Exploring Oxygenated Compounds for Efficient Transition Metal-Catalyzed Molecular Transformations

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A Brief Encomium

"All that I am, or hope to be,

I owe to my dear parents:

Congteng & Pingxian

For providing me with unconditional love;

And to my beloved wife:

Shanshan

For inspiring me to be the greatest version of myself;

And to my angel sisters:

Yiqing(Amy) & Yixuan (Bella)

For filling my heart with unending love."

Abstract

Xi-Jie Dai Supervisor: Professor Chao-Jun Li

McGill University

This thesis advances the knowledge in two fundamentally important organic chemical transformations: (1) cleavage of carbon-oxygen bonds, and (2) formation of carbon-carbon bonds. Such advancement consists of four late transition metal-catalyzed reactions based on the oxygenated chemical feedstock. The development of all these synthetic methods will be discussed on a chapter-by-chapter basis (Chapter 2 & 3: cleavage of C–O bonds; Chapter 4 & 5: formation of C–C bonds).

Chapter 2 introduces our initial attempts to address a 40-year-old scientific challenge in the field of alcohol deoxygenation: how to selectively and efficiently remove hydroxyl groups in organic molecules without affecting other existing functional groups. We hypothesize a single-step, redox process to solve this problem, whereby the dehydrogenative oxidation of alcohols and the Wolff-Kishner reduction are combined. As a proof-of-concept discovery, the early development of this reaction is catalyzed by iridium complexes and mediated by hydrazine under forcing reaction conditions. This deoxygenation protocol proves effective for a wide range of simple activated alcohol substrates such as benzylic and allylic alcohols. Mechanistic studies indicate that the iridium hydride complex serves as the key intermediate in the catalytic turnover. The major limitation, however, is the poor reactivity and selectivity seen in aliphatic alcohol substrates.

Chapter 3 describes the adaptation of ruthenium(II) catalysis for the direct deoxygenation of primary aliphatic alcohols in a completely chemo- and regio-selective manner. Such a robust catalytic system, comprising $[Ru(p\text{-cymene})Cl_2]_2$ and 1,2-bis(dimethylphosphino)ethane, is vital to lower the activation energy barriers to the dehydrogenative oxidation of aliphatic alcohols, and makes this step more kinetically favorable. Equally important is the combination of KO*t*Bu, DMSO and *t*-BuOH, which promotes the subsequent Wolff-Kishner reduction at low temperature.

As a consequence, this method is more practical compared with the previous iridium-based protocol, proceeding under milder thermal conditions. Notably, its synthetic utility is demonstrated by the selective cleavage of the carbon-oxygen bonds in both simple and complex organic molecules such as steroids and alkaloids.

Chapter 4 presents a novel approach to mask naturally occurring carbonyl compounds (i.e. aldehydes and ketones) as more sustainable alkyl carbanion equivalents for formation of carbon-carbon bonds via carbonyl addition reactions. Traditionally, such transformations are only possible with organometallic reagents, which rely on petroleum-derived chemical feedstocks and a stoichiometric quantity of metal. Accessing this umpolung reactivity of carbonyl compounds largely attributes to the ruthenium(II) catalytic system discovered in the previous deoxygenation chemistry. By fine-tuning the basicity in the reaction system, preformed carbonyl-derived hydrazones intercept another carbonyl compounds to form new carbon-carbon bonds, presumably via a Zimmerman-Traxler chair-like transition state. This chemical transformation delivers a wide range of synthetically valuable secondary and tertiary alcohols under very mild reaction conditions. Additional highlights include excellent functional group compatibility and good stereochemical control governed by chiral amido and phosphine ligands.

Chapter 5 focuses on the further exploration of such umpolung reactivity for formation of carbon-carbon bonds via conjugate addition reactions. Inspired by the softness of ruthenium(II) pre-catalyst, which bears a resemblance to that of 'soft' transition metals such as Cu, Rh, Ni, etc. in the classical 1,4-conjugate addition, we presume that this ruthenium(II)-based catalytic system may be more effective for conducting nucleophilic conjugate additions. Indeed, a variety of highly functionalized aromatic carbonyl compounds are used as latent benzyl carbanions, to couple with electron-deficient α,β-unsaturated compounds including esters, ketones, sulfones, phosphonates, and amides. Two bidentate phosphine ligands (dppp and dmpe) are found to facilitate this process in a complementary manner, largely depending on electronic profiles of the carbonyl compounds.

Chapter 6 summarizes all research present in this thesis and contributions to knowledge advancement.

Résumé

Cette thèse fait progresser la connaissance de deux transformations fondamentalement important es en chimie organique : (1) la rupture des liaisons carbone-oxygène, et (2) la formation de liaisons carbone-carbone. Une telle avancée repose sur quatre réactions hautement originales de réaction catalysées par des métaux de transition, à partir de matière première et de dérivés chimiques composés d'atome d'oxygène. Le développement de toutes ces méthodes de synthèse sera discuté chapitre par chapitre (Chapitre 2 & 3: rupture des liaisons C–O, Chapitre 4 & 5: formation des liaisons C–C).

Le chapitre 2 présente nos premières tentatives pour aborder un défi scientifique datant de 40 ans dans le domaine de la désoxygénation d'alcools: comment éliminer sélectivement et efficacement les groupes hydroxyles dans les molécules organiques sans affecter d'autres fonctions chimiques. Pour résoudre ce problème, nous proposons un processus redox en une seule étape combinant l'oxydation déshydrogénante d'alcools suivie de la réduction de Wolff-Kishner. Le développement de la réaction catalysée par un complexe d'iridium et assistée par l'intermédiaire d'hydrazine dans de fortes conditions oxydantes, démontre la faisabilité de notre hypothèse. Ce protocole de désoxygénation s'avère efficace pour une large gamme de fonctions alcools activées, telles que les fonctions alcools benzyliques et allyliques. Des études mécanistiques indiquent que le complexe d'hydrure d'iridium sert d'intermédiaire clef dans la régénération catalytique. Cependant, la principale limitation observée est la faible réactivité et la faible sélectivité vis-à-vis des alcools aliphatiques.

Le chapitre 3 décrit l'adaptation de la catalyse au ruthénium(II) pour la désoxygénation directe d'alcools primaires et aliphatiques, d'une manière complètement chimio- et régiosélective. Pour abaisser les barrières énergétiques d'activation de l'oxydation déshydrogénante d'alcools aliphatiques et rendre cette étape thermodynamiquement favorable, il a été vital de développer un système catalytique robuste comprenant du $[Ru(p\text{-cymene})Cl_2]_2$ et du 1,2-bis(diméthylphosphino)éthane. La combinaison de KO*t*Bu, DMSO et *t*-BuOH, favorisant la

réduction de Wolff-Kishner suivante, à basse température, est tout aussi importante. Par conséquent, cette méthode est nettement plus fonctionnelle, vis-à-vis du précédent protocole reposant sur la catalyse à l'iridium, en opérant dans des conditions thermiques nettement plus douces. Particulièrement, son utilité synthétique est démontrée avec élégance par la scission sélective des liaisons carbone-oxygène dans des molécules organiques simples et complexes telles que les stéroïdes et les alcaloïdes.

Le chapitre 4 présente une nouvelle approche pour utiliser les composés carbonylés naturels (c'est-à-dire les aldéhydes et les cétones) en tant que source masquée de carbanion pour la formation de liaisons carbone-carbone, via des réactions d'addition sur des dérivés carbonylés. Traditionnellement, de telles transformations ne sont possibles qu'avec des réactifs organométalliques, composés de matières premières dérivées du pétrole et d'une quantité stœchiométrique de métal. La clef pour accéder à cette réactivité umpolung des composés carbonylés est largement attribuable au système catalytique au ruthénium(II) découvert dans la réaction de désoxygénation précédente. En ajustant la basicité dans le système réactionnel, les dérivés d'hydrazones, préformés, s'additionnent à d'autres composés carbonylés pour former de nouvelles liaisons carbone-carbone. Cette addition est accomplie par l'intermédiaire d'un état de transition Zimmerman-Traxler, en forme chaise. Une large gamme d'alcools secondaires et tertiaires, possédant une grande valeur synthétique, est fournie dans des conditions réactionnelles très douces grâce à cette transformation unique. Parmi les autres points saillants, figurent une excellente compatibilité des groupes fonctionnels et un bon contrôle stéréochimique, contrôlé par des ligands chiraux amide et phosphine.

Le chapitre 5 se concentre sur l'exploration plus approfondie de la réactivité umpolung pour la formation de liaisons carbone-carbone, via des réactions d'addition conjuguées. Inspiré par la nature molle du pré-catalyseur au ruthénium(II), qui ressemble à celui des métaux de transition "mous" tels que le Cu, le Rh, le Ni, etc. dans la classique addition conjuguée 1,4, on suppose que le système catalytique à base de ruthénium(II) peut être plus efficace afin de mener des additions nucléophiles conjuguées. En effet, pour la première fois, des composés carbonylés aromatiques hautement fonctionnalisés sont utilisés en tant que carbanions benzyliques masqués pour s'additionner à des composés α, β-insaturés possédants des groupes déficients en électrons, comme

des esters, des cétones, des sulfones, des phosphonates et des amides. Deux ligands phosphines bidentés (dppp et dmpe) facilitent ce procédé de manière complémentaire, en grande partie dépendant des profils électroniques des composés carbonylés.

Le chapitre 6 résume toutes les recherches présentées dans cette thèse et les contributions à l'avancement des connaissances.

Acknowledgements

My sincere gratitude goes first and foremost to my supervisor, Professor Chao-Jun Li, for your constant guidance, stimulation and encouragement throughout my Ph.D. pursuit. I feel grateful and privileged to be under the tutelage of such an incredibly supportive and wise advisor. I appreciate your coaching (time, ideas and funding) on my professional growth as an independent scientist. Your sheer joy and passion for pursuing great chemistry has been insatiable and contagious. In particular, the strong faith you put in me when roads ahead were getting tough ends up bumping into some really interesting chemistry.

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To my most beloved parents, Congteng and Pingxian: I owe to you nearly everything that I have accomplished to this stage. Thank you for raising me with unconditional love and nurturing a strong-willed character in me against adversity and setbacks. I would like to extend my deepest gratitude to my wonderful parents-in-law, Jianwei and Haiping: Thank you for being always supportive over years and trusting me to bring the ultimate happiness to your precious daughter. I could not have been so successful in the Ph.D. program without backups from four of you, particularly two great moms.

To my amazing and beautiful wife, Shanshan Mi: Marrying you is the best decision I have ever made in my life. Being with you oversea in Canada pushes me to a whole new level of maturity. Because of you, I am today a much better man in all aspects of life than what I was years ago. Regardless of what uncertainties that would kick in our next chapter of life, the future looks brighter than ever. I cannot thank you enough for all sacrifice you made to our little family.

Lastly, to my darling daughters, Yiqing(Amy) Dai and Yixuan (Bella) Dai: thank you for making me smile and filling my heart with warmth and love at the end of heavy days. I am thrilled and motivated by your ever-increasing curiosities to be a greater daddy today than yesterday.

Table of Contents

List of Schemes

List of Figures

List of Tables

List of Abbreviations

A^3-coupling alkyne-aldehyde-amine coupling

Ac acetyl

acac acetylacetone

APCI atmospheric pressure chemical ionization

Ar aryl

BINAP 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl

Bn benzyl

Boc *tert*-butoxycarbonyl

br broad singlet (^{1}H NMR) or broad (IR)

*n*Bu *n*-butyl

*t*Bu *tert*-butyl

Bz benzoyl

C–C carbon-carbon

C–H carbon-hydrogen

C–X carbon-heteroatom

CDC cross-dehydrogenative-coupling

cod 1,5-cyclooctadiene

Cp cyclopentadienyl

Cp* pentamethylcyclopentadienyl

Cy cyclohexyl

d doublet (^{1}H NMR)

dd doublet of doublets (^{1}H NMR)

DBU 1,8-diazabicyclo[5.4.0]undec-7-ene

DCE 1,2-dichloroethane

DCM dichloromethane

DEAD diethylazodicarboxylate

DFT density functional theory

DIPEA N,N-diisopropylethylamine

DME 1,2-dimethoxyethane

DMF dimethylformamide

DMSO dimethyl sulfoxide

DPEphos (oxydi-2,1-phenylene)bis(diphenylphosphine)

dppb bis(diphenylphosphino)butane

dppbenz 1,2-bis(diphenylphosphino)benzene

dppe bis(diphenylphosphino)ethane

dppf bis(diphenylphosphino)ferrocene

dppp bis(diphenylphosphino)propane

dr diastereomeric ratio

ee enantiomeric excess

ESI electrospray ionization

Et ethyl

eth ethylene

FT fourier transform

HAS Homolytic Aromatic Substitution

HRMS high-resolution mass spectroscopy

Hz Hertz

equiv equivalents

INT intermediate

*i*Pr *iso*-propyl

IR infrared spectroscopy

J coupling constant

[M] metal

m meta

m multiplet (^{1}H NMR) or medium (IR)

Me methyl

m.p. melting point

MS Mass spectrometry

n normal

NBE norbornylene

NBSH *o*-nitrobenzenesulfonylhydrazine

NHC N-Heterocyclic Carbene

NMR nuclear magnetic resonance spectroscopy

Nu nucleophile

[O] oxidative conditions

o ortho

OAc acetoxy

OTf trifluoromethanesulfonate

p para

Ph phenyl

ppm parts per million

PTFE polytetrafluoroethylene

Py pyridine

q quartet (^{1}H NMR)

quin quintet (^{1}H NMR)

QTOF quadrupole-time of flight

rac racemic

rt room temperature

s singlet (^{1}H NMR) or strong (IR)

sep septet (^{1}H NMR)

SET single electron transfer

t triplet (^{1}H NMR)

t tert

T temperature

TBP *tert*-butyl peroxide

temp. temperature

TFA trifluoroacetyl

TfOH triflic acid

THF tetrahydrofuran

TLC thin-layer chromatography

Ts para-toluenesulfonyl

TS transition state

UV ultraviolet

w weak (IR)

WK Wolff-Kishner

Xantphos 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene

XRD X-ray Powder Diffraction

Contributions of Co-Authors

This thesis includes six chapters. Chapter 1 is an introduction and Chapters 6 presents conclusions, contributions to the knowledge and prospects of the current thesis. The main part consists of four publications (Chapters 2-5). All the work has been accomplished in partial fulfillment of my Ph.D. degree in Chemistry under the tutelage of Professor Chao-Jun Li. Thus, he has been the corresponding author on all published manuscripts. All experimental sections included in this thesis were performed by myself with a few exceptions: Dr. Jian-Lin Huang provided preliminary scope results and jointly examined the reaction scope (Chapter 2); Dr. Zheng-Wang Chen and Dr. Feng Wang prepared some of the alcohol substrates (Chapter 3); Dr. Haining Wang jointly performed all experiments (Chapter 4 & 5).

This thesis has made original contributions to advance knowledge in two fundamental chemical transformations: cleavage of carbon-oxygen bonds and formation of carbon-carbon bonds:

1. Cleavage of carbon-oxygen bonds: the development of a redox-based, single-step deoxygenation strategy (Chapter 2 & 3) simultaneously addresses the challenges regarding step economy and selectivity, a 40-year-old scientific problem since the discovery of Barton-McCombie deoxygenation.

2. Formation of carbon-carbon bonds: naturally occurring carbonyls could be used as latent alkyl carbanion equivalents for versatile carbon-carbon bond-forming processes, including Grignard-type carbonyl addition reactions (Chapter 4), Michael-type conjugate addition reactions (Chapter 5), imine addition reactions and carbonyl olefination reactions. These reactions are fundamentally important in contemporary organic synthesis, yet traditionally rely on petroleum-derived chemical feedstocks (i.e. organohalides) and a stoichiometric quantity of metal.

Consequently, the following publications have resulted from these contributions, and are the basis of, or are discussed in this thesis:

1. Huang, J.-L., **Dai, X.-J.**, and Li, C.-J. (2013) Iridium-catalyzed direct dehydroxylation of alcohols. *European Journal of Organic Chemistry*. 6496-6500.

2. **Dai, X.-J.**, and Li, C.-J. (2016) En route to a practical primary alcohol deoxygenation. *Journal of the American Chemical Society*. **2016**, *138*: 5433-5440.

3. Wang, H.[†], **Dai, X.-J.**[†], and Li, C.-J. (2016) Aldehydes as alkyl carbanion equivalents for additions to carbonyl compounds. *Nature Chemistry*. **2016**, *9*, 374-378 ([†]indicates *co-first authorship*).

4. **Dai, X.-J.**[†], Wang, H.[†], and Li, C.-J. (2017) Carbonyls as latent carbanions for conjugate additions. *Angewandte Chemie International Edition.* **2017**, *56*, 6302-6306 ([†]indicates *co-first authorship*).

5. Chen, N.[†], **Dai, X.-J.**[†], Wang, H.[†], and Li, C.-J. (2017) Umpolung addition of aldehydes to aryl imines. *Angewandte Chemie International Edition*. **2017**, *56,* 6260-6263 ([†]indicates *co-first authorship*).

6. Wei, W.[†], **Dai, X.-J.**[†], Wang, H., Yang, X., and Li, C.-J. (2017) Ruthenium(II)-catalyzed olefination via carbonyl reductive cross-coupling. *Chemical Science.* **2017**, *submitted* (†indicates *co-first authorship*).

The final publication comprised a book chapter that I wrote as a research summary in the field of cross-dehydrogenative-coupling (CDC), which was entitled oxidation adjacent to nitrogen as one of the chapters in *Comprehensive Organic Synthesis*, 2nd edition.

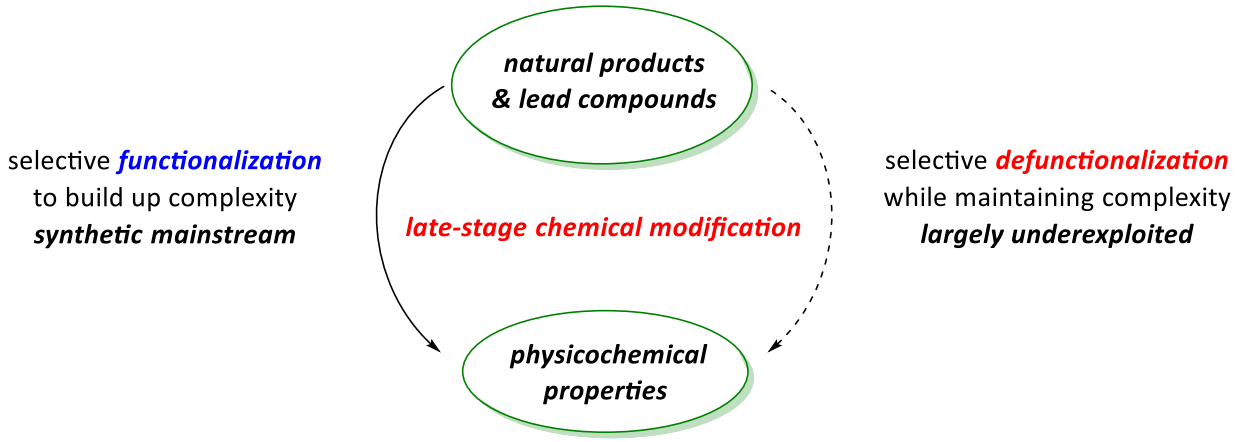
7. **Dai, X.-J.**, Li, C.-J. (2014) Oxidation adjacent to nitrogen. In: Gary A. Molander and Paul Knochel (eds.), *Comprehensive Organic Synthesis*, 2nd edition, Vol 7, Oxford: Elsevier; **2014**, pp. 242-261.

Chapter 1 : A Quest for Efficient Alcohol Deoxygenation via Metal-Catalyzed Dehydrogenative Activation

1.1 Perspective

1.1.1 Late-Stage Chemical Modification of Organic Molecules

Selective functionalization in organic molecules lies at the center of synthetic organic chemistry. Over the centuries, synthetic chemists have concentrated on the discovery of new reactions that allow facile construction of various chemical bonds in molecules to achieve complexity. As a result, progressive advances have been made in this field.[1] In particular, the late-stage interconversion of functional groups in high-value chemicals and drug-like candidates in a

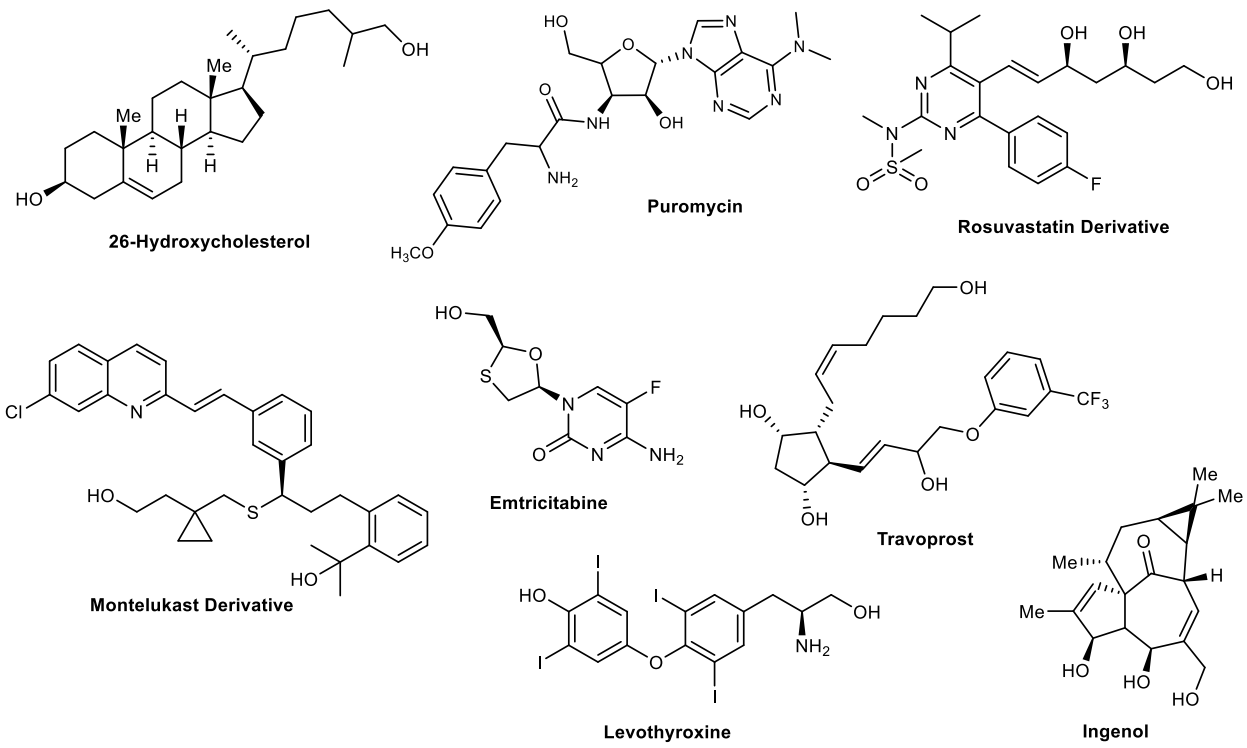


Scheme 1-1 Synthetic Toolbox for Late-Stage Chemical Modification

predictable and efficient manner enables rapid diversification and streamlines bioactive testing of closely related analogues.[2] An equally crucial chemical transformation, yet historically being considered latent, is the opposite direction—selective defunctionalization. Its significance can be justified by fine-tuning of the desired physico-chemical properties[3] (e.g. hydrogen-bond donors

and acceptors, solubility and permeability, etc.) of complex natural products and lead-like compounds, especially at the late stage of total synthesis or drug discovery, when an accurate removal of a specific functional group is required without affecting others (Scheme 1-1). Surprisingly, scarce endeavors have been geared toward this direction since the elaboration of functionalization methods at the beginning of the 21st century.

1.1.2 Significance of Efficient and Selective Alcohol Deoxygenation Methods



Scheme 1-2 Representative Complex Oxygenated Molecules, Pharmaceutical Drugs and Derivatives

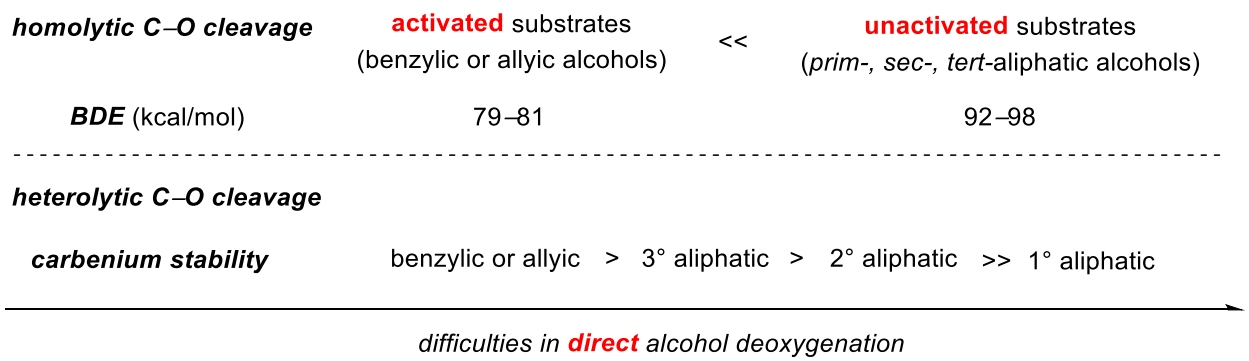
Under this context, one of the long-lasting challenges in the field of alcohol deoxygenation is how to selectively and efficiently replace hydroxy groups by hydrogen atoms in organic molecules bearing other functionalities (e.g. unprotected hydroxy groups bound to different types of carbons than the target ones, unprotected amines, etc.) without excessive chemical transformations.[4] Chemical tools (or synthetic methods) devised to address this challenge have become increasingly vital in the synthesis of complex oxygen- and nitrogen-bearing organic compounds (Scheme 1-2),

as well as in nucleoside and carbohydrate chemistry.[5] In fact, many deoxy derivatives of aminoglycoside and nucleoside antibiotics exhibit higher efficacy against resistant bacterial strains than their corresponding hydroxy precursors, as enzymatic deactivation (e.g. phosphorylation) is often problematic in the latter situation.[6]

Apart from great appeal in organic synthesis and drug-related development, strategies to remove hydroxy groups from biomass-derived feedstocks have attracted increased attention with the growing societal demand for sustainability.[7] A majority of these renewable feedstocks comprises highly oxygenated organic components (polyol structure with multiple hydroxy groups) which present enormous challenges (e.g. poor solubility in organic solvents, thermal instability, limited functionalization capability, etc.) to any deoxy chemical manipulation, especially with high selectivity. Hence, the conversion of biomass-derived feedstocks into fuels or other valuable chemicals with less oxygen contents by efficient synthetic means is rather difficult.

1.1.3 Fundamental Challenges and Our Proposed Solution

Depending on the nature of the chemical process (radical or ionic fission), C–O bonds present in alcohols and other oxygenated organic molecules are cleaved in either a homolytic or a heterolytic manner. However, none of them is able to proceed easily in one step because of thermodynamic and kinetic barriers (Scheme 1-3). In terms of thermodynamics, strong C–O bonds feature large bond dissociation energy (BDE),[8] especially for aliphatic hydroxy groups (BDE: 92–98 kcal/mol). In other words, unactivated C(sp^3)–O bonds in aliphatic alcohols are much stronger than activated ones at benzylic or allylic positions, and hence significantly less reactive when it comes to common single-step deoxygenation strategies (i.e. hydrogenolysis, homolysis, etc.). As a consequence, such a huge activation energy barrier has to be overcome by robust catalysis or intensive thermal energy for achieving the single-step homolytic C–O bond cleavage. Moreover, unlike secondary or tertiary aliphatic alcohols which can be directly deoxygenated via a Lewis acid-assisted activation/hydride reduction sequence, it is much more challenging to remove oxygen from primary alcohols in a single-step manner owing to the relatively unstable carbenium intermediates. On the other hand, most good nucleophiles are themselves strong bases while most alcohols are weak acids. For this matter, the acid-base interaction between nucleophiles and alcohols, rather than a direct S_N2 substitution of hydroxy groups, will become predominant in nearly all cases.



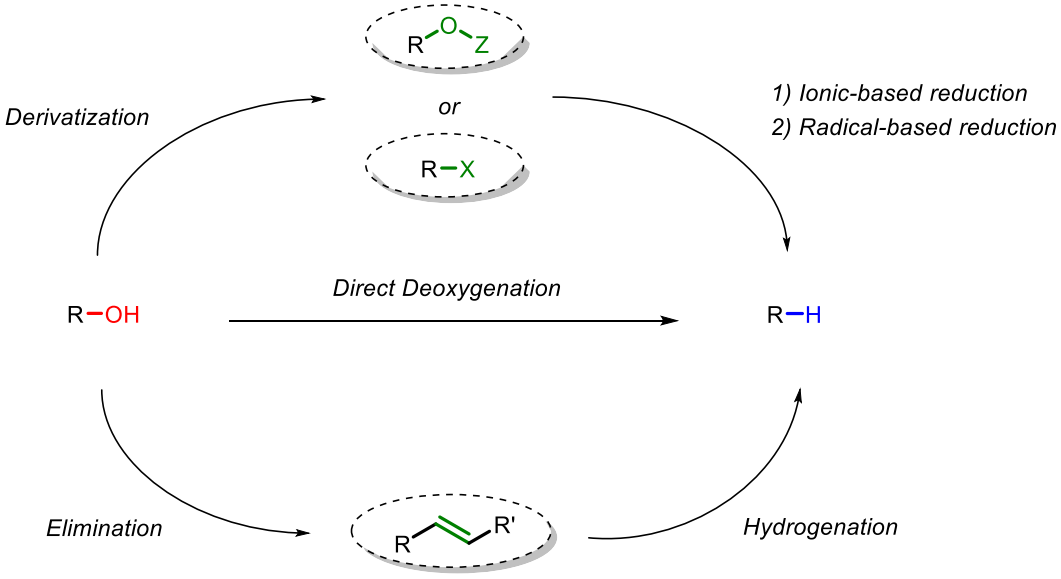
Scheme 1-3 Fundamental Thermodynamics of Various Alcohols.

Even if there was an exception, the direct heterolytic C–O bond dissociation by S_N2-type nucleophilic substitution would have produced strongly basic hydroxide anion (OH^-) as a poor leaving group,[9] and led to a thermodynamically unfavored process. To bypass these intrinsic barriers, most known synthetic methods for alcohol deoxygenation involve more reactive intermediates (alcohol derivatives) with better leaving group ability, and generally require two-step chemical transformation. Despite the fact that two-step deoxygenation strategies are widely applied in total synthesis, a few elegant single-step methods have been reported on various alcohol substrates. Mechanistically, all these exisiting deoxygenation protocols are either radical-based or ionic-based. Aligned with our long-term academic pursuit — to explore new reacvitivies from more efficient chemical transformations — we conceived a catalytic redox-based approach as a step-economic alternative to address selectivity issues in the field of alcohol deoxygenation. This redox design capitalizes on late-transition-metal catalysis and combines two known chemical reactions: the dehydrogenative oxidation of alcohols and the Wolff-Kishner (WK) reduction. In other words, utilizing better reactivity of carbonyl compounds (i.e. electrophilicity of carbon-oxygen double bonds) is envisioned, and the key concern is if the initial oxidation and the subsequent reduction will be compatible. In the next two chapters (Chapter 2 and 3), the concept of this redox-based hypothesis will be reintroduced in detail. The current chapter will briefly cover two-step deoxygenation methodologies, and recent developments in single-step deoxygenation methodology. The short revisit of contemporary deoxygenation methods will then be followed by some landmark papers in both the alcohol dehydrogenation and the WK reduction. Lastly, it will provide an overview of the rest of the chapters in this thesis.

1.2 Modern Alcohol Deoxygenation Methods

1.2.1 Introduction

Alcohol deoxygenation has long been a field of extensive study and popularity in organic chemistry.[10] Although past decades have witnessed enormous progress in this field, a majority of the deoxygenation methods consists of a two-step approach featuring the successive derivatization and reduction processes. Alternatively, an elimination-hydrogenation sequence represents a viable pathway for the same purpose. Complementary to the two-step approach is the single-step deoxygenation protocol, which has been predominately demonstrated in the context of benzylic, allylic alcohols, and aliphatic secondary and tertiary alcohols, but remained a challenging subject for sterically unhindered substrates such as primary aliphatic alcohols. In this section, we discuss

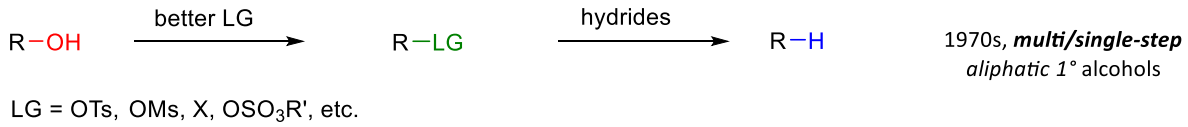


Scheme 1-4 Reaction Pathways for Alcohol Deoxygenation

different deoxygenation strategies based on their mechanistic profiles, with special emphasis on the deoxygenation of alcohols containing sp^3 C–O bonds (Scheme 1-4).

1.2.2 Ionic-Based Two-Step Deoxygenation Approach

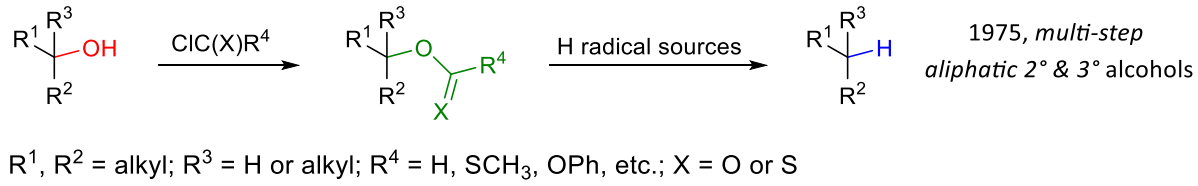
Classical ionic-based alcohol deoxygenation methods involve the formation of more chemically reactive alcohol derivatives via S_N2-type nucleophilic substitution, or *O*-functionalization, and their subsequent reduction in the presence of various hydride sources (Scheme 1-5). Representative intermediates in this stepwise transformation include tosylates,[11] mesylates,[12] sulfates,[13] organic halides,[14] and thiolates[15]. In principle, these ionic deoxygenation methods are quite effective towards simple and sterically unhindered alcohols (e.g. primary alcohols). However, stoichiometric amounts of chemical reagents employed in both steps result in the production of undesirable organic wastes. Apart from the stoichiometric problems, their limitations appear to be twofold: 1) unreactive sterically encumbered hydroxy groups in S_N2-type substitution reactions, and 2) poor chemoselective and regioselective control in polyfunctional, complex compounds bearing indiscriminate hydroxy groups and amines.



Scheme 1-5 Ionic S_N2-Based Two-Step Deoxygenation

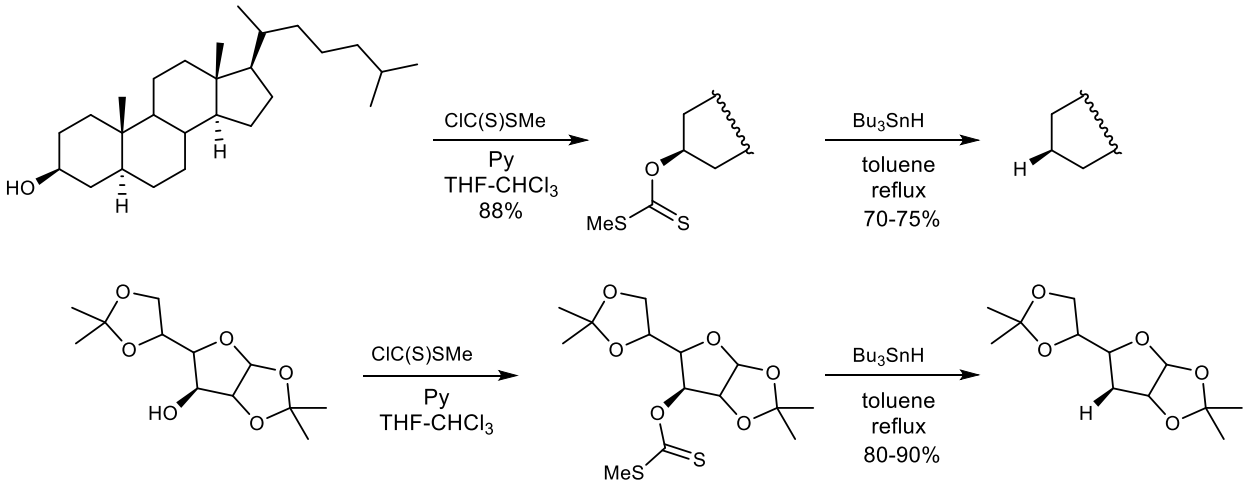
1.2.3 Radical-Based Two-Step Deoxygenation Approach

Radical deoxygenation, or the homolytic cleavage of a C–O bond to yield carbon radicals, can be realized by the β-fragmentation of suitable alcohol derivatives and the subsequent interception of hydrogen radicals (Scheme 1-6). Unlike the ionic-based deoxygenation which occurs under acidic or basic conditions, radical reactions commonly take place under neutral conditions, compatible with the presence of many sensitive functional groups in complex organic molecules. Importantly, radicals are less highly solvated and less susceptible to steric factors or dipole repulsion than ions, and hence radical-based methods are more advantageous for sterically congested alcohols with secondary or tertiary hydroxy groups. Perhaps the best-known method in this category is the Barton-McCombie deoxygenation of aliphatic alcohols, in which tributylstannane was used to reduce reactive carbonothioyl intermediates such as *O*-alkyl thioesters or xanthates.[16] The original,



Scheme 1-6 Radical-Based Two-Step Deoxygenation

stepwise protocol discovered in 1975 proves to be extremely effective on the removal of secondary hydroxy groups met in steroids and sugars, and tolerates various functional groups including carbonyls, esters, lactones and polyenes (Scheme 1-7).[16a] This ground-breaking chemical transformation rapidly finds its synthetic application in the subsequent deoxygenation of nucleosides.[5a, 5b] Such an important chemical modification of nucleosides holds promise for a profound impact on carbohydrate chemistry, as the enhanced biological activity can



Scheme 1-7 Barton-McCombie Deoxygenation of Secondary Alcohols

potentially be conferred on polyhydroxylated antibiotics. While the original Barton-McCombie deoxygenation is quite efficient for secondary alcohols, the fragmentation of the thiocarbonyl intermediates derived from primary alcohols was not observed under the normal reaction conditions.[17] Barton *et al.* later demonstrated the possible deoxygenation of hindered primary alcohols with neopentyl substitution, albeit at considerably higher temperature.[18] In addition, the one-pot procedure was further devised for the unhindered primary alcohol deoxygenation.[19] The

deoxygenation of tertiary alcohols, on the other hand, was often complicated by the competing Chugaev elimination owing to the thermal instability of the corresponding thiocarbonyl derivatives.[20] The mild reaction conditions and a wide range of functional groups accommodated in the Barton and McCombie's seminal discovery have spurred broad interests in developing analogous deoxygenation methods. In turn, such deoxygenations have seen considerable use in organic synthesis for the late-stage modification of synthetic intermediates or natural products. These variations employ, by and large, different thioacyl fragments and hydrogen sources. The main disadvantage of the Barton-McCombie reaction is the use of stoichiometric tributylstannane as the hydrogen donor, which is toxic, expensive and difficult to remove from the reaction mixture. Therefore, while this deoxygenation method has gained significant popularity over years in the academic community, stannanes make it a particularly undesirable chemical process for the synthesis of pharmaceuticals in drug industry.

To circumvent the stoichiometry issues regarding the tin reagent, Fu *et al.* have proposed the use of a catalytic amount of tributylstannane in the presence of a silane-based reducing reagent PMHS.[21] The reduction step excluding tin-based reagents has also been devised. Tris(trimethylsilyl)silane serves as a comparable donor to tributylstannane, and it can be used in combination with triethylborane to reduce 2'-bromonucleosides.[22] Organophosphorus compounds with P–H bonds such as dialkyl phosphites and hypophosphorous acids are inexpensive, low toxicity hydrogen donors, but larger amounts of AIBN as the radical initiator are required.[23] Other recent efforts to bypass scale-up problems include the use of sodium formate as the hydrogen source, with stoichiometric tetrabutylammonium peroxydisulfate initiating radicals,[24] as well as the combination of a trialkylborane-water complex (trimethylborane) and oxygen.[25] In the latter case, the oxidation of trimethylborane by air initiated the catalytic cycle, affording the methyl radical. Theoretical calculations suggested that O–H homolysis in borane-water complex is roughly as endothermic as the homolysis of tributylstannane, yet much lower than that of pure water. To seek practical routes that completely avoid the consumption of tin-based reagents, photosensitized electron-transfer deoxygenation utilizing simple benzoyl esters was reported by Saito and co-workers, which exhibits high selectivity on secondary alcohols in preference to primary ones.[26] The application of electrochemistry to the efficient deoxygenation based on benzoyl esters was also exploited for various types of alcohols.[27] Apart from the extensive use of

thiocarbonyls and benzoyl esters, phosphites were explored as reactive intermediates in the radical-based approach, delivering a comparatively clean and selective deoxygenation process of secondary and tertiary alcohols.[28]

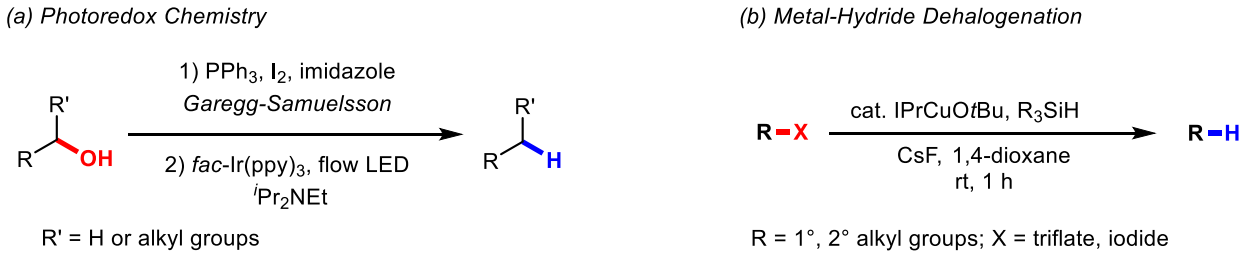
Besides being a two-step process, another commonality between the classical ionic and radical deoxygenation methods is the initial S_N2 displacement of alcohols to obtain more reactive intermediates that are much easier subject to either heterolytic or homolytic C–O bond dissociation in the succeeding reduction. One of the major downsides associated with these deoxygenation methods, regardless of via an ionic or a radical pathway, is an overall low step-efficiency. This raises an issue on inefficient chemical syntheses, particularly problematic for the synthesis of complex natural products. Another key issue that remains unanswered is how to remove hydroxy groups without affecting other functional groups present in the same molecules, or how to achieve great chemoselectivity. The employment of S_N2 substitution in the first step of the deoxygenation process implies the inferior chemoselectivity between various alcohols (i.e. to discriminate aliphatic primary and secondary hydroxy groups), and between alcohols and other functional groups that have much stronger nucleophilicity such as free amines. Driven by the ever-increasing desire for efficient chemical transformations,[29] the synthetic community calls for more direct conversions of hydroxy groups into deoxygenated C–H bonds. As stated in the previous perspective section, however, the direct deoxygenation of aliphatic alcohols is more kinetically challenging than that of benzylic or allylic alcohols, with primary aliphatic alcohols being the most difficult substrate. A few elegant attempts in this direction will be discussed next with a focus on alcohols containing sp^3 hybridized C–O bonds.

1.2.4 One-Step (or Two-Step, One-Pot) Deoxygenation Approach

There are commonly three intermediates involved in the one-step deoxygenation process for aliphatic alcohols: organohalides, alkyldiazenes and carbenium species. While the former two are often seen in the direct deoxygenation of primary and secondary aliphatic alcohols, the last one is well-established for that of tertiary aliphatic alcohols.

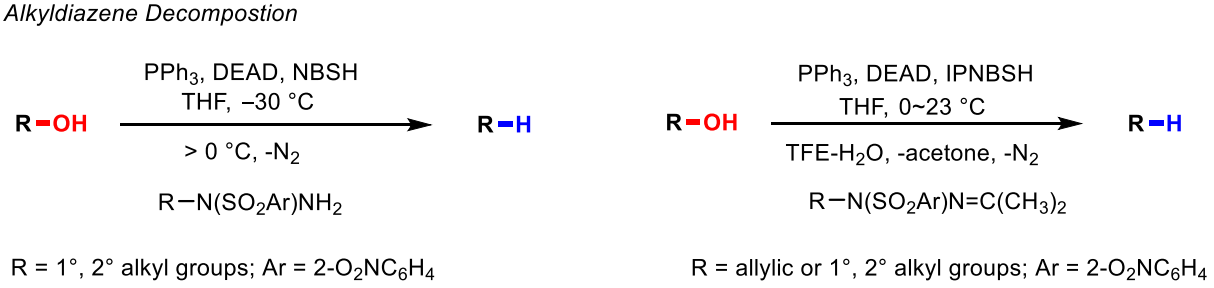
1.3.1.1 Direct Deoxygenation via S_N2 Substitution

Similar to two-step deoxygenation methods, the S_N2 substitution containing various intermediates provides a formally one-step route for unhindered primary or secondary aliphatic alcohols. For instance, phosphonium anhydride was developed as a potent oxophile to activate several simple primary alcohols by forming the corresponding phosphonium ethers.[30] These activated ethers were subsequently reduced by an external hydride source such as borohydride. However, the reaction rate became severely affected with sterically hindered secondary alcohols. Organohalides are reactive intermediates that many researchers relied on for single-step deoxygenation. Stephenson and co-workers devised the sequential Garegg-Samuelsson reaction to obtain alkyl organoiodide intermediates which underwent visible light photocatalyzed dehalogenation using flow chemistry (Scheme 1-8, a).[31] Alternatively, a photochemical-mediated method was reported using CBr_4, DMF, and a catalytic amount of $[Au_2(dppm)_2]Cl_2$, composing the initial bromination followed by the photoredox reduction.[32] Lalic *et al.* proved that the reduction of alcohol-derived triflates and iodides can be catalyzed by the NHC copper catalyst in the presence of silyl hydrides at ambient temperature (Scheme 1-8, b).



Scheme 1-8 Two-Step, One-Pot Deoxygenation via Organohalides

Another reactive intermediate is the monoalkyl diazene species, initially developed in the late 90's by Myers *et al.* for the single-step reductive deoxygenation of unhindered primary and secondary alcohols and further improved by Movassaghi and others in 2007 (Scheme 1-9). The early discovery involves a simple S_N2 Mitsunobu displacement of alcohols with *o*-nitrobenzenesulfonylhydrazine (NBSH), followed by the exclusion of N_2 via alkyldiazene decomposition to yield the hydrocarbons. A strict control over the reaction temperature (i.e. –30 °C)

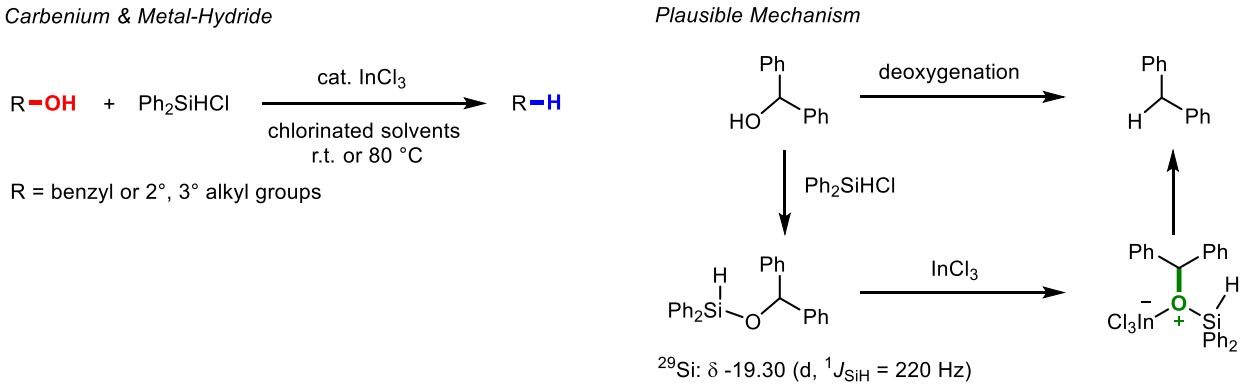


Scheme 1-9 One-Step Deoxygenation via Alkyldiazenes

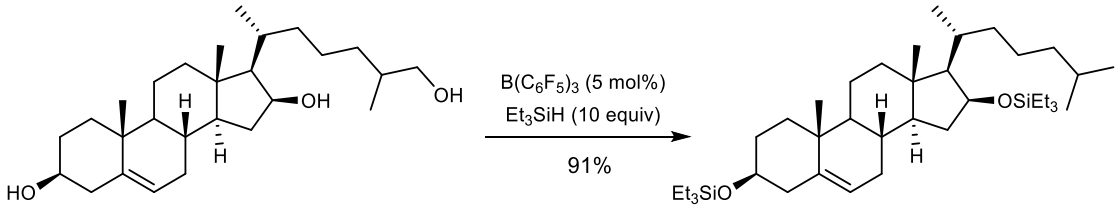
was required for the Mitsunobu reaction before the subsequent decomposition taking place at room temperature.

1.3.1.2 Lewis Acid-Catalyzed Deoxygenation

Lewis acids are known to activate sp^3 C–O bonds in alcohols for a single-step deoxygenation process with a subsequent hydride reduction.[33] They are mostly used in stoichiometric quantities. The formation of carbenium (carbon cation, e.g. α-oxocarbenium) or oxonium intermediates is typically involved upon the activation of alcohols. In line with previous discussion in the section **1.1.3**, the trend of reactivity based on different alcohols is expected to be as follows: benzylic or allylic > tertiary aliphatic > secondary aliphatic >> primary aliphatic. This difference in reactivity can be easily understood based on the relative stability of carbenium intermediates. For instance,

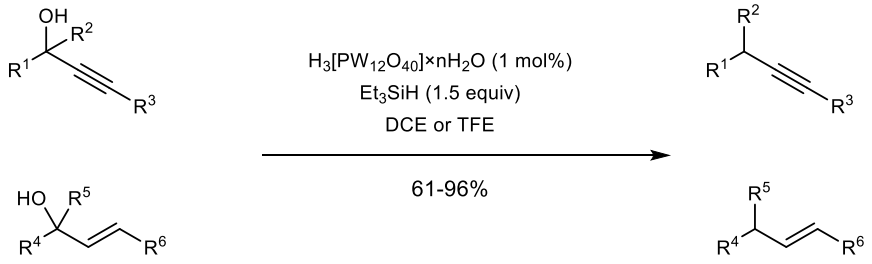


Scheme 1-10 Indium-Catalyzed Direct Deoxygenation via Stabilized Carbenium Intermediates



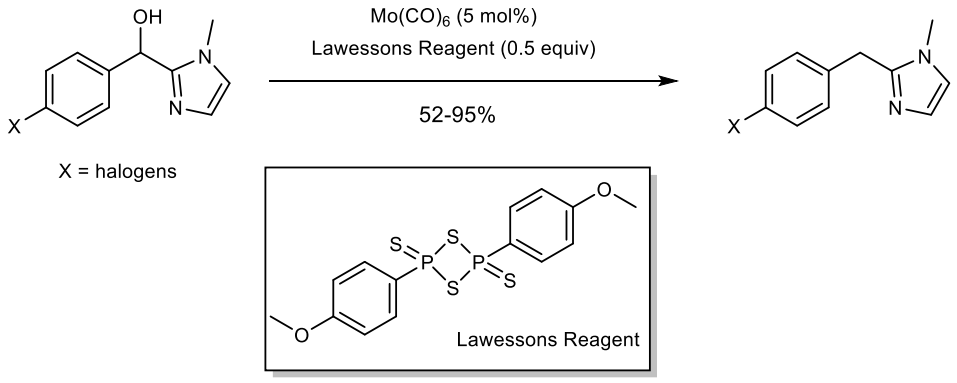
Scheme 1-11 $B(C_6F_5)_3$-Catalyzed Chemoselective Deoxygenation in Steroids

silyl hydrides were used to reduce secondary benzylic or tertiary aliphatic alcohols at ambient temperature, a reduction catalyzed by a catalytic amount of trivalent indium halides (i.e. $InCl_3$).[34] The corresponding oxonium intermediates, observed by ^{29}Si NMR, were proposed as the key intermediate to turnover the catalytic cycle (Scheme 1-10).[35] Although this chemistry was mostly illustrated by simple alcohols, it did enable the chemoselective deoxygenation of diols containing both benzylic secondary hydroxy group and primary hydroxy group in one step, with the removal of the former. In addition, other functionalities such as esters, halogens and nitro groups can



Scheme 1-12 Direct Deoxygenation of Propargylic and Allylic Alcohols

remain intact under the reaction conditions. The reversal order of reactivity is also possible, which was reported by Gevorgyan *et al.* using a catalytic amount of $B(C_6F_5)_3$ and $HSiEt_3$ as hydride source.[36] Under such scenario, the chemoselective deoxygenation of primary alcohols efficiently occurred in steroids bearing two secondary alcohols, with both protected as silyl ethers in the end (Scheme 1-11).[37] There are many other Lewis acid-catalyzed examples on allylic and propargylic alcohols. The heteropolyacid $H_3[PW_{12}O_{40}]\times nH_2O$ deoxygenates allylic and propargylic alcohols under mild reaction conditions in moderate to high yields, using Et_3SiH as a reducing agent (Scheme 1-12).[38] Other Lewis acids such as $Ca(NTf_2)_2$ and $Bi(OTf)_3$ are effective towards the deoxygenation of propargylic, allylic and benzylic alcohols. While Bu_4NPF_6 was used



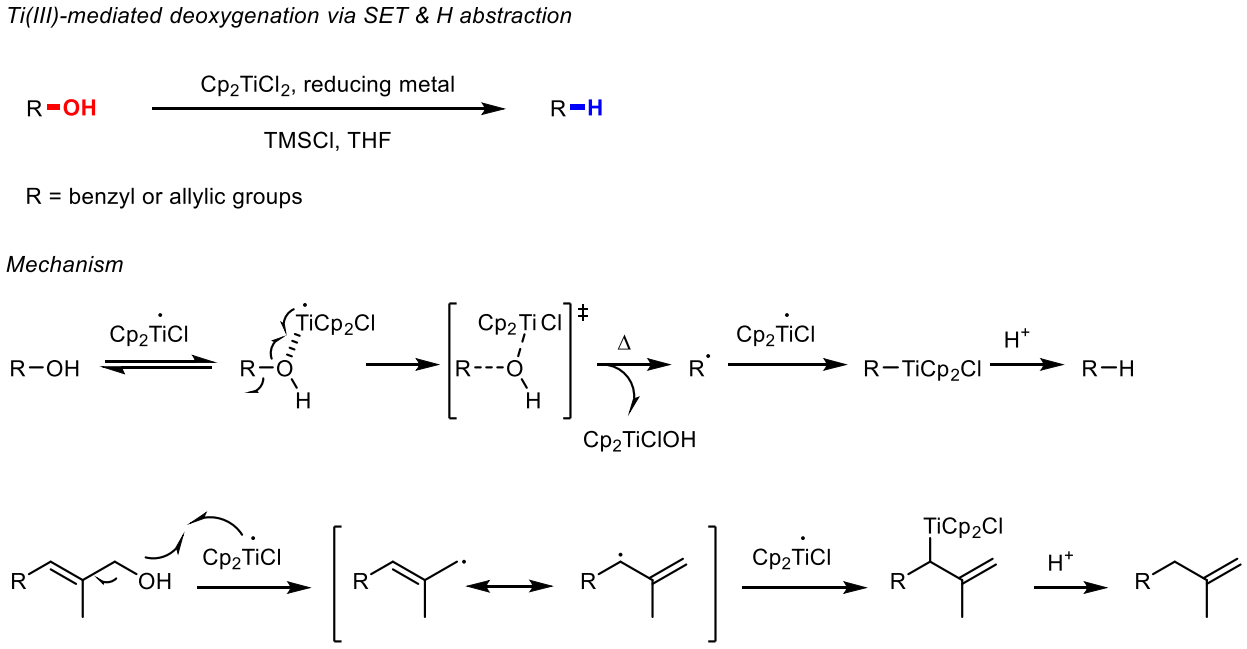
Scheme 1-13 Molybdenum-Catalyzed Direct Deoxygenation of Benzylic Alcohols

as an additive to enhance the $Ca(NTf_2)_2$-catalyzed deoxygenation,[39] the medium of $Bi(OTf)_3$-catalyzed reaction was the ionic liquid [BMIM][BF4].[40] Molybdenum hexacarbonyl, known for the cleavage of C–S bonds, was also employed as Lewis acid in the catalytic deoxygenation of alcohols. In combination with Lawesson´s reagent, a chemical used to convert carbonyl compounds into thiocarbonyls, $Mo(CO)_6$ catalyzed the deoxygenation of benzylic alcohols bearing heterocycle rings in high yields (Scheme 1-13).[41]

1.3.1.3 Titanium(III)-Mediated Radical Deoxygenation

With respect to activated alcohols such as benzylic or allylic alcohols, a single electron transfer (SET) process mediated by a trivalent titanium complex is typically involved in their direct deoxygenation. Low-valent titanium species have long been known for activating C–O bonds to form olefins in the McMurry coupling reaction. It was also applied to the deoxygenation of benzylic and allylic alcohols.[42] In 1980, Sato *et al.* showed that $TiCl_4$ or titanocene dichloride, Cp_2TiCl_2 catalyzed the deoxygenation of allyl and benzyl alcohols and allyl ethers in the presence of $LiAlH_4$.[43] Recently, Barrero and co-workers described such a protocol utilizing a stoichiometric amount of Nugent's reagent (Cp_2TiCl), generated *in situ* from Cp_2TiCl_2 in the presence of reducing metals like magnesium or zinc, to homolytically break the C–O bond (Scheme 1-14).[44] The key to success is the oxophilic trivalent titanium species, and the relatively low C–O bond activation energy of activated alcohols. Depending on the nature of substrates (alcohol or carbonyl compounds), the radical evolved from Cp_2TiCl can be either captured by a hydrogen donor via

hydrogen atom transfer, delivering an overall deoxygenation process, or can recouple with another radical. In the latter case, the recoupling of the radical intermediate often yields a C–C double bond. Isomerization of the double bond sometimes occurred in the deoxygenation of allyl alcohols. This process is driven by the formation of the most stable radical intermediate. Apart from titanium(III) reagents, $WCl_2(PMe_3)_4$ and $WH_2Cl_2(PMe_3)_4$ could deoxygenate methanol by forming tungsten alkoxide species as key intermediates.[45] The alkyl radical generated by the homolysis of the C–O bond was driven by the thermodynamically favored tungsten-oxo triple bond formation.



Scheme 1-14 Titanium(III)-Mediated Direct Deoxygenation of Benzylic or Allylic Alcohols

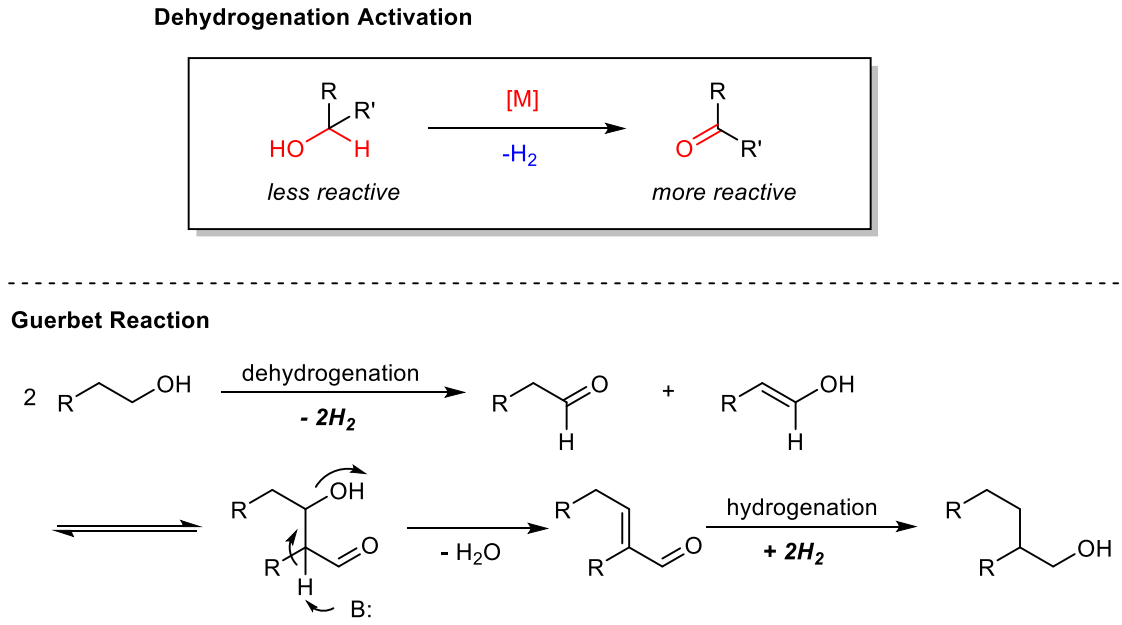
While all these direct deoxygenation protocols improve the step-efficiency compared to the classical two-step methods, they generally do not have good chemoselectivity over different aliphatic hydroxy groups, especially in complex molecules (e.g. to discriminate primary alcohols from secondary ones). Another challenge that remains elusive in this field, despite all the progress made in increasing step efficiency, is how to selectively remove hydroxy groups from molecules bearing more nucleophilic functional groups without tedious protection-deprotection manipulations. One such representative is the unprotected amines ubiquitously found in natural products and bioactive molecules. Organic nitrogen compounds also constitute over 90% of the

200 top-selling drugs, and feature in many named organic reactions. However, the presence of free amines in alcohols raises concerns on all S_N2-based direct deoxygenation processes owing to the stronger nucleophilicity of nitrogen atoms. Thus, protecting amines is necessary prior to the deoxygenation of molecules such as amino alcohols. To avoid this problematic scenario, we decided to study a mechanistically different deoxygenation pathway based on the dehydrogenative alcohol oxidation and the Wolff-Kishner reduction. This non-ionic and redox-based approach could provide a viable solution to simultaneously address the challenges regarding step-efficiency and selectivity.

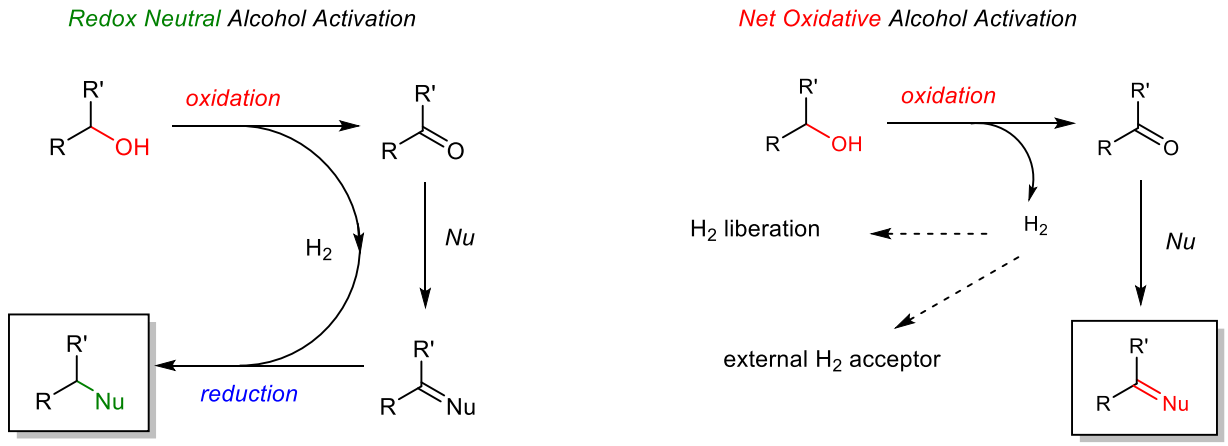
1.3 Transition-Metal-Catalyzed Alcohol Dehydrogenation

The rise of green chemistry has popularized bond-forming methods that promote atom economy and avoid mutagenic chemicals.[29c] Organometallic catalysis has thus taken a pivotal role in activating the less reactive chemical substrates such as RH or ROH by catalytic dehydrogenative oxidation. These transition-metal-catalyzed dehydrogenation strategies share two common characteristics: (1) a less reactive compound (i.e. alcohol) is converted into a more reactive species (i.e. carbonyl compound) with very high atom economy; and (2) unfunctionalized alcohols or alkanes are used as synthetic building blocks without any pre-functionalization such as halogenation, triflation, tosylation and so forth. Dehydrogenation of alcohols to more reactive carbonyl compounds in higher oxidation states enables the subsequent bond constructions that would otherwise be impossible on the parent alcohols (Scheme 1-15). This type of transformation has drawn much attention in recent years, and been referred to as "hydrogen borrowing methodology",[46] the "hydrogen autotransfer process",[47] or simply "hydrogen transfer".[48] In fact, the earliest known examples in this field date back more than 100 years. The dehydrogenative activation of alcohols followed by their concomitant dimerization to yield β-branched primary alcohols, a chemical transformation now known as the Guerbet reaction (Scheme 1-15).[49]

Capitalizing on the reactive carbonyl intermediates, this dehydrogenative activation mode has evolved into two main research domains over the past few years: (1) a redox neutral process with the returning of H_2 to the unsaturated intermediates newly formed from functionalization of



Scheme 1-15 Metal-Catalyzed Dehydrogenative Alcohol Activation and the Guerbet Reaction



Scheme 1-16 Two Main Research Domains in Alcohol Dehydrogenation

carbonyl compounds, and (2) a net oxidative process with the transfer of H_2 to external hydrogen acceptors without hydrogenating the functionalized carbonyl derivatives (Scheme 1-16). Depending on the choice of metal catalysts and nucleophiles, many useful chemical transformations can thus take place, among others, alkylation, allylation, esterification, amidation, and hydroacylation. Homogeneous catalysts for these reactions are generally ruthenium and

iridium complexes, whereby reaction conditions vary. But many require the basic solution with moderate heating. Although its unclear which catalytic steps require base, a basic moiety is viewed as a key ingredient in the dehydrogenation via a metal monohydride intermediate.[50] We will selectively discuss some exemplary reactions classified by two different activation modules in this field.

1.3.1 Redox-Neutral *N*-Alkylation Reactions

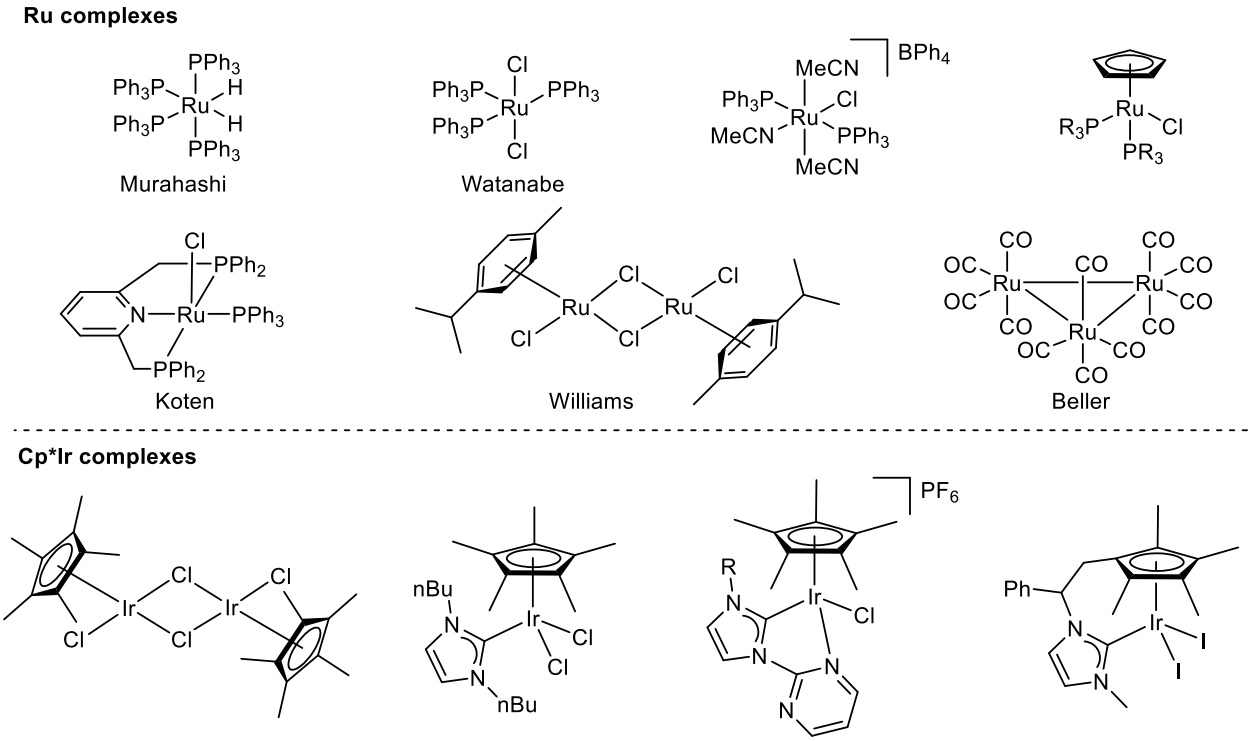
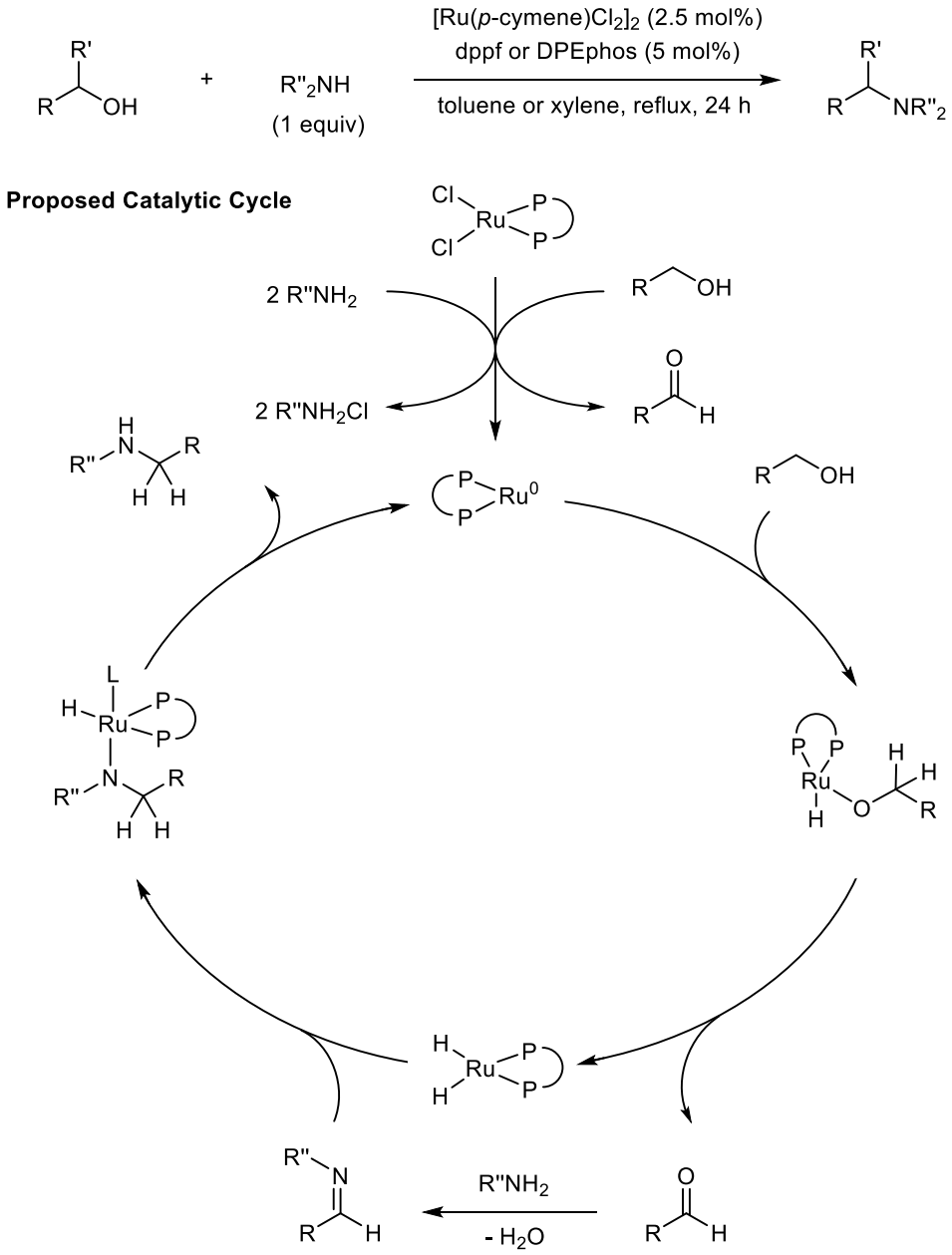


Figure 1-1 Representative Ruthenium and Iridium Complexes for *N*-Alkylation of Alcohols

Several representative ruthenium pre-catalysts and pentamethylcyclopentadienyl (Cp*) complexes of iridium widely used in *N*-alkylation of alcohols are listed above (Figure 1-1). Early work utilizing ruthenium complexes in *N*-alkylation was reported by the Murahashi group and the Watanabe group.[51] In 1982, Murahashi and co-workers showed aliphatic amines were competent substrates in a $RuH_2(PPh_3)_4$-catalyzed N-alkylation.[52] On the contrary, aryl amines were largely ineffective in this reaction. Watanabe *et al.* successfully demonstrated the use of aminoarenes by

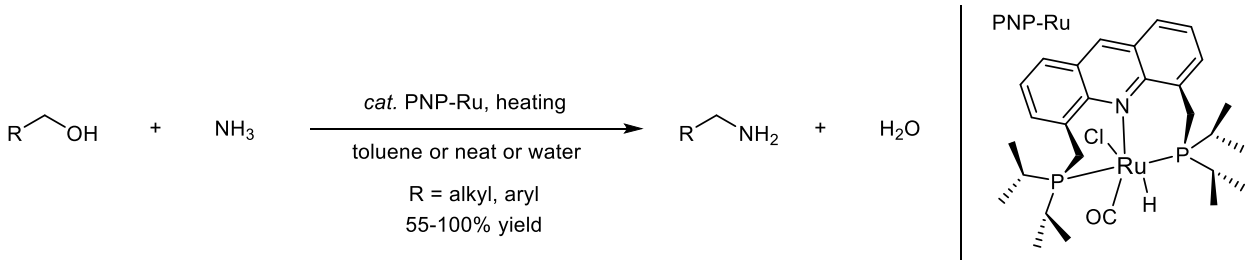
switching to $[RuCl_2(PPh_3)_3]$ and monophosphine complexes of type $[RuCl_3L]$.[53] *N*-Alkylation of heterocyclic aryl amines has also been reported using a variety of ruthenium complexes.[54] The



Scheme 1-17 $[Ru(p\text{-cymene})Cl_2]_2$/Diphosphines for *N*-Alkylation and Its Catalytic Cycle

ruthenium pre-catalyst $[Ru(p\text{-cymene})Cl_2]_2$ and bis(diphenylphosphino)ferrocene (dppf) were demonstrated by Williams and co-workers as an efficient catalyst system for *N*-alkylation of

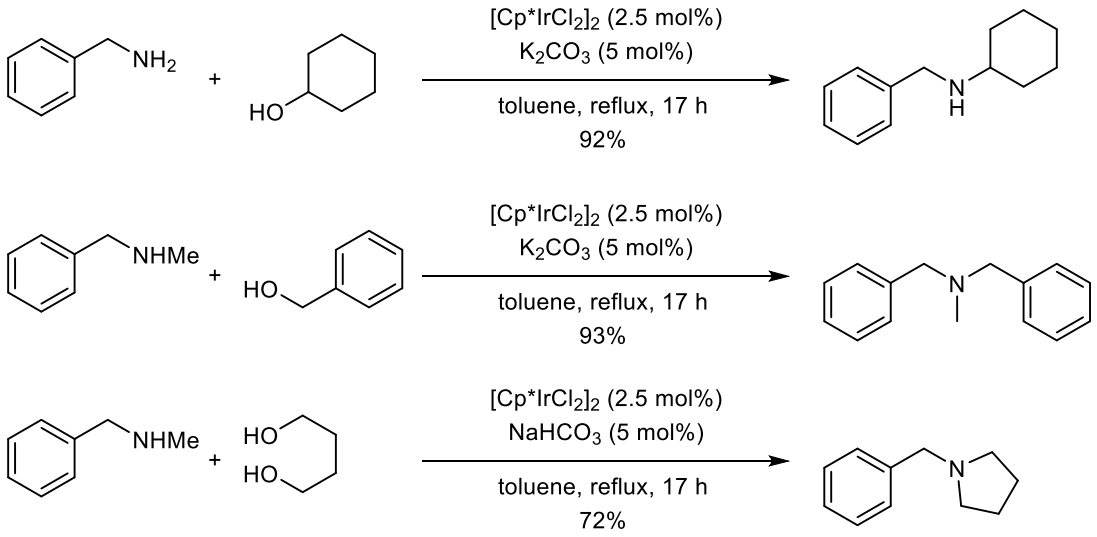
amines with primary alcohols (Scheme 1-17).[55] Other chelating phosphines were found to be inferior, producing a large amount of ester side product. Several primary or secondary amines including anilines were employed as substrates, but no secondary alcohols were reported in the study. Similarly, a combination of $[Ru(p\text{-cymene})Cl_2]_2$ and DPEphos catalytic system was later found to be active for the alkylation of sulfonamides and N-alkylbenylamines.[56] Recent work by Williams *et al.* explored $Ru(PPh_3)_3(CO)H_2$ and xantphos for the synthesis of benzimidazoles via hydrogen transfer reactions. The addition of piperidinium acetate was found to be beneficial to the alkylation, presumably by forming the iminium ion to facilitate nucleophilic attack.[57] Collectively, Williams *et al.* proposed a tentative mechanism for the *N*-alkylation on the basis of the $[Ru(p\text{-cymene})Cl_2]_2$/diphosphine combination (Scheme 1-17). Coordination of a diphosphine with the ruthenium would lead to the formation of the complex $Ru(P\text{-}P)Cl_2$. Activation of $Ru(P\text{-}P)Cl_2$ by exchange of a chloride with alcohol, and loss of HCl could give a ruthenium(0) complex. β-Hydride transfer from the alkoxy complex then leads to ruthenium hydride complex by loss of the aldehyde. Dissociation of the aldehyde and its condensation with amine yields an imine. The returning of H_2, presumably from the dihydride complex, to the imine leads to the amido complex. Its reductive elimination affords the amine product and regenerates the ruthenium(0) complex. When the *N*-alkylation involves a secondary amine, the intermediate iminium species would not be able to bind through the nitrogen, and the reaction could proceed either via an η^2 iminium complex, or via the enamine.



Scheme 1-18 PNP-Ru Pincer Complex in Amine Synthesis

Milstein and co-workers have developed many robust ruthenium pincer complexes in the context of dehydrogenative alcohol oxidation. For example, an air-stable PNP-type ruthenium pincer catalyst proves to be efficient in the selective synthesis of primary amines from alcohols and ammonia, precluding the traditional need for stoichiometric amounts of toxic chemical reagents,

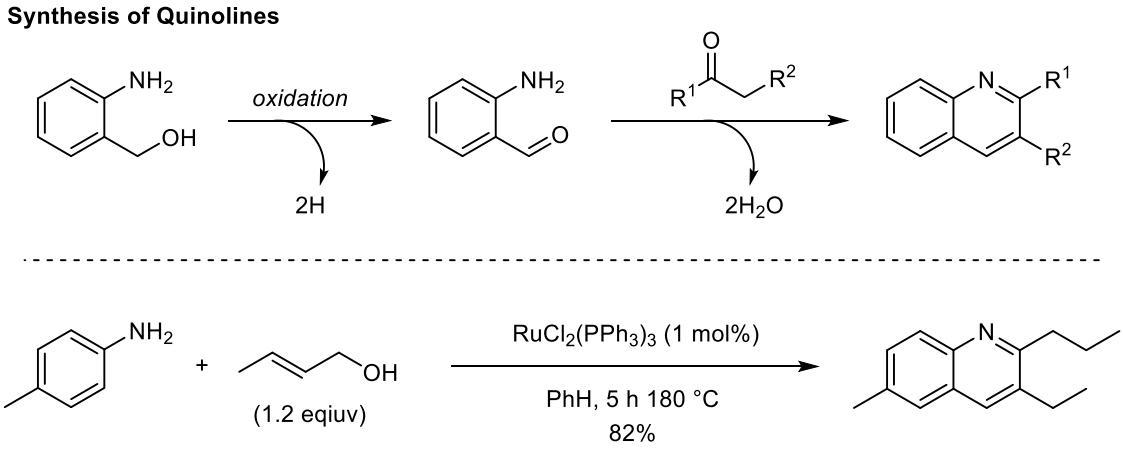
high pressure, and harsh reaction conditions (Scheme 1-18).[58] Notably, this reaction can even proceed in the absence of solvent or "on water".



Scheme 1-19 $[Cp^*IrCl_2]_2$ in *N*-Alkylation Reactions

Besides ruthenium complexes, Cp*Ir complexes have also shown good reactivity in catalyzing *N*-alkylation reactions. For instance, Fujita and Yamaguchi pioneered several hydrogen transfer reactions such as *N*-alkylation utilizing alcohols (Scheme 1-19).[59] A broad spectrum of amine and alcohol substrates were compatible, including both primary and secondary variants. A catalytic base was required in most cases, likely for activating the catalyst. In spite of the high catalyst loading (5 mol%), excellent yields of monoalkylated product were obtained. The cyclization of amino alcohols and the cyclization of primary amines with diols were subsequently reported.[60] Ishii *et al.* identified another efficient iridium catalytic system for transfer hydrogenation:[61] dppp-bound $[Ir(cod)Cl]_2$ complex in the presence of Cs_2CO_3. $[Ir(cod)Cl]_2$ was also used by Williams and co-workers to accomplish the *N*-alkylation of amines with alcohols; another biphosphine dppf was applied to the monoalkylation of primary amines with primary alcohols.[62] Imine side product was formed when using benzyl alcohol as substrate, suggesting an incomplete hydrogenation. Moreover, a C–N bond formation proceeded through a dehydrogenation—aza-Wittig—hydrogenation process, a variant of similar C–C bond-forming Wittig chemistry.[63]

Synthesis of structurally more complex heterocycles can be accomplished via these alkylation processes. Considering the Friedlander quinoline synthesis for example, the traditional use of amino benzaldehydes is replaced by that of amino benzyl alcohols. Upon the dehydrogenation of



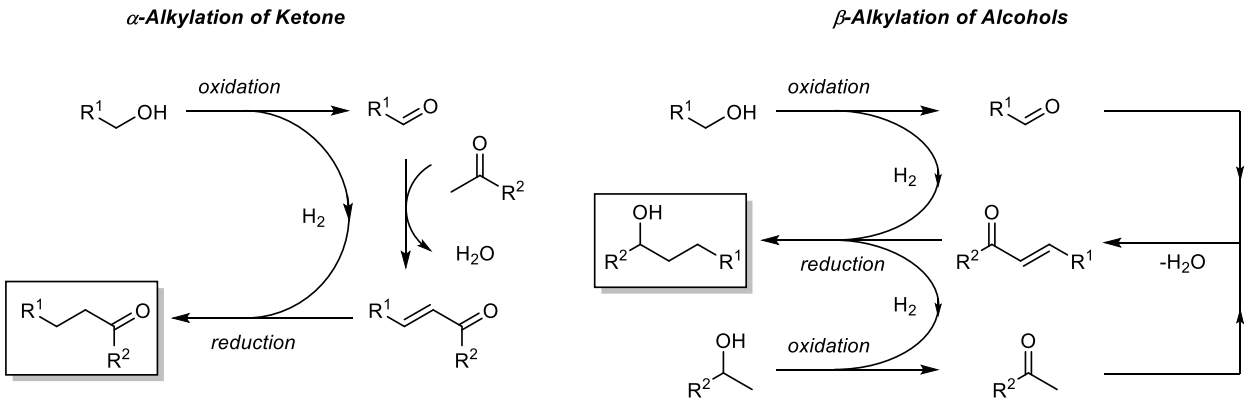
Scheme 1-20 Two Types of Alkylation in the Alcohol Dehydrogenation

the latter species, the intermediates formed are competent for a tandem Friedlander-type condensation (Scheme 1-20). The ketone coupling partner is produced from a secondary alcohol through dehydrogenation, with $RuCl_2(PPh_3)_3$ providing the highest yield.[64] There are many other ruthenium and iridium complexes which can catalyze this reaction in the presence of stoichiometric amounts of strong base, such as KOH or KO*t*Bu. Remarkably, the use of a strong base alone can promote the overall synthesis in a transition-metal-free manner.[65]

1.3.2 Redox-Neutral α-Alkylation Reactions

A good number of carbon nucleophiles have been explored in the same manner as amines in the hydrogen borrowing chemistry. To form new C–C bonds, the unactivated precursors of these nucleophiles typically require deprotonation or oxidation prior to their nucleophilic attack to carbonyl intermediates. Recent progress in the field of hydrogen transfer have brought this alkylation reaction, being performed traditionally with heterogeneous species, within the realm of homogeneous transition-metal catalysis. Depending on whether the carbonyl is formed *in situ* or used directly as the coupling partner, the reaction can be termed either as α-alkylation of ketones or β-alkylation of alcohols (Scheme 1-21). Stoichiometry of the overall alkylating process suggests

that the coupling product of an alcohol with another alcohol would remain as the alcohol unless hydrogen is transferred to a sacrificial hydrogen acceptor or liberated as gas. If an alcohol is coupled with a ketone, the formation of both the ketone and the alcohol product is possible.

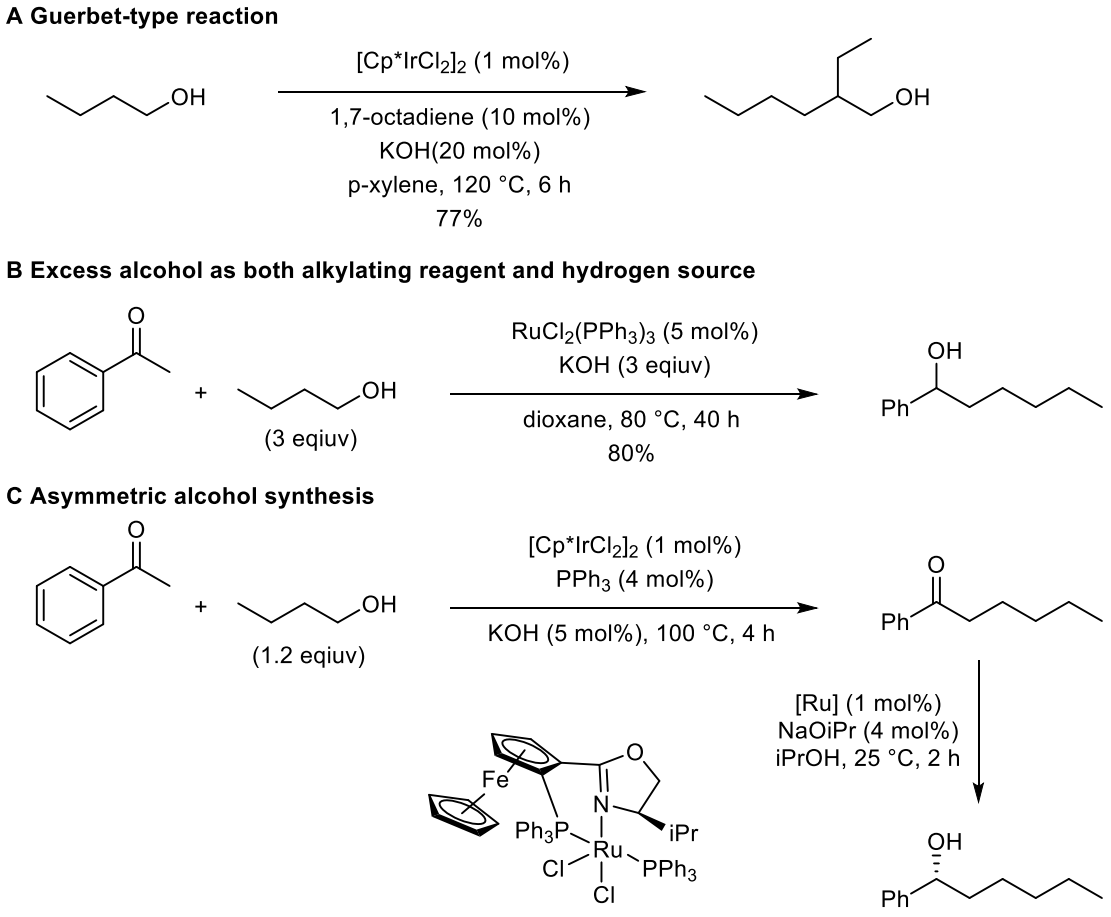


Scheme 1-21 Two Types of Alkylation in the Alcohol Dehydrogenation

However, the latter was only viable when the ketone was further reduced by an excess amount of alcohol or hydrogen donor. Dimerization of primary alcohols to form the Guerbet-type products have been made possible under basic conditions with different metal complexes such as, among others, complexes of ruthenium, rhodium, palladium and iridium (A, Scheme 1-22).[66] Cho *et al.* reported $RuCl_2(PPh_3)_3$-catalyzed alkylation reactions using either benzyl or aliphatic alcohols for the formation of α-alkylated ketone products (B, Scheme 1-22).[67] While dioxane served as the hydrogen donor for the selective production of the hydrogenated alcohol product, a large excess of 1-dodecene was required as the external hydrogen acceptor to deliver the ketone product. Moreover, β-alkylation of primary and secondary alcohol also took place smoothly with the same catalytic system.[68] $[RuCl_2(dmso)_4]$ was exploited in both β-alkylation of alcohols and *α*-alkylation of ketones.[69] Again, the use of 1,4-dioxane as a solvent proved beneficial to the reaction, implying its role as a hydrogen donor consistent with other studies. Studies conducted by Ramon and Yus indicate that the hydride attack, rather than hydrogenation, is involved in the reduction of α,β-unsaturated ketones. This conclusion could be applicable to other scenarios in hydrogen transfer reactions, such as imine reduction in *N*-alkylation reactions.

Though α-alkylation of ketones and β-alkylation of alcohols are closely related, some transition metal complexes appear to be quite selective. In other words, catalysts that are active for one

process remain inert for the other. For instance, $[Ir(cod)Cl]_2$ combined with PPh_3 and base is active for α-alkylation of ketones, but fails in giving the desired products in the β-alkylation.[70] A handful of ruthenium and iridium complexes are reported only suitable for β-alkylation reactions.[71]

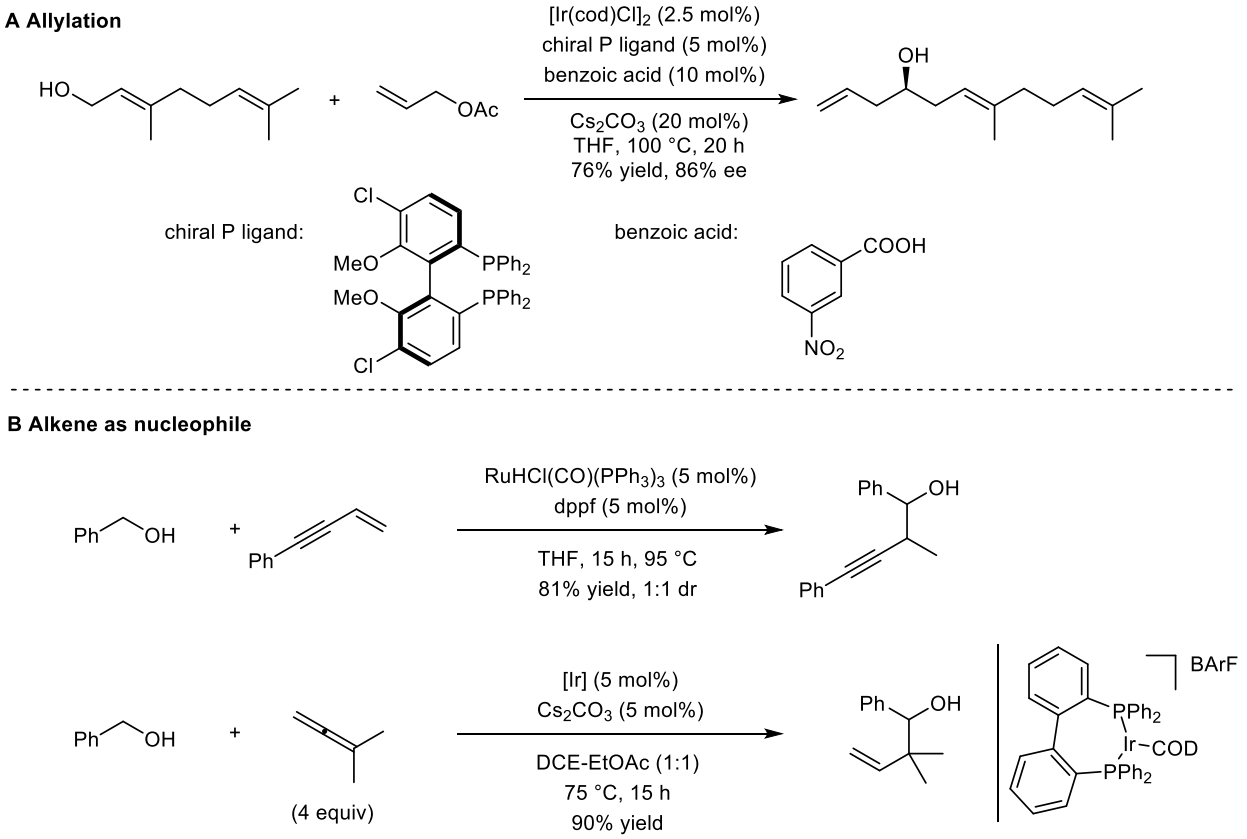


Scheme 1-22 Exemplary Alkylation Reactions in the Alcohol Dehydrogenation

The alcohol production via this alkylation process can be stereoselective given the proper chiral ligand framework in the hydrogenation step. A stepwise procedure was conducted for an asymmetric α-alkylation of ketones using two different catalysts (C, Scheme 1-22).[72] $[Cp^*IrCl_2]_2$ was used to initiate the coupling of an alcohol and a ketone, whereas a ruthenium complex containing a chiral bidentate P, N ligand catalyzed the enantioselective transfer hydrogenation of the resulting ketone at room temperature.

1.3.3 Redox-Neutral Reactions Using Other Nucleophiles

Apart from carbon nucleophiles, metallic nucleophilic species can be made available through a transition-metal-catalyzed hydrogenation of unsaturated compounds. Following this concept,



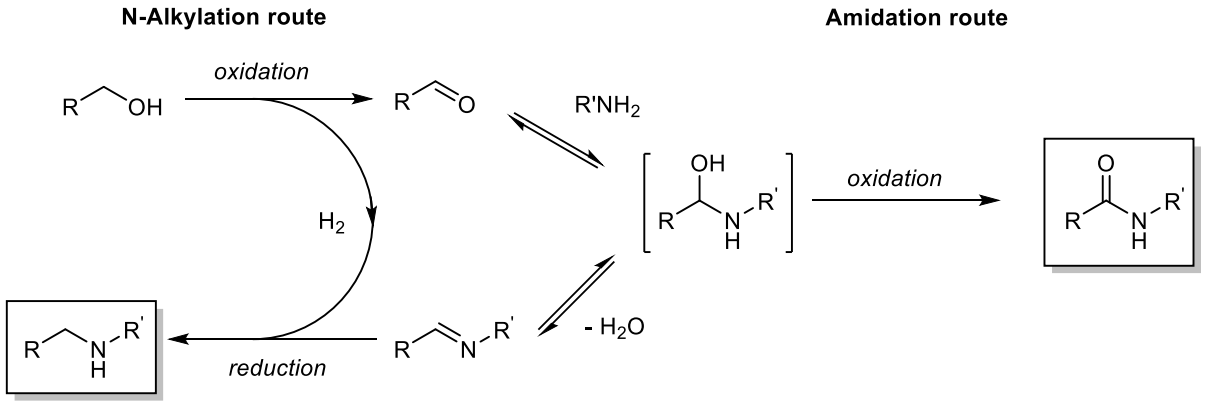
Scheme 1-23 Carbonyl Addition Reactions via Alcohol Dehydrogenation

Krische and co-workers have pioneered a series of net 'redox neutral' chemical transformations: carbonyl allylations, crotylations, vinylations, and propargylations. All of them are transition-metal-catalyzed carbonyl addition reactions that hinge on dehydrogenative activation of alcohols. To be more specific, aldehydes generated *in situ* from alcohols react with the metallic nucleophilic species hydrogenated *in situ* from unsaturated compounds in the presence of ruthenium or iridium catalysts. One obvious advantage using metal-based nucleophiles is the ability to induce chirality in the C–C bond forming step in the presence of chiral ligands. Stereoselective product formation has been seen for allylations using allyl acetate as an achiral allyl donor; the active catalyst is formed in situ with chelating chiral phosphine ligand as well as a benzoic acid derivative that is thought to form a metallocyclic species with the metal precursor (A, Scheme 1-23).[73] Asymmetric

induction can be achieved with a variety of aryl alcohols in good yield and excellent stereoselectivity. Pre-catalysts $RuHCl(CO)(PPh_3)_3$ and $[Ir(cod)Cl]_2$ are used in conjunction with chelating phosphines in an alcohol-diene coupling (B, Scheme 1-23).[74]

1.3.4 Net Oxidative Amidation

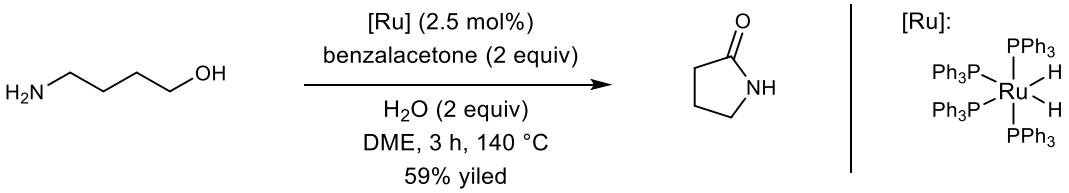
The alkylation and allylation reactions discussed so far are all net redox neutral processes, meaning that the hydrogen liberated from the alcohol is returned to the product. There are some exceptions to this phenomenon, in which cases the final hydrogenation does not occur, leading to an overall oxidative transformation. Consequently, the final product is produced in a higher oxidation state than the starting materials. Construction of amide bonds from alcohols and amines via this approach is conceptually appealing to synthetic chemists, yet challenging owing to the competing *N*-alkylation process (Scheme 1-24). Up till now, how much these two processes might overlap, or affect each other, is still unclear from the mechanistic standpoint. In addition, the number of transition metal complexes active for amide formation is much smaller than that for N-alkylation, and many of them require judicious ligand design especially in the absence of hydrogen acceptors.



Scheme 1-24 Two Routes Diverged from Alcohol Activation in the Presence of Amines

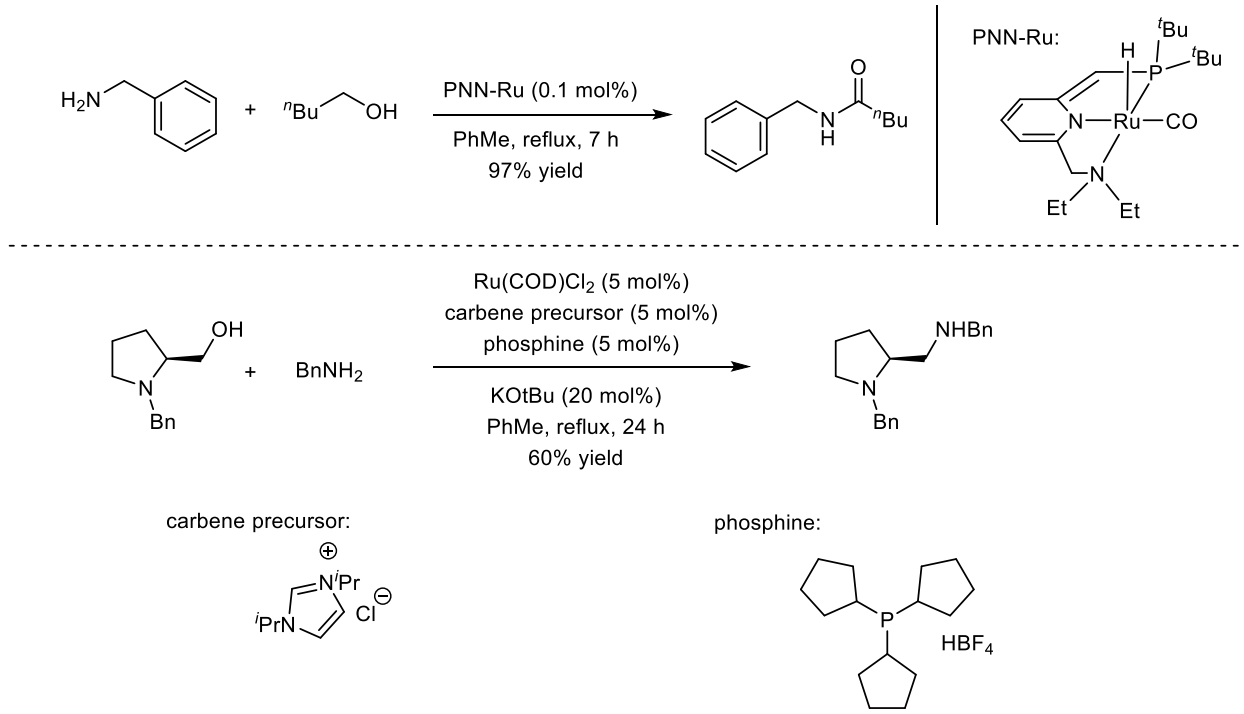
With aid of hydrogen acceptors, commercially available ruthenium complexes can be ideal catalysts for forming amide bonds. Murahashi *et al.* reported an intramolecular lactamization catalyzed by $RuH_2(PPh_3)_4$ using amino alcohols as starting materials at an elevated temperature. Either five- or six-membered lactam rings were efficiently constructed in the presence of a

hydrogen acceptor (Scheme 1-25).[75] The addition of excess water was found to be beneficial to yield lactams, as otherwise the formation of cyclic amines was observed. A plausible rationale for such observation is that extra water could slow down dehydration to form the imine from the hemiaminal intermediate, through which both *N*-alkylation and amidation likely proceed. Under such circumstances, the hemiaminal would be irreversibly dehydrogenated to generate the amide. Regardless, it remains elusive as to what properties predispose metal complexes to one pathway over the other. $[Cp^*RhCl_2]_2$ was later employed as catalyst in the presence of acetone as hydrogen acceptor for a similar lactamization process under mild basic conditions. But, the substrate scope of this reaction is only limited to aromatic amino alcohols, even though seven-membered lactams can be formed. Williams and co-workers reported the formation of amides from alcohols and amines from $[Ru(p\text{-cymene})Cl_2]_2$ in the presence of dppb and Cs_2CO_3 and a hydrogen acceptor in refluxing *tert*-butanol.[76]



Scheme 1-25 Synthesis of Lactam from Amino Alcohols

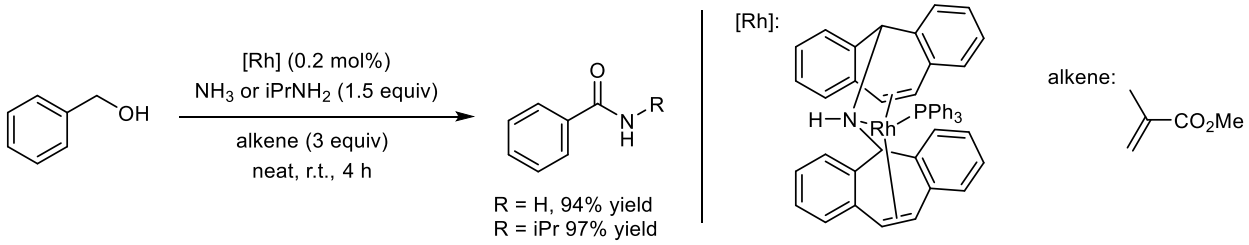
Milstein and co-workers pioneered a series of acceptorless amidation reactions based on an elegant catalyst design. (Scheme 1-26).[77] In all these cases, dihydrogen gas is ultimately released from the reaction system, accompanied with oxidation of the substrate. The PNN-ruthenium pincer complex was designed based on the dearomatization-aromatization of ligands on metal to ease the dihydrogen liberation and perform the amidation under neutral conditions. There is no need for the participation of any base or catalyst activator. Aliphatic primary alcohols can intermolecularly react with primary and secondary amines to form secondary and tertiary amides in excellent yields. Alternatively, Madsen and co-workers devised a Ru-NHC complex for the same purpose. (Scheme 1-26).[78] In this case, the active complex was pre-synthesized *in situ* from $[Ru(cod)Cl_2]$, imidazolium salt, phosphine, and a catalytic amount of base. While secondary amides were obtained in good to excellent yields, only one example of a tertiary amide was reported in moderate yield. Contrary to the Milstein's report, the reaction requires longer time to reach completion.



Scheme 1-26 Synthesis of Amides via Acceptorless Alcohol Deoxygenation

Heating is always required in chemical reactions via alcohol dehydrogenative activation as it provides kinetic driving force to the endothermic oxidation process. But there are very few exceptions. Grutzmacher and co-workers have demonstrated the unprecedented activity of a rhodium complex in the oxidative amidation, accommodating a wide array of alcohols at room temperature (Scheme 1-27).[79] Both primary amines and ammonia were successfully coupled with alcohols to produce primary and secondary amides, respectively. A ligand-based Lewis basic site of the rhodium complex was proposed to play a crucial role in the catalytic cycle. Computational studies suggested that this basic site allowed the dehydrogenation to occur via a metal-monohydride mechanism. With regard to the formation of carboxylic acid side products, the authors proposed that the nucleophilic ruthenium hydroxy species might attack the aldehyde-associated rhodium complex; the resulting hemiacetal would then undergo β-elimination to form the product. This mechanistic hypothesis is crucial in that it suggests the full involvement of the metal in the reaction pathway, including in the formation of the hemiacetal intermediate.

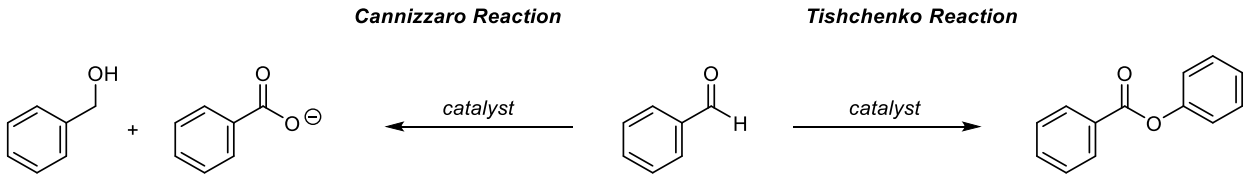
Taking advantage of the Beckmann rearrangement, Williams and co-workers developed a two-step, one-pot synthesis of primary amides from hydroxylamine and alcohols.[80] The reaction features the initial $[Cp^*IrCl_2]_2$-catalyzed dehydrogenative alcohol oxidation with Cs_2CO_3 in refluxing toluene, and the subsequent rearrangement of oxime to the corresponding amide.



Scheme 1-27 Synthesis of Amides at Room Temperature

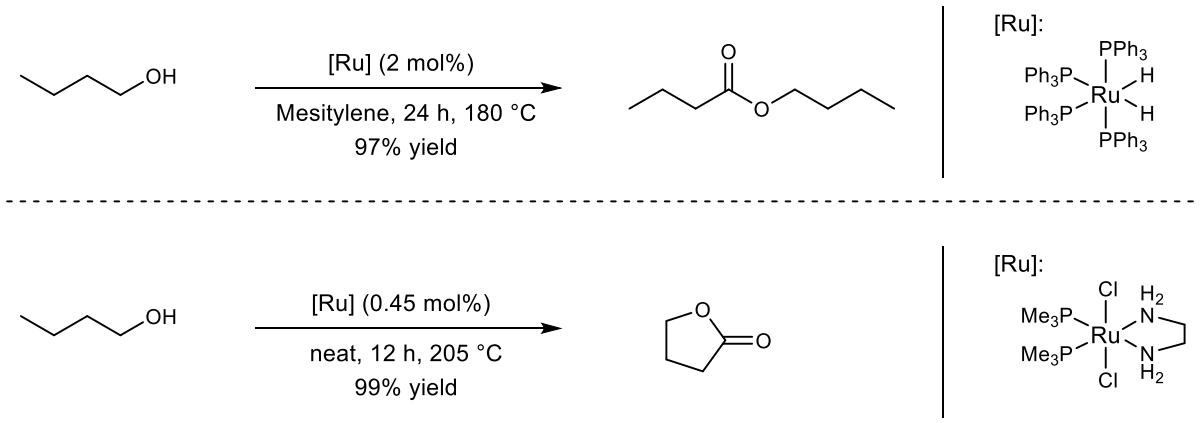
1.3.5 Net Oxidative Esterification

When alcohols replace amines as coupling partners, the oxidative esterification rather than amidation can be readily envisioned. Since most hydrogen transfer reactions occur at elevated temperature under basic conditions, two well-known name organic reactions may be able to complicate the desired esterification products: the Tishchenko reaction and the Cannizzaro reaction (Scheme 1-28). The formation of esters in the Tishchenko process is resulted from the dimerization of aldehydes, in which transition-metal complexes, lanthanide alkoxides, or alkali alkoxides serve as catalysts. The Cannizzaro reaction features a base-catalyzed disproportionation of aldehydes to form carboxylates and alcohols.



Scheme 1-28 Named Reactions Related to Ester Formation from Benzaldehyde

Parallel reactivity of metal complexes is observed in the ester formation via the oxidative activation and dimerization of alcohols, as well as in the Tishchenko reaction (Scheme 1-29).

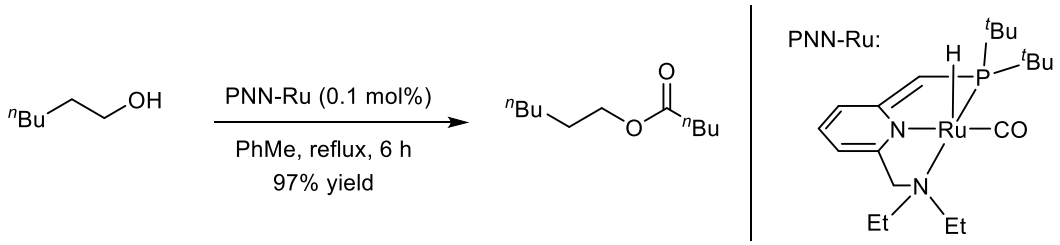


Scheme 1-29 Esterification of Primary Alcohols via Dehydrogenation

$RuH_2(PPh_3)_4$ is a known catalyst for both reactions.[81] However, Murahashi *et al.* argued that the esterification reaction going through alcohol dehydrogenation might not undergo a Tishchenko-type mechanism. This argument was supported by the inability of $RuH_2(PPh_3)_4$ to catalyze esterification from aldehydes.[81c] Catalysts in this class include the Shvo's complex $[(\eta^4\text{-}C_4Ph_4CO)Ru(CO)_3]_2$ as well as $Ru_3(CO)_{12}$. Both of them are capable of ester and lactone formation at elevated temperatures in the absence of base.[82] However, the acceptorless dehydrogenation is feasible in the case of Shvo's complex and $RuH_2(PPh_3)_4$ whereas $Ru_3(CO)_{12}$ commonly requires an external hydrogen acceptor. Synthesis of polyesters was catalyzed by $Ru_3(CO)_{12}$ when diols, excluding 1,4- and 1,5-diols, were used.[83] The ruthenium bis-phosphine diamine complex was capable of catalyzing lactone formation via an acceptorless dehydrogenation at elevated temperatures.[84]

Similar to the oxidative amidation, the PNN-ruthenium pincer complex developed by Milstein and co-workers is also active for the esterification process, affording esters in the absence of base via dehydrogenation of primary alcohols (Scheme 1-30).[85] Esterification at room temperature was again made possible by a cationic rhodium catalyst precursor developed by Grutzmacher and co-workers. The products were either esters or carboxylic acids using a hydrogen acceptor. Several iridium complexes are employed in the oxidative esterification, such as an iridium hydride species[86] and a Cp*Ir complex with a chelating N, O ligand.[87] A similar catalyst was used in the Tishchenko reaction of aldehydes at room temperature under basic conditions.[88] An asymmetric lactonization, starting from prochiral diols, was also possible using a chiral N, O ligand.[89] Ishii *et al.* showed that $[Ir(coe)Cl]_2$ can perform the oxidative dimerization of primary alcohols to esters

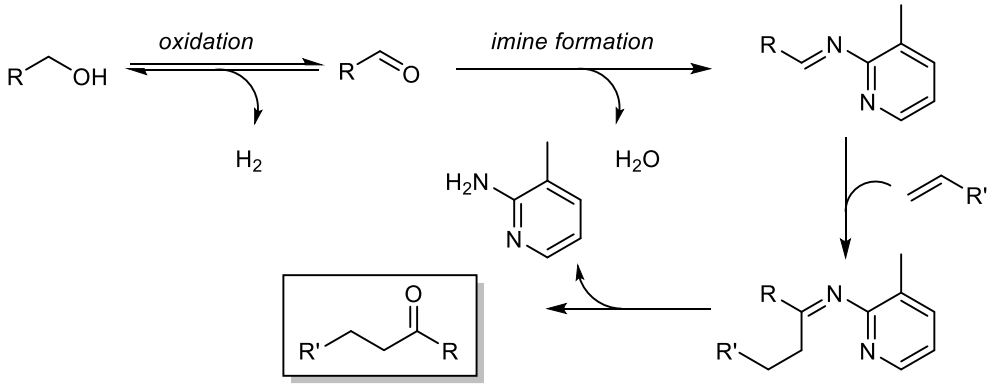
under neutral conditions.[90] Milstein and co-workers devised a PNP-ruthenium pincer complex for acetal formation based on alcohols.[91] While the ester is obtained in the presence of base, the acetal is formed under neutral conditions.



Scheme 1-30 Esterification of Primary Alcohols via Acceptorless Dehydrogenation

1.3.6 Net Oxidative Hydroacylation

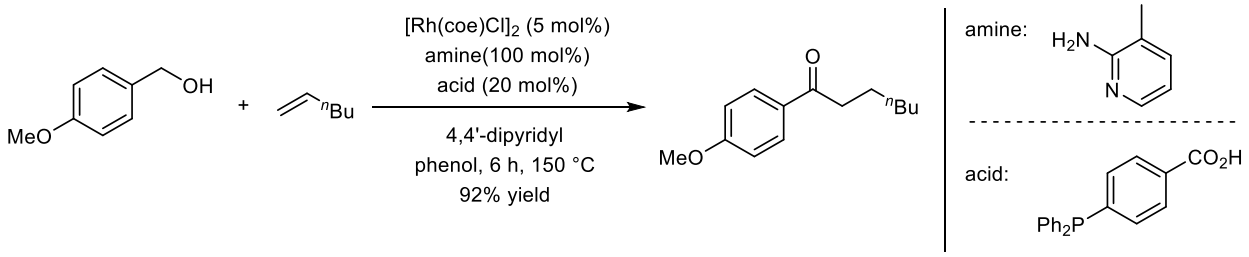
Hydroacylation, or the coupling of alkenes with carbonyls and imines, can also proceed by dehydrogenating alcohols (Scheme 1-31).[92] Jun and co-workers reported a $RhCl_3 \cdot H_2O/PPh_3$-catalzyed hydroacylation of benzyl alcohols with terminal olefins in the presence of 2-amino-4-



Scheme 1-31 Hydroacylation via Alcohol Dehydrogenation

picoline. The mechanism was pictured as the participation of aldehydes, generated *in situ*, in a hydroamination process by condensing with amines in the catalytic cycle. The ultimate hydrolysis of the newly formed imine leads to the formally acylated product.[93] Interestingly, the recycling of catalyst is possible, but requires an unconventional biphasic solvent system developed by the same

group, whereby $[Rh(coe)Cl]_2$ was used as the precatalyst.[94] (Scheme 1-32). Further variations include the use of a recyclable self-assembling organic catalyst.[95]

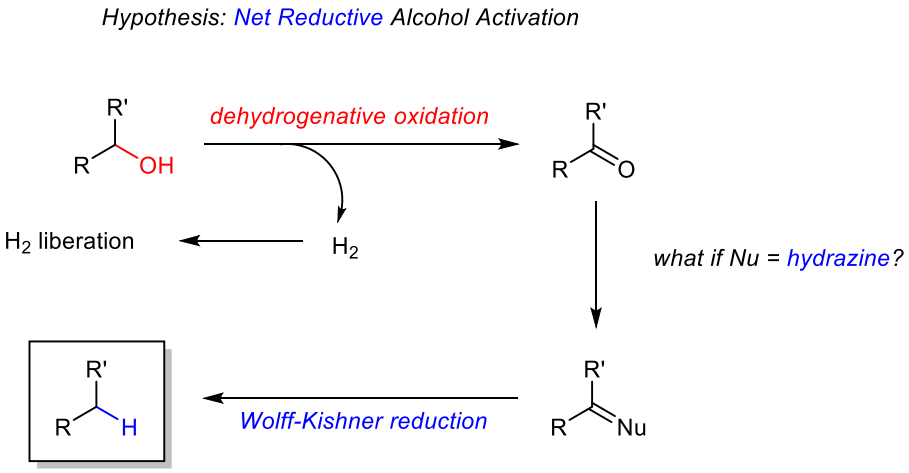


Scheme 1-32 Hydroacylation of Primary Alcohols and Terminal Olefins

1.4 Overview of Thesis

The studies reviewed above in the dehydrogenative activation of alcohols demonstrate the viability of chemical transformations based on *in situ* generation of reactive carbonyl intermediates (aldehydes and ketones). In addition, the literature recapped in the field of alcohol deoxygenation reveals a long-standing challenge (i.e. the selective alcohol deoxygenation in a single-step, efficient process). Inspired by the existing modules of alcohol activation (Scheme 1-16), we questioned if hydrazine can serve as an alternative nucleophile to react with the carbonyl intermediate generated *in-situ* from the alcohol (Scheme 1-33). The overall chemical transformation, combining the oxidative dehydrogenation with the Wolff-Kishner reduction, would then produce the corresponding alkane in a single step. This thesis presents our original contributions to two basic chemical transformations: C–O bond cleavage and C–C bond formation, both of which originated from this very idea. Four chapters will be included to further elaborate on these topics.

Chapter 2 introduces our initial attempts to address the abovementioned problem in alcohol deoxygenation: how to selectively and efficiently remove hydroxyl groups in organic compounds without affecting other functionalities in the same molecule. As a proof-of-concept, the early development of our redox-based hypothesis is catalyzed by iridium complexes and mediated by hydrazine under forcing reaction conditions. While this deoxygenation protocol proves efficient



Scheme 1-33 Our Redox-Based Hypothesis for Alcohol Deoxygenation

on a wide range of benzylic and allylic alcohols, the synthetic utility is constrained by its forcing reaction conditions and relatively poor reactivity seen for aliphatic alcohol substrates. Mechanistic studies indicate that the iridium hydride complex serves as the key intermediate in the catalytic turnover.

Chapter 3 describes the utilization of a ruthenium(II)-based catalyst for achieving a direct deoxygenation of primary aliphatic alcohols under milder and practical conditions. Such a robust catalytic system, comprising $[Ru(p\text{-cymene})Cl_2]_2$ and 1,2-bis(dimethylphosphino)ethane, is vital to kinetically facilitate the dehydrogenative oxidation of aliphatic alcohols. Equally important is the combination of KO*t*Bu, DMSO and *t*-BuOH, which promotes the subsequent Wolff-Kishner reduction at low temperature. Notably, the synthetic application of this method is demonstrated by the cleavage of the carbon-oxygen bonds in both simple and complex organic molecules such as steroids and alkaloids, with complete chemo- and regio-selectivity.

Chapter 4 presents an umpolung approach to utilize naturally occurring carbonyl compounds (i.e. aldehydes and ketones) as alkyl carbanion equivalents for carbon-carbon bond formation via carbonyl addition reactions. Such addition reactions are traditionally executed only by organometallic reagents, relying on petroleum-derived chemical feedstocks and a stoichiometric quantity of metal. Discovering this umpolung reactivity of carbonyl compounds largely attributes

to the ruthenium(II) catalytic system developed earlier for the deoxygenation chemistry. By lowering the basicity in the reaction system, preformed carbonyl-derived hydrazones attack another carbonyl compounds, presumably via a Zimmerman-Traxler chair-like transition state. Consequently, a wide range of synthetically valuable secondary and tertiary alcohols are produced under very mild reaction conditions, with excellent functional group compatibility and good stereochemical control.

Chapter 5 further explores this umpolung reactivity of carbonyl compounds for formation of new carbon-carbon bonds via conjugate addition reactions. Inspired by the softness of ruthenium(II) pre-catalyst, we conduct conjugate additions to electron-deficient α,β-unsaturated compounds using a variety of highly functionalized aromatic carbonyl compounds as latent benzyl carbanions. A vast array of electron-deficient α,β-unsaturated compounds are accommodated including esters, ketones, sulfones, phosphonates, and amides. Two bidentate phosphine ligands (dppp and dmpe) promote this process in a complementary manner, consistent with electronic profiles of the carbonyl substrates.

Chapter 6 summarizes all research presented in this thesis and contributions to knowledge advancement.

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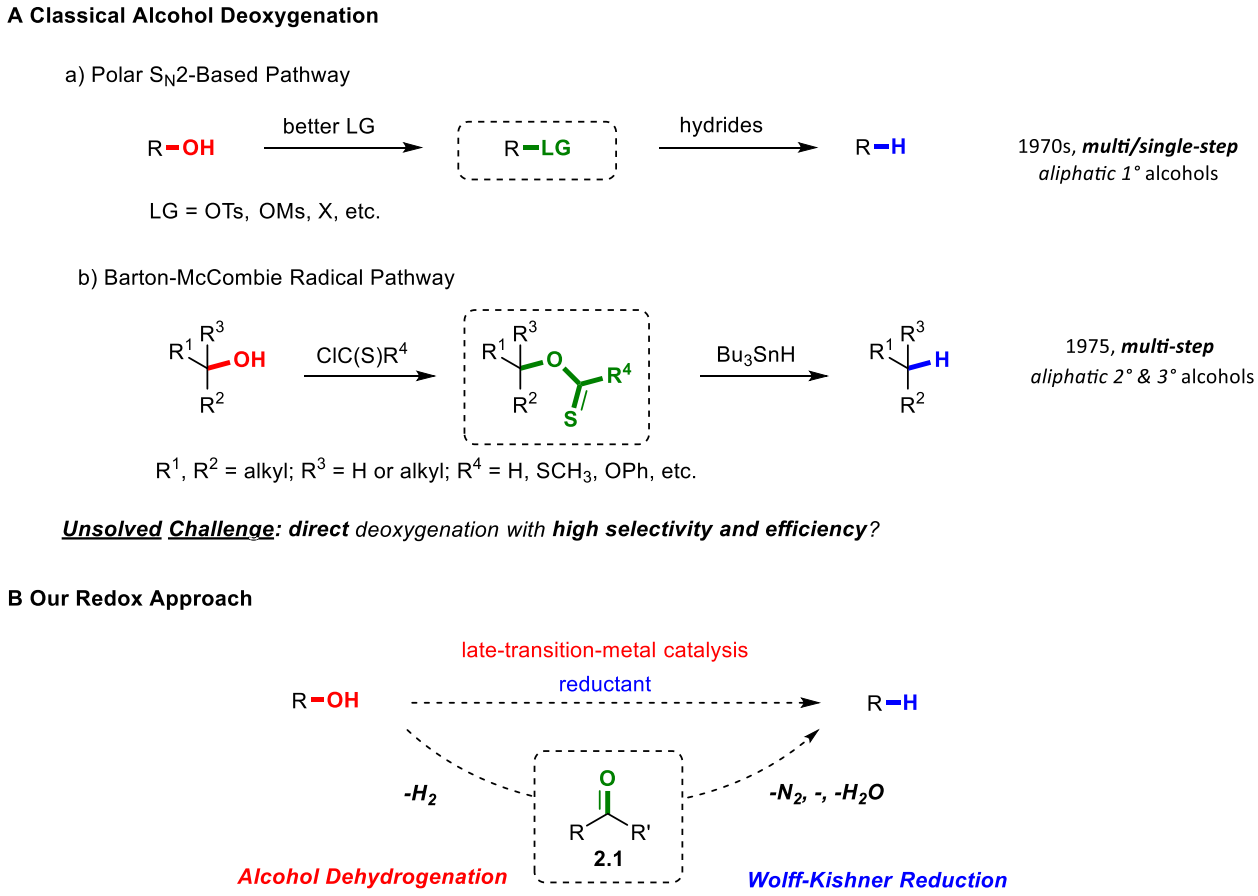
Chapter 2 : Iridium-Catalyzed Direct Deoxygenation of Activated Alcohols

2.1 Preface

Chapter 2 and 3 describe on our redox-based design to address synthetic challenges regarding efficiency and selectivity in the field of alcohol deoxygenation. Two different catalytic systems have been developed for such purposes. This chapter describes our early-stage development of an iridium-based deoxygenation catalytic protocol, with a proof-of-concept success in generating alkanes from benzylic and allylic alcohols. The project was initiated by Dr. Jianlin Huang (Postdoctoral Fellow 2011-2013) in the Li lab. My contribution to this work included optimizing reaction conditions, carrying out of the control experiments to probe the reaction mechanism, expanding the reaction scope, and leading the preparation of the manuscript. This work was published in *European Journal of Organic Chemistry* **2013**, 6496–6500.

2.2 Introduction

Cleavage of C–O bonds in alcohols to form hydrocarbons, or alcohol deoxygenation, is one of the fundamental chemical transformations in organic chemistry. It continuously plays an indispensable role in the synthesis of complex organic molecules and natural products bearing multifunctional groups.[1] As discussed in Chapter 1 (section 1.1.2), the significance of a selective and efficient deoxygenation process can be justified not only in the context of late-stage chemical modification,[2] but also in that of biomass conversion.[3] Modern deoxygenation methods are mostly two-step processes, comprising pre-activation of alcohols via S_N2 derivatization followed by radical-based or ionic-based reduction (Scheme 2-1-A, a).[4] The Barton-McCombie deoxygenation, discovered in 1975, is still regarded as the most robust synthetic method for removing secondary hydroxy groups in steroids and sugar derivatives (Scheme 2-1-A, b).[5] However, it requires



Scheme 2-1 Classical Alcohol Deoxygenation and Our Redox Approach

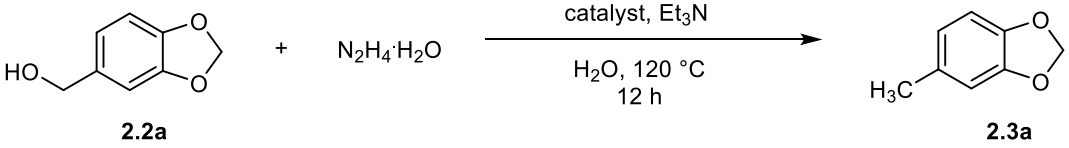
two-step conversions with overall low atom efficiency. The ever-increasing desire to increase efficiency in chemical transformations calls for a more direct deoxygenation process. Several synthetic attempts in this direction have been mentioned in Chapter 1 (section 1.2.4). Yet, few of them have good chemoselectivity on molecules that contain multiple different hydroxy groups or unprotected amines. We therefore questioned if carbonyl compounds, obtained via alcohol dehydrogenation, could be utilized as reactive species rather than commonly used ones such as organohalides, thioesters, tosylates, mesylates, alkyldiazenes, etc. To achieve the formal single-step deoxygenation reaction, the classical Wolff-Kishner reduction would then be applied to remove the oxygen atom from the *in-situ* generated carbonyl compound **2.1**. This redox-based deoxygenation approach is mechanistically distinct from all known pertinent methods, combining the dehydrogenative alcohol oxidation with the Wolff-Kishner reduction (Scheme 2-1-B).

2.3 Results and Discussion

2.3.1 Optimization of Reaction Conditions

To test our hypothesis, we decided to investigate a few iridium catalysts used in studies on alkylation of amines with alcohols.[6] Piperonyl alcohol **2.2a** and hydrazine hydrate (2 equiv) were subjected to H_2O in the presence of $[Cp^*IrCI_2]_2$ (1.0 mmol %) and Et_3N (1 equiv) (Table 2-1). To our delight, the corresponding deoxygenated product **2.3a** was detected using various iridium- and ruthenium-based complexes after 12 h reaction at 120 °C (entries 1-9). The experimental outcome suggested that iridium complexes displayed higher catalytic activity than ruthenium ones, whereas neither rhodium nor iron complexes showed any catalytic activity in this reaction (entries 10 and 11). Among all the iridium catalysts tested, Vaska's complex $(PPh_3)_2IrCl(CO)$ gave the best result, and the desired product **2.3a** was detected in 32% yield (entry 2). Comparable yields were also obtained using iridium-pincer complex (PCP)IrH(Cl) (PCP = C_6H_3-2,6-$(CH_2PBu^t_2)_2$) and iridium dimer complex $[(C_8H_{12})Ir(OMe)]_2$ (entries 1 and 3). The effort to make iridium center more Lewis acidic by adding silver triflate turned out to be slightly detrimental to the reaction outcome (entry 8).

Table 2-1[a] Catalyst Reactivity in Deoxygenation of Piperonyl Alcohol



2.2a **2.3a**

entry	catalyst	**2.3a** (%)[b]
1	(PCP)IrH(Cl)	29
2	$(PPh_3)_2IrCl(CO)$	32

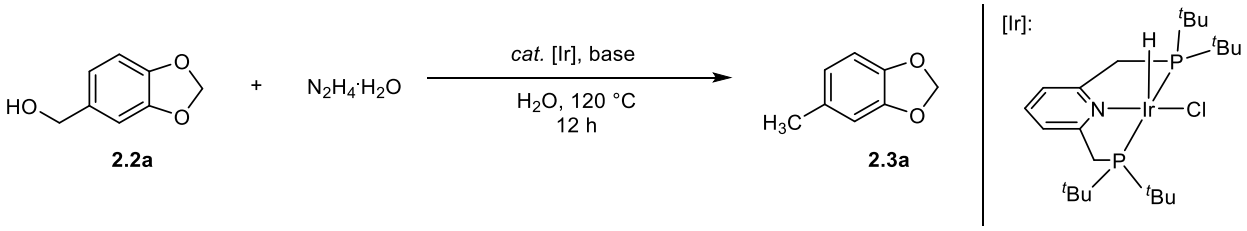
3	$[(C_8H_{12})Ir(OMe)]_2$	31
4	$(PPh_3)_3Ru(CO)H_2$	9
5	$(PPh_3)_3Ru(CO)(Cl)H$	15
6	$[Ir(cod)Cl]_2$	22
7	$[Cp^*IrCl_2]_2$	10
8[c]	$(PPh_3)_2IrCl(CO)$	22
9	$[Ru(p\text{-cymene})Cl_2]_2$	9
10	Rh(COD)Cl	-
11	$FeCl_2{\cdot}4H_2O$	-

[a]Reaction conditions: **2.2a** (15 mg, 0.1 mmol), hydrazine hydrate (10 mg, 0.2 mmol), catalyst (1 mol %), base (0.1 mmol), H_2O (0.1 mL), under an air atmosphere. [b]Determined by ^1H NMR using nitromethane as an internal standard. [c]AgOTf (2 mol %) was used as an additive.

Subsequently, a variety of inorganic and organic bases were examined (Table 2-2). While many carbonate and bicarbonate salts failed in providing good yield (entries 1, 3 and 5), the presence of cesium carbonate promoted the formation of **2.3a** in 21% yield (entry 2). Organic bases gave slightly better results, among which Et_3N was found to be the best (entry 7). Encouraged by these results, we next investigated the influence of solvents (Table 2-3). Polar solvents such as chloroform, MeOH and DMSO were better reaction media than other solvents. MeOH provided the highest yield (entry 2). Intriguingly, other protic polar solvents including EtOH, *i*-PrOH, *t*-BuOH and *t*-AmyOH were all inferior under the same reaction conditions (entries 11-13). The reactivity boost seen in MeOH can potentially be attributed to the rapid formation of CO which

goes through the dehydrogenation process and thus stabilizes the iridium complex at high temperature. In addition, our attempt to run this reaction under neat conditions proved to be fruitless (entry 14).

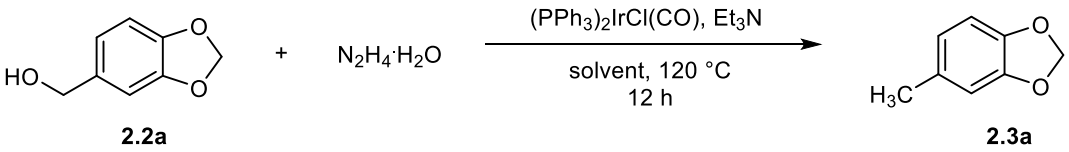
Table 2-2[a] Base Screening in Deoxygenation of Piperonyl Alcohol



entry	base	**2.3a** (%)[b]
1	$NaHCO_3$	8
2	Cs_2CO_3	21
3	$KHCO_3$	<5
4	DIEPA	14
5	K_2CO_3	<5
6	DBU	17
7	Et_3N	25

[a]Reaction conditions: **2.2a** (15 mg, 0.1 mmol), hydrazine hydrate (10 mg, 0.2 mmol), catalyst (1 mol %), base (0.1 mmol), H_2O (0.1 mL), under an air atmosphere. [b]Determined by ^{1}H NMR using nitromethane as an internal standard.

Table 2-3[a] Various Solvents in Deoxygenation of Piperonyl Alcohol



2.2a **2.3a**

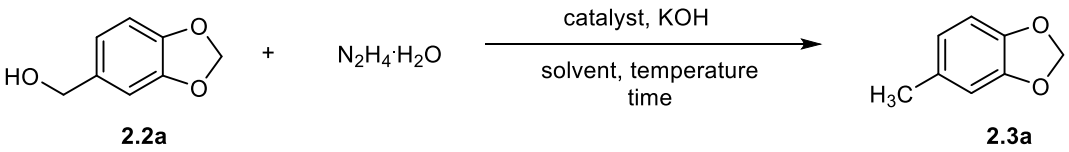
entry	solvent	**2.3a** (%)[c]
1	$CHCl_3$	29
2	MeOH	38
3	DMSO	24
4	Acetone	<5
5	Dioxane	13
6	MeCN	14
7	Cyclohexane	13
8	THF	13
9	Benzene	0
10	EtOH	<5
11	*i*-PrOH	<5
12	*t*-AmOH	7
13	*t*-BuOH	0

14		neat	7

[a]Reaction conditions: **2.2a** (15 mg, 0.1 mmol), hydrazine hydrate (10 mg, 0.2 mmol), catalyst (1 mol %), base (0.1 mmol), H_2O (0.1 mL), under an air atmosphere. [b]Determined by ^1H NMR using nitromethane as an internal standard.

Further reaction optimizations are summarized in Table 2-4. A spike in the yield was obtained by replacing Et_3N (1 equiv) with KOH (2 equiv) as the base (entry 1); this was attempted in view of the fact that the latter is commonly used in the Wolff-Kishner reduction. While optimizing the conditions, we discovered that this reaction was insensitive to air. Moreover, all ^1H NMR signals of the crude reaction mixture can be ascribed to either **2.2a** or **2.3a**, which indicated the possible consumption of **2.2a**. Because of above observations, our attention was eventually switched to the reaction temperature. A higher reaction temperature was found to be beneficial to this reaction, as shown by the increased yield (59 and 70% at 120 ^oC and 160 ^oC, respectively; entry 1 *vs* entry 2). Notably, an increased reaction concentration resulted in a shorter reaction time and a nearly quantitative yield (entry 3); this yield was unaffected by an argon atmosphere (entry 4). The product was obtained in only 50% yield under solvent-free conditions even after 10 h (entry 5). Furthermore, control experiments demonstrated that both iridium catalyst and hydrazine hydrate were indispensable for this deoxygenation, as no reaction occurred in the absence of either reagent (entries 6 and 7). It is noteworthy that the use of $(PPh_3)_3Ru(CO)(Cl)H$ also afforded the product, albeit in a slightly lower yield relative to that obtained with $(PPh_3)_2IrCl(CO)$ (entry 8). Temperature control experiments indicated that the yield of desired product was not proportional to the temperature increase once it is over 120 ^oC (entries 11-15). Under the optimized reaction conditions, we selected a couple more ruthenium and rhodium catalysts to test in the reaction (entries 16-21). None of them provided comparable yields.

Table 2-4[a] Further Reaction Optimizations



2.2a **2.3a**

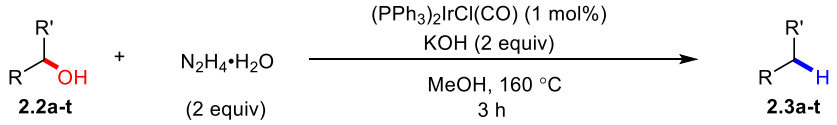
entry	catalysts	solvent[b]	T (℃)	t (h)	**2.3a** (%)[c]
1	$(PPh_3)_2IrCl(CO)$	MeOH	120	12	59
2	$(PPh_3)_2IrCl(CO)$	MeOH	160	12	70
3[d]	$(PPh_3)_2IrCl(CO)$	MeOH	160	3	99
				2	96
4[d,e]	$(PPh_3)_2IrCl(CO)$	MeOH	160	3	95
5	$(PPh_3)_2IrCl(CO)$	neat	160	12	50
6[d]	none	MeOH	160	3	0
7[d,f]	$(PPh_3)_2IrCl(CO)$	MeOH	160	3	0
8[d]	$(PPh_3)_3Ru(CO)(Cl)H$	MeOH	160	3	92
9[g]	$(PPh_3)_2IrCl(CO)$	MeOH	140	12	63
10[h]	$(PPh_3)_2IrCl(CO)$	MeOH	160	6	83
				3	70
11	$(PPh_3)_2IrCl(CO)$	H_2O	120	12	26
12	$(PPh_3)_2IrCl(CO)$	H_2O	140	12	29

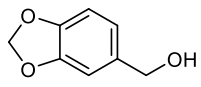
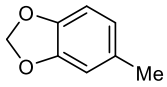
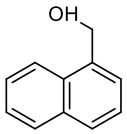
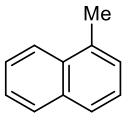
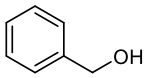
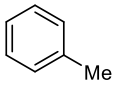
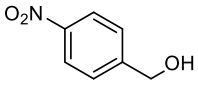
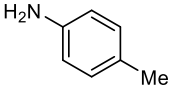
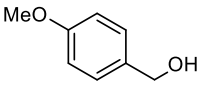
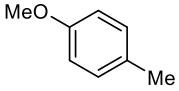
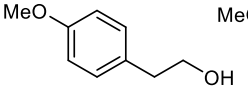
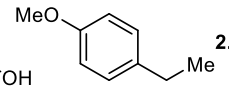
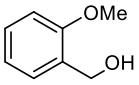
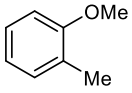
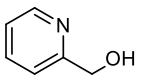
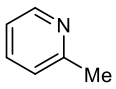
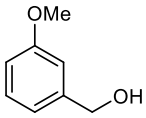
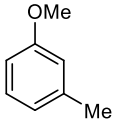
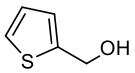
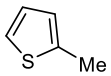
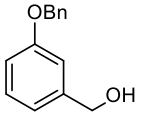
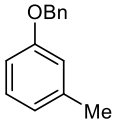
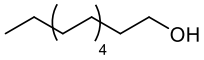
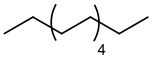
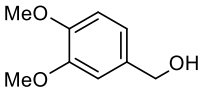
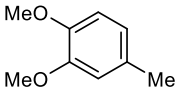
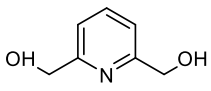
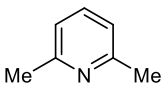
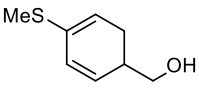
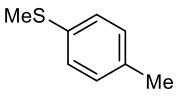
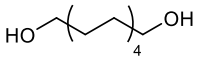
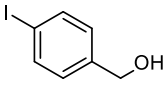
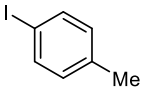
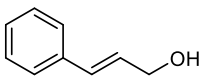
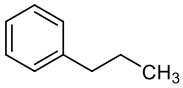
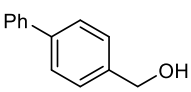
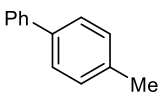
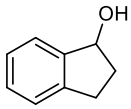
13	$(PPh_3)_2IrCl(CO)$	H_2O	160	12	37
14	$(PPh_3)_2IrCl(CO)$	H_2O	180	12	39
15	$(PPh_3)_2IrCl(CO)$	H_2O	200	12	30
16	$Ru(COD)Cl_2$	MeOH	160	3	6
17	$(PPh_3)_3Ru(CO)H_2$	MeOH	160	3	66
18	$[Ru(p\text{-cymene})Cl_2]_2$	MeOH	160	3	21
19	Rh(COD)Cl	MeOH	160	3	22
20	$(PPh_3)_2RhCl(CO)$	MeOH	160	3	5
21[i]	Milstein catalyst	MeOH	160	3	22

[a]Reaction conditions: **2.2a** (15 mg, 0.1 mmol), hydrazine hydrate (10 mg, 0.2 mmol), catalyst (1 mol %), base (0.2 mmol), under an air atmosphere. [b]Solvent (0.1 mL) was used (c = 1 M), unless otherwise noted. [c]Determined by ^{1}H NMR using nitromethane as an internal standard. [d]10 μL MeOH was used (c = 10 M). [e]Under an argon atmosphere. [f]Without hydrazine hydrate. [g]Et_3N (0.1 mmmol) was used as a base. [h]25 μL MeOH was used (c = 4 M). [i]Milstein catalyst: carbonylhydrido[6-(di-t-butylphosphinomethylene)-2-(N,N-diethylaminomethyl)-1,6-dihydropyridine] ruthenium(II), CAS No.: 863971-63-5.

2.3.2 Scope of Alcohol Substrates

Table 2-5[a] Scope of Ir(I)-Catalyzed Direct Alcohol Deoxygenation



Entry	Substrate	Product	Yield (%)[b]	Entry	Substrate	Product	Yield (%)[b]
1			**2.3a**, 99 (89)	11			**2.3k**, 77 (74)
2			**2.3b**, 98	12[c]			**2.3l**, 60 (51)
3			**2.3c**, 99 (90)	13			**2.3c**, 98 (88)
4			**2.3d**, 58 (50)	14			**2.3n**, 87 (62)
5			**2.3e**, 93 (86)	15			**2.3o**, 66 (55)
6			**2.3f**, 80 (75)	16			**2.3p**, 72
7			**2.3g**, 99 (93)	17[d,e]			**2.3q**, 77 (64)
8			**2.3h**, 90 (82)	18[d,e]			**2.3r**, 48
9			**2.3i**, 82 (73)	19[f]			**2.3s**, 96 (81)
10			**2.3j**, 92 (88)	20[f]			**2.3t**, 46 (43)

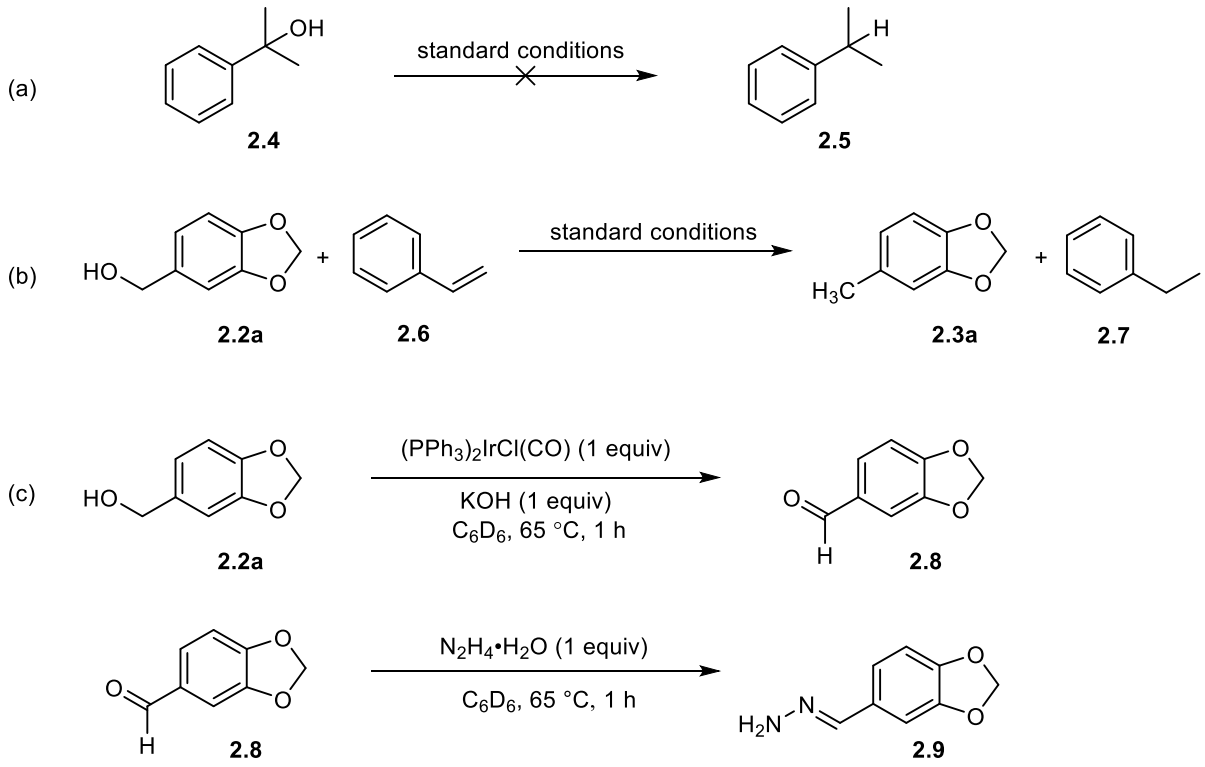
[a]Reaction conditions: **2.2a-t** (0.3 mmol), hydrazine hydrate (30 mg, 0.6 mmol), $(PPh_3)_2IrCl(CO)$ (2.3 mg, 1 mol %), KOH (34 mg, 0.6 mmol), MeOH (30 μL), 160 °C, 3 h, under an air atmosphere. [b]Determined by

[1]H NMR using nitromethane as an internal standard; isolated yields are given in parentheses. [c]MeOH (90 μL) was used (c = 3 M). [d]Reaction conditions: **2.2a-t** (0.3 mmol), hydrazine hydrate (60 mg, 1.2 mmol), $(PPh_3)_2IrCl(CO)$ (1 mol %), KOH (68 mg, 1.2 mmol), MeOH (30 μL), 160 °C, 3h, under an air atmosphere. [e]A trace amount of mono-deoxygenated product was detected. [f]Reaction time: 12 h.

Under the optimized conditions, the substrate scope was explored using hydrazine hydrate (2 equiv) as the reducing reagent, $(PPh_3)_2IrCl(CO)$ (1 mol %) as the catalyst, KOH (2 equiv) as the base in MeOH (c = 10 M) at 160 °C under an air atmosphere for 3 h (Table 2-5). In general, benzylic alcohols showed excellent reactivity, including those with both electron-donating and electron-withdrawing substituents (entries 1-12); nearly quantitative yields were obtained for electron-rich benzylic alcohols in almost all cases (entries 1-3 and entry 7). Interestingly, the yield decreased significantly (99% to 58%) upon moving the methoxy group from the *para* position to the *ortho* position, whereas the *meta* isomer remained unaffected (entry 3). This decrease in the yield of the product obtained with the use of the *ortho* isomer can possibly be attributed to the ready chelation of the *ortho*-methoxy group and hydroxy groups to the iridium catalyst; this chelation occupies the empty coordination site, which is required for the activation of the β C–H bond. Next, primary alcohols other than benzylic alcohols were tested and most of them gave satisfactory results (entries 13-19). To our delight, the reaction scope could be extended to heteroaromatic, heterocyclic, aliphatic alcohols and diols, as the direct deoxygenation of these candidates has not been previously reported (entries 14-18).[7] Significantly, both the hydroxy group and the C=C double bond can be efficiently reduced by employing this deoxygenation strategy (entry 19), whereas the carbon-carbon double bond remains intact in the previous Ti(III)-promoted strategy.[7a] However, only a moderate yield was observed for the secondary cyclic alcohol **2.2t** (entry 20), possibly as a result of increased steric hindrance, which offers potential regioselective deoxygenation of molecules bearing multiple hydroxy groups.

2.3.3 Mechanistic Studies

To explore the mechanism of this iridium-catalyzed deoxygenation reaction, several control experiments were conducted under the optimized conditions (Scheme 2-2). Tertiary 2-phenyl-2-propanol **2.4** did not react with hydrazine hydrate due to its lack of a *β*-H (Scheme 2-2, a). In addition, an intermolecular reaction between piperonyl alcohol **2.2a** and styrene **2.6** provided the

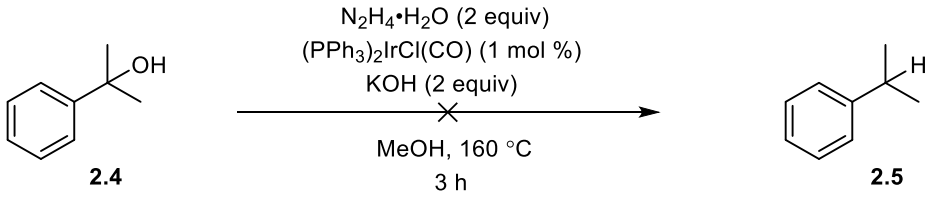


Scheme 2-2 Control Experiments for Mechanistic Understanding

corresponding deoxygenated product **2.3a** and ethylbenzene **2.7**, both in quantitative yield, and this implies that hydrogen gas generated *in situ* can participate in the hydrogenation of double bond catalyzed by Vaska's complex (Scheme 2-2, b). Anticipating two key intermediates (the aldehyde and the hydrazone) in the overall deoxygenation process, we also carried out a ^{1}H NMR spectroscopy experiment in deuterated benzene to detect them separately (Scheme 2-2, c). As expected, a small amount of piperonyl aldehyde **2.8** was detected by ^{1}H NMR spectroscopy upon treatment of piperonyl alcohol **2.2a** with $(PPh_3)_2IrCl(CO)$ (1 equiv) and KOH (1 equiv) at 65 ^{o}C for 1 h. However, **2.8** was not observed in the absence of base even if the reaction mixture was heated. The subsequent addition of hydrazine hydrate (1 equiv) to that reaction mixture led to the formation of a trace amount of piperonyl hydrazone **2.9**. Moreover, a quartet peak was observed in ^{1}H NMR spectrum around −10 ppm ($J_{P\text{-}H}$ = 21.6 Hz), which can be assigned to the Ir–H bond. Below are details of these control experiments.

2.3.3.1 Deoxygenation of Tertiary Alcohols

An Ace pressure glass tube was charged with $(PPh_3)_2IrCl(CO)$ (2.3 mg, 0.003 mmol), KOH (34 mg, 0.6 mmol), 2-phenyl-2-propanol (41 mg, 0.3 mmol), $N_2H_4 \cdot H_2O$ (29 μL, 0.6 mmol) and MeOH (30 μL) under an air atmosphere. The Ace tube was sealed and the reaction mixture was stirred at 160 °C for 3 h (Scheme 2-3). After that, the reaction mixture was cooled to room temperature, and filtered through a short column of silica by flushing it with CH_2Cl_2 (10 mL). The filtrate was dried over Na_2SO_4 and concentrated under reduced pressure to give the residue, which was further subjected to ^1H NMR by using nitromethane (8.1 μL, 0.15 mmol) as an internal standard (Figure 2-1).



Scheme 2-3 Deoxygenation of 2-Phenyl-2-propanol

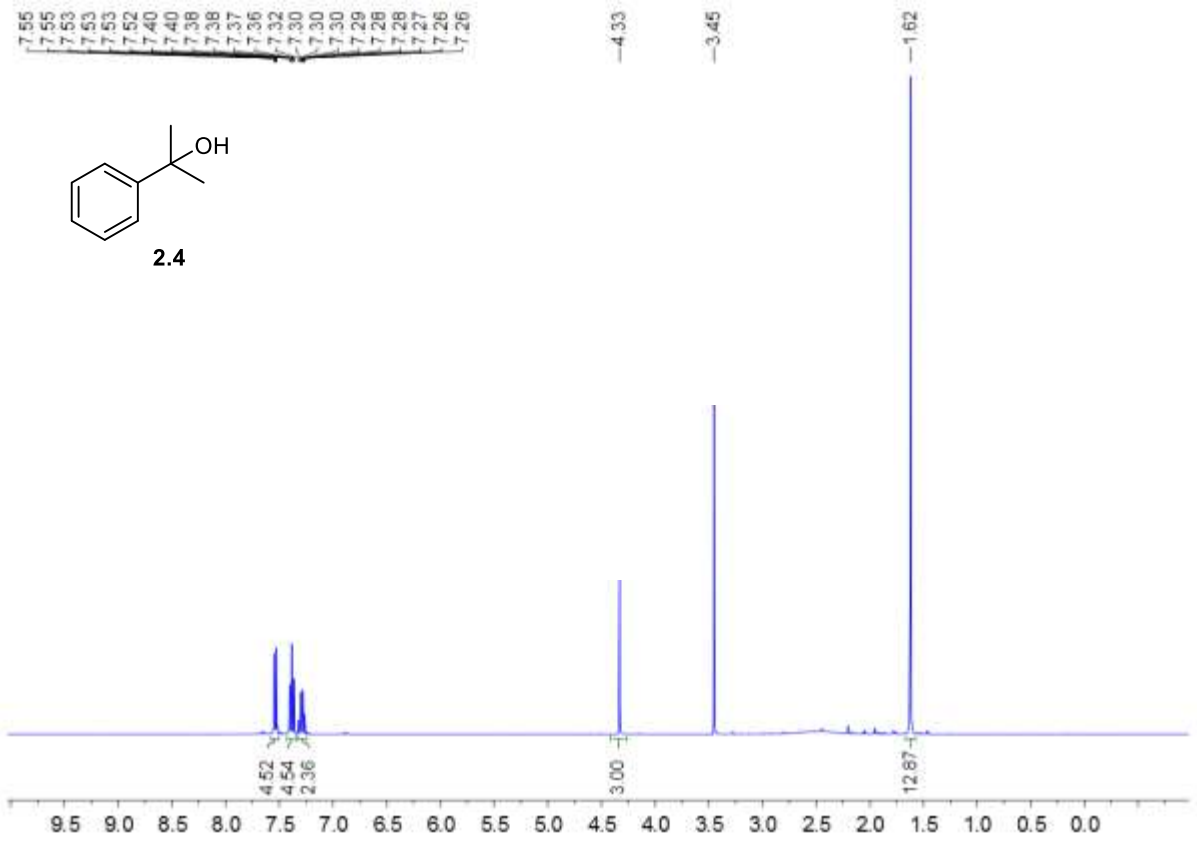
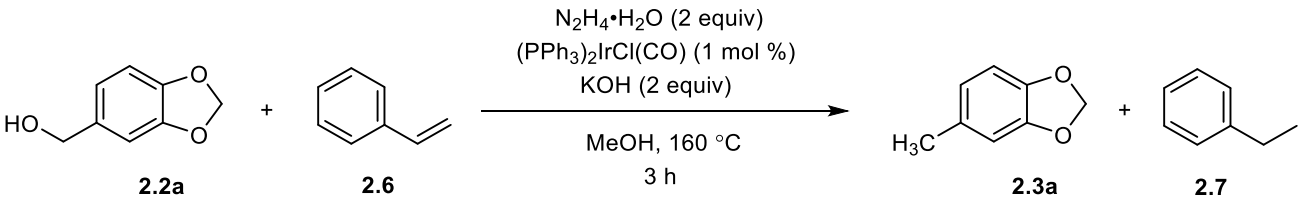


Figure 2-1 ^{1}H NMR Spectrum of the Crude Reaction Mixture in $CDCl_3$. (0.15 mmol CH_3NO_2)

2.3.3.2 Cross-Over Experiment

An Ace pressure glass tube was charged with $(PPh_3)_2IrCl(CO)$ (2.3 mg, 0.003 mmol), KOH (34 mg, 0.6 mmol), piperonyl alcohol (46 mg, 0.3 mmol), styrene (34 μL, 0.3 mmol), $N_2H_4{\cdot}H_2O$ (29 μL, 0.6 mmol) and MeOH (30 μL) under an air atmosphere. The Ace tube was sealed and the reaction mixture was stirred at 160 ºC for 3 h (Scheme 2-4). After that, the reaction mixture was cooled to room temperature, and filtered through a short column of silica plug by flushing it with CH_2Cl_2 (10 mL). The filtrate was dried over Na_2SO_4 and concentrated under reduced pressure to give the residue, which was further subjected to ^{1}H NMR by using nitromethane (5.4 μL, 0.1 mmol) as an internal standard (Figure 2-3).



Scheme 2-4 Deoxygenation in the Presence of an External Hydrogen Acceptor

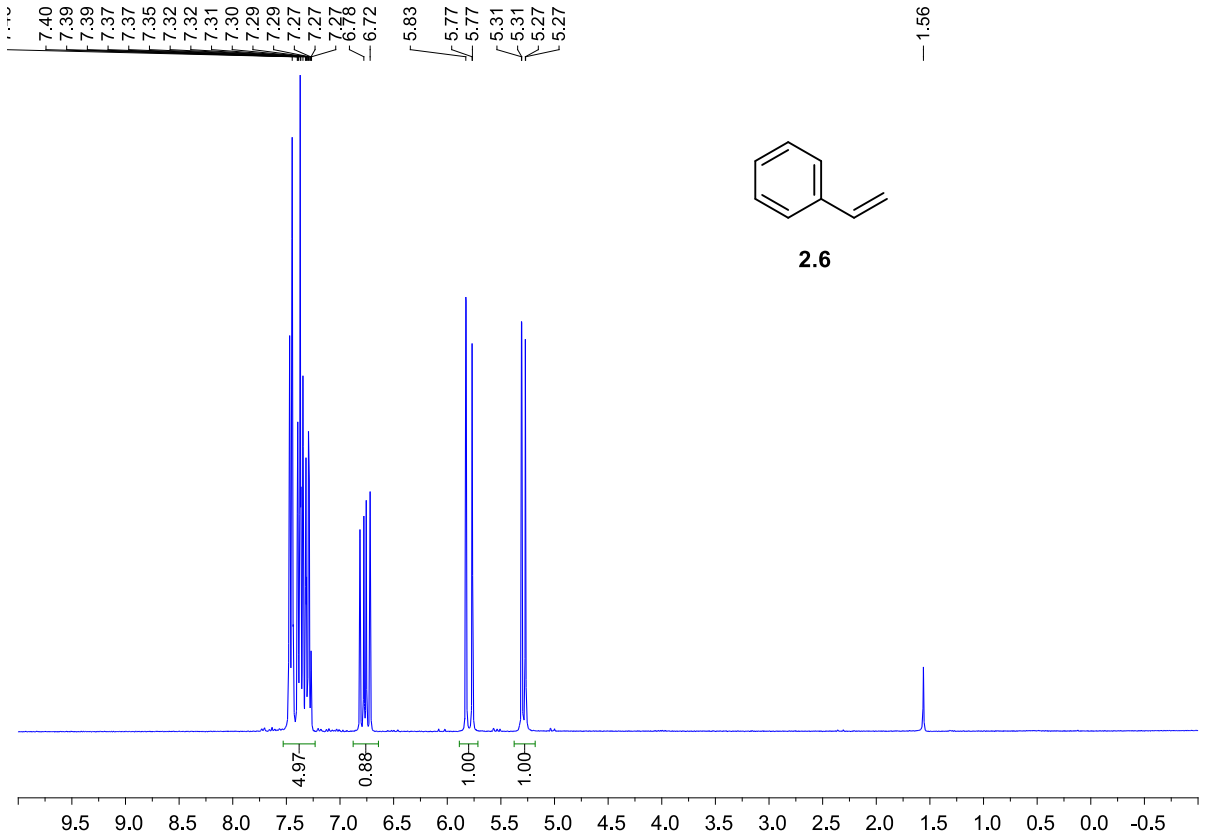


Figure 2-2 ^{1}H NMR Spectrum of Styrene in $CDCl_3$.

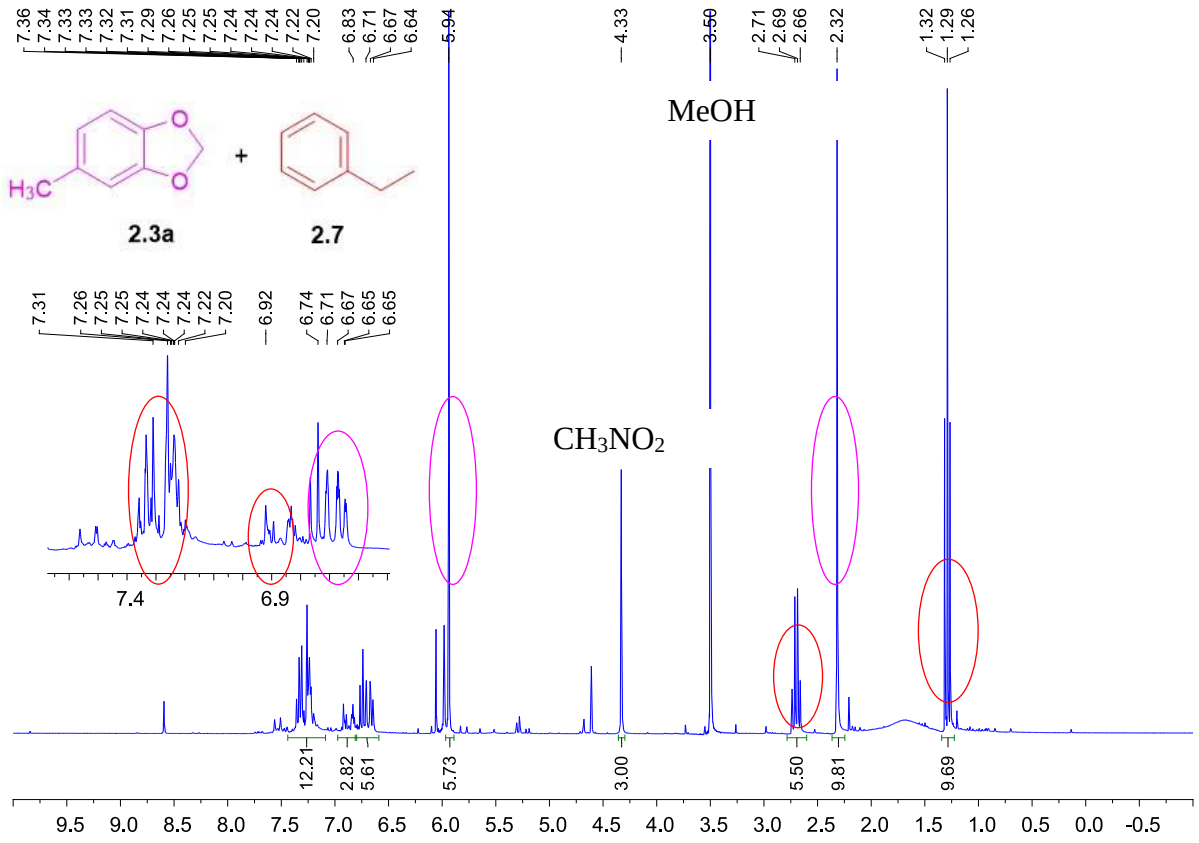


Figure 2-3 ^{1}H NMR Spectrum of the Crude Reaction Mixture in $CDCl_3$. (0.1 mmol CH_3NO_2)

2.3.3.3 ^{1}H NMR Monitoring Experiments

A NMR tube was charged with piperonyl alcohol (15 mg, 0.098 mmol), a stoichiometric amount of $(PPh_3)_2IrCl(CO)$ (76 mg, 0.098 mmol) in C_6D_6 (0.5 mL). The mixture was frozen by liquid nitrogen and vacuumed/ charged with argon three times. Then, (1) the mixture was warmed to room temperature and sonicated for 30 min (Step 1, Figure 2-4); (2) The mixture was kept in the oil bath at 65 ^{o}C for 1 h and sonicated for 30 min (Step 2, Figure 2-5); (3) KOH (5.5 mg, 0.098 mmol) was added into the mixture and repeated step 2 (Step 3, Figure 2-6); (4) $N_2H_4{\cdot}H_2O$ (4.7 μL, 0.098 mmol) was added into the mixture and repeated step 2 (Step 4, Figure 2-7 and Figure 2-8).

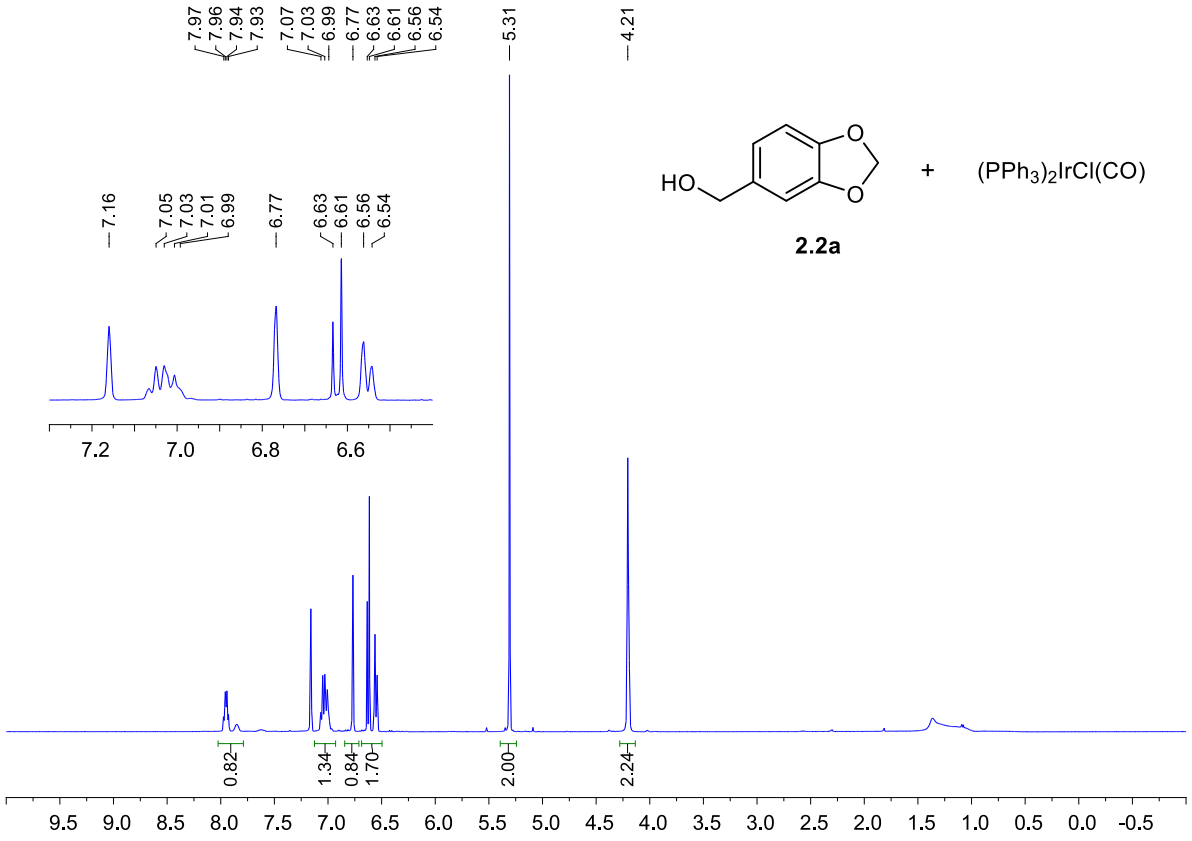


Figure 2-4 ^{1}H NMR Spectrum of Step 1 in C_6D_6. (Room Temperature)

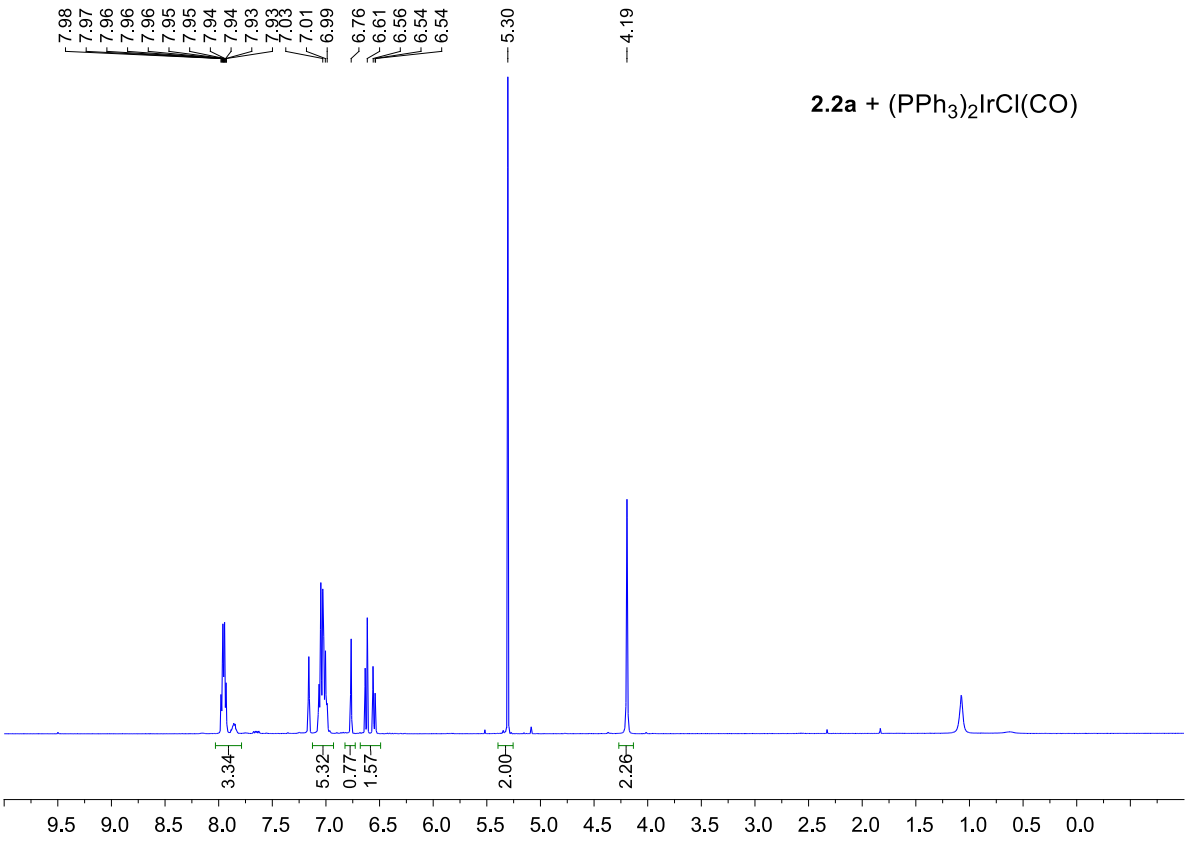


Figure 2-5 ^{1}H NMR Spectrum of Step 2 in C_6D_6. (65 ^{o}C)

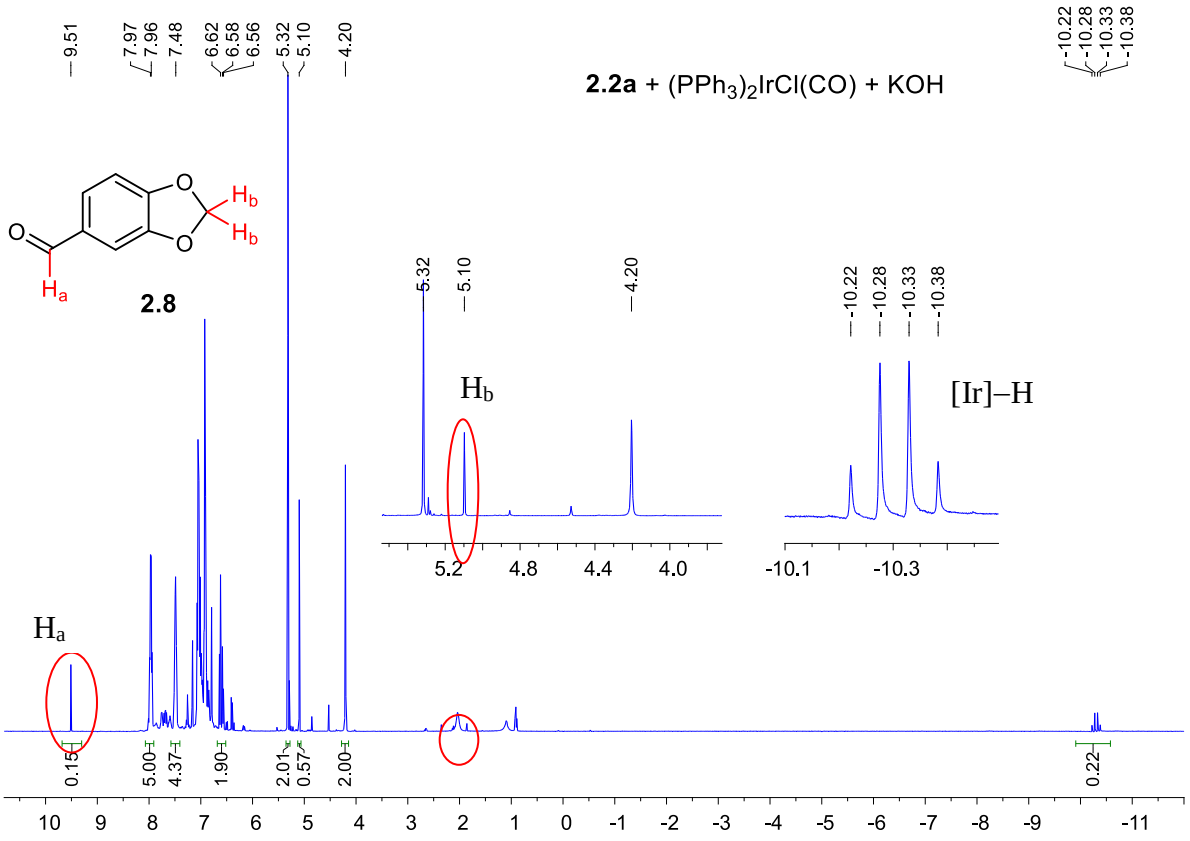


Figure 2-6 ^{1}H NMR Spectrum of Step 3 in C_6D_6. (65 ^{o}C)

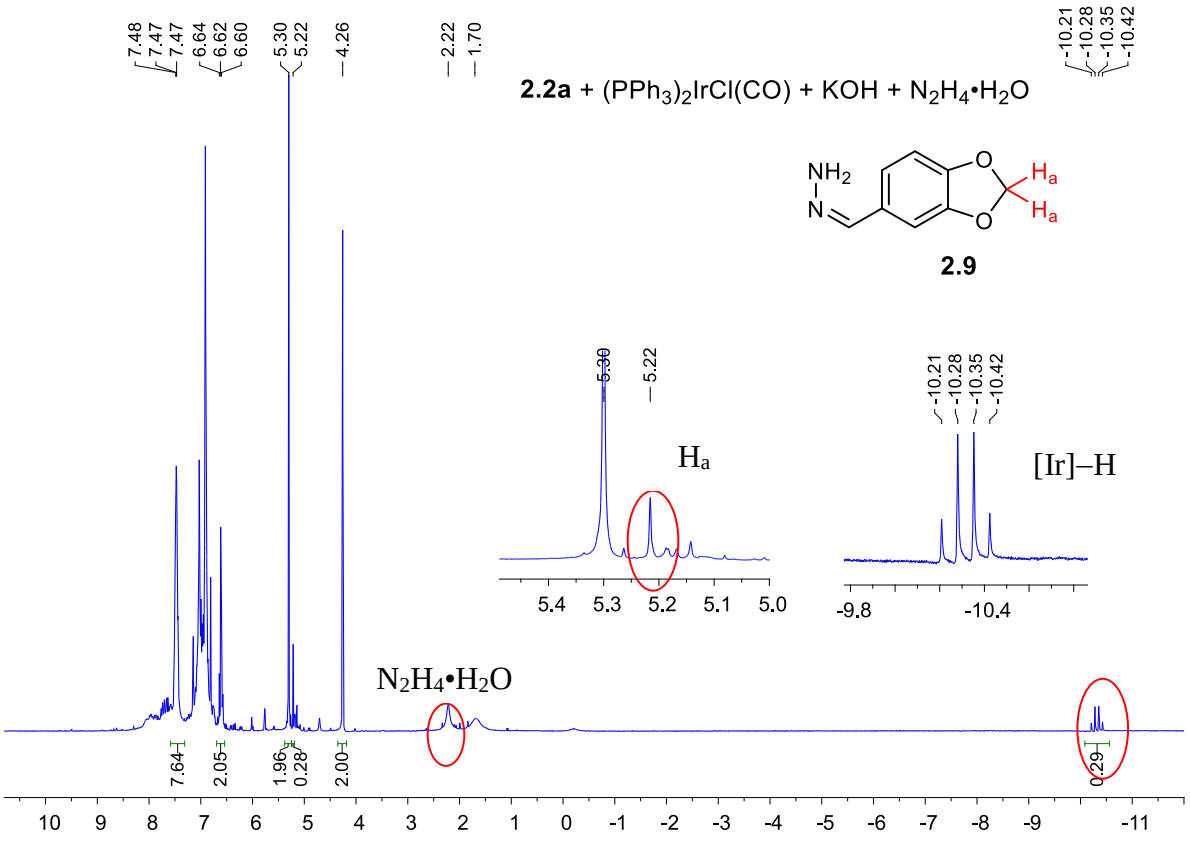


Figure 2-7 ^{1}H NMR Spectrum of Step 4 in C_6D_6. **(**65 ^{o}C)

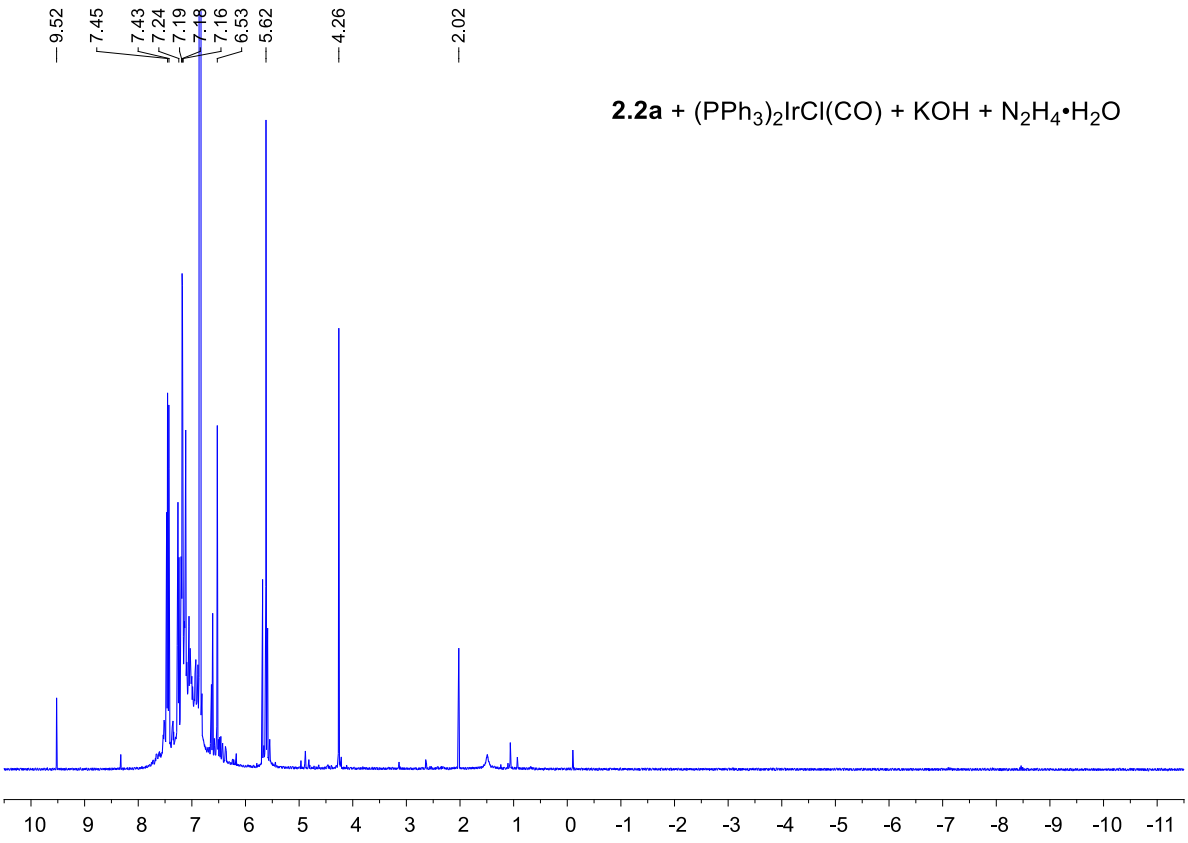
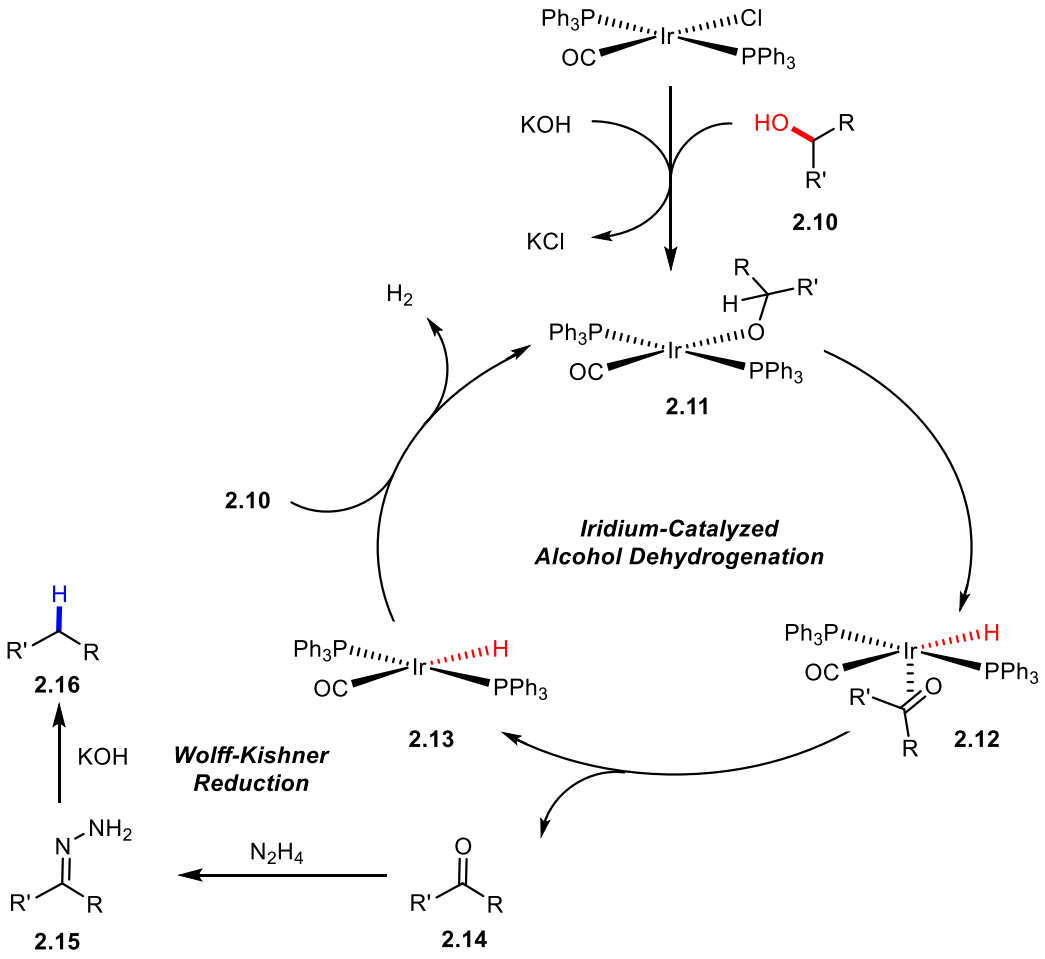


Figure 2-8 ^{1}H NMR Spectrum of Step 4 in C_6D_6. (An Excess Amount of KOH, 65 ^{o}C)

2.3.4 Proposed Mechanism on Ir-Catalyzed Direct Alcohol Deoxygenation

Based on experimental results obtained as well as the literature studies on the "borrowing hydrogen" strategy[8] and the Wolff-Kishner reduction,[9] a tentative mechanism for this iridium-catalyzed direct deoxygenation of alcohols is proposed in Scheme 2-5. Given that the activation of alcohols cannot happen without the involvement of a base, we postulate the initial ligand association of the Vaska's complex with alcohol **2.10** to afford iridium alkoxide species **2.11** in the presence of KOH. Subsequent β-H elimination occurs on **2.11** to form iridium complex **2.12** under heating conditions. The carbonyl compound which is *in-situ* generated and bound to **2.12**



Scheme 2-5 Deoxygenation in the Presence of the External Hydrogen Acceptor

dissociates from the iridium metal center to give rise to the corresponding alkane **2.16** following the Wolff-Kishner reduction. After ligand dissociation of the carbonyl compound from **2.12**, iridium hydride complex **2.13** is protonated by another alcohol molecule to regenerate active species **2.11**, with the concomitant release of hydrogen gas. Interestingly, if any hydrogen acceptors are present in this catalytic system, their double bonds can simultaneously be reduced through the insertion and protonation sequence (Table 2-5, entry 19 and Scheme 2-2, b). However, the role of iridium complexes other than Vaska's complex in the catalytic cycle is still unclear at this stage and needs further investigations.

2.4 Conclusions

In conclusion, we have developed a proof-of-concept deoxygenation method featuring iridium-catalyzed, redox-based process to form C–H bonds in a simple and efficient fashion. This reaction is proposed to proceed through a dehydrogenative alcohol oxidation/Wolff-Kishner reduction sequence. The present approach highlights a useful alternative to the classical multistep deoxygenation strategy of alcohols, especially for benzylic and allylic primary alcohols. Notably, even water can be used as a solvent for the reaction. Further efforts to expand the reaction scope, to clarify the reaction mechanism, and to explore the synthetic applications of this reaction are currently in progress in our laboratory.

2.5 Experimental

2.5.1 General Considerations

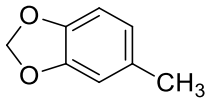
Experiment. All reactions were carried out under an atmosphere of air. All work-up and purification procedures were carried out with reagent-grade solvents. Analytical thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F254 pre-coated plates (0.25 mm). Flash column chromatography was performed with E. Merck silica gel 60 (230–400 mesh). Unless stated otherwise, all reagents were commercially available and used without further purification in this study.

Spectroscopy. Nuclear magnetic resonance (NMR) spectra were recorded on a Varian MERCURY plus-300 spectrometer (^{1}H 300 MHz, ^{13}C 75 MHz), a Varian MERCURY plus-400 spectrometer (^{1}H 400 MHz, ^{13}C 100 MHz) or a Varian MERCURY plus-500 spectrometer (^{1}H 500 MHz, ^{13}C 125 MHz). Chemical shifts for both ^{1}H NMR and ^{13}C NMR spectra are expressed in parts per million (ppm) units downfield from TMS, with the solvent residue peak as the chemical shift standard ($CDCl_3$: δ 7.26 ppm in^{1}H NMR; δ 77.0 ppm in ^{13}C NMR). Data are reported as following: chemical shift, multiplicity (s = singlet, d = doublet, dd = doublet of doublets, t = triplet, td = triplet of doublets, q = quartet, m = multiplet, br = broad signal), coupling constant (Hz), and integration.

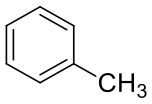
2.5.2 General Synthetic Procedure for Alcohol Deoxygenation

An Ace pressure glass tube (4 cm) was charged with $(PPh_3)_2IrCl(CO)$ (2.3 mg, 0.003 mmol), KOH (34 mg, 0.6 mmol), the alcohol (0.3 mmol), $N_2H_4 \cdot H_2O$ (29 μL, 0.6 mmol) and MeOH (30 μL) under an air atmosphere. The Ace tube was sealed and the reaction mixture was stirred at 160 °C for 3 h [*Warning: reaction is under pressure and potentially hazardous; and should be performed under protection of a blast shield*]. After that, the reaction mixture was cooled to room temperature, and filtered through a short column of silica by flushing it with CH_2Cl_2 (10 mL). The filtrate was dried over Na_2SO_4 and concentrated under reduced pressure to give the residue, which was first subjected to ^1H NMR by using nitromethane (5.4 μL, 0.1 mmol) as an internal standard; and further purified by preparative TLC, or flash chromatography on silica gel to afford the desired product.

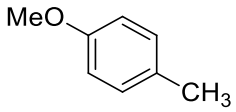
2.5.3 Spectroscopic Data



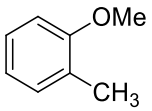
3,4-(Methylenedioxy)toluene (2.3a) (CAS Registered Number: 7145-99-5). Following **the general procedure**, the dehydroxylation of alcohol **2.2a** afforded **2.3a** in 89% yield (37.5 mg, 0.3 mmol) as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$): δ 6.75-6.60 (m, 3H), 5.92 (s, 2H), 2.29 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.4, 145.2, 131.4, 121.4, 109.5, 108.0, 100.6, 21.1. Spectral properties are consistent with literature values.[1]



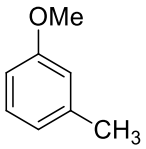
Toluene (2.3b) (CAS Registered Number: 108-88-3). Following **the general procedure**, the dehydroxylation of alcohol **2.2b** afforded **2.3b** in 98% NMR yield by using nitromethane as an internal standard. ^1H NMR (300 MHz, $CDCl_3$): δ 7.31-7.12 (m, 5H), 2.36 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.8, 129.1 (2C), 128.2 (2C), 125.3, 21.4. Spectral properties are consistent with a commercial chemical.



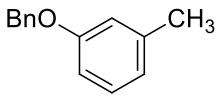
1-Methoxy-4-methylbenzene (2.3b) (CAS Registered Number: 104-93-8). Following **the general procedure**, the dehydroxylation of alcohol **2.2c** afforded **2.3b** in 90% yield (32.8 mg, 0.3 mmol) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.11 (m, 2H), 6.82 (m, 2H), 3.78 (3H, s), 2.31 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.4, 129.84 (2C), 129.78 (2C), 113.6, 55.2, 20.4. Spectral properties are consistent with literature values.[10]



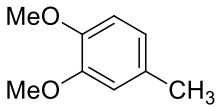
1-Methoxy-2-methylbenzene (2.3d) (CAS Registered Number: 578-58-5). Following **the general procedure**, the dehydroxylation of alcohol **2.2d** afforded **2.3d** in 50% yield (18.3 mg, 0.3 mmol) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.22-7.15 (m, 2H), 6.91-6.84 (m, 2H), 3.85 (s, 3H), 2.25 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.6, 130.6, 126.7, 126.5, 120.2, 109.9, 55.2, 16.2. Spectral properties are consistent with literature values.[11]



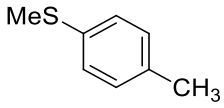
1-Methoxy-3-methylbenzene (2.3e) (CAS Registered Number: 100-84-5). Following **the general procedure**, the dehydroxylation of alcohol **2.2e** afforded **2.3e** in 86% yield (31.5 mg, 0.3 mmol) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.22-7.15 (m, 2H), 6.91-6.84 (m, 2H), 3.83 (s, 3H), 2.39 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.5, 139.4, 129.1, 121.4, 114.7, 110.7, 55.0, 21.5. Spectral properties are consistent with literature values.[12]



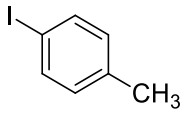
1-(Benzyloxy)-3-methylbenzene (2.3f) (CAS Registered Number: 834-25-3). Following **the general procedure**, the dehydroxylation of alcohol **2.2f** afforded **2.3f** in 75% yield (44.5 mg, 0.3 mmol) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51-7.34 (m, 5H), 7.25-7.19 (m, 1H), 6.89-6.81 (m, 3H), 5.09 (s, 2H), 2.38 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.8, 139.5, 137.1, 129.2, 128.5 (2C), 127.8, 127.4 (2C), 121.7, 115.7, 111.6, 69.8, 21.5. Spectral properties are consistent with literature values.[13]



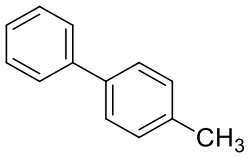
1,2-Dimethoxy-4-methylbenzene (2.3g) (CAS Registered Number: 494-99-5). Following **the general procedure**, the dehydroxylation of alcohol **2.2f** afforded **2.3f** in 93% yield (42.4 mg, 0.3 mmol) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.79-6.66 (m, 3H), 3.86 (s, 3H), 3.85 (s, 3H), 2.31 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.6, 146.7, 130.3, 120.6, 112.3, 111.1, 55.8, 55.6, 20.9. Spectral properties are consistent with literature values.[10]



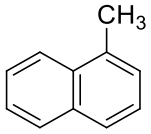
4-Methylthioanisole (2.3h) (CAS Registered Number: 623-13-2). Following **the general procedure**, the dehydroxylation of alcohol **2.2h** afforded **2.3h** in 82% yield (33.9 mg, 0.3 mmol) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.21 (m, 2H), 7.12 (m, 2H), 2.48 (s, 3H), 2.34 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.0, 134.6, 129.5 (2C), 127.2 (2C), 20.9, 16.4. Spectral properties are consistent with literature values.[14]



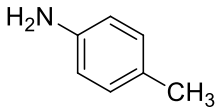
1-Iodo-4-methylbenzene (2.3i) (CAS Registered Number: 624-31-7). Following **the general procedure**, the dehydroxylation of alcohol **2.2i** afforded **2.3i** in 73% yield (47.9 mg, 0.3 mmol) as a light yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.58 (m, 2H), 6.94 (m, 2H), 2.32 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 137.4, 137.2 (2C), 131.1 (2C), 90.2, 21.0. Spectral properties are consistent with literature values.[15]



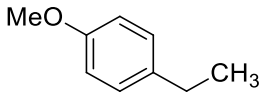
4-Methylbiphenyl (2.3j) (CAS Registered Number: 644-08-6). Following **the general procedure**, the dehydroxylation of alcohol **2.2j** afforded **2.3j** in 88% yield (44.4 mg, 0.3 mmol) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.67-7.63 (m, 2H), 7.59-7.55 (m, 2H), 7.52-7.46 (m, 2H), 7.42-7.36 (m, 1H), 7.33-7.30 (m, 2H), 2.46 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 141.1, 138.3, 137.0, 129.4 (2C), 128.7 (2C), 127.0, 126.9 (4C), 21.1. Spectral properties are consistent with literature values.[16]



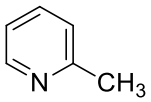
1-Methylnaphthalene (2.3k) (CAS Registered Number: 90-12-0). Following **the general procedure**, the dehydroxylation of alcohol **2.2k** afforded **2.3k** in 74% yield (31.6 mg, 0.3 mmol) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.07 (m, 1H), 7.92 (m, 1H), 7.78 (m, 1H), 7.63-7.50 (m, 2H), 7.48-7.35 (m, 2H), 2.77 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 134.2, 133.5, 132.6, 128.5, 126.5, 126.3, 125.7, 125.53, 125.49, 124.1, 19.4. Spectral properties are consistent with literature values.[17]



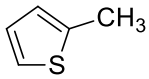
***p*-Toluidine (2.3l)** (CAS Registered Number: 106-49-0). Following **the general procedure**, the dehydroxylation of alcohol **2.2l** afforded **2.3l** in 51% yield (16.3 mg, 0.3 mmol) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.99 (m, 2H), 6.63 (m, 2H), 3.50 (s, br, 2H), 2.27 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.7, 129.7 (2C), 127.7, 115.2 (2C), 20.4. Spectral properties are consistent with literature values.[18]



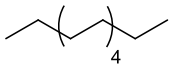
1-Ethyl-4-methoxybenzene (2.3m) (CAS Registered Number: 104-45-0). Following **the general procedure**, the dehydroxylation of alcohol **2.2m** afforded **2.3m** in 88% yield (35.9 mg, 0.3 mmol) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.15 (m, 2H), 6.86 (m, 2H), 3.81 (s, 3H), 2.63 (q, J = 7.6 Hz, 2H), 1.24 (t, J = 7.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.6, 136.3, 128.7 (2C), 113.7 (2C), 55.2, 27.9, 15.9. Spectral properties are consistent with literature values.[19]



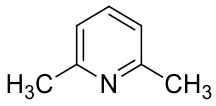
2-Methylpyridine (2.3n) (CAS Registered Number: 109-06-8). Following **the general procedure**, the dehydroxylation of alcohol **2.2n** afforded **2.3n** in 62% yield (17.3 mg, 0.3 mmol) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.41 (s, 1H), 7.55-7.40 (m, 1H), 7.06-6.92 (m, 2H), 2.47 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.2, 148.9, 136.0, 123.0, 120.4, 24.3. Spectral properties are consistent with literature values.[20]



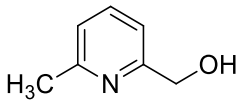
2-Methylthiophene (2.3o) (CAS Registered Number: 554-14-3). Following **the general procedure**, the dehydroxylation of alcohol **2.2o** afforded **2.3o** in 55% yield (16.2 mg, 0.3 mmol) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.05 (m, 1H), 6.90-6.86 (m, 1H), 6.75-6.72 (m, 1H), 2.48 (d, *J* = 1.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.5, 126.9, 125.1, 123.0, 15.0. Spectral properties are consistent with a commercial chemical.



Dodecane (2.3p) (CAS Registered Number: 112-40-3). Following **the general procedure**, the dehydroxylation of alcohol **2.2p** afforded **2.3p** in 72% NMR yield by using nitromethane as an internal standard. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.27 (m, 20H), 0.86 (d, *J* = 6.8 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 32.1 (2C), 29.9 (4C), 29.6 (2C), 22.9 (2C), 14.0 (2C). Spectral properties are consistent with a commercial chemical.

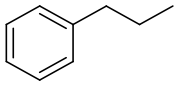


2,6-Dimethylpyridine (2.3q) (CAS Registered Number: 108-48-5). Following **the general procedure**, the dehydroxylation of alcohol **2.2q** afforded **2.3q** in 64% yield (20.5 mg, 0.3 mmol) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.71 (t, *J* = 7.7 Hz, 1H), 7.20 (d, *J* = 7.7 Hz, 2H), 4.79 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.5 (2C), 136.4, 120.0 (2C), 24.4 (2C). Spectral properties are consistent with a commercial chemical.

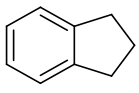


6-Methyl-2-pyridinemethanol (2.3qa) (CAS Registered Number: 1122-71-0). Following **the general procedure**, the dehydroxylation of alcohol **2.2q** afforded **2.3qa** in 10% yield (3.7 mg, 0.3 mmol) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.57 (t, *J* = 7.7 Hz, 1H), 7.05 (dd, *J* = 11.2, 7.7 Hz, 2H), 4.72 (s, 2H), 2.56 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.0, 157.3, 137.1, 121.8, 117.4, 63.8, 24.1. Spectral properties are consistent with a commercial chemical.

Decane (2.3r) (CAS Registered Number: 124-18-5). Following **the general procedure**, the dehydroxylation of alcohol **2.2r** afforded **2.3r** in 48% NMR yield by using nitromethane as an internal standard. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.39 (m, 4H), 1.25 (m, 12H), 0.87 (d, *J* = 6.8 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 32.2 (2C), 29.9 (2C), 29.5 (2C), 22.9 (2C), 14.2 (2C). Spectral properties are consistent with a commercial chemical.



Propylbenzene (2.3s) (CAS Registered Number: 103-65-1). Following **the general procedure**, the dehydroxylation of alcohol **2.2s** afforded **2.3s** in 81% yield (29.2 mg, 0.3 mmol) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.30-7.25 (m, 1H), 7.20-7.15 (m, 1H), 2.59 (t, *J* = 7.3 Hz, 1H), 1.65 (sextet, *J* = 7.3 Hz, 3H), 0.95 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 142.7, 128.4 (2C), 128.2 (2C), 125.6, 38.1, 24.6, 13.8. Spectral properties are consistent with literature values.[21]



Indane (2.3t) (CAS Registered Number: 496-11-7). Following **the general procedure**, the dehydroxylation of alcohol **2.2t** afforded **2.3t** in 43% yield (15.2 mg, 0.3 mmol) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.22-7.26 (m, 2H), 7.16-7.10 (m, 2H), 2.93 (t, *J* = 7.4 Hz, 4H),

2.08 (tt, apparent quin, J = 7.4 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 144.1 (2C), 125.9 (2C), 124.3 (2C), 32.8 (2C), 25.3. Spectral properties are consistent with literature values.[22]

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Chapter 3 : Ruthenium-Catalyzed Selective and Practical Deoxygenation of Primary Aliphatic Alcohols

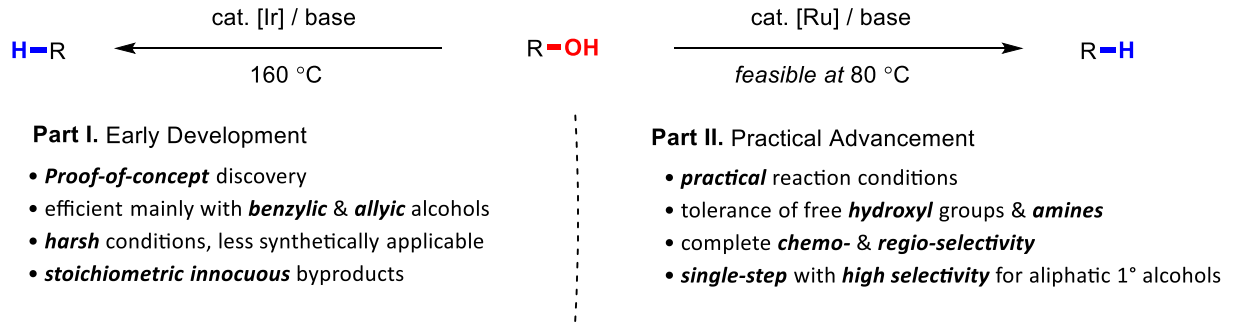
3.1 Preface

This chapter describes our pursuit of the redox-based, direct and chemoselective deoxygenation of primary aliphatic alcohols under practical reaction conditions. To this end, a catalytic system composed of a ruthenium(II) pre-catalyst and an electron-rich bidentate phosphine ligand was successfully developed as an alternative to the iridium-based system discussed in Chapter 2. More importantly, the method presented in the current chapter demonstrates its synthetic efficiency and utility in the context of both simple and complex molecular settings. I spent nearly two years — the longest among all projects in my Ph.D. studies — on this project. Towards the end of this project, Dr. Zheng-Wang Chen and Dr. Feng Wang (Visiting Scholars 2014-2015) in the Li lab were particularly acknowledged for their assistance in preparation of some complex alcohol substrates. This work was published in *Journal of the American Chemical Society* **2016**, *138*: 5433–5440.

3.2 Introduction

To recap the perspective from the beginning of Chapter 1 (section 1.1.1), selective defunctionalization of a specific chemical bond in any given organic molecules has historically been less of a mainstream academic interest than selective functionalization. Perhaps the lack of attention or enthusiasm in this direction can be attributed to the paucity of reliable synthetic methods. Nevertheless, methods that are selective and efficient to defunctionalize targeted chemical bonds at late stage of chemical synthesis is highly valuable, as they provide chemical tools for the fine-tuning of molecular structure and physico-chemical properties (e.g., hydrogen-bond donors and acceptors, lipophilicity, etc.). A long-lasting challenge in this context is how to

selectively and directly remove sp^3 C–O bonds from aliphatic alcohols, in the presence of other functionalities such as free hydroxyl groups and amines, without excessive chemical transformations.[1] While the Barton-McCombie radical deoxygenation has been extensively utilized to remove sterically encumbered aliphatic hydroxyl groups in complex molecules,[2] the deoxygenation of less sterically hindered alcohols is typically accomplished through the ionic reductive mechanism.[3] The major downside of these classical methods is the requirement for multistep transformations, resulting in low step-efficiency. This raises an issue related to inefficient chemical syntheses, particularly when it comes to the functional group interconversion in complex molecules at a late stage.[4] To overcome this poor step economy, a few pioneering efforts in the 1990s have targeted direct deoxygenation of unhindered aliphatic alcohols via S_N2 displacement using stoichiometric reagents.[5] Nevertheless, limited functional group tolerance and poor selectivity generally render the aforementioned strategies less synthetically attractive. To date, there is not a direct catalytic deoxygenation method for aliphatic alcohols with great selectivity and efficiency, especially one that is compatible with free hydroxyl groups and amines ubiquitously present in biological molecules, such as steroids and alkaloids.[6]



Scheme 3-1 Our Two-Stage Development on Redox-Based Alcohol Deoxygenation

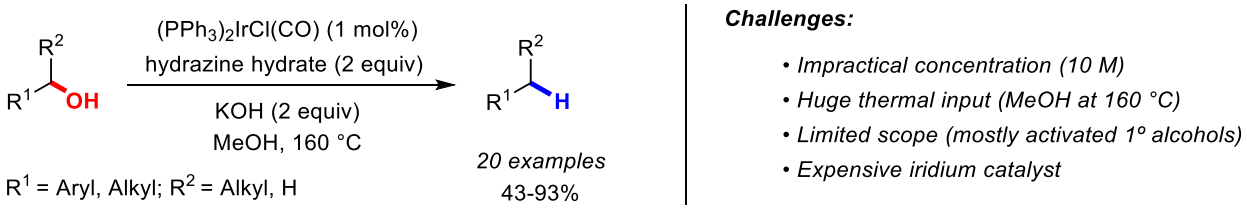
The development of a redox-based, single-step deoxygenation method in this thesis consists of two parts (Scheme 3-1): (1) The first part focuses on the early development using an iridium catalyst, which has been discussed in the previous chapter; and (2) the second part, or the present chapter discloses a significant and practical advancement catalyzed by a ruthenium complex, leading to an efficient and selective deoxygenation method for aliphatic primary alcohols. Its synthetic appeal lies in four key characteristics: (1) The reaction can be performed under practical conditions; (2)

good functional group tolerance and chemoselectivity in both simple and complex molecular settings, in particular leaving free hydroxyl groups and amines unaffected; (3) complete regioselectivity, demonstrated by the monodeoxygenation of steroids with multiple cyclic secondary hydroxyl groups; and (4) a synthetically benign strategy with stoichiometric nitrogen, hydrogen and water as innocuous byproducts.[7]

3.3 Results and Discussion

3.3.1 Proof-of-Concept Development and Limitations

As illustrated in Chapter 2, our redox-based hypothesis for the direct deoxygenation proved to be experimentally feasible when activated alcohols such as benzylic and allylic alcohols were used in the presence of hydrazine hydrate and strong base under iridium catalysis (Scheme 3-2).[8] Such proof-of-concept studies offer a mechanistically distinct approach to address the challenge of step economy. However, some critical issues remained unsolved and thus constrained this preliminary result from being synthetically appealing (Scheme 3-2). They are (1) significantly less



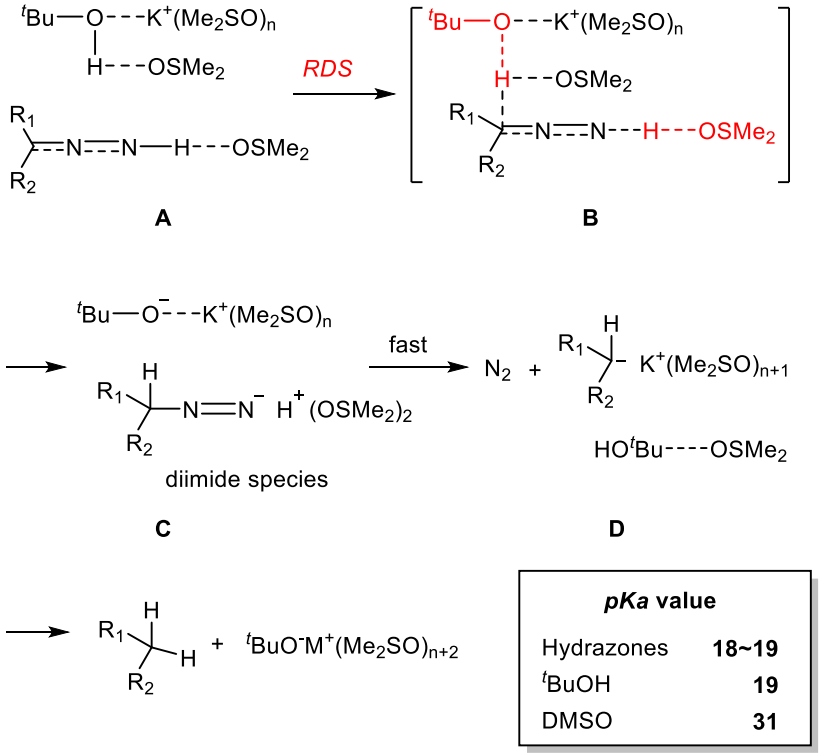
Scheme 3-2 Iridium-Catalyzed Alcohol Deoxygenation and Remaining Challenges

reactivity shown for aliphatic alcohols (our ultimate target) than their benzylic and allylic counterparts, especially when other functional groups are present; (2) stoichiometric quantity of strong base and massive thermal input in a sealed reaction vessel (MeOH at 160 °C with interior pressure built up over the course of the reaction), which are similar to the conditions used in the classical WK reduction; and (3) highly concentrated solution (10 M) for a complete conversion of starting materials, which is particularly not amenable to a practical scale-up with solid substrates.

To circumvent these limitations, we reasoned that a different catalyst and a milder set of reaction conditions (less basic, lower temperature, pressure and concentration) could potentially lead to significant progress on the deoxygenation of aliphatic alcohols, resolving issues related to both reactivity and chemoselectivity.

3.3.2 Studies on the Modified Low-Temperature WK Reaction

Subsequently, we embarked on studies to make this catalytic redox-based deoxygenation method more practical. Ruthenium-based complexes were selected as alternative catalysts because they were as effective as iridium complexes in our early studies from Chapter 2, yet more cost-effective.



Scheme 3-3 Modified Low-Temp WK Reduction Using DMSO/KO*t*Bu/*t*-BuOH

In the 1960s and 1970s, several reports revealed beneficial effects of DMSO along with the other two ingredients — KO*t*Bu and *t*-BuOH — on the rate of the low-temperature Wolff-Kishner reduction.[9] Using mixture of DMSO/KO*t*Bu/*t*-BuOH with a certain ratio, the WK reaction

becomes much more rapid and thus proceeds at nearly ambient temperature, as opposed to the high temperature required in the original protocol. In fact, it is well established by Szmant and others that the rate-determining step of the WK reaction involves the concerted formation of a carbon-hydrogen bond and breaking of a nitrogen-hydrogen bond.[10] In other words, the formation of the diimide anion **C** is kinetically the slowest step (Scheme 3-3). To accelerate the rate of this step, DMSO serves simply as a superior hydrogen acceptor while *t*-BuOH acts as a hydrogen donor. The presence of DMSO also causes a decrease in the acidity of alcohols complexed by alkoxide ions **A** in the proton-transfer process.[11]

3.3.3 Optimization on Low-Temperature Alcohol Deoxygenation

Inspired by a few studies on modified low-temperature WK reductions,[12] we attempted to combine such a mixture (*t*-BuOH as additive, DMSO as solvent) with [Ru(*p*-cymene)Cl_2]$_2$/dppb **(L_{16})** catalytic system developed by Williams *et al.* for the alcohol dehydrogenation.[13] With this combination, a trace amount of the desired product **3.2a** was detected under relatively mild thermal conditions (80 °C, 20 h). This outcome was indeed encouraging, as such a low-temperature alcohol dehydrogenation has rarely been reported in the past,[14] not to mention the more thermal demanding WK reduction. Subsequent screenings of various catalysts, ligands, bases, or other parameters had little to no effect on reaction yields, suggesting a major impediment to the catalytic cycle. We surmised that DMSO, a well-known dative ligand,[15] might be problematic when it was used as a solvent, because saturation of the ruthenium complex by DMSO might leave the ruthenium center with no empty coordination site. To verify this assumption, the volume of DMSO was decreased to 20 µL (1.4 equiv of **3.1a**). A spike in the yield of **3.2a** was observed.

3.3.3.1 Evaluation of Catalysts and Ligands

We tested a variety of ruthenium and iridium catalysts in the DMSO/KO*t*Bu/*t*-BuOH system, among which the reactivity of ruthenium-based catalysts was generally superior to that of iridium-based ones. The catalytic system consisting of [Ru(*p*-cymene)Cl_2]$_2$/bidentate phosphine ligands outperformed the Vaska's complex used in our early studies (Table 3-1, entry 5 vs entry 9), as well as other robust pincer-based ruthenium and iridium catalysts (Figure 3-1) specifically designed for the acceptorless alcohol dehydrogenation (Table 3-1, entries 10-14).[16] Variations on loadings of

ligands and base suggested that 5 mol% dppp and 50 mol% KO*t*Bu was optimal (Table 3-2, entry 3).

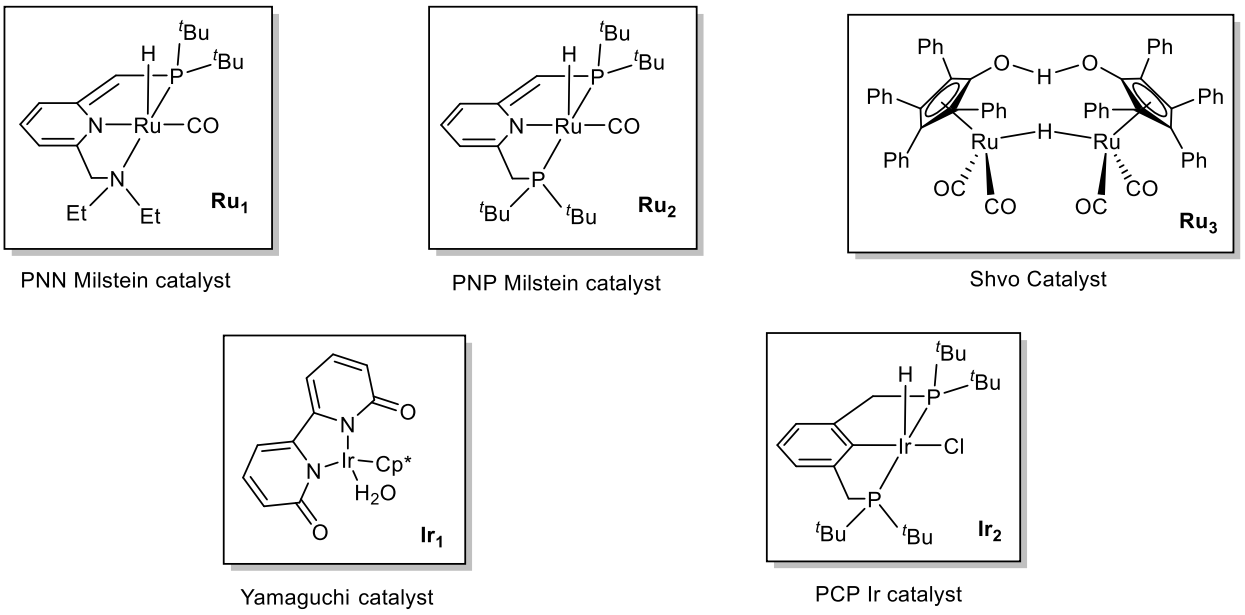
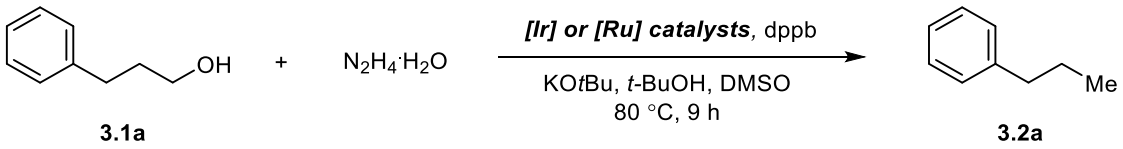


Figure 3-1 Metal Complexes Designed for Acceptorless Alcohol Dehydrogenation

Table 3-1 Catalyst Screening



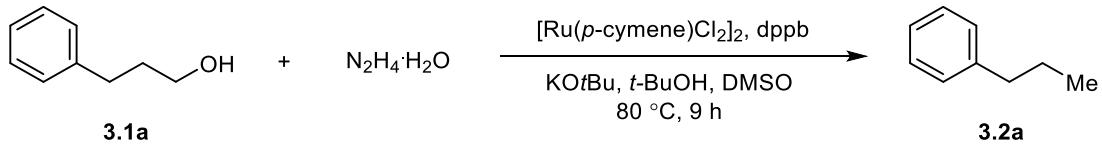
3.1a 3.2a

Entry	[Ru] or [Ir] catalysts	**3.2a** (%)[b]	Entry	[Ru] or [Ir] catalysts	**3.2a** (%)[b]
1	$[Rh(COD)Cl_2]_2$	N.D.	8	$[(CO)_3RuCl_2]_2$	N.D.
2	$[Ir(COD)Cl_2]_2$	7	9	$(PPh_3)_3Ir(CO)Cl$	5
3	$RuCl_3$	27	10[c]	Ru_1	16
4	$[PhRuCl_2]_2$	22	11[c]	Ru_2	13
5	$[Ru(p\text{-cymene})CI_2]_2$	33	12[c]	Ru_3	N.D.

6	$CpRu(PPh_3)_2Cl$	N.D.	13[c]	Ir_1	9
7	$Ru(CO)H_2PPh_3$	N.D.	14[c]	Ir_2	12

[a]Reaction conditions: **3.1a** (0.2 mmol, 27.2 µL), [Ru] or [Ir] catalysts: dimer (2.5 mol %), monomer (5 mol %), dppb (5 mol %), KO*t*Bu (0.1 mmol, 11.2 mg), $N_2H_4{\cdot}H_2O$ (0.24 mmol, 13 µL), *t*-BuOH (0.2 mmol, 18 µL), DMSO (0.28 mmol, 20 µL), sealed V-shape microvial, under an argon atmosphere. [b]Determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard. [c]1 mol % catalysts were used without dppb ligand.

Table 3-2 Loadings of Ligand and Base

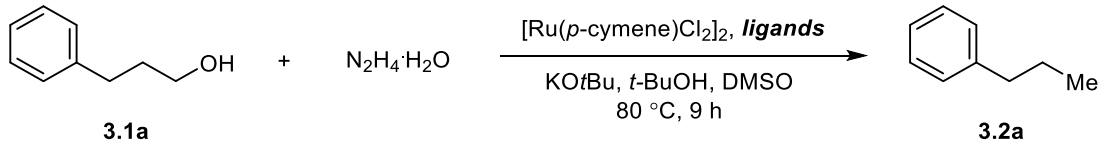


3.1a **3.2a**

Entry	dppb (mol %)	KO*t*Bu (equiv)	**3.2a** (%)[b]
1	2.5	0.5	18
2	10	0.5	15
3	5	0.5	23
4	5	0.25	N.D.
5	5	1	26

[a]Reaction conditions: **3.1a** (0.2 mmol, 27.2 µL), [Ru(*p*-cymene)Cl_2]$_2$ (2.5 mol %), DMSO (0.28 mmol, 20 µL), $N_2H_4{\cdot}H_2O$ (0.24 mmol, 13 µL), *t*-BuOH (0.2 mmol, 18.8 µL), sealed V-shape microvial, under an argon atmosphere. [b]Determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard.

Table 3-3 Ligand Screening



3.1a **3.2a**

Entry	Monodentate P Ligands	**3.2a** (%)[b]	Entry	Monodentate P Ligands	**3.2a** (%)[b]
1	Me_3P (**L_1**)	3	6	(p-$MeOC_6H_4$)$_3$P (**L_6**)	9
2	tBu_3P (**L_2**)	2	7	$(PhO)_3P$ (**L_7**)	N.D.
3	Cy_3P (**L_3**)	5	8	(2-furyl)$_3$P (**L_8**)	11
4	cataCXium A (**L_4**)	8	9	*t*-BuDavephos (**L_9**)	10
5	PPh_3 (**L_5**)	8	10	Ruphos (**L_{10}**)	8

Entry	Bidentate P	Bite Angle (°)[19-20]	**3.2a** (%)[b]	Entry	Bidentate P	Bite Angle (°)[19-20]	**3.2a** (%)[b]
11	dppm (**L_{11}**)	72	12	20	*rac*-BINAP (**L_{20}**)	93	2
12	dppe (**L_{12}**)	85	15	21	(*R*)-tol-BINAP (**L_{21}**)	-	5
13	dppe(ethylene) (**L_{13}**)	-	6	22	Xantphos (**L_{22}**)	111	16
14	dmpe (**L_{14}**)	85	53	23	DPEphos (**L_{23}**)	103	6
15	dppp (**L_{15}**)	91	18	24	dppf (**L_{24}**)	96	27
16	dppb (**L_{16}**)	98	33	25	dcpf (**L_{25}**)	-	10

17	dcpb (**L17**)	-	16	26	DIOP (**L26**)	98	18
18	dpph (**L18**)	-.	22	27	(S)-Phanephos (**L27**)	103	9
19	dppo (**L19**)	-	26	28	Norphos (**L28**)	123	14

Entry	Bidentate N Ligands	**3.2a** (%)[b]	Entry	Bidentate N Ligands	**3.2a** (%)[b]
29	TMEDA (**L33**)	7	32	TMBDA (**L36**)	4
30	TEEDA (**L34**)	9	33	**L37**	N.D.
31	NBEDA (**L35**)	6	34	**L38**	N.D.

Entry	Tridentate P Ligands	**3.2a** (%)[b]	Entry	NHC Ligands	**3.2a** (%)[b]
35	**L29**	2	37	IMeS (**L31**)	12
36	**L30**	7	38	I*i*PrS (**L32**)	10

[a]Reaction conditions: **3.1a** (0.2 mmol, 27.2 µL), [Ru(*p*-cymene)CI_2]$_2$ (2.5 mol %), monodentate P ligands (10 mol %), bidentate P/ N ligands (5 mol %), tridentate P ligands (5 mol %), NHC ligands (5 mol %), KO*t*Bu (0.1 mmol, 11.2 mg), $N_2H_4 \cdot H_2O$ (0.24 mmol, 13 µL), *t*-BuOH (0.2 mmol, 18.8 µL), DMSO (0.28 mmol, 20 µL), sealed V-shape microvial, under an argon atmosphere. [b]Determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard.

Following the catalyst evaluation, we launched a thorough ligand investigation (Table 3-3). Most monodentate phosphine ligands, regardless of their electronic or steric properties, performed poorly in the reaction (Table 3-3, entries 1-10; Figure 3-2). Neither tridentate phosphine ligands nor NHC ligands increased the yields (Table 3-3, entries 35-38). Some bidentate amido ligands (Figure 3-3, **L37** and **L38**), giving enhanced H_2 production[17] and showing high efficiency at low temperature,[18] also failed under our conditions (Table 3-3, entries 33 and 34). The increased yields observed when using bidentate phosphine ligands with large bite angles (Table 3-3, entries 15, 16,

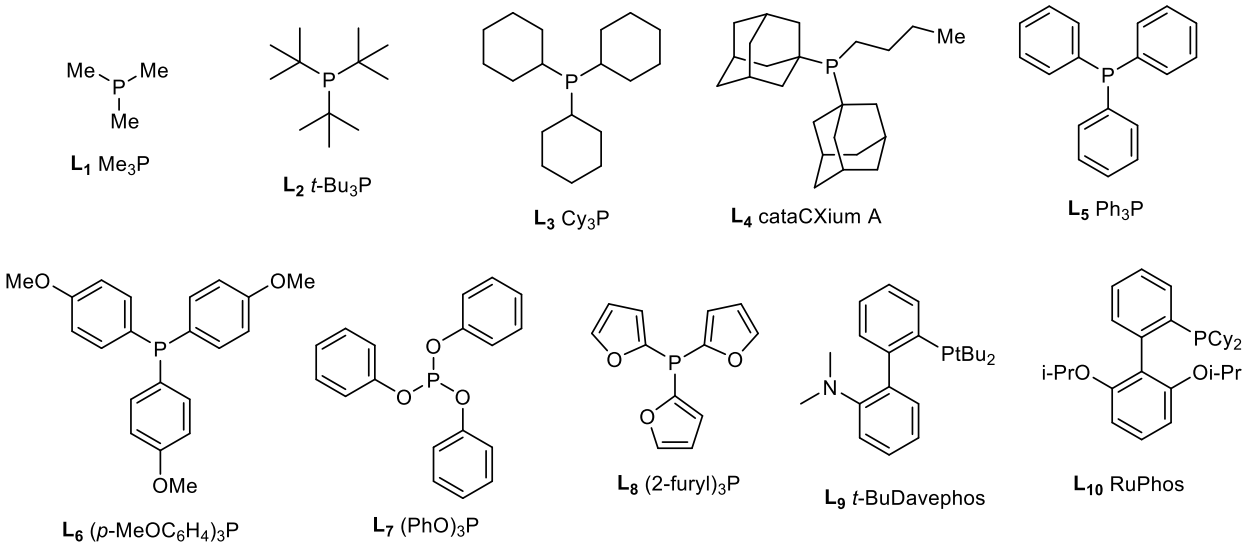
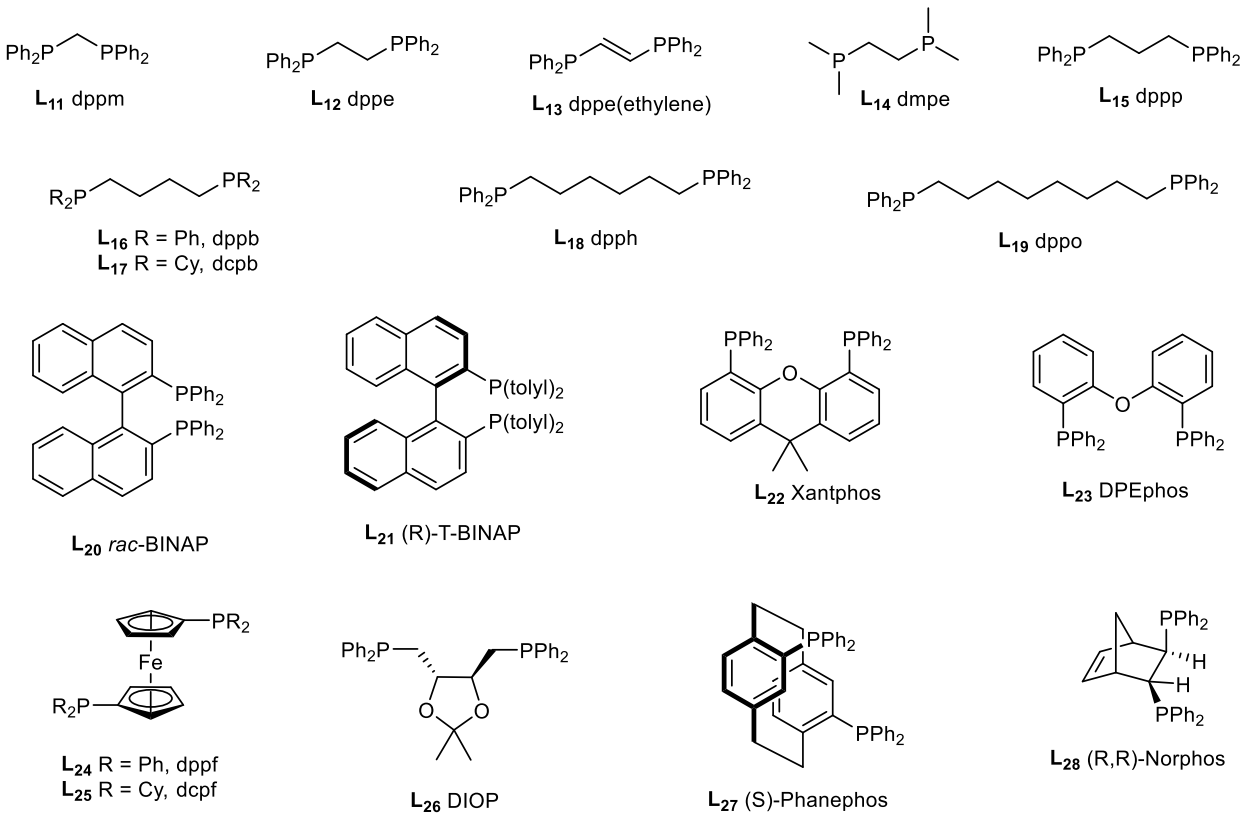


Figure 3-2 Monodentate Phosphine Ligands



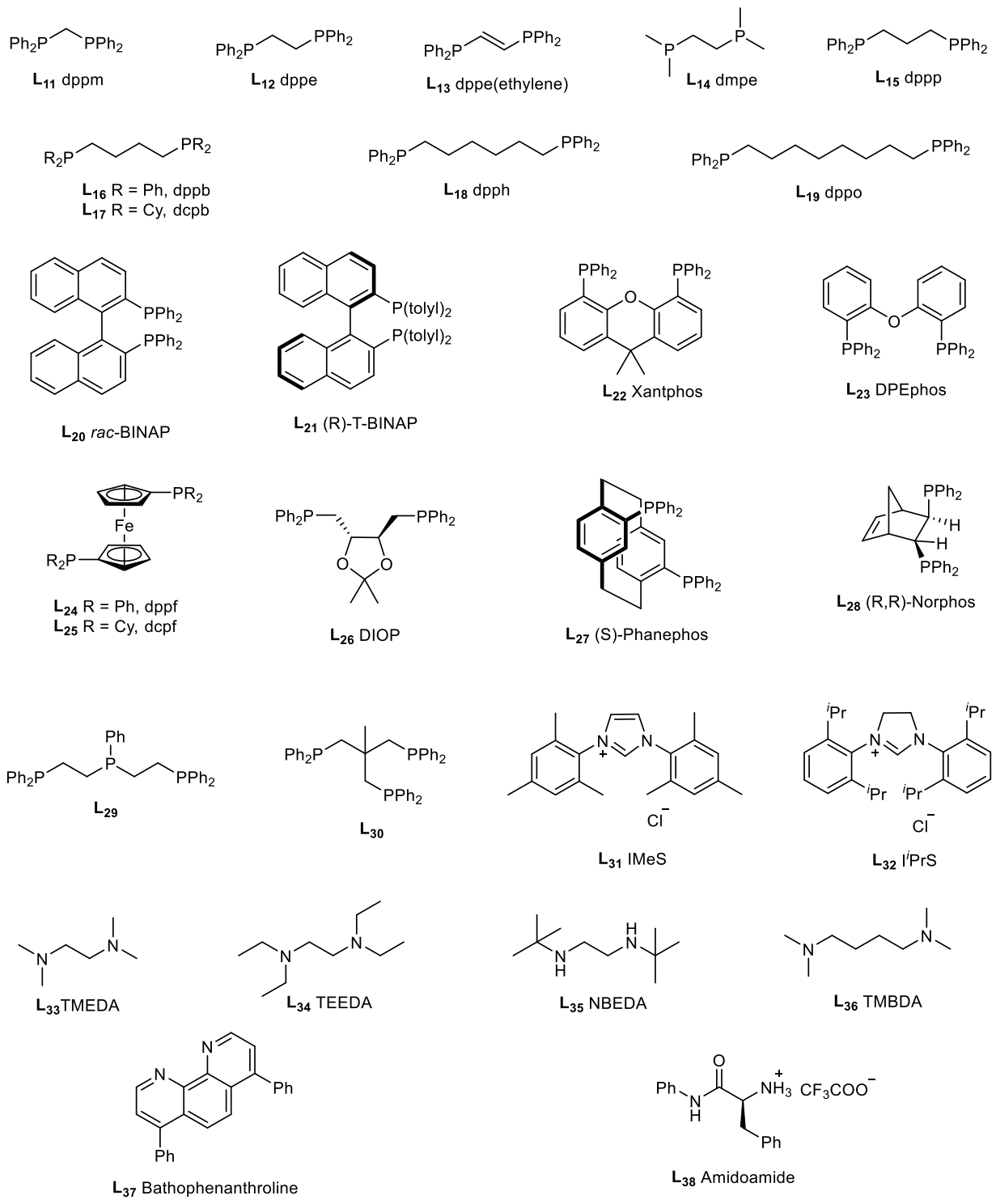


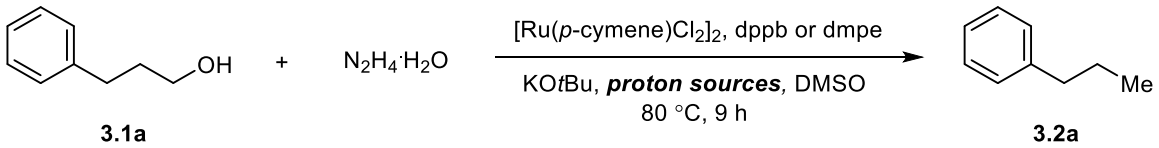
Figure 3-3 Bi- and Tri-Dentate Phosphine Ligands, NHCs and Bidentate Amido Ligands

24 and 26) led us to assume that bite angles might be of importance to the catalyst's reactivity.[19] Intriguingly, the use of 1,2-bis(dimethylphosphino)ethane (dmpe, **L14**) provided the highest

reactivity despite its comparably small bite angle, affording **3.2a** in 53% NMR yield (Table 3-3, entry 14).

3.3.3.2 Evaluation of DMSO and Protic Solvents

Table 3-4 Proton Sources



3.1a **3.2a**

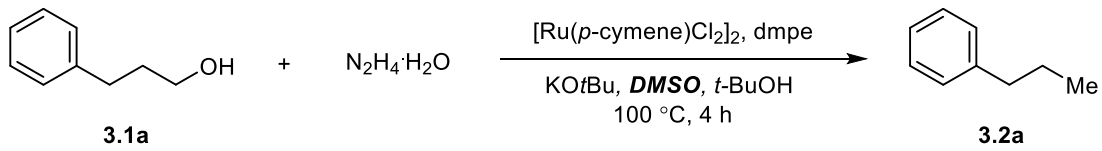
Entry	Proton Sources (**dppb** as ligand)	**3.2a** (%)[b]	Entry	Proton Sources (**dmpe** as ligand)	**3.2a** (%)[b]
1	*tert*-amyl alcohol	34	4	*tert*-amyl alcohol	37
2	3-methyl-3-pentanol	29	5	3-methyl-3-pentanol	35
3	*tert*-butanol	26	6	*tert*-butanol	53

[a]Reaction conditions: **3.1a** (0.2 mmol, 27.2 µL), [Ru(*p*-cymene)Cl_2]$_2$ (2.5 mol %), **dppb** or **dmpe** (5 mol %), KO*t*Bu (0.1 mmol, 11.2 mg), DMSO (0.28 mmol, 20 µL), $N_2H_4{\cdot}H_2O$ (0.24 mmol, 13 µL), **proton sources** (0.2 mmol), sealed V-shape microvial, under an argon atmosphere. [b]Determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard.

As suggested by studies on the low-temperature WK reactions, protic polar solvent was necessary in the reaction medium to create a strong dipole-dipole interaction (hydrogen bonding) with DMSO, as well as the hydrazone intermediate. To avoid dehydrogenative oxidation of alcohols, we selected tertiary alcohols instead of primary or secondary ones as proton sources. As shown in Table 3-4, the best reactivity was obtained with *t*-BuOH using dmpe as phosphine ligand (entry 6). However, we noticed that such reactivity was only accessible when *t*-BuOH was used as solvent and DMSO as additive. In other words, the volume of DMSO was critical in this reaction (Table 3-5). Examination on this issue reaffirmed that an excessive amount of DMSO is detrimental to the reaction under the optimized catalytic system (Table 3-5, entries 7 and 8), as we observed at the beginning of our investigation (section 3.3.3). Optimization of the volume of *t*-BuOH

suggested that this ruthenium-catalyzed deoxygenation can proceed in a more diluted solution than the previous iridium-based method (Table 3-6). Nevertheless, too much dilution led to yield attenuation (Table 3-6, entry 4). Intriguingly, the concentration profiles of DMSO and *t*-BuOH observed herein were quite opposite to that in the modified low-temperature WK studies.[9b, 9c] In the latter case, DMSO was employed as a solvent in the presence of substoichiometric *t*-BuOH.

Table 3-5 Volume of DMSO

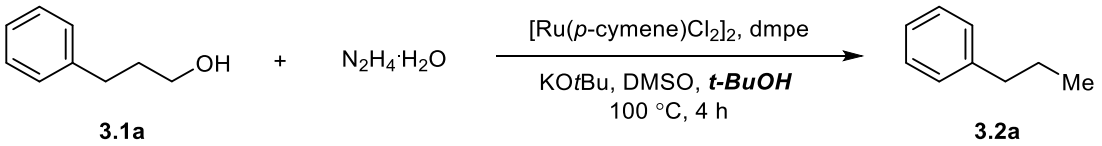


3.1a **3.2a**

Entry	DMSO (equiv, volume)	**3.2a** (%)[b]
1	-	15
2	5 mol %, 0.7 µL	64
3	20 mol %, 2.8 µL	67
4	60 mol %, 8.5 µL	65
5	1.2, 17 µL	61
6	2.4, 34 µL	55
7	7.2, 102 µL	14
8	14.4, 204 µL	10

[a]Reaction conditions: **3.1a** (0.2 mmol, 27.2 µL), [Ru(*p*-cymene)CI_2]$_2$ (1.5 mol %, 1.8 mg), dmpe (3 mol %, 1.0 µL), KO*t*Bu(0.1 mmol, 11.2 mg), $N_2H_4 \cdot H_2O$ (0.24 mmol, 13 µL), *t*-BuOH (0.2 mL), sealed V-shape microvial, under an argon atmosphere. [b]Determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard.

Table 3-6 Volume of *t*-BuOH



3.1a **3.2a**

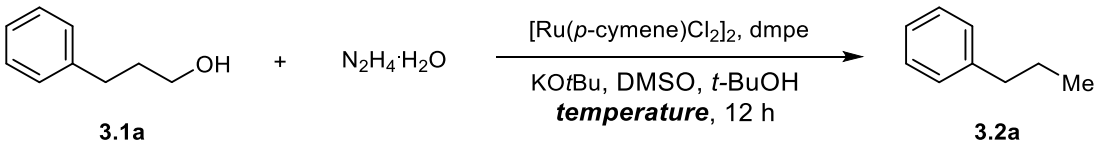
Entry	*t*-BuOH (volume)	**3.2a** (%)[b]
1	20 µL	55
2	0.1 mL	65
3	0.2 mL	67
4	0.4 mL	49

[a]Reaction conditions: **3.1a** (0.2 mmol, 27.2 µL), [Ru(*p*-cymene)CI_2]$_2$ (1.5 mol %, 1.8 mg), dmpe (3 mol %, 1.0 µL), DMSO (20 mol %, 2.8 µL), KO*t*Bu (0.1 mmol, 11.2 mg), $N_2H_4{\cdot}H_2O$ (0.24 mmol, 13 µL), sealed V-shape microvial, under an argon atmosphere. [b]Determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard.

3.3.3.3 Other Reaction Parameters

Temperature control indicated that 100 °C was ideal for obtaining maximum efficiency of the reaction (Table 3-7, entry 1). While a moderate yield was obtained by lowering the temperature to 80 °C (Table 3-7, entry 3), a further temperature decrease to 70 °C was associated with a significant

Table 3-7 Temperature Variations



3.1a **3.2a**

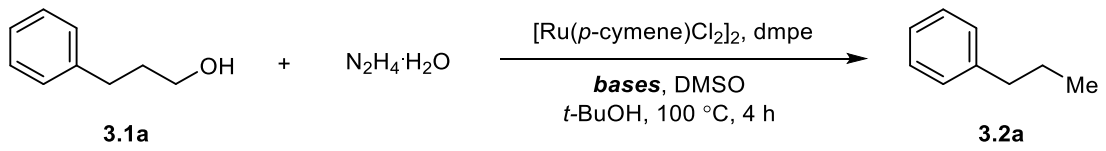
Entry	Temperature (°C)	**3.2a** (%)[b]

1	100	95
2	90	85
3	80	67
4	70	30

[a]Reaction conditions: **3.1a** (0.2 mmol, 27.2 µL), [Ru(*p*-cymene)CI_2]$_2$ (1.5 mol %, 1.8 mg), dmpe (3 mol %, 1.0 µL), DMSO (20 mol %, 2.8 µL), KO*t*Bu (0.1 mmol, 11.2 mg), $N_2H_4{\cdot}H_2O$ (0.24 mmol, 13 µL), *t*-BuOH (0.2 mL), sealed V-shape microvial, under an argon atmosphere. [b]Determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard.

erosion of the yield (Table 3-7, entry 4). Most inorganic bases were effective in promoting the deoxygenation in the current catalytic system (Table 3-8). Organic bases, on the other hand, were largely ineffective. Among all bases examined, KO*t*Bu stood out and provided the highest yield (Table 3-8, entry 10). This outcome is consistent with the basicity rationale from studies on the DMSO/KO*t*Bu/*t*-BuOH system. Significantly, a substoichiometric amount of base was sufficient to promote this transformation, unlike the stoichiometric quantity required in the conventional WK reduction. An approximate linear kinetic relationship at 100 °C was established between the reaction yield and time, whereby **3.1a** was mostly consumed within 4 h and completely consumed after 12 h (Table 3-10, entries 4 and 7). It is of importance to note that neither dehydrating reagents such as molecular sieves nor anhydrous hydrazine sources can improve the reaction yield, given that strictly anhydrous conditions are generally adopted in nearly all modified low-temperature WK reductions (Table 3-11; Table 3-12, entry 3). Other hydrazine salts proved to be inferior reducing reagents for this reaction (Table 3-12, entries 1 and 2).

Table 3-8 Choice of Base

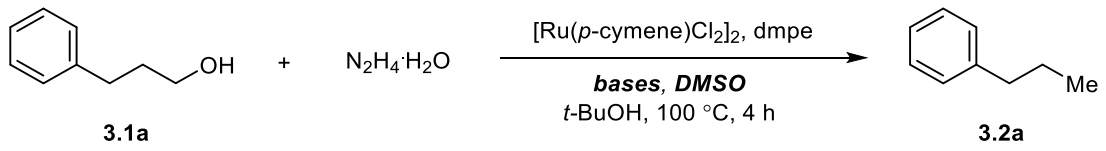


3.1a **3.2a**

Entry	Base (0.5 equiv)	**3.2a** (%)[b]	Entry	Base (0.5 equiv)	**3.2a** (%)[b]
1	$LiOH·H_2O$	N.D.	6	Et_3N	N.D.
2	NaOH	46	7	DIPEA	N.D.
3	KOH	56	8	Cs_2CO_3	44
4	$CsOH·H_2O$	50	9	NaO*t*Bu	58
5	K_3PO_4	19	10	KO*t*Bu	67
6	DBU	N.D.	11	K_2CO_3	N.D.

[a]Reaction conditions: **3.1a** (0.2 mmol, 27.2 µL), [Ru(*p*-cymene)Cl_2]$_2$ (1.5 mol %), dmpe (3 mol %), bases (0.5 equiv), DMSO (20 mol %, 2.8 µL), $N_2H_4·H_2O$ (0.24 mmol, 13 µL), *t*-BuOH (0.2 mL), sealed V-shape microvial, under an argon atmosphere. [b]Determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard.

Table 3-9 Base and Loading of DMSO

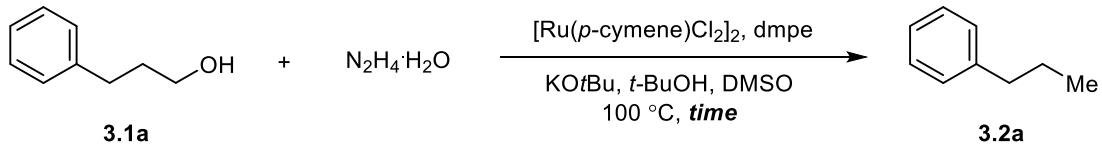


3.1a **3.2a**

Entry	Base	DMSO (mol %)	**3.2a** (%)[b]
1	KOH	20	56
2	KOH	-	30
3	NaO*t*Bu	20	58
4	NaO*t*Bu	-	23
5	KO*t*Bu	20	67
6	KO*t*Bu	-	15

[a]Reaction conditions: **3.1a** (0.2 mmol, 27.2 µL), [Ru(*p*-cymene)Cl_2]$_2$ (1.5 mol %, 1.8 mg), dmpe (3 mol %, 1.0 µL), $N_2H_4 \cdot H_2O$ (0.24 mmol, 13 µL), *t*-BuOH (0.12 mL), sealed V-shape microvial, under an argon atmosphere. [b]Determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard.

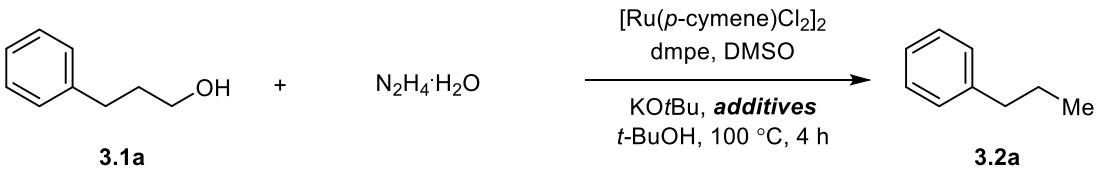
Table 3-10 Kinetic Profile



Entry	Time	**3.2a** (%)[b]
1	30 min	15
2	1 h	28
3	2 h	48
4	3 h	56
5	4 h	74
6	8 h	83
7	12 h	95

[a]Reaction conditions: **3.1a** (0.2 mmol, 27.2 µL), [Ru(*p*-cymene)Cl_2]$_2$ (1.5 mol %, 1.8 mg), dmpe (3 mol %, 1.0 µL), DMSO (20 mol %, 2.8 µL), KO*t*Bu (0.1 mmol, 11.2 mg), $N_2H_4 \cdot H_2O$ (0.24 mmol, 13 µL), *t*-BuOH (0.1 mL), sealed V-shape microvial, under an argon atmosphere. [b]Determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard.

Table 3-11 Molecular Sieve Additive

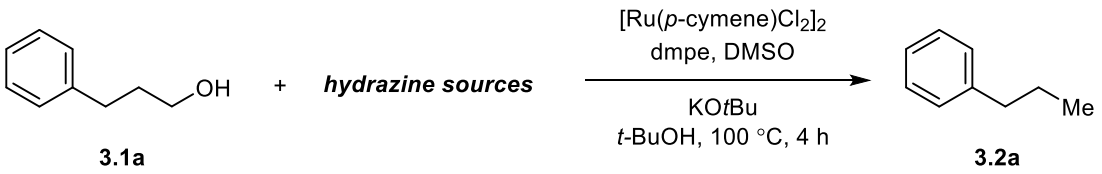


3.1a **3.2a**

Entry	Additives	**3.2a** (%)[b]
1	3Å MS	66
2	4Å MS	67
3	-	74

[a]Reaction conditions: **3.1a** (0.2 mmol, 27.2 µL), [Ru(*p*-cymene)CI_2]$_2$ (1.5 mol %, 1.8 mg), dmpe (3 mol %, 1.0 µL), DMSO (20 mol %, 2.8 µL), KO*t*Bu (0.1 mmol, 11.2 mg), $N_2H_4{\cdot}H_2O$ (0.24 mmol, 13 µL), molecular sieves (40 mg, absorption capacity 19%), *t*-BuOH (0.1 mL), sealed V-shape microvial, under an argon atmosphere. [b]Determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard.

Table 3-12 Hydrazine Sources



3.1a **3.2a**

Entry	Hydrazine Sources	**3.2a** (%)[b]
1	$N_2H_4{\cdot}H_2SO_4$	-
2[c]	$N_2H_4{\cdot}HCl$	42
3	N_2H_4 in THF (anhydrous, 1.0 M) (co-solvent effect)	18

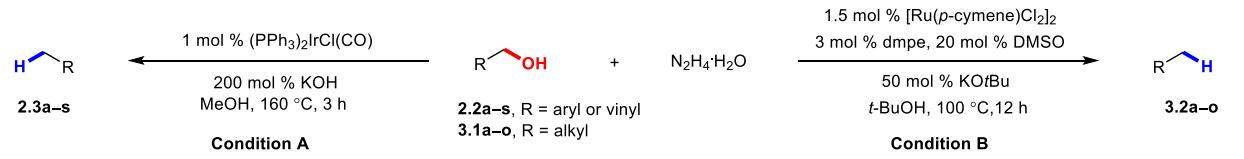
[a]Reaction conditions: **3.1a** (0.2 mmol, 27.2 µL), [Ru(*p*-cymene)CI_2]$_2$ (1.5 mol %, 1.8 mg), dmpe (3 mol %, 1.0 µL), DMSO (20 mol %, 2.8 µL), KO*t*Bu (0.1 mmol, 11.2 mg), hydrazine sources

(0.2 mmol), *t*-BuOH (0.1 mL), sealed V-shape microvial, under an argon atmosphere. [b]Determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard. [c]KO*t*Bu (0.3 mmol, 33.6 mg).

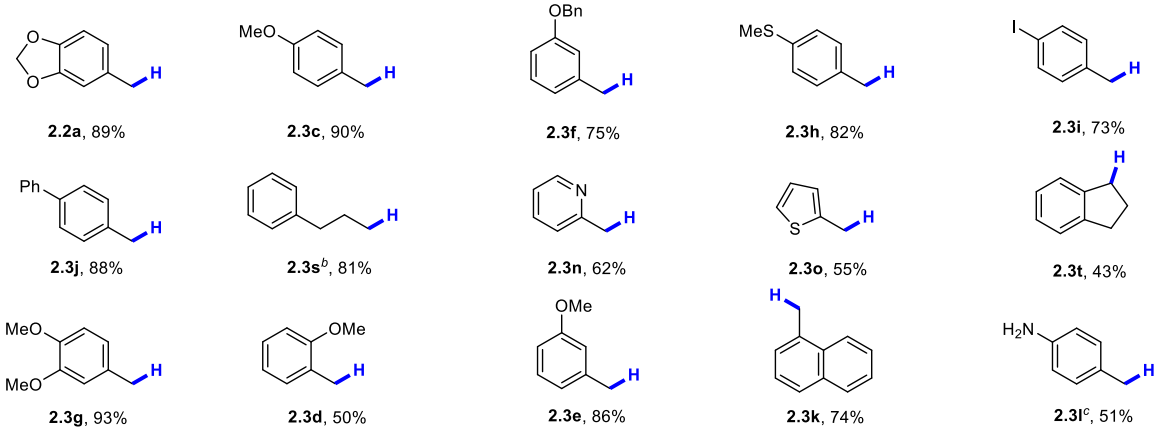
3.3.4 Scope of Alcohol Substrates

With this practical set of reaction conditions, we moved on to test a wide range of aliphatic primary alcohols. Below is a summary of substrate scope from both iridium-based and ruthenium-based deoxygenation protocols (Table 3-13). To our delight, good to excellent yields were obtained by using the ruthenium-based catalyst system in nearly all cases (Table 3-13, condition B). Complete conversions were seen in all linear aliphatic primary alcohols, regardless of their backbone lengths (**3.2a**, **3.2b**, **3.2e**). Slightly lower yields were obtained for branched substrates with substituents at β positions (**3.2c**, **3.2l**). In terms of functional group tolerance, thioether (**3.2d**), isolated internal double and triple bonds (**3.2j**, **3.2k**), phenolic hydroxyl group (**3.2m**), and Boc (*tert*-butyloxycarbonyl) (**3.2i**) all remained untouched. Amines are key moieties encountered in many pharmaceutical drugs and bioactive molecules. Their more nucleophilic nitrogen atoms usually make the chemoselective deoxygenation of aliphatic alcohols with amine functionalities (i.e., amino alcohols) problematic. This difficulty is even more profound when it comes to the direct deoxygenation protocol, and thereby no precedent exists under such circumstances. Gratifyingly, the direct cleavage of C–O bonds occurred smoothly with great chemoselectivity in both acyclic amino alcohol **3.2f** and cyclic amino alcohols (**3.2g**, **3.2h**), even though the *N*-alkylation might have occurred as a side reaction under ruthenium catalysis.[21] Excellent efficiency and chemoselectivity of our current practical protocol are demonstrated in bioactive molecules. For instance, **3.1n** derived from (+)-biotin was quantitatively deoxygenated, without affecting the ureido and thioether groups**.** However, functional groups labile to basic conditions (i.e., amides, esters, etc.) tend to hydrolyze under current conditions. For instance, the deoxygenation of **3.1o** was accompanied by the complete hydrolysis of the acyl group on its aniline moiety, giving rise to **3.2o** in nearly quantitative yield. It is also noteworthy to mention that our catalytic redox design by and large suppressed the formation of azines (5 % or less in most cases), which represents a major side reaction in all modified WK-type reductions.[9b, 9c, 12]

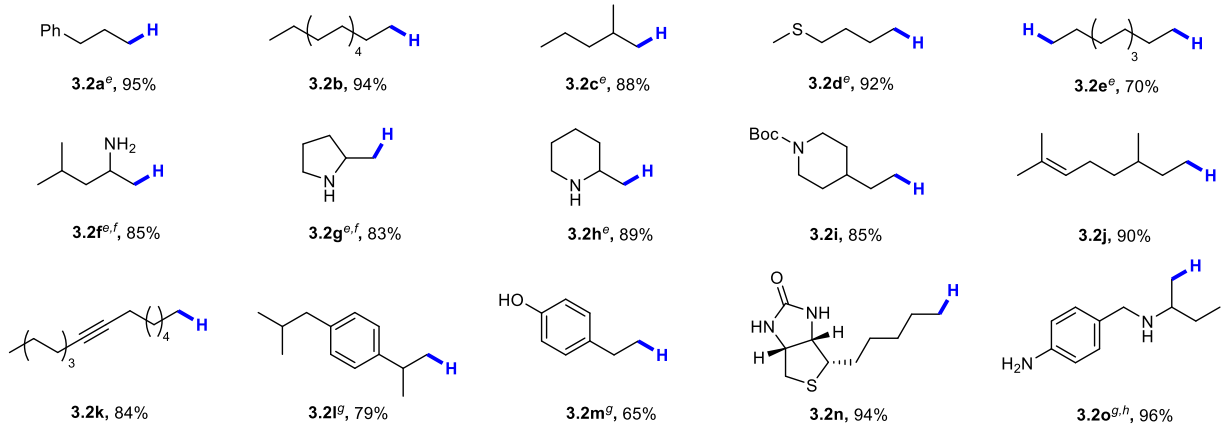
Table 3-13 Substrate Scope of Redox-Based, Catalytic, Direct Deoxygenation



Condition A[a]: *benzylic & allylic 1° or 2° alcohols*



Condition B[d]: *aliphatic 1° alcohols*

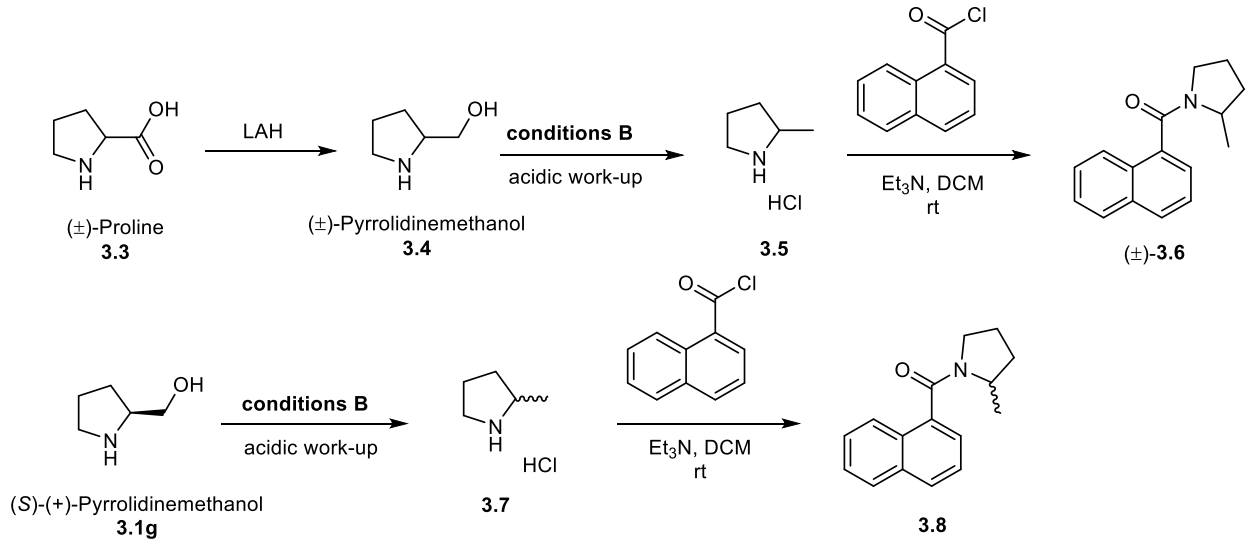


[a]Condition A: **2.2a-s** (0.3 mmol), hydrazine hydrate (0.6 mmol), $(PPh_3)_2IrCl(CO)$ (2.3 mg, 1 mol %), KOH (34 mg, 0.6 mmol), MeOH (30 µL), 160 °C, 3 h, under an air atmosphere, isolated yields were obtained unless noted otherwise. [b]**2.3s**: cinnamyl alcohol. [c]**2.3l**: 4-nitrobenzyl alcohol. [d]Condition B: **3.1a-o** (0.2 mmol), $[Ru(p\text{-cymene})Cl_2]_2$ (1.5 mol %), dmpe (3 mol %), hydrazine hydrate (0.24 mmol), KO*t*Bu (0.1 mmol), DMSO (20 mol %), *t*-BuOH (0.2 mL), 100 °C, 12 h, under Ar, isolated yields were obtained. [e]NMR yields were determined using 1,3,5-trimethoxybenzene as an internal standard. [f]Racemization occurred on both enantiomerically pure

amino alcohols. [g]Reaction time: 24 h. [h]**3.1o**: *N*-(4-([(1-hydroxybutan-2-yl)amino]methyl)phenyl)acetamide.

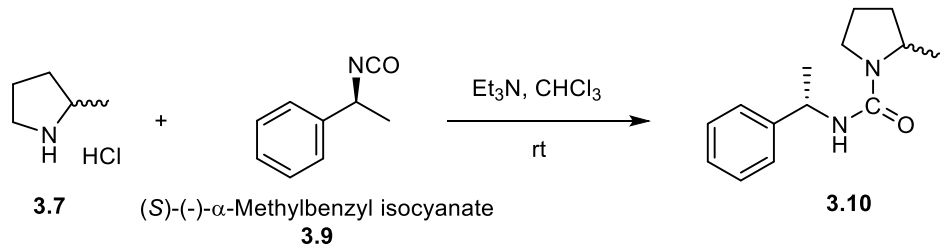
3.3.5 Racemization of Chiral Amino Alcohols

The current basic reaction conditions raise concerns on racemization when encountering some enantioenriched compounds. Starting from enantiomerically pure amino alcohols **3.1f** and **3.1g**, we thought that the racemization could have occurred on both **3.1f** and **3.1g** according to the proposed mechanism. We therefore designed both indirect and direct experiments to verify this racemization hypothesis as indicated below:



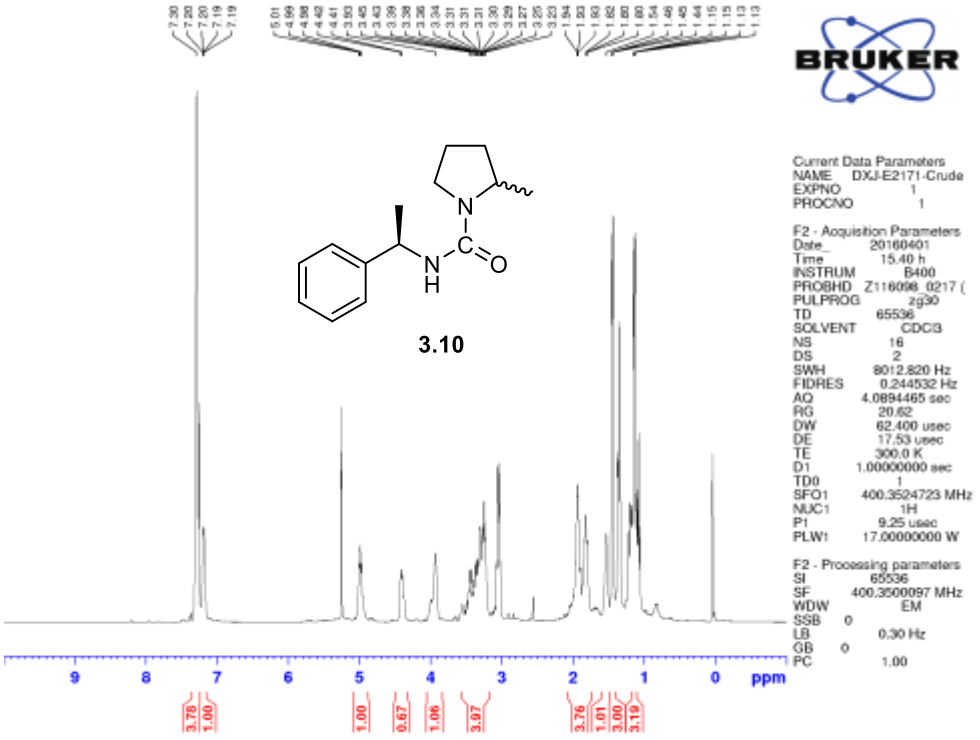
Scheme 3-4 Direct Evidence of Racemization on Amino Alcohols

Direct experimental evidence (Scheme 3-4): The amidation of 2-methylpyrrolidine HCl salt **3.7** and 1-naphthoyl chloride was conducted to produce the corresponding amide compound **3.8**. Unfortunately, we could not separate the two enantiomers using a set of chiral columns that we had in hand.



Scheme 3-5 Indirect Evidence of Racemization on Amino Alcohols

Indirect experimental evidence (Scheme 3-5): 2-methylpyrrolidine HCl salt **3.7** was treated with enantiomerically pure (*S*)-(-)-α-methylbenzyl isocyanate **3.9** to create the corresponding urea compound **3.10** with two chiral centers. The crude residue and the purified diastereoisomeric mixture were subjected to NMR spectroscopy, respectively. The ^{1}H NMR spectrum of the crude mixture suggested that the racemization occurs on **3.7** under the present deoxygenation conditions (Figure 3-4). However, we were unable to determine the diastereoisomeric ratio due to the overlap



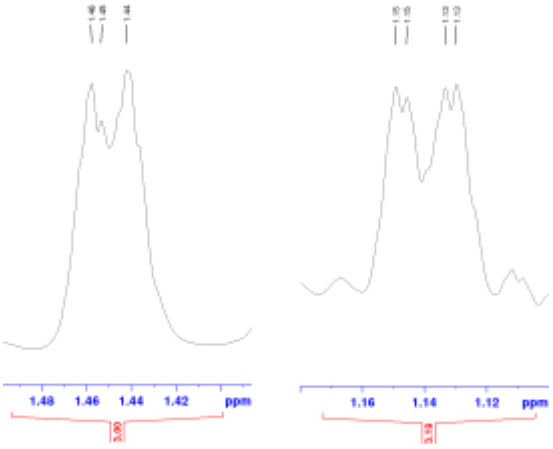
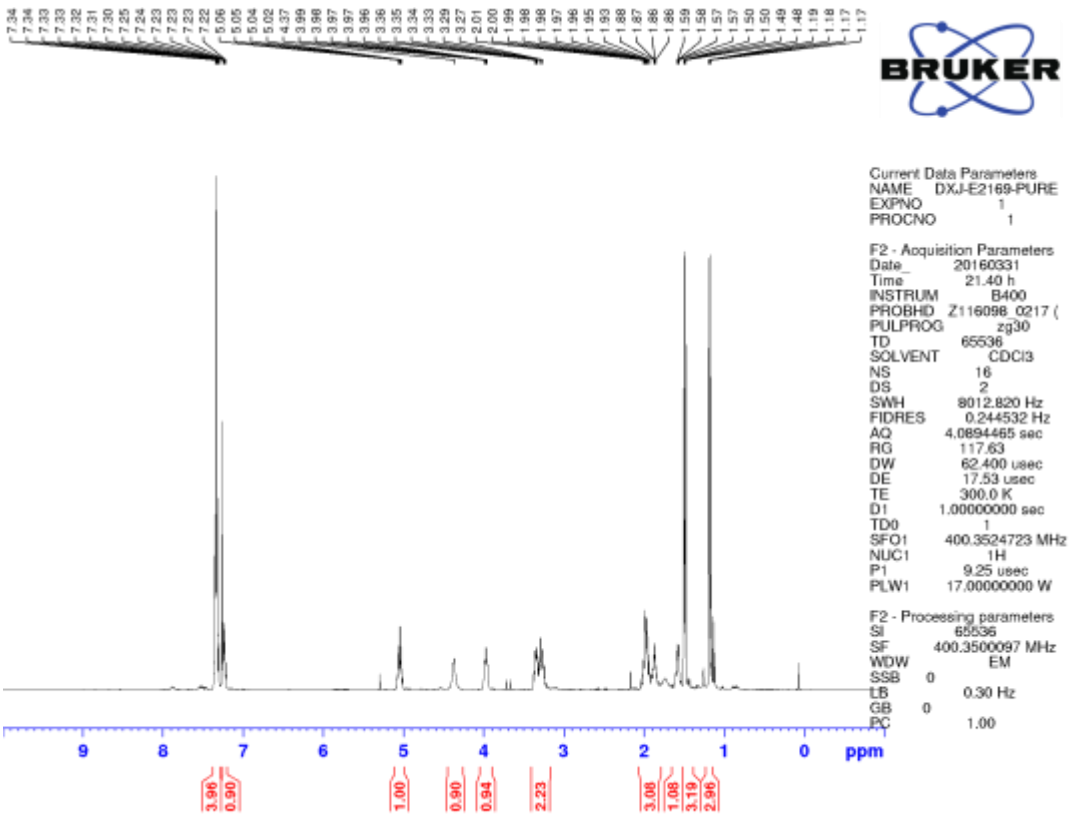


Figure 3-4 Crude ^{1}H NMR of Reaction Mixture to Yield **3.10**

of the corresponding methyl peaks, shown in the expanded spectrum. On the other hand, both ^{1}H NMR and ^{13}C NMR spectra of the purified mixtures further confirmed the existence of the two diastereoisomers (Figure 3-5 and Figure 3-6). These observations suggest that racemization of chiral amino alcohols occurs during the deoxygenation process.



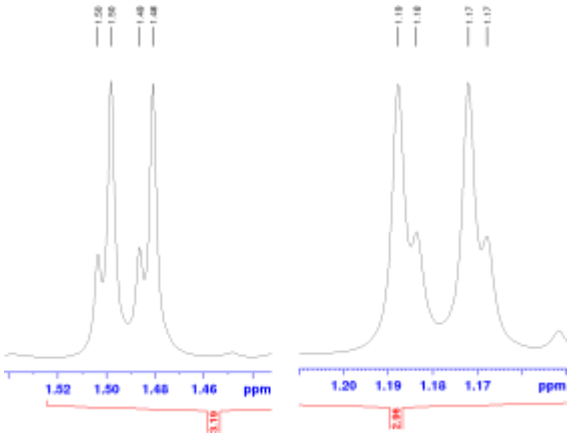


Figure 3-5 Purified ^{1}H NMR of Diastereoisomers of **3.10**

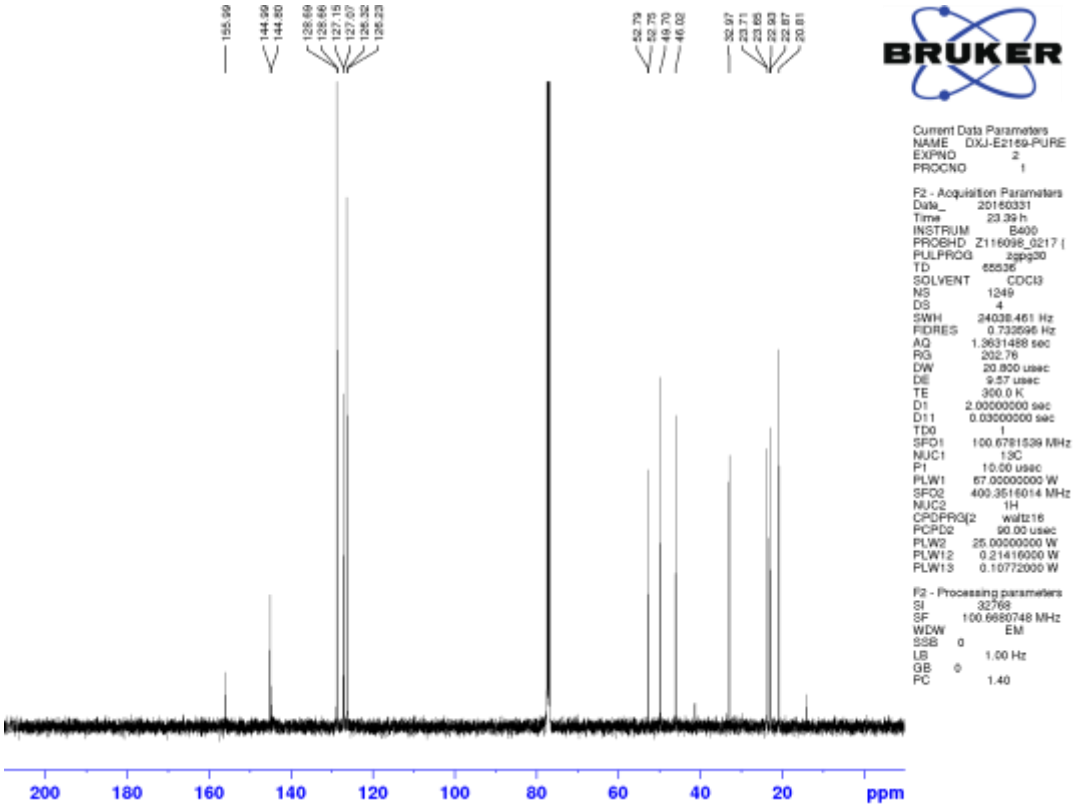
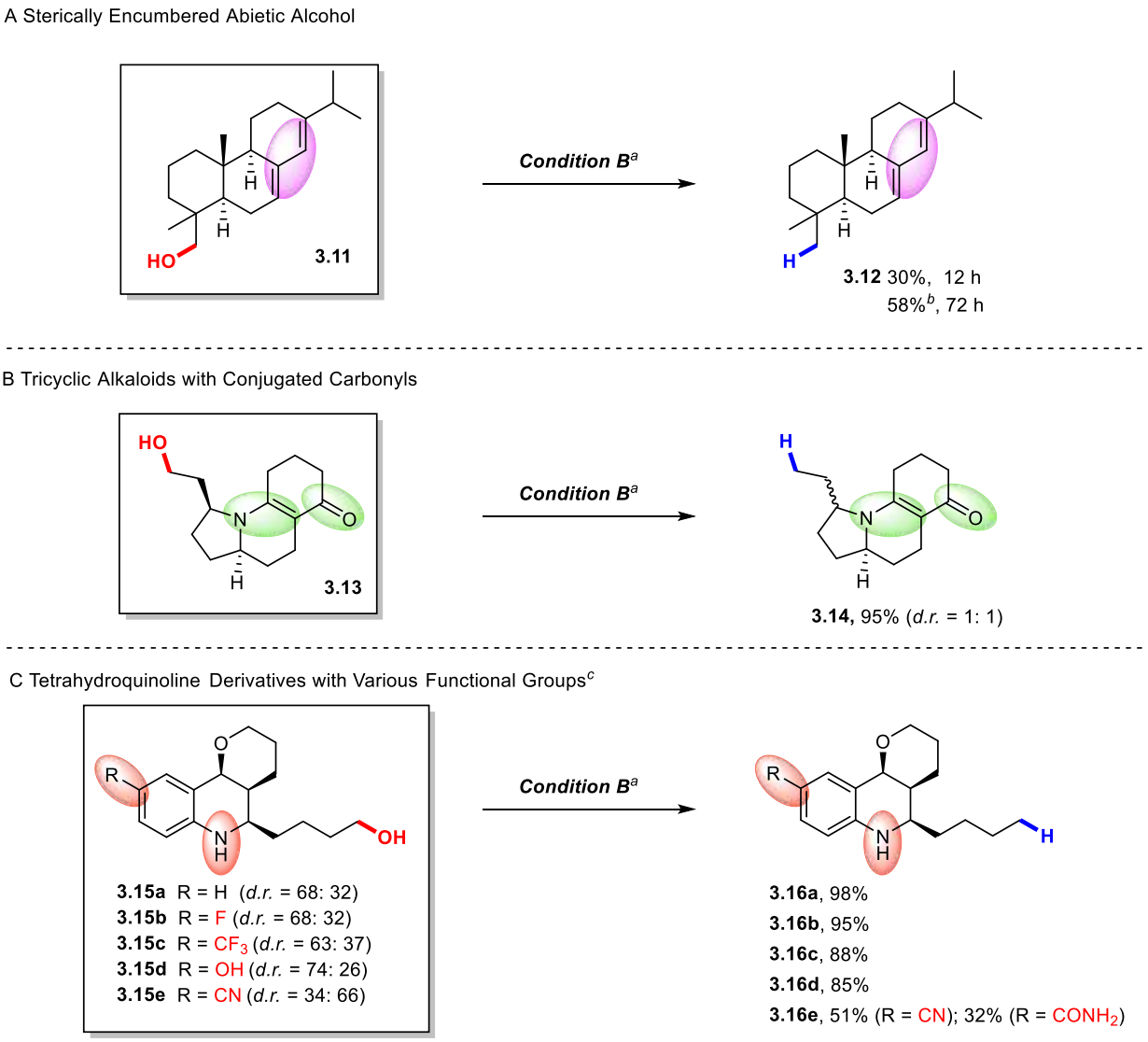


Figure 3-6 Purified ^{13}C NMR of Diastereoisomers of **3.10**

3.3.6 Chemoselective Direct Deoxygenation in Complex Molecules



[a]Condition B: **3.11**, **3.13**, and **3.15a-e** (0.1 mmol), $[Ru(p\text{-cymene})Cl_2]_2$ (1.5 mol %), dmpe (3 mol %), hydrazine hydrate (0.24 mmol), KO*t*Bu (0.1 mmol), DMSO (20 mol %), *t*-BuOH (0.2 mL), 100 °C, 12 h, under Ar, isolated yields were obtained. [b]$[Ru(p\text{-cymene})Cl_2]_2$ (3 mol %), dmpe (6 mol %), hydrazine hydrate (0.36 mmol). [c]See ref 23 for the preparation of **3.15a-e**.

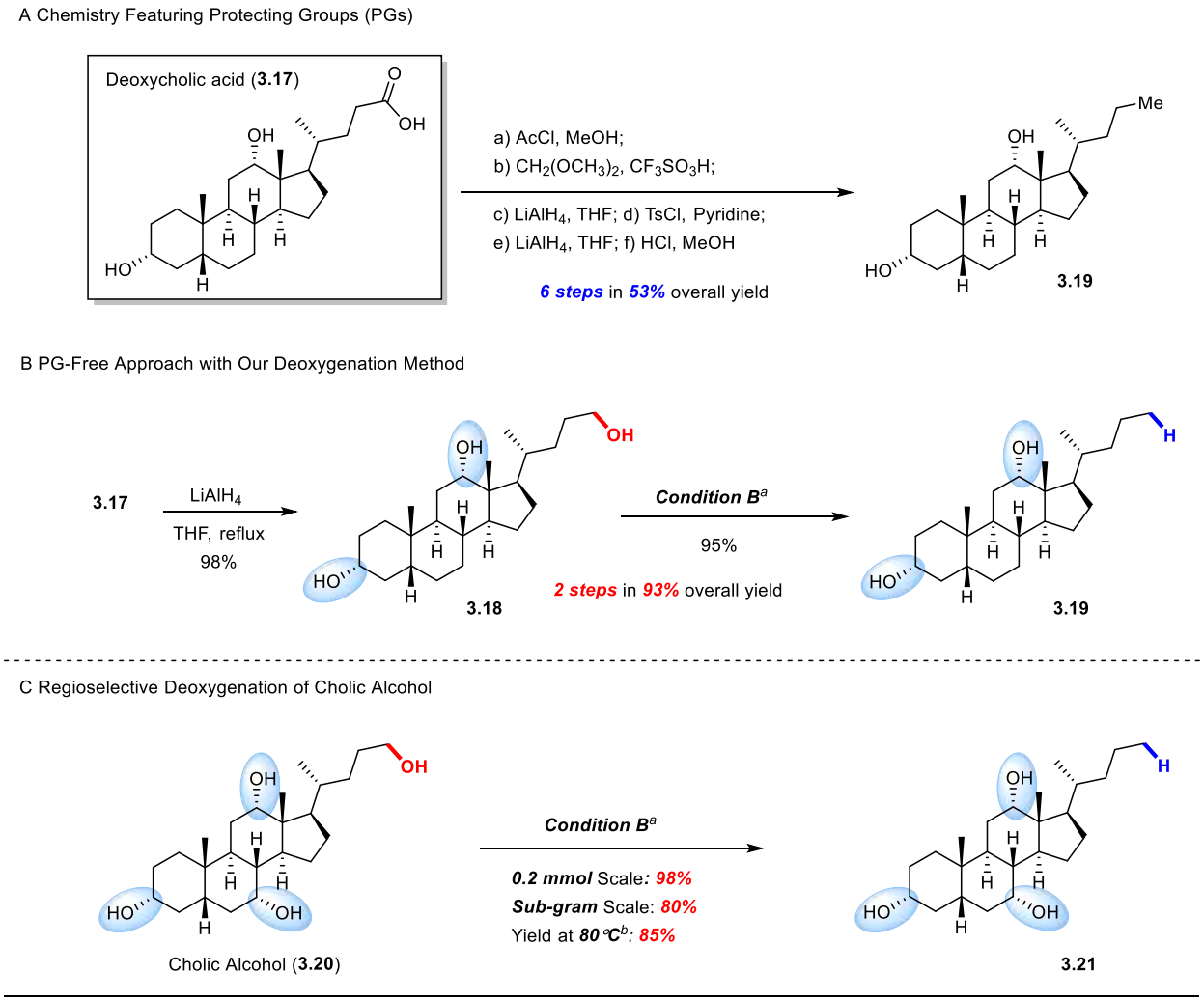
Scheme 3-6 Chemoselective Direct Deoxygenation in Complex Molecules

Chemoselectivity is and has always been a major challenge in modern synthetic chemistry.[22] To make our deoxygenation method more synthetically attractive, we decided to study the

chemoselectivity in complex molecular settings. Abietic alcohol **3.11**, possessing a conjugated double bond and a neopentyl quaternary carbon center, was chosen as our first target. Our initial attempt provided the deoxygenated product **3.12** in only 30% yield under the standard conditions. We reasoned that the sluggish reaction was due to the sterically encumbered neopentyl quaternary carbon center in **3.11**. Thus, it was difficult for the active ruthenium species to approach that carbon and perform an effective dehydrogenative oxidation. To restore reactivity, we doubled the amount of [Ru(*p*-cymene)Cl_2]$_2$ and dmpe (**L_{14}**), affording a reasonable 58% yield after a prolonged reaction time (Scheme 3-6-A). Tricyclic heterocycle alkaloid **3.13**, a key intermediate in the total synthesis of (+)-gephyrotoxin,[23] has the α,β-unsaturated carbonyl group in the molecule. The complete chemoselective deoxygenation was observed quantitatively in **3.13**, although epimerization occurred of the pyrrolidine ring (Scheme 3-6-B). This epimerization was likely due to the sequential base-catalyzed retro-Michael/Michael addition processes. Rapid assembly of the tetrahydroquinoline skeleton and its structural modifications have attracted continuous synthetic interest over the past decades. Based on our early development of an $InCl_3$-catalyzed protocol to synthesize tetrahydroquinoline alcohols,[24] we now disclose their further structural modification using our deoxygenation method. These tetrahydroquinoline alcohols (**3.15a**-**e**, Scheme 3-6-C) displayed exceptional reactivity under current conditions, producing the corresponding deoxygenated tetrahydroquinoline derivatives in excellent yields, with the ratio of relative stereochemistry unchanged (**3.16a**-**e**, Scheme 3-6-C). Equally important was the compatibility of varying functional groups on the aryl rings such as fluorine, trifluoromethyl, and the phenolic hydroxyl group. An exception was the nitrile group in **3.15e**, as partial hydrolysis to the amide was observed. To summarize, this two-step synthetic approach allows a rapid and efficient access to deoxygenated tetrahydroquinoline derivatives for future biological studies, as some of their hydroxylated precursors have shown promising antitumor bioactivities.[24]

3.3.7 Chemoselective Direct Monodeoxygenation in Steroids

Multiple hydroxyl groups in the same molecule raise an issue of chemoselectivity when synthetic chemists try to selectively discriminate one hydroxyl group from another. Based on the relatively sluggish rate displayed by the sterically encumbered substrate **3.11**, we envisaged the possibility of controlling chemoselectivity through the pre-existing steric bias in natural products.



[a]Condition B: **3.18** or **3.20** (0.2 mmol), [Ru(*p*-cymene)Cl_2]$_2$ (1.5 mol %), dmpe (3 mol %), hydrazine hydrate (0.24 mmol), KO*t*Bu (0.1 mmol), DMSO (20 mol %), *t*-BuOH (0.4 mL), 100 °C, 12 h, under Ar. [b]Conditions: **3.20** (0.1 mmol), [Ru(*p*-cymene)Cl_2]$_2$ (1.5 mol %), dmpe (3 mol %), hydrazine hydrate (0.12 mmol), KO*t*Bu (0.05 mmol), DMSO (20 mol %), *t*-BuOH (0.2 mL), 80 °C, 48 h, under Ar.

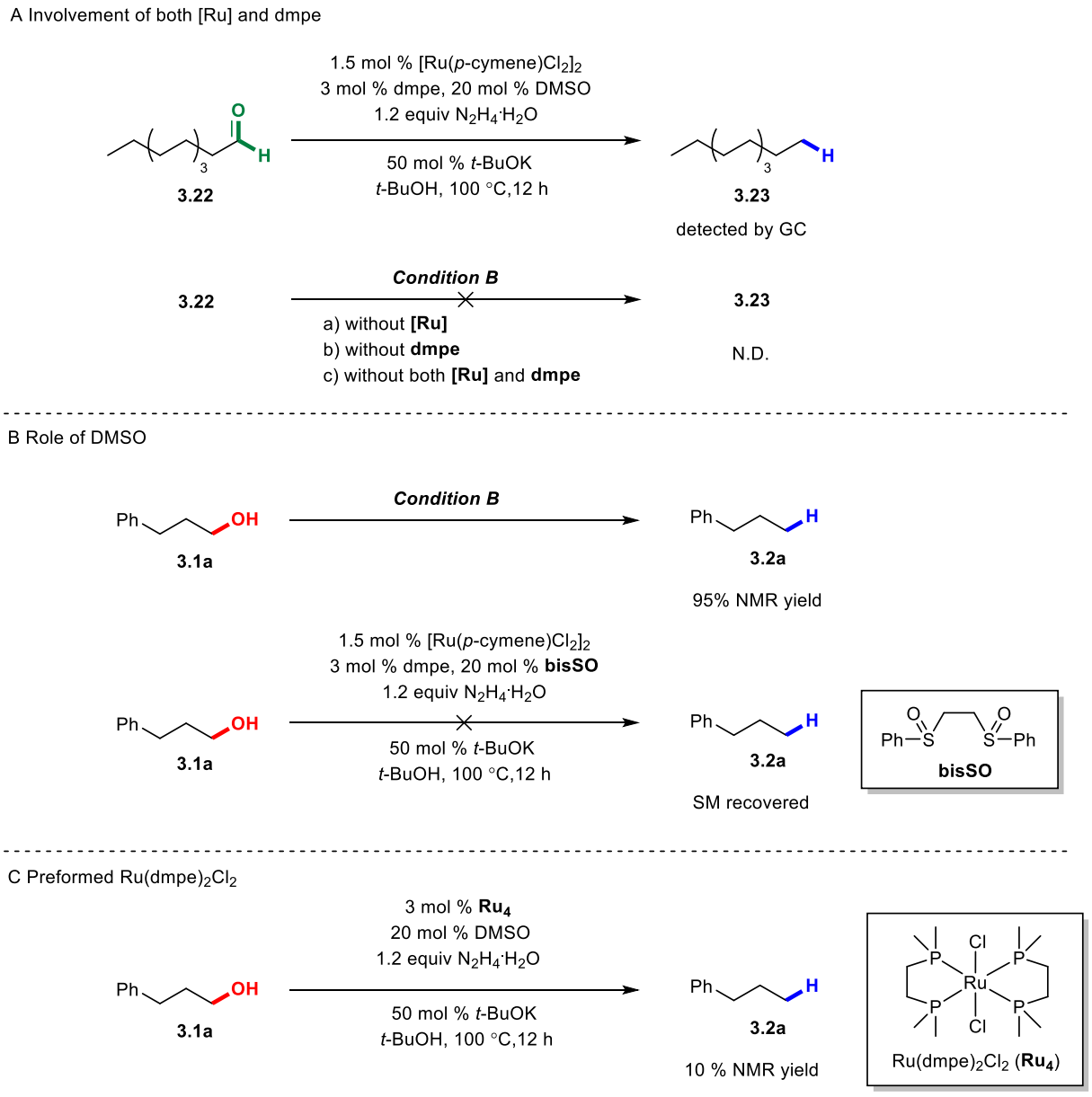
Scheme 3-7 Chemoselective Direct Mono-deoxygenation in Steroids

Therefore, steroids became our targets of interest. Deoxycholic alcohol (**3.18**), which can be easily obtained from deoxycholic acid (**3.17**) through a $LiAlH_4$ reduction, contains three hydroxyl groups: one acyclic, primary alcohol and two cyclic, secondary alcohols. Review of the literature indicated

that no synthetic method was available to selectively deoxygenate **3.18**.[25] Following our steric bias rationale, complete regioselectivity and remarkable reactivity were shown on the least sterically hindered acyclic primary hydroxyl group in **3.18**. In comparison with a traditional synthetic route to access **3.19** (Scheme 3-7-A),[26] where protection-deprotection strategies are adapted in a six-step synthesis, our method features a two-step approach to obtain **3.19** in 93% yield (Scheme 3-7-B). 3α,7α,12α-Trihydroxycholane (**3.21**), another challenging steroidal derivative to synthesize, is an important precursor of seroflocculating agents and amphiphiles.[27] Conventional synthetic approaches are associated with a mixture of over-reduced products.[28] Using our protocol, the mono-deoxygenation of cholic alcohol (**3.20**) proceeded smoothly, furnishing **3.21** in quantitative yield on a small scale (0.2 mmol) and slightly diminished yield on a sub-gram scale (2 mmol). Remarkably, the mono-deoxygenation of **3.20** took place smoothly even at 80 °C, giving **3.21** in 85% yield after 24 h (Scheme 3-7-C).

3.3.8 Studies on the Reaction Mechanism

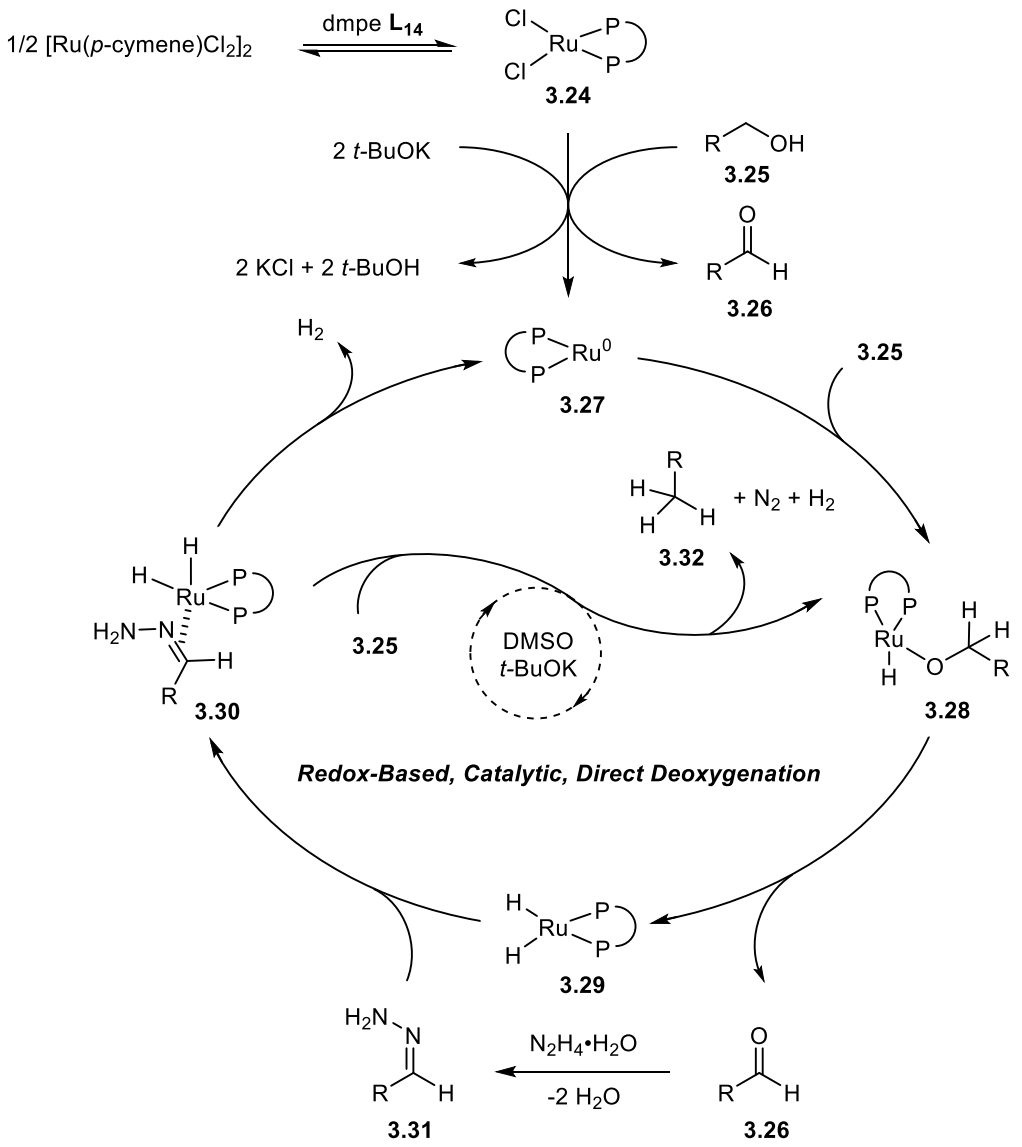
Several control experiments were conducted to shed light on the mechanism of this redox deoxygenation chemistry. Starting from decanal **3.22**, decane **3.23** was captured by GC-MS under standard conditions, whereas no product was detected in the absence of [Ru(*p*-cymene)Cl_2]$_2$ and dmpe. This result suggested the critical involvement of both metal and ligand in the reductive transformation (Scheme 3-8-A). To better understand the exact role of DMSO, a structurally similar bisSO ligand (1,2-bis(phenylsulfinyl)ethane) was tested, yet no product was observed (Scheme 3-8-B). Accordingly, it appeared that DMSO was more than just a ligand in our current catalytic system. Interestingly, the use of presynthesized Ru(dmpe)$_2Cl_2$ (**Ru$_4$**) dramatically decreased the overall efficiency, indicating that it was not the active metal species (Scheme 3-8-C). We also confirmed the production of hydrogen and nitrogen gas over the course of the reaction, by analyzing the headspace of the reaction vial with GC-MS.



Scheme 3-8 Control Experiments for Mechanistic Insights

3.3.9 Tentative Mechanism of Ruthenium(II)-Catalyzed Deoxygenation

We tentatively postulate a mechanism herein based on all our experimental data, in addition to studies from others (Scheme 3-9).[12,13,16a] According to the well-established mechanism in the alcohol amination catalyzed by a [Ru(*p*-cymene)Cl_2]$_2$/diphosphine system, the bidentate phosphine coordinated complex **3.24** is initially generated by a ligand exchange of [Ru(*p*-



Scheme 3-9 Proposed Catalytic Cycle

cymene)$Cl_2]_2$ with **L_{14}**. A ruthenium(0) complex **3.27** can then be formed via an alcohol association followed by the loss of HCl in the presence of base. Oxidative addition of the alcohol provides the alkoxy hydride complex **3.28**, which further undergoes *β*-hydride elimination to produce the chelated aldehyde complex. Dissociation of aldehyde **3.26**, hydrazone formation and association of hydrazone **3.31** to ruthenium dihydride complex **3.29** provide **3.30**. Its reductive decomposition, in the presence of DMSO and KO*t*Bu, leads to the desired deoxygenated product **3.2a**, with concomitant release of hydrogen and nitrogen gas. The regeneration of **3.27** presumably

goes through the reductive elimination of **3.30**. Unlike all low-temperature modified WK reduction, only a catalytic amount of DMSO and substoichiometric amount of KO*t*Bu are required in our method, suggesting an unconventional rate acceleration due to the participation of [Ru(*p*-cymene)Cl_2]$_2$ and dmpe.

3.4 Failed Alcohol Substrates

New synthetic methods have rarely been flawless with respect to the reaction scope, and this chemistry is certainly no exception. Apart from the racemization found in a few enantioenriched substrates, we have quite a few problematic substrates that either remain unreactive or contain incompatible functional groups under standard conditions (Figure 3-7). Failed alcohol substrates are classified into several groups, including those containing functionalities labile under basic conditions like ester **3.37**, amide (**3.36**, **3.39**, **3.40**), and those bearing proximal chelating heteroatoms, in particular oxygen atoms (**3.32-3.35**, **3.43**). In the latter cases, starting materials were completely recovered.

3.5 Conclusions

To summarize Chapter 2 and 3, we have discovered and developed a direct catalytic alcohol deoxygenation protocol based on redox chemistry. Our early studies show that deoxygenation of benzylic and allylic alcohols can be realized using iridium catalysis in a single step via a sequential redox process (dehydrogenation/WK reduction). However, the harsh reaction conditions and limited scope make it less synthetically applicable. Our later development catalyzed by a ruthenium complex focuses on aliphatic primary alcohols and improves the chemoselectivity of the deoxygenation process under practical reaction conditions. We have demonstrated its synthetic viability, both efficiency and selectivity, by using molecules with varying degrees of complexity and a number of different functional groups. Significantly, our current method can be successfully implemented on the highly chemoselective direct deoxygenation of alkaloids and regioselective direct mono-deoxygenation of steroids with multiple secondary hydroxyl groups on both milligram

Figure 3-7 Unsuccessful Primary Alcohols in the Ruthenium-Catalyzed Deoxygenation Method

and sub-gram scales. Striking features of our method also include relatively mild thermal conditions, as well as innocuous byproducts. The indispensable roles of ruthenium catalyst, bidentate phosphine ligand dmpe (**L14**), a catalytic amount of DMSO, and a substoichiometric amount of base imply a transition-metal-assisted reductive WK transformation. While further experimental evidence is required to elucidate the mechanism of this deoxygenation chemistry, our new redox-based approach has great potential to become a useful synthetic tool for the direct sp^3 C–O defunctionalization in complex molecules.

3.6 Experimental

3.6.1 General Considerations

Reaction Setup: All reactions were carried out in flamed-dried V-shaped microwave reaction vials, covered by aluminum seals with PTFE-faced silicone septa, under an atmosphere of Argon unless otherwise stated. All reported reaction temperatures correspond to oil bath temperatures. All air and moisture sensitive catalysts, ligands, and reagents were stored and charged in MBRAUN UNIlab Pro Glove Box Workstation.

Purifications: All work-up and purification procedures were carried out with reagent-grade solvents. Analytical thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F_{254} pre-coated plates (0.25 mm). Flash column chromatography was performed with E. Merck silica gel P60 (40–63 μm particle size, 230–400 mesh) (SiO_2). Unless otherwise specified, "SiO_2" refers to P60 grade silica gel. Visualization was accomplished with UV light and/or iodine (I_2) or ceric ammonium molybdate (CAM) solution or potassium permanganate ($KMnO_4$) solution. Retention factor (R_f) values reported were measured using a 10 × 2 cm TLC plate in a developing chamber containing the solvent system (10 mL) described. Automated flash column chromatography was performed on Biotage Isolera™ Spektra Systems with ACI™.

Solvents: Reaction solvents *tert*-butanol (*t*-BuOH) (ACS grade), *tert*-amyl alcohol (TAA) (ACS grade), 3-methyl-3-pentanol (ACS grade) were distilled over CaH_2 prior to use. Dimethyl sulfoxide (DMSO), tetrahydrofuran (THF) and toluene were taken directly from the *Pure Solvent MD-7* purification system (Innovative Technology). Solvents for filtration, transfers, chromatography, and recrystallization were dichloromethane (CH_2Cl_2) (ACS grade, amylene stabilized), ether (Et_2O) (Fisher, BHT stabilized ACS grade), acetone (ACS grade), ethyl acetate (EtOAc) (Fisher, ACS grade), hexane (Fisher, ACS grade), pentane (ACS grade), methanol (ACS grade).

Chemicals: In the model study, 3-phenyl-1-propanol (Aldrich) was distilled over CaH_2 prior to use. Other commercially available chemicals that were used without further purification are: $[Ru(p\text{-cymene})CI_2]_2$ (Aldrich), $[Rh(COD)Cl_2]_2$ (Aldrich), $[Ir(COD)Cl_2]_2$ (Aldrich), $RuCl_3$ (Aldrich), $[PhRuCl_2]_2$ (Aldrich), $CpRu(PPh_3)_2Cl$ (Aldrich), $Ru(CO)H_2PPh_3$ (Alfa), $[(CO)_3RuCl_2]_2$ (Strem), PNN Milstein catalyst Ru_1 (Strem), Shvo catalyst Ru_3 (Strem), Me_3P (Aspira), $t\text{-}Bu_3P$ (Alfa), Cy_3P (Fluka), cataCXium A (Alfa), Ph_3P (Aldrich), $(p\text{-}MeOC_6H_4)_3P$ (Strem), $(PhO)_3P$ (Aldrich), $(2\text{-furyl})_3P$ (Aldrich), *t*-BuDavephos (Aldrich), RuPhos (Aldrich), dppm (Strem), dppe (Strem), dppe(ethylene) (Alfa), dmpe (Aldrich & Aspira), dppp (Aldrich), dppb (Aldrich), dcpb (Aspira), dpph (Aldrich), *rac*-BINAP (Aldrich), (R)-T-BINAP (Strem), Xantphos (Aldrich), DPEphos (Aldrich), dppf (Aldrich), dcpf (Aspira), DIOP (Aldrich & Aspira), (S)-Phanephos (Aldrich), (R,R)-Norphos (Strem), IMeS (Aldrich), I^iPrS (Aldrich), TMEDA (Aldrich), TEEDA (Aldrich), NBEDA (Aldrich), TMBDA (Aldrich), Bathophenanthroline (Aldrich), potassium *tert*-butoxide (Aldrich), $N_2H_4{\cdot}H_2O$ (Reagent Grade, 64-65% wt, Aldrich), N_2H_4 in THF solution (anhydrous, 1.0 M, Aldrich), $N_2H_4{\cdot}H_2SO_4$ (Aldrich), $N_2H_4{\cdot}HCl$ (Fischer), 1,3,5-trimethoxybenzene (Aldrich), 1-naphthoyl chloride (Aldrich), (*S*)-(-)-α-Methylbenzyl isocyanate (Aldrich).

In literature preparations, these chemicals are commercially available: $RuCl_2(PPh_3)_3$ (Aldrich), $[RuHCl(PPh_3)_3(CO)]$ (Aldrich), *t*-Bu-PNP (Aldrich), $NiBr_2(PPh_3)_2$ (Aldrich), zinc powder (Aldrich), Bu_4NI (Aldrich), 2-Bromo-3-methoxypyridine (Aldrich), $(Cp^*IrCl_2)_2$ (Alfa), AgOTf (Aldrich), *t*-BuONa (Aldrich), Boc-Phe-OH (Fluka), 1,3-dicyclohexylcarbodiimide (Aldrich), di-*tert*-butyl dicarbonate (Boc_2O) (Biochem/Aldrich). Both 3Å and 4Å molecular sieve (powder) were activated in furnace at 400 °C overnight prior to use. All liquid simple primary alcohol

substrates were distilled over CaH_2, and solid ones were recrystallized prior to use. Other complex substrates, if not commercially available, were prepared according to the known literature.

NMR Spectroscopy: Nuclear magnetic resonance (^1H, ^{13}C {^1H} and ^{31}P {^1H} NMR) spectra were recorded on a Bruker AV500 equipped with a 60-position SampleXpress sample changer (^1H, 500 MHz; ^{13}C, 125 MHz; ^{31}P, 202 MHz), a Varian MERCURY plus-500 spectrometer (^1H, 500 MHz; ^{13}C, 125 MHz) or Bruker AV400 spectrometer (^1H, 400 MHz; ^{13}C, 100 MHz). Chemical shifts for both ^1H NMR and ^{13}C NMR spectra were expressed in parts per million (ppm) units downfield from TMS, with the solvent residue peak as the chemical shift standard ($CDCl_3$: δ 7.28 ppm in ^1H NMR; δ 77.0 ppm in ^{13}C NMR; MeOD: δ 3.31 ppm in ^1H NMR; δ 49.0 ppm in ^{13}C NMR; C_6D_6: δ 7.16 ppm in ^1H NMR; δ 128.1 ppm in ^{13}C NMR; DMSO-d_6: δ 2.50 ppm in ^1H NMR; δ 39.5 ppm in ^{13}C NMR). Data were reported as following: chemical shift, multiplicity (s = singlet, d = doublet, dd = doublet of doublets, t = triplet, td = triplet of doublets, q = quartet, quin = quintet, sep = septet, m = multiplet, br = broad singlet), coupling constants *J* (Hz), and integration.

Infrared Spectroscopy: Infrared (IR) spectra were collected using a Fourier Transform-Infrared Attenuated Total Reflection Bruker Vertex 80/80v high resolution spectrometer in 400-4000 cm^{-1} as a thin film. IR absorbance was quoted in wavenumbers (cm^{-1}) with the abbreviations br. (broad), s (strong), m (medium) or w (weak).

Mass Spectrometry: Mass spectrometry (MS) was performed by the McGill Chemistry Department Mass Spectrometry Facility. High Resolution Mass spectra were recorded using electrospray ionization (ESI+) and/or atmospheric pressure chemical ionization APCI (+/-), performed either on "Exactive Plus Orbitrap" a ThermoScientific high resolution accurate mass (HR/AM) FT mass spectrometer, or a Bruker Daltonics Maxis Impact quadrupole-time of flight (QTOF) mass spectrometer.

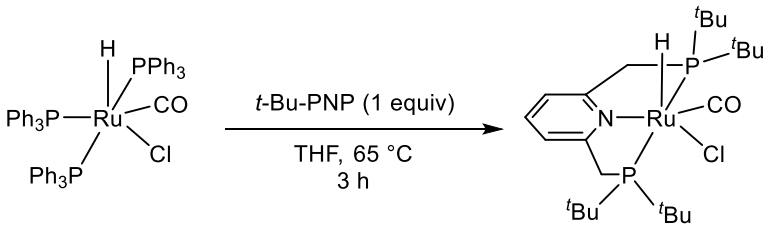
Melting Points: Melting points (m.p.) were determined by thermogravimetric analysis using a Mettleo Toledo TGA/DSC I Star System.

3.6.2 General Synthetic Procedure of Alcohol Deoxygenation

3.6.2.1 Preparation of Catalysts & Ligands

The following catalysts & ligands were prepared according to literature procedures: PNP Milstein catalyst (**Ru2**),[29] Yamaguchi catalyst (**Ir1**),[14b,16d,30] *trans*-[Ru(dmpe)Cl_2]$_2$ (**Ru4**),[31] 1,8-bis(diphenylphosphanyl)octane (dppo, **L19**),[32] Amidoamide ligand (**L38**).[18]

Synthesis of PNP Milstein pre-catalyst (**p-Ru2**)



p-Ru2

To a suspension of [RuHCl(PPh_3)$_3$(CO)] (95.3 mg, 0.1 mmol) in THF (5 mL) was added *t*-Bu-PNP (40 mg, 0.1 mmol), and the mixture was stirred and heated at 65 °C for 3 h, then cooled to room temperature. The yellow solution was filtered and the filtrate was evaporated under vacuum to dryness. The residue yellow oil was dissolved in minimum THF (1 mL) and pentane (10 mL) was added slowly to precipitate the yellow solid, which was filtered and dried under vacuum to afford **p-Ru2** (40 mg, 70%).

Data for **p-Ru2**:

^{1}H NMR: (500 MHz, C_6D_6)

δ 6.79 (t, 1H, *J* = 7.8 Hz, pyridine-H_4), 6.46 (d, 2H, *J* = 7.8 Hz, pyridine-$H_{3,5}$), 3.78 (dt, 2H, *J* = 16.0, 3.6 Hz), 2.89 (dt, 2H, *J* = 16.0, 3.6 Hz), 1.52 (t, 18H, *J* = 6.7 Hz), 1.12 (t, 18H, *J* = 6.7 Hz), –14.53 (t, 1H, *J* = 19.2 Hz).

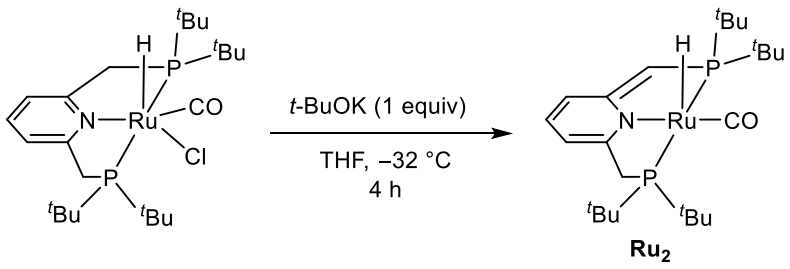
^{13}C NMR: (125 MHz, C_6D_6)

δ 209.8, 163.4 (t, *J* = 5.2 Hz), 136.4, 119.5 (t, *J* = 4.5 Hz), 38.0 (t, *J* = 6.2 Hz), 37.8 (t, *J* = 5.8 Hz), 35.3 (t, *J* = 9.8 Hz), 30.8 (t, *J* = 2.6 Hz), 29.8 128.2 (2C), 125.6, 38.1, 24.6, 13.8.

^{31}P NMR: (202 MHz, C_6D_6)

δ 90.82, 90.78.

Synthesis of PNP Milstein catalyst (**Ru$_2$**)



To a solution of **p-Ru$_2$** (15 mg, 0.03 mmol) in THF (3 mL) was added KO*t*Bu (3.0 mg, 0.03 mmol) at –32 °C, the mixture was stirred at room temperature for 4 hours, then filtered. The blue filtrate was concentrated under vacuum, then 5 mL pentane was added to precipitate a blue-green solid, which was filtered and washed with pentane (3 × 2 mL), then dried under vacuum to afford complex **Ru$_2$** (11 mg, 80%).

Data for **Ru$_2$**:

^{1}H NMR: (500 MHz, C_6D_6)

δ 6.39–6.47 (m, 2H), 5.46 (d, 1H, *J* = 5.5 Hz), 3.74 (d, 2H, *J* = 3.7 Hz), 2.71–2.83 (m, 2H), 1.37 (d, 9H, *J* = 13.5 Hz), 1.28 (d, 9H, *J* = 13Hz), 1.02 (t, 18H, *J* = 13.9 Hz), –25.77 (t, 1H, *J* = 16.4 Hz).

^{13}C NMR: (125 MHz, C_6D_6)

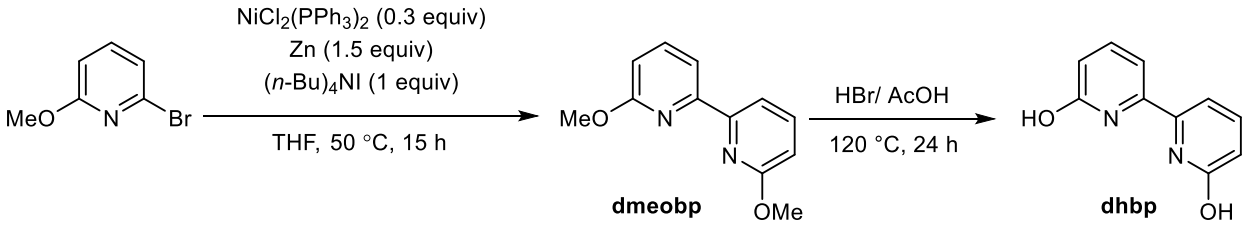
δ 209.2, 173.3 (d, *J* = 16.5 Hz), 160.6, 132.0 (t, *J* = 1.6 Hz), 114.9 (d, *J* = 18.1 Hz), 98.2 (d, *J* = 11.1 Hz), 66.6 (d, *J* = 49.8 Hz), 40.6 (d, *J* = 20.8 Hz), 35.82 (dd, *J* = 12.5, 1.6 Hz), 35.76 (d, *J* =

16.3 Hz), 34.4, 33.9 (d, *J* = 15.3 Hz), 29.6 (d, *J* = 5.6 Hz), 29.3 (d, *J* = 4.8 Hz), 29.0 (d, *J* = 4.7 Hz), 28.9 (d, *J* = 5.1 Hz).

^{31}P NMR: (202 MHz, C_6D_6)

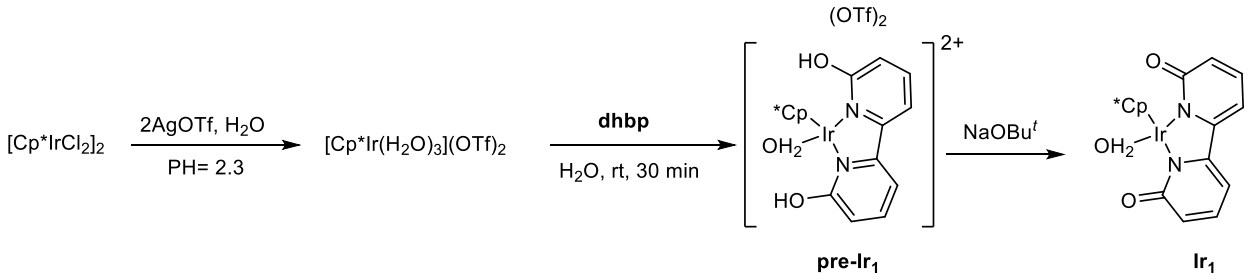
AB system, δ d_A: 82.9 (dd, *J* = 215.4, 4.6 Hz), d_B: 74.3 (dd, *J* = 215.4, 4.0 Hz).

Synthesis of 6,6'-dihydroxy-2,2'-bipyridine (**dhbp**)



To a stirred solution of $NiBr_2(PPh_3)_2$ (981 mg, 1.32 mmol), zinc powder (392 mg, 6 mmol), and Bu_4NI (1.47 g, 4 mmol) in THF (10 mL) was slowly added the solution of 2-bromo-3-methoxypyridine (752 mg, 4 mmol) in THF (5 mL) under argon at 50 °C. The reaction was further stirred for 15 h. Then the mixture was poured into aqueous ammonia (2 M) solution and extracted with CH_2Cl_2 (3 × 10 mL). The organic layer was washed with water (3 × 10 mL), dried over $MgSO_4$ and evaporated. The concentrated residue was purified by flash chromatography on silica gel to afford 6,6'-dimethoxy-2,2'-bipyridine (dmeobp) as a white solid (761 mg, 88%). 6,6'-dimethoxy-2,2'-bipyridine (dmeobp) was further dissolved in the solution of HBr and acetic acid (33%) and brought to reflux for 24 h. After that, the reaction mixture was concentrated and washed by acetone (3 × 10 mL). The resulting light yellowish solid (flake-shape) was suspended in water with pH = 1. The careful neutralization of this milky suspension with NaOH (1 M) at its boiling point, followed by filtration afforded 6,6'-dihydroxy-2,2'-bipyridine (**dhbp**) as a white solid (639 mg, 85%).

Synthesis of Yamaguchi catalyst (**Ir$_1$**)



The pH of a mixture of $(Cp^*IrCl_2)_2$ (100 mg, 0.125 mmol) and AgOTf (162 mg, 0.62 mmol) in H_2O (5 mL) is 2.3. The solution was stirred at ambient temperature for 12 h under an argon atmosphere, and the precipitating AgCl was removed by filtration. The solvent was evaporated and dried in vacuo to yield a yellow powder of $[Cp^*Ir(H_2O)_3](OTf)_2$ (167 mg, 98%).

Under an atmosphere of argon, $[Cp^*Ir(H_2O)_3](OTf)_2$ (167 mg, 0.25 mmol) was placed in a flask. Water (12 mL) and 6,6'-dihydroxy-2,2'-bipyridine (dhbp) (59 mg, 0.25 mmol) were added, and the mixture was stirred for 30 min at room temperature. Evaporation of the solvent in vacuo gave a yellow powder of **pre-Ir$_1$** in 93% yield (193 mg, 0.25 mmol). Yellow crystals of **pre-Ir$_1$** were obtained by recrystallization from methanol-diethyl ether.

Data for **pre-Ir$_1$**:

^{1}H NMR: (500 MHz, D_2O)

δ 8.03 (t, *J* = 8.0 Hz, 2H), 7.84 (d, *J* = 7.6 Hz, 2H), 7.20 (d, *J* = 8.4 Hz, 2H), 1.56 (s, 15H).

^{13}C NMR: (125 MHz, D_2O)

δ 164.1, 154.6, 144.1, 120.2 (q, *J* = 317.4 Hz), 116.0, 114.0, 89.3, 9.2.

In a flask, **pre-Ir$_1$** (153 mg, 0.22 mmol) was placed. Water (10 mL) and *t*-BuONa (44 mg, 0.44 mmol) were added, and the mixture was stirred for 30 min at room temperature. Yellow solution gradually changed to green suspension. The suspension was filtered. The residue was washed with water and dried to give **Ir$_1$** as a green powder (58 mg, 50 %).

Data for **Ir$_1$**:

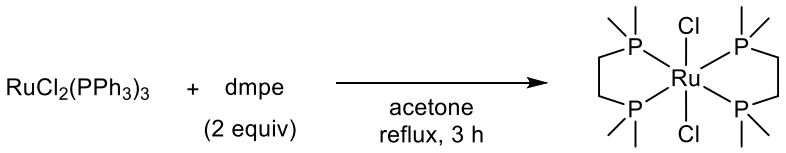
^{1}H NMR: (500 MHz, MeOD)

δ 7.39 (dd, *J* = 8.6, 7.2 Hz, 2H), 6.89 (d, *J* = 7.2 Hz, 2H), 6.32 (d, *J* = 8.6 Hz, 2H), 1.59 (s, 15H).

^{13}C NMR: (125 MHz, MeOD)

δ 170.9, 157.5, 139.4, 117.2, 106.9, 88.3, 9.3.

Synthesis of *trans*-[Ru(dmpe)Cl_2]$_2$ (**Ru$_4$**)



Ru$_4$

A Schlenk tube was charged with dmpe (84 µL, 0.5 mmol) and $RuCl_2(PPh_3)_3$ (240 mg, 0.25 mmol) and dry acetone (10 mL) in the glove box. The tube was sealed, moved outside of the box, and refluxed for 3 h till the yellow suspension was formed. After that, the reaction was cooled to room temperature, filtered and the solvent removed under vacuum to give a yellow solid residue. This was washed with hexane (2 x 10 mL) and dried under vacuum to give **Ru$_4$** (106 mg, 90%) as a pale yellow solid.

Data for **Ru$_4$**:

^{1}H NMR: (500 MHz, C_6D_6)

δ 1.50 (s, 8H), 1.35 (s, 24H).

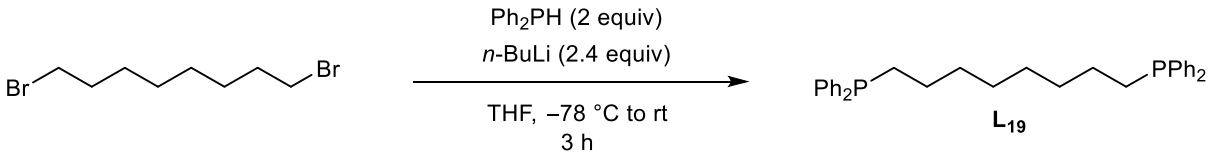
^{13}C NMR: (125 MHz, C_6D_6)

δ 29.4 (quin, J = 12.8 Hz), 12.6 (t, J = 6.4 Hz).

^{31}P NMR: (202 MHz, C_6D_6)

δ 38.9.

Synthesis of 1,8-bis(diphenylphosphanyl)octane (**L$_{19}$**)



A lithium diphenylphosphide solution was prepared by the slow addition of diphenylphosphine (174 µL, 1 mmol) into *n*-BuLi (0.48 mL, 1.2 mmol, 2.5 M in hexane) THF solution at −78 °C. The reaction mixture was stirred for 20 mins. 1,8-dibromooctane (0.5 mmol, 92 µL) was slowly added into the lithium diphenylphosphide solution dropwise using a syringe while the solution was stirred at −78 °C. The reaction was allowed to gradually proceed for 3 hours at room temperature and then the solvent was removed by a rotary evaporator. The product was extracted by dichloromethane (20 mL). After that, the reaction was filtered and the solvent removed under vacuum to give **L$_{19}$** as a white powder (187 mg, 85%).

Data for **L$_{19}$**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.39–7.46 (m, 8H), 7.29–7.37 (m, 12H), 1.99–2.07 (m, 4H), 1.34–1.48 (m, 8H), 1.20–1.29 (m, 4H).

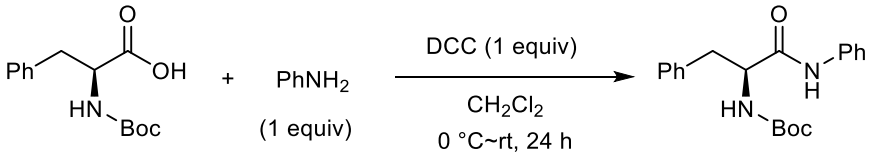
^{13}C NMR: (125 MHz, $CDCl_3$)

δ 138.8 (4C), 132.7 (d, *J* = 18.2 Hz) (8C), 128.4 (4C), 128.3 (d, *J* = 6.3 Hz) (8C), 31.1 (d, *J* = 12.8 Hz) (2C), 29.0 (2C), 28.0 (d, *J* = 10.2 Hz) (2C), 25.8 (d, *J* = 15.6 Hz) (2C).

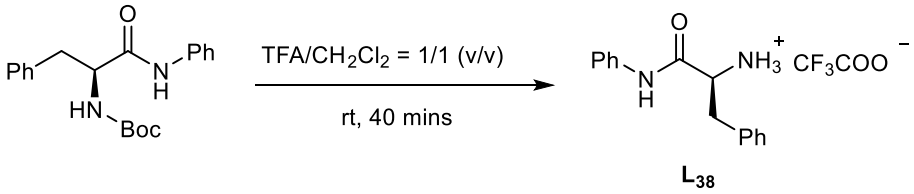
^{31}P NMR: (202 MHz, $CDCl_3$)

δ −16.0.

Synthesis of amidoamide ligand (**L_{38}**)



The Boc-Phe-OH (1.59 g, 6 mmol) was dissolved in dry dichloromethane (30 mL) and cooled in an ice bath. To the solution was added 1,3-dicyclohexylcarbodiimide (DCC) (1.23 g, 6.0 mmol) in small portions followed by stirring in an ice bath for 15 min. Aniline (0.55 mL, 6.0 mmol) was then added to the solution, and the reaction was allowed to warm to room temperature and stir for 24 h. The reaction was filtered, and the filtrate was washed twice with deionized water. The organic fractions were combined and dried over anhydrous magnesium sulfate. The solution was filtered, and the filtrate was recovered and concentrated under vacuum. Hexane was added, and a white solid was filtered.



L_{38}

The Boc-amino amide was quantitatively transferred to a flask, and a 50: 50 (v/ v) solution of trifluoroacetic acid (10 equiv) in dichloromethane was added. The reaction was stirred at room temperature for 40 min, and then solvent was removed under vacuum. Diethyl ether was added to

the residue to precipitate a white solid. **L38** was filtered as a solid and washed several times with ether and allowed to dry (1.26 g, 60%). This compound was stable under ambient conditions.

Data for **L38**:

^{1}H NMR: (500 MHz, DMSO-d_6)

δ 10.47 (s, 1H), 8.41 (s, 3H), 7.46–7.56 (m, 2H), 7.19–7.37 (m, 7H), 7.05–7.15 (m, 1H), 4.19 (m, 1H), 3.05–3.22 (m, 2H).

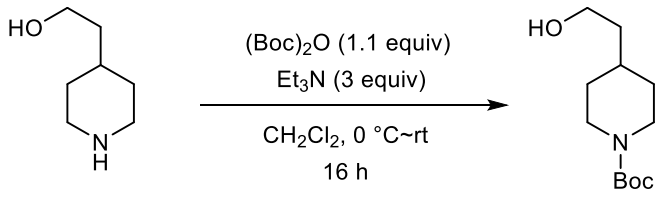
^{13}C NMR: (125 MHz, DMSO-d_6)

δ 166.8, 137.9, 134.8, 129.5 (2C), 128.9 (2C), 128.6 (2C), 127.2, 124.2, 119.7 (2C), 54.3, 37.1.

3.6.2.2 Preparation of Substrates

The following alcohol substrates were prepared according to literature procedures 4-(2-hydroxyethyl)piperidine-1-carboxylic acid *tert*-butyl ester **3.1i**,[33] 2-(4-isobutylphenyl)propan-1-ol **3.1l**, (+)-biotinol **3.1n**, *N*-(4-{[(1-hydroxybutan-2-yl)amino]methyl}phenyl)acetamide **3.1o**,[34] abietic alcohol **3.11**, tetrahydroquinoline alcohols **3.15a-e**,[24] deoxycholic alcohol **3.18**, cholic alcohol **3.20**.

Synthesis of 4-(2-hydroxyethyl)piperidine-1-carboxylic acid *tert*-butyl ester (**3.1i**)



3.1i

To a cold solution of 4-piperidine ethanol (1.25 g, 10 mmol) in 50 mL of CH_2Cl_2 was added dropwise a solution of di-*tert*-butyl dicarbonate (2.38 g, 11 mmol) and triethylamine (4.3 mL, 30 mmol) in 200 mL of CH_2Cl_2. The mixture was stirred in an ice bath for 1 h and subsequently at room temperature for 16 h. A saturated sodium carbonate solution (100 mL) was added, the organic layer was collected, and the aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were dried over sodium sulfate and evaporated to give **3.1i** as a colorless oil (2.3 g, 98%).

Data for **3.1i**:

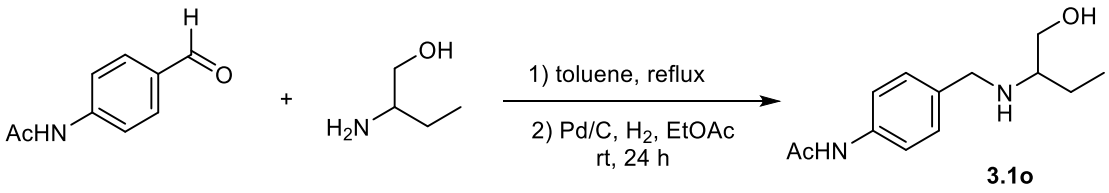
^{1}H NMR: (500 MHz, $CDCl_3$)

δ 4.02–4.11 (m, 2H), 3.69 (t, 2H, J = 6.6 Hz), 2.64–2.73 (m, 2H), 1.77 (s, br, OH), 1.51–1.70 (m, 5H), 1.45 (s, 9H), 1.07–1.17 (m, 2H).

^{13}C NMR: (125 MHz, $CDCl_3$)

δ 154.8, 79.2, 60.1, 43.9 (2C), 39.2, 32.5, 32.1 (2C), 28.4 (3C).

Synthesis of *N*-(4-{[(1-hydroxybutan-2-yl)amino]methyl}phenyl)acetamide (**3.1o**)



To a solution of 2-aminobutan-1-ol (445 mg, 5 mmol) in 50 mL toluene was added dropwise a solution of *N*-(4-formylphenyl)acetamide (852 mg, 5.2 mmol) in 10 mL of toluene. The mixture was heated under reflux and stirred for 1 h using a Dean-Stark separator. Evaporation of the solvent resulted in the crude imine product as a white solid. Without further purification, a solution of the appropriate this crude mixture and 5% Pd/C catalyst (3.0 g) in ethyl acetate (50 mL) was stirred

vigorously under the flow of H_2 at room temperature for 24 h. The solution was then filtered through celite and evaporated to afford the **3.1o** as a white solid (649 mg, 55%).

Data for **3.1o**:

^{1}H NMR: (500 MHz, MeOD)

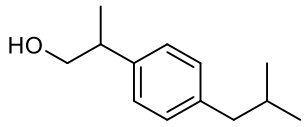
δ 7.48–7.55 (m, 2H), 7.26–7.34 (m, 2H), 3.80 (d, 2H, *J* = 13.0 Hz), 3.73 (d, 2H, *J* = 13.0 Hz), 3.64 (dd, 1H, *J* = 11.1, 4.4 Hz), 3.44 (dd, 1H, *J* = 11.1, 6.7 Hz), 2.53–2.62 (m, 1H), 2.11 (s, 3H), 1.51–1.63 (m, 1H), 1.39–1.50 (m, 1H), 0.92 (t, 3H, *J* = 7.5 Hz).

^{13}C NMR: (125 MHz, MeOD)

δ 171.6, 139.4, 130.3 (2C), 121.3 (2C), 62.9, 61.1, 51.0, 23.9, 23.8, 10.6.

General procedure for $LiAlH_4$ reduction of carboxylic acid compounds.

The solution of carboxylic acid compounds (5 mmol) in dry THF (60 mL) was added dropwise to a suspension of powdered $LiAlH_4$ (1.12 g, 29.4 mmol) in dry THF (30 mL) at room temperature. The reaction mixture was refluxed and stirred overnight. To this mixture was added 60 mL water and 50 mL H_2SO_4 (1 M), stirring for 1 h. The mixture was extracted with ethyl acetate (23 × 60 mL). After drying with anhydrous $MgSO_4$ and evaporating the solvent, the residue was purified by silica gel column chromatography to yield the corresponding alcohol substrates.



2-(4-Isobutylphenyl)propan-1-ol (**3.1l**)

Following **the general $LiAlH_4$ reduction procedure**, **3.1l** was obtained as a colorless oil (912 mg, 95%).

Data for **3.1l**:

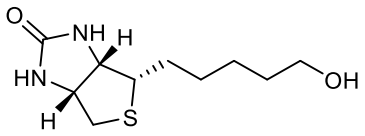
TLC: R_f 0.5 (2:1 hexane/EtOAc) [UV/I_2/CAM]

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.11–7.19 (m, 4H), 3.74 (d, *J* = 13.0 Hz, 2H), 3.70 (d, *J* = 6.8 Hz, 1H), 2.94 (qq, apparent sextet, *J* = 6.9 Hz, 1H), 2.48 (d, *J* = 7.2 Hz, 2H), 1.86 (qqt, apparent sep, *J* = 6.8 Hz, 1H), 1.29 (d, *J* = 7.0 Hz, 3H), 0.94 (d, *J* = 6.6 Hz, 6H).

^{13}C NMR: (125 MHz, $CDCl_3$)

δ 140.7, 140.0, 129.3 (2C), 127.1 (2C), 68.7, 45.0, 42.0, 30.2, 22.4 (2C), 17.6.



(+)-Biotinol (**3.1n**)

Following **the general $LiAlH_4$ reduction procedure**, **3.1n** was obtained as a white solid (1012 mg, 88%).

Data for **3.1n**:

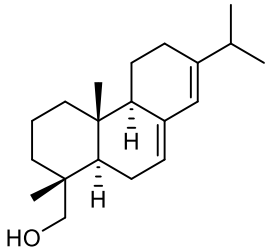
TLC: R_f 0.1 (10:1 EtOAc/MeOH) [UV/I_2/CAM]

^{1}H NMR: (500 MHz, MeOD)

δ 4.49 (ddd, apparent dd, *J* = 7.8, 4.9 Hz, 1H), 4.30 (dd, *J* = 7.8, 4.5 Hz, 1H), 3.66 (d, *J* = 6.4 Hz, 3H), 3.21 (ddd, apparent quintet, *J* = 4.8 Hz, 1H), 2.92 (dd, *J* = 12.7, 4.9 Hz, 1H), 2.70 (d, *J* = 13Hz, 1H), 1.70–1.79 (m, 1H), 1.30–1.57 (m, 6H).

^{13}C NMR: (125 MHz, MeOD)

δ 166.1, 63.4, 61.6, 60.0, 57.1, 41.0, 33.4, 30.1, 29.7, 26.9.



Abietic alcohol (**3.11**)

Following **the general $LiAlH_4$ reduction procedure**, **3.11** was obtained as a colorless oil (1296 mg, 90%).

Data for **3.11**:

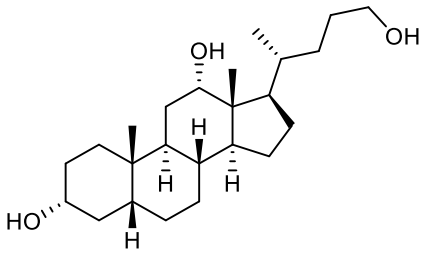
TLC: R_f 0.45 (5:1 hexane/EtOAc) [UV/I_2/CAM]

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 5.79 (s, 1H), 5.41 (t, *J* = 2.5 Hz, 1H), 3.36 (d, *J* = 10.9 Hz, 1H), 3.13 (d, *J* = 10.9 Hz, 1H), 2.18–2.28 (m, 1H), 1.74–2.12 (m, 8H), 1.50–1.66 (m, 3H), 1.16–1.46 (m, 3H), 1.03 (d, *J* = 6.8 Hz, 3H), 1.02 (d, *J* = 6.8 Hz, 3H), 0.93 (s, 3H), 0.88 (s, 3H), 0.84 (s, 3H).

^{13}C NMR: (125 MHz, $CDCl_3$)

δ 145.1, 135.5, 122.4, 120.9, 72.0 50.7, 43.4, 38.8, 37.4, 35.6, 34.8, 34.6, 27.5, 23.8, 22.6, 21.4, 20.8, 18.1, 17.6, 14.2.



Deoxycholic alcohol (**3.18**)

Following **the general $LiAlH_4$ reduction procedure**, **3.18** was obtained as a colorless oil (1776 mg, 94%).

Data for **3.18**:

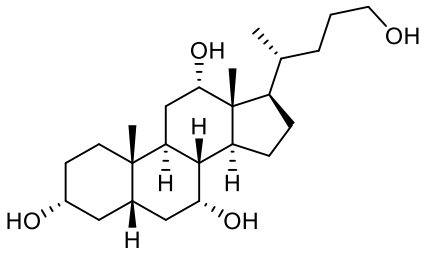
TLC: R_f 0.15 (3:1 hexane/EtOAc) [I_2/CAM]

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 4.00 (s, 1H), 3.57–3.69 (m, 3H), 2.06 (s, br, 3H, OH), 1.34–1.92 (m, 20H), 1.23–1.32 (m, 2H), 1.04–1.18 (m, 3H), 1.00 (d, J = 6.6 Hz, 3H), 0.95–1.03 (m, 1H), 0.92 (s, 3H), 0.70 (s, 3H).

^{13}C NMR: (125 MHz, $CDCl_3$)

δ 73.2, 71.8, 63.5, 48.2, 47.6, 46.5, 42.1, 36.4, 36.0, 35.3, 35.2, 34.1, 33.6, 31.7, 30.5, 29.4, 28.5, 27.6, 27.1, 26.1, 23.6, 23.1, 17.7, 12.7.



Cholic alcohol (**3.20**)

Following **the general $LiAlH_4$ reduction procedure**, **3.20** was obtained as a colorless oil (1812 mg, 92%).

Data for **3.20**:

TLC: R_f 0.1 (8:1 CH_2Cl_2/MeOH) [I_2/CAM]

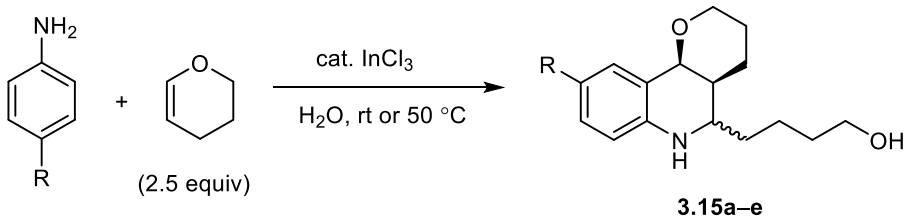
^{1}H NMR: (500 MHz, MeOD)

δ 3.98 (dd, apparent t, *J* = 2.8 Hz, 1H), 3.82 (ddd, apparent d, *J* = 2.8 Hz, 1H), 3.53 (ddd, apparent dt, *J* = 6.6, 2.4 Hz, 2H), 3.35–3.43 (m, 1H), 2.23–2.35 (m, 2H), 1.36–2.03 (m, 19H), 1.24–1.35 (m, 1H), 1.07–1.18 (m, 2H), 1.04 (d, *J* = 6.6 Hz, 3H), 0.94 (s, 3H), 0.74 (s, 3H).

^{13}C NMR: (125 MHz, MeOD)

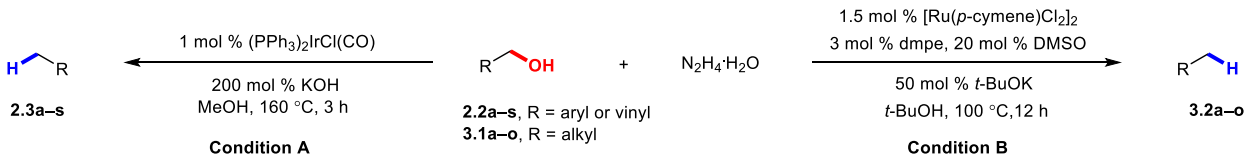
δ 74.1, 72.9, 69.1, 63.6, 48.3, 47.4, 43.2, 43.0, 41.0, 40.5, 37.1, 36.5, 35.9, 35.8, 33.2, 31.2, 30.4, 29.6, 28.8, 27.9, 24.2, 23.2, 18.0, 13.0.

General procedure for the synthesis of tetrahydroquinoline alcohols (**3.15a-e**)



3.15a–e

A mixture of aromatic amine (2 mmol), 3,4-dihydro-*2H*-pyran (5 mmol), and indium trichloride (0.2-0.4 mmol) in 10 mL of water was stirred at room temperature or at 50-60 °C, and the reaction progress was monitored by TLC. When the reaction was completed, the reaction mixture was extracted with ethyl ether or methylene chloride. The combined organic phases were dried and concentrated. The crude materials were separated by column chromatography to give tetrahydroquinoline alcohols **3.15a-e**. The data of **3.15a-e** were in accordance with our previous report.[24]



3.6.2.3 General Reaction Procedure for Condition A

An Ace pressure glass tube (4 cm) was charged with $(PPh_3)_2IrCl(CO)$ (2.3 mg, 0.003 mmol), KOH (34 mg, 0.6 mmol), the alcohol **2.2a-s** (0.3 mmol), $N_2H_4{\cdot}H_2O$ (29 μL, 0.6 mmol) and MeOH (30 μL) under an air atmosphere. The Ace tube was sealed and the reaction mixture was stirred at 160 ^oC for 3 h [*Warning: reaction is under pressure and potentially hazardous; and should be performed under protection of a blast shield*]. After that, the reaction mixture was cooled to room temperature, and filtered through a short column of silica by flushing it with CH_2Cl_2 (10 mL). The filtrate was dried over Na_2SO_4 and concentrated under reduced pressure to give the residue, which was first subjected to ^1H NMR by using nitromethane (5.4 μL, 0.1 mmol) as an internal standard; and further purified by preparative TLC, or flash chromatography on silica gel to afford the desired product **2.3a-s**.

3.6.2.4 General Reaction Procedure for Condition B

A flamed-dried V-shape microwave reaction vial (10 cm^3) equipped with a magnetic stir bar was charged with $[Ru(p\text{-cymene})Cl_2]_2$ (1.8 mg, 1.5 mol %), KO*t*Bu (11.2 mg, 0.1 mmol, 0.5 equiv). The reaction vial was then transferred to the glovebox and charged with dmpe (1.0 μL, 3.0 mol %), before being sealed with a rubber septum. The reaction vial was then moved out of the glovebox, put under an argon atmosphere and sequentially charged with primary aliphatic alcohol **3.1a-o** (0.2 mmol, 1.0 equiv), DMSO (2.8 μL, 20 mol%), *t*-BuOH (0.2 mL) and hydrazine hydrate (13 μL, 0.24 mmol, 64-65 wt%, 1.2 equiv). With Argon protection, the rubber septum was replaced by an aluminum seal containing a PTFE-faced silicone septum. The reaction mixture was then heated to an indicated temperature for 12 h [*Warning: reaction with hydrazine monohydrate is potentially hazardous; and should be performed with appropriate personal protection*]. Typically, reaction completion was tracked by a characteristic color change of the solution from dark

red/brown (beginning) to light brown/yellow (exact colors might vary depending on substrates). Upon completion, the reaction vial was removed from the oil bath, and cooled to room temperature. A distinctive gas (N_2 and H_2) release sound was heard when the aluminum seal was opened.

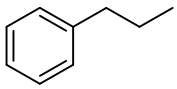
Note: Some of substrates (i.e. **3.1e**, **3.1i**, **3.11**, etc.) were subject to a slightly different reaction conditions. Please refer to the footnotes in the corresponding tables or schemes.

3.6.2.5 General Work-Up Procedure

Due to the volatility of most deoxygenated alkanes (in particular short carbon backbones), 1,3,5-trimethoxybenzene (16.8 mg, 0,1 mmol) was directly added into the reaction mixture as an internal standard upon completion of the reaction. A small amount of reaction mixture (roughly 20 μL) was filtered through a short plug made of neutral Al_2O_3 and anhydrous Na_2SO_4, flushed by $CDCl_3$ (0.7 mL), analyzed by GC-MS, and subjected to ^{1}H NMR for yield determination.

For non-volatile alkanes with low polarity, the reaction was quenched by a few drops of *sat.* NH_4Cl upon its completion, diluted by H_2O (2.0 mL), and extracted by Et_2O (3 x 2 mL). For non-volatile alkanes with high polarity, such as 5β-cholane-3α,12α-diol (**3.19**) and 3α, 7α, 12α-trihydroxycholane (**3.21**), the reaction mixture was diluted by methanol (2.0 mL). The combined organic layer was concentrated in vacuo. The crude residue was further purified by either preparative thin-layer-chromatography (PTLC), or flash column chromatography (FCC) to obtain the isolate yields.

3.6.3 Spectroscopic Data



Propylbenzene (**3.2a**)

Following **the general reaction procedure for condition B** from 3-phenyl-1-propanol **3.1a** (27.5 μL, 0.2 mmol), **3.2a** was obtained in 95% ^{1}H NMR yield using 1,3,5-trimethoxybenzene as an internal standard.

Data for **3.2a**:

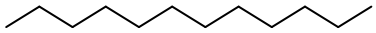
TLC: R_f 0.80 (pentane) [UV/I_2/CAM]

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.30–7.25 (m, 3H), 7.20–7.15 (m, 2H), 2.59 (t, *J* = 7.3 Hz, 2H), 1.65 (sextet, *J* = 7.3 Hz, 2H), 0.95 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR: (125 MHz, $CDCl_3$)

δ 142.7, 128.4 (2C), 128.2 (2C), 125.6, 38.1, 24.6, 13.8.



Dodecane (**3.2b**)

Following **the general reaction procedure for condition B** from 1-dodecanol **3.1b** (36.5 μL, 0.2 mmol), **3.2b** was obtained as a colorless oil (32.2 mg, 95%) by purification through flash chromatography on silica gel.

Data for **3.2b**:

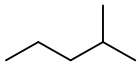
TLC: R_f 0.80 (pentane) [I_2/CAM]

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 1.22–1.36 (m, 20H), 0.90 (t, *J* = 7.0 Hz, 6H).

^{13}C NMR: (125 MHz, $CDCl_3$)

δ 31.9 (2C), 29.70 (2C), 29.66 (2C), 29.4 (2C), 22.7 (2C), 14.1 (2C).



2-Methylpentane (**3.2c**)

Following **the general reaction procedure for condition B** from 2-methylpentan-1-ol **3.1c** (25 µL, 0.2 mmol), **3.2c** was obtained in 88% ^{1}H NMR yield using 1,3,5-trimethoxybenzene as an internal standard.

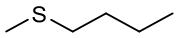
Data for **3.2c**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 1.48–1.58 (m, 1H), 1.24–1.34 (m, 2H), 1.10–1.18 (m, 2H), 0.84–0.92 (m, 9H).

^{13}C NMR: (125 MHz, $CDCl_3$)

δ 41.9, 28.0, 22.7 (2C), 20.8, 14.2.



n-Butylmethylsulfide (**3.2d**)

Following **the general reaction procedure for condition B** from 4-(methylthio)butan-1-ol **3.1d** (24.3 µL, 0.2 mmol), **3.2d** was obtained in 92% ^{1}H NMR yield using 1,3,5-trimethoxybenzene as an internal standard.

Data for **3.2d**:

TLC: R_f 0.80 (pentane) [I_2/CAM]

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 2.47 (t, *J* = 5.0 Hz, 2H), 2.07 (s, 3H), 1.56 (tt, apparent quin, *J* = 7.4 Hz, 2H), 1.39 (qt, apparent quin, *J* = 7.4 Hz, 2H), 0.9 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR: (125 MHz, $CDCl_3$)

δ 34.2, 31.4, 22.0, 15.5, 13.8.

Decane (**3.2e**)

Following **the general reaction procedure for condition B** from 1,10-decanediol **3.1e** (34.8 mg, 0.2 mmol), **3.2e** was obtained as a colorless oil (19.8 mg, 70%) by purification through flash chromatography on silica gel.

Data for **3.2e**:

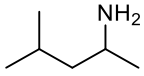
TLC: R_f 0.8 (pentane) [I_2/CAM]

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 1.25–1.35 (m, 16H), 0.91 (t, *J* = 7.0 Hz, 6H).

^{13}C NMR: (125 MHz, $CDCl_3$)

δ 32.0 (2C), 29.70 (2C), 29.4 (2C), 22.7 (2C), 14.1 (2C).



4-Methylpentan-2-amine (**3.2f**)

Following **the general reaction procedure for condition B** from (S)-(+)-Leucinol **3.1f** (26.5 µL, 0.2 mmol), racemic **3.2f** was obtained in 85% ^{1}H NMR yield using 1,3,5-trimethoxybenzene as an internal standard.

Data for **3.2f**:

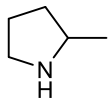
TLC: R_f 0.75 (pentane) [I_2/CAM]

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 2.93 (sextet, *J* = 6.9 Hz, 1H), 1.63 (sextet, *J* = 6.6 Hz, 1H), 1.12–1.21 (m, 2H), 1.03 (d, *J* = 6.3 Hz, 3H), 0.87 (d, *J* = 6.6 Hz, 6H).

^{13}C NMR: (125 MHz, $CDCl_3$)

δ 50.1, 44.7, 25.1 (2C), 23.4, 22.5.



2-Methylpyrrolidine (**3.2g**)

Following **the general reaction procedure for condition B** from (S)-(+)-2-pyrrolidinemethanol **3.1g** (19.7 µL, 0.2 mmol), racemic **3.2g** was obtained in 83% ^{1}H NMR yield using 1,3,5-trimethoxybenzene as an internal standard.

Data for **3.2g**:

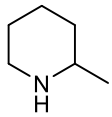
TLC: R_f 0.75 (pentane) [I_2/CAM]

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 2.96–3.09 (m, 2H), 2.78–2.90 (m, 1H), 1.65–1.91 (m, 4H), 1.17–1.25 (m, 1H), 1.14 (d, *J* = 6.3 Hz, 3H).

^{13}C NMR: (125 MHz, $CDCl_3$)

δ 54.5, 46.7, 33.7, 25.7, 21.1.



2-Methylpiperidine (**3.2h**)

Following **the general reaction procedure for condition B** from 2-piperidinemethanol **3.1h** (23 mg, 0.2 mmol), **3.2h** was obtained in 89% ^{1}H NMR yield using 1,3,5-trimethoxybenzene as an internal standard.

Data for **3.2h**:

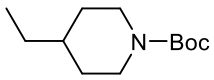
TLC: R_f 0.75 (pentane) [I_2/CAM]

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 2.96–3.09 (m, 1H), 2.53–2.62 (m, 2H), 1.73–1.83 (m, 1H), 1.51–1.64 (m, 2H), 1.29–1.47 (m, 3H), 1.04 (d, *J* = 6.3 Hz, 3H).

^{13}C NMR: (125 MHz, $CDCl_3$)

δ 53.6, 48.3, 36.0, 27.5, 26.2, 23.4.



tert-Butyl 4-ethylpiperidine-1-carboxylate (**3.2i**)

Following **the general reaction procedure for condition B** from *tert*-butyl 4-(2-hydroxyethyl)piperidine-1-carboxylate **3.1i** (45.8 mg, 0.2 mmol), **3.2i** was obtained as a colorless oil (36.2 mg, 85%) by purification through flash chromatography on silica gel.

Data for **3.2i**:

TLC: R_f 0.65 (2:1 hexane/EtOAc) [I_2/CAM]

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 4.00–4.17 (m, 2H), 2.68 (t, *J* = 12.3 Hz, 2H), 1.62–1.70 (m, 2H), 1.46 (s, 9H), 1.22–1.32 (m, 3H), 1.01–1.12 (m, 2H), 0.90 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR: (125 MHz, $CDCl_3$)

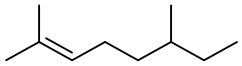
δ 154.9, 79.1, 44.1 (2C), 37.7 (2C), 31.8, 29.2, 28.5 (3C), 11.1.

IR: (neat)

ν (cm^{-1}) 2965 (m), 2926 (m), 2854 (m), 1693 (s), 1412 (s), 1365 (s), 1340 (w), 1314 (w), 1278 (m), 1250 (m), 1230 (s), 1175 (s), 1150 (s), 1092 (m), 1012 (m), 980 (m), 932 (w), 867 (m), 812 (w), 769 (m), 561 (w), 460 (w).

HRMS: (ESI, *m/z*)

calcd for $C_{12}H_{23}NNaO_2$ $[M+Na]^+$ 236.1621, found: 236.1618



2,6-Dimethyloct-2-ene (**3.2j**)

Following **the general reaction procedure for condition B** from β-citronellol **3.1j** (0.2 mmol, 36.5 µL), **3.2j** was obtained as a colorless oil (25 mg, 90%) by purification through flash chromatography on silica gel.

Data for **3.2j**:

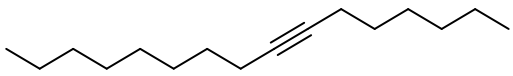
TLC: R_f 0.8 (pentane) [I_2/CAM]

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 5.10–5.16 (m, 1H), 1.90–2.06 (m, 2H), 1.71 (s, 3H), 1.63 (s, 3H), 1.30–1.40 (m, 3H), 1.10–1.20 (m, 2H), 0.88 (t, J = 7.3 Hz, 3H), 0.88 (d, J = 6.5 Hz, 3H).

^{13}C NMR: (125 MHz, $CDCl_3$)

δ 130.9, 125.1, 36.7, 34.0, 29.4, 25.7, 25.6, 19.1, 17.6, 11.3.



Hexadec-7-yne (**3.2k**)[35]

Following **the general reaction procedure for condition B** from 7-hexadecyn-1-ol **3.1k** (55 µL, 0.2 mmol), **3.2k** was obtained as a colorless oil (37.2 mg, 84%) by purification through flash chromatography on silica gel.

Data for **3.2k**:

TLC: R_f 0.65 (pentane) [I_2/CAM]

^{1}H NMR: (500 MHz, $CDCl_3$)

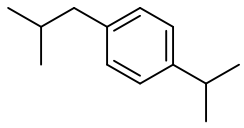
δ 2.16 (t, *J* = 7.0 Hz, 1H), 1.45–1.53 (m, 4H), 1.22–1.43 (m, 16H), 1.04 (d, *J* = 6.8 Hz, 3H), 0.91 (t, *J* = 7.0 Hz, 3H), 0.90 (t, *J* = 6.9 Hz, 3H).

^{13}C NMR: (125 MHz, $CDCl_3$)

δ 80.2 (2C), 31.8, 31.4, 29.22, 29.17, 29.14 (2C), 28.9, 28.5, 22.7, 22.6, 18.8 (2C), 14.1, 14.0.

IR: (neat)

ν (cm^{-1}) 2957 (m), 2927 (m), 2857 (m), 2401(w), 2384 (w), 2352 (w), 2328 (m), 2251 (m), 2214 (w), 1715 (w), 1678 (w), 1459 (m), 1379 (m), 1332 (w), 1112 (w), 723 (m), 420 (w).



1-Isobutyl-4-isopropylbenzene (**3.2l**)

Following **the general reaction procedure for condition B** from 2-(4-isobutylphenyl)propan-1-ol **3.1l** (38.4 mg, 0.2 mmol), **3.2l** was obtained as a colorless oil (27.8 mg, 79%) by purification through flash chromatography on silica gel.

Data for **3.2l**:

TLC: R_f 0.65 (Pentane) [I_2/CAM]

^{1}H NMR: (500 MHz, $CDCl_3$)

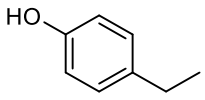
δ 7.14–7.18 (m, 2H), 7.07–7.12 (m, 2H), 2.90 (qq, apparent sep, *J* = 6.9 Hz, 1H), 2.47 (d, *J* = 7.1 Hz, 2H), 1.88 (qqt, apparent sep, *J* = 6.8 Hz, 1H), 1.27 (d, *J* = 6.9 Hz, 6H), 0.93 (d, *J* = 6.9 Hz, 6H).

^{13}C NMR: (125 MHz, $CDCl_3$)

δ 146.0, 139.0, 129.0 (2C), 126.1 (2C), 45.0, 30.7, 30.2, 24.1 (2C), 22.4 (2C).

HRMS: (ESI, *m/z*)

calcd for $C_{13}H_{21}$ $[M+H]^+$ 175.1481, found: 175.1481



4-Ethylphenol (**3.2m**)

Following **the general reaction procedure for condition B** from 4-(2-hydroxyethyl)phenol **3.1m** (38.4 mg, 0.2 mmol), **3.2m** was obtained as a colorless oil (27.8 mg, 79%) by purification through flash chromatography on silica gel.

Data for **3.2m**:

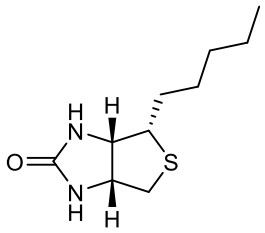
TLC: R_f 0.5 (3:1 hexane/EtOAc) [UV/I_2/CAM]

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.06–7.11 (m, 2H), 6.75–6.80 (m, 2H), 4.64 (s, br, 1H), 2.60 (q, *J* = 7.6 Hz, 2H), 1.22 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR: (125 MHz, $CDCl_3$)

δ 153.4, 136.5, 128.9 (2C), 115.1 (2C), 28.0, 15.9.



(+)-Deoxybiotin (**3.2n**)

Following **the general reaction procedure for condition B** from (+)-biotinol **3.1n** (46 mg, 0.2 mmol), **3.2n** was obtained as a white solid (39 mg, 91%) by purification through flash chromatography on silica gel.

Data for **3.2n**:

TLC: R_f 0.4 (10:1 EtOAc/MeOH) [I_2/CAM]

mp: 180.15–180.56 °C (MeOH)

^{1}H NMR: (500 MHz, MeOD)

δ 4.49 (ddd, apparent dd, *J* = 7.8, 4.9 Hz, 1H), 4.29 (dd, *J* = 7.8, 4.5 Hz, 1H), 3.20 (ddd, apparent quintet, *J* = 4.8 Hz, 1H), 2.93 (dd, *J* = 12.7, 4.9 Hz, 1H), 2.70 (d, *J* = 13.0 Hz, 1H), 1.67–1.77 (m, 1H), 1.53–1.62 (m, 1H), 1.29–1.48 (m, 6H), 0.92 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR: (125 MHz, MeOD)

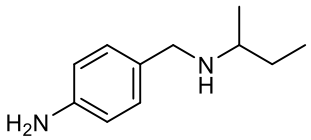
δ 166.2, 63.5, 61.6, 57.3, 41.0, 32.9, 30.1, 29.8, 23.6, 14.3.

IR: (neat)

ν (cm^{-1}) 3215 (w), 2958 (m), 2932 (m), 2853 (m), 2383 (w), 1690 (s), 1467 (m), 1428 (m), 1325 (w), 1315 (w), 1293 (w), 1259 (w), 1230 (w), 1206 (w), 1167 (w), 1099 (w), 1020 (w), 973 (w), 919 (w), 871 (w), 834 (m), 759 (w), 720 (w), 685 (w), 646 (w), 611 (w), 569 (w).

HRMS: (ESI, *m/z*)

calcd for $C_{10}H_{19}N_2OS$ $[M+H]^+$ 215.1213, found: 215.1211



4-[(sec-Butylamino)methyl]aniline (**3.2o**)

Following **the general reaction procedure for condition B** from *N*-(4-{[(1-hydroxybutan-2-yl)amino]methyl}phenyl)acetamide **3.1o** (46 mg, 0.2 mmol), **3.2o** was obtained as a light yellow oil (34.2 mg, 96%) by purification through flash chromatography on silica gel.

Data for **3.2o**:

TLC: R_f 0.25 (5:1 acetone/MeOH) [UV/I_2/CAM]

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.20–7.25 (m, 2H), 6.64–6.69 (m, 2H), 3.82 (d, *J* = 13.0 Hz, 1H), 3.74 (d, *J* = 13.0 Hz, 1H), 2.72 (qt, apparent sextet, *J* = 6.4 Hz, 1H), 1.65–1.75 (m, 1H), 1.45–1.54 (m, 1H), 1.19 (d, *J* = 6.4 Hz, 3H), 0.92 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR: (125 MHz, $CDCl_3$)

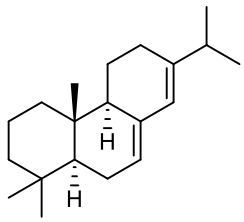
δ 146.7, 130.9 (2C), 130.6, 115.2 (2C), 53.0, 47.9, 26.7, 16.4, 10.0.

IR: (neat)

ν (cm^{-1}) 3348 (br.), 2964 (w), 2928 (w), 2877 (w), 2405 (w), 2384 (w), 2351 (w), 2328 (w), 2251 (w), 1612 (m), 1545 (m), 1518 (s), 1459 (m), 1408 (m), 1376 (m), 1318 (m), 1273 (w), 1216 (w), 1182 (w), 1121 (w), 1041 (w), 1016 (w), 825 (m), 673 (w), 654 (w), 618 (m), 580 (m).

HRMS: (ESI, *m/z*)

calcd for $C_{11}H_{19}N_2$ $[M+H]^+$ 179.1543, found: 179.1541



Abieta-7,13-diene (**3.12**)

Following **the general reaction procedure for condition B** from abietic alcohol **3.11** (28.8 mg, 0.1mmol), **3.12** was obtained as a colorless oil (15 mg, 58%) by purification through flash chromatography on silica gel.

Data for **3.12**:

TLC: R_f 0.8 (hexane) [UV/I_2/CAM]

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 5.80 (s, 1H), 5.45 (t, *J* = 2.5 Hz, 1H), 1.92–2.28 (m, 5H), 1.78–1.89 (m, 3H), 1.52–1.64 (m, 1H), 1.41–1.51 (m, 2H), 1.16–1.30 (m, 3H), 1.02–1.08 (m, 1H), 1.03 (d, *J* = 6.8 Hz, 3H), 1.02 (d, *J* = 6.8 Hz, 3H), 0.93 (s, 3H), 0.88 (s, 3H), 0.81 (s, 3H).

^{13}C NMR: (125 MHz, $CDCl_3$)

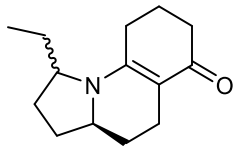
δ 145.1, 135.5, 122.6, 121.5, 51.0, 50.3, 42.4, 39.3, 34.91, 34.87, 33.3, 32.9, 27.6, 24.0, 22.7, 21.9, 21.4, 20.9, 18.9, 13.6.

IR: (film)

ν (cm^{-1}) 2931 (w), 2254 (w), 1711 (m), 1502 (w), 1439 (w), 1363 (w), 1223 (w), 1090 (w), 909 (m), 729 (s), 648 (w), 530 (w).

HRMS: (APCI, *m/z*)

calcd for $C_{20}H_{33}$ $[M+H]^+$ 273.2577, found: 273.2575



(*3aS*)-1-(2-Ethyl)-2,3,3a,4,5,7,8,9,-octahydro-*1H*-pyrrolo[1,2-a]quinolin-6-one (**3.14**)

Following **the general reaction procedure for condition B** from (1S, *3aS*)-1-(2-hydroxyethyl)-2,3,3a,4,5,7,8,9-octahydropyrrolo[1,2-a]quinolin-6(*1H*)-one **3.13** (23.5 mg, 0.1 mmol), **3.14** was obtained as a light yellow oil (20.8 mg, 95%) with diastereomeric ratio (1.1: 1) by purification through flash chromatography on silica gel.

Data for **3.14** (mix of diastereoisomers):

TLC: R_f 0.45 (10:1 EtOAc/MeOH) [I_2/CAM]

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 3.82–3.92 (m, 1H), 3.65–3.74 (m, 1H), 3.38–3.47 (m, 1H), 3.24–3.33 (m, 1H), 2.71–2.80 (m, 1H), 2.62–2.70 (m, 1H), 2.30–2.60 (m, 7H), 2.01–2.22 (m, 7H),1.80–1.99 (m, 6H), 1.44–1.74 (m, 6H),1.18–1.40 (m, 4H), 0.82–0.95 (m, 6H).

^{13}C NMR: (125 MHz, $CDCl_3$)

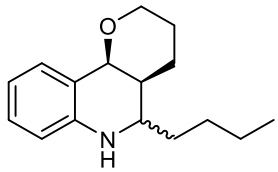
δ 193.3, 192.6, 159.60, 159.56, 106.7, 105.3, 60.4 (2C), 59.4, 58.1, 35.8, 35.4, 30.8, 29.6, 28.57, 28.55, 28.3, 28.10, 28.09, 27.5, 27.3, 27.1, 21.9, 21.8, 21.3, 20.0, 11.1, 9.6.

IR: (neat)

ν (cm^{-1}) 2934 (m), 2876 (m), 1715 (w), 1601 (w), 1526 (s), 1432 (s), 1352 (w), 1320 (m), 1300 (m), 1227 (w), 1184 (s), 1141 (w), 1124 (w), 1088 (w), 1043 (w), 957 (w), 854 (w), 726 (w), 678 (m), 567 (w), 504 (w).

HRMS: (ESI, *m/z*)

calcd for $C_{14}H_{22}NO$ $[M+H]^+$ 220.1696, found: 220.1695



5-butyl-3,4,3.1a,5,6,3.15b-hexahydro-*2H*-pyrano[3,2-c]quinoline (**3.16a**)

Following **the general reaction procedure for condition B** from tetrahydroquinoline alcohol **3.15a** (52.2 mg, 0.2 mmol), **3.16a** was obtained as a mixture of diastereoisomers (48 mg, 98%, *cis/ trans* = 68: 32) by purification through flash chromatography on silica gel. Further purification on the preparative thin layer chromatography afforded each diastereoisomer.

Data for **3.16a-*cis*** (light yellow oil):

TLC: R_f 0.5 (10:1 hexane/EtOAc) [UV/I_2/CAM]

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.39 (m, 1H), 7.04 (m, 1H), 6.76 (m, 1H), 6.54 (m, 1H), 5.08 (d, *J* = 5.7 Hz, 1H), 3.58–3.64 (m, 1H), 3.44 (ddd, apparent td, *J* = 12.0, 2.1 Hz, 1H), 3.38 (ddd, apparent td, *J* = 7.0, 2.1 Hz, 1H), 2.01–2.11 (m, 1H), 1.32–1.78 (m, 11H), 0.96 (t, *J* = 6.9 Hz, 3H).

^{13}C NMR: (125 MHz, $CDCl_3$)

δ 145.0, 127.9, 127.6, 120.3, 117.8, 113.9, 72.4, 60.7, 54.2, 35.5, 31.8, 28.0, 25.5, 22.7, 17.8, 14.0.

Data for **3.16a-*trans*** (light pinky oil):

TLC: R_f 0.45 (10:1 hexane/EtOAc) [UV/I_2/CAM]

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.22 (m, 1H), 7.07 (m, 1H), 6.69 (m, 1H), 6.55 (m, 1H), 4.47 (d, *J* = 3.2 Hz, 1H), 3.92–3.98 (m, 1H), 3.71 (ddd, apparent td, *J* = 10.4, 3.1 Hz, 1H), 3.57 (ddd, apparent td, *J* = 8.4, 3.6 Hz, 1H), 1.94–2.01 (m, 1H), 1.32–1.86 (m, 11H), 0.96 (t, *J* = 6.9 Hz, 3H).

^{13}C NMR: (125 MHz, $CDCl_3$)

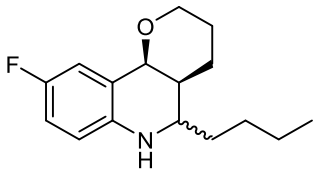
δ 144.5, 130.2, 128.9, 120.5, 117.2, 114.2, 73.8, 67.0, 49.8, 36.4, 32.8, 27.2, 24.2, 22.9, 22.8, 14.1.

IR: (neat)

ν (cm^{-1}) 3372 (w), 2932 (m), 2862 (m), 1713 (w), 1609 (m), 1585 (w), 1485 (s), 1467 (s), 1379 (w), 1351 (w), 1318 (m), 1278 (w), 1220 (w), 1202 (w), 1184 (w), 1154 (w), 1124 (w), 1089 (s), 1070 (s), 1033 (m), 910 (m), 862 (w), 786 (w), 748 (s), 731 (s), 702 (w), 671(w), 540 (w), 498 (w).

HRMS: (ESI, *m/z*)

calcd for $C_{16}H_{24}NO$ $[M+H]^+$ 246.1858, found: 246.1857



5-Butyl-9-fluoro-3,4,3.1a,5,6,3.15b-hexahydro-*2H*-pyrano[3,2-c]quinoline (**3.16b**)

Following **the general reaction procedure for condition B** from tetrahydroquinoline alcohol **3.15b** (55.8 mg, 0.2 mmol), **3.16b** was obtained as a mixture of diastereoisomers (50 mg, 95%, *cis/ trans* = 68: 32) by purification through flash chromatography on silica gel. Further purification on the preparative thin layer chromatography afforded each diastereoisomer.

Data for **3.16b-*cis*** (colorless oil):

TLC: R_f 0.5 (10:1 hexane/EtOAc) [UV/I_2/CAM]

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.11 (m, 1H), 6.77 (m, 1H), 6.76 (m, 1H), 5.02 (d, J = 5.7 Hz, 1H), 3.60–3.65 (m, 1H), 3.40 (ddd, apparent td, J = 11.9, 2.1 Hz, 1H), 3.38 (ddd, apparent td, J = 7.0, 2.1 Hz, 1H), 2.00–2.07 (m, 1H), 1.30–1.78 (m, 11H), 0.96 (t, J = 7.0 Hz, 3H).

^{13}C NMR: (125 MHz, $CDCl_3$)

δ 156.3 (d, $J_{C,F}$ = 235.0 Hz), 141.2, 121.9 (d, $J_{C,F}$ = 5.7 Hz), 114.77 (d, $J_{C,F}$ = 7.3 Hz), 114.76 (d, $J_{C,F}$ = 22.9 Hz), 113.6 (d, $J_{C,F}$ = 22.4 Hz), 72.3, 60.9, 54.3, 35.2, 31.9, 28.0, 25.3, 22.7, 17.8, 14.0.

Data for **3.16b-*trans*** (light yellow oil):

TLC: R_f 0.45 (10:1 hexane/EtOAc) [UV/I_2/CAM]

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 6.96 (m, 1H), 6.81 (m, 1H), 6.49 (m, 1H), 4.45 (d, *J* = 3.4 Hz, 1H), 3.87–3.94 (m, 1H), 3.71 (ddd, apparent td, *J* = 11.3, 3.1 Hz, 1H), 3.50 (ddd, apparent td, *J* = 8.2, 3.8 Hz, 1H), 1.90–1.98 (m, 1H), 1.32–1.86 (m, 11H), 0.96 (t, *J* = 6.9 Hz, 3H).

^{13}C NMR: (125 MHz, $CDCl_3$)

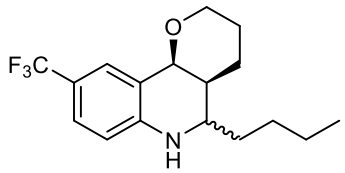
δ 155.6 (d, $J_{C,F}$ = 235.5 Hz), 140.7, 121.3, 115.9 (d, $J_{C,F}$ = 22.8 Hz), 115.8 (d, $J_{C,F}$ = 21.7 Hz), 115.1, 73.1, 66.7, 50.4, 36.2, 32.8, 27.3, 24.1, 22.9, 22.8, 14.1.

IR: (neat)

ν (cm^{-1}) 3372 (w), 2931 (m), 2861 (m), 1620 (w), 1499 (s), 1467 (s), 1377 (w), 1304 (w), 1251 (m), 1215 (w), 1186 (w), 1144 (w), 1087 (m), 1061 (m), 942 (w), 907 (m), 868 (m), 806 (s), 787 (m), 733 (w), 666 (w), 618 (w), 571 (w), 532 (w), 480(w), 452 (w), 431 (w).

HRMS: (ESI, *m/z*)

calcd for $C_{16}H_{23}FNO$ $[M+H]^+$ 264.1764, found: 264.1767



5-Butyl-9-trifluoromethyl-3,4,3.1a,5,6,3.15b-hexahydro-*2H*-pyrano[3,2-c]quinolone (**3.16c**)

Following **the general reaction procedure for condition B** from tetrahydroquinoline alcohol **3.15c** (32.9 mg, 0.1 mmol)**, 3.16c** was obtained as a mixture of diastereoisomers (27.5 mg, 88%, *cis/ trans* = 63: 37) by purification through flash chromatography on silica gel. Further purification on the preparative thin layer chromatography afforded each diastereoisomer.

Data for **3.16c-*cis*** (colorless oil):

TLC: R_f 0.45 (10:1 hexane/EtOAc) [UV/I_2/CAM]

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.11 (m, 1H), 6.77 (m, 1H), 6.76 (m, 1H), 5.02 (d, J = 5.7 Hz, 1H), 3.60–3.65 (m, 1H), 3.40 (ddd, apparent td, J = 11.9, 2.1 Hz, 1H), 3.38 (ddd, apparent td, J = 7.0, 2.1 Hz, 1H), 2.00–2.07 (m, 1H), 1.64–1.78 (m, 2H), 1.30–1.58 (m, 9H), 0.96 (t, J = 7.0 Hz, 3H).

^{13}C NMR: (125 MHz, $CDCl_3$)

δ 147.6, 126.1, 125.1 (quintet, $J_{C,F}$ = 4.2 Hz), 123.9, 119.5, 119.2 (q, $J_{C,F}$ = 32.4 Hz), 113.0, 71.9, 60.7, 53.9, 34.9, 31.6, 27.9, 25.3, 22.7, 17.8, 14.0.

Data for **3.16c-*trans*** (light yellow oil):

TLC: R_f 0.4 (10:1 hexane/EtOAc) [UV/I_2/CAM]

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 6.96 (m, 1H), 6.81 (m, 1H), 6.49 (m, 1H), 4.45 (d, J = 3.4 Hz, 1H), 3.87–3.94 (m, 1H), 3.71 (ddd, apparent td, J = 11.3, 3.1 Hz, 1H), 3.50 (ddd, apparent td, J = 8.2, 3.8 Hz, 1H), 1.90–1.98 (m, 1H), 1.32–1.86 (m, 11H), 0.96 (t, J = 6.9 Hz, 3H).

^{13}C NMR: (125 MHz, $CDCl_3$)

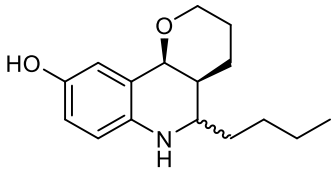
δ 147.0, 127.5 (d, $J_{C,F}$ = 3.9 Hz), 126.0 (q, $J_{C,F}$ = 3.7 Hz), 125.1, 123.8, 119.5, 113.6, 73.1, 66.8, 50.0, 35.8, 32.8, 27.1, 24.1, 22.80, 22.76, 14.0.

IR: (neat)

ν (cm^{-1}) 3358 (w), 2930 (m), 2863 (m), 1734 (w), 1619 (m), 1523 (w), 1464 (w), 1381 (w), 1320 (s), 1303 (m), 1256 (m), 1217 (m), 1160 (s), 1137 (m), 1102 (s), 1085 (s), 1066 (s), 961 (w), 940 (m), 912 (w), 896 (w), 861 (w), 818 (m), 752 (w), 710 (w), 688 (w), 634 (m), 616 (m), 539 (m), 496 (m).

HRMS: (ESI, *m/z*)

calcd for $C_{17}H_{21}F_3NO$ $[M-H]^+$ 312.1570, found: 312.1565



5-Butyl-9-hydroxyl-3,4,3.1a,5,6,3.15b-hexahydro-*2H*-pyrano[3,2-c]quinolone (**3.16d**)

Following **the general reaction procedure for condition B** from tetrahydroquinoline alcohol **3.15d** (22.7 mg, 0.1 mmol), **3.16d** was obtained as a mixture of diastereoisomers (22.2 mg, 85%, *cis/ trans* = 74: 26) by purification through flash chromatography on silica gel. Further purification on the preparative thin layer chromatography afforded each diastereoisomer.

Data for **3.16d-*cis*** (colorless oil):

TLC: R_f 0.5 (2 :1 hexane/EtOAc) [UV/I_2/CAM]

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 6.96–7.00 (m, 1H), 6.60–6.66 (m, 1H), 6.45–6.50 (m, 1H), 5.06 (d, *J* = 5.7 Hz, 1H), 3.59–3.66 (m, 1H), 3.45 (ddd, apparent td, *J* = 12.0, 2.0 Hz, 1H), 3.30 (ddd, apparent td, *J* = 7.0, 1.9 Hz, 1H), 2.01–2.08 (m, 1H), 1.64–1.75 (m, 2H), 1.20–1.58 (m, 9H), 0.95 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR: (125 MHz, $CDCl_3$)

δ 148.6, 138.6, 121.9, 115.7, 115.5, 113.7, 72.6, 61.0, 54.6, 35.6, 31.9, 28.0, 25.4, 22.7, 17.8, 14.0.

Data for **3.16d-*trans*** (light yellow oil):

TLC: R_f 0.45 (2 :1 hexane/EtOAc) [UV/I_2/CAM]

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 6.72–6.76 (m, 1H), 6.59–6.65 (m, 1H), 6.47–6.56 (m, 1H), 4.45 (d, *J* = 3.4 Hz, 1H), 3.87–3.94 (m, 1H), 3.71 (ddd, apparent td, *J* = 10.3, 2.9 Hz, 1H), 3.51 (ddd, apparent td, *J* = 8.1, 3.5 Hz, 1H), 1.94–2.01 (m, 1H), 1.33–1.88 (m, 11H), 0.96 (t, *J* = 6.9 Hz, 3H).

^{13}C NMR: (125 MHz, $CDCl_3$)

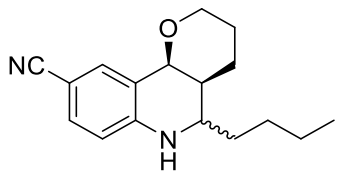
δ 147.7, 138.7, 121.8, 116.9, 116.4, 115.7, 73.5, 66.8, 50.8, 36.7, 33.0, 27.4, 24.3, 23.1, 22.9, 14.0.

IR: (neat)

ν (cm^{-1}) 3357 (br.), 2933 (m), 2862 (m), 2403 (w), 2384 (w), 2351 (w), 2328 (w), 2251 (w), 1708 (m), 1616 (w), 1500 (s), 1467 (m), 1439 (m), 1380 (m), 1335 (m), 1279 (m), 1226 (m), 1185 (w), 1173 (w), 1087 (m), 1064 (m), 1038 (m), 909 (m), 877 (w), 811 (m), 729 (s), 647 (m), 618 (w), 531 (m), 441 (m).

HRMS: (ESI, *m/z*)

calcd for $C_{16}H_{24}NO_2$ $[M+H]^+$ 262.1802, found: 262.1798



5-Butyl-9-cyano-3,4,3.1a,5,6,3.15b-hexahydro-*2H*-pyrano[3,2-c]quinolone (**3.16e**)

Following **the general reaction procedure for condition B** from tetrahydroquinoline alcohol **3.15e** (28.6 mg, 0.1 mmol), **3.16e** was obtained as a mixture of diastereoisomers (13.8 mg, 51%, *cis/ trans* = 34: 66) by purification through flash chromatography on silica gel. Further purification on the preparative thin layer chromatography afforded each diastereoisomer.

Data for **3.16e-*cis*** (light yellow oil):

TLC: R_f 0.5 (5:1 hexane/EtOAc) [UV/I_2/CAM]

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.63 –7.66 (m, 1H), 7.28–7.31 (m, 1H), 6.43–6.47 (m, 1H), 5.00 (d, *J* = 5.6 Hz, 1H), 3.62–3.68 (m, 1H), 3.45 (ddd, apparent td, *J* = 7.1, 2.5 Hz, 1H), 3.37 (ddd, apparent td, *J* = 12.0, 2.1 Hz, 1H), 2.03–2.12 (m, 1H), 1.20–1.80 (m, 11H), 0.97 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR: (125 MHz, $CDCl_3$)

δ 148.4, 132.2, 132.1, 120.6, 120.0, 113.3, 99.2, 71.5, 60.7, 53.8, 34.6, 31.4, 27.8, 25.3, 22.6, 17.8, 13.9.

Data for **3.16e-*trans*** (light reddish oil):

TLC: R_f 0.45 (5:1 hexane/EtOAc) [UV/I_2/CAM]

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.49–7.51 (m, 1H), 7.28–7.31 (m, 1H), 6.47–6.51 (m, 1H), 4.46 (d, *J* = 3.1 Hz, 1H), 3.85–3.92 (m, 1H), 3.70 (ddd, apparent td, *J* = 11.7, 3.0 Hz, 1H), 3.58 (ddd, apparent td, *J* = 8.1, 3.8 Hz, 1H), 1.58–1.92 (m, 6H), 1.47–1.57 (m, 2H), 1.32–1.46 (m, 4H), 0.96 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR: (125 MHz, $CDCl_3$)

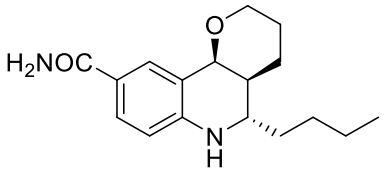
δ 147.9, 134.6, 132.8, 120.4, 119.9, 113.8, 98.3, 72.5, 66.7, 50.2, 35.4, 32.9, 27.1, 24.0, 22.7 (2C), 14.0.

IR: (neat)

ν (cm^{-1}) 3359 (m), 2931 (m), 2860 (m), 2212 (s), 1716 (w), 1610 (s), 1516 (s), 1466 (m), 1378 (w), 1325 (m), 1310 (m), 1278 (w), 1258 (w), 1211 (m), 1188 (w), 1160 (w), 1137 (m), 1087 (m), 1060 (m), 1005 (w), 912 (m), 890 (m), 819 (s), 771 (w), 730 (s), 585 (m), 474 (m).

HRMS: (APCI, *m/z*)

calcd for $C_{17}H_{23}N_2O$ $[M+H]^+$ 271.1805, found: 271.1803



5-Butyl-9-carboxamide-3,4,3.1a,5,6,3.15b-hexahydro-*2H*-pyrano[3,2-c]quinolone (**3.16e'**)

Following **the general reaction procedure for condition B** from tetrahydroquinoline alcohol **3.15e** (28.6 mg, 0.1 mmol), **3.16e'** was obtained as a single *trans* diastereoisomer, and appeared as light yellow oil (9 mg, 32%) by purification through flash chromatography on silica gel.

Data for 3.16e'-*trans*:

TLC: R_f 0.35 (EtOAc) [UV/I_2/CAM]

^{1}H NMR: (500 M Hz, $CDCl_3$)

δ 7.68–7.71 (m, 1H), 7.58–7.62 (m, 1H), 6.51–6.55 (m, 1H), 5.91 (s, br, 2H), 4.49 (d, *J* = 3.1 Hz, 1H), 3.89–3.95 (m, 1H), 3.71 (ddd, *J* = 9.4, 2.8 Hz, 1H), 3.60 (ddd, apparent td, *J* = 8.2, 3.7 Hz, 1H), 1.88–1.96 (m, 1H), 1.32–1.86 (m, 11H), 0.96 (t, *J* = 6.9 Hz, 3H).

^{13}C NMR: (125 MHz, $CDCl_3$)

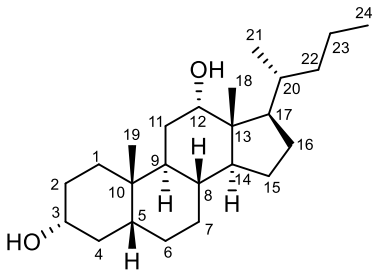
δ 169.4, 147.8, 130.0, 129.1, 120.7, 119.2, 113.6, 73.3, 66.9, 50.0, 35.8, 32.8, 27.1, 24.0, 22.8, 22.7, 14.0.

IR: (neat)

ν (cm^{-1}) 3342 (br.), 3267 (br.), 2931 (m), 2860 (m), 2351 (w), 2212 (w), 1708 (m), 1651 (s), 1611 (s), 1575 (m), 1520 (m), 1466 (w), 1435 (w), 1371 (s), 1328 (m), 1308 (m), 1273 (m), 1222 (m), 1123 (w), 1086 (m), 1060 (m), 1004 (w), 948 (w), 895 (m), 829 (m), 770 (m), 733 (m), 672 (w), 662 (w), 600 (m), 530 (w).

HRMS: (ESI, *m/z*)

calcd for $C_{17}H_{25}N_2O_2$ $[M+H]^+$ 289.1911, found: 289.1907



5β-Cholane-3α,12α-diol (**3.19**)

Following **the general reaction procedure for condition B** from deoxycholic alcohol **3.18** (37.8 mg, 0.1 mmol), **3.19** was obtained as a white solid (34.4 mg, 95%) by purification through flash chromatography on silica gel.

Data for **3.19**:

TLC: R_f 0.35 (1:1 hexane/EtOAc) [I_2/ CAM]

m.p.: 167.59–169.19 °C (MeOH)

^{1}H NMR: (500 M Hz, $CDCl_3$)

δ 4.01 (dd, apparent t, *J* = 2.8 Hz, 1H), 3.62 (dddd, apparent sep, *J* = 5.2 Hz, 1H), 1.96 (s, br, 2H), 0.99–1.91 (m, 26H), 0.97 (d, *J* = 6.6 Hz, 3H), 0.92 (s, 3H), 0.88 (t, *J* = 7.1 Hz, 3H), 0.70 (s, 3H).

^{13}C NMR: (125 MHz, $CDCl_3$)

δ 73.3, 71.8, 48.3, 47.8, 46.5, 42.1, 38.2, 36.4, 36.0, 35.3, 35.2, 34.1, 33.6, 30.5, 28.4, 27.6, 27.1, 26.1, 23.7, 23.1, 19.3, 17.6, 14.5, 12.6.

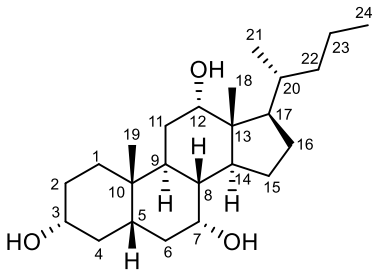
IR: (neat)

ν (cm^{-1}) 3369 (br.), 2931 (s), 2866 (s), 1657 (w), 1449 (m), 1377 (m), 1308 (w), 1255 (w), 1115 (w), 1090 (m), 1041 (s), 1014 (m), 968 (w), 944 (w), 915 (w), 853 (w), 797 (w), 735 (w), 683 (w), 609 (w), 454 (w).

HRMS: (ESI, *m/z*)

calcd for $C_{24}H_{42}O_2$ $[M+Cl]^-$ 397.2879, found: 397.2887

calcd for $C_{25}H_{43}O_4$ $[M+HCOO]^-$ 407.3167, found: 407.3173



3α, 7α, 12α-Trihydroxycholane (**3.21**)

Following **the general reaction procedure for condition B** from cholic alcohol **3.20** (78.8 mg, 0.2 mmol), **3.21** was obtained as a white solid (74 mg, 98%) by purification through flash chromatography on silica gel.

Data for **3.21**:

TLC: R_f 0.4 (9:1 CH_2Cl_2/MeOH) [I_2/CAM]

m.p.: 186.55–187.74 °C (MeOH/H_2O)

^{1}H NMR: (500 M Hz, MeOD)

δ 3.96 (dd, apparent s, 1H), 3.79 (ddd, apparent d, J = 2.8 Hz, 1H), 3.37 (dddd, apparent sep, J = 5.3 Hz, 1H), 2.20–2.32 (m, 2H), 1.03–2.03 (m, 22H), 1.00 (d, J = 6.6 Hz, 3H), 0.92 (s, 3H), 0.88 (t, J = 7.1 Hz, 3H), 0.71 (s, 3H).

^{13}C NMR: (125 MHz, MeOD)

δ 74.3, 73.0, 69.2, 48.5, 47.6, 43.4, 43.1, 41.2, 40.6, 39.8, 37.2, 36.6, 36.1, 36.0, 31.3, 29.7, 29.0, 28.0, 24.4, 23.3, 20.6, 18.2, 15.0, 13.1.

IR: (neat)

ν (cm^{-1}) 3369 (br.), 2940 (s), 2866 (s), 2488 (br.), 1649 (w), 1446 (m), 1377 (m), 1292 (w), 1214 (w), 1117 (w), 1080 (m), 1046 (w), 1003 (w), 973 (s), 914 (w), 857 (w), 734 (w), 670 (w), 666 (w), 642 (w), 611 (m), 558 (w), 498 (w).

HRMS: (ESI, *m/z*)

calcd for $C_{24}H_{42}O_3Na$ $[M+Na]^+$ 401.3032, found: 401.3036

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Chapter 4 : Aldehydes as Alkyl Carbanion Equivalents for Additions to Carbonyl Compounds

4.1 Preface

This chapter describes the development of a ruthenium-catalyzed synthetic method utilizing carbonyl compounds, mainly aldehydes, as alkyl carbanion equivalents for new carbon-carbon bond formation via carbonyl addition reactions. This discovery is heavily rooted in the ruthenium-based deoxygenation chemistry (Chapter 3). Dr. Haining Wang (Postdoctoral Fellow 2014-2017 in the Li lab) first observed the alcohol product. All experimental studies in the current project were jointly performed between Dr. Haining Wang and me. My additional contribution to this work included conceiving a mechanistic picture of this chemistry and leading the preparation of the manuscript. The computation study was mainly carried out by Dr. Haining Wang. Zoë Hearne proofread the manuscript. Pierre Querard and Zheng Huang (the Lumb lab) donated compound **4.9b** and chiral (*S*,*S*)-DPEN ligand, respectively. This work was published in *Nature Chemistry* **2016**, *9*, 374-378.

4.2 Introduction

Last four decades have witnessed the development of synthetic methods for the polarity reversal, or formally known as umpolung in German, of the natural reactivity of functional groups, which proves to be a significant conceptual breakthrough in organic chemistry.[1] This concept, in spite of the early recognition,[2] owes much of its active research later to Corey and Seebach in the mid 1960s.[3]

There are mainly three classes of nucleophilic acylating reagents that were put forth by Seebach,[4] including unprotected acyl or acyl-analogous equivalents **A**, vinyl ether-type protected acyl anions

B and acetal-type protected anions **C** (Figure 4-1). In addition, aldehyde hydrazones **D** are considered as latent nucleophilic acylating reagents. The earliest example in this category is

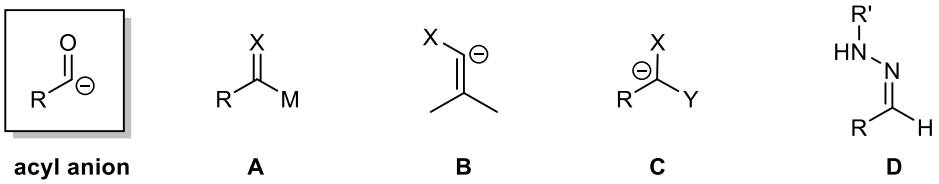
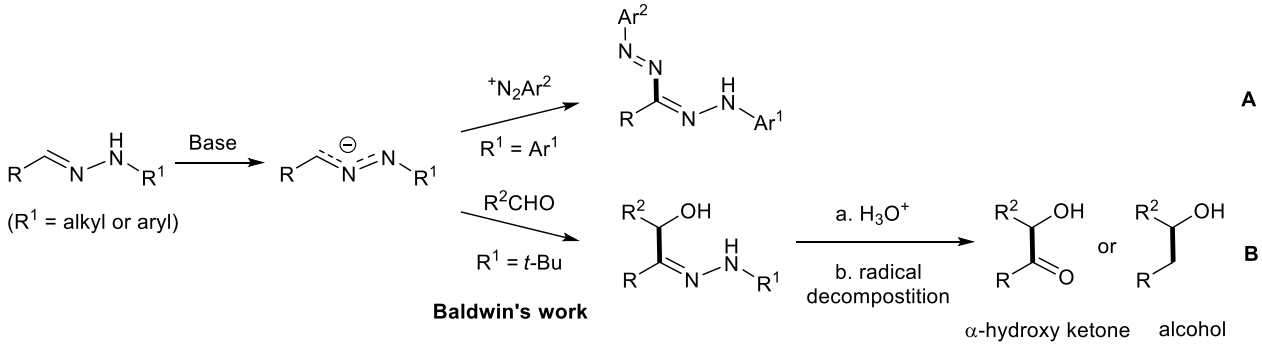


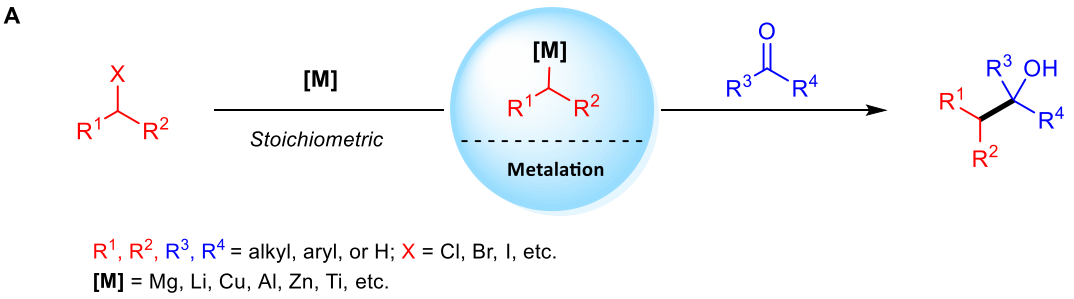
Figure 4-1 Four Classes of Acyl Anion Equivalents

aldehyde monophenylhydrazones. They can react with strong electrophiles when deprotonated, using either the terminus nitrogen or the azomethine carbon. For example, their reactions with diazonium ions lead to the formation of formazanes (Scheme 4-1-A).[5] Baldwin *et al.* expanded the reaction scope by replacing the phenyl residue of mono-substituted hydrazones with more sterically encumbered substituents (e.g. *tert*-butyl, trityl, diphenyl-4-pyridylmethyl) (Scheme 4-1-B).[6] This change in sterics makes it possible for the formation of new carbon-carbon bonds between sterically bulky aldehyde hydrazones and relatively weak electrophiles (i.e. when compared to diazonium ions) such as alkyl halides, aldehydes and ketones. Upon hydrolysis of the hydrazone, the parent carbonyl group gets recovered to yield the corresponding α-hydroxy ketone. In the case of carbonyl addition reactions, however, the lithium salts of these hydrazones had to be pre-formed, with subsequent C–C bond formation and removal of bulky substituents on azo-intermediates via radical decomposition.[6e,6f]



Scheme 4-1 Mono-substituted Aldehyde Hydrazones as Anions for Chemical Bond Formation

Nucleophilic addition of organometallic reagents to carbonyl compounds, to form new carbon–carbon bonds, is a fundamental process in contemporary organic synthesis.[7] This simple alkylation process, complementary to the reduction of carbonyl compounds, provides a reliable method for generating a wide array of alcohol products. These alcohols are frequently encountered as key building blocks in the synthesis of complex pharmaceutical drugs and biologically active molecules. The discovery of Grignard reagents as carbanion equivalents,[8] and their subsequent additions to carbonyl compounds, marked a milestone in synthetic chemistry, enabling facile access to a diverse range of alcohols using preformed organomagnesium reagents with high generality, reactivity, and easy manipulation.[9] Since then, other organometallic reagents,[10] such



R^1, R^2, R^3, R^4 = alkyl, aryl, or H; X = Cl, Br, I, etc.
[M] = Mg, Li, Cu, Al, Zn, Ti, etc.

R^1, R^2, R^3, R^4 = alkyl, aryl, or H;
[M] = Ir, Rh, Ru, Cu, Ni, etc.

R^1, R^2, R^3, R^4 = alkyl, aryl, or H;
[M] = Ru

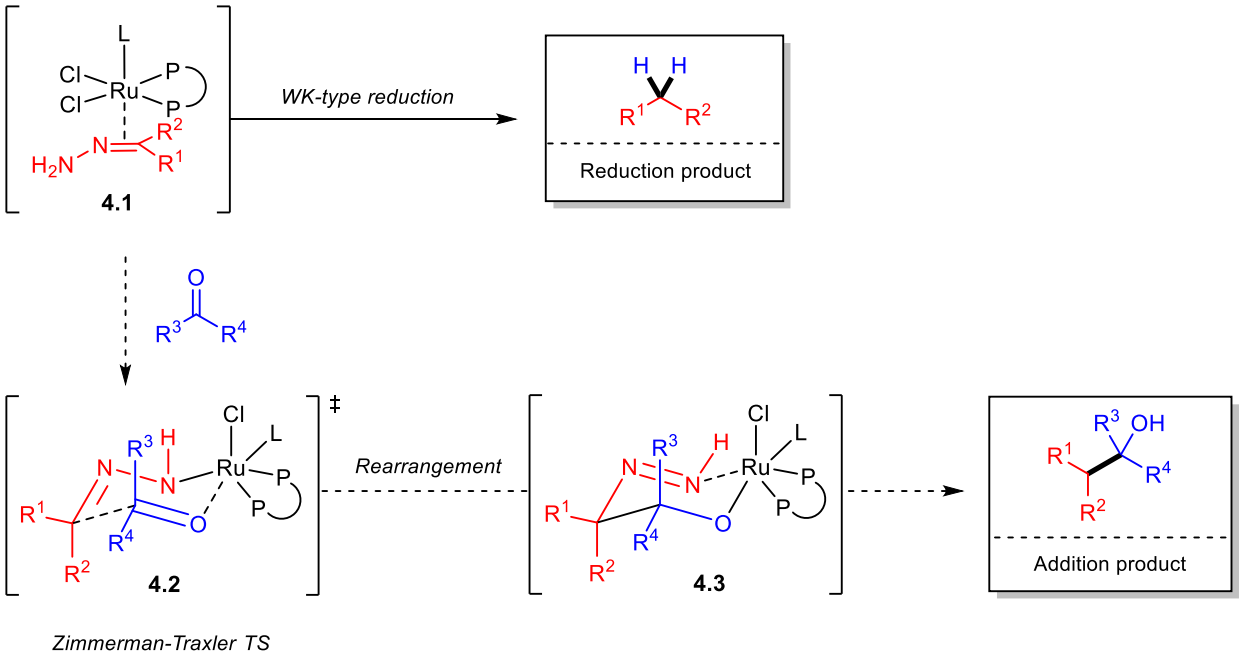
Scheme 4-2 Synthetic Strategies to Access Secondary and Tertiary Alcohols by Carbonyl Addition Reactions

as those based on zinc,[11] aluminum,[12] copper,[13] and titanium,[14] have been sought and utilized to achieve better selectivity. However, preparation of these robust organometallic reagents requires stoichiometric quantities of metal (Scheme 4-2-A). Despite considerable advances, and the abundance of organometallic reagents developed for additions to carbonyl compounds, three key challenges have endured. Firstly, the dependence on stoichiometric, pre-formed organometallic reagents in carbonyl addition reactions produces copious metal waste. This is particularly problematic for large-scale synthesis, as it complicates synthetic operations and raises environmental concerns. In addition, petroleum-derived chemical feedstocks (i.e. organic halides) are typically used to prepare organometallic reagents. Their paucity in nature constrains the types of nucleophiles accessible to perform carbonyl addition reactions without prior functionalization.[15] Furthermore, the high nucleophilicity and basicity of most organometallic reagents generally result in poor selectivity, making these reagents inferior candidates in late-stage chemical transformations where highly functionalized molecules are present.

To address these challenges, much effort has been devoted to developing catalytic and asymmetric methods to produce enantioenriched alcohols, whereby π-unsaturated hydrocarbons (alkenes or alkynes) act as carbanion precursors (Scheme 4-2-B). Krische and co-workers have pioneered stereoselective coupling reactions between diverse π-unsaturated reactants and aldehydes under hydrogenative conditions catalyzed by late transition metals.[16] Hoveyda and colleagues have successfully developed copper-catalyzed borylative enantioselective additions to carbonyl compounds using olefin-derived nucleophiles.[17] Montgomery, Jamison and co-workers have designed nickel-based catalysts for stereoselective aldehyde additions, in which alkynes are employed as carbanion equivalents.[18] To synthesize more sterically encumbered tertiary alcohols, Buchwald, Liu and colleagues have devised enantioenriched alkyl copper intermediates, synthesized from olefins, for additions to ketones.[19] The catalytic generation of carbanion equivalents from either alkenes or alkynes, elegantly exemplified in these reports, has successfully addressed some of the long-standing challenges facing organometallic reagents. Nevertheless, as

chemical industry shifts from using petrochemicals to renewable feedstocks, the synthetic community is increasingly giving attention to more sustainable and efficient chemical syntheses.[20]

In this context, development of carbanion equivalents that originate from naturally occurring chemical feedstocks, require only a catalytic quantity of metal, have improved compatibility towards benign protic solvents and various functional groups, and generate innocuous byproducts would be desirable for additions to carbonyl compounds. We herein report such alkyl carbanion equivalents, derived from the naturally prevalent carbonyls with umpolung reactivity,[21] for carbonyl addition reactions (Scheme 4-2-C). Very recently, we have pioneered a ruthenium-catalyzed redox system for direct primary alcohol deoxygenation.[22] This practical deoxygenation chemistry evolved from our initial iridium-based system,[23] and proved to be highly chemo- and regioselective in complex molecules such as alkaloids and steroids. The proposed mechanism



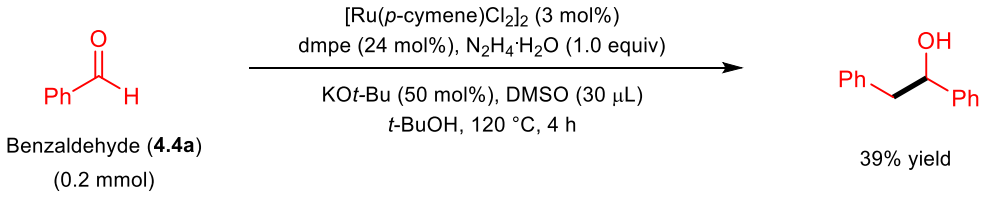
Scheme 4-3 A Hypothesis Based on Our Previous Deoxygenation Chemistry

involves the *in-situ* generation of a ruthenium-coordinated hydrazone intermediate **4.1**, followed by a ruthenium-assisted Wolff-Kishner (WK) reduction under relatively low-temperature conditions (Scheme 4-3). Intriguingly, when benzylic alcohols were subjected to the same catalytic reaction conditions, a trace amount of reductive C–C coupling product — the carbonyl addition

product — was observed. On the basis of this serendipitous discovery, we hypothesized that the coordinately unsaturated ruthenium complex in **4.1** might rapidly metallate another carbonyl compound, and subsequently rearrange to give intermediate **4.3**, via Zimmerman-Traxler chair-like transition state **4.2**.[24] As a consequence, formation of the reductive C–C coupling product might be kinetically favored over the WK-type reduction product upon N_2 extrusion (Scheme 4-3). Aligned with this hypothesis, we further considered whether naturally occurring carbonyl compounds, via umpolung chemistry, could serve as sustainable alkyl carbanion equivalents in carbonyl addition reactions.

4.3 Results and Discussion

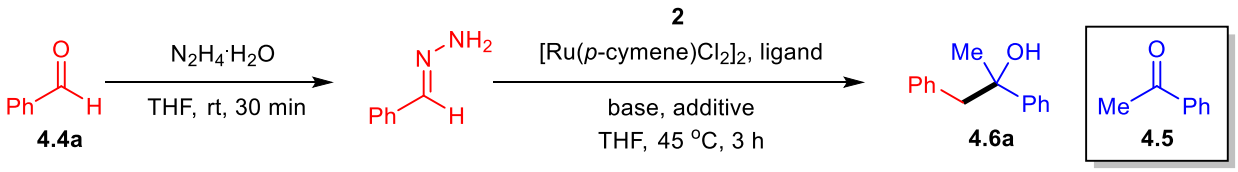
4.3.1 Optimization of Reaction Conditions



Scheme 4-4 Initial Experiment to Verify Our Hypothesis

We commenced our studies by evaluating benzaldehyde **4.4a** in the ruthenium catalytic system developed for our deoxygenation chemistry.[22b] We were delighted to observe the deoxygenated homo-coupling product in 39 % yield at 120 °C after four hours (Scheme 4-4). The cross-coupling scenario was further examined between benzaldehyde **4.4a** (as a nucleophilic carbonyl partner) and acetophenone **4.5** (as an electrophilic carbonyl partner). Subsequent screenings suggested that the reaction was kinetically favored, as it was completed within three hours at temperatures as low as 45 °C. Next, a revised procedure was developed by replacing *in situ* generated hydrazone with preformed hydrazone derived from **4.4a**. This effort turned out to be beneficial to the overall reaction as attenuated yields were seen for both deoxygenated (from **4.4a**) and asymmetric azine byproduct (between hydrazone and **4.5**), providing alcohol product **4.6a** in higher yield. We found

Table 4-1 A Model Study on Nucleophilic Addition of Benzaldehyde to Acetophenone



entry	ligand	base	additive	**4.6a** (%)
1	-	K_3PO_4	CsF	13
2	dppe	K_3PO_4	CsF	78
3	dppp	K_3PO_4	CsF	92
4	dppf	K_3PO_4	CsF	58
5	dmpe	-	CsF	3
6	dmpe	K_2CO_3	CsF	57
7	dmpe	Cs_2CO_3	CsF	51
8	dmpe	*t*-BuOK	CsF	82
9	dmpe	K_3PO_4	CsF	95
10	dmpe	K_3PO_4	-	85

Reaction conditions: **4.4a** (25 µL, 0.24 mmol, 1.2 equiv.), $N_2H_4{\cdot}H_2O$ (13 µL, 0.26 mmol, 1.3 equiv.), THF (0.1 mL), rt, 30 min; **4.5** (23.5 µL, 0.20 mmol, 1.0 equiv.), [Ru(*p*-cymene)Cl_2]$_2$ (0.9 mg, 0.0015 mmol, 0.75 mol%), ligand (0.003 mmol, 1.5 mol%), base (0.05 mmol, 25 mol%), CsF (15 mg, 0.10 mmol, 50 mol%), 45 °C, 3 h, under N_2. Yields were determined by crude ^{1}H NMR using mesitylene as an internal standard.

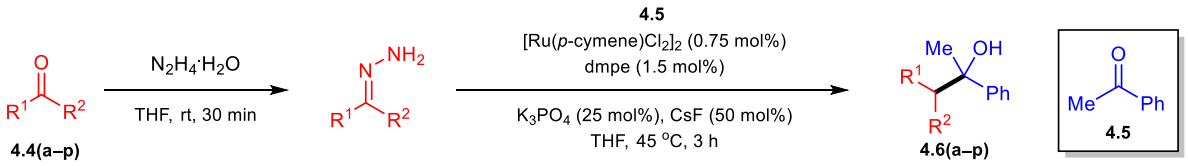
that the success of this reaction depended upon three critical factors: ligand, base and additive (Table 4-1). Among all the catalysts and ligands tested, our previous catalytic system, consisting of [Ru(*p*-cymene)Cl_2]$_2$ and 1,2-bis(dimethylphosphino)ethane (dmpe), showed the highest reactivity (entries 1–4 vs 9).[22b] Base is indispensable for the catalytic cycle. Our attempt without base only produced trace amounts of product (entry 5). Unlike the deoxygenation chemistry, however, strong basicity does not benefit the formation of new carbon-carbon bonds. In most cases, moderate or even weak bases delivered satisfactory yields (entries 6–8), amongst which potassium phosphate (K_3PO_4) proved ideal (entry 9). Equally important is the fact that cesium fluoride (CsF) serves as an efficient additive to enhance catalysis (entry 9 vs 10). A similar

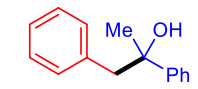
observation was reported earlier in the palladium-catalyzed cross-coupling reactions.[25] It should be noted that this enhancement was only observed when both cesium and fluoride ions were present. Starting from a catalytic amount, we discovered that more CsF generally led to faster reactions, with substoichiometric quantities being optimal.

4.3.2 Scope with Respect to Nucleophilic Carbonyl Partners

With the optimized conditions in hand, we sought to explore the scope of nucleophilic carbonyl partners in this new umpolung chemistry (Table 4-2). In general, both electron-deficient and electron-rich aromatic aldehydes (**4.6a-k**) perform well under the standard reaction conditions, with a variety of functional groups remaining untouched (trifluoromethyls, nitriles, ethers, halogens, amines). Of particular note is the nitrile group, which is known to inhibit the formation of Grignard reagents.[26] Importantly, a high tolerance of various functional groups featured by these nucleophilic carbonyl precursors makes them complementary to the highly functionalized Grignard reagents — a rapidly advancing field over the past decade.[9d, 27] In addition to good functional group compatibility, we have also identified a minor influence on reaction efficiency with respect to differing arene substituent patterns. Compared to *para*- and *meta*-substituted compounds, *o*-chlorobenzaldehyde is the least reactive, likely due to the slightly increased steric hindrance (**4.6e-g**). In addition, we found that elevated temperatures were essential for aromatic ketones to undergo the transformation, albeit with attenuated yield (**4.6l**). We reasoned that this reduced reactivity was more likely caused by a steric, rather than an electronic difference between aromatic aldehyde **4.4a** and ketone **4.4l**. Aliphatic aldehydes can be used as nucleophilic carbonyl partners in our current system, although they showed low reactivity towards formation of alcohols (**4.6m**, **4.6n**). Instead, more elimination and asymmetric azine products were predominant under such circumstances. Aldehydes with heteroaromatic substituents (i.e. furyl, pyridyl) at the α position were also reactive, affording reasonable quantities of alkylation products (**4.6o**, **4.6p**). In particular, the good compatibility shown by 2-pyridyl group in this chemistry is intriguing, as poor reactivity of ruthenium catalyst might have been expected due to its strong chelate effect.

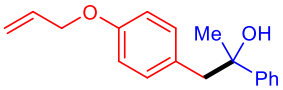
Table 4-2 Scope with Respect to Nucleophilic Carbonyl Partners



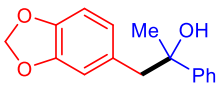


4.6a, 94%

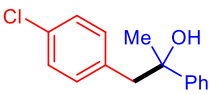
4.6b, 58%



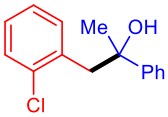
4.6c, 98%



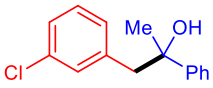
4.6d, 86%



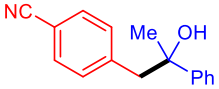
4.6e, 85%



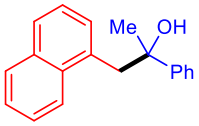
4.6f, 65%



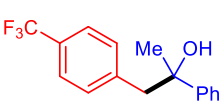
4.6g, 94%



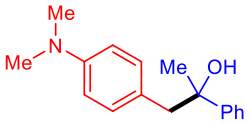
4.6h, 43%



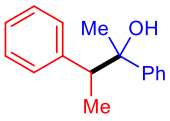
4.6i, 97%



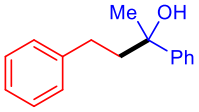
4.6j, 95%



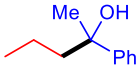
4.6k, 67%



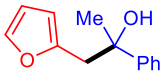
4.6l, 30%[a]



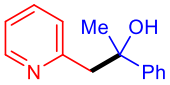
4.6m, 23%[b]



4.6n, 20%[b]



4.6o, 75%



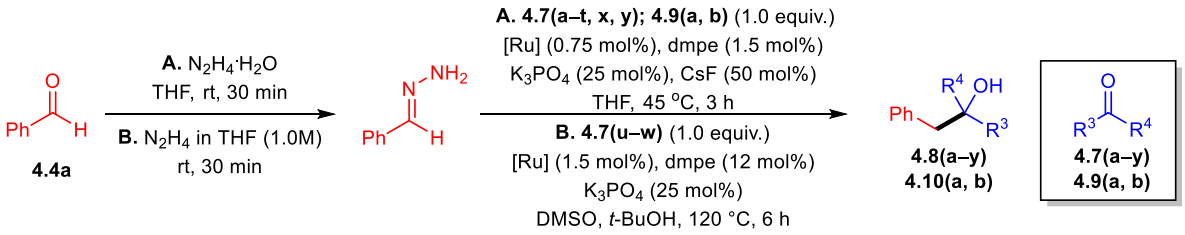
4.6p, 53%

Reaction conditions: **4.4(a-p)** (0.48 mmol), $N_2H_4{\cdot}H_2O$ (0.52 mmol), THF (0.2 mL), rt, 30 min; **4.5** (0.40 mmol), [Ru(*p*-cymene)Cl_2]$_2$ (0.75 mol%), dmpe (1.5 mol%), K_3PO_4 (25 mol%), CsF (50 mol%), 45 °C, 3 h, under N_2. Isolated yields were reported (average of two runs). [a]Reaction was conducted at 80 °C for 20 h. [b]Using KO*t*Bu (25 mol%) instead of K_3PO_4.

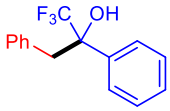
4.3.3 Scope with Respect to Electrophilic Carbonyl Partners

Having studied the scope of nucleophilic carbonyl partners, we turned our attention to electrophilic partners (Table 4-3, aromatic and aliphatic ketones, aromatic and aliphatic aldehydes). The generality of this umpolung chemistry was validated by excellent reactivity seen across a broad

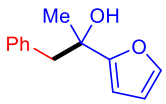
Table 4-3 Scope with Respect to Electrophilic Carbonyl Partners



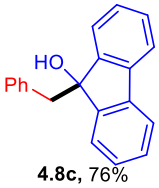
Aromatic & Aliphatic Ketones[a]



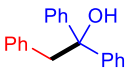
4.8a, 89%



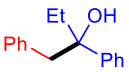
4.8b, 80%



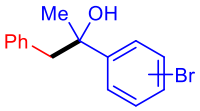
4.8c, 76%



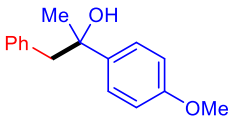
4.8d, 65%



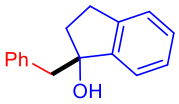
4.8e, 93%



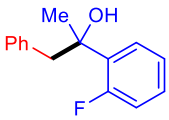
4.8f: 4-Br, 86%
4.8g: 2-Br, 71%



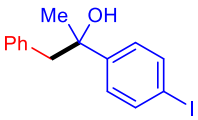
4.8h, 93%



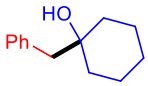
4.8i, 70%



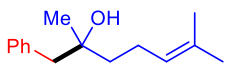
4.8j, 84%



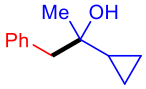
4.8k, 79%



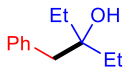
4.8l, 88%



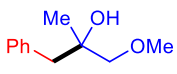
4.8m, 71%



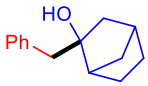
4.8n, 85%



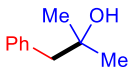
4.8o, 50%



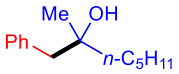
4.8p, 55%



4.8q, 56%

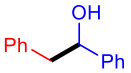


4.8r, 82%

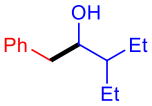


4.8s, 75%

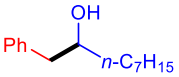
Aromatic & Aliphatic Aldehydes[b]



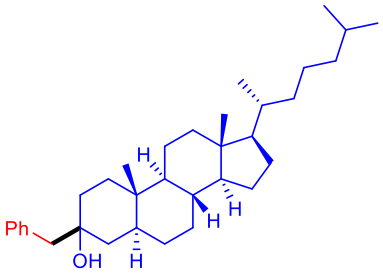
4.8u, 48%



4.8v, 61%

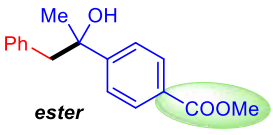


4.8w, 50%

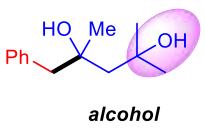


4.8t, 68%

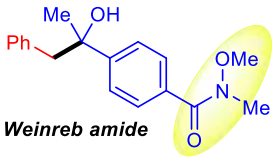
Highlighted Compatible Functional Groups[a]



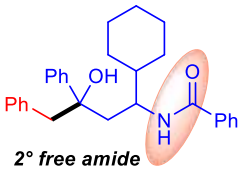
4.8x, 88%



4.8y, 50%



4.10a, 77%



4.10b, 85%

[a]**Reaction condition A** for ketones: **4.4a** (0.48 mmol), $N_2H_4{\cdot}H_2O$ (0.52 mmol), THF (0.2 mL), rt, 30 min; **4.7(a-t, x, y)**; **4.9(a, b)** (0.40 mmol), [Ru(*p*-cymene)Cl_2]$_2$ (0.75 mol%), dmpe (1.5 mol%), K_3PO_4 (25

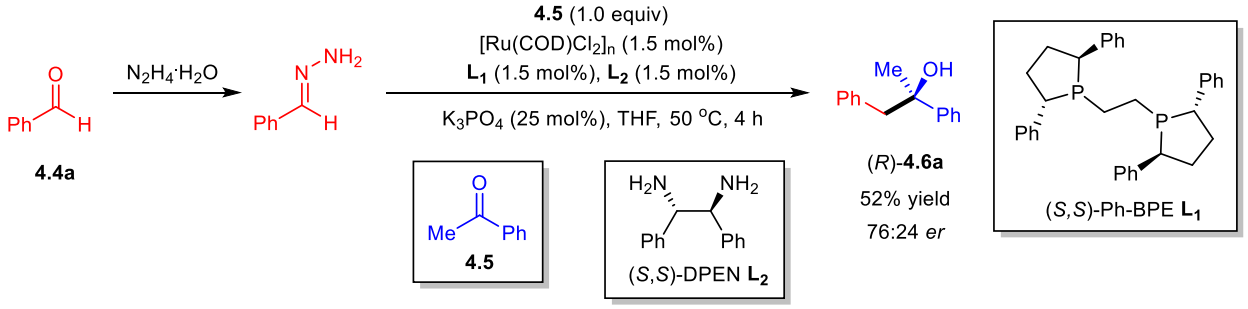
mol%), CsF (50 mol%), 45 °C, 3 h, under N_2. Isolated yields are reported (average of two runs). [b]**Reaction condition B** for aldehydes: **4.4a** (0.24 mmol), anhydrous N_2H_4 in THF (1.0 M, 0.3 mmol), rt, 30 min; **4(u-w)** (0.2 mmol), [Ru(*p*-cymene)Cl_2]$_2$ (1.5 mol%), dmpe (12 mol%), K_3PO_4 (25 mol%) , DMSO (30 μL), *t*-BuOH (100 μL), 120 °C, 6 h, under N_2. Isolated yields are reported (average of two runs).

tolerated under reaction conditions. Specifically, good to excellent yields were obtained for aromatic ketones (**4.8a-k**, **4.8x**, **4.10a**, **4.10b**, 65-93% yield); moderate to excellent yields for aliphatic ketones (**4.8l-t**, **4.8y**, 50-88% yield), and moderate yields for both aromatic and aliphatic aldehydes (**4.8u-w**, 48-61% yield, major byproducts are alkenes). Relatively complex substrates were also accommodated in this transformation, as exemplified by alkylation of an oxo-steroid compound in good yield (**4.8t**, 68% yield). Reduction in reactivity owing to steric bias, previously observed for nucleophilic partners (**4.4a** vs **4.4l**), was similarly observed with electrophilic partners (**4.8o** vs **4.8r**). It is important to note that tetrahydrofuran (THF) is replaced by *tert*-butanol (*t*-BuOH) as reaction solvent when aldehydes are used as electrophilic partners (**4.8u-w**). This result clearly indicates that the carbonyl-derived carbanion equivalent is compatible with alcoholic solvents. In line with this observation, we questioned whether this carbanion equivalent might have better chemoselectivity than traditional organometallic reagents. Indeed, unique chemoselectivity was demonstrated by tolerance to commonly reactive functional groups. Under the standard conditions described, moderate to excellent yields were obtained from aromatic ketones featuring ester, unprotected *tert*-alcohol, Weinreb amide, and unprotected *sec*-amide (**4.8x**, **4.8y**, **4.10a**, **4.10b**, 50-88% yield). Given the distinct chemoselectivity displayed by the carbonyl-derived carbanion equivalents, orthogonal reactivity could be readily achieved through further diversification on residual functional groups (i.e. ester and Weinreb amide). Moreover, survival of the unprotected *sec*-amide implies potential applications of this carbanion equivalent in peptide chemistry.

4.3.4 Enantioselective Approach

To access more synthetically useful enantioenriched alcohols, we decided to probe the asymmetric version of this chemistry. When the chiral ligands (*S*,*S*)-Ph-BPE **L₁** and (*S*,*S*)-DPEN **L₂** were combined with [Ru(COD)Cl_2]$_n$ in our model study, (*R*)-**4.6a** was obtained in 52 % yield with 76:24 *er* (Scheme 4-5). This preliminary result suggested that chiral ligands were involved in the C–C

formation step. As a result, high levels of stereocontrol could be feasible with the appropriate chiral ligand framework. Taken together, our findings show both great chemoselectivity of the current chemistry and potential for stereoselectivity.

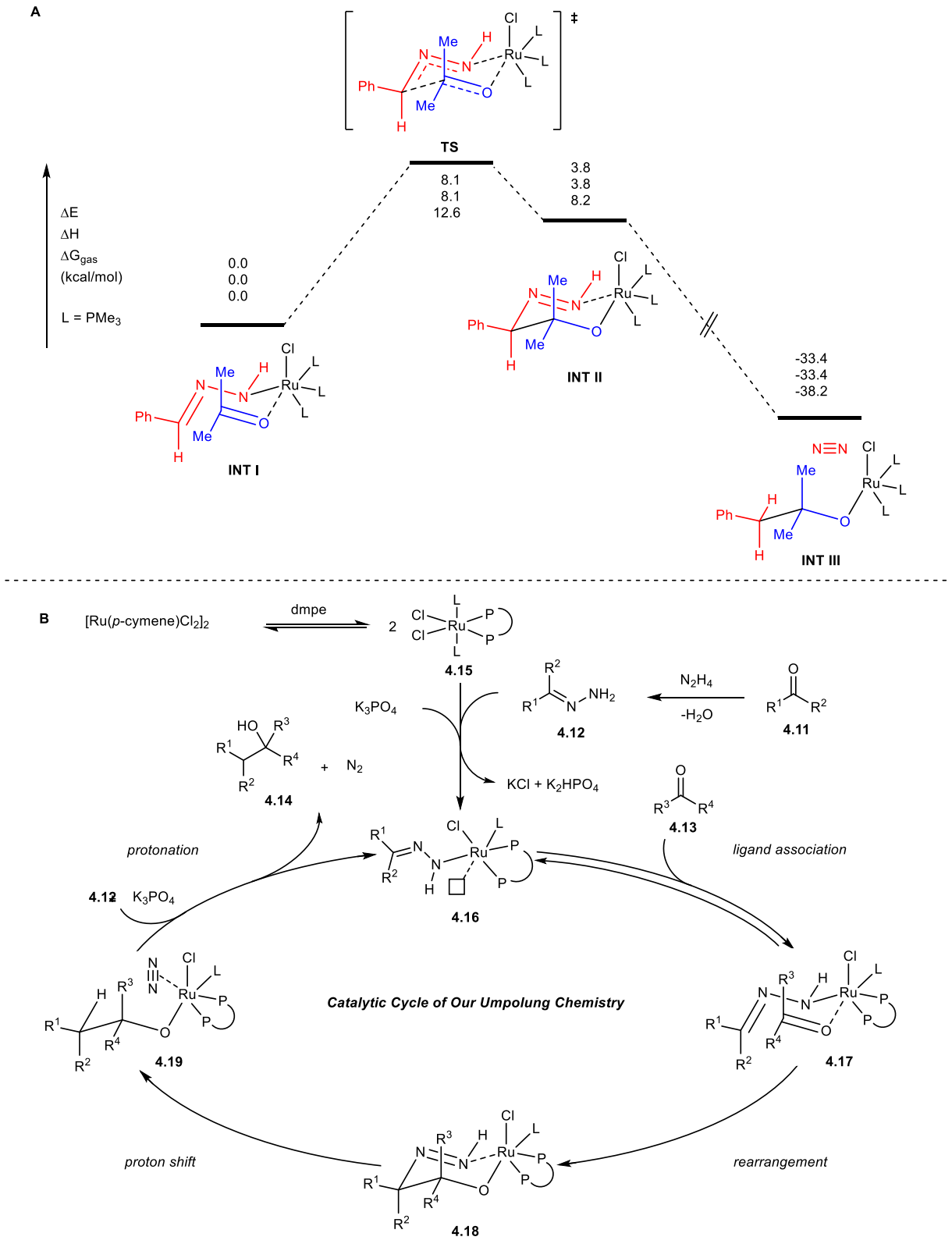


Scheme 4-5 Preliminary Results on the Enantioselective Carbonyl Addition

4.3.5 Preliminary DFT Calculation and Plausible Mechanism

To better understand this new umpolung chemistry, we launched the Density Functional Theory (DFT) calculations to study the fundamental thermodynamics, specifically with regard to the formation of our initially hypothesized six-membered ring intermediate **4.3** (Scheme 4-3). Our DFT model study included the hydrazone derived from benzaldehyde and acetone as substrates. To simplify the overall calculation process, trimethylphosphine (PMe_3), instead of dmpe, was chosen as the ancillary ligand coordinating to the ruthenium metal (Scheme 4-6-A, see section 4.5.5 for details). We calculated the change in Gibbs free energy $\triangle G$ for the intramolecular sigmatropic rearrangement of **INT I** to give **INT II** via **TS**, and the subsequent intramolecular tautomerization to form **INT III** via N_2 exclusion. The calculation data suggests a relatively low energy barrier (12.6 kcal/mol, $\Delta G^{\ddagger}$ value) from **INT I** to **TS**, which is in line with the mild thermal input (45°C, oil bath). In addition, our preliminary DFT calculation indicates a huge thermodynamic sink for the remaining steps, in particular from **INT II** to **INT III** with N_2 release, which explains that the rest of the catalytic cycle is thermodynamically favored.

Guided by our proof-of-concept hypothesis, collectively with all the positive experimental outcomes and preliminary DFT calculation data, we postulated a catalytic cycle for this new umpolung chemistry (Scheme 4-6-B). The bidentate phosphine coordinated complex **4.15** is



Scheme 4-6 Proposed Catalytic Cycle with DFT Calculation Support

initially generated by a ligand dissociation/association between [Ru(*p*-cymene)Cl_2]$_2$ and dmpe, followed by a ligand association with carbonyl-derived hydrazone **4.12** and carbonyl **4.13** in the presence of K_3PO_4, giving rise to complex **4.16** and **4.17** respectively. The formation of **4.17** sets a stage for the intramolecular rearrangement. This concerted rearrangement process yields the key six-membered ring intermediate **4.18** by forming a new carbon-carbon bond between **4.11** and **4.13**.[28] Driven by both the increase in entropy and the decrease in enthalpy, a base-assisted intramolecular proton shift occurs at terminus nitrogen atom of **4.18** with the concomitant N_2 exclusion, providing complex **4.19**. Upon the protonation of **4.19** to generate the desired carbonyl addition product **4.14**, **4.16** is regenerated as the active catalyst with the completion of the entire catalytic cycle.

4.4 Conclusions

In summary, we have described a catalytic, ruthenium-based, umpolung strategy to use aldehydes as alkyl carbanion equivalents for additions to carbonyl compounds. The full potential of this novel chemistry is yet to be revealed, as it is currently limited by accessible nucleophilic carbonyls, safety and toxicity issues concerning hydrazine. Nevertheless, many applications based on the key characteristics of these new carbonyl-derived carbanion equivalents can be envisioned. Highlighted features of this chemistry are: naturally prevalent carbonyls as renewable chemical feedstocks, a catalytic amount of both metal and ligand, benign stoichiometric byproducts, good functional group tolerance with unique chemoselectivity (ester, Weinreb amide, free amide and hydroxyl group), and enantioselective control. We believe that this chemistry is a stepping stone towards carbon–carbon bond-forming processes built upon more sustainable chemical feedstocks. With a deeper understanding of this reaction, new strategies using carbonyl-derived carbanion equivalents for chemical bond formation beyond carbon–carbon bonds will likely emerge.

4.5 Experimental

4.5.1 General Considerations

Reaction Setup: All reactions were carried out in flame-dried V-shaped microwave reaction vials which were covered by aluminum seals with PTFE-faced silicone septa, under an atmosphere of nitrogen unless otherwise stated. All reaction temperatures corresponded to oil bath temperatures. All air and moisture sensitive catalysts, ligands, and reagents were stored and charged in MBRAUN UNIlab Pro Glove Box Workstation unless otherwise stated.

Purifications: All work-up and purification procedures were carried out with reagent-grade solvents. Analytical thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F_{254} pre-coated plates (0.25 mm). Flash column chromatography was performed with E. Merck silica gel P60 (40–63 μm particle size, 230–400 mesh) (SiO_2). Unless otherwise specified, "SiO_2" refers to P60 grade silica gel. Visualization was accomplished with UV light and/or iodine (I_2) or Vanillin solution. Retention factor (R_f) values reported were measured using a 10 × 2 cm TLC plate in a developing chamber containing the solvent system (10 mL) described. Automated flash column chromatography was performed on Biotage Isolera™ Spektra Systems with ACI™.

Solvents: *tert*-butanol (*t*-BuOH) (ACS grade) was distilled over CaH_2 prior to use. Dimethyl sulfoxide (DMSO), tetrahydrofuran (THF), toluene were taken directly from the *Pure Solvent MD-7* purification system (Innovative Technology). Solvents for filtration, transfers, chromatography, and recrystallization were dichloromethane (CH_2Cl_2) (ACS grade, amylene stabilized), ether (Et_2O) (Fisher, BHT stabilized ACS grade), acetone (ACS grade), ethyl acetate (EtOAc) (Fisher, ACS grade), hexane (Fisher, ACS grade), pentane (ACS grade), methanol (ACS grade).

Chemicals: In the model study, benzaldehyde (Aldrich) and acetophenone (Aldrich) were distilled prior to use. Other chemicals that are commercially available, and used without further purification: $[Ru(p\text{-cymene})Cl_2]_2$ (Aldrich), $[Ru(COD)Cl_2]_n$ (Aldrich), dppe (Strem), dmpe (Aldrich & Aspira), dppp (Aldrich), dppf (Aldrich), potassium *tert*-butoxide (Aldrich), potassium phosphate (Aldrich), potassium carbonate (Aldrich), cesium carbonate (Aldrich), cesium fluoride (Aldrich), hydrazine hydrate (Reagent Grade, 64–65% wt, Aldrich), anhydrous hydrazine (THF, 1.0 M, Aldrich), mesitylene (Aldrich), anhydrous sodium sulfate. All liquid carbonyls were distilled and solid ones were recrystallized prior to use. The following carbonyls were prepared according to literature procedures: methyl 4-acetylbenzoate **4.7x**,[29] 4-acetyl-*N*-methoxy-*N*-methylbenzamide **4.9a**,[30] *N*-(1-cyclohexyl-3-oxo-3-henylpropyl)benzamide **4.9b**.[31]

NMR Spectroscopy: Nuclear magnetic resonance (^{1}H and ^{13}C NMR) spectra were recorded on a Bruker AV500 equipped with a 60-position SampleXpress sample changer (^{1}H, 500 MHz; ^{13}C, 125 MHz), a Varian MERCURY plus-500 spectrometer (^{1}H, 500 MHz; ^{13}C, 125 MHz) or Bruker AV400 spectrometer (^{1}H, 400 MHz; ^{13}C, 100 MHz). Chemical shifts for both ^{1}H NMR and ^{13}C NMR spectra are expressed in parts per million (ppm) units downfield from TMS, with the solvent residue peak as the chemical shift standard ($CDCl_3$: δ 7.26 ppm in ^{1}H NMR; δ 77.00 ppm in ^{13}C NMR). Data are reported as following: chemical shift, multiplicity (s = singlet, d = doublet, dd = doublet of doublets, t = triplet, td = triplet of doublets, q = quartet, quin = quintet, sep = septet, m = multiplet, br = broad singlet), coupling constants *J* (Hz), and integration.

Infrared Spectroscopy: Infrared (IR) spectra were collected using a Fourier Transform-Infrared Attenuated Total Reflection Bruker Vertex 80/80v high resolution spectrometer in 400–4000 cm^{-1} as a thin film. IR absorbances are quoted in wavenumbers (cm^{-1}) with the abbreviations: br. (broad), s (strong), m (medium) or w (weak).

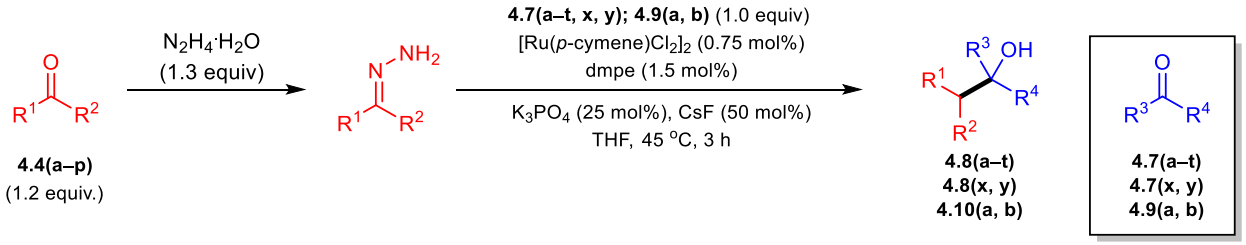
Mass Spectrometry: Mass spectrometry (MS) was performed by the McGill Chemistry Department Mass Spectrometry Facility. High resolution mass spectra were recorded using electrospray ionization (ESI+) and/or atmospheric pressure chemical ionization APCI (+/-), performed either on "Exactive Plus Orbitrap" a ThermoScientific high resolution accurate mass (HR/AM) FT mass spectrometer, or a Bruker Daltonics Maxis Impact quadrupole-time of flight (QTOF) mass spectrometer.

HPLC Analysis: High performance liquid chromatography (HPLC) analyses were performed on a Agilent Technologies 1260 Infinity instrument equipped with a quaternary pump, using Daicel Chiralcel IC Columns (250 mmL × 4.6 mm ϕ). UV absorption was monitored at 215 nm.

Characterization of Alcohol Products: The following alcohol products were newly synthesized by current method: **4.6c**, **4.6d**, **4.6k**, **4.6o**, **4.6p**, **4.8e**, **4.8h**, **4.8j**, **4.8k**, **4.8p**, **4.8t**, **4.8v**, **4.8x**, **4.10a**, **4.10b**. Known compounds were noted with references in the spectroscopic data section.

4.5.2 General Synthetic Procedure

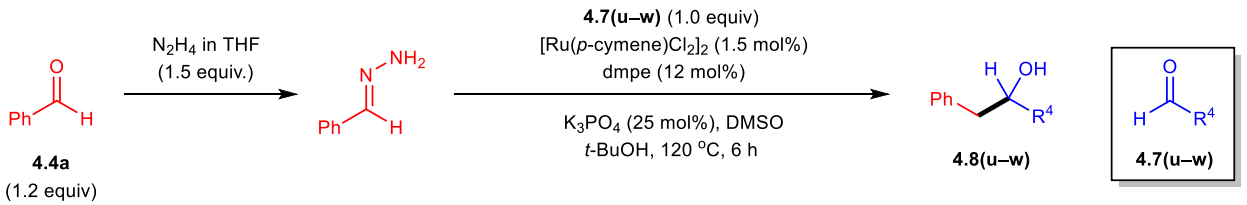
4.5.2.1 General Procedure A (Ketones as Electrophilic Carbonyl Partners)



A flame-dried V-shape microwave reaction vial (10 cm^3) equipped with a magnetic stir bar was charged with [Ru(*p*-cymene)Cl_2]$_2$ (1.8 mg, 0.003 mmol, 0.75 mol%), K_3PO_4 (21.2 mg, 0.1 mmol, 25 mol%). The reaction vial was transferred to the glovebox and charged with dmpe (1.0 μL, 0.006 mmol, 1.5 mol%) and CsF (30 mg, 0.20 mmol, 50 mol%) before being sealed by a rubber septum. The reaction vial was moved out of the glovebox and sequentially charged with ketones **4.7(a-t**, **x**, **y)** (0.4 mmol, 1.0 equiv), **hydrazone solution A** (250 μL). The reaction mixture was heated to 45 ^oC in an oil bath. Upon stirring for 3 hours, the reaction mixture was filtered through a plug of silica gel with EtOAc (2 mL) as eluent, concentrated, and purified by flash chromatography (hexane/ethyl acetate 90:10 as eluent) to give the corresponding alcohols. For certain substrates **4.7(x**, **y)**, prolonged reaction time (6-8 h) was necessary for the full conversion.

Hydrazone solution A: A mixture of carbonyls (0.48 mmol, 1.2 equiv) and hydrazine monohydrate (26 μL, 0.52 mmol, 64–65 wt%, 1.3 equiv) in THF (0.2 mL) solution was stirred for 30 minutes at room temperature. Prior to injection of this hydrazone solution A into the reaction mixture, a small amount of anhydrous Na_2SO_4 was added.

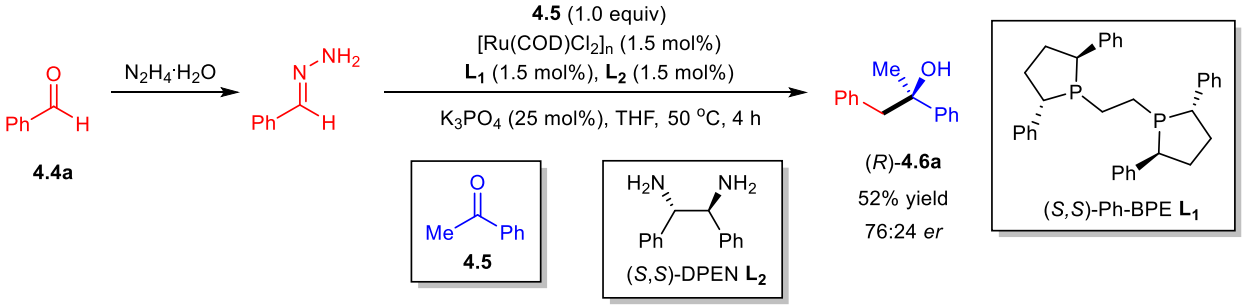
4.5.2.2 General Procedure B (Aldehydes as Electrophilic Carbonyl Partners):



A flame-dried V-shape microwave reaction vial (10 cm^3) equipped with a magnetic stir bar was charged with [Ru(*p*-cymene)Cl_2]$_2$ (1.8 mg, 0.003 mmol, 1.5 mol%), K_3PO_4 (10.6 mg, 0.05 mmol, 5 mol%). The reaction vial was transferred to the glovebox and charged with dmpe (4.0 μL, 0.024 mmol, 12 mol%) before being sealed by a rubber septum. The reaction vial was moved out of the glovebox and sequentially charged with aldehydes **4.7(u-w)** (0.2 mmol, 1.0 equiv), DMSO (30 μL), *t*-BuOH (100 μL), and **hydrazone solution B** (325 μL). With N_2 protection, the rubber septum was replaced by an aluminum seal containing a PTFE-faced silicone septum. The reaction mixture was heated to 120 °C in an oil bath. Upon stirring for 6 hours, the reaction mixture was filtered through a plug of silica gel with EtOAc (2 mL) as eluent, concentrated, and purified by silica gel chromatography (hexane /ethyl acetate 90:10 as eluent) to give the corresponding alcohols.

Hydrazone solution B: A mixture of benzaldehyde (25 μL, 0.24 mmol, 1.2 equiv) and hydrazine solution (1.0 M in THF) (300 μL, 0.30 mmol, 1.5 equiv) was stirred for 30 minutes at room temperature.

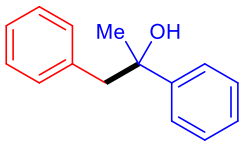
4.5.2.3 General Procedure for the Enantioselective Reaction:



A flame-dried V-shape microwave reaction vial (10 cm^3) equipped with a magnetic stir bar was charged with [$RuCl_2$(COD)]n (0.8 mg, 0.003 mmol, 1.5 mol%), (*S*,*S*)-Ph-BPE (1.5 mg, 0.003 mmol, 1.5 mol%), (*S*,*S*)-DPEN (0.7 mg, 0.003 mmol, 1.5 mol%), and K_3PO_4 (10.6 mg, 0.05 mmol, 25 mol%). The reaction vial was sequentially charged with acetophenone **4.5** (23.5 µL, 0.20 mmol, 1.0 equiv) and **hydrazone solution A** (140 µL) under N_2 atmosphere. The reaction mixture was heated to 50 ^oC in an oil bath. Upon stirring for 4 hours, the reaction mixture was filtered through a plug of silica gel with dichloromethane (2 mL) as eluent, concentrated, and purified by flash chromatography (hexane/ethyl acetate 90:10 as eluent) to give the corresponding alcohol **4.6a** as a colorless oil (22.0 mg, 52% yield, 76:24 *er*), $[\alpha]_D^{20}$ = 30.6 (c = 0.8, $CHCl_3$). Absolute configuration was assigned as (*R*) on the basis of data reported in the literature.[32]

Hydrazone solution A: A mixture of benzaldehyde (25 µL, 0.24 mmol, 1.2 equiv) and hydrazine monohydrate (15 µL, 0.30 mmol, 64-65 wt%, 1.5 equiv) in THF (0.1 mL) solution was stirred for 30 minutes at room temperature. Prior to injection of this hydrazone solution A into the reaction mixture, a small amount of anhydrous Na_2SO_4 was added.

4.5.3 Spectroscopic Data



1,2-Diphenylpropan-2-ol **(4.6a)**[33]

Following the **general procedure A**, **4.6a** was obtained from the coupling between benzaldehyde **4.4a** (48 µL, 0.48 mmol) and acetophenone (47 µL, 0.4 mmol), as a colorless oil (79.4 mg, 94%) after flash chromatography.

Data for **4.6a**:

TLC: R_f 0.25 (9:1 hexane/EtOAc) [UV/I_2/Vanillin]

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.44 – 7.39 (m, 2H), 7.37 – 7.31 (m, 2H), 7.29 – 7.21 (m, 4H), 7.03 – 6.99 (m, 2H), 3.15 (d, *J* = 13.3 Hz, 1H), 3.04 (d, *J* = 13.3 Hz, 1H), 1.87 (s, br, 1H), 1.58 (s, 3H).

^{13}C NMR: (125 MHz, $CDCl_3$)

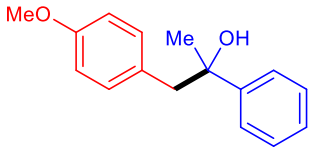
δ 147.6, 136.8, 130.6, 128.0, 126.63, 126.62, 125.0, 74.4, 50.5, 29.4.

IR: (neat)

ν (cm^{-1}) 3445 (br.), 3027 (w), 2971 (w), 1489 (m), 1444 (m), 1038 (m), 699 (s).

HRMS: (ESI, *m/z*)

calcd for $C_{15}H_{16}ONa[M+Na]^+$ 235.1093, found: 235.1092.



1-(4-Methoxyphenyl)-2-phenylpropan-2-ol **(4.6b)**[34]

Following the **general procedure A**, **4.6b** was obtained from the coupling between *p*-anisaldehyde **4.4b** (58.4 µL, 0.48 mmol) and acetophenone (47 µL, 0.4 mmol), as a colorless oil (56.1 mg, 58%) after flash chromatography.

Data for **4.6b**:

TLC: R_f 0.19 (9:1 hexane/EtOAc) [UV/I_2/Vanillin]

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.40 (dt, *J* = 3.1, 1.7 Hz, 2H), 7.37 – 7.30 (m, 2H), 7.29 – 7.21 (m, 1H), 6.95 – 6.86 (m, 2H), 6.81 – 6.71 (m, 2H), 3.77 (s, 3H), 3.08 (d, J = 13.5 Hz, 1H), 2.97 (d, *J* = 13.5 Hz, 1H), 1.82 (s, br, 1H), 1.56 (s, 3H).

^{13}C NMR: (125 MHz, $CDCl_3$)

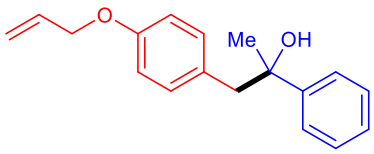
δ 158.4, 147.6, 131.5, 128.6, 128.0, 126.5, 125.0, 113.5, 74.4, 55.2, 49.6, 29.4.

IR: (neat)

ν (cm^{-1}) 3452 (br.), 2930 (w), 1445 (m), 1245(m), 1029 (m), 699 (m).

HRMS: (ESI, *m/z*)

calcd for $C_{16}H_{18}O_2Na[M+Na]^+$ 265.1199, found: 265.1198.



1-(4-(Allyloxy)phenyl)-2-phenylpropan-2-ol **(4.6c)**

Following the **general procedure A**, **4.6c** was obtained from the coupling between *p*-allyloxybenzaldehyde **4.4c** (73.6 µL, 0.48 mmol) and acetophenone (47 µL, 0.4 mmol), as a colorless oil (105 mg, 98%) after flash chromatography.

Data for **4.6c**:

TLC: R_f 0.21 (9:1 hexane/EtOAc) [UV/I_2/Vanillin]

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.42 (dt, *J* = 3.1, 1.8 Hz, 2H), 7.38 – 7.31 (m, 2H), 7.30 – 7.23 (m, 1H), 6.96 – 6.86 (m, 2H), 6.84 – 6.75 (m, 2H), 6.07 (ddt, *J* = 17.2, 10.6, 5.3 Hz, 1H), 5.42 (dq, *J* = 17.3, 1.6 Hz, 1H), 5.30

(dq, *J* = 10.5, 1.4 Hz, 1H), 4.52 (dt, *J* = 5.3, 1.5 Hz, 2H), 3.11 (d, *J* = 13.5 Hz, 1H), 2.99 (d, *J* = 13.5 Hz, 1H), 1.86 (s, br, 1H), 1.58 (s, 3H).

^{13}C NMR: (125 MHz, $CDCl_3$)

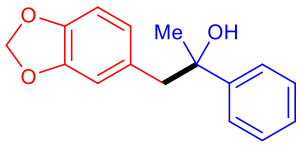
δ 157.5, 147.6, 133.4, 131.6, 128.9, 128.0, 126.6, 125.0, 117.6, 114.3, 74.4, 68.7, 49.6, 29.4.

IR: (neat)

ν (cm^{-1}) 3450 (br.), 2971 (w), 1446 (m), 1066 (m), 700 (s).

HRMS: (ESI, *m/z*)

calcd for $C_{18}H_{20}O_2Na[M+Na]^+$ 291.1355, found: 291.1354.



1-(1,3-Benzodioxole-5-yl)-2-phenylpropan-2-ol **(4.6d)**

Following the **general procedure A**, **4.6d** was obtained from the coupling between piperonal **4.4d** (72 mg, 0.48 mmol) and acetophenone (47 µL, 0.4 mmol), as a colorless oil (88.1 mg, 86%) after flash chromatography.

Data for **4.6d**:

TLC: R_f 0.16 (9:1 hexane/EtOAc) [UV/I_2/Vanillin]

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.46 – 7.39 (m, 2H), 7.39 – 7.31 (m, 2H), 7.31 – 7.23 (m, 1H), 6.70 (d, *J* = 7.8 Hz, 1H), 6.54 – 6.43 (m, 2H), 5.92 (s, 2H), 3.08 (d, *J* = 13.5 Hz, 1H), 2.96 (d, *J* = 13.5 Hz, 1H), 1.91 (s, br, 1H), 1.58 (s, 3H).

^{13}C NMR: (125 MHz, $CDCl_3$)

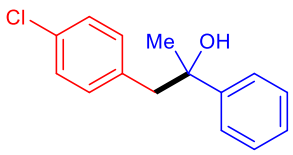
δ 147.5, 147.3, 146.3, 130.4, 128.1, 126.7, 124.9, 123.6, 110.9, 107.9, 100.8, 74.4, 50.1, 29.4.

IR: (neat)

ν (cm^{-1}) 3550 (br.), 2971 (w), 1488 (m), 1038 (s), 700 (s).

HRMS: (ESI, *m/z*)

calcd for $C_{16}H_{16}O_3Na[M+Na]^+$ 279.0992, found: 279.0990.



1-(4-Chlorophenyl)-2-phenylpropan-2-ol **(4.6e)**[34]

Following the **general procedure A**, **4.6e** was obtained from the coupling between 4-chlorobenzaldehyde **4.4e** (67.5 mg, 0.48 mmol) and acetophenone (47 µL, 0.4 mmol), as a colorless oil (83.6 mg, 85%) after flash chromatography.

Data for **4.6e**:

TLC: R_f 0.21 (9:1 hexane/EtOAc) [UV/I_2/Vanillin]

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.40 – 7.31 (m, 4H), 7.28 – 7.21 (m, 1H), 7.19 – 7.12 (m, 2H), 6.93 – 6.86 (m, 2H), 3.08 (d, *J* = 13.4 Hz, 1H), 2.99 (d, *J* = 13.4 Hz, 1H), 1.79 (s, br, 1H), 1.57 (s, 3H).

^{13}C NMR: (125 MHz, $CDCl_3$)

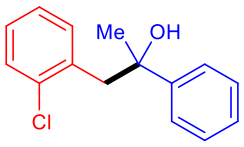
δ 147.1, 135.3, 132.5, 131.9, 128.11, 128.05, 126.8, 124.9, 74.5, 49.8, 29.3.

IR: (neat)

ν (cm^{-1}) 3446 (br.), 2971 (w), 1446 (m), 1068 (m), 700 (s).

HRMS: (ESI, *m/z*)

calcd for $C_{15}H_{15}OClNa[M+Na]^+$ 269.0704, found: 269.0703.



1-(2-Chlorophenyl)-2-phenylpropan-2-ol **(4.6f)**[35]

Following the **general procedure A**, **4.6f** was obtained from the coupling between 2-chlorobenzaldehyde **4.4f** (54 µL, 0.48 mmol) and acetophenone (47 µL, 0.4 mmol), as a colorless oil (64 mg, 65%) after flash chromatography.

Data for **4.6f**:

TLC: R_f 0.15 (9:1 hexane/EtOAc) [UV/I_2/Vanillin]

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.51 – 7.46 (m, 2H), 7.41 – 7.33 (m, 3H), 7.32 – 7.25 (m, 1H), 7.21 – 7.08 (m, 3H), 3.40 (d, *J* = 13.7 Hz, 1H), 3.18 (d, *J* = 13.7 Hz, 1H), 2.01 (s, br, 1H), 1.60 (s, 3H).

^{13}C NMR: (125 MHz, $CDCl_3$)

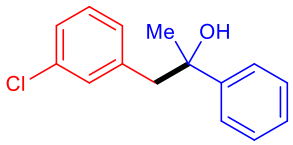
δ 147.7, 135.2, 135.0, 132.6, 129.4, 128.1, 127.9, 126.8, 126.2, 124.9, 75.2, 46.4, 28.8.

IR: (neat)

ν (cm^{-1}) 3442 (br.), 2973 (w), 1492 (m), 1473 (m), 1092 (m), 1065 (m), 1052 (m), 1028 (m), 767 (m), 746 (m), 732 (m), 699 (m).

HRMS: (ESI, *m/z*)

calcd for $C_{15}H_{15}ClNaO$ $[M+Na]^+$ 269.0704, found: 269.0701.



1-(3-Chlorophenyl)-2-phenylpropan-2-ol **(4.6g)**[33, 35]

Following the **general procedure A**, **4.6g** was obtained from the coupling between 3-chlorobenzaldehyde **4.4g** (54 µL, 0.48 mmol) and acetophenone (47 µL, 0.4 mmol), as a colorless oil (92.5 mg, 94%) after flash chromatography.

Data for **4.6g**:

TLC: R_f 0.23 (9:1 hexane/EtOAc) [UV/I_2/Vanillin]

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.39 (dt, *J* = 3.0, 1.8 Hz, 2H), 7.37 – 7.31 (m, 2H), 7.27 (tt, *J* = 6.2, 1.3 Hz, 1H), 7.19 (ddd, *J* = 8.0, 1.8, 1.2 Hz, 1H), 7.14 (t, *J* = 7.8 Hz, 1H), 7.02 (t, *J* = 1.7 Hz, 1H), 6.87 (d, *J* = 7.5 Hz, 1H), 3.09 (d, *J* = 13.4 Hz, 1H), 3.00 (d, *J* = 13.4 Hz, 1H), 1.79 (s, br, 1H), 1.57 (s, 3H).

^{13}C NMR: (125 MHz, $CDCl_3$)

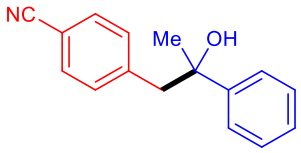
δ 147.1, 138.9, 133.7, 130.7, 129.1, 128.7, 128.1, 126.9, 126.7, 124.9, 74.4, 50.1, 29.2.

IR: (neat)

ν (cm^{-1}) 3445 (br.), 2971 (w), 1081 (m), 699 (s).

HRMS: (ESI, *m/z*)

calcd for $C_{15}H_{15}ClNaO$ $[M+Na]^+$ 269.0704, found: 269.0701.



4-(2-Hydroxy-2-phenylpropyl)benzonitrile **(4.6h)**[35]

Following the **general procedure A**, **4.6h** was obtained from the coupling between 4-formylbenzonitrile **4.4h** (62.9 mg, 0.48 mmol) and acetophenone (47 µL, 0.4 mmol), as an off-white solid (40.8 mg, 43%) after flash chromatography.

Data for **4.6h**:

TLC: R_f 0.1 (5:1 hexane/EtOAc) [UV/I_2/Vanillin]

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.45 – 7.43 (m, 2H), 7.36 – 7.29 (m, 4H), 7.28 – 7.23 (m, 1H), 7.10 – 7.04 (m, 2H), 3.13 (d, *J* = 13.2 Hz, 1H), 3.08 (d, *J* = 13.2 Hz, 1H), 1.80 (s, br, 1H), 1.60 (s, 3H).

^{13}C NMR: (125 MHz, $CDCl_3$)

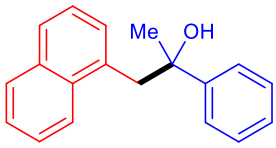
δ 146.6, 142.7, 131.5, 131.3, 128.2, 127.1, 124.8,119.0, 110.3, 74.6, 50.6, 29.5.

IR: (neat)

ν (cm^{-1}) 3546 (br.), 2981 (w), 2220 (m), 1493 (m), 1447 (m), 1413 (m), 1091 (m), 1059 (m), 1027 (m), 767 (s), 734 (s), 554 (s).

HRMS: (ESI, *m/z*)

calcd for $C_{16}H_{15}NNaO$ $[M+Na]^+$ 260.1046, found: 260.1055.



1-(Naphthalen-1-yl)-2-phenylpropan-2-ol **(4.6i)**[36]

Following the **general procedure A**, **4.6i** was obtained from the coupling between 2-naphthaldehyde **4.4i** (74.9 mg, 0.48 mmol) and acetophenone (47 µL, 0.4 mmol), as an off-white solid (101.7 mg, 97%) after flash chromatography.

Data for **4.6i**:

TLC: R_f 0.1 (5:1 hexane/EtOAc) [UV/I_2/Vanillin]

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 8.17 – 8.10 (m, 1H), 7.90 – 7.83 (m, 1H), 7.82 – 7.74 (m, 1H), 7.55 – 7.44 (m, 4H), 7.43 – 7.32 (m, 3H), 7.33 – 7.24 (m, 1H), 7.20 – 7.18 (m, 1H), 3.62 (d, *J* = 13.9 Hz, 1H), 3.56 (d, *J* = 13.9 Hz, 1H), 1.92 (s, br, 1H), 1.62 (s, 3H).

^{13}C NMR: (125 MHz, $CDCl_3$)

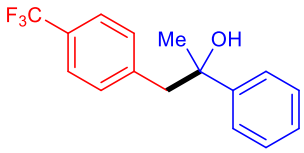
δ 147.9, 133.9, 133.22, 133.20, 129.2, 128.5, 128.1, 127.4, 126.6, 125.7, 125.4, 125.0, 124.9, 124.8, 75.2, 46.2, 29.4.

IR: (neat)

ν (cm^{-1}) 3446 (br.), 3056 (w), 2971 (w), 1493 (m), 1446 (m), 1396 (m), 1097 (m), 1067 (m), 1027 (m), 944 (m), 911 (w), 863 (w), 800 (s), 781 (s), 765 (s), 699 (s),.

HRMS: (ESI, *m/z*)

calcd for $C_{19}H_{18}NaO$ $[M+Na]^+$ 285.1250, found: 285.1248.



1-(4-(Trifluoromethyl)phenyl)-2-phenylpropan-2-ol **(4.6j)**[35]

Following the **general procedure A**, **4.6j** was obtained from the coupling between 4-(trifluoromethyl)benzaldehyde **4.4j** (65.5 µL, 0.48 mmol) and acetophenone (47 µL, 0.4 mmol), as a light yellow oil (106 mg, 95%) after flash chromatography.

Data for **4.6j**:

TLC: R_f 0.25 (9:1 hexane/EtOAc) [UV/I_2/Vanillin]

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.50 – 7.45 (m, 2H), 7.43 – 7.31 (m, 4H), 7.31 – 7.26 (m, 1H), 7.14 – 7.09 (m, 2H), 3.18 (d, *J* = 13.3 Hz, 1H), 3.10 (d, *J* = 13.3 Hz, 1H), 1.79 (s, br, 1H), 1.61 (s, 3H).

^{13}C NMR: (125 MHz, $CDCl_3$)

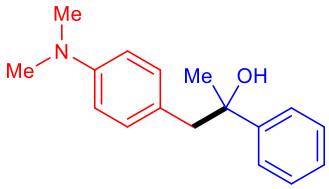
δ 147.0, 141.1, 130.8, 128.8 (q, *J* = 32.4 Hz), 128.2 =, 127.0, 124.9, 124.7 (q, *J* = 3.7 Hz), 124.3 (d, *J* = 271.9 Hz), 74.5, 50.3, 29.4.

IR: (neat)

ν (cm^{-1}) 3438 (br.), 2971 (w), 1494 (m), 1447 (m), 1322 (s), 1162 (s), 1110 (s), 1066 (s), 1028 (s), 1019 (m), 741 (m), 699 (s).

HRMS: (ESI, *m/z*)

calcd for $C_{16}H_{15}F_3NaO$ $[M+Na]^+$ 303.0967, found: 303.0969.



1-(4-(Dimethylamino)phenyl)-2-phenylpropan-2-ol **(4.6k)**

Following the **general procedure A**, **4.6k** was obtained from the coupling between 4-(dimethylamino)benzaldehyde **4.4k** (71.6 mg, 0.48 mmol) and acetophenone (47 µL, 0.4 mmol), as an off-white solid (68.3 mg, 67%) after flash chromatography.

Data for **4.6k**:

TLC: R_f 0.05 (9:1 hexane/EtOAc) [UV/I_2/Vanillin]

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.45 – 7.40 (m, 2H), 7.36 – 7.30 (m, 2H), 7.28 – 7.22 (m, 1H), 6.90 – 6.84 (m, 2H), 6.64 – 6.59 (m, 2H), 3.06 (d, *J* = 13.6 Hz, 1H), 2.93 (d, *J* = 13.6 Hz, 1H), 2.91 (s, 6H), 1.94 (s, br, 1H), 1.55 (s, 3H).

^{13}C NMR: (125 MHz, $CDCl_3$)

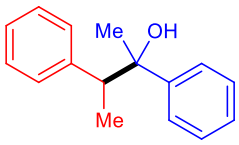
δ 149.5, 148.0, 131.3, 128.0, 126.4, 125.0, 124.2, 112.4, 74.4, 49.5, 40.6, 29.4.

IR: (neat)

ν (cm^{-1}) 3427 (br.), 2971 (w), 1519 (s), 719 (m), 700 (s).

HRMS: (ESI, *m/z*)

calcd for $C_{17}H_{22}ON[M+H]^+$ 256.1696, found: 256.1692.



2,3-Diphenylbutan-2-ol **(4.6l)**[37]

Following the **general procedure A**, **4.6l** was obtained as diastereoisomers (*d.r.* = 13/1) from the coupling between acetophenone **4.4l** (56.4 µL, 0.48 mmol) and acetophenone (47 µL, 0.4 mmol), as a colorless oil (27 mg, 30%) after flash chromatography.

Data for **4.6l** (major diastereoisomer):

TLC: R_f 0.35 (9:1 hexane/EtOAc) [UV/I_2/Vanillin]

^{1}H NMR: (400 MHz, $CDCl_3$)

δ 7.36 – 7.17 (m, 8H), 7.12 – 7.02 (m, 2H), 3.17 (q, *J* = 7.2 Hz, 1H), 1.57 (s, 3H), 1.27 (d, *J* = 7.2 Hz, 3H).

^{13}C NMR: (100 MHz, $CDCl_3$)

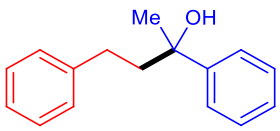
δ 146.9, 142.1, 129.3, 127.8, 127.7, 126.59, 126.56, 125.7, 76.4, 51.0, 25.8, 15.6.

IR: (neat)

ν (cm^{-1}) 3461 (br.), 2971 (w), 1446 (m), 1067 (m), 772 (m), 700 (s).

HRMS: (ESI, *m/z*)

calcd for $C_{16}H_{18}ONa[M+Na]^+$ 249.1250, found: 249.1248.



2,4-Diphenylbutan-2-ol **(4.6m)**[38]

Following the **general procedure A**, **4.6m** was obtained from the coupling between phenylacetaldehyde **4.4m** (56.4 µL, 0.48 mmol) and acetophenone (47 µL, 0.4 mmol), as a light yellow oil (20.8 mg, 23%) after flash chromatography.

Data for **4.6m**:

TLC: R_f 0.30 (5:1 hexane/EtOAc) [UV/I_2/Vanillin]

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.52 –7.46 (m, 2H), 7.42 – 7.35 (m, 2H), 7.31 – 7.22 (m, 3H), 7.19 – 7.10 (m, 3H), 2.63 (ddd, *J* = 13.6, 11.3, 5.8 Hz, 1H), 2.46 (ddd, *J* = 13.6, 11.3, 5.8 Hz, 1H), 2.21 – 2.09 (m, 2H), 1.78 (s, br, 1H), 1.63 (s, 3H).

^{13}C NMR: (125 MHz, $CDCl_3$)

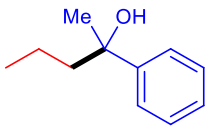
δ 147.5, 142.2, 128.35, 128.28, 128.2, 126.6, 125.7, 124.7, 74.7, 45.9, 30.5, 30.4.

IR: (neat)

ν (cm^{-1}) 3426 (br.), 3059 (w), 1445 (m), 1060 (m), 715 (m), 697 (s).

HRMS: (ESI, *m/z*)

calcd for $C_{16}H_{18}ONa[M+Na]^+$ 249.1250, found: 249.1248.



2-Phenylpentan-2-ol **(4.6n)**[39]

Following the **general procedure A**, **4.6n** was obtained from the coupling between propionaldehyde **4.4n** (34.6 µL, 0.48 mmol) and acetophenone (47 µL, 0.4 mmol), as a light yellow oil (13 mg, 20%) after flash chromatography.

Data for **4.6n**:

TLC: R_f 0.25 (5:1 hexane/EtOAc) [UV/I_2/Vanillin]

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.46 – 7.40 (m, 2H), 7.37 – 7.30 (m, 2H), 7.26 – 7.21 (m, 1H), 1.85 – 1.72 (m, 2H), 1.56 (s, 3H), 1.35 – 1.22 (m, 1H), 1.21 – 1.09 (m, 1H), 0.85 (t, J = 7.4 Hz, 3H).

^{13}C NMR: (125 MHz, $CDCl_3$)

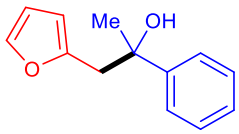
δ 148.1, 128.1, 126.5, 124.8, 74.7, 46.5, 30.1, 17.3, 14.4.

IR: (neat)

ν (cm^{-1}) 3364 (br.), 2927 (w), 1463 (m), 1046 (m), 793 (m), 703 (s).

HRMS: (ESI, *m/z*)

calcd for $C_{11}H_{16}ONa[M+Na]^+$ 187.1089, found: 187.1093.



1-(Furan-2-yl)-2-phenylpropan-2-ol **(4.6o)**

Following the **general procedure A**, **4.6o** was obtained from the coupling between furfural **4.4o** (39.8 µL, 0.48 mmol) and acetophenone (47 µL, 0.4 mmol), as a light yellow oil (60.5 mg, 75%) after flash chromatography.

Data for **4.6o**:

TLC: R_f 0.25 (5:1 hexane/EtOAc) [UV/I_2/Vanillin]

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.47 – 7.42 (m, 2H), 7.36 – 7.32 (m, 2H), 7.31 (d, *J* = 1.8 Hz, 1H), 7.27 – 7.22 (m, 1H), 6.26 (dd, *J* = 3.1, 1.9 Hz, 1H), 5.96 (d, *J* = 2.8 Hz, 1H), 3.17 (d, *J* = 14.9 Hz, 1H), 3.11 (d, *J* = 14.9 Hz, 1H), 2.36 (s, br, 1H), 1.56 (s, 3H).

^{13}C NMR: (125 MHz, $CDCl_3$)

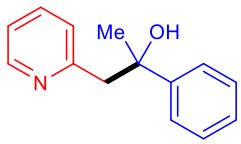
δ 151.9, 147.2, 141.8, 128.1, 126.7, 124.7, 110.3, 108.2, 74.1, 42.7, 29.5.

IR: (neat)

ν (cm^{-1}) 3454 (br.), 2976 (w), 1495 (m), 1069 (m), 772 (m), 700 (s).

HRMS: (ESI, *m/z*)

calcd for $C_{13}H_{14}O_2Na[M+Na]^+$ 225.0884, found: 225.0886.



2-Phenyl-1-(pyridin-2-yl)propan-2-ol **(4.6p)**

Following the **general procedure A**, **4.6p** was obtained from the coupling between 2-formylpyridine **4.4p** (45.6 µL, 0.48 mmol) and acetophenone (47 µL, 0.4 mmol), as a light yellow oil (45.2 mg, 53%) after flash chromatography.

Data for **4.6p**:

TLC: R_f 0.20 (5:1 hexane/EtOAc) [UV/I_2/Vanillin]

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 8.44 (d, *J* = 4.2 Hz, 1H), 7.52 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.47 – 7.42 (m, 2H), 7.28 – 7.21 (m, 2H), 7.17 – 7.06 (m, 2H), 6.96 (d, *J* = 7.7 Hz, 1H), 6.65 (s, br, 1H), 3.29 (d, *J* = 14.5 Hz, 1H), 3.25 (d, *J* = 14.5 Hz, 1H), 1.57 (s, 3H).

^{13}C NMR: (125 MHz, $CDCl_3$)

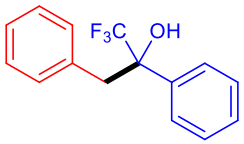
δ 159.2, 148.1, 148.0, 136.8, 127.8, 126.1, 124.9, 124.4, 121.5, 74.6, 48.9, 30.6.

IR: (neat)

ν (cm^{-1}) 3450 (br.), 2968 (w), 1490 (m), 1066 (m), 765 (m), 698 (s).

HRMS: (ESI, *m/z*)

calcd for $C_{14}H_{16}NO[M]^+$ 214.1220, found: 214.1226.



1,1,1-Trifluoro-2,3-diphenylpropan-2-ol **(4.8a)**[40]

Following the **general procedure A**, **4.8a** was obtained from the coupling between benzaldehyde (48 µL, 0.48 mmol) and trifluoroacetophenone **4.7a** (56 µL, 0.4 mmol), as a light yellow oil (94.7 mg, 89%) after flash chromatography.

Data for **4.8a**:

TLC: R_f 0.1 (9:1 hexane/EtOAc) [UV/I_2/Vanillin]

^{1}H NMR: (400 MHz, $CDCl_3$)

δ 7.59 – 7.52 (m, 2H), 7.44 – 7.31 (m, 3H), 7.29 – 7.16 (m, 3H), 7.04 – 6.95 (m, 2H), 3.46 (d, *J* = 13.9 Hz, 1H), 3.42 (d, *J* = 13.9 Hz, 1H), 2.44 (s, br, 1H).

^{13}C NMR: (100 MHz, $CDCl_3$)

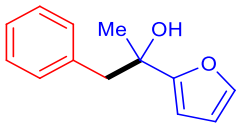
δ 137.1, 133.0, 130.7, 128.5, 128.4, 128.2, 127.5, 126.39, 126.38, 125.5 (q, *J* = 285.9 Hz), 77.0 (q, *J* = 27.8 Hz), 41.8.

IR: (neat)

ν (cm^{-1}) 3559 (br.), 3032 (w), 1455 (m), 1033 (m), 960 (s), 700 (s).

HRMS: (ESI, *m/z*)

calcd for $C_{15}H_{13}F_3NaO$ $[M+Na]^+$ 289.0811, found: 289.0810.



1-Phenyl-2-furylpropan-2-ol **(4.8b)**[34]

Following the **general procedure A**, **4.8b** was obtained from the coupling between benzaldehyde (48 µL, 0.48 mmol) and 2-acetyl furan **4.7b** (40 µL, 0.4 mmol), as a colorless oil (64.5 mg, 80%) after flash chromatography.

Data for **4.8b**:

TLC: R_f 0.1 (8:1 hexane/EtOAc) [UV/I_2/Vanillin]

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.40 (dd, *J* = 1.8, 0.9 Hz, 1H), 7.28 – 7.17 (m, 3H), 6.99 – 6.93 (m, 2H), 6.29 (dd, *J* = 3.2, 1.8 Hz, 1H), 6.05 (dd, *J* = 3.3, 0.9 Hz, 1H), 3.22 (d, *J* = 13.3 Hz, 1H), 3.08 (d, *J* = 13.3 Hz, 1H), 2.05 (s, br, 1H), 1.53 (s, 3H).

^{13}C NMR: (125 MHz, $CDCl_3$)

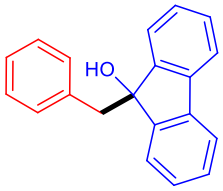
δ 158.9, 141.3, 136.5, 130.2, 128.1, 126.7, 110.2, 105.2, 71.9, 48.0, 26.5.

IR: (neat)

ν (cm^{-1}) 3398 (br.), 3030 (w), 1496 (m), 1449 (m), 1217 (m), 1153 (s), 700 (s).

HRMS: (ESI, *m/z*)

calcd for $C_{13}H_{14}NaO_2$ $[M+Na]^+$ 225.0886, found: 225.0886.



9-Benzyl-9*H*-fluoren-9-ol **(4.8c)**[41]

Following the **general procedure A**, **4.8c** was obtained from the coupling between benzaldehyde (48 µL, 0.48 mmol) and fluoren-9-one **4.7c** (72 mg, 0.4 mmol), as a colorless oil (82.6 mg, 76%) after flash chromatography.

Data for **4.8c**:

TLC: R_f 0.25 (8:1 hexane/EtOAc) [UV/I_2/Vanillin]

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.56 – 7.52 (m, 3H), 7.36 – 7.22 (m, 6H), 7.19 – 7.10 (m, 3H), 7.01 – 6.94 (m, 2H), 3.30 (s, 2H), 2.09 (s, br, 1H).

^{13}C NMR: (125 MHz, $CDCl_3$)

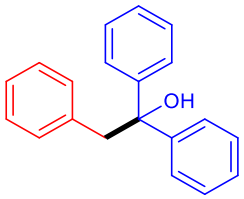
δ 148.2, 139.3, 136.3, 130.7, 128.9, 127.52, 127.49, 126.4, 124.2), 119.9, 82.3, 45.8.

IR: (neat)

ν (cm^{-1}) 3272 (br.), 3026 (w), 1450 (m), 1042 (m), 1002 (m), 696 (m), 664 (m).

HRMS: (ESI, *m/z*)

calcd for $C_{20}H_{16}NaO$ $[M+Na]^+$ 295.1093, found: 295.1100.



1,1,2-Triphenylethan-1-ol **(4.8d)**[33]

Following the **general procedure A**, **4.8d** was obtained from the coupling between benzaldehyde (48 µL, 0.48 mmol) and benzophenone **4.7d** (73 mg, 0.4 mmol), as a colorless oil (71.2 mg, 65%) after flash chromatography.

Data for **4.8d**:

TLC: R_f 0.15 (8:1 hexane/EtOAc) [UV/I_2/Vanillin]

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.46 – 7.41 (m, 4H), 7.34 – 7.27 (m, 4H), 7.27 – 7.21 (m, 2H), 7.20 – 7.13 (m, 3H), 6.93 – 6.88 (m, 2H), 3.66 (s, 2H), 2.31 (s, br, 1H).

^{13}C NMR: (125 MHz, $CDCl_3$)

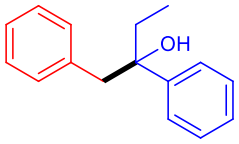
δ 146.6, 135.8, 130.9, 128.05, 128.03, 126.9, 126.8, 126.2, 77.7, 47.9.

IR: (neat)

ν (cm^{-1}) 3548 (br.), 3027 (w), 1446 (m), 1365 (m), 1229 (m), 1052 (m), 1031 (m), 1006 (m), 989 (m), 708 (s), 694 (s), 598 (s), 565 (s).

HRMS: (ESI, *m/z*)

calcd for $C_{20}H_{18}NaO$ $[M+ Na]^+$ 297.1250, found: 297.1250.



1,2-Diphenylbutan-2-ol **(4.8e)**

Following the **general procedure A**, **4.8e** was obtained from the coupling between benzaldehyde (48 µL, 0.48 mmol) and propiophenone **4.7e** (53.2 µL, 0.4 mmol), as a colorless oil (84.1 mg, 93%) after flash chromatography.

Data for **4.8e**:

TLC: R_f 0.36 (9:1 hexane/EtOAc) [UV/I_2/Vanillin]

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.38 – 7.29 (m, 4H), 7.28 – 7.16 (m, 4H), 7.02 – 6.94 (m, 2H), 3.18 (d, *J* = 13.4 Hz, 1H), 3.08 (d, *J* = 13.4 Hz, 1H), 2.03 (dq, *J* = 14.9, 7.5 Hz, 1H), 1.87 (dq, *J* = 14.6, 7.3 Hz, 1H), 1.81 (s, br, 1H), 0.78 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR: (125 MHz, $CDCl_3$)

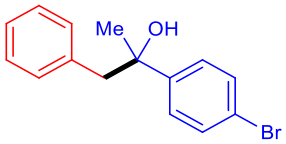
δ 145.5, 136.4, 130.7, 128.0, 127.9, 126.6, 126.4, 125.6, 76.9, 49.4, 34.5, 7.8.

IR: (neat)

ν (cm^{-1}) 3460 (br.), 2970 (w), 768 (m), 700 (s).

HRMS: (ESI, *m/z*)

calcd for $C_{16}H_{18}ONa[M+Na]^+$ 249.1250, found: 249.1249.



2-(4-Bromophenyl)-1-phenylpropan-2-ol **(4.8f)**[34]

Following the **general procedure A**, **4.8f** was obtained from the coupling between benzaldehyde (48 μL, 0.48 mmol) and 4'-bromoacetophenone **4.7f** (79.6 mg, 0.4 mmol), as a colorless oil (99.7 mg, 86%) after flash chromatography.

Data for **4.8f**:

TLC: R_f 0.23 (9:1 hexane/EtOAc) [UV/I_2/Vanillin]

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.45 (d, *J* = 8.6 Hz, 2H), 7.27 (d, *J* = 8.7 Hz, 2H), 7.26 – 7.19 (m, 3H), 7.04 – 6.95 (m, 2H), 3.10 (d, *J* = 13.4 Hz, 1H), 3.00 (d, *J* = 13.4 Hz, 1H), 1.89 (s, br, 1H), 1.55 (s, 3H).

^{13}C NMR: (125 MHz, $CDCl_3$)

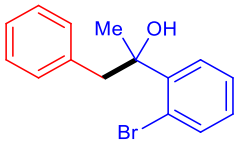
δ 146.6, 136.3, 131.0, 130.5, 128.2, 126.9, 126.8, 120.6, 74.2, 50.3, 29.4.

IR: (neat)

ν (cm^{-1}) 3445 (br.), 2971 (w), 1008 (m), 700 (s).

HRMS: (ESI, *m/z*)

calcd for $C_{15}H_{14}OBr[M–H]^+$ 289.0234, found: 289.0233.



2-(2-Bromophenyl)-1-phenylpropan-2-ol **(4.8g)**[42]

Following the **general procedure A**, **4.8g** was obtained from the coupling between benzaldehyde (48 µL, 0.48 mmol) and 2-bromoacetophenone **4.7g** (54 µL, 0.4 mmol), as a colorless oil (82 mg, 71%) after flash chromatography.

Data for **4.8g**:

TLC: R_f 0.3 (9:1 hexane/EtOAc) [UV/I_2/Vanillin]

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.67 – 7.62 (m, 1H), 7.52 – 7.47 (m, 1H), 7.25 – 7.17 (m, 4H), 7.14 – 7.07 (m, 1H), 7.07 – 6.99 (m, 2H), 3.68 (d, *J* = 13.6 Hz, 1H), 3.29 (d, *J* = 13.6 Hz, 1H), 2.48 (s, br, 1H), 1.77 (s, 3H).

^{13}C NMR: (125 MHz, $CDCl_3$)

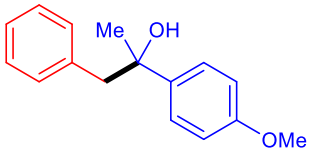
δ 144.9, 136.7, 135.0, 130.5, 128.5, 128.3, 128.1, 127.4, 126.6, 120.2, 75.5, 46.0, 27.3.

IR: (neat)

ν (cm^{-1}) 3373 (br.), 3025 (w), 1494 (m), 1478 (m), 1100 (m), 1081 (m), 1059 (m), 764 (s), 727 (s), 700 (s).

HRMS: (ESI, *m/z*)

calcd for $C_{15}H_{15}BrNaO$ $[M+Na]^+$ 313.0198, found: 313.0189.



2-(4-Methoxyphenyl)-1-phenylpropan-2-ol **(4.8h)**[34]

Following the **general procedure A**, **4.8h** was obtained from the coupling between benzaldehyde (48 μL, 0.48 mmol) and 4'-methoxyacetophenone **4.7h** (60 mg, 0.4 mmol), as a colorless oil (90 mg, 93%) after flash chromatography.

Data for **4.8h**:

TLC: R_f 0.16 (9:1 hexane/EtOAc) [UV/I_2/Vanillin]

^{1}H NMR: (400 MHz, $CDCl_3$)

δ 7.41 – 7.37 (m, 2H), 7.35 – 7.30 (m, 2H), 7.27 – 7.22 (m, 1H), 6.92 – 6.87 (m, 2H), 6.79 – 6.73 (m, 2H), 3.77 (s, 3H), 3.08 (d, *J* = 13.2 Hz, 1H), 2.96 (d, *J* = 13.2 Hz, 1H), 1.82 (s, br, 1H), 1.56 (s, 3H).

^{13}C NMR: (100 MHz, $CDCl_3$)

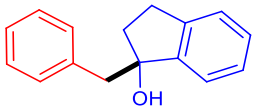
δ 158.4, 147.6, 131.5, 128.6, 128.0, 126.6, 125.0, 113.5, 74.4, 55.2, 49.6, 29.4.

IR: (neat)

ν (cm^{-1}) 3451 (br.), 2932 (w), 1511 (m), 1245(m), 1246 (m), 863 (m), 702 (m).

HRMS: (ESI, *m/z*)

calcd for $C_{16}H_{18}O_2Na[M+Na]^+$ 265.1199, found: 265.1199.



1-Benzyl-2,3-dihydro-1H-inden-1-ol **(4.8i)**

Following the **general procedure A**, **4.8i** was obtained from the coupling between benzaldehyde (48 µL, 0.48 mmol) and 1-indanone **4.7i** (53 mg, 0.4 mmol), as a light yellow oil (63.1 mg, 70%) after flash chromatography.

Data for **4.8i**:

TLC: R_f 0.05 (9:1 hexane/EtOAc) [UV/I_2/Vanillin]

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.33 – 7.17 (m, 7H), 7.17 – 7.10 (m, 2H), 3.14 (d, *J* = 13.3 Hz, 1H), 3.03 (d, *J* = 13.3 Hz, 1H), 2.90 (ddd, *J* = 16.0, 8.6, 3.7 Hz, 1H), 2.60 (dt, *J* = 15.4, 7.6 Hz, 1H), 2.40 (ddd, *J* = 13.0, 8.0, 3.7 Hz, 1H), 2.03 – 1.93 (m, 2H).

^{13}C NMR: (125 MHz, $CDCl_3$)

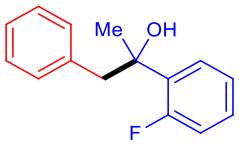
δ 147.1, 143.0, 137.1, 130.5, 128.3, 128.0, 126.6, 126.5, 124.8, 123.1, 83.5, 46.5, 40.1, 29.4.

IR: (neat)

ν (cm^{-1}) 3373 (br.), 3025 (w), 2936 (w), 1494 (m), 1478 (m), 1454 (m), 1439 (m), 1154 (m), 1100 (m), 764 (s), 727 (s), 700 (s).

HRMS: (ESI, *m/z*)

calcd for $C_{16}H_{16}NaO$ $[M+Na]^+$ 247.1093, found: 247.1094.



2-(2-Fluorophenyl)-1-phenylpropan-2-ol **(4.8j)**

Following the **general procedure A**, **4.8j** was obtained from the coupling between benzaldehyde (48 µL, 0.48 mmol) and 2-fluoroacetophenone **4.7j** (49 µL, 0.4 mmol), as a colorless oil (77 mg, 84%) after flash chromatography.

Data for **4.8j**:

TLC: R_f 0.2 (9:1 hexane/EtOAc) [UV/I_2/Vanillin]

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.37 – 7.30 (m, 1H), 7.28 – 7.16 (m, 4H), 7.10 – 6.97 (m, 4H), 3.35 (d, *J* = 13.4 Hz, 1H), 3.13 (d, *J* = 13.4 Hz, 1H), 2.11 (s, br, 1H), 1.66 (d, *J* = 1.1 Hz, 3H).

^{13}C NMR: (125 MHz, $CDCl_3$)

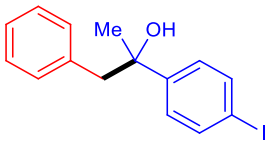
δ 159.5 (d, *J* = 244.5 Hz), 136.6, 133.9 (d, *J* = 11.9 Hz), 130.4, 128.7 (d, *J* = 8.5 Hz), 128.1, 127.4 (d, *J* = 4.5 Hz), 126.7, 124.0 (d, *J* = 3.4 Hz), 115.8 (d, *J* = 24.0 Hz), 73.5 (d, *J* = 4.4 Hz), 48.0 (d, *J* = 4.3 Hz), 28.2 (d, *J* = 3.8 Hz).

IR: (neat)

ν (cm^{-1}) 3456 (br.), 3063 (w), 1579 (m), 1495 (m), 1484 (m), 1445 (m), 1374 (m), 1351 (m), 1062 (m), 757 (s).

HRMS: (ESI, *m/z*)

calcd for $C_{15}H_{15}FNaO$ $[M+Na]^+$ 253.0999, found: 253.0998.



2-(4-Iodophenyl)-1-phenylpropan-2-ol **(4.8k)**

Following the **general procedure A**, **4.8k** was obtained from the coupling between benzaldehyde (48 µL, 0.48 mmol) and 4-iodoacetophenone **4.7k** (98.4 mg, 0.4 mmol), as a colorless oil (106.9 mg, 79%) after flash chromatography.

Data for **4.8k**:

TLC: R_f 0.1 (9:1 hexane/EtOAc) [UV/I_2/Vanillin]

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.68 – 7.61 (m, 2H), 7.27 – 7.18 (m, 3H), 7.18 – 7.11 (m, 2H), 7.04 – 6.96 (m, 2H), 3.09 (d, *J* = 13.4 Hz, 1H), 2.99 (d, *J* = 13.4 Hz, 1H), 1.76 (s, br, 1H), 1.53 (s, 3H).

^{13}C NMR: (125 MHz, $CDCl_3$)

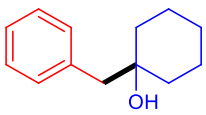
δ 147.3, 137.0, 136.3, 130.5, 128.2, 127.2, 126.8, 92.2, 74.2, 50.3, 29.4.

IR: (neat)

ν (cm^{-1}) 3443 (br.), 3027 (w), 1494 (m), 1031 (s), 949 (w), 861 (m), 758 (m), 719 (s), 701 (s).

HRMS: (ESI, *m/z*)

calcd for $C_{15}H_{16}INaO$ $[M+Na]^+$ 361.0060, found: 361.0050.



1-Benzylcyclohexan-1-ol **(4.8l)**[43]

Following the **general procedure A**, **4.8l** was obtained from the coupling between benzaldehyde (48 µL, 0.48 mmol) and cyclohexanone **4.7l** (44 µL, 0.4 mmol), as a white solid (67 mg, 88%) after flash chromatography.

Data for **4.8l**:

TLC: R_f 0.1 (9:1 hexane/EtOAc) [UV/I_2/Vanillin]

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.35 – 7.17 (m, 5H), 2.75 (s, 2H), 1.68 – 1.37 (m, 9H), 1.35 – 1.19 (m, 2H).

^{13}C NMR: (125 MHz, $CDCl_3$)

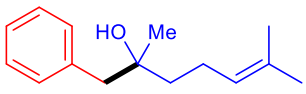
δ 137.2, 130.6, 128.1, 126.4, 71.1, 48.7, 37.3, 25.8, 22.1.

IR: (neat)

ν (cm^{-1}) 3360 (br.), 2926 (m), 1495 (m), 1062 (m), 1034 (s), 698 (s).

HRMS: (ESI, *m/z*)

calcd for $C_{13}H_{18}NaO$ $[M+Na]^+$ 213.1250, found: 213.1249.



2,6-Dimethyl-1-phenylhept-5-en-2-ol **(4.8m)**[44]

Following the **general procedure A**, **4.8m** was obtained from the coupling between benzaldehyde (48 µL, 0.48 mmol) and 6-methyl-5-hepten-2-one **4.7m** (58.8 µL, 0.4 mmol), as a colorless oil (62 mg, 71%) after flash chromatography.

Data for **4.8m**:

TLC: R_f 0.30 (9:1 hexane/EtOAc) [UV/I_2/Vanillin]

^{1}H NMR: (400 MHz, $CDCl_3$)

δ 7.35 – 7.16 (m, 5H), 5.18 – 5.03 (m, 1H), 2.80 (d, *J* = 13.3 Hz, 1H), 2.73 (d, *J* = 13.3 Hz, 1H), 2.12 (q, *J* = 7.4 Hz, 2H), 1.68 (s, 3H), 1.63 (s, 3H), 1.53 – 1.46 (m, 2H), 1.36 (s, br, 1H), 1.16 (s, 3H).

^{13}C NMR: (100 MHz, $CDCl_3$)

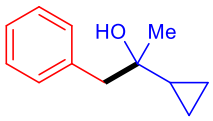
δ 137.5, 131.6, 130.5, 128.1, 126.4, 124.4, 72.5, 48.1, 41.6, 26.4, 25.7, 22.7, 17.7.

IR: (neat)

ν (cm^{-1}) 3440 (br.), 2970 (w), 1490 (m), 1445 (m), 619 (s).

HRMS: (ESI, *m/z*)

calcd for $C_{15}H_{22}ONa[M+Na]^+$ 241.1563, found: 241.1561.



2-Cyclopropyl-1-phenylpropan-2-ol **(4.8n)**[45]

Following the **general procedure A**, **4.8n** was obtained from the coupling between benzaldehyde (48 µL, 0.48 mmol) and cyclopropyl methyl ketone **4.7n** (39.6 µL, 0.4 mmol), as a colorless oil (59.9 mg, 85%) after flash chromatography.

Data for **4.8n**:

TLC: R_f 0.27 (9:1 hexane/EtOAc) [UV/I_2/Vanillin]

^{1}H NMR: (400 MHz, $CDCl_3$)

δ 7.37 – 7.19 (m, 5H), 2.89 (d, *J* = 13.1 Hz, 1H), 2.84 (d, *J* = 13.1 Hz, 1H), 1.14 (s, br, 1H), 1.12 (s, 3H), 0.99 – 0.87 (m, 1H), 0.45 – 0.23 (m, 4H).

^{13}C NMR: (100 MHz, $CDCl_3$)

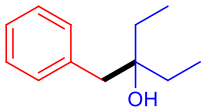
δ 137.5, 130.6, 128.0, 126.3, 71.0, 49.1, 25.9, 20.8, 0.73, 0.70.

IR: (neat)

ν (cm^{-1}) 3451 (br.), 2971 (w), 1372 (m), 753 (m), 700 (s).

HRMS: (ESI, *m/z*)

calcd for $C_{12}H_{16}ONa[M+Na]^+$ 199.1093, found: 199.1093.



3-Benzylpentan-3-ol **(4.8o)**[46]

Following the **general procedure A**, **4.8o** was obtained from the coupling between benzaldehyde (48 µL, 0.48 mmol) and 3-pentanone **4.7o** (42.4 µL, 0.4 mmol), as a colorless oil (35.6 mg, 50%) after flash chromatography.

Data for **4.8o**:

TLC: R_f 0.26 (9:1 hexane/EtOAc) [UV/I_2/Vanillin]

^{1}H NMR: (400 MHz, $CDCl_3$)

δ 7.36 – 7.22 (m, 5H), 2.77 (s), 1.49 (q, *J* = 7.5 Hz, 4H), 1.21 (s), 1.21 (s, br, 1H), 0.96 (t, *J* = 7.5 Hz, 6H).

^{13}C NMR: (100 MHz, $CDCl_3$)

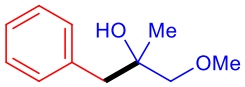
δ 137.5, 130.6, 128.2, 126.3, 74.5, 44.8, 30.4, 8.0.

IR: (neat)

ν (cm^{-1}) 3415 (br.), 2931 (w), 1376 (m), 700 (s).

HRMS: (ESI, *m/z*)

calcd for $C_{12}H_{18}ONa[M+Na]^+$ 201.1250, found: 201.1251.



1-Methoxy-2-methyl-3-phenylpropan-2-ol **(4.8p)**

Following the **general procedure A**, **4.8p** was obtained from the coupling between benzaldehyde (48 µL, 0.48 mmol) and methoxyacetone **4.7p** (36.8 µL, 0.4 mmol), as a colorless oil (67 mg, 55%) after flash chromatography.

Data for **4.8p**:

TLC: R_f 0.1 (9:1 hexane/EtOAc) [UV/I_2/Vanillin]

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.33 – 7.27 (m, 2H), 7.27 – 7.18 (m, 3H), 3.41 (s, 3H), 3.22 (d, *J* = 8.9 Hz, 1H), 3.15 (d, *J* = 8.9 Hz, 1H), 2.82 (s, 2H), 1.77 (s, br, 1H), 1.14 (s, 3H).

^{13}C NMR: (125 MHz, $CDCl_3$)

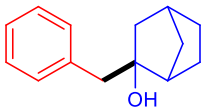
δ 137.4, 130.4, 128.1, 126.4, 78.8, 72.3, 59.1, 45.2, 23.8.

IR: (neat)

ν (cm^{-1}) 3451 (br.), 2926 (m), 1414 (m), 1380 (m), 1262 (m), 1229 (m), 1217 (m), 1034 (s), 698 (s).

HRMS: (ESI, *m/z*)

calcd for $C_{11}H_{16}NaO_2$ $[M+Na]^+$ 203.1043, found: 203.1040.



2-Benzylbicyclo[2.2.1]heptan-2-ol **(4.8q)**[47]

Following the **general procedure A**, **4.8q** was obtained from the coupling between benzaldehyde (48 µL, 0.48 mmol) and norcamphor **4.7q** (44 mg, 0.4 mmol), as a colorless oil (45 mg, 56%) after flash chromatography.

Data for **4.8q**:

TLC: R_f 0.15 (9:1 hexane/EtOAc) [UV/I_2/Vanillin]

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.36 – 7.22 (m, 5H), 2.88 (d, *J* = 13.5 Hz, 1H), 2.78 (d, *J* = 13.5 Hz, 1H), 2.25 (tt, *J* = 4.3, 1.3 Hz, 1H), 2.17 – 2.10 (m, 1H), 1.89 (ddq, *J* = 12.2, 8.9, 2.8 Hz, 1H), 1.74 (ddd, *J* = 12.9, 4.6, 2.8 Hz, 1H), 1.67 (dt, *J* = 10.1, 2.1 Hz, 1H), 1.63 – 1.52 (m, 1H), 1.42 (s, br, 1H), 1.38 – 1.24 (m, 3H), 1.11 (dd, *J* = 12.9, 3.3 Hz, 1H).

^{13}C NMR: (125 MHz, $CDCl_3$)

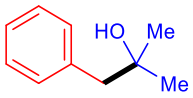
δ 137.7, 130.5, 128.3, 126.5, 79.2, 47.9, 45.8, 45.7, 38.6, 37.4, 28.6, 22.1.

IR: (neat)

ν (cm^{-1}) 3450 (br.), 2947 (m), 2868 (m), 1452 (m), 1353 (m), 1270 (m), 1254 (m), 1003 (s), 702 (s).

HRMS: (ESI, *m/z*)

calcd for $C_{14}H_{18}NaO$ $[M+Na]^+$ 225.1250, found: 225.1247.



2-Methyl-1-phenylpropan-2-ol **(4.8r)**[48]

Following the **general procedure A**, **4.8r** was obtained from the coupling between benzaldehyde (48 µL, 0.48 mmol) and acetone **4.7r** (29.4 µL, 0.4 mmol), as a colorless oil (49 mg, 82%) after flash chromatography.

Data for **4.8r**:

TLC: R_f 0.16 (9:1 hexane/EtOAc) [UV/I_2/Vanillin]

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.34 – 7.28 (m, 2H), 7.28 – 7.24 (m, 1H), 7.24 – 7.19 (m, 2H), 2.77 (s, 2H), 1.49 (s, br, 1H), 1.23 (s, 6H).

^{13}C NMR: (125 MHz, $CDCl_3$)

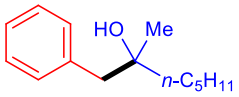
δ 137.7, 130.5, 128.2, 126.5, 70.7, 49.7, 29.2.

IR: (neat)

ν (cm^{-1}) 3388 (br.), 2970 (w), 2930(w), 1123(m), 725 (s), 700 (s).

HRMS: (ESI, *m/z*)

calcd for $C_{10}H_{14}ONa[M+Na]^+$ 173.0937, found: 173.0939



2-Methyl-1-phenylheptan-2-ol **(4.8s)**[49]

Following the **general procedure A**, **4.8s** was obtained from the coupling between benzaldehyde (48 µL, 0.48 mmol) and 2-heptanone **4.7s** (55.7 µL, 0.4 mmol), as a colorless oil (61.8 mg, 75%) after flash chromatography.

Data for **4.8s**:

TLC: R_f 0.30 (9:1 hexane/EtOAc) [UV/I_2/Vanillin]

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.35 – 7.28 (m, 2H), 7.28 – 7.19 (m, 3H), 2.79 (d, *J* = 13.3 Hz, 1H), 2.73 (d, *J* = 13.3 Hz, 1H), 1.52 – 1.38 (m, 4H), 1.38 – 1.23 (m, 5H), 1.15 (s, 3H), 0.91 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR: (125 MHz, $CDCl_3$)

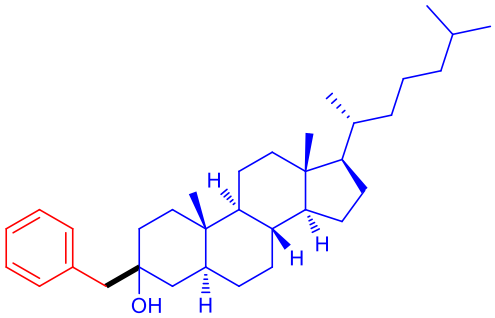
δ 137.6, 130.5, 128.2, 126.4, 72.5, 48.0, 41.9, 32.4, 26.5, 23.7, 22.7, 14.1.

IR: (neat)

ν (cm^{-1}) 3427 (br.), 2931 (w), 1248 (m), 701 (s).

HRMS: (ESI, *m/z*)

calcd for $C_{14}H_{22}ONa[M+Na]^+$ 229.1563, found: 229.1560.



(*5S,8R,9S,10S,13R,14S,17R*)-3-Benzyl-10,13-dimethyl-17-((*R*)-6-methylheptan-2-yl)hexadecahydro-*1H*-cyclopenta[a]phenanthren-3-ol **(4.8t)**

Following the **general procedure A**, **4.8t** was obtained from the coupling between benzaldehyde (24 µL, 0.24 mmol) and 4.8a-cholestan-3-one **4.7t** (77.2 mg, 0.2 mmol), as a white solid (65 mg, 68%) after flash chromatography.

Data for **4.8t**:

TLC: R_f 0.45 (9:1 hexane/EtOAc) [UV/I_2/Vanillin]

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.34 – 7.24 (m, 3H), 7.24 – 7.18 (m, 2H), 2.71 (s, 2H), 1.95 (dt, *J* = 12.6, 3.4 Hz, 1H), 1.85 – 1.75 (m, 1H), 1.68 – 1.35 (m, 11H), 1.35 – 1.25 (m, 5H), 1.25 – 1.05 (m, 10H), 1.05 – 0.94 (m, 3H), 0.94 – 0.81 (m, 10H), 0.74 (s, 3H), 0.64 (s, 3H).

^{13}C NMR: (125 MHz, $CDCl_3$)

δ 137.1, 130.6, 128.1, 126.4, 71.3, 56.5, 56.2, 54.2, 50.4, 42.6, 40.8, 40.1, 40.0, 39.5, 36.2, 35.79, 35.75, 35.5, 33.8, 33.3, 32.0, 28.5, 28.2, 28.0, 24.2, 23.8, 22.8, 22.5, 21.0, 18.6, 12.1, 11.2.

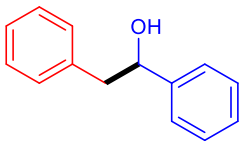
IR: (neat)

ν (cm^{-1}) 3440 (br.), 2867 (m), 1440 (m), 1353 (m), 1270 (m), 1230 (m), 1217 (m), 704 (m).

HRMS: (ESI, *m/z*)

calcd for $C_{34}H_{54}NaO$ $[M+Na]^+$ 501.4067, found: 501.4076.

calcd for $C_{34}H_{54}KO$ $[M+K]^+$ 517.3806, found: 517.3815.



1,2-Diphenylethan-1-ol **(4.8u)**

Following the **general procedure B**, **4.8u** was obtained from the coupling between benzaldehyde (24 µL, 0.24 mmol) and benzaldehyde **4.4a/4.7u** (20 µL, 0.2 mmol), as a white solid (19 mg, 48%) after flash chromatography.

Data for **4.8u**:

TLC: R_f 0.19 (9:1 hexane/EtOAc) [UV/I_2/Vanillin]

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.40 – 7.18 (m, 5H), 4.91 (dd, *J* = 8.5, 4.8 Hz, 1H), 3.06 (dd, *J* = 13.6, 4.8 Hz, 1H), 3.00 (dd, *J* = 13.6, 8.5 Hz, 1H), 1.81 (s, br, 1H).

^{13}C NMR: (125 MHz, $CDCl_3$)

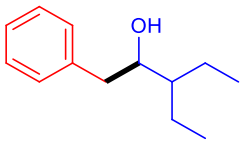
δ 143.8, 138.0, 129.5, 128.5, 128.4, 127.6, 126.6, 125.9, 75.3, 46.1.

IR: (neat)

ν (cm^{-1}) 3371 (br.), 3027 (w), 1028 (m), 756 (m), 698 (m).

HRMS: (ESI, *m/z*)

calcd for $C_{14}H_{14}ONa[M+Na]^+$ 221.0937, found: 221.0936.



3-Ethyl-1-phenylpentan-2-ol **(4.8v)**

Following the **general procedure B**, **4.8v** was obtained from the coupling between benzaldehyde (48 µL, 0.48 mmol) and 2-ethylbutanal **4.7v** (49.2 µL, 0.4 mmol), as a colorless oil (46.8 mg, 61%) after flash chromatography.

Data for **4.8v**:

TLC: R_f 0.36 (9:1 hexane/EtOAc) [UV/I_2/Vanillin]

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.35 – 7.29 (m, 2H), 7.25 – 7.20 (m, 3H), 3.84 (ddd, *J* = 9.7, 4.5, 3.4 Hz, 1H), 2.84 (dd, *J* = 13.6, 3.3 Hz, 1H), 2.62 (dd, *J* = 13.6, 9.7 Hz, 1H), 1.60 – 1.49 (m, 3H), 1.47 – 1.30 (m, 3H), 0.99 – 0.90 (m, 6H).

^{13}C NMR: (125 MHz, $CDCl_3$)

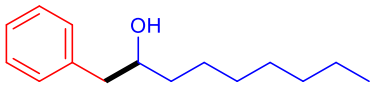
δ 139.4, 129.3, 128.6, 126.4, 74.1, 46.3, 40.7, 22.1, 21.4, 11.8, 11.7.

IR: (neat)

ν (cm^{-1}) 3422 (br.), 2959 (w), 2853 (w), 1454 (m), 1030 (m), 699 (s).

HRMS: (ESI, *m/z*)

calcd for $C_{13}H_{20}ONa[M+Na]^+$ 215.1406, found: 215.1410.



1-Phenylnonan-2-ol **(4.8w)**[50]

Following the **general procedure B**, **4.8w** was obtained from the coupling between benzaldehyde (48 µL, 0.48 mmol) and octanal **4.7w** (62.5 µL, 0.4 mmol), as a colorless oil (44 mg, 50%) after flash chromatography.

Data for **4.8w**:

TLC: R_f 0.32 (9:1 hexane/EtOAc) [UV/I_2/Vanillin]

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.36 – 7.28 (m, 2H), 7.25 – 7.19 (m, 3H), 3.88 – 3.73 (m, 1H), 2.84 (dd, *J* = 13.6, 4.2 Hz, 1H), 2.65 (dd, *J* = 13.6, 8.4 Hz, 1H), 1.59 – 1.44 (m, 4H), 1.36 – 1.18 (m, 9H), 0.88 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR: (125 MHz, $CDCl_3$)

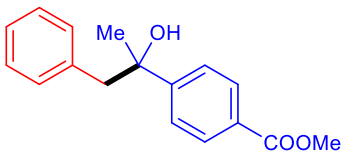
δ 138.7, 129.4, 128.6, 126.4, 72.7, 44.1, 36.9, 31.8, 29.6, 29.3, 25.8, 22.7, 14.1.

IR: (neat)

ν (cm^{-1}) 3379 (br.), 2923 (w), 1454 (w), 699 (m).

HRMS: (ESI, *m/z*)

calcd for $C_{15}H_{24}ONa[M+Na]^+$ 243.1719, found: 243.1723.



Methyl 4-(2-hydroxy-1-phenylpropan-2-yl)benzoate **(4.8x)**

Following the **general procedure A**, **4.8x** was obtained from the coupling between benzaldehyde (48 µL, 0.48 mmol) and methyl 4-acetylbenzoate **4.7x** (98.4 mg, 0.4 mmol), as a light yellow oil (95 mg, 88%) after flash chromatography.

Data for **4.8x**:

TLC: R_f 0.15 (5:1 hexane/EtOAc) [UV/I_2/Vanillin]

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 8.02 – 7.95 (m, 2H), 7.49 – 7.43 (m, 2H), 7.24 – 7.17 (m, 3H), 7.01 – 6.93 (m, 2H), 3.91 (s, 3H), 3.14 (d, *J* = 13.4 Hz, 1H), 3.04 (d, *J* = 13.4 Hz, 1H), 2.01 (s, br, 1H), 1.58 (s, 3H).

^{13}C NMR: (125 MHz, $CDCl_3$)

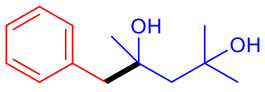
δ 167.0, 152.7, 136.1, 130.5, 129.4, 128.5, 128.1, 126.8, 125.1, 74.5, 52.0, 50.2, 29.4.

IR: (neat)

ν (cm^{-1}) 3489 (br.), 2951 (w), 1704 (s), 1227 (s), 1112 (s), 1092 (m), 1017 (m), 828 (m), 776 (m), 725 (m), 700 (s).

HRMS: (ESI, *m/z*)

calcd for $C_{17}H_{18}NaO_3$ $[M+Na]^+$ 293.1148, found: 293.1140.



2-Benzyl-4-metyl-2,4-pentanediol **(4.8y)**[51]

Following the **general procedure A**, **4.8y** was obtained from the coupling between benzaldehyde (24 µL, 0.24 mmol) and 4-Hydroxy-4-methyl-2-pentanone **4.7y** (25µL, 0.2 mmol), as a colorless oil (21 mg, 50%) after flash chromatography.

Data for **4.8y**:

TLC: R_f 0.3 (6:4 hexane/EtOAc) [UV/I_2/Vanillin]

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.34 – 7.27 (m, 2H), 7.27 – 7.23 (m, 1H), 7.23 – 7.18 (m, 2H), 3.40 (s, br, 1H), 2.93 (d, *J* = 13.2 Hz, 1H), 2.89 (s, 1H), 2.72 (d, *J* = 13.2 Hz, 1H), 1.87 (d, *J* = 14.8 Hz, 1H), 1.71 (d, *J* = 14.8 Hz, 1H), 1.36 (s, 3H), 1.33 (s, 3H), 1.28 (s, 3H).

^{13}C NMR: (125 MHz, $CDCl_3$)

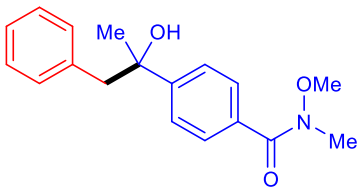
δ 137.2, 130.7, 128.1, 126.5, 73.8, 72.0, 50.9, 50.8, 32.7, 31.2, 28.6.

IR: (neat)

ν (cm^{-1}) 3349 (br.), 2970 (s), 2363 (s), 1378 (s), 1172 (s), 702 (s).

HRMS: (ESI, *m/z*)

calcd for $C_{13}H_{20}NaO_2$ $[M+Na]^+$ 231.1356, found: 231.1356.



4-(2-Hydroxy-1-phenylpropan-2-yl)-*N*-methoxy-*N*-methylbenzamide **(4.10a)**

Following the **general procedure A**, **4.10a** was obtained from the coupling between benzaldehyde (48 µL, 0.48 mmol) and 4-acetyl-*N*-methoxy-*N*-methylbenzamide **4.9a** (98.4 mg, 0.4 mmol), as a colorless oil (92 mg, 77%) after flash chromatography.

Data for **4.10a**:

TLC: R_f 0.25 (1:1 hexane/EtOAc) [UV/I_2/Vanillin]

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.67 – 7.62 (m, 2H), 7.45 – 7.40 (m, 2H), 7.23 – 7.18 (m, 3H), 7.02 – 6.96 (m, 2H), 3.56 (s, 3H), 3.36 (s, 3H), 3.12 (d, *J* = 13.4 Hz, 1H), 3.03 (d, *J* = 13.4 Hz, 1H), 1.87 (s, br, 1H), 1.58 (s, 3H).

^{13}C NMR: (125 MHz, $CDCl_3$)

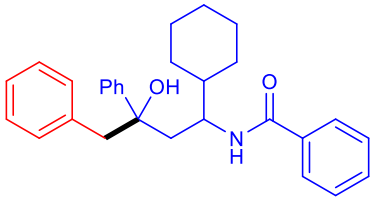
δ 169.8, 150.2, 136.3, 132.3, 130.5, 128.11, 128.08, 126.8, 124.7, 74.4, 61.0, 50.4, 33.8, 29.3.

IR: (neat)

ν (cm^{-1}) 3424 (br.), 2933 (w), 1624 (s), 1495 (m), 1453 (m), 1373 (s), 1218 (m), 1093 (m), 978 (m), 847 (m), 737 (m), 701 (s).

HRMS: (ESI, *m/z*)

calcd for $C_{18}H_{21}NNaO_3$ $[M+Na]^+$ 322.1414, found: 322.1412.



N-(1-Cyclohexyl-3-hydroxy-3,4-diphenylbutyl)benzamide **(4.10b)**

Following the **general procedure A**, **4.10b** was obtained from the coupling between benzaldehyde (12 µL, 0.12 mmol) and *N*-(1-cyclohexyl-3-oxo-3-phenylpropyl)benzamide **4.9b** (33.5 mg, 0.1 mmol), as a colorless oil (36 mg, 85%) after flash chromatography.

Data for **4.9b**:

TLC: R_f 0.3 (3:1 hexane/EtOAc) [UV/I_2/Vanillin]

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.74 – 7.68 (m, 2H), 7.50 – 7.44 (m, 1H), 7.43 – 7.35 (m, 2H), 7.29 – 7.25 (m, 4H), 7.23 – 7.18 (m, 1H), 7.17 – 7.11 (m, 3H), 6.93 – 6.86 (m, 2H), 6.46 (d, *J* = 7.6 Hz, 1H), 3.66 (dddd, *J* = 14.8, 9.4, 7.6, 3.1 Hz, 1H), 3.44 (s, br, 1H), 3.18 (d, *J* = 13.4 Hz, 1H), 3.06 (d, *J* = 13.4 Hz, 1H), 2.36 (dd, *J* = 14.8, 3.1 Hz, 1H), 2.00 (dd, *J* = 14.8, 9.4 Hz, 1H), 1.79 – 1.44 (m, 6H), 1.29 – 0.93 (m, 5H).

^{13}C NMR: (125 MHz, $CDCl_3$)

δ 167.3, 144.7, 136.1, 134.7, 131.3, 130.7, 128.4, 128.1, 127.9, 126.9, 126.64, 126.55, 125.6, 51.5, 50.4, 43.9, 42.7, 29.0, 28.4, 26.5, 26.3, 26.2.

IR: (neat)

ν (cm^{-1}) 3377 (br.), 2919 (br.), 1614 (s), 1543 (s), 1495 (m), 1445 (m), 775 (m).

HRMS: (ESI, *m/z*)

calcd for $C_{29}H_{33}NNaO_2$ $[M+Na]^+$ 450.2404, found: 450.2397.

4.5.4 HPLC Chromatography of Chiral Alcohol Products

HPLC Condition

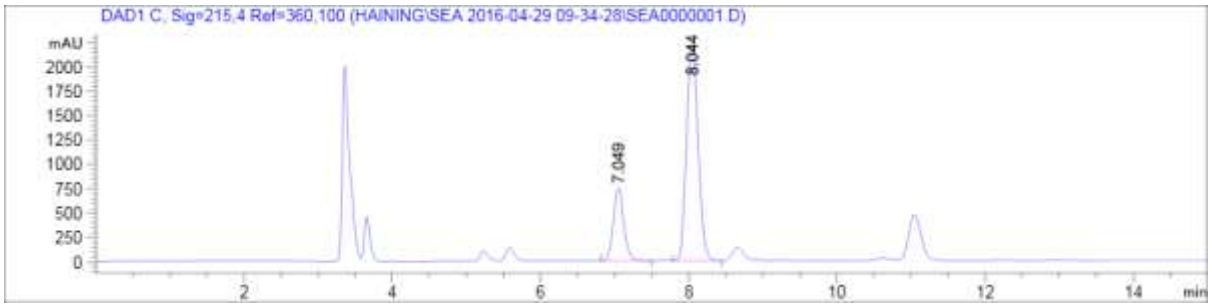
Column: Chiralpak IC, Daicel Corporation;

Eluent: Hexanes/IPA (99/1);

Flow rate: 1.0 mL/min;

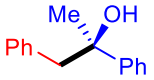
Detection: UV215 nm.

HPLC Chromatography of Chiral **4.6a**



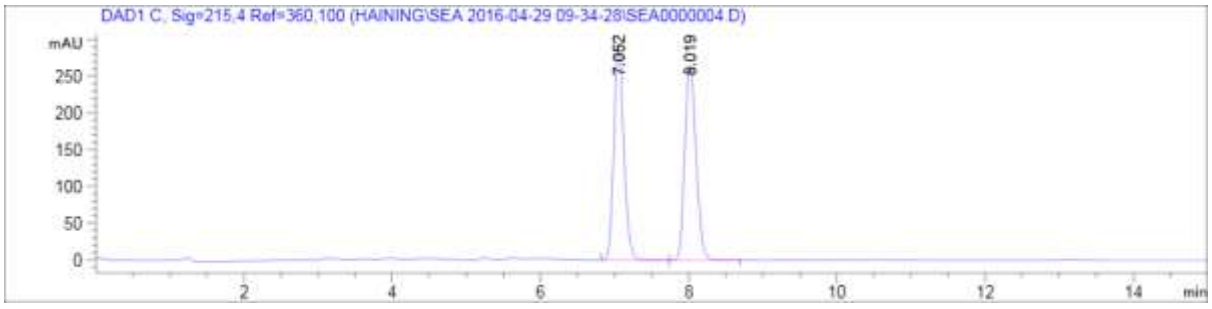
Signal 3: DAD1 C, Sig=215,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.049	VB	0.1511	7342.10596	744.30774	23.5232
2	8.044	VV	0.1679	2.38701e4	2211.19360	76.4768
Totals :				3.12123e4	2955.50134	



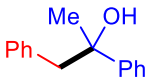
(R)-**4.6a,** 52% yield, 76:24 *er*

HPLC Chromatography of Racemic **4.6a**



Signal 3: DAD1 C, Sig=215,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.052	BB	0.1460	2759.44409	292.72055	49.7964
2	8.019	BB	0.1622	2782.01440	265.68942	50.2036
Totals :				5541.45850	558.40997	



(±)-4.6a

4.5.5 Preliminary Computational Calculation

All the calculations were carried out at the B3LYP/6-31G(d) level (LanL2DZ for Ru), using the Gaussian 09 rev. D.01 suite of programs. Harmonic frequencies were calculated at the same level to characterize the stationary points and to determine the zeropoint energies (ZPE). Intrinsic reaction coordinate (IRC) studies were performed in ambiguous cases to confirm the relation of the transition states with the corresponding minima.

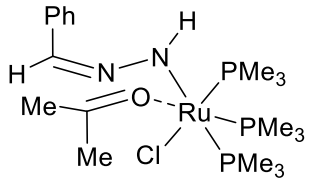
i. Complete Reference of Gaussian 09

Gaussian 09, Revision D.01, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, T. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, O. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, and D. J. Fox, Gaussian, Inc., Wallingford CT, 2013.

ii. Cartesian Coordinates for the Optimized Structures

Atomic Cartesian coordinates and computed energies (atomic units) for the stationary points calculated with basis set [B3LYP/6-31G(d) (C, H, O, P) LanL2DZ (Ru).

Structure **INT I**



INT I

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Sum of electronic and thermal Energies= -2510.481591

Sum of electronic and thermal Enthalpies= -2510.480647

Sum of electronic and thermal Free Energies= -2510.591972

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2	7	-0.000008434	0.000002749	0.000003716
3	7	0.000013976	-0.000003422	-0.000000146
4	1	-0.000013138	-0.000010622	0.000007088

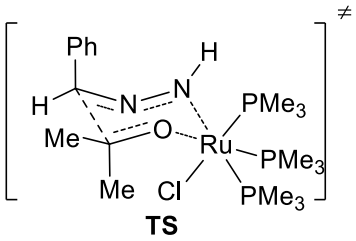
5	44	-0.000007922	-0.000010893	-0.000000862
6	15	-0.000003661	0.000004112	0.000005583
7	15	0.000003199	0.000010094	-0.000006818
8	17	-0.000009276	0.000003707	-0.000000719
9	15	-0.000006371	-0.000004563	0.000010658
10	8	0.000006675	-0.000004080	-0.000021225
11	6	-0.000006643	0.000007381	0.000011384
12	6	-0.000001576	-0.000000111	0.000009745
13	6	0.000001281	0.000004192	0.000005396
14	6	-0.000002605	0.000001928	0.000006597
15	6	0.000000819	0.000006472	0.000007594
16	1	0.000002134	0.000006595	0.000004710
17	6	-0.000002113	0.000001212	0.000009903
18	1	-0.000003902	-0.000001640	0.000008443
19	6	-0.000000645	0.000003691	0.000009707
20	1	0.000002059	0.000007724	0.000008055
21	1	-0.000003759	0.000000365	0.000011162
22	1	-0.000000931	0.000005145	0.000011185
23	1	-0.000027975	-0.000035107	0.000032798
24	6	0.000003277	0.000006963	0.000000539

25	1	0.000004766	0.000005775	0.000001671
26	1	-0.000000049	0.000003350	-0.000001992
27	1	0.000005230	0.000003135	-0.000000681
28	6	0.000006786	-0.000001555	-0.000012382
29	1	0.000011392	0.000025390	-0.000003387
30	1	0.000004901	0.000008457	0.000002262
31	1	0.000005291	0.000006093	0.000000486
32	6	-0.000000508	0.000006277	0.000005914
33	1	0.000000700	0.000003646	0.000004453
34	1	-0.000001370	0.000001240	0.000006377
35	1	0.000001528	0.000005029	0.000004839
36	6	0.000001726	-0.000000849	0.000001034
37	1	0.000000412	-0.000006140	0.000002157
38	1	-0.000001692	0.000000230	0.000003153
39	1	-0.000003681	-0.000001538	-0.000000227
40	6	-0.000005284	-0.000002294	0.000000918
41	1	-0.000002694	-0.000007393	-0.000001724
42	1	-0.000006379	-0.000008878	-0.000003776
43	1	-0.000001379	-0.000006189	-0.000003743
44	6	-0.000011552	-0.000005569	0.000005755

45	1	0.000006601	-0.000005930	-0.000006353
46	1	-0.000007401	-0.000007546	0.000003582
47	1	-0.000004648	-0.000004269	0.000006277
48	6	0.000006177	-0.000003939	-0.000013290
49	1	-0.000000303	-0.000003609	-0.000008506
50	1	0.000000687	-0.000007429	-0.000007868
51	1	-0.000001481	-0.000003549	-0.000009095
52	6	0.000003407	-0.000001256	-0.000006141
53	1	0.000003128	-0.000002151	-0.000011895
54	1	0.000001984	-0.000005074	-0.000009011
55	1	0.000003650	-0.000000163	-0.000009796
56	6	0.000004609	-0.000001154	-0.000011353
57	1	0.000004799	0.000004910	-0.000007108
58	1	0.000002651	-0.000000468	-0.000008754
59	1	0.000005296	0.000001265	-0.000007915
60	6	0.000003354	-0.000004816	-0.000001388
61	1	0.000002721	0.000002817	-0.000004961
62	1	0.000001851	0.000004413	-0.000001072
63	1	0.000003988	0.000003720	-0.000004339
64	6	0.000003056	-0.000003717	-0.000009196

65	1	-0.000001124	-0.000002346	-0.000001540
66	1	-0.000002249	-0.000004201	-0.000002705
67	1	-0.000001378	-0.000008657	0.000002824

Structure **TS**



TS

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Sum of electronic and thermal Energies= -2510.468699

Sum of electronic and thermal Enthalpies= -2510.467755

Sum of electronic and thermal Free Energies= -2510.571824

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1	6	0.000013619	-0.000007885	0.000004195
2	7	0.000010368	-0.000005440	-0.000003358

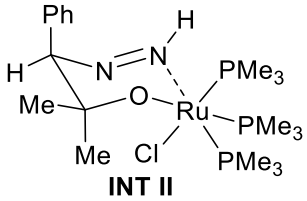
3	7	0.000001097	-0.000002611	0.000003382
4	1	0.000011459	0.000018319	-0.000001474
5	44	-0.000017313	0.000002893	-0.000000468
6	15	-0.000003104	0.000001844	-0.000008964
7	15	0.000000861	0.000003423	-0.000001256
8	17	-0.000000257	-0.000015460	-0.000007266
9	15	0.000003734	0.000000189	0.000003747
10	8	-0.000002156	0.000012839	0.000001794
11	6	-0.000007437	-0.000002972	-0.000011671
12	6	0.000000389	-0.000003204	-0.000005647
13	6	0.000000192	-0.000002142	-0.000003707
14	6	0.000002939	-0.000004196	-0.000002419
15	6	-0.000000003	-0.000003107	-0.000004306
16	1	-0.000001684	-0.000001027	-0.000003633
17	6	0.000002942	-0.000004894	-0.000003903
18	1	0.000003599	-0.000004778	-0.000001822
19	6	0.000001627	-0.000004412	-0.000004609
20	1	-0.000001013	-0.000002345	-0.000005230
21	1	0.000004155	-0.000006097	-0.000003763
22	1	0.000001723	-0.000004973	-0.000005421

23	1	-0.000016453	0.000002599	0.000008456
24	6	-0.000006771	0.000004765	0.000004873
25	1	-0.000004069	0.000003346	0.000001625
26	1	-0.000000641	0.000003437	0.000002851
27	1	-0.000005290	-0.000001366	0.000000236
28	6	-0.000005440	0.000005756	-0.000009512
29	1	0.000003970	-0.000004231	-0.000001623
30	1	-0.000004401	0.000004217	-0.000000967
31	1	-0.000004368	0.000003628	0.000000187
32	6	-0.000002148	0.000004297	0.000003324
33	1	-0.000002724	0.000003755	0.000001202
34	1	-0.000000683	0.000001536	0.000000712
35	1	0.000002820	0.000001799	0.000005406
36	6	-0.000003582	-0.000002999	0.000006506
37	1	0.000003188	0.000005761	0.000000517
38	1	-0.000000275	0.000008463	0.000008955
39	1	-0.000002630	0.000000007	0.000008751
40	6	0.000003119	0.000004427	0.000008418
41	1	0.000005589	0.000003249	0.000012052
42	1	0.000001638	-0.000004735	0.000001411

43	1	-0.000001493	0.000007589	0.000000987
44	6	0.000004861	0.000006103	0.000002649
45	1	-0.000001958	-0.000002739	0.000004571
46	1	0.000005068	0.000001357	0.000003778
47	1	0.000002035	-0.000008435	0.000008037
48	6	-0.000002413	0.000001652	-0.000000457
49	1	-0.000001112	0.000001380	0.000004109
50	1	0.000001339	-0.000002397	0.000001701
51	1	-0.000002316	0.000001133	-0.000001107
52	6	-0.000000062	0.000002095	-0.000001501
53	1	-0.000001937	0.000000211	-0.000002866
54	1	-0.000000319	-0.000002228	-0.000003466
55	1	-0.000001142	-0.000000407	-0.000004375
56	6	-0.000001281	0.000002734	0.000001224
57	1	-0.000004473	0.000003760	-0.000001059
58	1	-0.000003023	0.000003116	0.000005307
59	1	-0.000003021	0.000002119	-0.000001151
60	6	-0.000003590	-0.000010876	0.000000232
61	1	-0.000001553	-0.000001866	-0.000006405
62	1	-0.000000316	-0.000003443	-0.000005662

63	1	-0.000001913	-0.000000225	-0.000005416
64	6	0.000006513	-0.000003741	-0.000001822
65	1	0.000000264	0.000000761	-0.000002923
66	1	0.000009594	-0.000007809	0.000002562
67	1	0.000015661	-0.000001518	0.000005467

Structure **INT II**



INT II

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Sum of electronic and thermal Energies= -2510.475470

Sum of electronic and thermal Enthalpies= -2510.474526

Sum of electronic and thermal Free Energies= -2510.578965

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Number	Number	X	Y	Z

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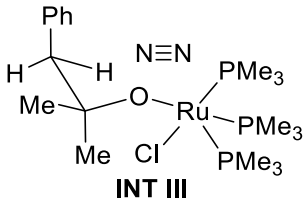
3	7	0.000003248	-0.000002913	0.000001283
4	1	0.000002801	0.000004201	-0.000002129
5	44	-0.000001692	0.000015415	-0.000004157
6	15	-0.000003567	-0.000012197	0.000006292
7	15	0.000000694	-0.000005667	-0.000000011
8	17	-0.000000610	0.000008879	0.000005465
9	15	0.000002910	-0.000001563	0.000010660
10	8	-0.000011795	-0.000005151	-0.000014367
11	6	0.000013137	0.000004121	0.000011275
12	6	0.000000540	-0.000001494	-0.000012833
13	6	-0.000003392	-0.000007471	-0.000003493
14	6	0.000004297	-0.000004368	-0.000002938
15	6	0.000002198	-0.000006986	-0.000006788
16	1	-0.000002181	-0.000006143	-0.000005916
17	6	0.000000120	-0.000003759	-0.000006527
18	1	0.000003870	-0.000000583	-0.000005769
19	6	0.000000698	-0.000003917	-0.000011145
20	1	-0.000001880	-0.000007975	-0.000009076

21	1	0.000004069	-0.000002904	-0.000009111
22	1	0.000001230	-0.000007346	-0.000010822
23	1	-0.000002423	0.000020480	0.000019584
24	6	-0.000003271	-0.000003261	0.000007428
25	1	-0.000002503	-0.000003226	-0.000000511
26	1	0.000002056	0.000000232	-0.000000461
27	1	-0.000003117	0.000001698	-0.000000427
28	6	-0.000001580	-0.000009316	-0.000000547
29	1	-0.000001541	-0.000004904	-0.000010530
30	1	-0.000004064	-0.000006321	0.000001100
31	1	-0.000006489	-0.000000193	0.000001789
32	6	-0.000003023	-0.000005542	-0.000002636
33	1	-0.000000540	-0.000003481	-0.000003535
34	1	0.000001246	0.000000919	-0.000011627
35	1	0.000001478	0.000000079	-0.000004822
36	6	0.000005252	0.000002371	0.000000869
37	1	-0.000001077	0.000004467	0.000005433
38	1	-0.000000386	0.000003209	0.000000087
39	1	0.000003634	0.000005146	0.000000535
40	6	0.000003419	0.000014161	-0.000001500

41	1	0.000005598	0.000007035	0.000002099
42	1	0.000004326	0.000003452	0.000005034
43	1	0.000003664	0.000002049	0.000007689
44	6	0.000005741	0.000003044	0.000000370
45	1	0.000006802	0.000004933	-0.000002149
46	1	0.000006639	0.000005974	-0.000001139
47	1	0.000005105	0.000003196	-0.000002753
48	6	-0.000001752	0.000007700	0.000010044
49	1	-0.000002038	0.000004691	0.000005165
50	1	0.000001699	0.000004635	0.000005999
51	1	-0.000003265	0.000003873	0.000010281
52	6	0.000003790	-0.000001002	0.000005012
53	1	-0.000004314	0.000003478	0.000008481
54	1	-0.000003475	0.000006163	0.000006362
55	1	-0.000004914	0.000001107	0.000004790
56	6	-0.000006265	-0.000001390	0.000006262
57	1	-0.000005985	-0.000000157	0.000004959
58	1	-0.000003966	0.000000931	0.000006842
59	1	-0.000004614	0.000001368	0.000009383
60	6	-0.000001039	-0.000002947	-0.000001029

61	1	-0.000004617	-0.000001640	0.000001350
62	1	-0.000001760	-0.000003894	-0.000002077
63	1	-0.000002513	-0.000002265	-0.000005423
64	6	0.000001039	-0.000000072	-0.000000066
65	1	0.000000632	0.000000511	0.000000214
66	1	-0.000000357	0.000002171	0.000000215
67	1	0.000000585	0.000002921	-0.000000733

Structure **INT III**



INT III

Sum of electronic and zero-point Energies= -2510.576010

Sum of electronic and thermal Energies= -2510.534874

Sum of electronic and thermal Enthalpies= -2510.533930

Sum of electronic and thermal Free Energies= -2510.652787

Center Number	Atomic Number	Forces (Hartrees/Bohr) X	Y	Z
1	6	-0.000001355	0.000002093	-0.000006572
2	7	0.000001597	0.000016831	-0.000012843
3	7	0.000007239	0.000012704	-0.000006024
4	44	-0.000002417	-0.000005933	0.000002118
5	15	-0.000003060	-0.000003138	-0.000000634
6	15	-0.000000745	0.000001386	0.000012315
7	17	-0.000002960	0.000008032	0.000002062
8	15	0.000006796	-0.000000039	-0.000001000
9	8	-0.000005389	-0.000001090	-0.000008396
10	6	0.000006443	-0.000002639	0.000005681
11	6	-0.000000418	0.000003762	-0.000002614
12	6	0.000001298	0.000001406	-0.000009430
13	6	0.000002625	0.000006138	-0.000005806
14	6	0.000000231	0.000003603	-0.000010697
15	1	-0.000000803	-0.000001927	-0.000010842

16	6	0.000003367	0.000009636	-0.000005240
17	1	0.000003507	0.000008860	-0.000002092
18	6	0.000002393	0.000008092	-0.000008238
19	1	0.000000706	0.000001611	-0.000012556
20	1	0.000003966	0.000013068	-0.000003544
21	1	0.000002952	0.000008963	-0.000009383
22	1	0.000000010	-0.000002453	-0.000008336
23	6	-0.000004538	-0.000013286	0.000000563
24	1	-0.000003897	-0.000015128	0.000001874
25	1	-0.000001964	-0.000008420	-0.000000033
26	1	-0.000003552	-0.000007984	0.000004153
27	6	-0.000004841	-0.000011073	0.000005915
28	1	-0.000002803	-0.000009369	0.000004938
29	1	-0.000004212	-0.000015191	0.000003876
30	1	-0.000002866	-0.000009951	0.000010127
31	6	-0.000003725	-0.000013126	-0.000004274
32	1	-0.000004364	-0.000014417	-0.000004625
33	1	-0.000000928	-0.000006999	-0.000006256
34	1	-0.000003660	-0.000010692	-0.000006281
35	6	0.000002185	-0.000003365	-0.000005554

36	1	-0.000001706	-0.000002262	-0.000001903
37	1	-0.000002444	-0.000004864	-0.000006053
38	1	-0.000000032	0.000000339	-0.000006839
39	6	0.000003611	0.000008388	-0.000003323
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41	1	0.000002972	0.000009139	-0.000000615
42	1	0.000001877	0.000008058	0.000000896
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46	1	0.000000712	-0.000000022	-0.000009940
47	6	0.000000567	0.000003670	0.000005642
48	1	0.000002342	0.000007763	0.000009261
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50	1	0.000002047	0.000007626	0.000013113
51	6	0.000001616	0.000001864	0.000015963
52	1	0.000000808	0.000001554	0.000018057
53	1	0.000002283	0.000003204	0.000011325
54	1	-0.000003531	-0.000001208	0.000011707
55	6	0.000000532	-0.000003936	0.000010771

56	1	-0.000001872	-0.000005052	0.000012727
57	1	-0.000002908	-0.000004303	0.000009658
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59	6	-0.000001933	-0.000003662	-0.000001718
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61	1	-0.000000907	-0.000003914	-0.000000809
62	1	-0.000001804	-0.000007769	-0.000004166
63	6	-0.000000786	0.000004128	0.000005873
64	1	0.000002329	0.000001876	0.000005313
65	1	0.000000769	0.000000534	0.000007812
66	1	0.000001163	0.000001724	0.000005691
67	1	0.000004599	0.000005478	-0.000003912

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Chapter 5 : Carbonyls as Latent Alkyl Carbanions for Conjugate Additions

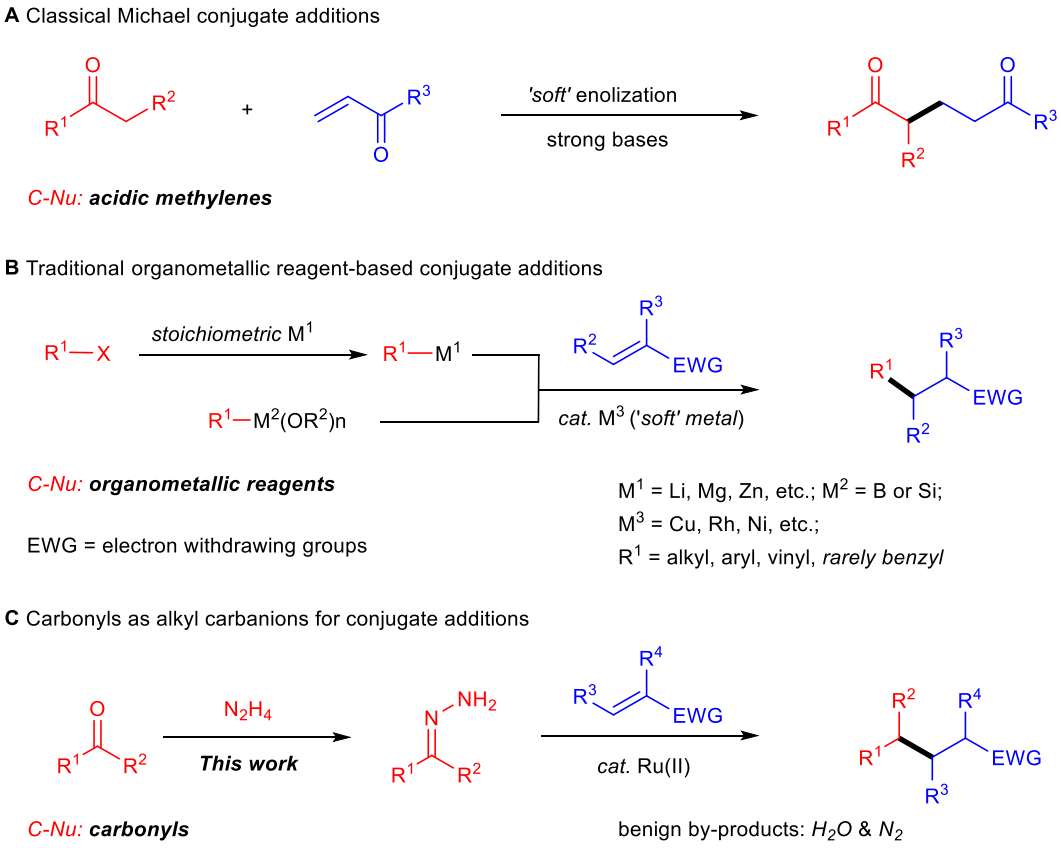
5.1 Preface

This chapter describes a continuous development of ruthenium-catalyzed conjugate addition reactions utilizing carbonyl compounds as alkyl carbanion equivalents. The conceptual picture discussed herein is closely linked to that presented in the last chapter (Chapter 4). All experimental studies in the current project were jointly performed between Dr. Haining Wang (Postdoctoral Fellow 2014-2017 in the Li lab) and me. My additional contribution to this work included conceiving a mechanistic picture of this chemistry and leading the preparation of the manuscript. This work was published in *Angewandte Chemie International Edition* **2017**, *56*, 6302-6306).

5.2 Introduction

Conjugate addition of carbon nucleophiles to electron-deficient olefins represents one of the most reliable alkylation strategies for carbon-carbon bond formation with exclusive 1,4-regioselectivity.[1] Traditional conjugate additions to α,β-unsaturated carbonyl compounds and related electron-deficient olefins are generally accomplished in two ways: (1) via a 'hard' enolization of carbonyl derivatives bearing acidic methylene protons (Scheme 5-1, A),[5.5a-d] and (2) via a 'soft' transition metal-mediated or -catalyzed (e.g. copper,[2] rhodium[3] and other metals[4]) addition process, whereby stoichiometric organometallic or organometalloid reagents serve as

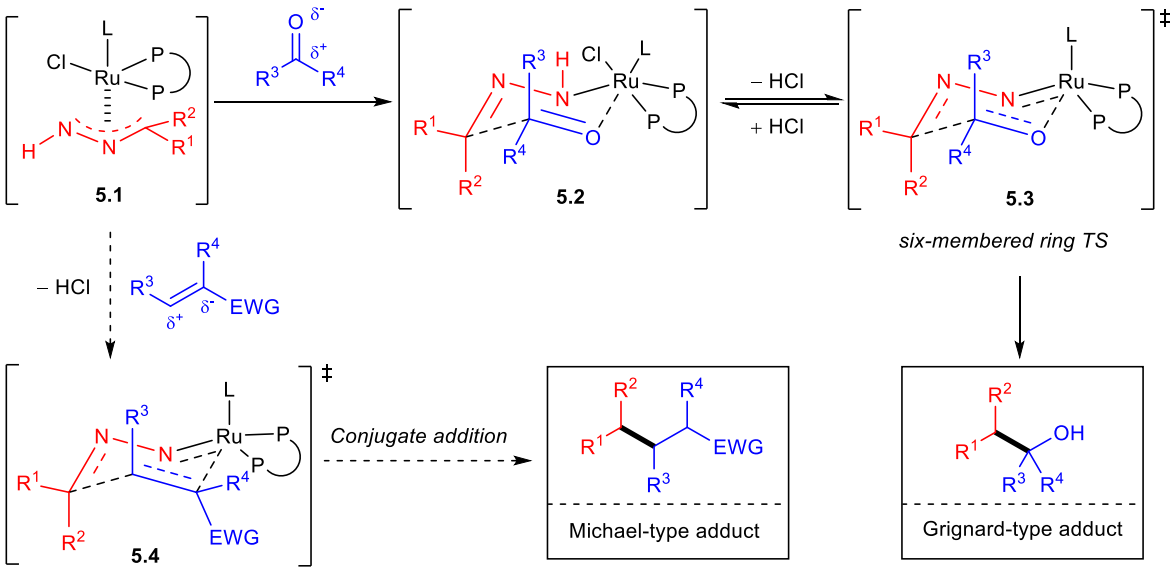
carbon nucleophiles (Scheme 5-1, B).[5] While tremendous progress has been made in controlling selectivity, particularly stereoselectivity,[2h,2i,3,4] the choice of carbon nucleophiles remains limited



Scheme 5-1 Carbon Nucleophiles in Conjugate Additions for the Formation of New C–C Bonds

for the purpose of chemical diversifications. Taking the most important organometallic reagent-based method as an example, stoichiometric amounts of metal are essential to generate carbon nucleophiles from petroleum-derived organohalides. Furthermore, the high reactivity and basicity of most organometallic reagents often make it challenging to realize broad functional group tolerance, and demand a strict control over low-temperature, anhydrous and oxygen-free reaction conditions.[2h] Limted types of carbon nucleophiles, along with innate constraints imposed by organometallic reagents, prompted us to explore viable carbanion alternatives for conjugate addition reactions. Herein, we report a ruthenium(II)-catalyzed conjugate addition of carbonyl

compounds,[6] masked as 'soft' alkyl carbanions via polarity reversal,[7] to a wide range of electron-deficient olefins under mild reaction conditions (Scheme 5-1, C), complementary to the organometallic reagent-based conjugate additions mediated or catalyzed by 'soft' transition metals.



Scheme 5-2 Our Hypothesis of Using Carbonyls as Alkyl Carbanions for Conjugate Additions

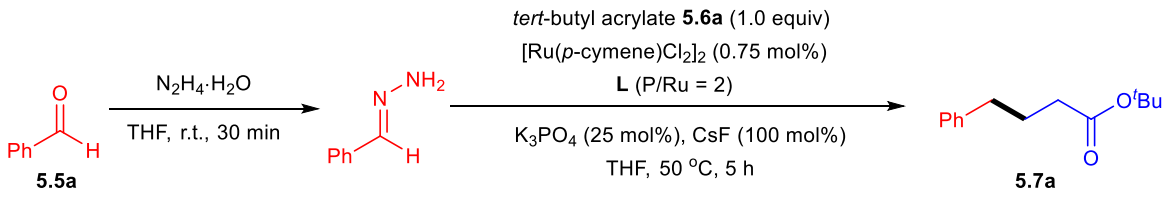
In Chapter 3, we described a ruthenium-based catalytic system for a direct deoxygenation of primary aliphatic alcohols, being highly chemo- and regio-selective in both simple and complex compounds.[8] Capitalizing on the ruthenium complex (**5.1**, Scheme 5-2) postulated in the deoxygenation chemistry, we made another discovery by engaging carbonyl compounds (**5.2**, Scheme 5-2) to form new carbon-carbon bonds, possibly via a Zimmerman-Traxler chair-like transition state (**5.3**, Scheme 5-2).[9] This chemistry was discussed in Chapter 4. We speculated that the polarized carbon-carbon double bonds in electron-deficient olefins might be an equally reactive substitute for carbonyl compounds in **5.3** (**5.4**, Scheme 5-2). In addition, the softness of ruthenium(II), bearing a resemblance to 'soft' metals in the classical conjugate addition,[10] led us to question if such homogenous ruthenium(II) catalysis could be even more effective for conducting nucleophilic conjugate additions than carbonyl additions.

5.3 Results and Discussion

5.3.1 Optimization of Reaction Conditions

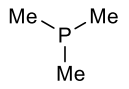
To verify this hypothesis, benzaldehyde **5.5a** and *tert*-butyl acrylate **5.6a** were chosen as model substrates in the pilot study. The preformed hydrazone from **5.5a** was treated with **5.6a** in the presence of $[Ru(p\text{-cymene})Cl_2]_2$, 1,2-bis(dimethylphosphino)ethane (dmpe, **L₃**), and K_3PO_4 in THF solution. To our delight, the desired Michael-type 1,4-adduct **5.7a** was obtained in 76% yield at 50 °C after 5 h, with a stoichiometric amount of CsF as additive (Table 5-1, entry 3).[11] It should be noted that no desired 1,4-adduct was produced in the absence of the ruthenium(II) pre-catalyst,[12] and a significantly lower yield was obtained without the participation of either phosphine ligands or cesium fluoride (40% and 65% ^{1}H NMR yield, respectively). Our early investigation on spectator ligands bound to the ruthenium(II) pre-catalyst suggested that significant enhancement in catalyst activity was achieved by using electron-rich phosphine ligands.[8,9] In contrast, strong σ-donors other than phosphines, including NHCs and charge-neutral amido ligands, were largely inferior. Aligned with this observation, studies on the influence of various electron-rich phosphine ligands were prioritized for optimization (Table 5-1). In fact, the conjugate addition of benzaldehyde-derived hydrazone to **5.6a** proceeded smoothly as long as certain phosphines were used as dative ligands, regardless of their denticity. Nevertheless, varying levels of catalyst activity were observed, resulting in yield variations of **5.7a**. For instance, monodentate tricyclohexylphosphine (PCy_3, **L₂**) was less efficient than bidentate 1,4-bis(dicyclohexylphosphino)butane (dcpb, **L₉**) (entry 2 vs 9). However, the use of trimethylphosphine (PMe_3, **L₁**) and **L₃** afforded comparable yields (entry 1 vs 3), presumably due

Table 5-1[a] Effect of Various Phosphine Ligands

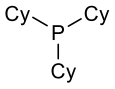


5.5a 5.7a

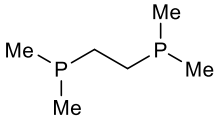
Entry	L	Yield (%)	Entry	L	Yield (%)
1	L_1	73	7	L_7	91
2	L_2	24	8	L_8	71
3	L_3	76	9	L_9	46
4	L_4	80	10	L_{10}	50
5	L_5	58	11	L_{11}	45
6	L_6	76	12	L_{12}	37



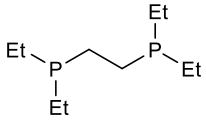
PMe_3 (L_1)



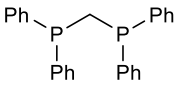
PCy_3 (L_2)



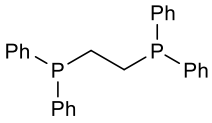
dmpe (L_3)



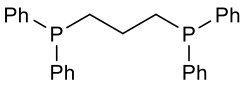
depe (L_4)



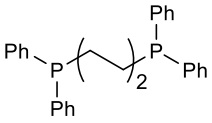
dppm (L_5)



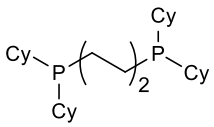
dppe (L_6)



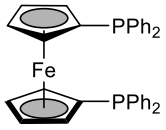
dppp (L_7)



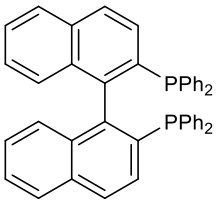
dppb (L_8)



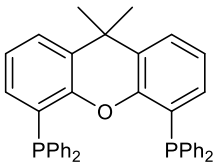
dcpb (L_9)



dppf (L_{10})



(±)-BINAP (L_{11})



Xantphos (L_{12})

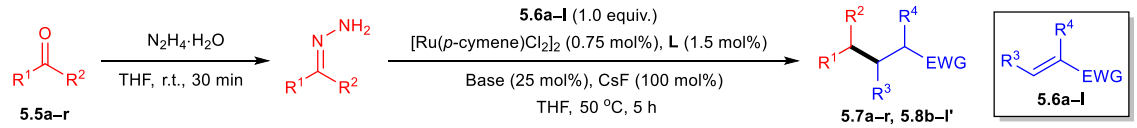
[a]Reaction conditions: **5.5a** (25 μL, 0.24 mmol), $N_2H_4{\cdot}H_2O$ (13 μL, 0.26 mmol), THF (100 μL), room temperature, 30 min; **5.6a** (30 μL, 0.2 mmol), $[Ru(p\text{-cymene})Cl_2]_2$ (0.9 mg, 0.75 mol%), $\mathbf{L_1}$ and $\mathbf{L_2}$ (3.0 mol%), or $\mathbf{L_3}$-$\mathbf{L_{12}}$ (1.5 mol%), K_3PO_4 (10.6 mg, 25 mol%), CsF (30 mg, 100 mol%), 50 °C, 5 h, under N_2. The volume of $N_2H_4{\cdot}H_2O$ was measured more precisely using the prepared stock THF solution, see details in the Supplementary Information. Yields were determined by ^1H NMR using mesitylene as an internal standard.

to their similar electronic and steric nature. On the other hand, diphenylphosphines linked by alkylidene bridges outperformed those by other linkers, including 1,1'-bis(diphenylphosphino)ferrocene (dppf, **L$_{10}$**), 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP, **L$_{11}$**) and 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (Xantphos **L$_{12}$**) (entries 5-8 vs 10-12). In the former case, the alkylidene linker with three carbons is optimal, as attenuated reactivity was shown in others with either longer or shorter linker. Finally, we concluded that 1,3-bis(diphenylphosphino)propane (dppp, **L$_7$**) was the preferred spectator ligand binding to [Ru(*p*-cymene)Cl$_2$]$_2$ in the current reaction.

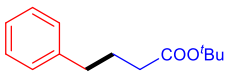
5.3.2 Reaction Scope

Under the optimized reaction conditions, **5.7a** was obtained in 91% yield (Table 5-1, entry 7). The scope of the optimized conjugate addition process was initially explored using aromatic carbonyl compounds as carbon nucleophiles in the presence of **L$_7$**. In general, moderate to excellent yields were obtained using a broad range of electron-rich and electron-poor aromatic aldehydes (Table 5-2, **5.5a-n**). A number of functional groups including allyl phenyl ether (**5.7h**), aryl ethers (**5.7g**, **5.7i**), aryl halides (**5.7b**, **5.7c**) and trifluoromethyls (**5.7d**, **5.7e**) were compatible with this transformation. Heteroaromatic aldehydes containing furans (**5.5k**), thiophenes (**5.5l**) and pyridines (**5.5m**) were also effective as nucleophilic coupling partners. A formally similar conjugate addition reaction (analogous to the formation of **5.7k** from **5.5k**) could go through a step-wise Kishner reduction of 2-furylhydrazone and the ene reaction.[13] Surprisingly, 2-pyridyl substituent does not cause any attenuation in catalyst reactivity, given that it is a well-known chelating ligand in transition metal catalysis.[14] On the contrary, steric encumbrance proves to be a stronger factor in catalytic reactivity, as significantly lower yield was obtained in aromatic ketone **5.5j** even at an elevated temperature, compared with aldehyde counterpart **5.5a**. In addition, poor to moderate yields were observed in electron-rich aromatic aldehydes (**5.7f-i**). To improve catalyst activity, a more cost-effective bidentate alkylphosphine — dmpe **L$_3$**, a stronger σ-donor but a

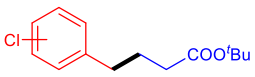
Table 5-2[a] Scope of Conjugate Additions Masking Carbonyls as Alkyl Carbanions



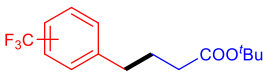
Scope of aromatic carbonyls (L: dppp L_7 *or* dmpe L_3, Base: K_3PO_4)



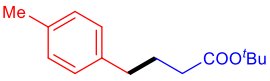
5.7a
L_7, 91%
L_3, 76%; 88%[b]



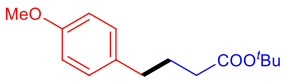
5.7b: 2-Cl, 5.7c: 4-Cl
L_7, 82% (**3b**); 98%(**3c**)
L_3, 67% (**3b**); 71%(**3c**)



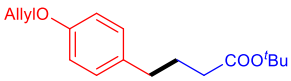
5.7d: 2-CF_3, 5.7e: 4-CF_3
L_7, 94% (**3d**); 90%(**3e**)
L_3, 83% (**3d**); 67%(**3e**)



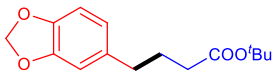
5.7f
L_7, 58%
L_3, 76%



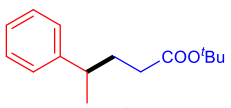
5.7g
L_7, 55%
L_3, 80%



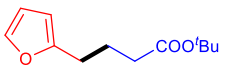
5.7h
L_7, 50%
L_3, 79%



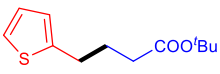
5.7i
L_7, 30%
L_3, 69%



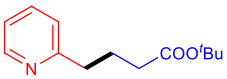
5.7j[c]
L_7, 23%
L_3, 50%



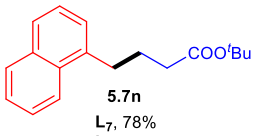
5.7k
L_7, 58%
L_3, 62%



5.7l
L_7, 57%
L_3, 64%

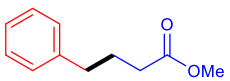


5.7m
L_7, 83%
L_3, 38%

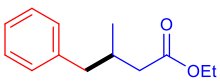


5.7n
L_7, 78%
L_3, 73%

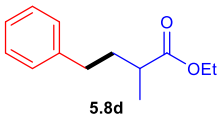
Scope of electron-deficient olefins



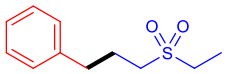
5.8b
L_7, 96%
L_3, 60%



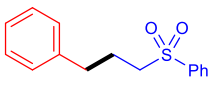
5.8c
L_7, 42%
L_3, 82%



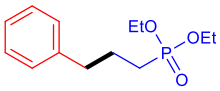
5.8d
L_7, 27%
L_3, 27%



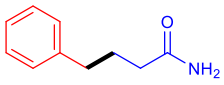
5.8e
L_7, 75%
L_3, 72%



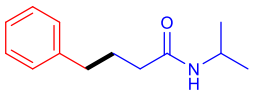
5.8f
L_7, 69%
L_3, 80%



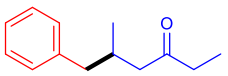
5.8g
L_7, 64%
L_3, 92%



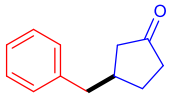
5.8h
L_7, 49%
L_3, 52%



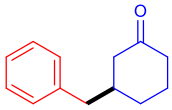
5.8i
L_7, 36%
L_3, 67%



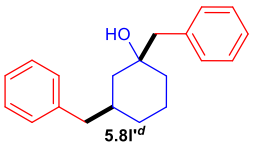
5.8j
L_7, 47%
L_3, 69%



5.8k
L_7, 74%
L_3, 62%

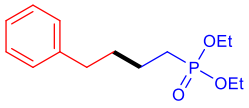


5.8l[c]
L_7, 39%
L_3, 44%; 0%[e]

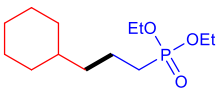


5.8l'[d]
L_7, 43%
L_3, 45%; 98%[e]

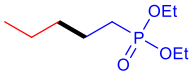
Scope of aliphatic aldehydes[f] (L: dppe L_4, Base: KO*t*Bu)



5.7o, 40%



5.7p, 44%



5.7q, 42%

[a]Reaction conditions: **5.5a–r** (0.24 mmol), $N_2H_4{\cdot}H_2O$ (13.3 μL, 0.26 mmol), THF (100 μL), room temperature, 30 min; **5.6a–l** (0.2 mmol), $[Ru(p\text{-cymene})Cl_2]_2$ (0.9 mg, 0.75 mol%), **L**: L_7 or L_3 (1.5 mol%),

Base: K_3PO_4 (10.6 mg, 25 mol%), CsF (30 mg, 100 mol%), 50 °C, 5 h, under N_2. Isolated yields were reported. [b]Gram-scale synthesis was conducted (**5.6a**, 10 mmol). [c]Both hydrazone synthesis and the subsequent conjugate addition were conducted at 80 °C for 24 h. [d]**5.8l** and **5.8l'** were isolated as a mixture in the reaction. [e]Hydrazone (2.4 equiv) was prepared from **5.5a** (0.48 mmol) and $N_2H_4 \cdot H_2O$ (26 µL, 0.52 mmol). [f]**5.5o-q** (0.24 mmol), **5.6g** (0.2 mmol), **L**: $\mathbf{L_4}$ (0.7 µL, 1.5 mol%), Base: KO*t*Bu (5.6 mg, 25 mol%). The volume of $\mathbf{L_4}$ was measured more precisely using the prepared stock THF solution.

weaker π-acceptor than $\mathbf{L_7}$ — was chosen, instead of 1,2-bis(diethylphosphino)ethane (depe, $\mathbf{L_4}$) which was better in the model study (Table 5-1, entry 4 vs 3). Indeed, the switch from L_7 to L_3 led to higher conversions and yields across all electron-rich aromatic aldehydes (**5.7f-i**, $\mathbf{L_3}$ vs $\mathbf{L_7}$). Notably, such a ligand switch overcame the steric disadvantage of aromatic ketones, providing a modest yield improvement (**5.7j**, $\mathbf{L_3}$ vs $\mathbf{L_7}$). As opposed to the increase of yields in electron-rich aromatic aldehydes, the erosion of yields was detected in most electron-deficient counterparts (**5.5a-e**, **1m**). Nevertheless, a synthetically valuable feature of the current chemistry is its ability to incorporate highly functionalized benzyl groups into α,β-unsaturated esters via conjugate additions.[15] Such benzyl incorporation has long been a non-trivial challenge in the classical organometallic reagent-based methods. Importantly, an effective gram-scale synthesis of **5.7a** (1.94 g, 88%) was carried out to demonstrate the practicability of the current method (Table 5-2, **5.7a** with $\mathbf{L_3}$).

Next, the scope of electron-deficient olefins was surveyed. Under standard reaction conditions, a broad spectrum of electron-deficient olefins was successfully coupled with benzaldehyde-derived hydrazone, affording the corresponding 1,4-addition products in moderate to excellent yields (Table 5-2, **5.8b**-**l**). Specifically, esters (**5.8a**-**d**), ketones (**5.8j**-**l**), sulfones (**5.8e**, **5.8f**), phosphonates (**5.8g**), and amides (**5.8h**, **5.8i**) were all accommodated, indicating the mildness of the reaction conditions and the broad functional group tolerance of this method. Exclusive 1,4-regioselectivity was observed in the acyclic enone and 2- cyclopentenone (**5.8j**, **5.8k**). In the case

of 2-cyclohexenone, however, more cyclic tertiary alcohol **5.8l'** was generated than the desired monobenzylated product **5.8l** (**L**$_7$, **5.8l'** vs **5.8l**). Doubling the amount of hydrazone (2.4 equiv) prepared from **5.5a** led to the exclusive formation of **5.8l'** in 98% yield. Intriguingly, the unorthodox dibenzylation featuring successive 1,4- and 1,2-addition did not occur on **5.6k**. This striking reactivity difference between **5.6k** and **5.6l** likely stemmed from the torsional ring strain increase in 5-membered rings, given the sp^2 hybridized carbon could have changed to sp^3 hybridized carbon through benzylation. Consistent with the negative steric influence seen earlier in aromatic ketones, reactivity of sterically bulky olefins dropped dramatically. For example, unlike linear propionates **5.6a** and **5.6b**, methyl substituent at the α position of propionate **5.6d** caused a drastic yield loss. By contrast, minor steric influence on reactivity was noticed in β-branched propionate **5.6c**. In cases where the use of **L**$_7$ provided low yields, a ligand switch to **L**$_3$ was generally necessary to increase yields (**5.8b**, **5.8f**-**j**), albeit with a few exceptions (**5.8d** and **5.8l**).

To further exploit the versatility of this chemistry, aliphatic aldehydes bearing different substituents (arylmethyl, cyclohexyl and ethyl) were examined in their conjugate additions to diethyl vinylphosphonate **5.6g** (Table 5-2, **5.7o**-**q**). Unfortunately, performing these reactions under standard conditions only afforded a trace amount of corresponding 1,4-addition products. Enlightened by our previous study on carbonyl additions,[31] we found that two parameters influence yields for reactions of aliphatic aldehydes: basicity and ligand. Combination of a strong base KO*t*Bu and an electron rich phosphine ligand **L**$_4$ delivered modest yields of the desired alkyl phosphonates in all cases. Although preliminary, success in coupling aliphatic aldehydes with electron-deficient olefins via conjugate additions is exciting because a majority of natural carbonyl compounds belong to this class.

5.4 Conclusions

In summary, we have developed carbonyls as latent alkyl carbanions for conjugate additions via the ruthenium(II)-catalzyed reductive coupling, with hydarzine as the key reductant. Such carbon nucleophiles can react with various electron-deficient olefins, complementary to the 'soft' metal-based carbanions in the classical conjugate additions. This reaction proceeds under mild conditions, and enables a variety of functional groups pre-installed on both coupling partners. Efforts to elucidate the pertinent mechanism, expand nucleophilic carbonyl partners, and develop an asymmetric variant are ongoing in our laboratory.

5.5 Experimental

5.5.1 General Considerations

Reaction Setup: All reactions were carried out in flame-dried V-shaped microwave reaction vials, covered by aluminum seals with PTFE-faced silicone septa, under an atmosphere of nitrogen unless otherwise stated. All reported reaction temperatures correspond to oil bath temperatures. All air and moisture sensitive catalysts, ligands, and reagents were stored and charged in MBRAUN UNI lab Pro Glove Box Workstation.

Purifications: All work-up and purification procedures were carried out with reagent-grade solvents. Analytical thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F_{254} pre-coated plates (0.25 mm). Flash column chromatography was performed with E. Merck silica gel P60 (40–63 μm particle size, 230–400 mesh) (SiO_2). Unless otherwise specified, "SiO_2" refers to P60 grade silica gel. Visualization was accomplished with UV light and/or iodine (I_2) or Vanillin solution. Retention factor (R_f) values reported were measured using a 10 × 2 cm TLC plate in a developing chamber containing the solvent system (10 mL) described. Automated flash column chromatography was performed on Biotage Isolera™ Spektra Systems with ACI™.

Solvents: Tetrahydrofuran (THF) and *N*,*N*-dimethylformamide (DMF) were taken directly from the *Pure Solvent MD-7* purification system (Innovative Technology). Solvents for filtration, transfers, and chromatography were ethyl acetate (EtOAc) (Fisher, ACS grade) and hexane (Fisher, ACS grade).

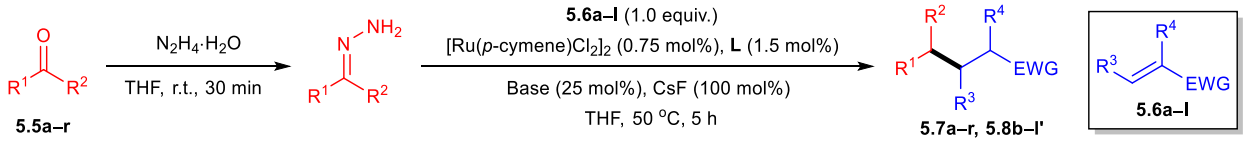
Chemicals: In the model study, benzaldehyde (Aldrich) and *tert*-butyl acrylate (Aldrich) were distilled prior to use. Other chemicals are commercially available and used without further purification: $[Ru(p\text{-cymene})Cl_2]_2$ (Aldrich), $\mathbf{L_{1\text{-}12}}$ (Aldrich), potassium *tert*-butoxide (Aldrich), potassium phosphate (Aldrich), cesium fluoride (Aldrich), hydrazine hydrate (Reagent Grade, 64–65% wt, Aldrich), mesitylene (Aldrich), anhydrous sodium sulfate. All liquid carbonyl compounds were distilled and solid ones were recrystallized prior to use.

NMR Spectroscopy: Nuclear magnetic resonance (^{1}H, ^{13}C and ^{31}P NMR) spectra were recorded on a Bruker AV500 equipped with a 60-position Sample Xpress sample changer (^{1}H, 500 MHz; ^{13}C, 125 MHz; ^{31}P, 202 MHz). Chemical shifts for both ^{1}H NMR and ^{13}C NMR spectra are expressed in parts per million (ppm) units downfield from TMS, with the solvent residue peak as the chemical shift standard ($CDCl_3$: δ 7.26 ppm in ^{1}H NMR; δ 77.16 ppm in ^{13}C NMR). Data are reported as following: chemical shift, multiplicity (s = singlet, d = doublet, dd = doublet of doublets, t = triplet, td = triplet of doublets, q = quartet, quin = quintet, sext = sextet, sep = septet, m = multiplet, br = broad singlet), coupling constants *J* (Hz), and integration.

Mass Spectrometry: Mass spectrometry (MS) was performed by the McGill Chemistry Department Mass Spectrometry Facility. High Resolution Mass spectra were recorded using electrospray ionization (ESI+), performed either on "Exactive Plus Orbitrap" a Thermo Scientific high resolution accurate mass (HR/AM) FT mass spectrometer, or a Bruker Daltonics Maxis Impact quadrupole-time of flight (QTOF) mass spectrometer.

Characterization of Products: The following compounds were newly synthesized by current method: **5.7b-5.7k**, **5.8d**, **5.8e**, **5.8i**, **5.8l'**, **5.7p**. Known compounds were noted with references in the spectroscopic data section.

5.5.2 General Synthetic Procedure for Alcohol Deoxygenation



5.5.2.1 General Procedure A (with Ligands: PMe_3, PCy_3, dmpe, and depe)

A flame-dried V-shape microwave reaction vial (10 cm^3) equipped with a magnetic stir bar was charged with [Ru(*p*-cymene)Cl_2]$_2$ (0.9 mg, 0.0015 mmol, 0.75 mol%) and K_3PO_4 (10.6 mg, 0.05 mmol, 25 mol%). The reaction vial was transferred into the glove box and charged with dmpe (0.5 μL, 0.003 mmol, 1.5 mol%) and CsF (30 mg, 0.20 mmol, 100 mol%) before being sealed with a rubber septum. The reaction vial was then moved out of the glove box and sequentially charged with α,β-unsaturated olefins (0.2 mmol, 1.0 equiv) and **hydrazone solution A** (~140 μL) under N_2 atmosphere. The reaction mixture was then heated to 50 °C in an oil bath. Upon stirring for 5 h, the reaction mixture was filtered through a plug of silica gel with EtOAc (2 mL) as eluent, concentrated, and purified by flash chromatography (hexane/ethyl acetate 90:10 as eluent) to give the corresponding products.

5.5.2.2 General Procedure B (with Other Phosphine Ligands)

A flame-dried V-shape microwave reaction vial (10 mL) equipped with a magnetic stir bar was charged with [Ru(*p*-cymene)Cl_2]$_2$ (0.9 mg, 0.0015 mmol, 0.75 mol%), dppp (1.3 mg, 0.003 mmol, 1.5 mol%) and DMF (25 μL). The mixture was then heated to 100 °C in an oil bath. Upon stirring for 10 min, the DMF was removed by vacuum. The reaction vial was then sequentially charged with K_3PO_4 (10.6 mg, 0.05 mmol, 25 mol%), CsF (30 mg, 0.20 mmol, 100 mol%), α,β-unsaturated

olefins (0.2 mmol, 1.0 equiv), and **hydrazone solution A** (~140 μL) under N_2 atmosphere. The reaction mixture was then heated to 50 °C in an oil bath. Upon stirring for 5 h, the reaction mixture was filtered through a plug of silica gel with EtOAc (2 mL) as eluent, concentrated, and purified by flash chromatography (hexane/ethyl acetate 90:10 as eluent) to give the corresponding products.

5.5.2.3 General Procedure C (for Aliphatic Aldehydes)

A flame-dried V-shape microwave reaction vial (10 cm^3) equipped with a magnetic stir bar was charged with [Ru(*p*-cymene)Cl_2]$_2$ (0.9 mg, 0.0015 mmol, 0.75 mol%) and KO*t*Bu (5.6a mg, 0.05 mmol, 25 mol%). The reaction vial was transferred into the glove box and charged with depe solution (3 μL, 1M in THF, 0.003 mmol, 1.5 mol%) and CsF (30 mg, 0.20 mmol, 100 mol%) before being sealed with a rubber septum. The reaction vial was then moved out of the glove box and sequentially charged with diethyl vinylphosphonate **5.6g** (30.7 μL, 0.2 mmol, 1.0 equiv) and **hydrazone solution A** (~140 μL) under N_2 atmosphere. The reaction mixture was then heated to 50 °C in an oil bath. Upon stirring for 5 h, the reaction mixture was filtered through a plug of silica gel with EtOAc (2 mL) as eluent, concentrated, and purified by flash chromatography (ethyl acetate as eluent) to give the corresponding products.

Hydrazone solution A: A mixture of carbonyl compounds (0.24 mmol, 1.2 equiv) and hydrazine monohydrate (13 μL, 0.26 mmol, 64–65 wt%, 1.3 equiv) in THF (0.1 mL) solution was stirred at room temperature for 30 min. Prior to injection of this **hydrazone solution A** into the reaction mixture, a small amount of anhydrous Na_2SO_4 was added.

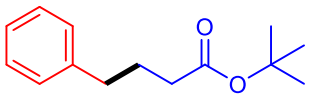
5.5.2.4 Gram-Scale Synthesis

A flame-dried flask (50 cm^3) equipped with a magnetic stir bar was charged with [Ru(*p*-cymene)Cl_2]$_2$ (46 mg, 0.075 mmol, 0.75 mol%) and K_3PO_4 (0.53 g, 2.5 mmol, 25 mol%). The flask was transferred into the glove box and charged with dmpe (25 μL, 0.15 mmol, 1.5 mol%) and CsF (1.52 g, 10 mmol, 100 mol%) before being sealed with a rubber septum. The flask was then moved

out of the glove box and sequentially charged with *tert*-butyl acrylate (**5.6a**) (1.46 mL, 10 mmol, 1.0 equiv) and **hydrazone solution B** (~6.8 mL) under N_2 atmosphere. The reaction mixture was then heated to 50 °C in an oil bath. Upon stirring for 5 h, the reaction mixture was filtered through a plug of silica gel with EtOAc (50 mL) as eluent, concentrated, and purified by flash chromatography (hexane/ethyl acetate 90:10 as eluent) to give the corresponding product **5.7a** as colorless oil (1.94 g, 88% yield).

Hydrazone solution B: A mixture of benzaldehyde (**5.5a**) (1.22 mL, 12 mmol, 1.2 equiv) and hydrazine monohydrate (630 µL, 13 mmol, 64–65 wt%, 1.3 equiv) in THF (5 mL) solution was stirred at room temperature for 30 min. Prior to injection of this **hydrazone solution B** into the reaction mixture, a small amount of anhydrous Na_2SO_4 was added.

5.5.3 Spectroscopic Data



tert-Butyl 4-phenylbutanoate **(5.7a)**[16]

Following the **general procedure B** in the presence of dppp (**L7**), **5.7a** was obtained from the conjugate addition of benzaldehyde **5.5a** (25 µL, 0.24 mmol) to *tert*-butyl acrylate **5.6a** (30 µL, 0.2 mmol), as a colorless oil (40.0 mg, 91% yield) after flash chromatography. Following the **general procedure A** in the presence of dmpe (**L3**), **5.7a** was isolated as a colorless oil (33.4 mg, 76% yield).

Data for **5.7a**:

TLC: R_f 0.85 (9:1 hexane/EtOAc) [UV/I_2/Vanillin]

^{1}H NMR: (500 MHz, $CDCl_3$, ppm)

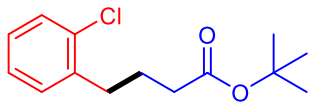
δ 7.31 – 7.26 (m, 2H), 7.22 – 7.15 (m, 3H), 2.64 (t, J = 7.5 Hz, 2H), 2.24 (t, J = 7.5 Hz, 2H), 1.91 (quin, J = 7.5 Hz, 2H), 1.45 (s, 9H).

^{13}C NMR: (125 MHz, $CDCl_3$, ppm)

δ 173.1, 141.8, 128.7, 128.5, 126.1 80.3, 35.3, 35.1, 28.3, 26.9.

HRMS: (ESI, *m/z*)

calcd for $C_{14}H_{20}O_2Na[M+Na]^+$ 243.1356, found: 243.1354.



tert-Butyl 4-(2-chlorophenyl)butanoate **(5.7b)**

Following the **general procedure B** in the presence of dppp (**L**$_7$), **5.7b** was obtained from the conjugate addition of 2-chlorobenzaldehyde **5.5b** (27 µL, 0.24 mmol) to *tert*-butyl acrylate **5.6a** (30 µL, 0.2 mmol), as a colorless oil (48.0 mg, 98% yield) after flash chromatography. Following the **general procedure A** in the presence of dmpe (**L**$_3$), **5.7b** was isolated as a colorless oil (36.2 mg, 71% yield).

Data for **5.7b**:

TLC: R_f 0.66 (9:1 hexane/EtOAc) [UV/I_2/Vanillin]

^{1}H NMR: (500 MHz, $CDCl_3$, ppm)

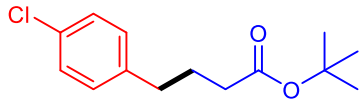
δ 7.33 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.22 (dd, *J* = 7.5, 1.9 Hz, 1H), 7.18 (td, *J* = 7.4, 1.4 Hz, 1H), 7.16 – 7.10 (m, 1H), 2.81 – 2.71 (m, 2H), 2.27 (t, *J* = 7.4 Hz, 2H), 1.92 (m, 2H), 1.46 (s, 9H).

^{13}C NMR: (125 MHz, $CDCl_3$, ppm)

δ 172.9, 139.4, 134.1, 130.6, 129.6, 127.6, 126.9, 80.3, 35.1, 32.9, 28.3, 25.2.

HRMS: (ESI, *m/z*)

calcd for $C_{14}H_{19}ClNaO_2$ $[M+Na]^+$ 277.0966, found: 277.0979.



tert-Butyl 4-(4-chlorophenyl)butanoate **(5.7c)**

Following the **general procedure B** in the presence of dppp (**L**$_7$), **5.7c** was obtained from the conjugate addition of 4-chlorobenzaldehyde **5.6c** (33.7 mg, 0.24 mmol) to *tert*-butyl acrylate **5.6a** (30 µL, 0.2 mmol), as a colorless oil (41.8 mg, 82% yield) after flash chromatography. Following the **general procedure A** in the presence of dmpe (**L**$_3$), **5.7c** was isolated as a colorless oil (34.1 mg, 67% yield).

Data for **5.7c**:

TLC: R_f 0.65 (9:1 hexane/EtOAc) [UV/I_2/Vanillin]

^{1}H NMR: (500 MHz, $CDCl_3$, ppm)

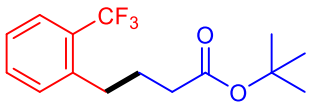
δ 7.26 (d, J = 8.4 Hz, 2H), 7.11 (d, J = 8.4 Hz, 2H), 2.67 – 2.51 (m, 2H), 2.22 (t, J = 7.4 Hz, 2H), 1.93 – 1.78 (m, 2H), 1.45 (s, 9H).

^{13}C NMR: (125 MHz, $CDCl_3$, ppm)

δ 172.9, 140.2, 131.8, 130.0, 128.6, 80.4, 34.9, 34.6, 28.3, 26.8.

HRMS: (ESI, *m/z*)

calcd for $C_{14}H_{19}ClNaO_2$ $[M+Na]^+$ 277.0961, found: 277.0966.



tert-Butyl 4-(2-(trifluoromethyl)phenyl)butanoate **(5.7d)**

Following the **general procedure B** in the presence of dppp (**L**$_7$), **5.7d** was obtained from the conjugate addition of 2-trifluoromethylbenzaldehyde **5.5d** (32 µL, 0.24 mmol) to *tert*-butyl acrylate **5.6a** (30 µL, 0.2 mmol), as a colorless oil (54.2 mg, 94% yield) after flash chromatography. Following the **general procedure A** in the presence of dmpe (**L**$_3$), **5.7d** was isolated as a colorless oil (47.9 mg, 83% yield).

Data for **5.7d**:

TLC: R_f 0.65 (9:1 hexane/EtOAc) [UV/I_2/Vanillin]

^{1}H NMR: (500 MHz, $CDCl_3$, ppm)

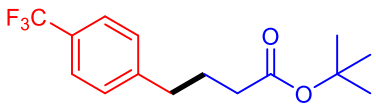
δ 7.61 (d, *J* = 7.9 Hz, 1H), 7.47 (t, *J* = 7.5 Hz, 1H), 7.35 (d, *J* = 7.7 Hz, 1H), 7.28 (t, *J* = 7.6 Hz, 1H), 2.87 – 2.72 (m, 2H), 2.30 (t, *J* = 7.4 Hz, 2H), 1.97 – 1.84 (m, 2H), 1.46 (s, 9H).

^{13}C NMR: (125 MHz, $CDCl_3$, ppm)

δ 172.8, 140.7 (q, $J_{C,F}$ = 1.8 Hz, 1C), 131.9, 131.2, 128.6 (q, $J_{C,F}$ = 30.4 Hz, 1C), 126.1, 126.0 (q, $J_{C,F}$ = 6.4 Hz, 1C), 124.7 (q, $J_{C,F}$ = 274.0 Hz, 1C), 80.4, 35.4, 31.9 (q, $J_{C,F}$ = 1.8 Hz, 1C), 28.2, 27.0.

HRMS: (ESI, *m/z*)

calcd for $C_{12}H_{18}NaO_2S$ $[M+Na]^+$ 249.0907, found: 249.0920.



tert-Butyl 4-(4-(trifluoromethyl)phenyl)butanoate **(5.7e)**

Following the **general procedure B** in the presence of dppp (**L**$_7$), **5.7e** was obtained from the conjugate addition of 4-trifluoromethylbenzaldehyde **5.5e** (32.7 µL, 0.24 mmol) to *tert*-butyl acrylate **5.6a** (30 µL, 0.2 mmol), as a colorless oil (51.8 mg, 90% yield) after flash chromatography. Following the **general procedure A** in the presence of dmpe (**L**$_3$), **5.7e** was isolated as a colorless oil (38.5 mg, 67% yield).

Data for **5.7e**:

TLC: R_f 0.55 (10:1 hexane/EtOAc) [UV/I_2]

^{1}H NMR: (500 MHz, $CDCl_3$, ppm)

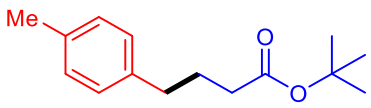
δ 7.56 – 7.51 (m, 2H), 7.31 – 7.27 (m, 2H), 2.70 (t, *J* = 7.7 Hz, 2H), 2.24 (t, *J* = 7.4 Hz, 2H), 1.92 (quin, *J* = 7.5 Hz, 2H), 1.45 (s, 9H).

^{13}C NMR: (125 MHz, $CDCl_3$, ppm)

δ 172.6, 145.7, 128.8, 128.3 (q, $J_{C,F}$ = 32.3 Hz, 1C), 125.3(q, $J_{C,F}$ = 3.7 Hz, 2C), 124.3 (q, $J_{C,F}$ = 271.6 Hz, 1C), 80.3, 34.9, 34.7, 28.1, 26.4.

HRMS: (ESI, *m/z*)

calcd for $C_{15}H_{19}F_3NaO_2$ $[M+Na]^+$ 311.1224, found: 311.1229.



tert-Butyl 4-phenylpentanoate **(5.7f)**

Following the **general procedure B** in the presence of dppp (**L**$_7$), **5.7f** was obtained from the conjugate addition of 4-methylbenzaldehyde **5.6f** (28 µL, 0.24 mmol) to *tert*-butyl acrylate **5.6a** (30 µL, 0.2 mmol), as a colorless oil (21.2 mg, 58% yield) after flash chromatography. Following the **general procedure A** in the presence of dmpe (**L**$_3$), **5.7f** was isolated as a colorless oil (35.6a mg, 76% yield).

Data for **5.7f**:

TLC: R_f 0.77 (9:1 hexane/EtOAc) [UV/I_2/Vanillin]

^{1}H NMR: (500 MHz, $CDCl_3$, ppm)

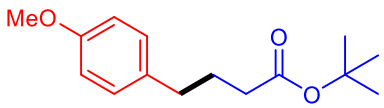
δ 7.16 – 7.04 (m, 4H), 2.67 – 2.55 (m, 2H), 2.34 (s, 3H), 2.25 (t, J = 7.5 Hz, 2H), 1.98 – 1.83 (m, 2H), 1.47 (s, 9H).

^{13}C NMR: (125 MHz, $CDCl_3$, ppm)

δ 173.0, 138.7, 135.4, 129.1, 128.5, 80.1, 35.1, 34.8, 28.2, 27.0, 21.1.

HRMS: (ESI, *m/z*)

calcd for $C_{15}H_{22}NaO_2$ $[M+Na]^+$ 257.1512, found: 257.1512.



tert-Butyl 4-(4-methoxyphenyl)butanoate **(5.7g)**

Following the **general procedure B** in the presence of dppp (**L**$_7$), **5.7g** was obtained from the conjugate addition of 4-methoxybenzaldehyde **5.5g** (29 µL, 0.24 mmol) to *tert*-butyl acrylate **5.6a**

(30 µL, 0.2 mmol), as a colorless oil (27.5 mg, 55% yield) after flash chromatography. Following the **general procedure A** in the presence of dmpe (**L3**), **5.7g** was isolated as a colorless oil (40.0 mg, 80% yield).

Data for **5.7g**:

TLC: R_f 0.78 (9:1 hexane/EtOAc) [UV/I_2/Vanillin]

^{1}H NMR: (500 MHz, $CDCl_3$, ppm)

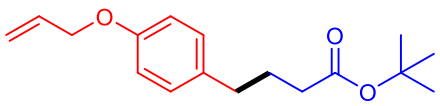
δ 7.10 (d, *J* = 8.6 Hz, 2H), 6.83 (d, *J* = 8.6 Hz, 2H), 3.79 (s, 3H), 2.58 (t, *J* = 7.8 Hz, 2H), 2.22 (t, *J* = 7.5 Hz, 2H), 1.91 – 1.78 (m, 2H), 1.45 (s, 9H).

^{13}C NMR: (125 MHz, $CDCl_3$, ppm)

δ 173.1, 158.0, 133.9, 129.5, 113.9, 80.2, 55.4, 35.0, 34.4, 28.3, 27.1.

HRMS: (ESI, *m/z*)

calcd for $C_{15}H_{22}NaO_3$ $[M+Na]^+$ 273.1464, found: 273.1461.



tert-Butyl 4-(4-(allyloxy)phenyl)butanoate **(5.7h)**

Following the **general procedure B** in the presence of dppp (**L7**), **5.7h** was obtained from the conjugate addition of 4-allyloxybenzaldehyde **5.5h** (37 µL, 0.24 mmol) to *tert*-butyl acrylate **5.6a** (30 µL, 0.2 mmol), as a colorless oil (27.6 mg, 50% yield) after flash chromatography. Following the **general procedure A** in the presence of dmpe (**L3**), **5.7h** was isolated as a colorless oil (43.7 mg, 79% yield).

Data for **5.7h**:

TLC: R_f 0.69 (9:1 hexane/EtOAc) [UV/I_2/Vanillin]

^{1}H NMR: (500 MHz, $CDCl_3$, ppm)

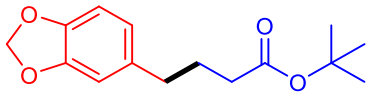
δ 7.08 (d, *J* = 8.6 Hz, 2H), 6.84 (d, *J* = 8.6 Hz, 2H), 6.06 (ddt, *J* = 17.2, 10.6, 5.3 Hz, 1H), 5.41 (dq, *J* = 17.3, 1.6 Hz, 1H), 5.28 (ddd, *J* = 10.5, 2.8, 1.4 Hz, 1H), 4.51 (dt, *J* = 5.3, 1.5 Hz, 2H), 2.62 – 2.50 (m, 2H), 2.22 (t, *J* = 7.5 Hz, 2H), 1.92 – 1.78 (m, 2H), 1.44 (s, 9H).

^{13}C NMR: (125 MHz, $CDCl_3$, ppm)

δ 173.1, 157.0, 134.1, 133.6, 129.5, 117.7, 114.8, 80.2, 69.0, 35.1, 34.4, 28.3, 27.1.

HRMS: (ESI, *m/z*)

calcd for $C_{17}H_{24}NaO_3$ $[M+Na]^+$ 299.1612, found: 299.1618.



tert-Butyl 4-(benzo[d][1,3]dioxol-5-yl)butanoate **(5.7i)**

Following the **general procedure B** in the presence of dppp (**L**$_7$), **5.7i** was obtained from the conjugate addition of piperonal **5.5i** (36 mg, 0.24 mmol) to *tert*-butyl acrylate **5.6a** (30 µL, 0.2 mmol), as a colorless oil (15.9 mg, 30% yield) after flash chromatography. Following the **general procedure A** in the presence of dmpe (**L**$_3$), **5.7i** was isolated as a colorless oil (36.5 mg, 69% yield).

Data for **5.7i**:

TLC: R_f 0.60 (9:1 hexane/EtOAc) [UV/I_2/Vanillin]

^{1}H NMR: (500 MHz, $CDCl_3$, ppm)

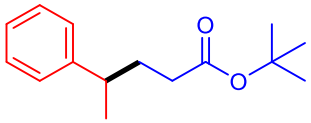
δ 6.72 (d, *J* = 7.9 Hz, 1H), 6.67 (d, *J* = 1.5 Hz, 1H), 6.62 (dd, *J* = 7.9, 1.6 Hz, 1H), 5.92 (s, 2H), 2.62 – 2.47 (m, 2H), 2.21 (t, *J* = 7.5 Hz, 2H), 1.93 – 1.77 (m, 2H), 1.45 (s, 9H).

^{13}C NMR: (125 MHz, $CDCl_3$, ppm)

δ 173.0, 147.7, 145.8, 135.6, 121.4, 109.1, 108.3, 100.9, 80.3, 35.0, 34.9, 28.3, 27.1.

HRMS: (ESI, *m/z*)

calcd for $C_{15}H_{20}NaO_4$ $[M+Na]^+$ 287.1246, found: 287.1254.



tert-Butyl 4-phenylpentanoate **(5.7j)**

Following the **general procedure B** in the presence of dppp (**L**$_7$), **5.7j** was obtained from the conjugate addition of acetophenone **5.5j** (28 µL, 0.24 mmol) to *tert*-butyl acrylate **5.6a** (30 µL, 0.2 mmol), as a colorless oil (10.8 mg, 23% yield) after flash chromatography. Following the **general procedure A** in the presence of dmpe (**L**$_3$), **5.7j** was isolated as a colorless oil (23.4 mg, 50% yield).

Data for **5.7j**:

TLC: R_f 0.78 (9:1 hexane/EtOAc) [UV/I_2/Vanillin]

^{1}H NMR: (500 MHz, $CDCl_3$, ppm)

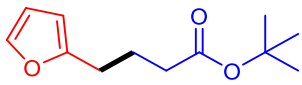
δ 7.30 (t, *J* = 7.5 Hz, 2H), 7.23 – 7.13 (m, 3H), 2.76 – 2.65 (m, 1H), 2.19 – 2.01 (m, 2H), 1.95 – 1.78 (m, 2H), 1.43 (s, 9H), 1.27 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR: (125 MHz, $CDCl_3$, ppm)

δ 173.2, 146.7, 128.6, 127.2, 126.2, 80.1, 39.5, 33.9, 33.5, 28.2, 22.3.

HRMS: (ESI, *m/z*)

calcd for $C_{15}H_{22}NaO_2$ $[M+Na]^+$ 257.1512, found: 257.1510.



tert-Butyl 4-(furan-2-yl)butanoate **(5.7k)**

Following the **general procedure B** in the presence of dppp (**L**$_7$), **5.7k** was obtained from the conjugate addition of furfural **5.5k** (20 µL, 0.24 mmol) to *tert*-butyl acrylate **5.6a** (30 µL, 0.2 mmol), as a colorless oil (24.4 mg, 58% yield) after flash chromatography. Following the **general**

procedure A in the presence of dmpe (**L**$_3$), **5.7k** was isolated as a colorless oil (26.0 mg, 62% yield).

Data for **5.7k**:

TLC: R_f 0.55 (9:1 hexane/EtOAc) [UV/I_2/Vanillin]

^{1}H NMR: (500 MHz, $CDCl_3$, ppm)

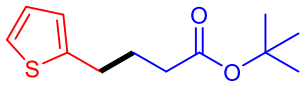
δ 7.31 – 7.27 (m, 1H), 6.27 (dd, *J* = 3.1, 1.9 Hz, 1H), 5.99 (dd, *J* = 3.1, 0.7 Hz, 1H), 2.66 (t, *J* = 7.4 Hz, 2H), 2.25 (t, *J* = 7.5 Hz, 2H), 1.92 (quin, *J* = 7.5 Hz, 2H), 1.44 (s, 9H).

^{13}C NMR: (125 MHz, $CDCl_3$, ppm)

δ 172.8, 155.4, 141.1, 110.2, 105.3, 80.3, 34.8, 28.2, 27.3, 23.6.

HRMS: (ESI, *m/z*)

calcd for $C_{12}H_{18}NaO_2S$ $[M+Na]^+$ 249.0907, found: 249.0920.



tert-Butyl 4-(thiophen-2-yl)butanoate **(5.7l)**

Following the **general procedure B** in the presence of dppp (**L**$_7$), **5.7l** was obtained from the conjugate addition of 2-thiophenecarboxaldehyde **5.5l** (23 µL, 0.24 mmol) to *tert*-butyl acrylate **5.6a** (30 µL, 0.2 mmol), as a light yellow solid (25.7 mg, 57% yield) after flash chromatography. Following the **general procedure A** in the presence of dmpe (**L**$_3$), **5.7l** was isolated as a light yellow solid (28.9 mg, 64% yield).

Data for **5.7l**:

TLC: R_f 0.4 (10:1 hexane/EtOAc) [UV/I_2/Vanillin]

^{1}H NMR: (500 MHz, $CDCl_3$, ppm)

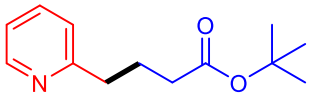
δ 7.12 (dd, *J* = 5.1, 1.1 Hz, 1H), 6.92 (dd, *J* = 5.1, 3.4 Hz, 1H), 6.79 (dd, *J* = 3.4, 1.1 Hz, 1H), 2.86 (t, *J* = 7.4 Hz, 2H), 2.26 (t, *J* = 7.4 Hz, 2H), 1.92 (quin, *J* = 7.4 Hz, 2H), 1.45 (s, 9H).

^{13}C NMR: (125 MHz, $CDCl_3$, ppm)

δ 172.6, 144.4, 126.7, 124.4, 123.1, 80.2, 34.6, 29.1, 28.1, 27.0.

HRMS: (ESI, *m/z*)

calcd for $C_{12}H_{18}NaO_2S$ $[M+Na]^+$ 249.0907, found: 249.0920.



tert-Butyl 4-(pyridin-2-yl)butanoate **(5.7m)**

Following the **general procedure B** in the presence of dppp (**L**$_7$), **5.7m** was obtained from the conjugate addition of 2-formylpyridine **5.5m** (28 µL, 0.24 mmol) to *tert*-butyl acrylate **5.6a** (30 µL, 0.2 mmol), as a colorless oil (36.6 mg, 83% yield) after flash chromatography. Following the **general procedure A** in the presence of dmpe (**L**$_3$), **5.7m** was isolated as a colorless oil (16.8 mg, 38% yield).

Data for **5.7m**:

TLC: R_f 0.15 (10:1 hexane/EtOAc) [UV/I_2/Vanillin]

^{1}H NMR: (500 MHz, $CDCl_3$, ppm)

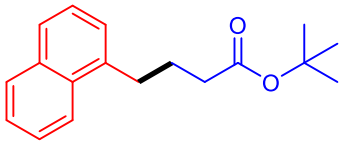
δ 8.53 (dd, *J* = 4.9, 1.8 Hz, 1H), 7.60 (td, *J* = 7.6, 1.8 Hz, 1H), 7.16 (d, *J* = 7.6, 1H), 7.12 (dd, *J* = 7.6, 4.9 Hz, 1H), 2.82 (t, *J* = 7.6 Hz, 2H), 2.27 (t, *J* = 7.5 Hz, 2H), 2.03 (quin, *J* = 7.6 Hz, 2H), 1.44 (s, 9H).

^{13}C NMR: (125 MHz, $CDCl_3$, ppm)

δ 172.7, 161.2, 149.0, 136.6, 123.0, 121.2, 80.2, 37.3, 34.9, 28.1, 25.1.

HRMS: (ESI, *m/z*)

calcd for $C_{13}H_{19}NNaO_2$ $[M+Na]^+$ 244.1305, found: 244.1308.



tert-Butyl 4-(naphthalen-1-yl)butanoate **(5.7n)**

Following the **general procedure B** in the presence of dppp (**L**$_7$), **5.7n** was obtained from the conjugate addition of 2-naphthaldehyde **5.5n** (33 µL, 0.24 mmol) to *tert*-butyl acrylate **5.6a** (30 µL, 0.2 mmol), as a colorless oil (42.1 mg, 78% yield) after flash chromatography. Following the **general procedure A** in the presence of dmpe (**L**$_3$), **5.7n** was isolated as a colorless oil (39.4 mg, 73% yield).

Data for **5.7n**:

TLC: R_f 0.55 (10:1 hexane/EtOAc) [UV/I_2/Vanillin]

^{1}H NMR: (500 MHz, $CDCl_3$, ppm)

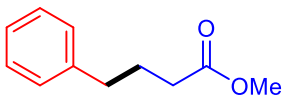
δ 8.10 – 8.05 (m, 1H), 7.88 – 7.83 (m, 1H), 7.74 – 7.70 (m, 1H), 7.55 – 7.45 (m, 2H), 7.42 – 7.37 (m, 1H), 7.35 – 7.30 (m, 1H), 3.11 (t, *J* = 7.7 Hz, 2H), 2.33 (t, *J* = 7.3 Hz, 2H), 2.05 (quin, *J* = 7.5 Hz, 2H), 1.47 (s, 9H).

^{13}C NMR: (125 MHz, $CDCl_3$, ppm)

δ 173.0, 137.9, 134.0, 132.0, 128.9, 126.9, 126.4, 126.0, 125.65, 125.60, 124.0, 80.3, 35.4, 32.5, 28.3, 26.2.

HRMS: (ESI, *m/z*)

calcd for $C_{18}H_{22}NaO_2$ $[M+Na]^+$ 293.1504, found: 293.1512.



Methyl 4-phenylbutanoate **(5.8b)**[17]

Following the **general procedure B** in the presence of dppp (**L**$_7$), **5.8b** was obtained from the conjugate addition of benzaldehyde **5.5a** (25 µL, 0.24 mmol) to methyl acrylate **5.6b** (18 µL, 0.2

mmol), as a colorless oil (42.1 mg, 96% yield) after flash chromatography. Following the **general procedure A** in the presence of dmpe (**L**$_3$), **5.8b** was isolated as a colorless oil (39.4 mg, 60% yield).

Data for **5.8b**:

TLC: R_f 0.5 (5:1 hexane/EtOAc) [UV/I_2/Vanillin]

^{1}H NMR: (500 MHz, $CDCl_3$, ppm)

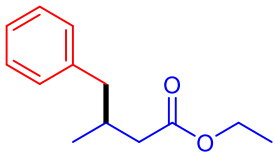
δ 7.31 – 7.26 (m, 2H), 7.22 – 7.16 (m, 3H), 3.67 (s, 3H), 2.65 (t, *J* = 7.5 Hz, 2H), 2.33 (t, *J* = 7.5 Hz, 2H), 1.96 (quin, *J* = 7.5 Hz, 2H).

^{13}C NMR: (125 MHz, $CDCl_3$, ppm)

δ 174.1, 141.5, 135.3, 128.6, 128.5, 126.1, 51.7, 35.3, 33.5, 26.6.

HRMS: (ESI, *m/z*)

calcd for $C_{11}H_{14}NaO_2$ $[M+Na]^+$ 201.0877, found: 201.0886.



Ethyl -3-methyl-4-phenylbutanoate **(5.8c)**[18]

Following the **general procedure B** in the presence of dppp (**L**$_7$), **5.8c** was obtained from the conjugate addition of benzaldehyde **5.5a** (25 µL, 0.24 mmol) to ethyl crotonate **5.6c** (24.9 µL, 0.2 mmol), as a colorless oil (17.3 mg, 42% yield) after flash chromatography. Following the **general procedure A** in the presence of dmpe (**L**$_3$), **5.8c** was isolated as a colorless oil (33.8 mg, 82% yield).

Data for **5.8c**:

TLC: R_f 0.55 (10:1 hexane/EtOAc) [UV/I_2/Vanillin]

^{1}H NMR: (500 MHz, $CDCl_3$, ppm)

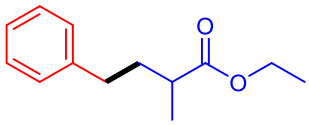
δ 7.31 – 7.25 (m, 2H), 7.22 – 7.14 (m, 3H), 4.11 (q, *J* = 7.2 Hz, 2H), 2.63 (dd, *J* = 13.4, 6.5 Hz, 1H), 2.50 (dd, *J* = 13.4, 7.4 Hz, 1H), 2.36 – 2.24 (m, 2H), 2.18 – 2.09 (m, 1H), 1.25 (t, *J* = 7.2 Hz, 3H), 0.94 (d, *J* = 6.5 Hz, 3H).

^{13}C NMR: (125 MHz, $CDCl_3$, ppm)

δ 173.2, 140.4, 129.4, 128.4, 126.1, 60.3, 43.2, 41.3, 32.4, 19.7, 14.4.

HRMS: (ESI, *m/z*)

calcd for $C_{13}H_{18}NaO_2$ $[M+Na]^+$ 229.1191, found: 229.1199.



Ethyl 2-methyl-4-phenylbutanoate **(5.8d)**

Following the **general procedure B** in the presence of dppp (**L$_7$**), **5.8d** was obtained from the conjugate addition of benzaldehyde **5.5a** (25 µL, 0.24 mmol) to ethyl methacrylate **5.6d** (25.5 µL, 0.2 mmol), as a colorless oil (11.1 mg, 27% yield) after flash chromatography. Following the **general procedure A** in the presence of dmpe (**L$_3$**), **5.8d** was isolated as a colorless oil (11.1 mg, 27% yield).

Data for **5.8d**:

TLC: R_f 0.55 (10:1 hexane/EtOAc) [UV/I_2/Vanillin]

^{1}H NMR: (500 MHz, $CDCl_3$, ppm)

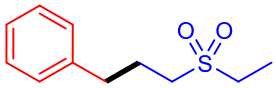
δ 7.31 – 7.25 (m, 2H), 7.22 – 7.14 (m, 3H), 4.13 (q, *J* = 7.3 Hz, 2H), 2.62 (t, *J* = 8.0 Hz, 2H), 2.46 (sext, *J* = 7.0 Hz, 1H), 2.06 – 1.96 (m, 1H), 1.77 – 1.67 (m, 1H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.19 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR: (125 MHz, $CDCl_3$, ppm)

δ 176.7, 141.9, 128.6, 128.5, 126.0, 60.4, 39.2, 35.6, 33.6, 17.3, 14.4.

HRMS: (ESI, *m/z*)

calcd for $C_{13}H_{18}NaO_2$ $[M+Na]^+$ 229.1196, found: 229.1199.



(3-(Ethylsulfonyl)propyl)benzene **(5.8e)**

Following the **general procedure B** in the presence of dppp (**L**$_7$), **5.8e** was obtained from the conjugate addition of benzaldehyde **5.5a** (25 µL, 0.24 mmol) to ethyl vinyl sulfone **5.6e** (20.9 µL, 0.2 mmol), as a colorless oil (31.8 mg, 75% yield) after flash chromatography. Following the **general procedure A** in the presence of dmpe (**L**$_3$), **5.8e** was isolated as a colorless oil (30.5 mg, 72% yield).

Data for **5.8e**:

TLC: R_f 0.15 (5:1 hexane/EtOAc) [UV/I_2/Vanillin]

^{1}H NMR: (500 MHz, $CDCl_3$, ppm)

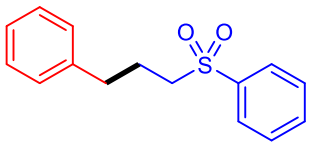
δ 7.35 – 7.26 (m, 2H), 7.25 – 7.15 (m, 3H), 2.99 – 2.89 (m, 4H), 2.85 – 2.68 (m, 2H), 2.24 – 2.13 (m, 2H), 1.35 (t, J = 7.5 Hz, 3H).

^{13}C NMR: (125 MHz, $CDCl_3$, ppm)

δ 140.0, 128.8, 128.6, 126.7, 51.1, 47.2, 34.4, 23.5, 6.7.

HRMS: (ESI, *m/z*)

calcd for $C_{11}H_{16}NaO_2S$ $[M+Na]^+$ 235.0755, found: 235.0763.



((3-Phenylpropyl)sulfonyl)benzene **(5.8f)**[19]

Following the **general procedure B** in the presence of dppp (**L**$_7$), **5.8f** was obtained from the conjugate addition of benzaldehyde **5.5a** (25 µL, 0.24 mmol) to phenyl vinyl sulfone **5.6f** (33.6

mg, 0.2 mmol), as a white solid (35.8 mg, 69% yield) after flash chromatography. Following the **general procedure A** in the presence of dmpe (**L**$_3$), **5.8f** was isolated as a white solid (41.5 mg, 80% yield).

Data for **5.8f**:

TLC: R_f 0.2 (5:1 hexane/EtOAc) [UV/I_2/Vanillin]

^{1}H NMR: (500 MHz, $CDCl_3$, ppm)

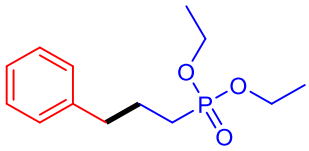
δ 7.91 – 7.86 (m, 2H), 7.68 – 7.63 (m, 1H), 7.59 – 7.53 (m, 2H), 7.30 – 7.24 (m, 2H), 7.23 – 7.17 (m, 1H), 7.12 – 7.08 (m, 2H), 3.10 – 3.05 (m, 2H), 2.70 (t, J = 7.5 Hz, 2H), 2.09 – 2.02 (m, 2H).

^{13}C NMR: (125 MHz, $CDCl_3$, ppm)

δ 140.0, 139.2, 133.8, 129.4, 128.7, 128.5, 128.2, 126.6, 55.6, 34.2, 24.3.

HRMS: (ESI, *m/z*)

calcd for $C_{15}H_{16}NaO_2S$ $[M+Na]^+$ 283.0756, found: 283.0763.



Diethyl (3-phenylpropyl)phosphonate **(5.8g)**[20]

Following the **general procedure B** in the presence of dppp (**L**$_7$), **5.8g** was obtained from the conjugate addition of benzaldehyde **5.5a** (25 µL, 0.24 mmol) to diethyl vinylphosphonate **5.6g** (30.7 µL, 0.2 mmol), as a light yellow oil (32.7 mg, 64% yield) after flash chromatography. Following the **general procedure A** in the presence of dmpe (**L**$_3$), **5.8g** was isolated as a light yellow oil (47.1 mg, 92% yield).

Data for **5.8g**:

TLC: R_f 0.3 (EtOAc) [UV/I_2/Vanillin]

^{1}H NMR: (500 MHz, $CDCl_3$, ppm)

7.32 – 7.25 (m, 2H), 7.24 – 7.13 (m, 3H), 4.20 – 4.00 (m, 4H), 2.70 (t, J = 7.5 Hz, 2H), 1.99 – 1.86 (m, 2H), 1.79 – 1.67 (m, 2H), 1.30 (t, J = 7.5 Hz, 6H).

^{13}C NMR: (125 MHz, $CDCl_3$, ppm)

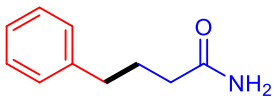
δ 141.2, 128.6, 128.5, 126.2, 61.5 (d, $J_{c,p}$ = 7.5 Hz), 36.5 (d, $J_{c,p}$ = 21.3 Hz), 25.1 (d, $J_{c,p}$ = 206.3 Hz), 24.4 (d, $J_{c,p}$ = 37.5 Hz,), 16.6 (d, $J_{c,p}$ = 7.5 Hz, 2C).

^{31}P NMR: (202 MHz, $CDCl_3$, ppm)

δ 32.1.

HRMS: (ESI, *m/z*)

calcd for $C_{13}H_{21}NaO_3P$ $[M+Na]^+$ 279.1115, found: 279.1121.



4-Phenylbutanamide **(5.8h)**[21]

Following the **general procedure B** in the presence of dppp (**L**$_7$), **5.8h** was obtained from the conjugate addition of benzaldehyde **5.5a** (25 µL, 0.24 mmol) to acrylamide **5.6h** (12.6 µL, 0.2 mmol), as a colorless oil (15.9 mg, 49% yield) after flash chromatography. Following the **general procedure A** in the presence of dmpe (**L**$_3$), **5.8h** was isolated as a colorless oil (17 mg, 52% yield).

Data for **5.8h**:

TLC: R_f 0.15 (1:1 hexane/EtOAc) [UV/I_2/Vanillin]

^{1}H NMR: (500 MHz, $CDCl_3$, ppm)

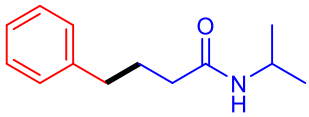
δ 7.32 – 7.24 (m, 2H), 7.23 – 7.15 (m, 3H), 5.39 (s, br, 2H), 2.68 (t, J = 7.5 Hz, 2H), 2.22 (t, J = 7.5 Hz, 2H), 1.98 (quin, J = 7.5 Hz, 2H).

^{13}C NMR: (125 MHz, $CDCl_3$, ppm)

δ 175.1, 141.5, 128.63, 128.55, 126.2, 35.2, 35.1, 27.0.

HRMS: (ESI, *m/z*)

calcd for $C_{10}H_{13}ONNa$ $[M+Na]^+$ 186.0889, found: 186.0891.



N-Isopropyl-4-phenylbutanamide **(5.8i)**

Following the **general procedure B** in the presence of dppp (**L**$_7$), **5.8i** was obtained from the conjugate addition of benzaldehyde **5.5a** (25 µL, 0.24 mmol) to *N*-isopropylacrylamide **5.6i** (22.6 mg, 0.2 mmol), as a white solid (14.7 mg, 36% yield) after flash chromatography. Following the **general procedure A** in the presence of dmpe (**L**$_3$), **5.8i** was isolated as a white solid (27.5 mg, 67% yield).

Data for **5.8i**:

TLC: R_f 0.4 (1:1 hexane/EtOAc) [UV/I_2/Vanillin]

^{1}H NMR: (500 MHz, $CDCl_3$, ppm)

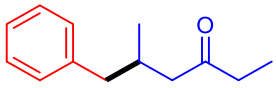
δ 7.31 – 7.26 (m, 2H), 7.21 – 7.15 (m, 3H), 5.23 (s, br, 1H), 4.08 (sep, *J* = 6.7 Hz, 1H), 2.65 (d, *J* = 7.5 Hz, 2H), 2.13 (d, *J* = 7.5 Hz, 2H), 1.96 (quin, *J* = 7.5 Hz, 2H), 1.13 (d, *J* = 6.7 Hz, 6H).

^{13}C NMR: (125 MHz, $CDCl_3$, ppm)

δ 171.9, 141.7, 128.6, 128.5, 126.1, 41.4, 36.2, 35.3, 27.3, 23.0.

HRMS: (ESI, *m/z*)

calcd for $C_{13}H_{19}NNaO$ $[M+Na]^+$ 228.1349, found: 228.1359.



5-Methyl-6-phenylhexan-3-one **(5.8j)**[22]

Following the **general procedure B** in the presence of dppp (**L**$_7$), **5.8j** was obtained from the conjugate addition of benzaldehyde **5.5a** (25 µL, 0.24 mmol) to (*E*)-4-hexen-3-one **5.6j** (19.6 mg,

0.2 mmol), as a colorless oil (17.9 mg, 47% yield) after flash chromatography. Following the **general procedure A** in the presence of dmpe (**L**$_3$), **5.8j** was isolated as a colorless oil (29.2 mg, 69% yield).

Data for **5.8j**:

TLC: R_f 0.95 (9:1 hexane/EtOAc) [UV/I_2/Vanillin]

^{1}H NMR: (500 MHz, $CDCl_3$, ppm)

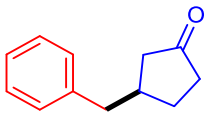
δ 7.31 – 7.26 (m, 2H), 7.22 – 7.17 (m, 1H), 7.17 – 7.12 (m, 2H), 2.57 (dd, *J* = 13.4, 6.7 Hz, 1H), 2.48 (dd, *J* = 13.3, 7.3 Hz, 1H), 2.42 – 2.28 (m, 5.8h), 2.23 (dd, *J* = 15.4, 7.6 Hz, 1H), 1.02 (t, *J* = 7.3 Hz, 3H), 0.90 (d, *J* = 6.5 Hz, 3H).

^{13}C NMR: (125 MHz, $CDCl_3$, ppm)

δ 211.4, 140.6, 129.3, 128.4, 126.1, 49.1, 43.3, 36.7, 31.3, 20.0, 7.9.

HRMS: (ESI, *m/z*)

calcd for $C_{13}H_{18}ONa[M+Na]^+$ 213.1250, found: 213.1248.



3-Benzylcyclopentanone **(5.8k)**[23]

Following the **general procedure B** in the presence of dppp (**L**$_7$), **5.8k** was obtained from the conjugate addition of benzaldehyde **5.5a** (25 µL, 0.24 mmol) to 2-cyclopenten-1-one **5.6k** (16.8 µL, 0.2 mmol), as a colorless oil (25.8 mg, 74% yield) after flash chromatography. Following the **general procedure A** in the presence of dmpe (**L**$_3$), **5.8k** was isolated as a colorless oil (21.6 mg, 62% yield).

Data for **5.8k**:

TLC: R_f 0.87 (9:1 hexane/EtOAc) [UV/I_2/Vanillin]

^{1}H NMR: (500 MHz, $CDCl_3$, ppm)

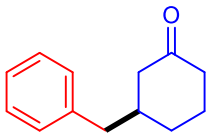
δ7.38 – 7.04 (m, 5H), 2.79 – 2.65 (m, 2H), 2.54 – 2.40 (m, 1H), 2.37 – 2.22 (m, 2H), 2.21 – 2.04 (m, 2H), 1.96-1.87 (m, 1H), 1.71 – 1.52 (m, 1H).

^{13}C NMR: (125 MHz, $CDCl_3$, ppm)

δ 219.4, 140.2, 128.9, 128.6, 126.4, 45.1, 41.6, 39.0, 38.5, 29.2.

HRMS: (ESI, *m/z*)

calcd for $C_{12}H_{14}NaO$ $[M+Na]^+$ 197.0932, found: 197.0937.



3-Benzylcyclohexan-1-one **(5.8l)**[24]

Following the **general procedure B** in the presence of dppp (**L**$_7$), **5.8l** was obtained from the conjugate addition of benzaldehyde **5.5a** (25 µL, 0.24 mmol) to 2-cyclohexen-1-one **5.6l** (19.4 µL, 0.2 mmol), as a colorless oil (14.6 mg, 39% yield) after flash chromatography. Following the **general procedure A** in the presence of dmpe (**L**$_3$), **5.8l** was isolated as a colorless oil (16.5 mg, 44% yield).

Data for **5.8l**:

TLC: R_f 0.45 (5:1 hexane/EtOAc) [UV/I_2/Vanillin]

^{1}H NMR: (500 MHz, $CDCl_3$, ppm)

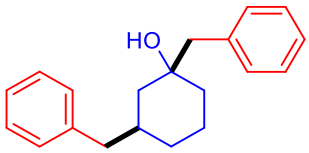
δ 7.31 – 7.26 (m, 2H), 7.23 – 7.18 (m, 1H), 7.15 – 7.10 (m, 2H), 2.68 – 2.57 (m, 2H), 2.41 – 2.32 (m, 2H), 2.30 – 2.22 (m, 1H), 2.10 – 2.00 (m, 3H), 1.91 – 1.84 (m, 1H), 1.67 – 1.55 (m, 1H), 1.43 – 1.32 (m, 1H).

^{13}C NMR: (125 MHz, $CDCl_3$, ppm)

δ 211.8, 139.6, 129.2, 128.5, 126.3, 48.0, 43.1, 41.6, 41.0, 31.0, 25.3.

HRMS: (ESI, *m/z*)

calcd for $C_{13}H_{16}NaO$ $[M+Na]^+$ 211.1087, found: 211.1093.



1,3-Dibenzylcyclohexan-1-ol **(5.8l')**

Following the **general procedure B** in the presence of dppp (**L**$_7$), **5.8l'** was obtained from the conjugate addition of benzaldehyde **5.5a** (25 µL, 0.24 mmol) to 2-cyclohexen-1-one **5.6l** (19.4 µL, 0.2 mmol), as a colorless oil (24.1 mg, 43% yield) after flash chromatography. Following the **general procedure A** in the presence of dmpe (**L**$_3$), **5.8l'** was isolated as a colorless oil (25.1 mg, 45% yield).

Data for **5.8l'**:

TLC: R_f 0.5 (5:1 hexane/EtOAc) [UV/I_2/Vanillin]

^{1}H NMR: (500 MHz, $CDCl_3$, ppm)

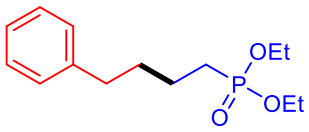
δ 7.34 – 7.22 (m, 5H), 7.21 – 7.15 (m, 3H), 7.15 – 7.11 (m, 2H), 2.73 (d, *J* = 13.2 Hz, 2H), 2.52 (dd, *J* = 13.3, 6.3 Hz, 1H), 2.42 (dd, *J* = 13.3, 8.0 Hz, 1H), 1.98 – 1.86 (m, 1H), 1.66 (d, *J* = 13.5, 2H), 1.57 – 1.45 (m, 3H), 1.36 – 1.25 (m, 2H), 1.12 (t, *J* = 6.7 Hz, 1H), 0.90-0.70 (m, 1H).

^{13}C NMR: (125 MHz, $CDCl_3$, ppm)

δ 140.9, 137.1, 130.8, 129.3, 128.3, 128.2, 126.6, 125.8, 71.7, 50.8, 44.1, 44.0, 36.9, 34.9, 32.2, 21.4.

HRMS: (ESI, *m/z*)

calcd for $C_{20}H_{24}NaO$ $[M+Na]^+$ 303.1715, found: 303.1719.



Diethyl (4-phenylbutyl)phosphonate **(5.7o)**[25]

Following the **general procedure C** in the presence of depe (**L4**), **5.7o** was obtained from the conjugate addition of phenylacetaldehyde **5.5o** (26.7 µL, 0.24 mmol) to diethyl vinylphosphonate **5.6g** (30.7 µL, 0.2 mmol), as a light yellow oil (21.5 mg, 40% yield) after flash chromatography.

Data for **5.7o**:

TLC: R_f 0.3 (EtOAc) [UV/I_2/Vanillin]

^{1}H NMR: (500 MHz, $CDCl_3$, ppm)

7.30 – 7.24 (m, 2H), 7.20 – 7.14 (m, 3H), 4.15 – 4.00 (m, 4H), 2.62 (t, J = 7.4 Hz, 2H), 1.80 – 1.60 (m, 6H), 1.30 (t, J = 7.1 Hz, 6H).

^{13}C NMR: (125 MHz, $CDCl_3$, ppm)

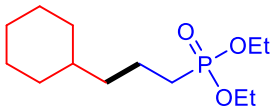
δ 142.1, 128.51, 128.47, 125.9, 61.6 (d, $J_{c,p}$ = 6.5 Hz), 35.6, 32.5 (d, $J_{c,p}$ = 16.6 Hz), 25.7 (d, $J_{c,p}$ = 140.8 Hz), 22.2 (d, $J_{c,p}$ = 4.8 Hz), 16.6 (d, $J_{c,p}$ = 6.2 Hz).

^{31}P NMR: (202 MHz, $CDCl_3$, ppm)

δ 32.2.

HRMS: (ESI, *m/z*)

calcd for $C_{14}H_{23}NaO_3P$ $[M+Na]^+$ 293.1277, found: 293.1280.



Diethyl (3-cyclohexylpropyl)phosphonate **(5.7p)**

Following the **general procedure C** in the presence of depe (**L4**), **5.7p** was obtained from the conjugate addition of phenylacetaldehyde **5.5p** (26.7 µL, 0.24 mmol) to diethyl vinylphosphonate **5.6g** (30.7 µL, 0.2 mmol), as a light yellow oil (23 mg, 44% yield) after flash chromatography.

Data for **5.7p**:

TLC: R_f 0.3 (EtOAc) [I_2/Vanillin]

^{1}H NMR: (500 MHz, $CDCl_3$, ppm)

4.14 – 4.02 (m, 5.8h), 1.73 – 1.54 (m, 9H), 1.31 (t, J = 7.1 Hz, 6H), 1.28 – 1.09 (m, 6H), 0.92 – 0.79 (m, 2H).

^{13}C NMR: (125 MHz, $CDCl_3$, ppm)

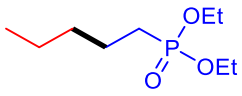
δ 61.5 (d, $J_{c,p}$ = 6.6 Hz), 38.6 (d, $J_{c,p}$ = 16.8 Hz), 37.4, 33.3, 26.8, 26.4, 26.1 (d, $J_{c,p}$ = 140.1 Hz), 19.9 (d, $J_{c,p}$ = 5.3 Hz), 16.6 (d, $J_{c,p}$ = 6.2 Hz).

^{31}P NMR: (202 MHz, $CDCl_3$, ppm)

δ 32.6.

HRMS: (ESI, *m/z*)

calcd for $C_{13}H_{27}NaO_3P$ $[M+Na]^+$ 285.1590, found: 285.1585.



Diethyl pentylphosphonate **(5.7q)**[26]

Following the **general procedure C** in the presence of depe (**L4**), **5.7q** was obtained from the conjugate addition of propionaldehyde **5.5q** (18 µL, 0.24 mmol) to diethyl vinylphosphonate **5.6g** (30.7 µL, 0.2 mmol), as a light yellow oil (17.5 mg, 42% yield) after flash chromatography.

Data for **5.7q**:

TLC: R_f 0.3 (EtOAc) [I_2/Vanillin]

^{1}H NMR: (500 MHz, $CDCl_3$, ppm)

δ 4.18 – 3.99 (m, 4H), 1.79 – 1.67 (m, 2H), 1.67 – 1.52 (m, 3H), 1.40 – 1.23 (m, 9H), 0.89 (t, J = 7.1 Hz, 3H).

^{13}C NMR: (125 MHz, $CDCl_3$, ppm)

δ 61.5 (d, J = 6.5 Hz), 32.9 (d, J = 16.9 Hz), 25.8 (d, J = 140.4 Hz), 22.3 (d, J = 1.0 Hz), 22.2 (d, J = 5.2 Hz), 16.6 (d, J = 6.0 Hz), 14.0.

^{31}P NMR: (202 MHz, $CDCl_3$, ppm)

δ 32.7.

HRMS: (ESI, *m/z*)

calcd for $C_9H_{21}NaO_3P$ $[M+Na]^+$ 231.1121, found: 231.1127.

5.6 References

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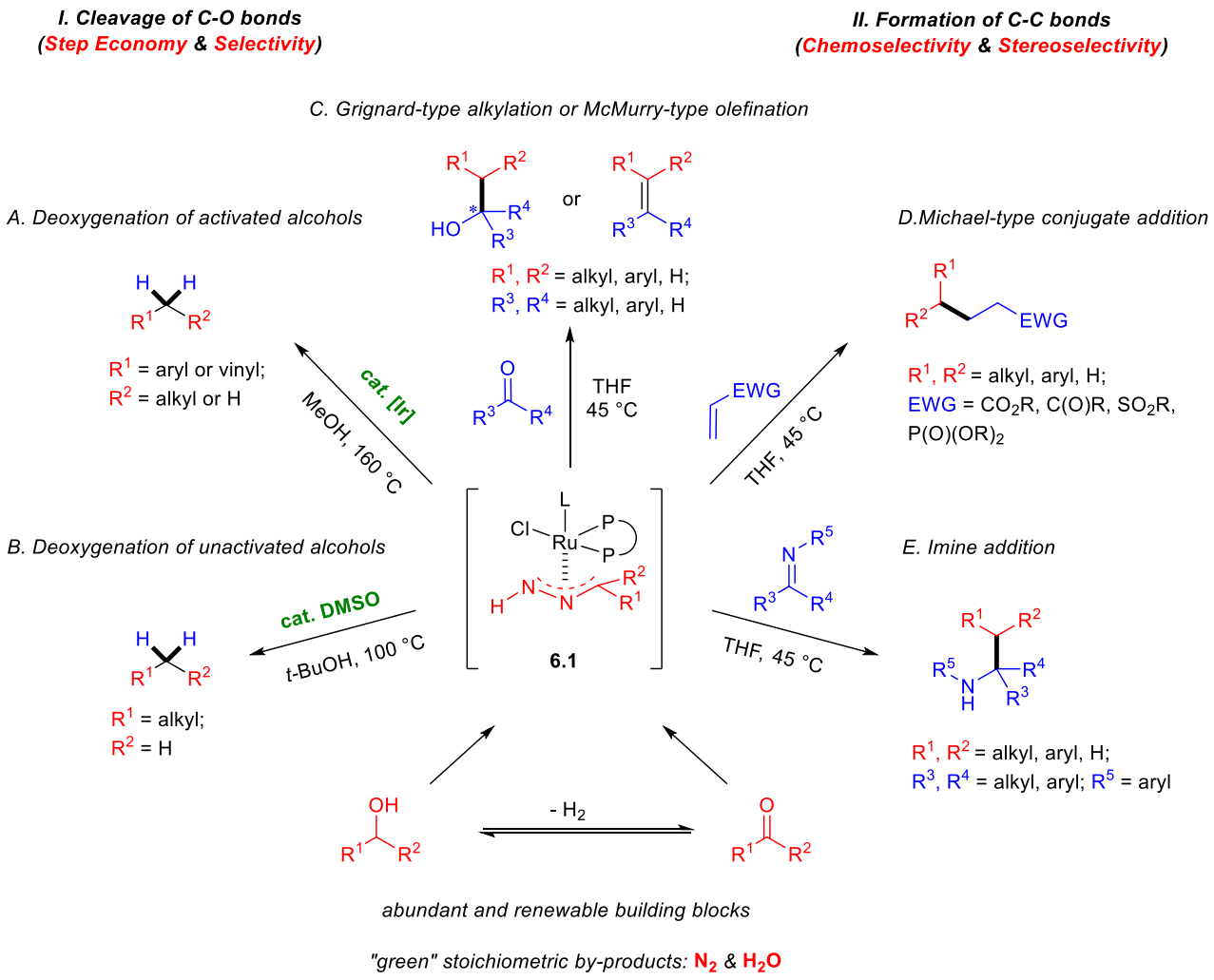
Chapter 6 : Conclusions and Prospects

6.1 Conclusions and Contributions to Knowledge

Over years, a main research focus in the Li group has been the exploration of novel chemical reactivity for sustainable molecular transformations.[1] Representative examples include Grignard-type reactions in water,[2] alkyne-aldehyde-amine coupling (A^3-coupling)[3] and cross-dehydrogenative-coupling (CDC) reactions.[4] Aligned with this major theme, we were surprised to learn how little efforts had been devoted to the development of selective and efficient defunctionalization methods, when comparing to the opposite mainstream interest — functionalization methods (Chapter 1). We were particularly intrigued by a long-standing challenge that remains elusive in the field of alcohol deoxygenation: to selectively and efficiently remove hydroxy groups (i.e. cleavage of C–O bonds) in naturally occurring organic molecules (e.g. carbohydrates and amino acids) that are often over-functionalized by hydroxyl or amine groups. Traditional deoxygenation methods feature inefficient two-step synthesis, and require even more steps (i.e. protection-deprotection) to differentiate multi hydroxy groups or amines in the same molecule. We therefore conceived a redox-based design combining the alcohol dehydrogenation with the Wolff-Kishner reduction to deliver a one-pot synthetic approach. A proof-of-concept study was completed by an iridium-catalyzed process for mostly benzylic and allylic alcohols under impractical reaction conditions (i.e. highly concentrated solution and extremely high temperature).[5] Despite limitations prevailed, this protocol proved the feasibility of our redox-based design — the first example that is mechanistically distinct in this field (Chapter



Scheme 6-1 Ruthenium-catalyzed Catalytic Molecular Transformations on Oxygen-Containing Organic Compounds

2; Scheme 6-1-A). Subsequent progress was achieved utilizing ruthenium-based catalytic system and DMSO/KO*t*Bu/*t*-BuOH, which was comparably much more practical from a synthetic utility perspective.[6] Notably, such advancement demonstrated its good efficiency and chemoselectivity for removing aliphatic primary hydroxy groups in both simple and complex molecules (Chapter 3; Scheme 6-1-B). Capitalizing on the proposed ruthenium complex **6.1** and the same ruthenium catalytic system developed in the deoxygenation chemistry (Scheme 6-1),[6] we further developed a series of chemical transformations to form carbon-carbon bonds. Exemplary reactions in this

new research area include Grignard-type carbonyl addition (Chapter 4; Scheme 6-1-C),[7] Michael-type conjugate addition (Chapter 5; Scheme 6-1-D),[8] imine addition,[9] and McMurry-type olefination.[10] These innovative reactions reductively convert readily available carbonyl compounds into catalytic alkyl carbanion equivalents for the further coupling reaction with the other electrophiles (carbonyls, imines, electron-deficient olefins), delivering synthetically important chemicals. In comparison, these transformations are traditionally accomplished using stoichiometric organometallic reagents which are commonly robust and sensitive towards air and protic solvents.

As it stands, certain aspects of these carbon-carbon bond-forming reactions – such as the safety and toxicity issues with hydrazine as well as the rarity and relatively high cost concerns associated with precious metal catalyst ruthenium – preclude them from being ideal in green chemistry and render the opportunity for further improvement. Nevertheless, they do open an avenue for converting naturally occurring carbonyl functionalities to carbanion equivalents, which is a stepping-stone toward more sustainable carbon-carbon bond-forming processes. Indeed, we believe that some of concerns abovementioned can be addressed via further modification of the metal catalyst (by, for instance, using earth-abundant metals and via catalyst immobilizations) or the reducing reagent. Unlike copious metal waste generated in other organometallic-based reactions, these reactions' production of only innocuous byproducts (e.g. N_2 and H_2O), their relatively mild reaction conditions, and tolerance toward a wide range of functional groups (as well as air and water), make them attractive to researchers across academia and industry.

6.2 References

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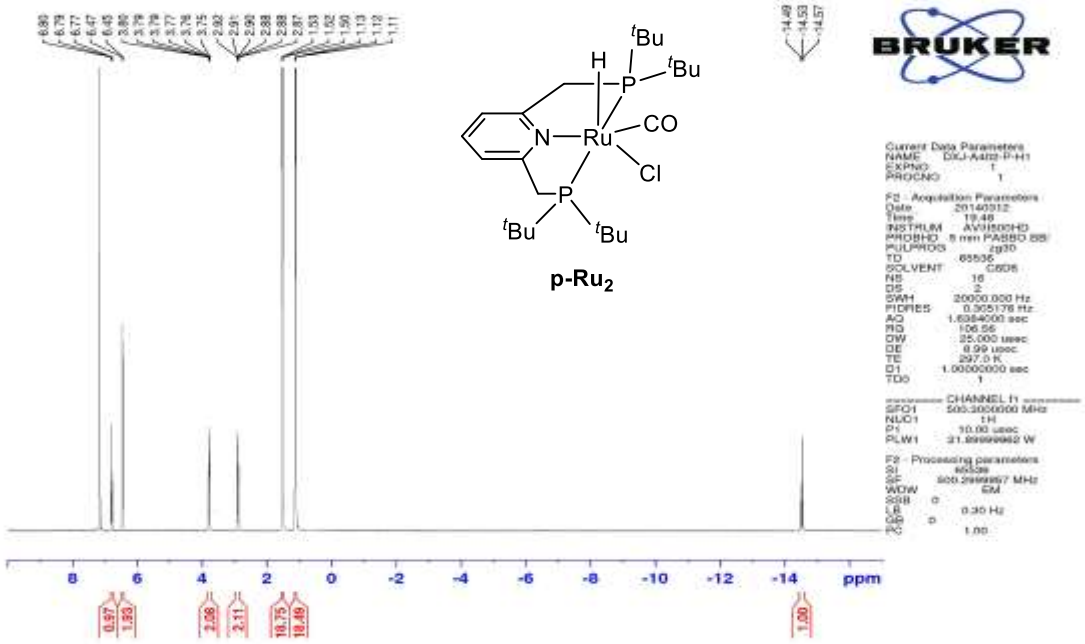
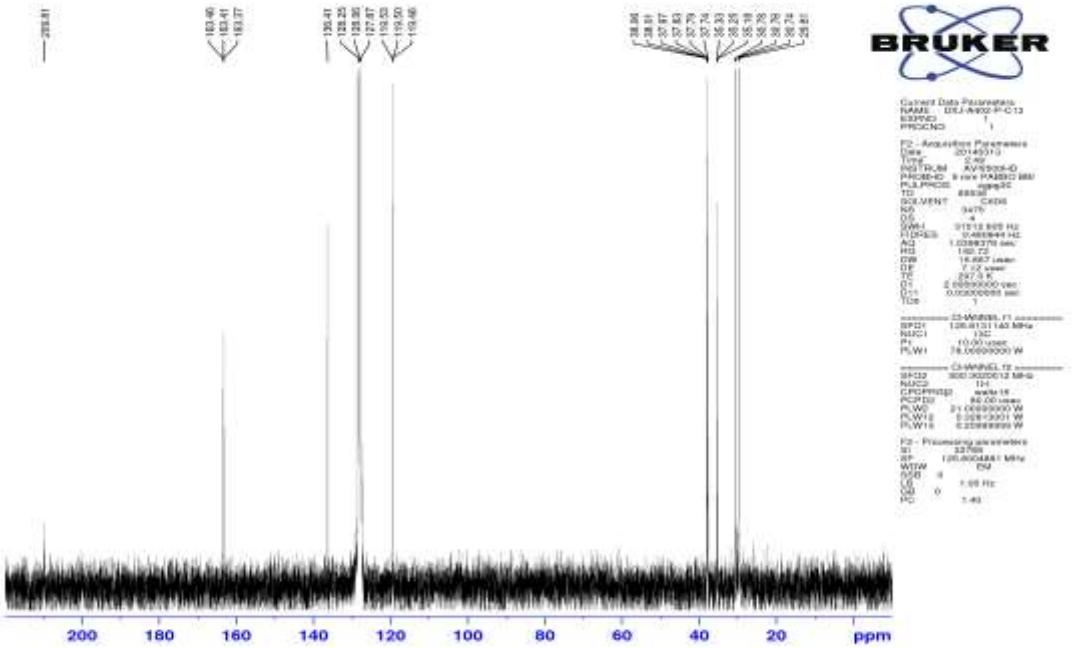
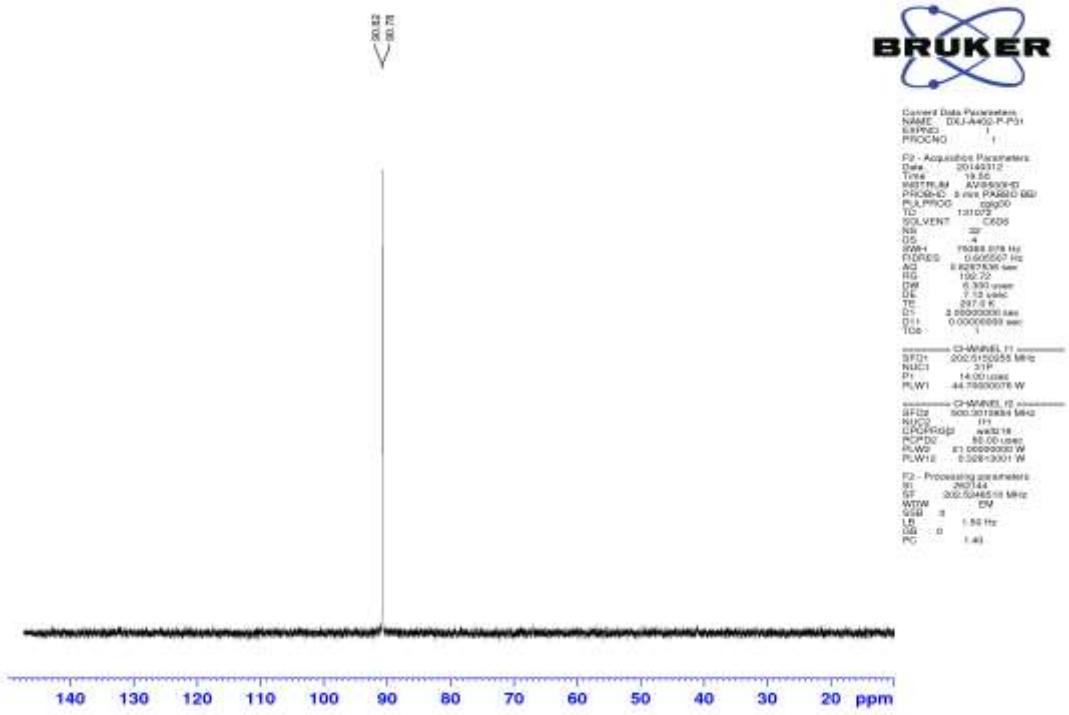
Appendix 1: NMR Data for Metal Complexes and Unknown Compounds in Chapter 3



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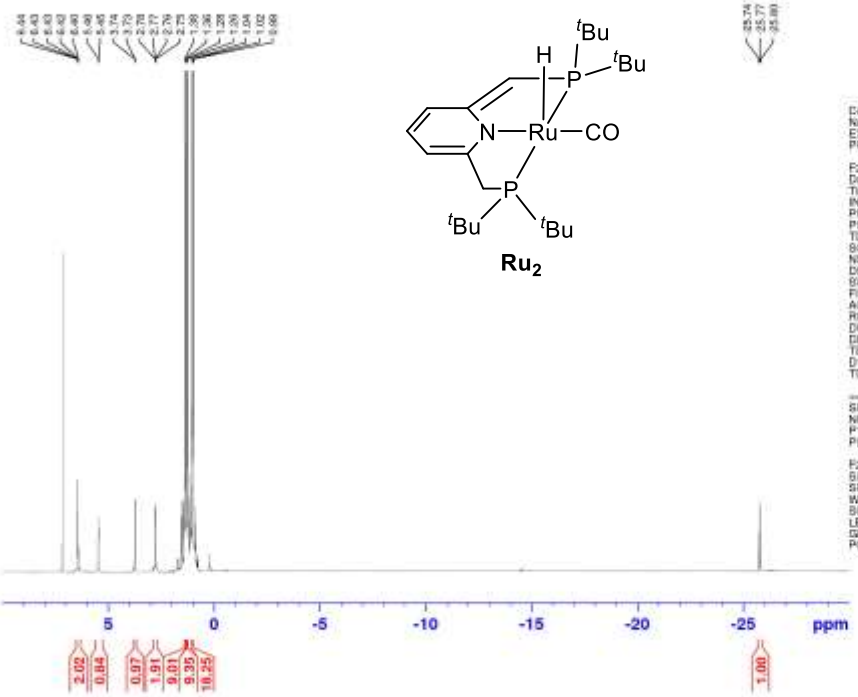
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N
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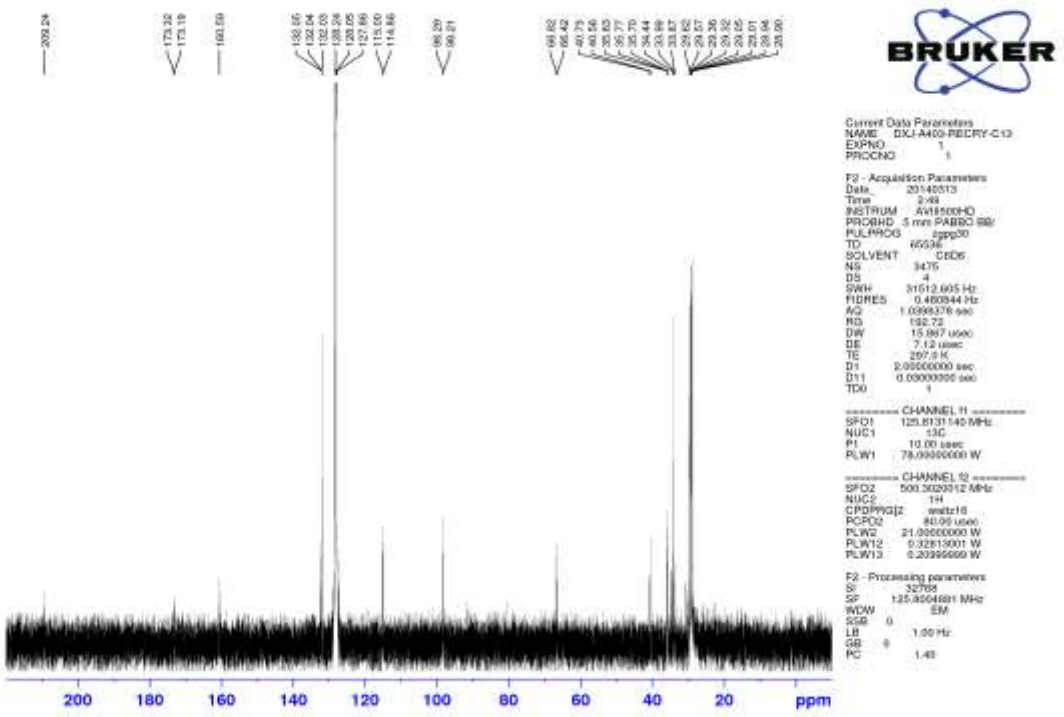
tBu

Ru_2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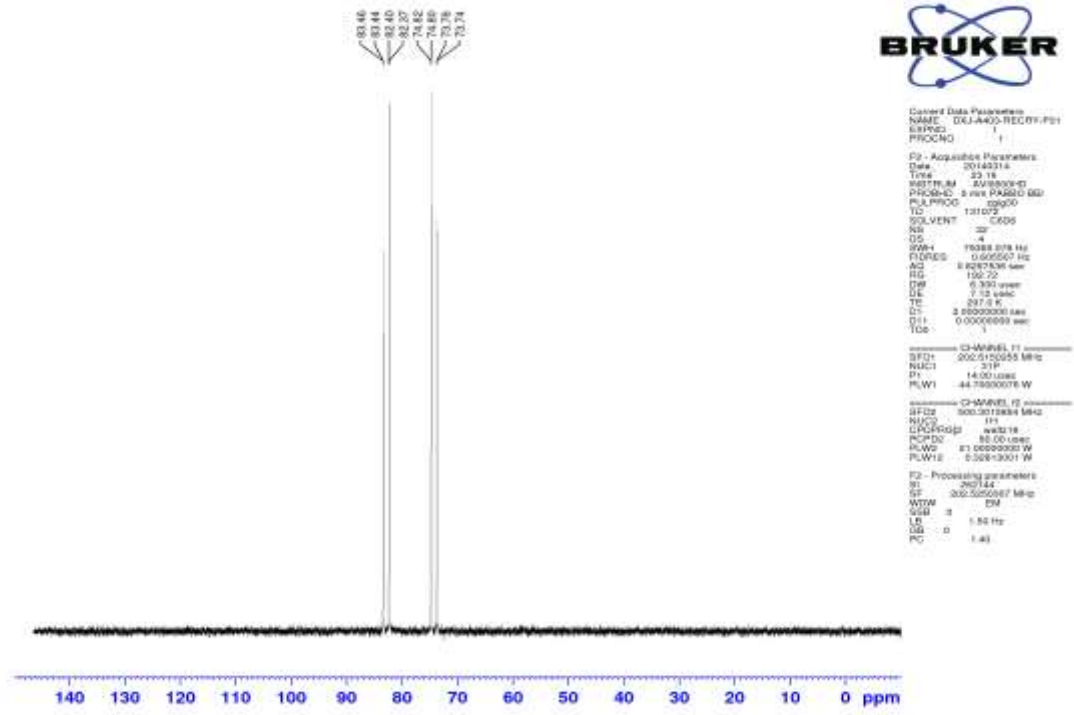
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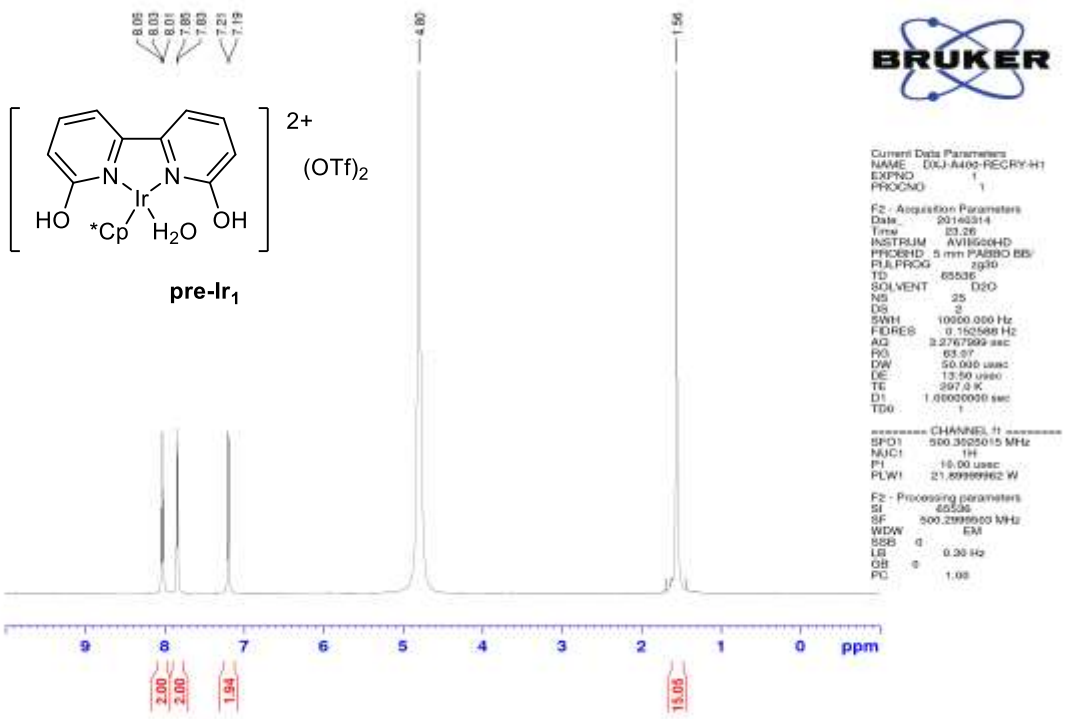
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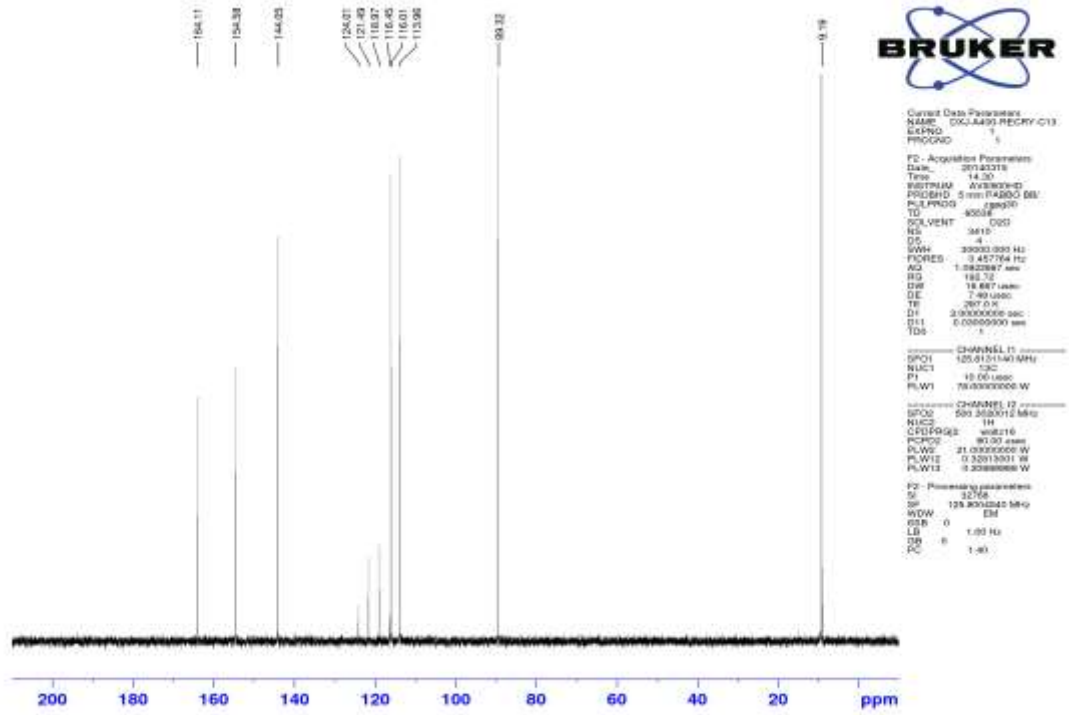
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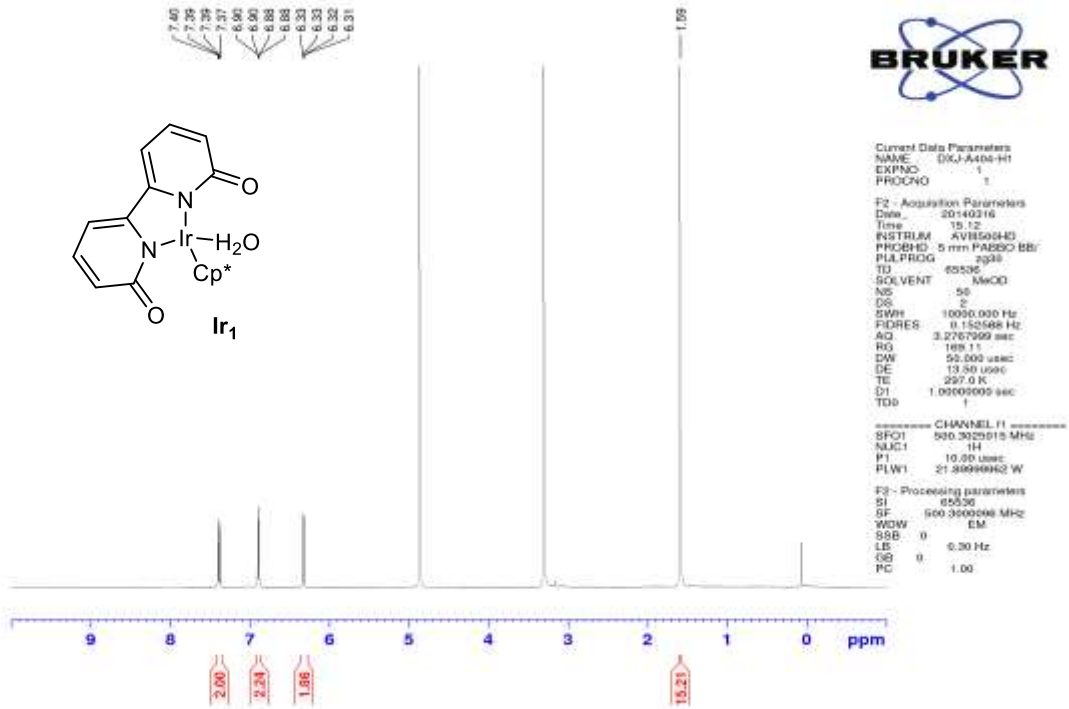
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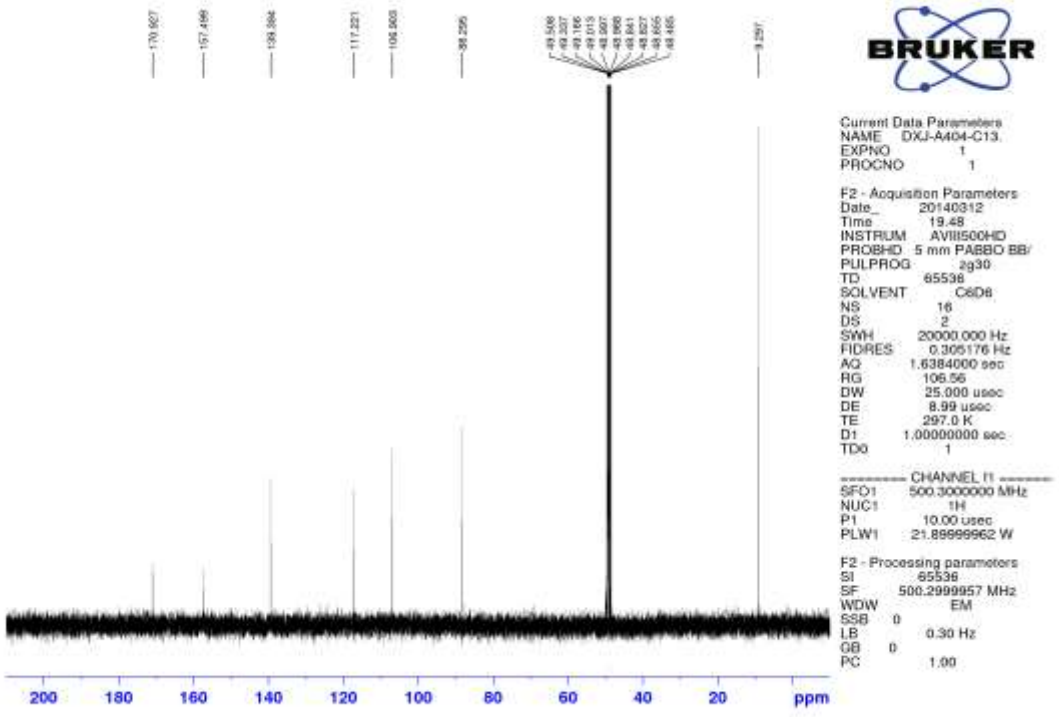
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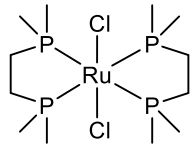
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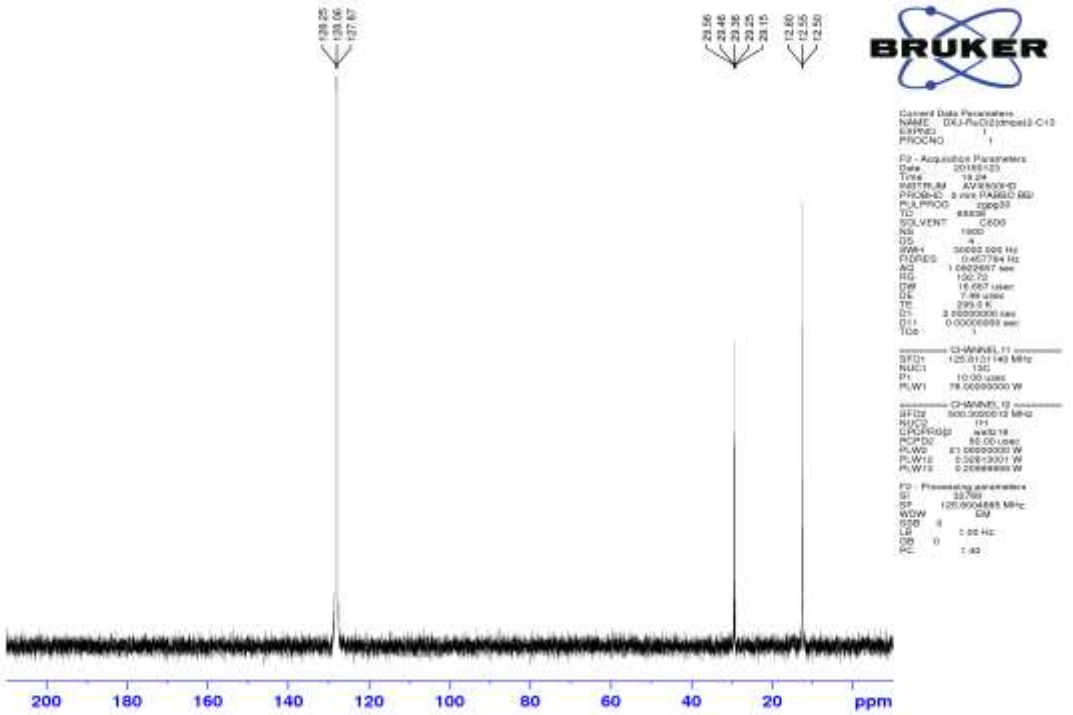
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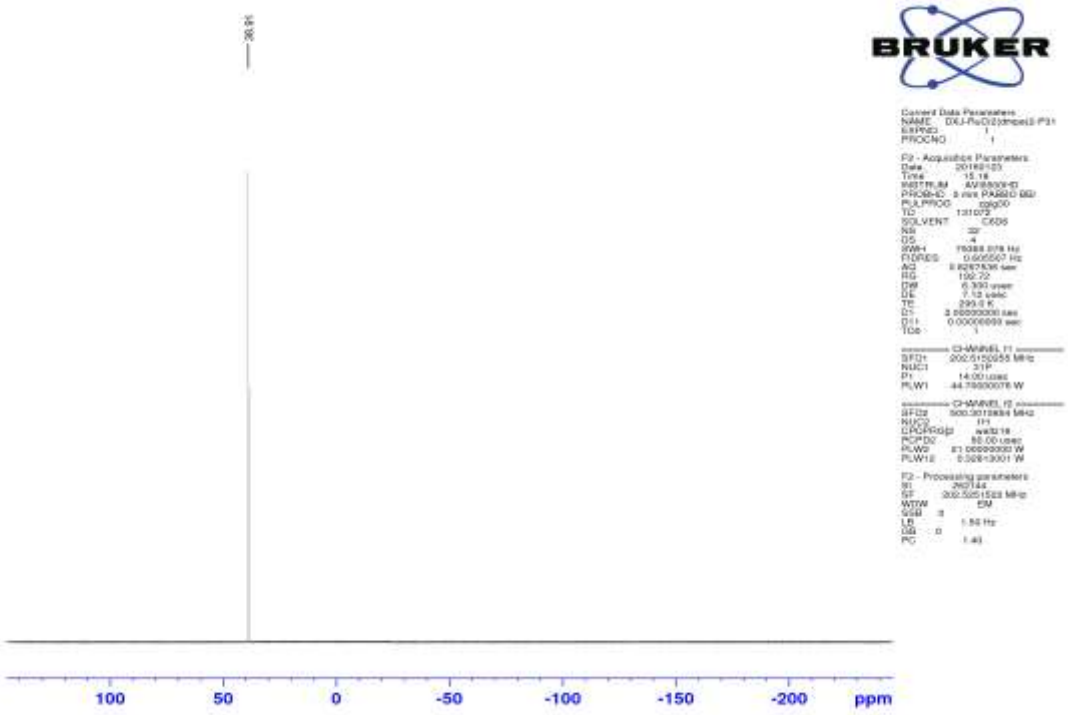
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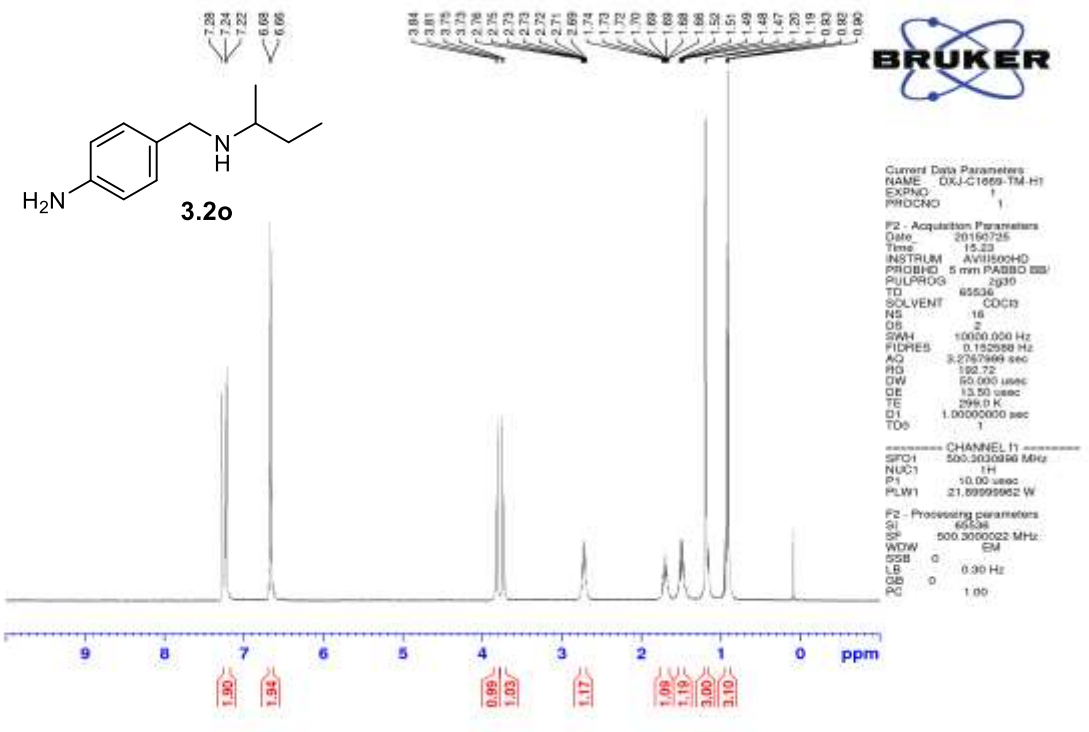
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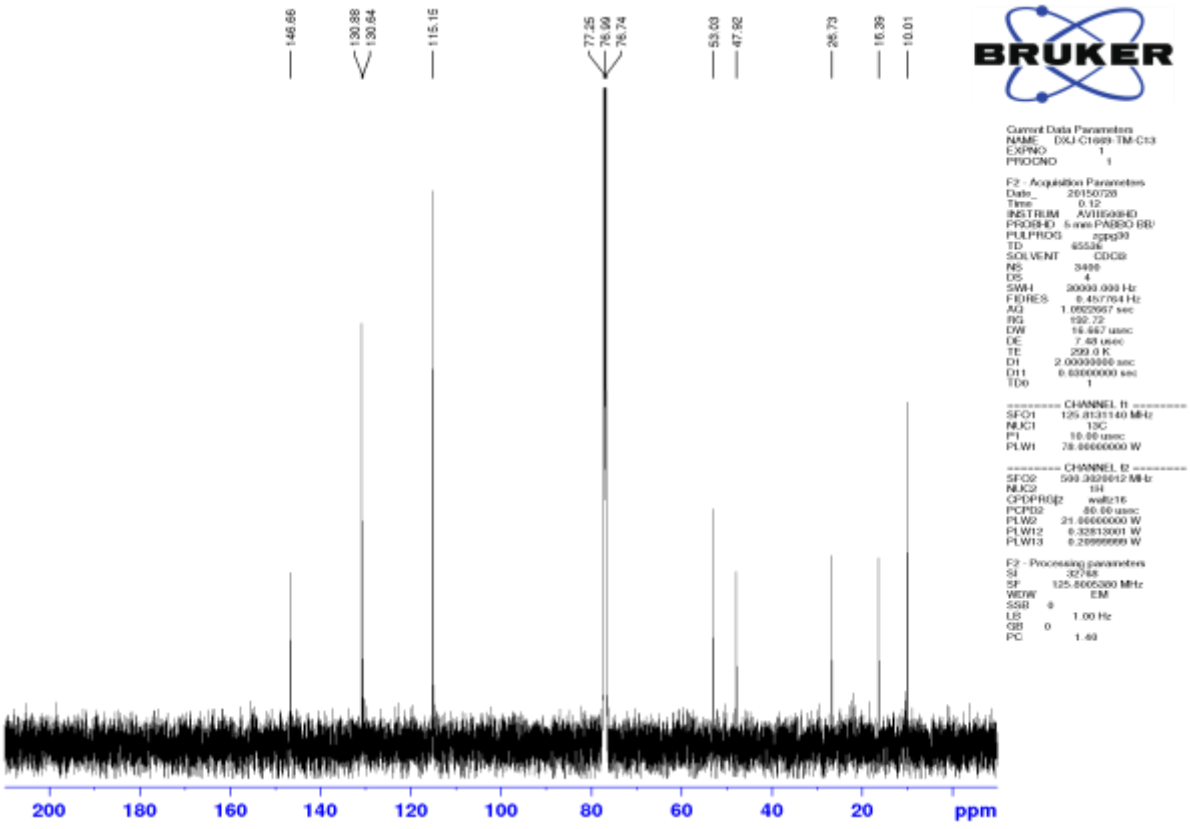
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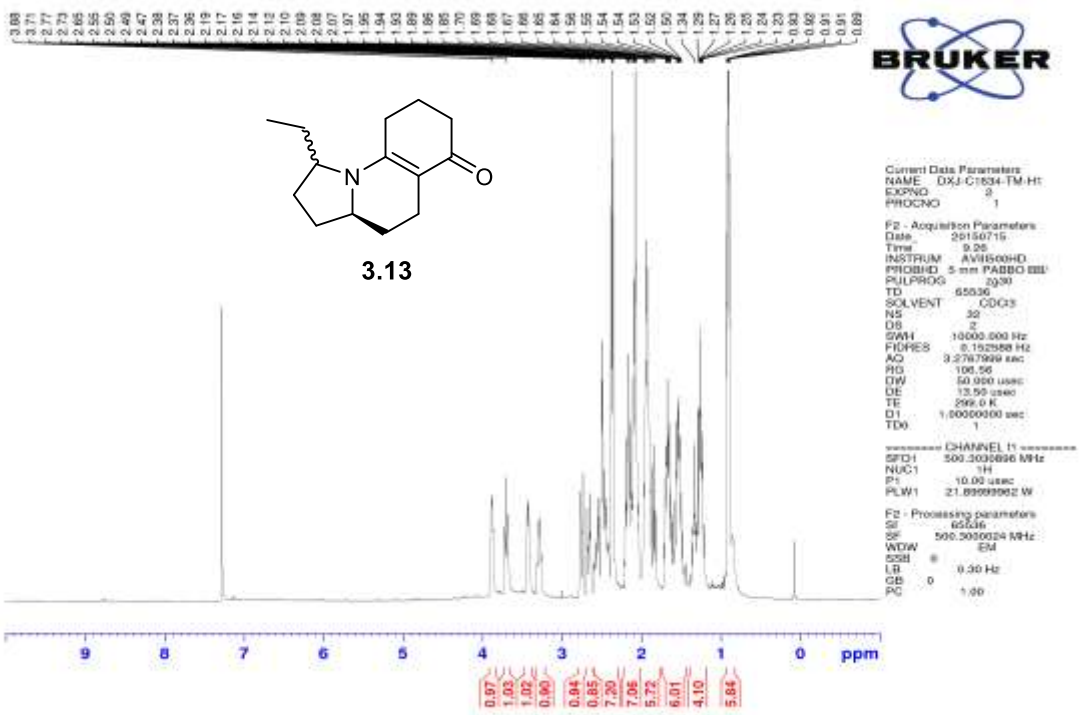
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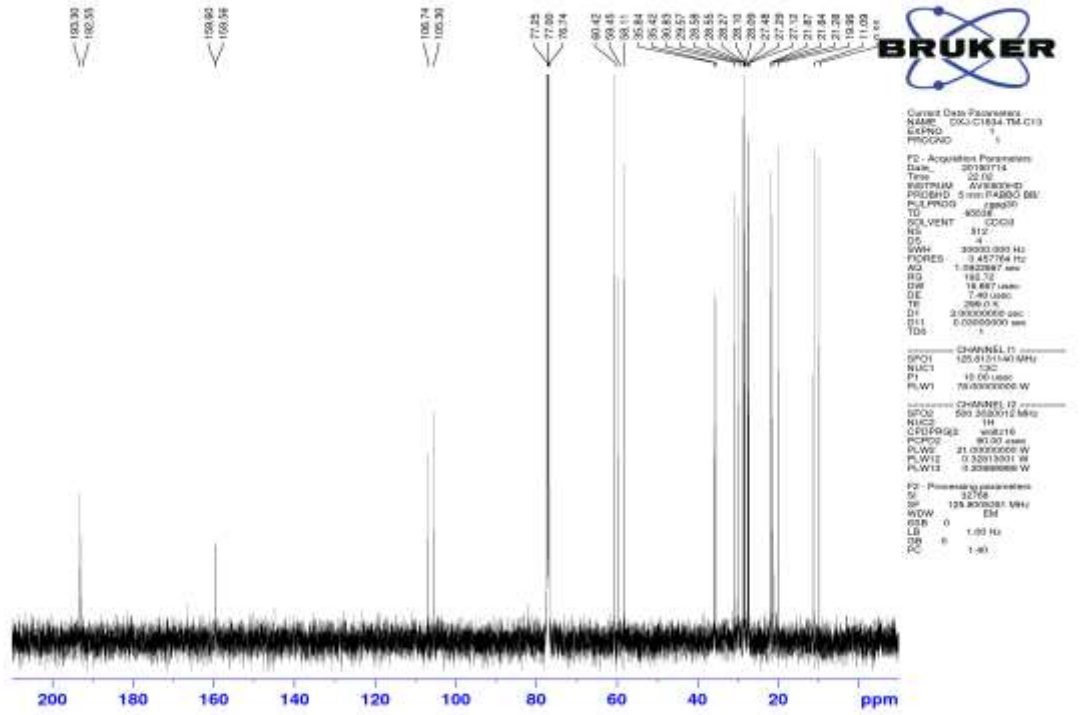
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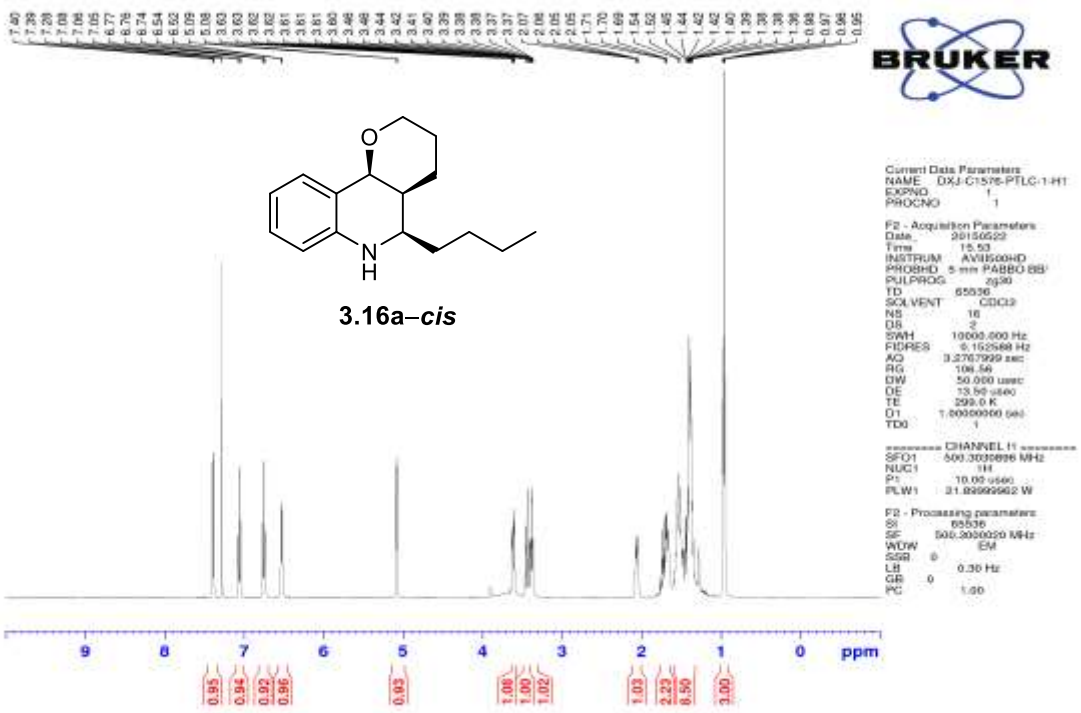

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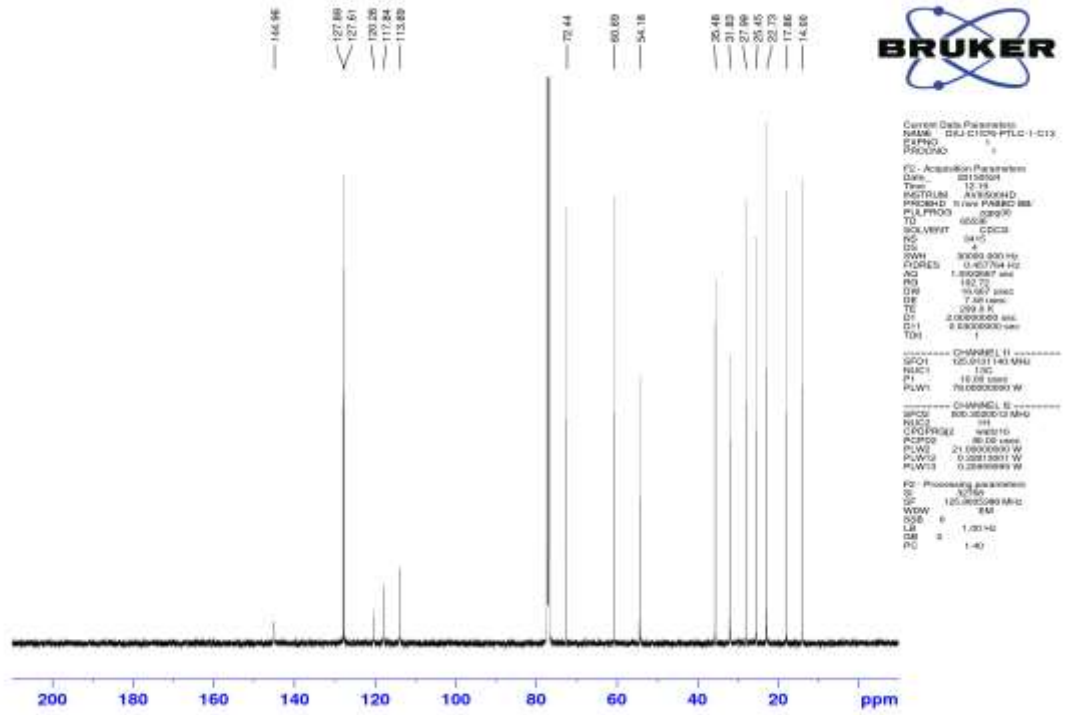

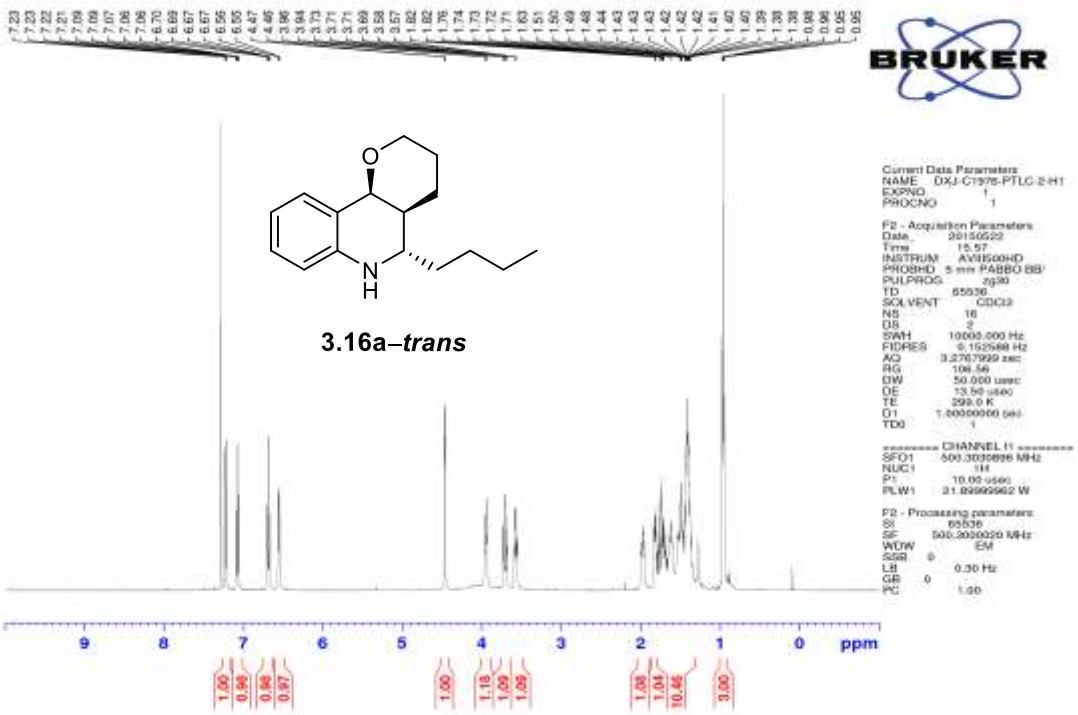
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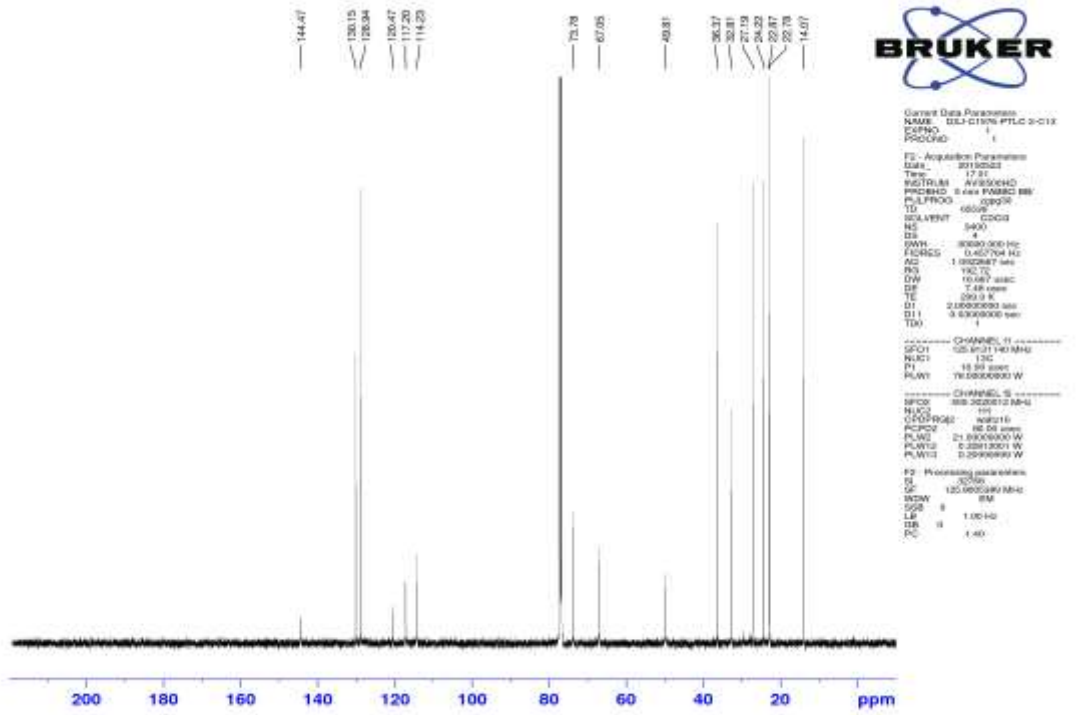
BRUKER
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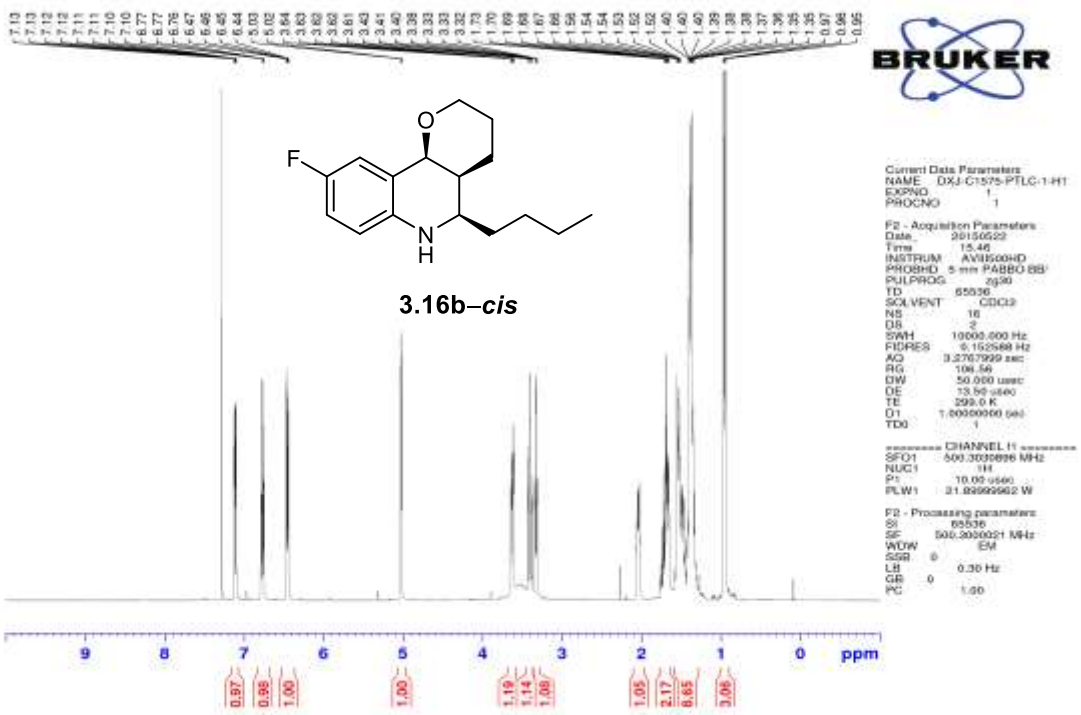
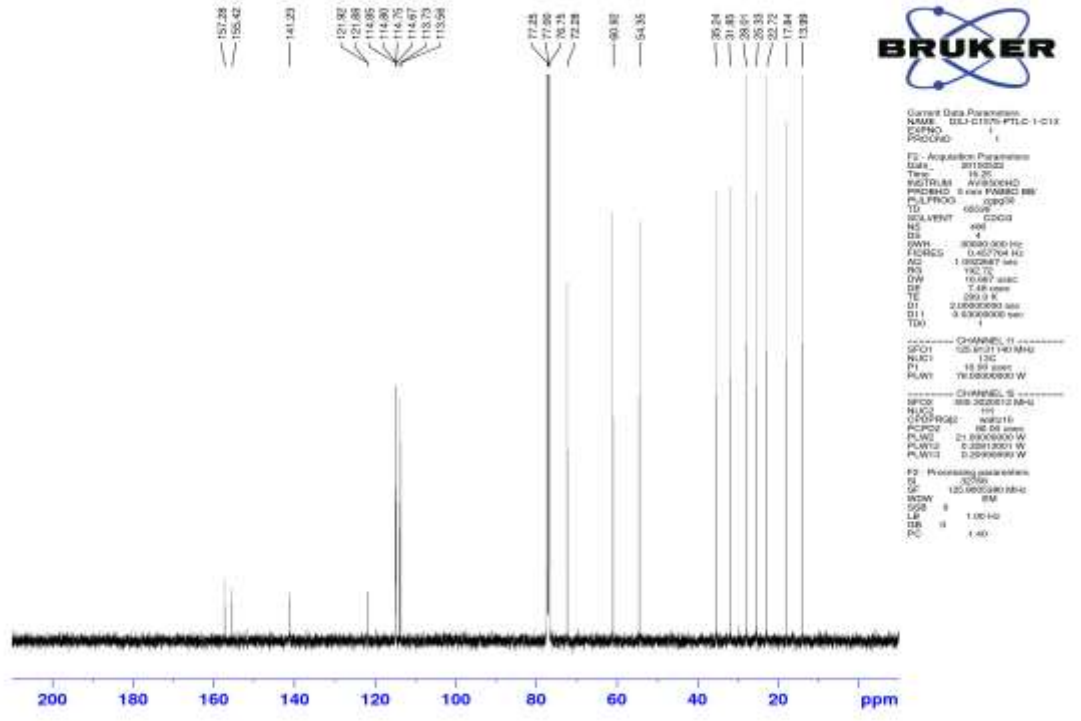
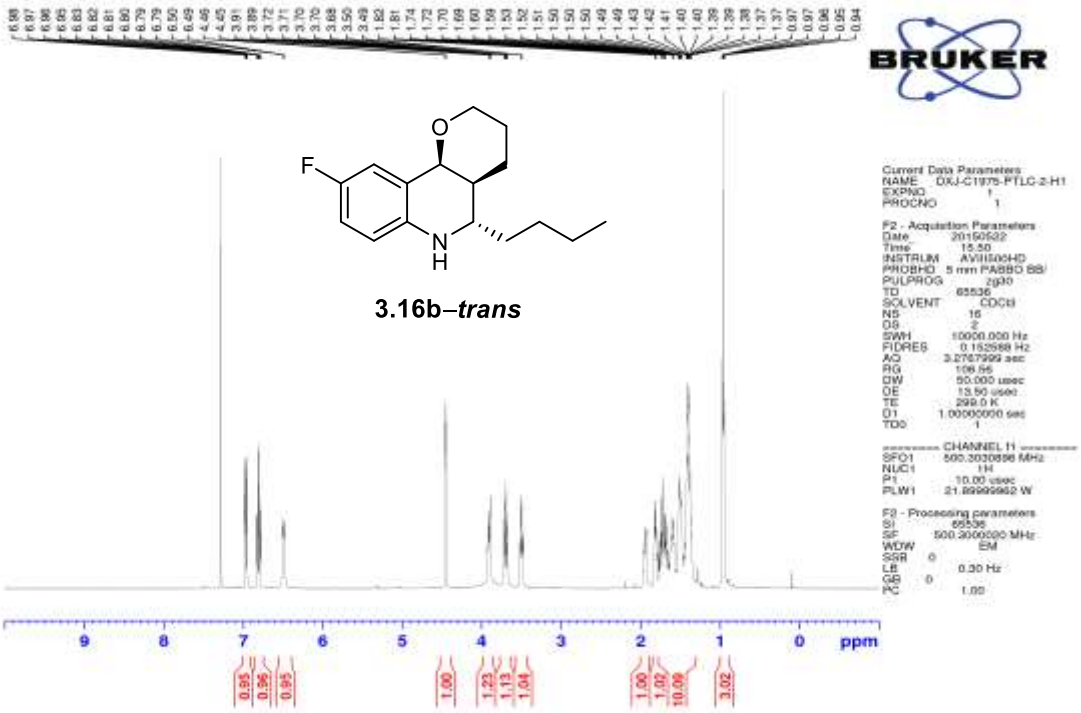
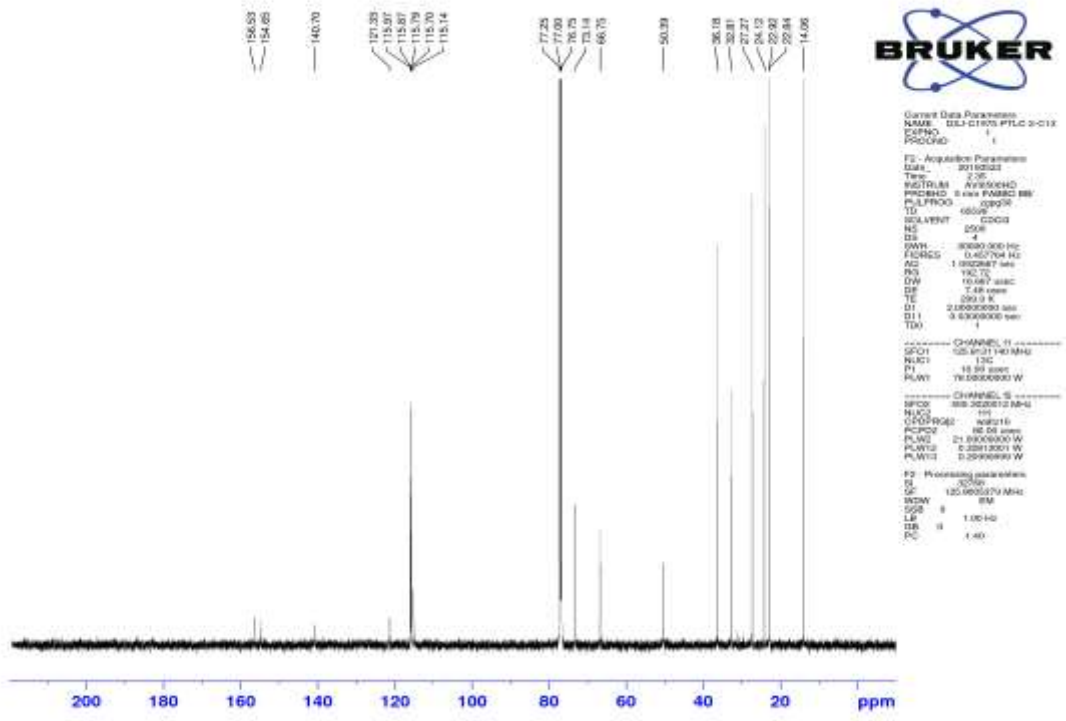


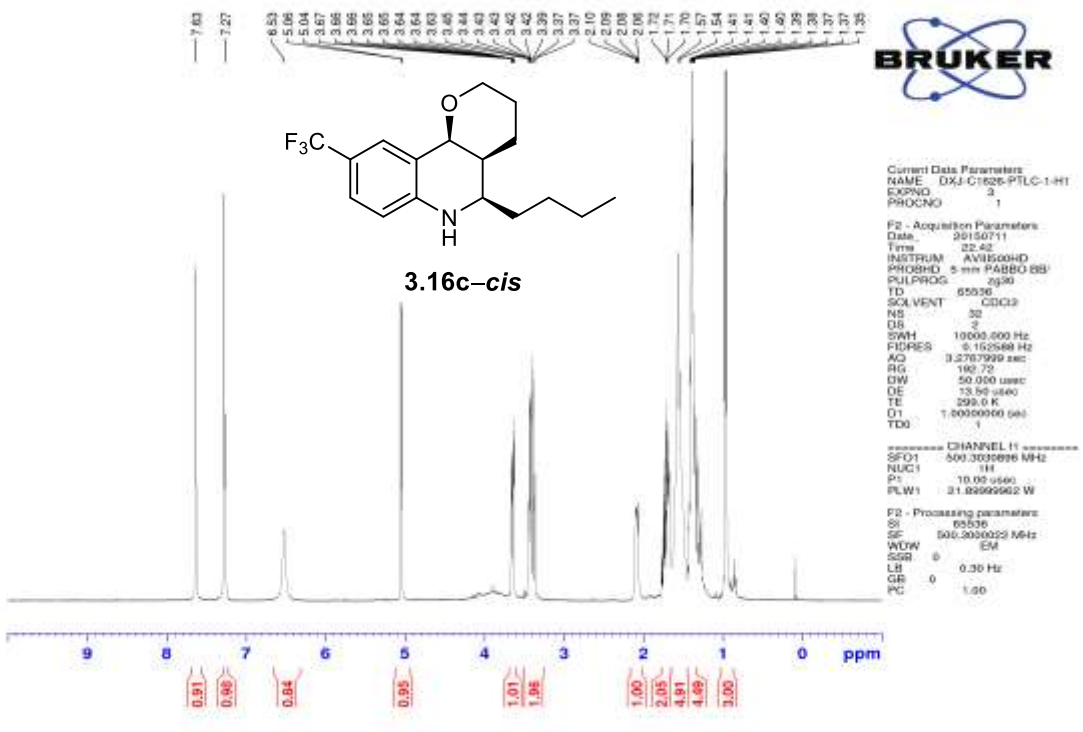
3.16b–*cis*



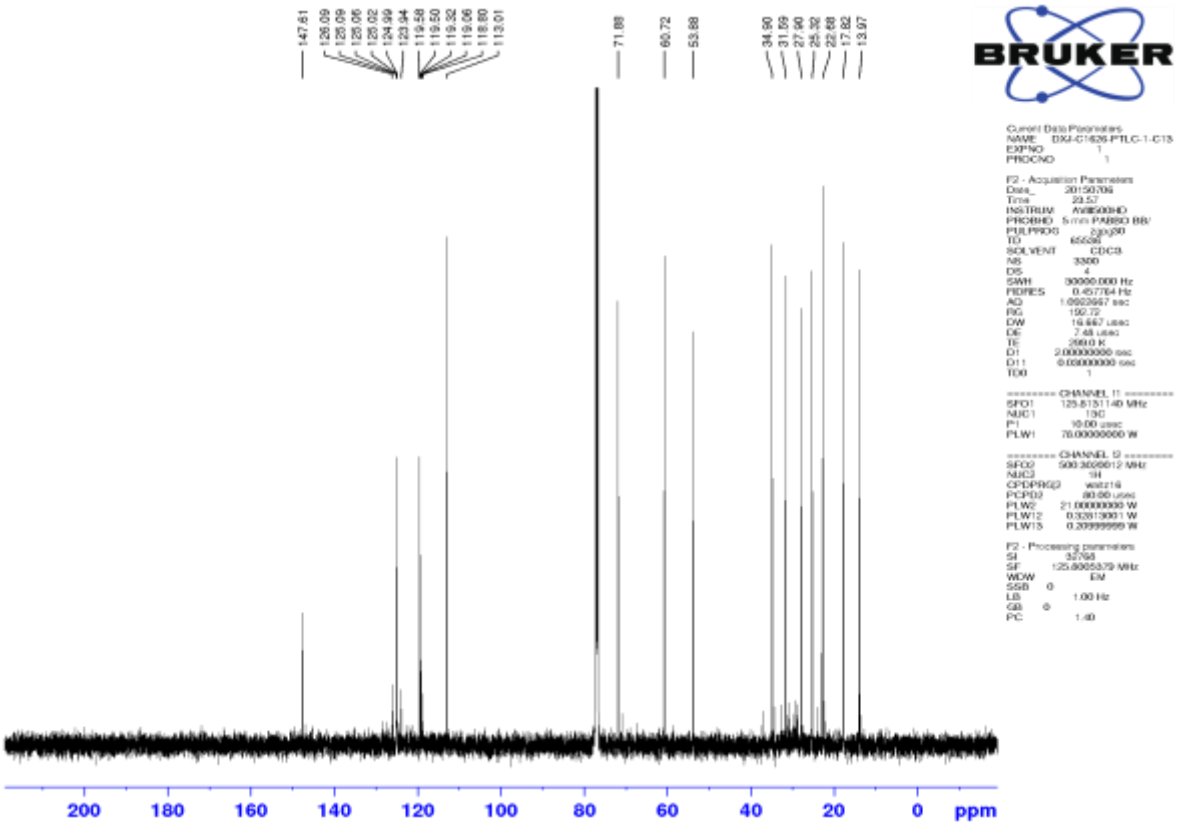


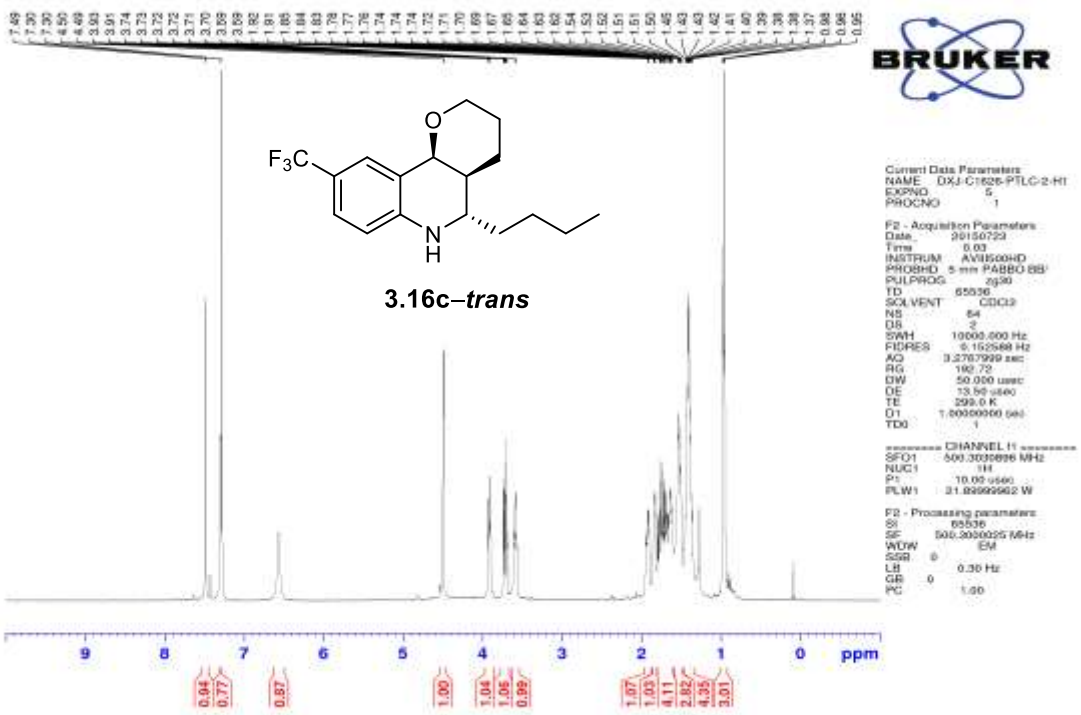
3.16b–*trans*

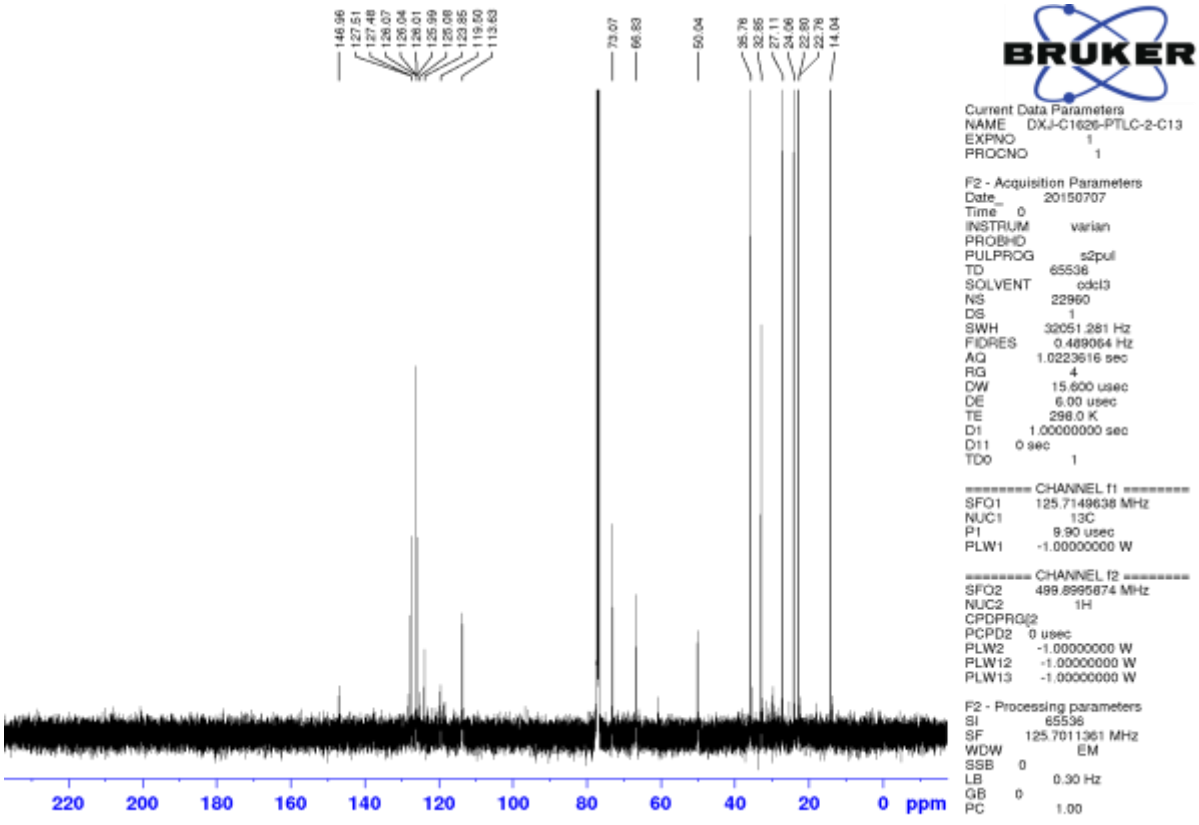


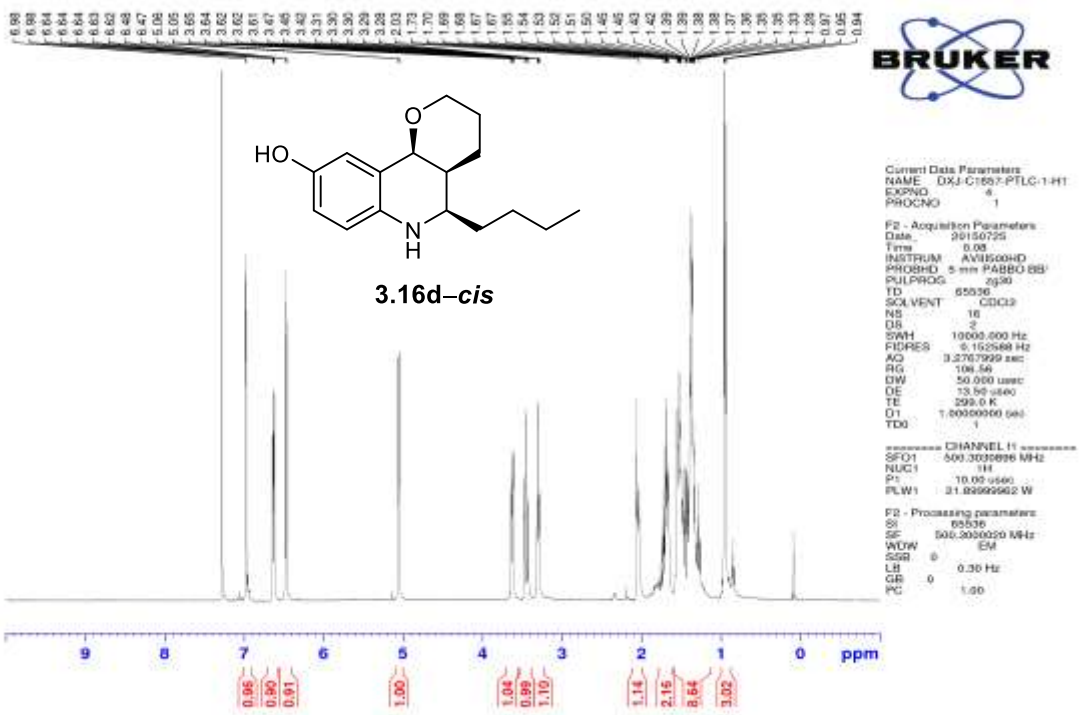


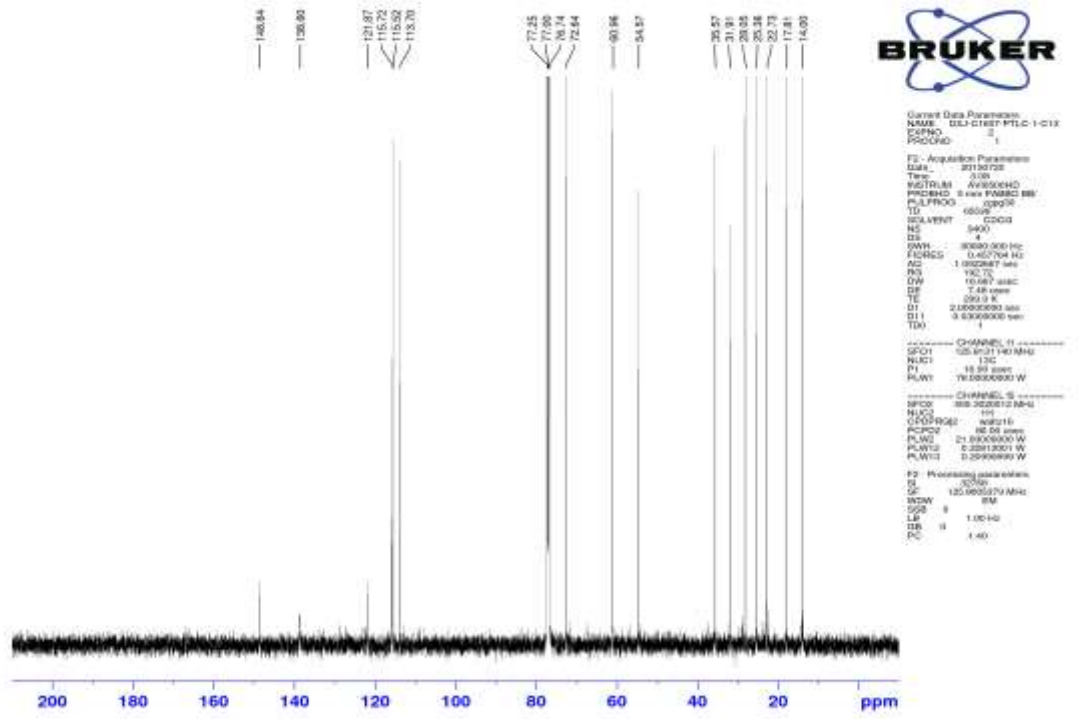
3.16c–*cis*

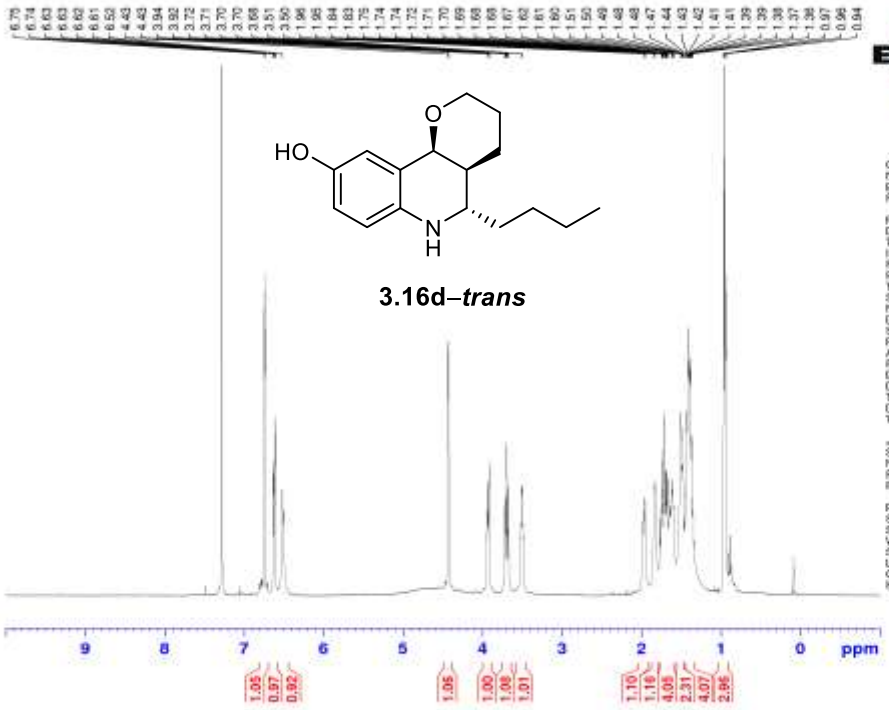



F3C
O
N
H
3.16c–*trans*
9
8
7
6
5
4
3
2
1
0
ppm
0.94
0.77
0.87
1.00
1.04
1.05
0.99
1.07
1.03
4.11
2.82
4.35
3.01
BRUKER
Current Data Parameters
NAME DXJ-C1626-PTLC-2-H1
EXPNO 5
PROCNO 1
F2 - Acquisition Parameters
Date_ 20150723
Time 0.03
INSTRUM AV600HD
PROBHD 5 mm PABBO BB/
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 64
DS 2
SWH 10000.000 Hz
FIDRES 0.152588 Hz
AQ 3.2767929 sec
RG 160.72
DW 50.000 usec
DE 13.50 usec
TE 298.0 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 500.3030886 MHz
NUC1 1H
P1 10.00 usec
PLW1 31.89999962 W
F2 - Processing parameters
SI 65536
SF 500.3030025 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

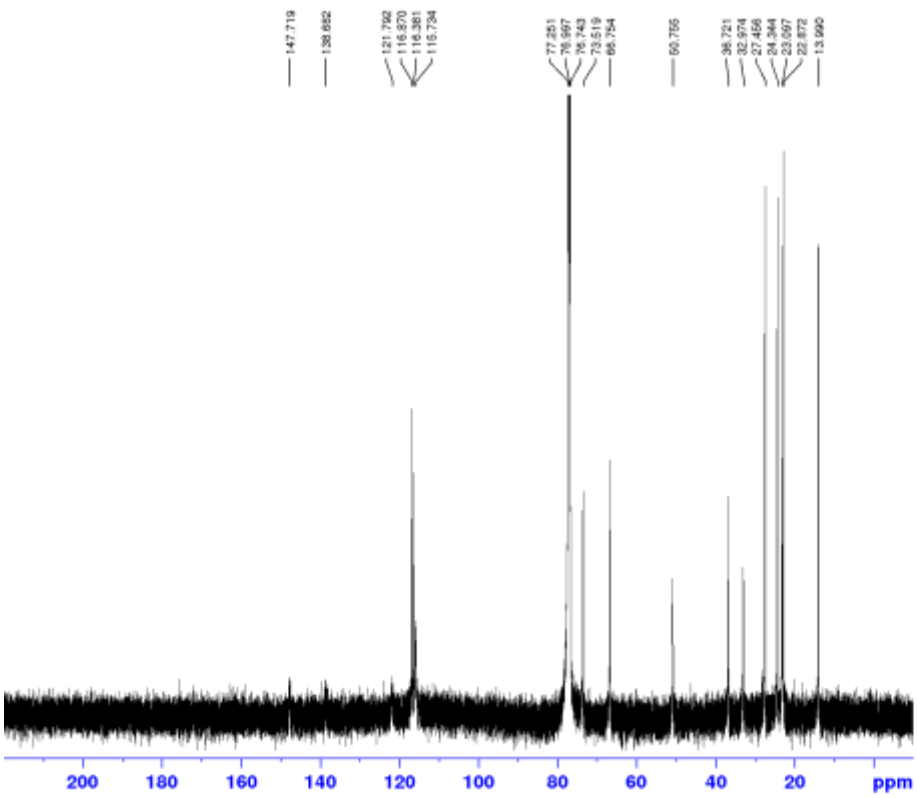

146.96
127.51
127.48
126.07
126.04
126.01
125.99
125.08
123.85
119.50
113.63
73.07
66.83
50.04
35.78
32.85
27.11
24.06
22.80
22.76
14.04
220
200
180
160
140
120
100
80
60
40
20
0
ppm
BRUKER
Current Data Parameters
NAME DXJ-C1626-PTLC-2-C13
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20150707
Time 0
INSTRUM varian
PROBHD
PULPROG s2pul
TD 65536
SOLVENT cdcl3
NS 22960
DS 1
SWH 32051.281 Hz
FIDRES 0.489064 Hz
AQ 1.0223616 sec
RG 4
DW 15.600 usec
DE 6.00 usec
TE 298.0 K
D1 1.00000000 sec
D11 0 sec
TD0 1
======== CHANNEL f1 ========
SFO1 125.7149638 MHz
NUC1 13C
P1 9.90 usec
PLW1 -1.00000000 W
======== CHANNEL f2 ========
SFO2 499.8995874 MHz
NUC2 1H
CPDPRG2
PCPD2 0 usec
PLW2 -1.00000000 W
PLW12 -1.00000000 W
PLW13 -1.00000000 W
F2 - Processing parameters
SI 65536
SF 125.7011361 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

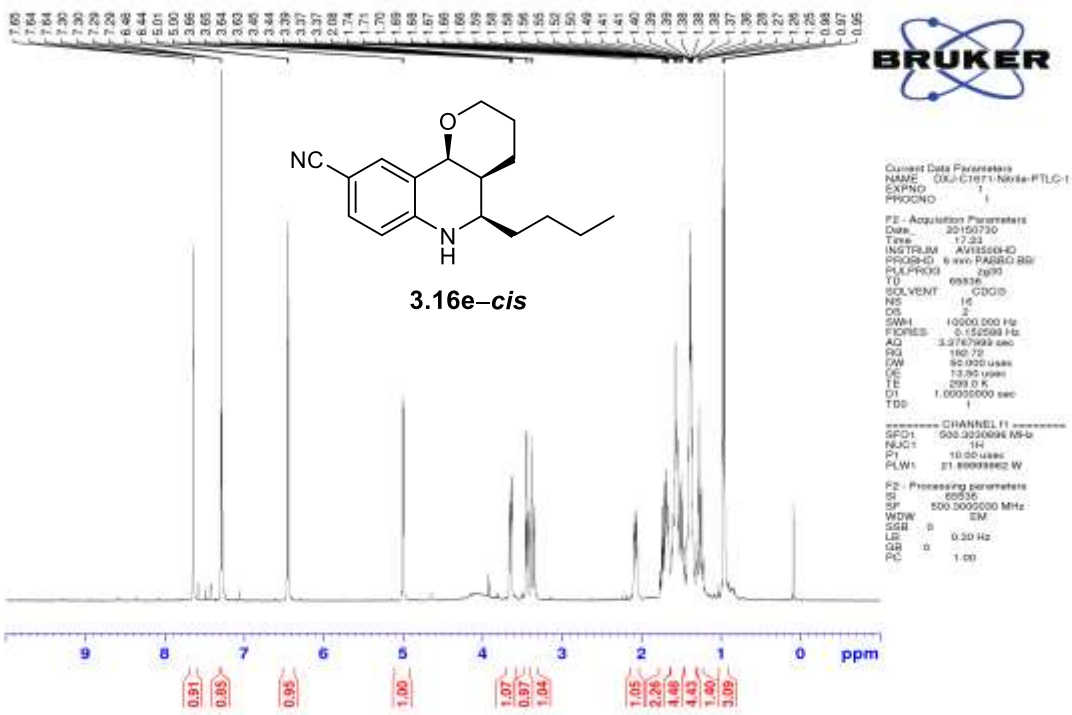

HO
O
N
H
3.16d–*cis*
BRUKER
9
8
7
6
5
4
3
2
1
0
ppm


BRUKER
200
180
160
140
120
100
80
60
40
20
ppm

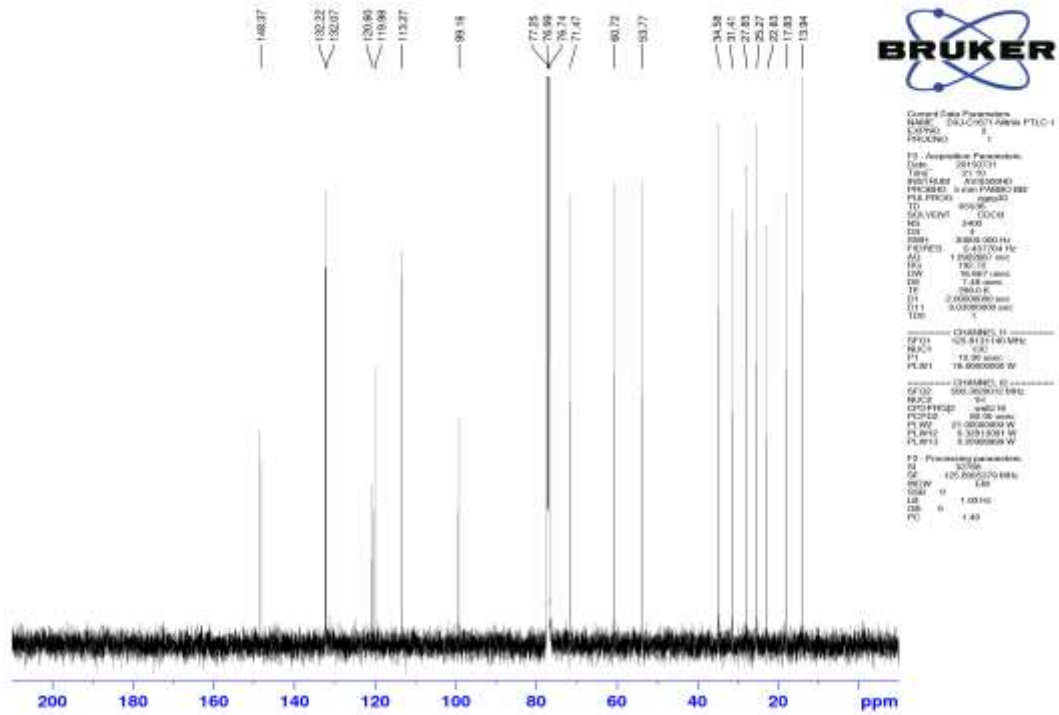


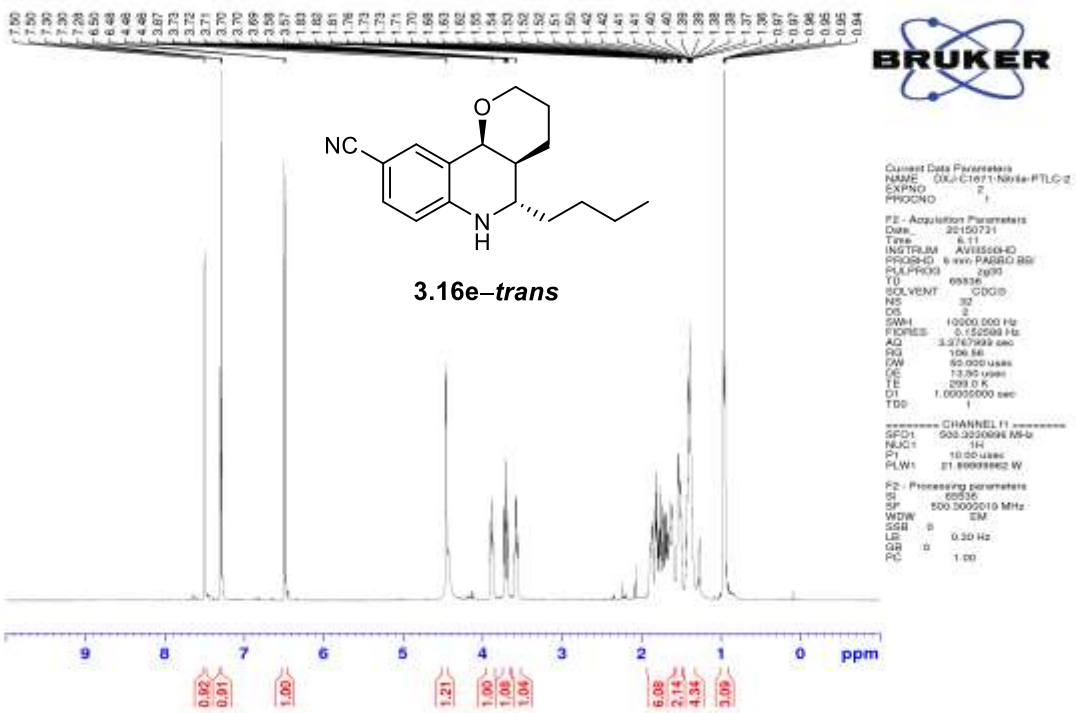
3.16d–*trans*



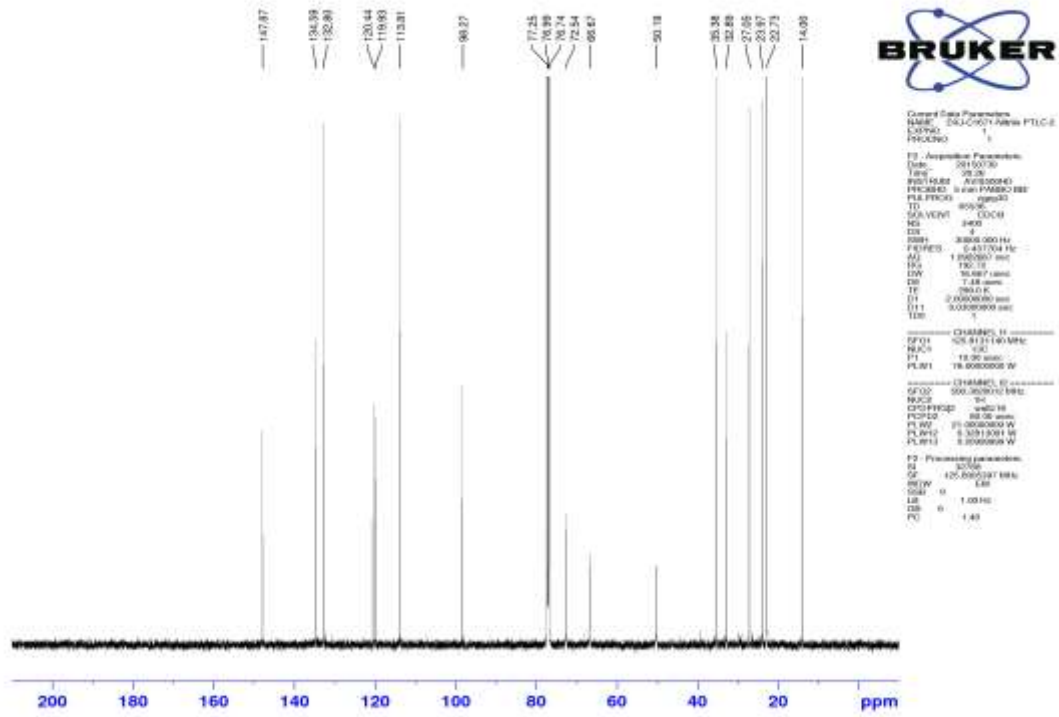


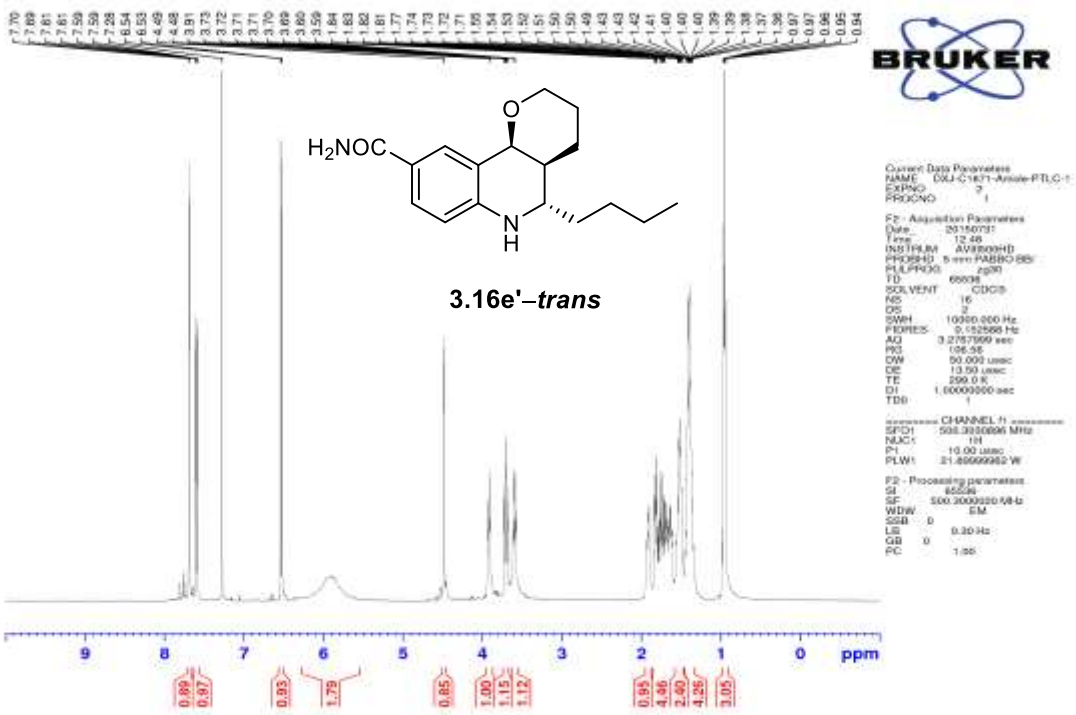
3.16e–*cis*



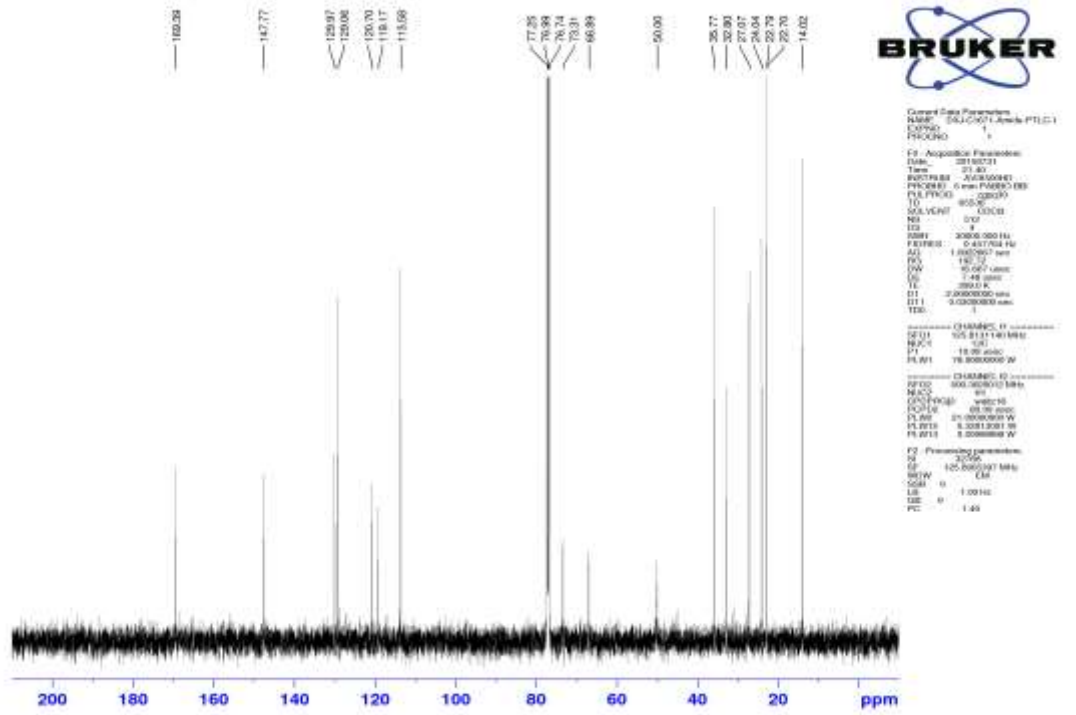

NC
O
N
H
9
8
7
6
5
4
3
2
1
0
ppm
0.92
0.91
1.00
1.21
1.00
1.08
1.04
6.08
2.14
4.34
3.09

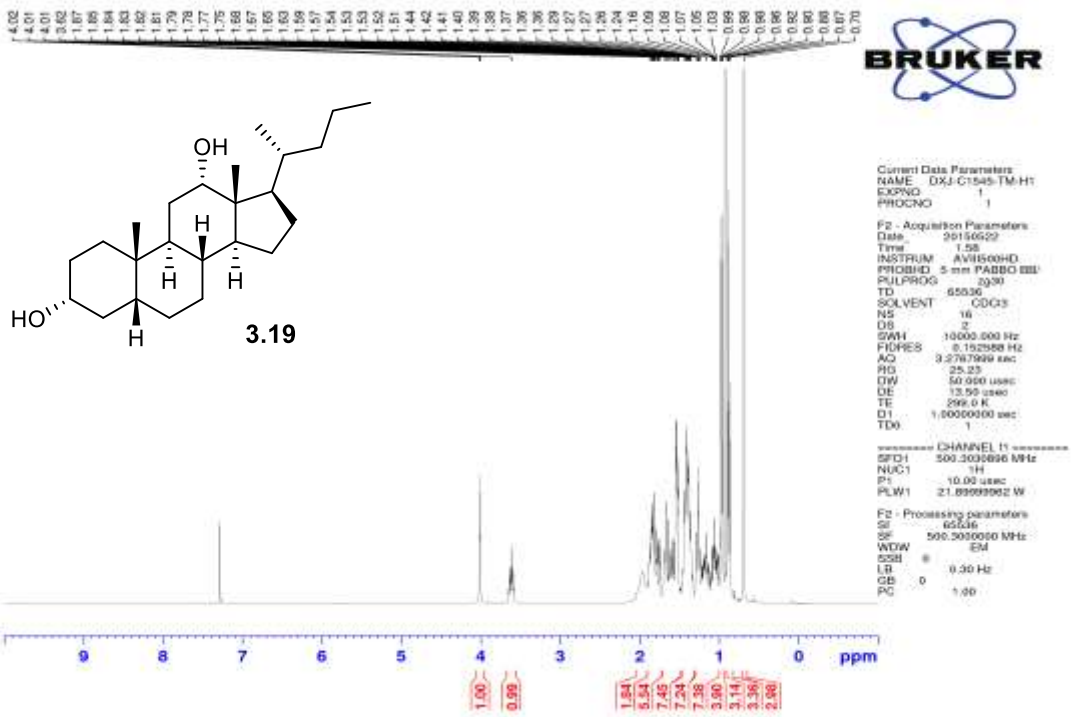
3.16e–*trans*

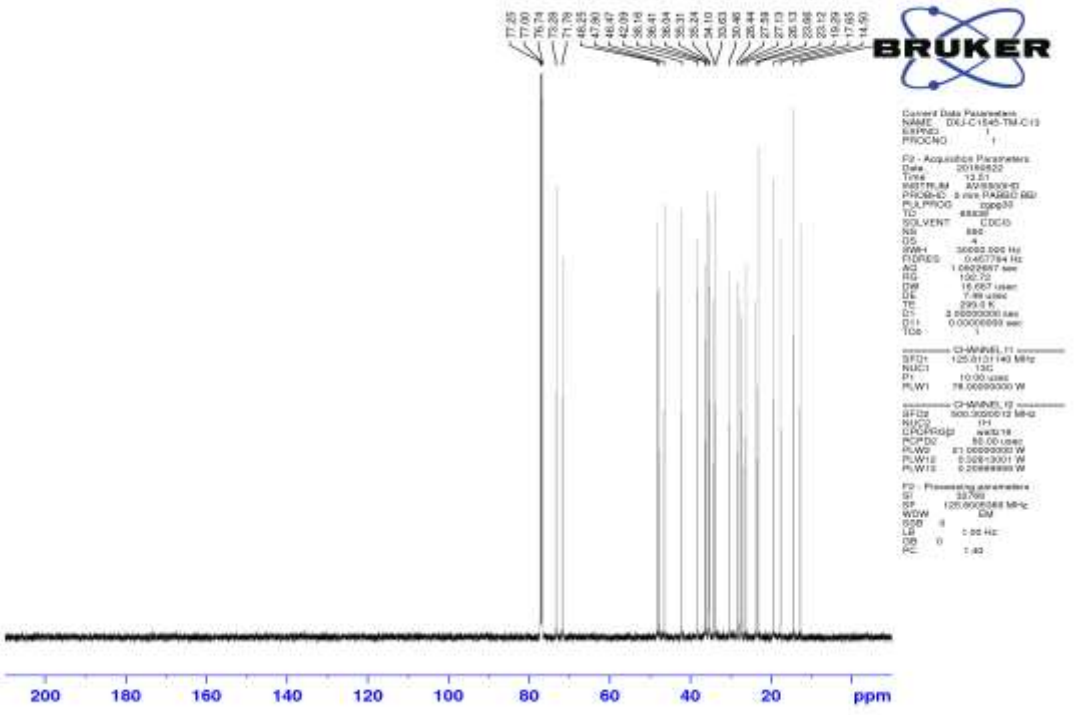

200
180
160
140
120
100
80
60
40
20
ppm

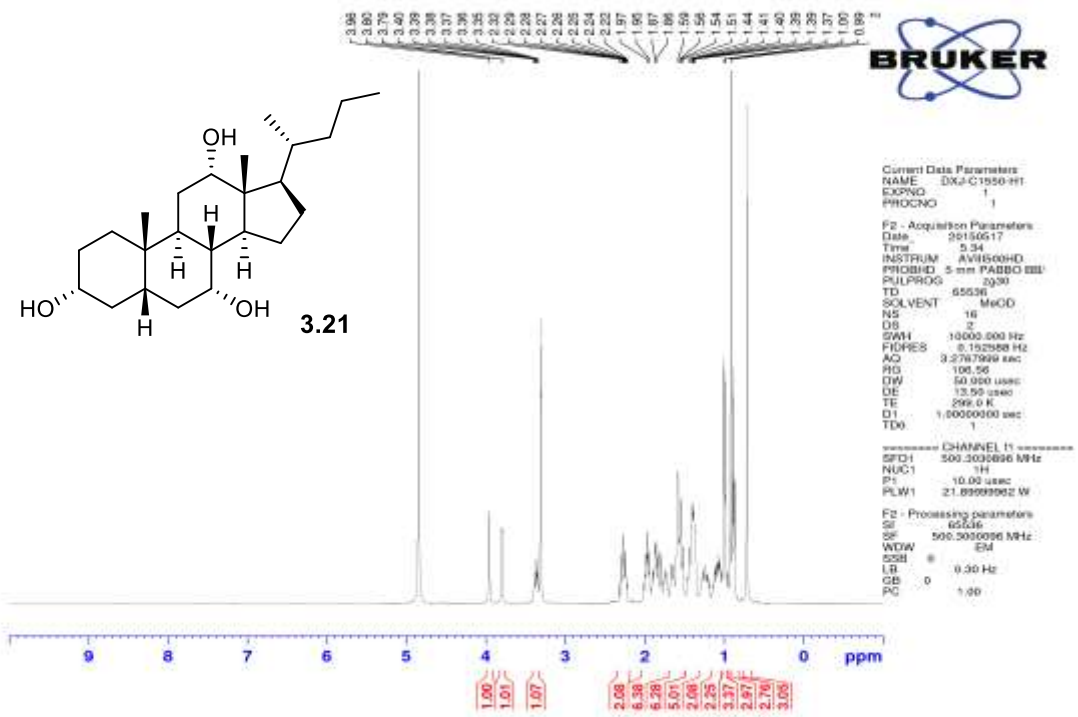

BRUKER
O
H2NOC
N
H
9
8
7
6
5
4
3
2
1
0
ppm

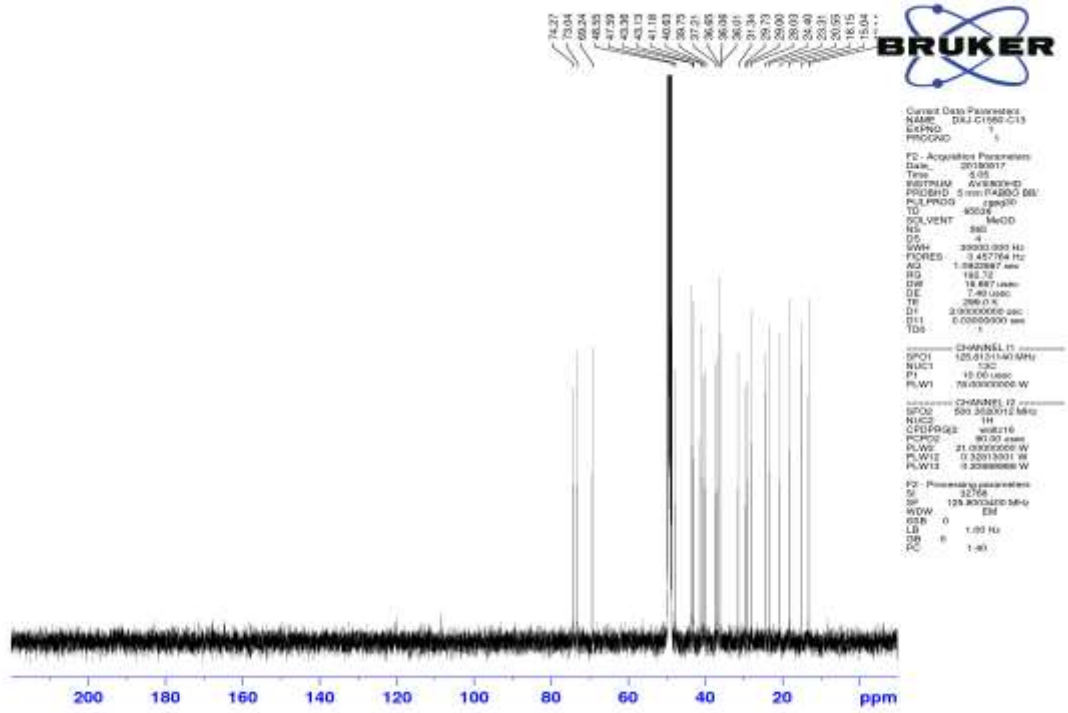
3.16e'–*trans*


BRUKER
200
180
160
140
120
100
80
60
40
20
ppm

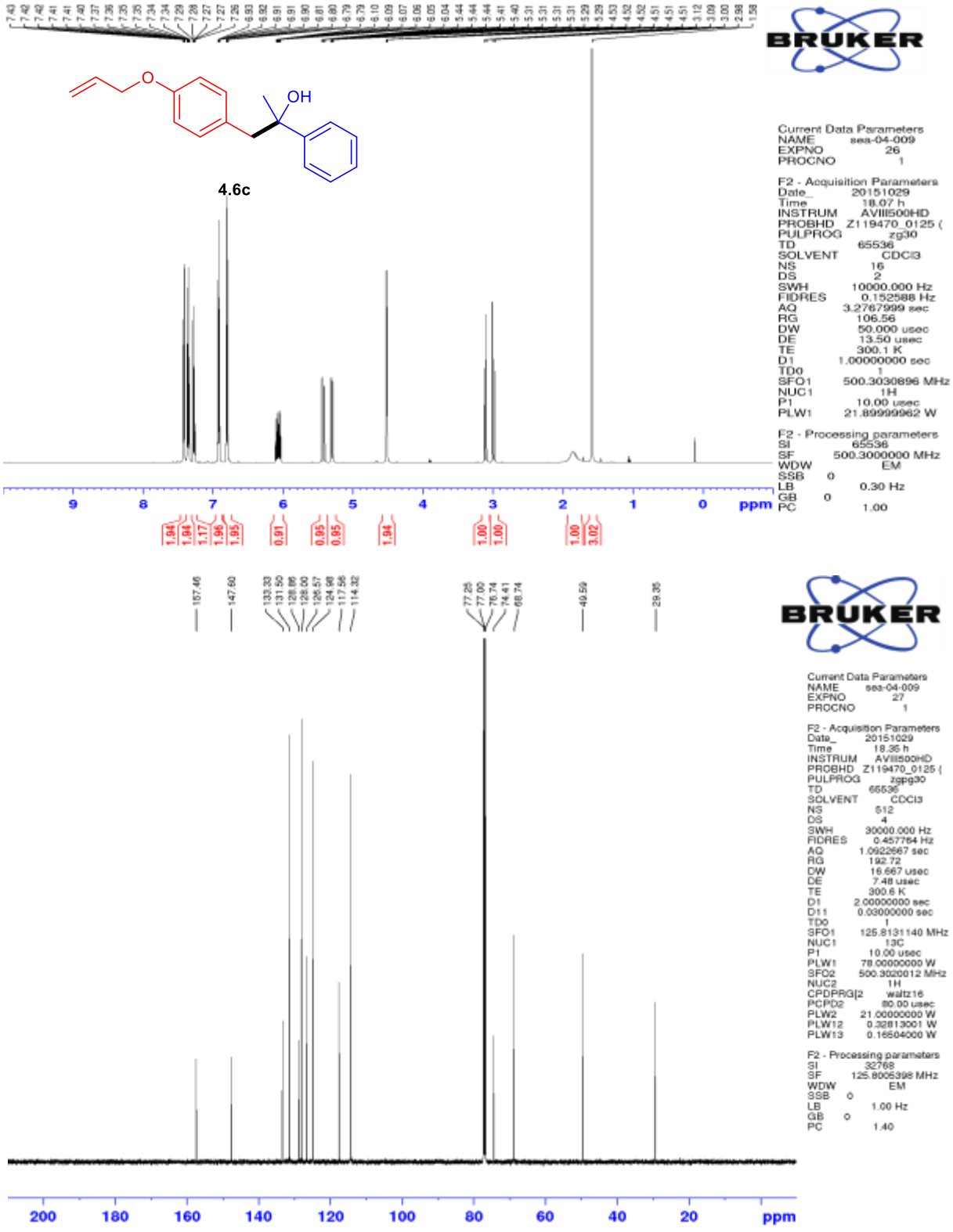

OH
H
H
H
HO
H
3.19
BRUKER
ppm

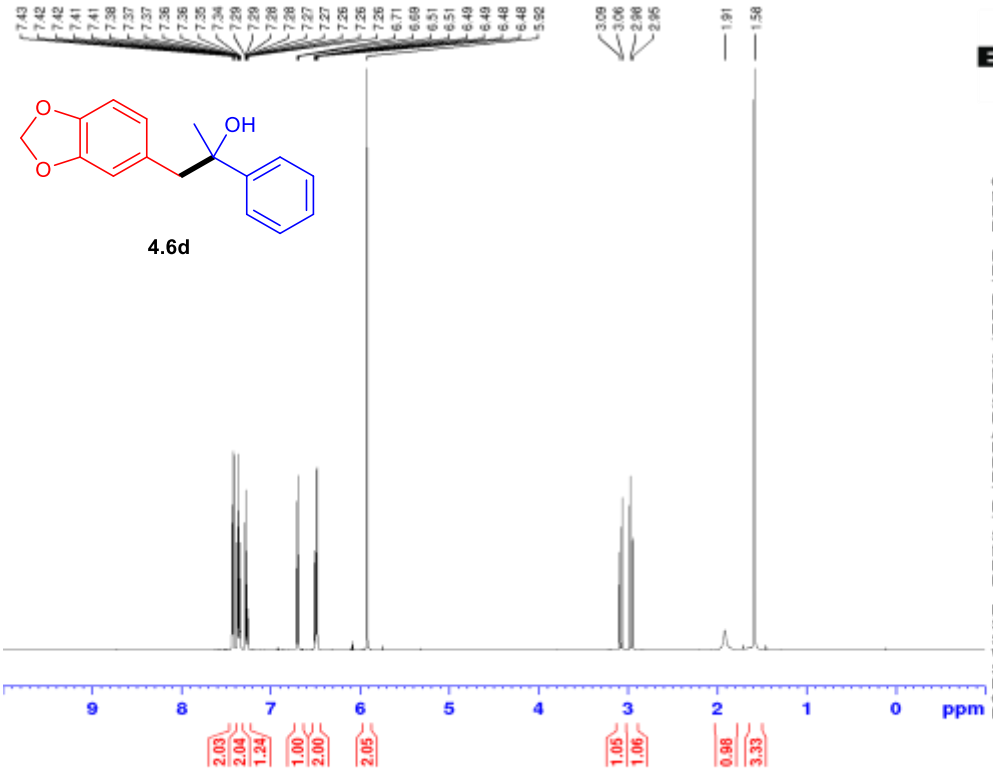

BRUKER
ppm


OH
H
H
H
HO
OH
H
3.21
BRUKER
ppm


BRUKER
200
180
160
140
120
100
80
60
40
20
ppm

Appendix 2: NMR Data for Unknown Compounds in Chapter 4



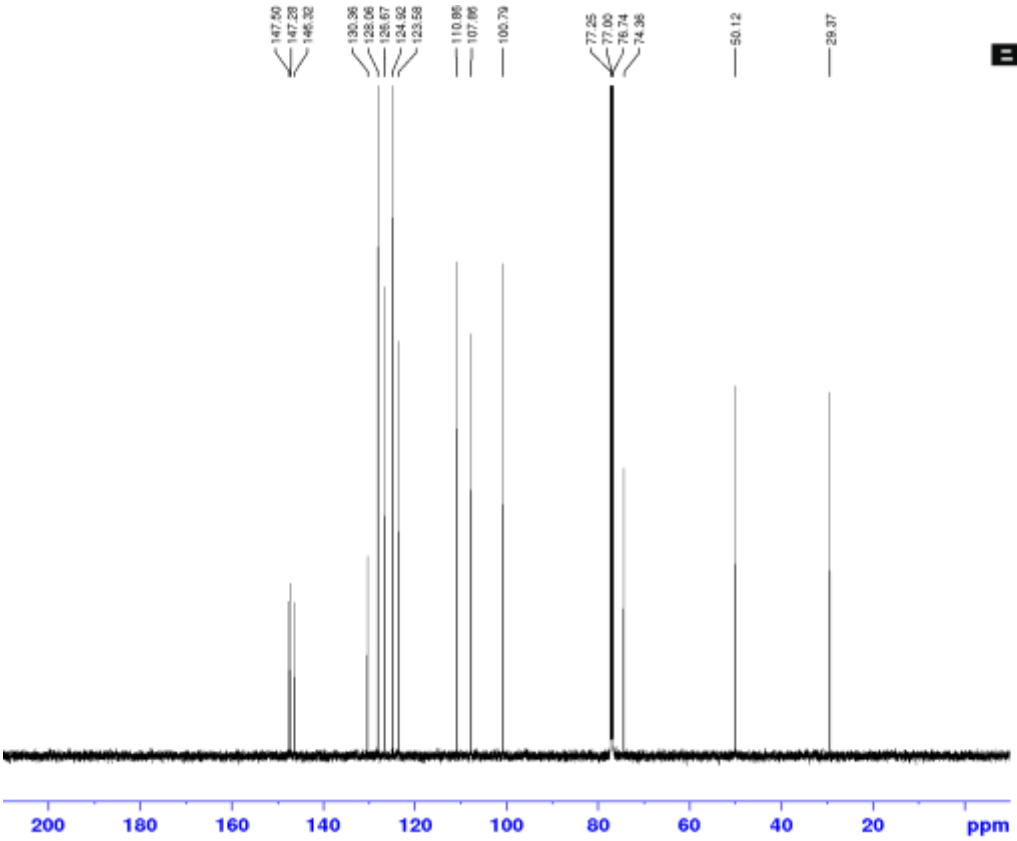


BRUKER

Current Data Parameters
NAME sea-04-009
EXPNO 24
PROCNO 1

F2 - Acquisition Parameters
Date_ 20151029
Time 17.34 h
INSTRUM AVIII500HD
PROBHD Z119470_0125 (
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 10000.000 Hz
FIDRES 0.152588 Hz
AQ 3.2767999 sec
RG 106.56
DW 50.000 usec
DE 13.50 usec
TE 300.1 K
D1 1.00000000 sec
TD0 1
SFO1 500.3030896 MHz
NUC1 1H
P1 10.00 usec
PLW1 21.89999962 W

F2 - Processing parameters
SI 65536
SF 500.3000000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

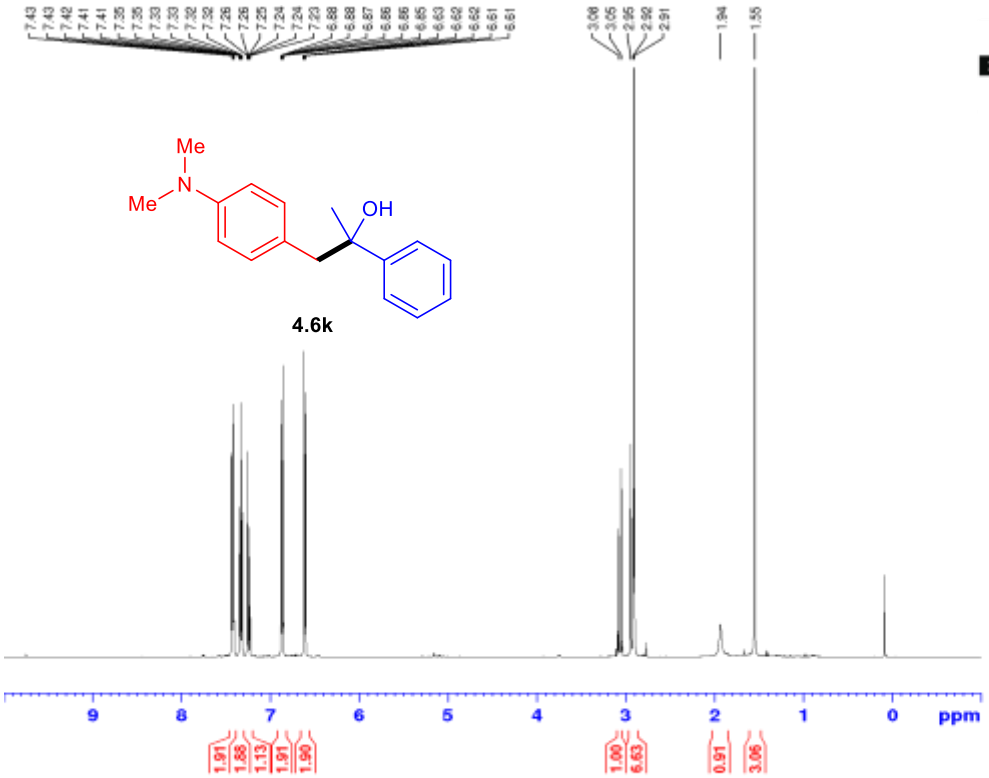


BRUKER

Current Data Parameters
NAME sea-04-009
EXPNO 25
PROCNO 1

F2 - Acquisition Parameters
Date_ 20151029
Time 18.02 h
INSTRUM AVIII500HD
PROBHD Z119470_0125 (
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 512
DS 4
SWH 30000.000 Hz
FIDRES 0.457764 Hz
AQ 1.0922667 sec
RG 192.72
DW 16.667 usec
DE 7.48 usec
TE 300.6 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
SFO1 125.8131140 MHz
NUC1 13C
P1 10.00 usec
PLW1 78.00000000 W
SFO2 500.3020012 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 80.00 usec
PLW2 21.00000000 W
PLW12 0.32813001 W
PLW13 0.16504000 W

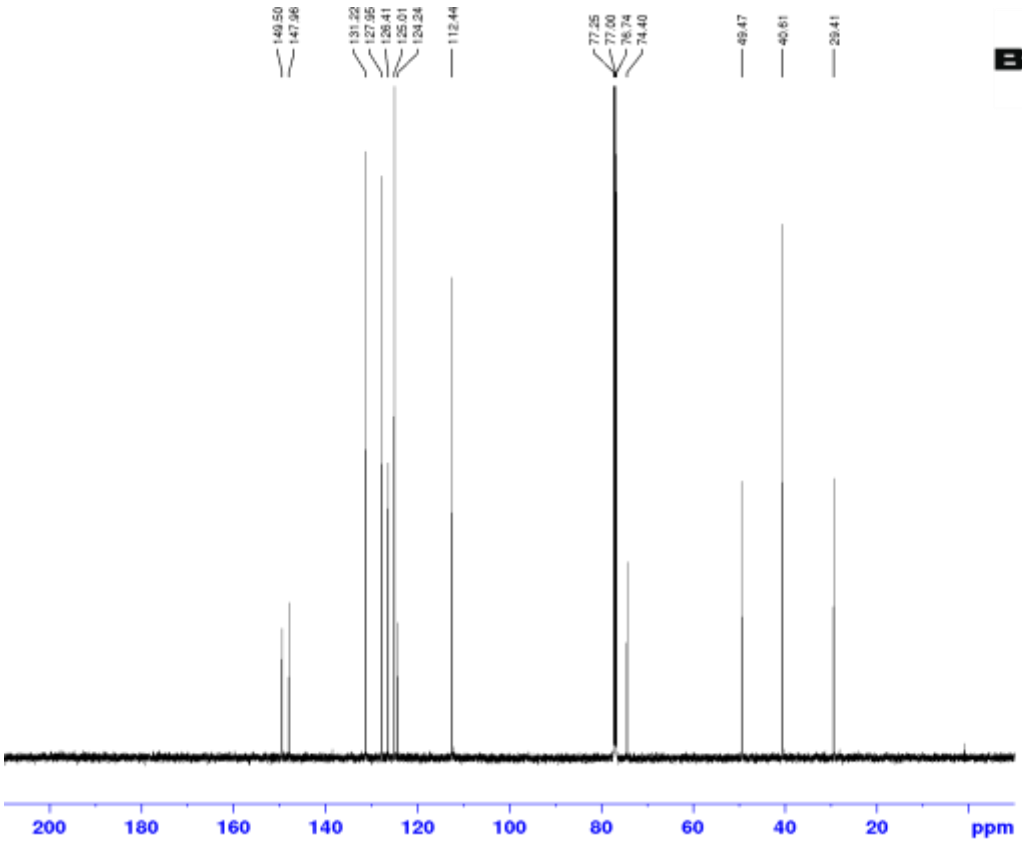
F2 - Processing parameters
SI 32768
SF 125.8005397 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40



Current Data Parameters
NAME sea-04-029
EXPNO 30
PROCNO 1

F2 - Acquisition Parameters
Date_ 20151223
Time 20.02 h
INSTRUM AVIII500HD
PROBHD Z119470_0125 (
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 10000.000 Hz
FIDRES 0.152588 Hz
AQ 3.2767999 sec
RG 87.38
DW 50.000 usec
DE 13.50 usec
TE 300.0 K
D1 1.00000000 sec
TD0 1
SFO1 500.3030896 MHz
NUC1 1H
P1 10.00 usec
PLW1 21.89999962 W

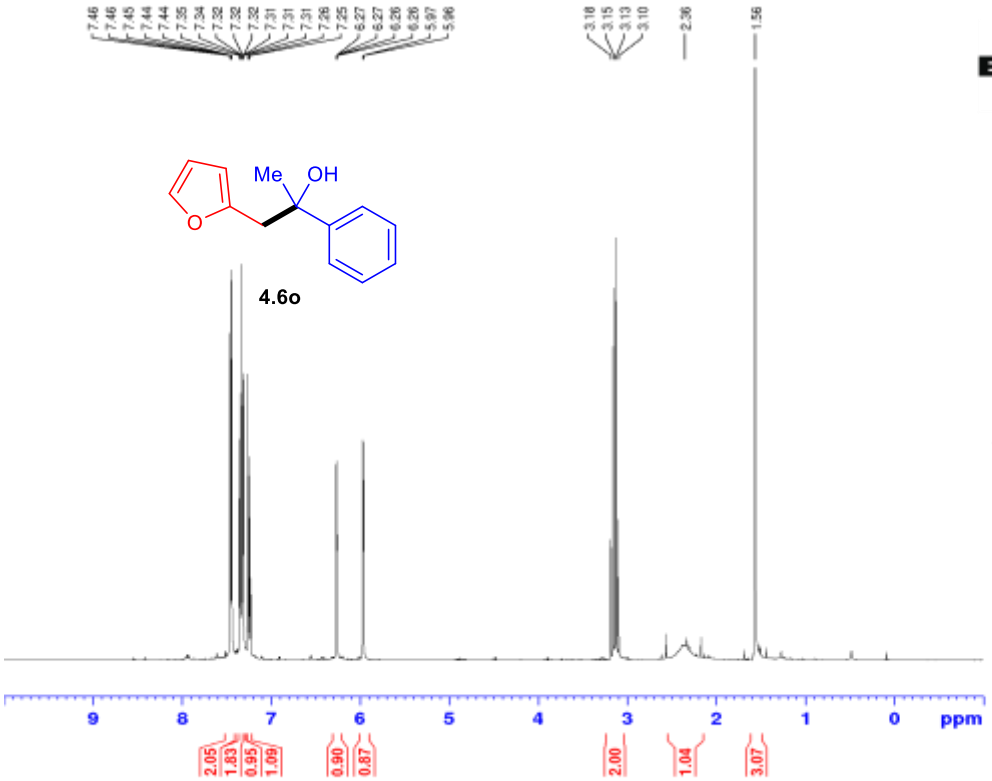
F2 - Processing parameters
SI 65536
SF 500.3000120 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00



Current Data Parameters
NAME sea-04-029
EXPNO 31
PROCNO 1

F2 - Acquisition Parameters
Date_ 20151224
Time 0.13 h
INSTRUM AVIII500HD
PROBHD Z119470_0125 (
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 512
DS 4
SWH 30000.000 Hz
FIDRES 0.457764 Hz
AQ 1.0922667 sec
RG 192.72
DW 16.667 usec
DE 7.48 usec
TE 300.0 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
SFO1 125.8131140 MHz
NUC1 13C
P1 10.00 usec
PLW1 78.00000000 W
SFO2 500.3020012 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 90.00 usec
PLW2 21.00000000 W
PLW12 0.32813001 W
PLW13 0.16504000 W

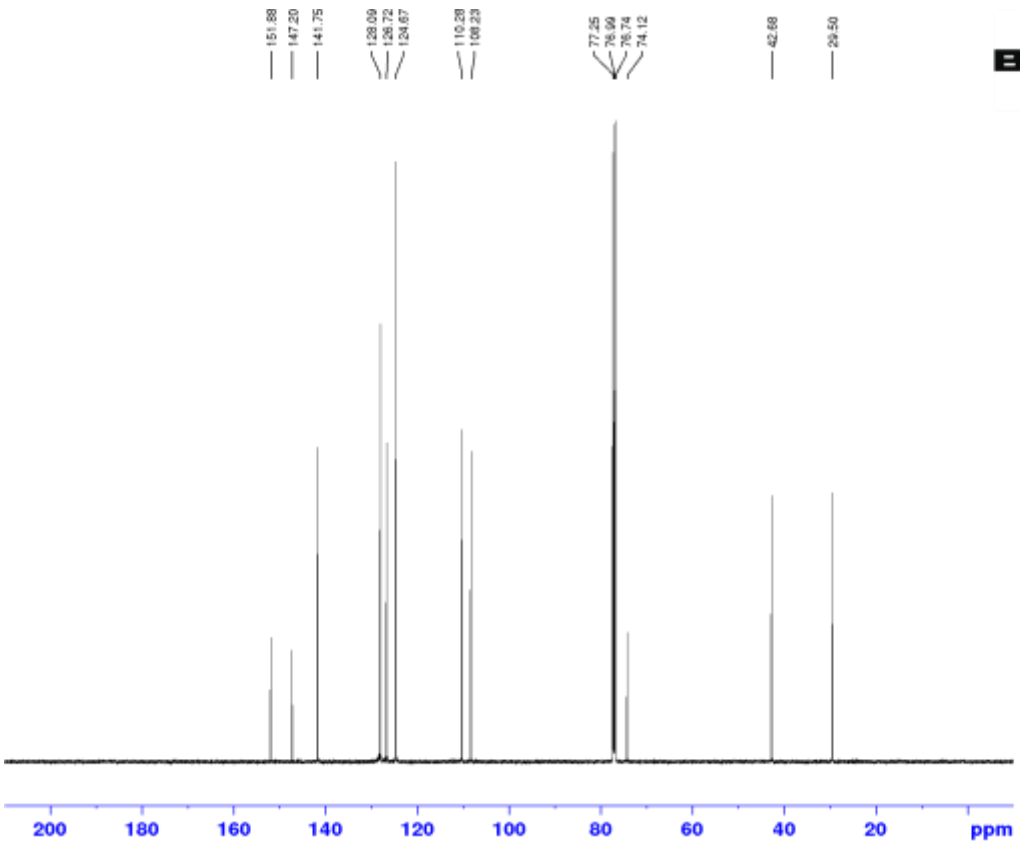
F2 - Processing parameters
SI 32768
SF 125.8005398 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40



Current Data Parameters
NAME DXJ-E2281-PURE
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date_ 20160507
Time 18.15 h
INSTRUM AVIII500HD
PROBHD Z119470_0125 (
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 10000.000 Hz
FIDRES 0.305176 Hz
AQ 3.2767999 sec
RG 87.38
DW 50.000 usec
DE 13.50 usec
TE 301.4 K
D1 1.00000000 sec
TD0 1
SFO1 500.3030896 MHz
NUC1 1H
P1 10.00 usec
PLW1 21.89999962 W

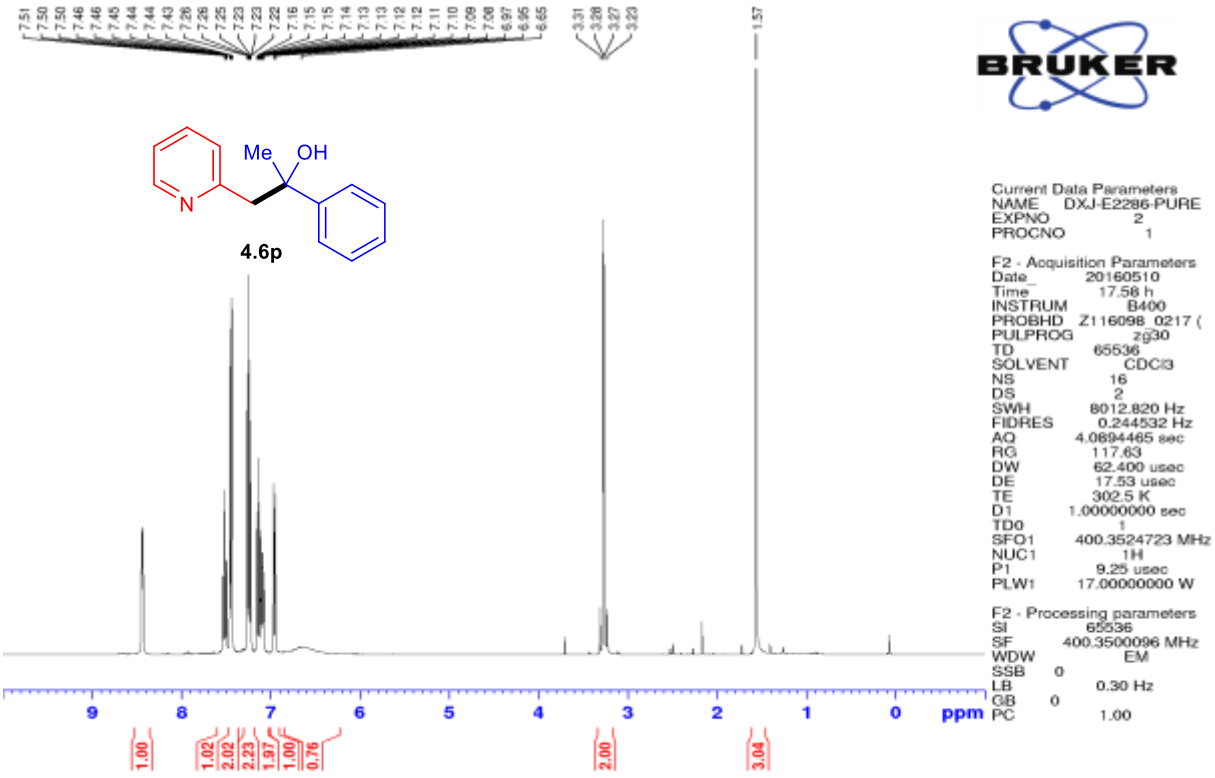
F2 - Processing parameters
SI 65536
SF 500.3000120 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00



Current Data Parameters
NAME DXJ-E2281-PURE
EXPNO 2
PROCNO 1

F2 - Acquisition Parameters
Date_ 20160507
Time 21.36 h
INSTRUM AVIII500HD
PROBHD Z119470_0125 (
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 1500
DS 4
SWH 30000.000 Hz
FIDRES 0.915527 Hz
AQ 1.0922667 sec
RG 192.72
DW 16.667 usec
DE 7.48 usec
TE 300.2 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
SFO1 125.8131140 MHz
NUC1 13C
P1 10.00 usec
PLW1 78.00000000 W
SFO2 500.3020012 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 80.00 usec
PLW2 21.00000000 W
PLW12 0.32813001 W
PLW13 0.16504000 W

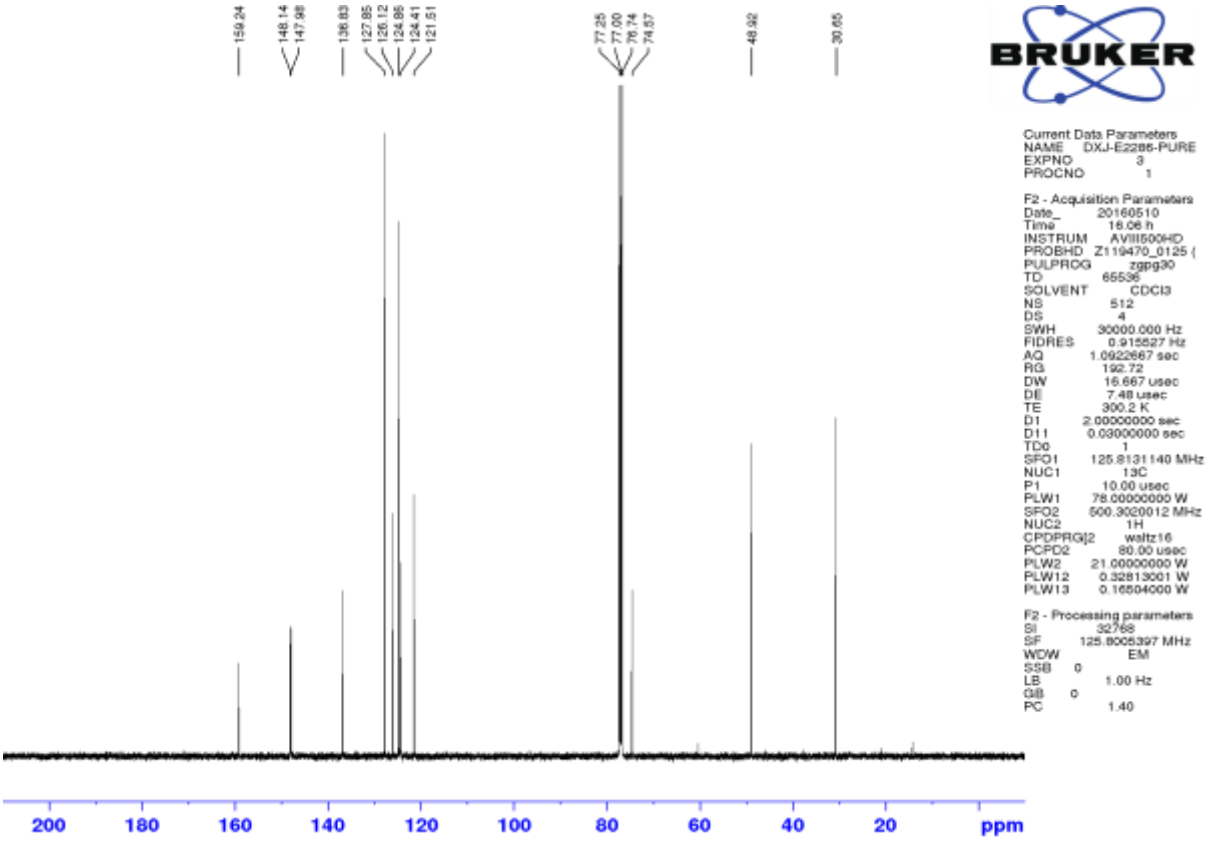
F2 - Processing parameters
SI 32768
SF 125.8005398 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40



Current Data Parameters
NAME DXJ-E2286-PURE
EXPNO 2
PROCNO 1

F2 - Acquisition Parameters
Date_ 20160510
Time 17.58 h
INSTRUM B400
PROBHD Z116098_0217 (
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 8012.820 Hz
FIDRES 0.244532 Hz
AQ 4.0894465 sec
RG 117.63
DW 62.400 usec
DE 17.53 usec
TE 302.5 K
D1 1.00000000 sec
TD0 1
SFO1 400.3524723 MHz
NUC1 1H
P1 9.25 usec
PLW1 17.00000000 W

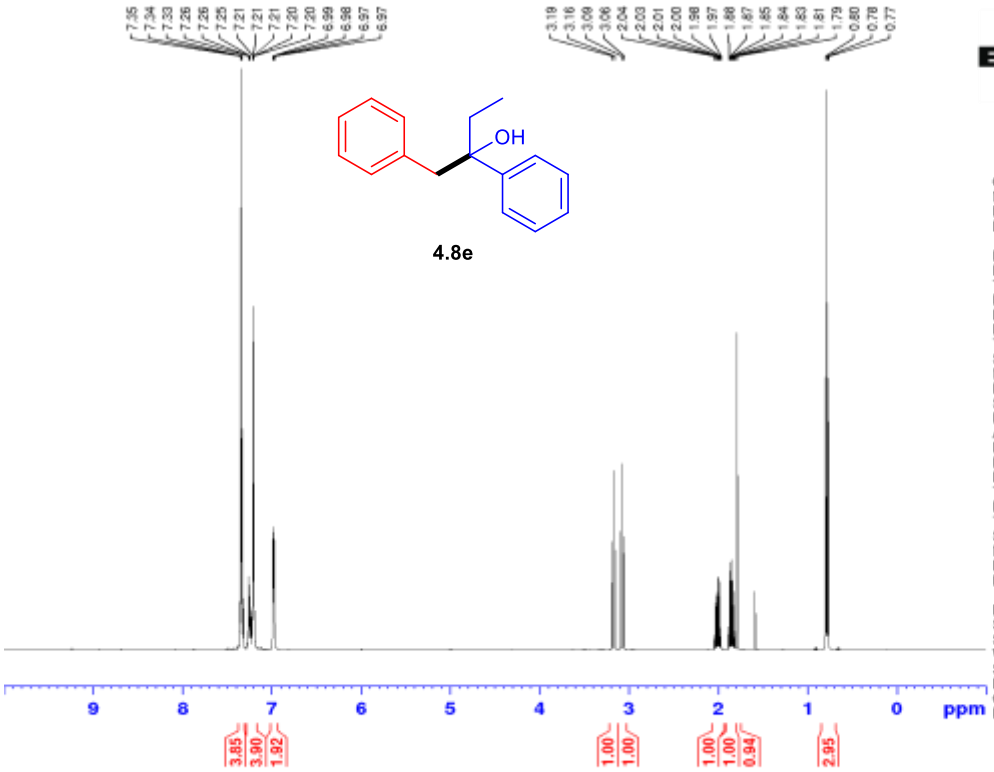
F2 - Processing parameters
SI 65536
SF 400.3500096 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00



Current Data Parameters
NAME DXJ-E2286-PURE
EXPNO 3
PROCNO 1

F2 - Acquisition Parameters
Date_ 20160510
Time 18.06 h
INSTRUM AVIII500HD
PROBHD Z119470_0125 (
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 512
DS 4
SWH 30000.000 Hz
FIDRES 0.915827 Hz
AQ 1.0922667 sec
RG 192.72
DW 16.667 usec
DE 7.48 usec
TE 300.2 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
SFO1 125.8131140 MHz
NUC1 13C
P1 10.00 usec
PLW1 78.00000000 W
SFO2 500.3020012 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 80.00 usec
PLW2 21.00000000 W
PLW12 0.32813001 W
PLW13 0.16504000 W

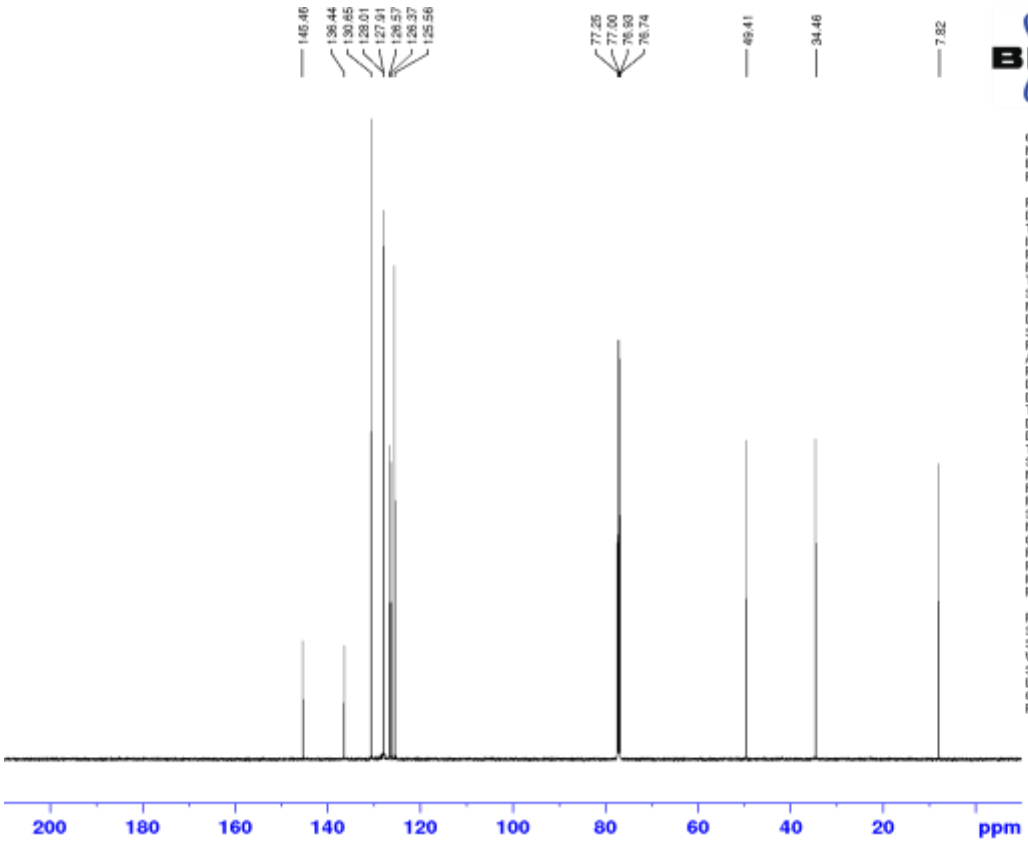
F2 - Processing parameters
SI 32768
SF 125.8005397 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40



Current Data Parameters
NAME sea-04-038
EXPNO 6
PROCNO 1

F2 - Acquisition Parameters
Date_ 20160106
Time 22.45 h
INSTRUM AVIII500HD
PROBHD Z119470_0125 (
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 10000.000 Hz
FIDRES 0.305176 Hz
AQ 3.2767999 sec
RG 50.67
DW 50.000 usec
DE 13.50 usec
TE 300.0 K
D1 1.00000000 sec
TD0 1
SFO1 500.3030896 MHz
NUC1 1H
P1 10.00 usec
PLW1 21.89999962 W

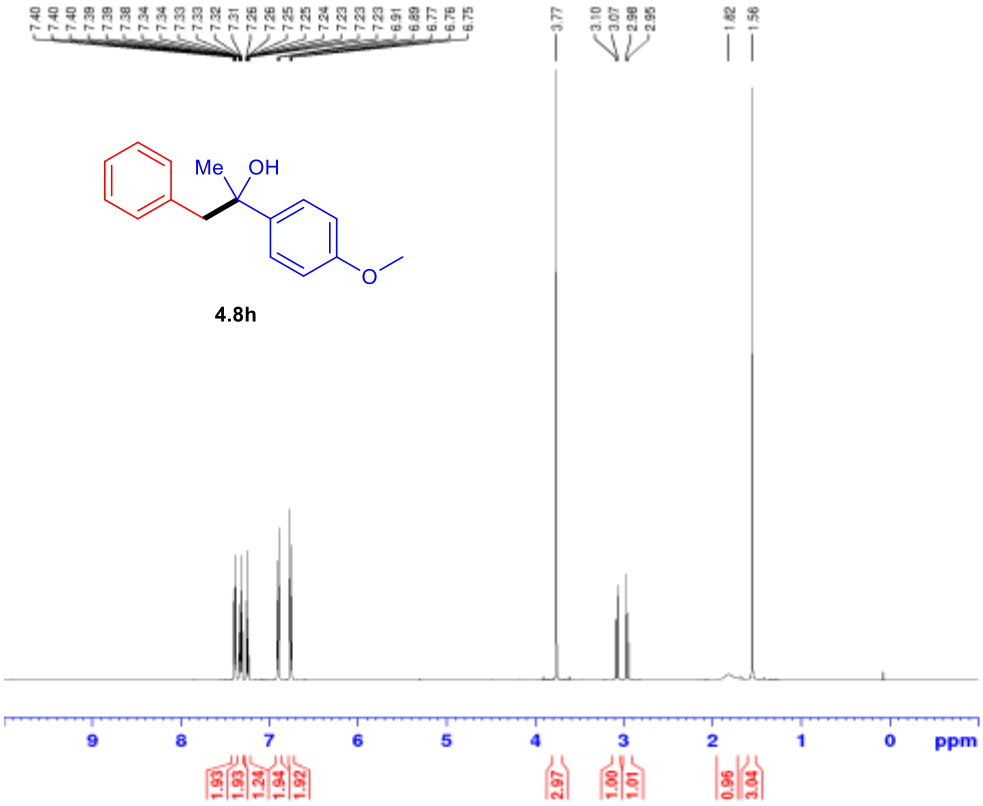
F2 - Processing parameters
SI 65536
SF 500.3000121 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00



Current Data Parameters
NAME sea-04-038
EXPNO 7
PROCNO 1

F2 - Acquisition Parameters
Date_ 20160106
Time 23.13 h
INSTRUM AVIII500HD
PROBHD Z119470_0125 (
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 512
DS 4
SWH 30000.000 Hz
FIDRES 0.915527 Hz
AQ 1.0922667 sec
RG 192.72
DW 16.667 usec
DE 7.48 usec
TE 300.0 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
SFO1 125.8131140 MHz
NUC1 13C
P1 10.00 usec
PLW1 78.00000000 W
SFO2 500.3020012 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 80.00 usec
PLW2 21.00000000 W
PLW12 0.32813001 W
PLW13 0.16604000 W

F2 - Processing parameters
SI 32768
SF 125.8006426 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

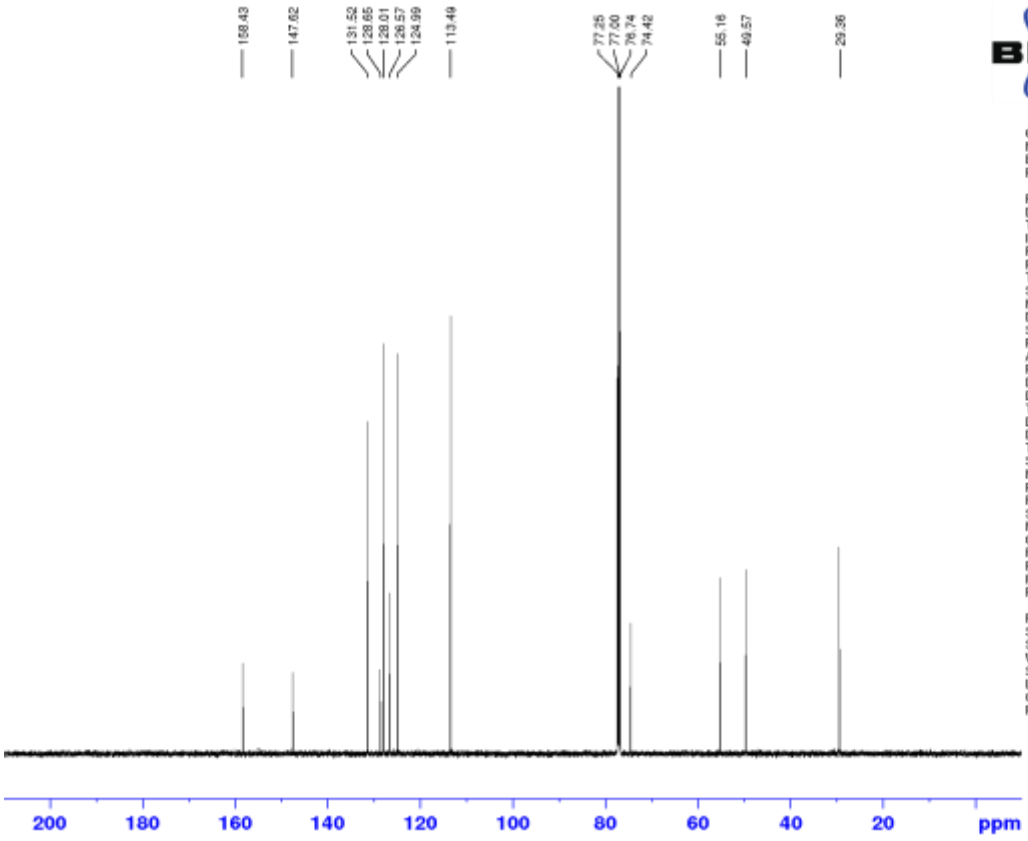


4.8h

Current Data Parameters
NAME sea-04-009
EXPNO 28
PROCNO 1

F2 - Acquisition Parameters
Date_ 20151029
Time 18.41 h
INSTRUM AVIII500HD
PROBHD Z119470_0125 (
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 10000.000 Hz
FIDRES 0.152588 Hz
AQ 3.2767999 sec
RG 106.56
DW 50.000 usec
DE 13.50 usec
TE 300.0 K
D1 1.00000000 sec
TD0 1
SFO1 500.3030896 MHz
NUC1 1H
P1 10.00 usec
PLW1 21.89999962 W

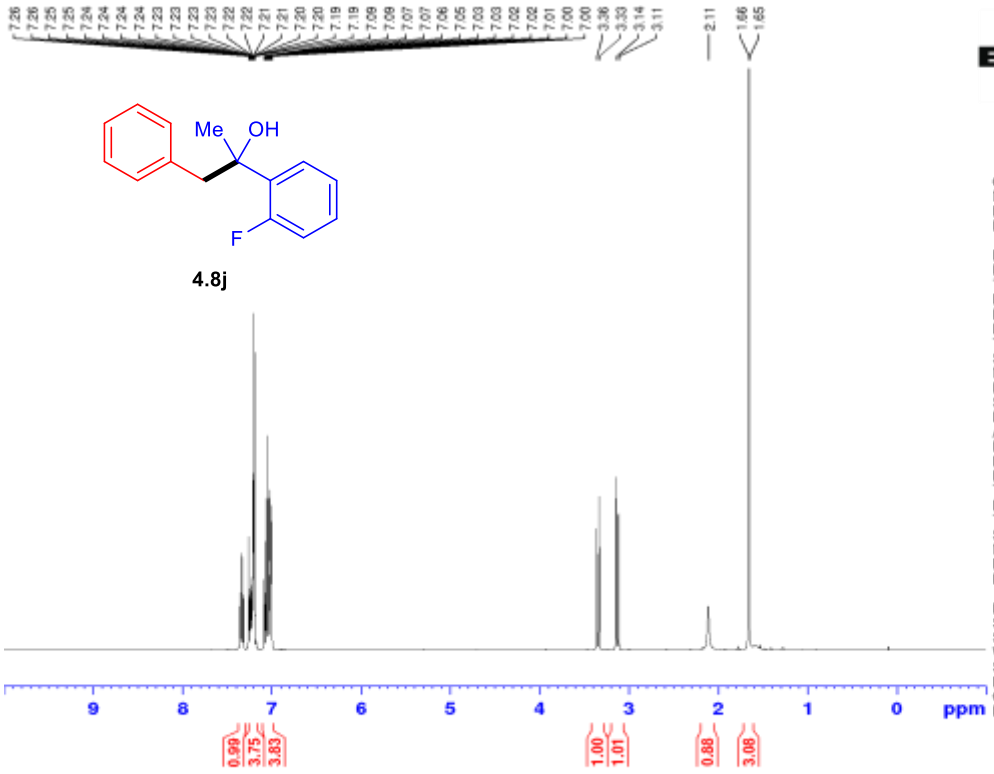
F2 - Processing parameters
SI 65536
SF 500.3000122 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00



Current Data Parameters
NAME sea-04-009
EXPNO 29
PROCNO 1

F2 - Acquisition Parameters
Date_ 20151030
Time 6.25 h
INSTRUM AVIII500HD
PROBHD Z119470_0125 (
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 512
DS 4
SWH 30000.000 Hz
FIDRES 0.457764 Hz
AQ 1.0922667 sec
RG 192.72
DW 16.667 usec
DE 7.48 usec
TE 300.0 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
SFO1 125.8131140 MHz
NUC1 13C
P1 10.00 usec
PLW1 78.00000000 W
SFO2 500.3020012 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 80.00 usec
PLW2 21.00000000 W
PLW12 0.32813001 W
PLW13 0.16504000 W

F2 - Processing parameters
SI 32768
SF 125.8005389 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

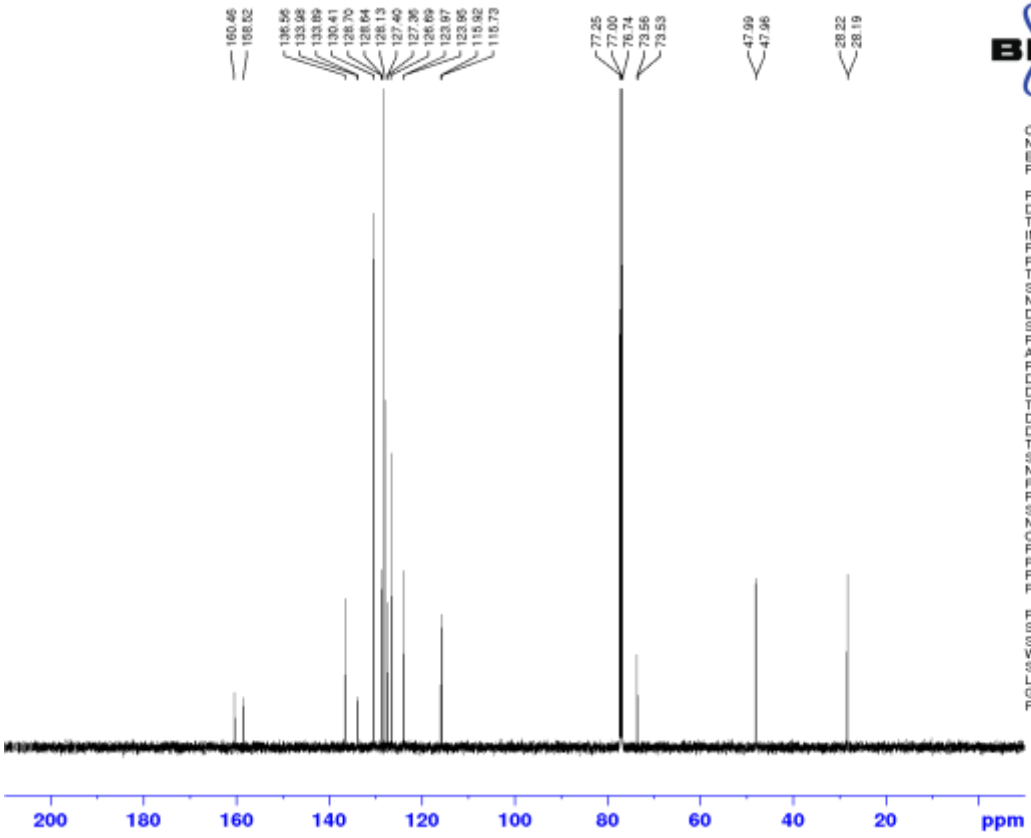


4.8j

Current Data Parameters
NAME DXJ-D2092-PURE
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date_ 20160120
Time 13.56 h
INSTRUM AVIII500HD
PROBHD Z119470_0125 (
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 10000.000 Hz
FIDRES 0.305176 Hz
AQ 3.2767999 sec
RG 87.38
DW 50.000 usec
DE 13.50 usec
TE 300.0 K
D1 1.00000000 sec
TD0 1
SFO1 500.3030896 MHz
NUC1 1H
P1 10.00 usec
PLW1 21.89999962 W

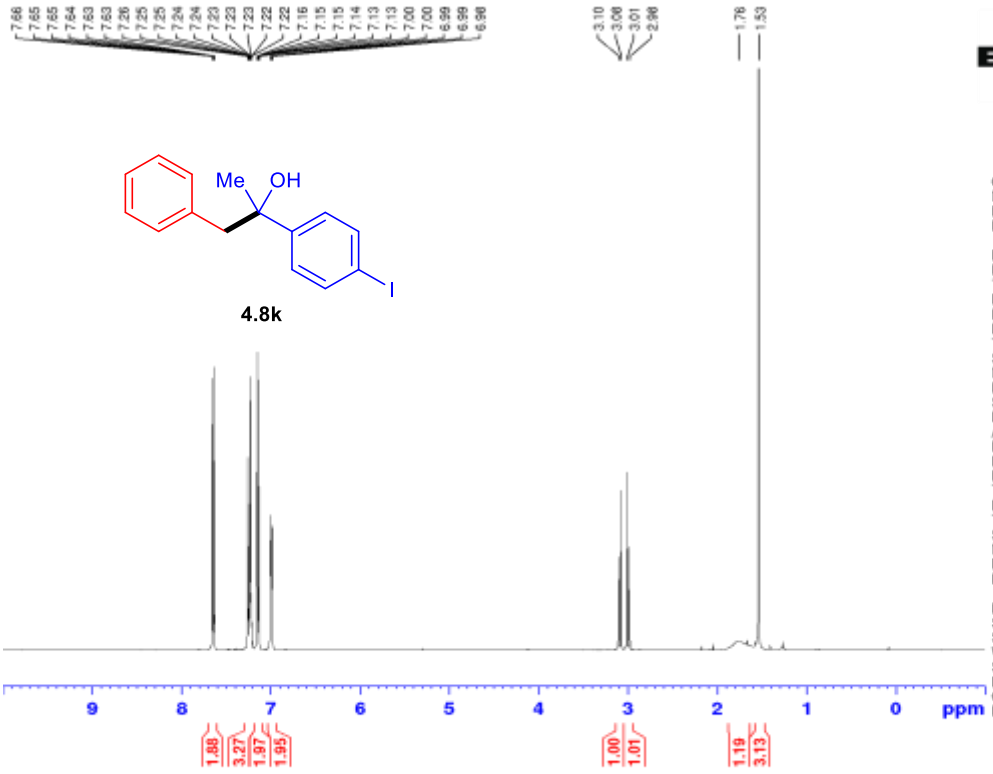
F2 - Processing parameters
SI 65536
SF 500.3000122 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00



Current Data Parameters
NAME DXJ-D2092-PURE
EXPNO 2
PROCNO 1

F2 - Acquisition Parameters
Date_ 20160120
Time 14.40 h
INSTRUM AVIII500HD
PROBHD Z119470_0125 (
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 150
DS 4
SWH 30000.000 Hz
FIDRES 0.915527 Hz
AQ 1.0922667 sec
RG 192.72
DW 16.667 usec
DE 7.48 usec
TE 300.0 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
SFO1 125.8131140 MHz
NUC1 13C
P1 10.00 usec
PLW1 78.00000000 W
SFO2 500.3020012 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 80.00 usec
PLW2 21.00000000 W
PLW12 0.32813001 W
PLW13 0.16504000 W

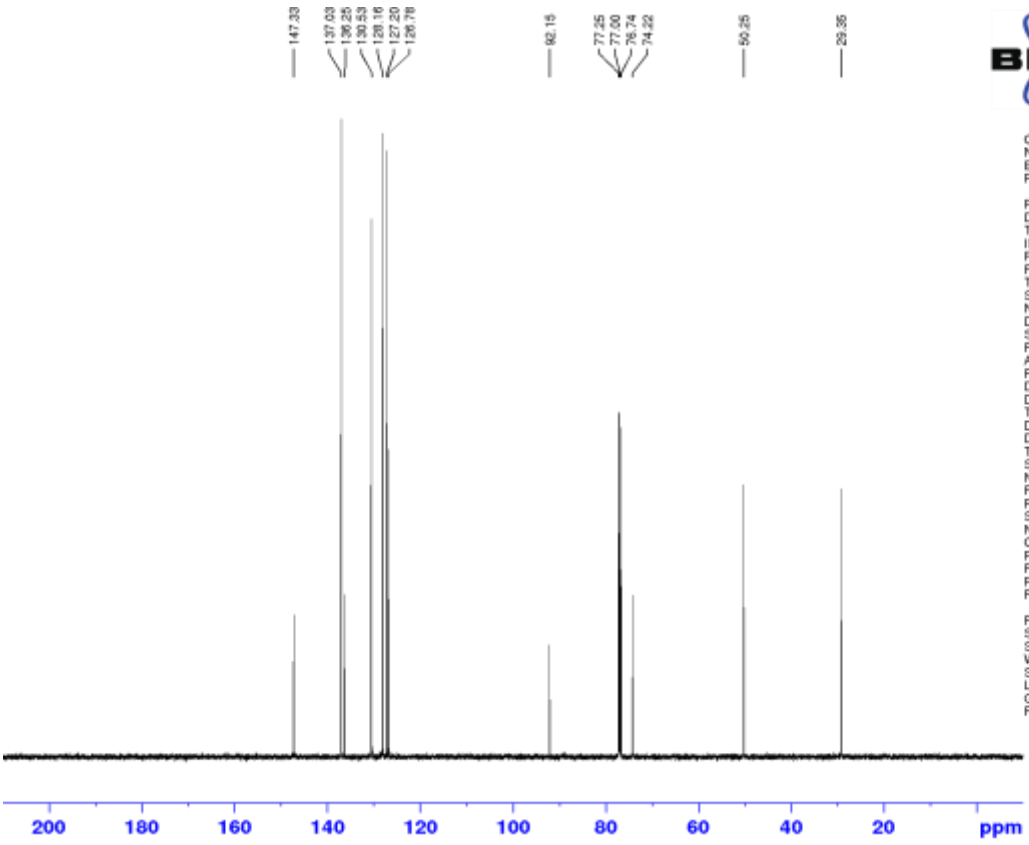
F2 - Processing parameters
SI 32768
SF 125.8005398 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40



Current Data Parameters
NAME DXJ-D2090-PURE
EXPNO 3
PROCNO 1

F2 - Acquisition Parameters
Date_ 20160120
Time 13.50 h
INSTRUM AVIII500HD
PROBHD Z119470_0125 (
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 10000.000 Hz
FIDRES 0.305176 Hz
AQ 3.2767999 sec
RG 106.56
DW 50.000 usec
DE 13.50 usec
TE 300.0 K
D1 1.00000000 sec
TD0 1
SFO1 500.3030896 MHz
NUC1 1H
P1 10.00 usec
PLW1 21.89999962 W

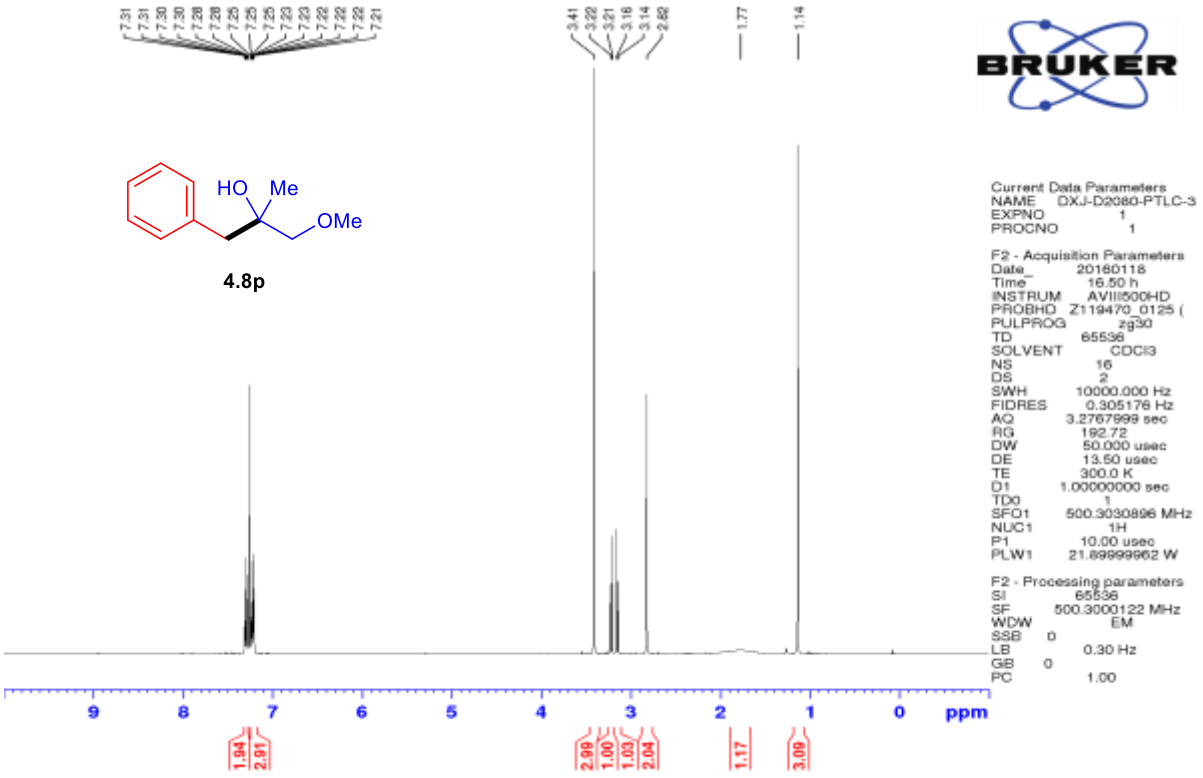
F2 - Processing parameters
SI 65536
SF 500.3000127 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

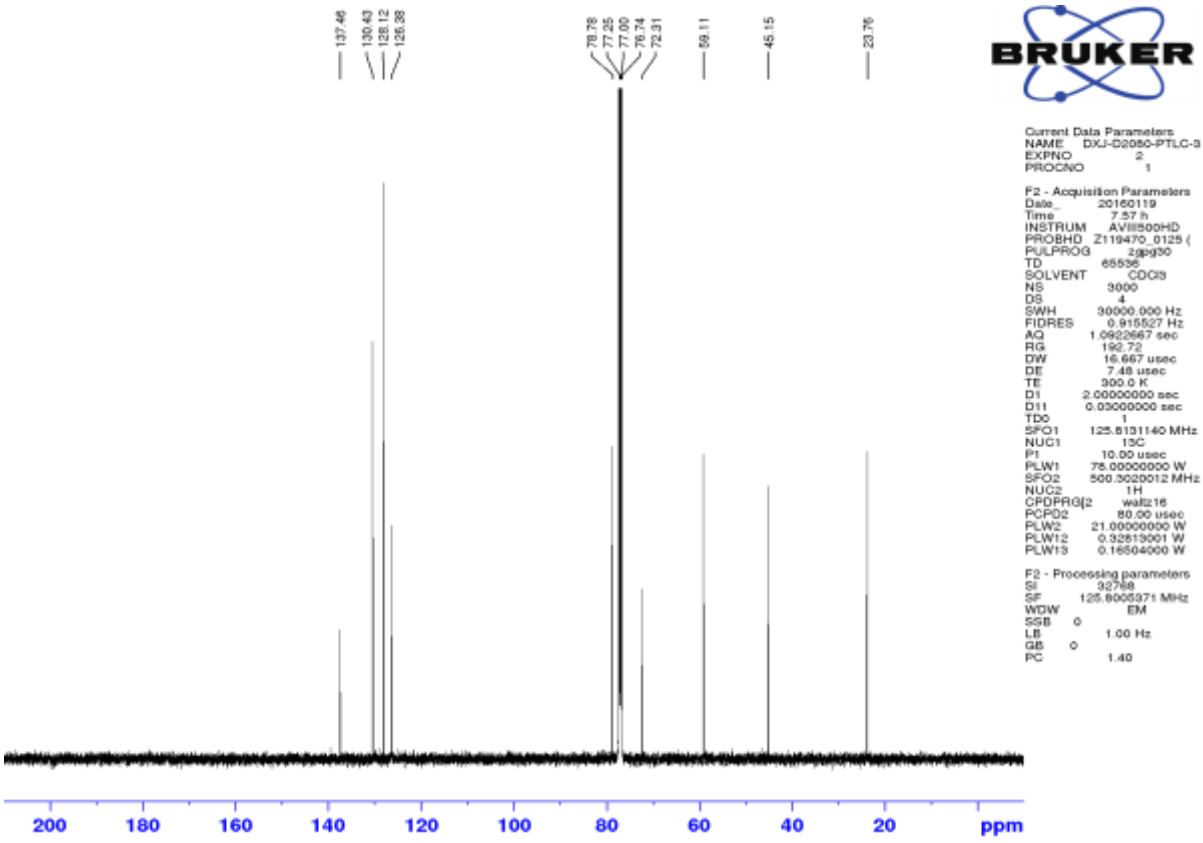


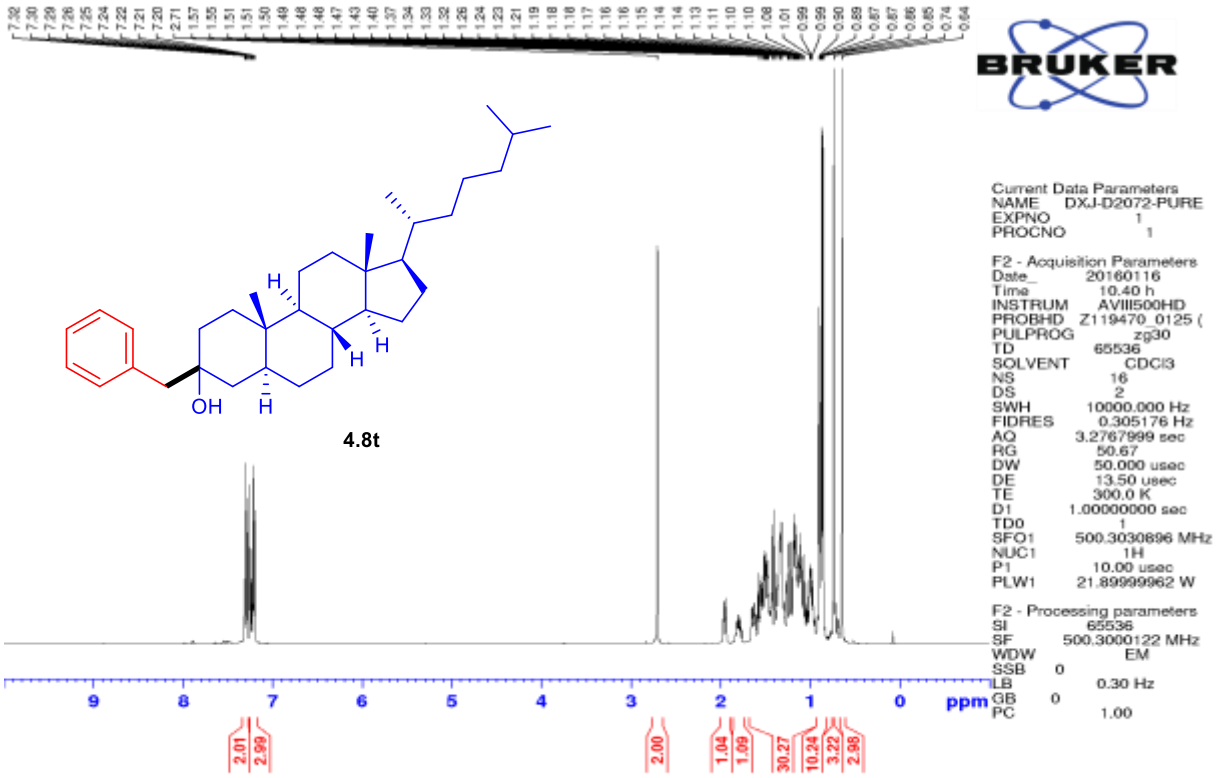
Current Data Parameters
NAME DXJ-D2090-PURE
EXPNO 2
PROCNO 1

F2 - Acquisition Parameters
Date_ 20160118
Time 17.02 h
INSTRUM AVIII500HD
PROBHD Z119470_0125 (
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 150
DS 4
SWH 30000.000 Hz
FIDRES 0.915527 Hz
AQ 1.0922667 sec
RG 192.72
DW 16.667 usec
DE 7.48 usec
TE 300.0 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
SFO1 125.8131140 MHz
NUC1 13C
P1 10.00 usec
PLW1 78.00000000 W
SFO2 500.3020012 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 80.00 usec
PLW2 21.00000000 W
PLW12 0.32813001 W
PLW13 0.16504000 W

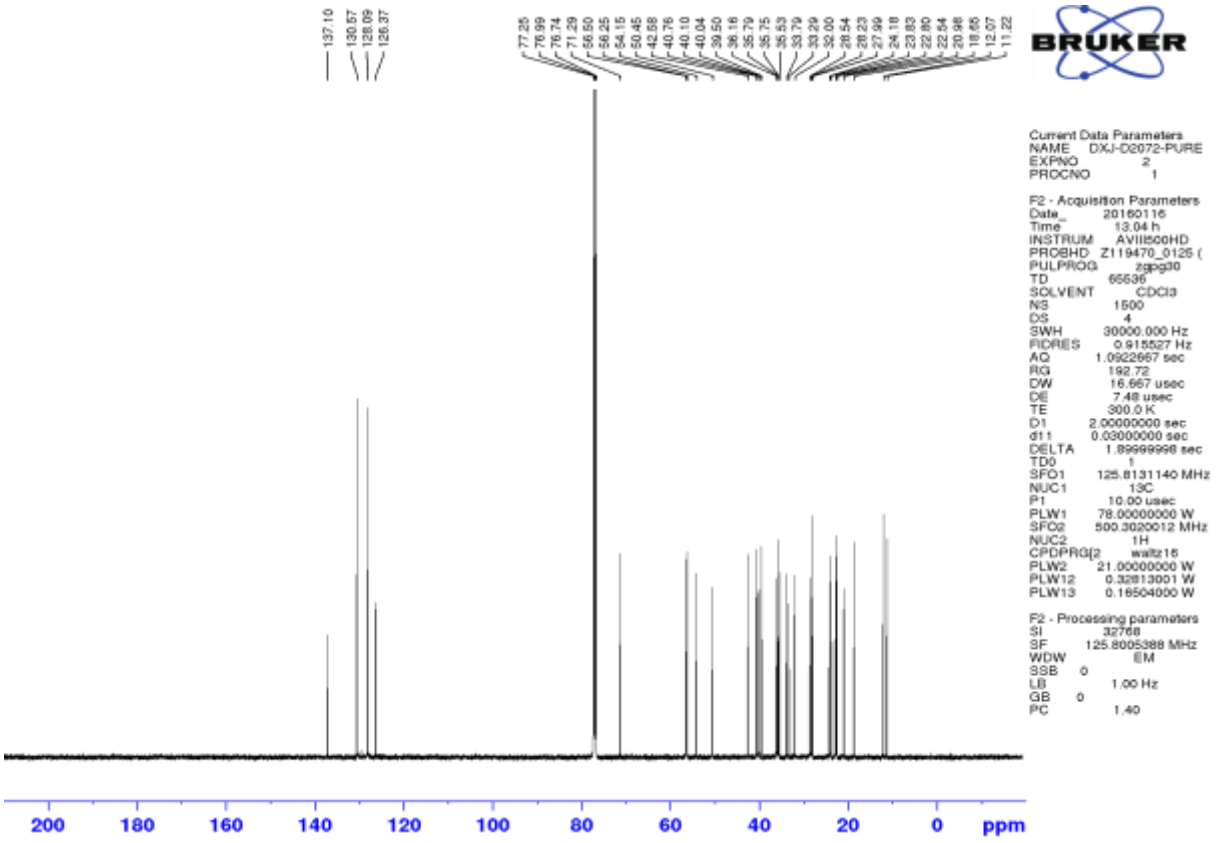
F2 - Processing parameters
SI 32768
SF 125.8005435 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

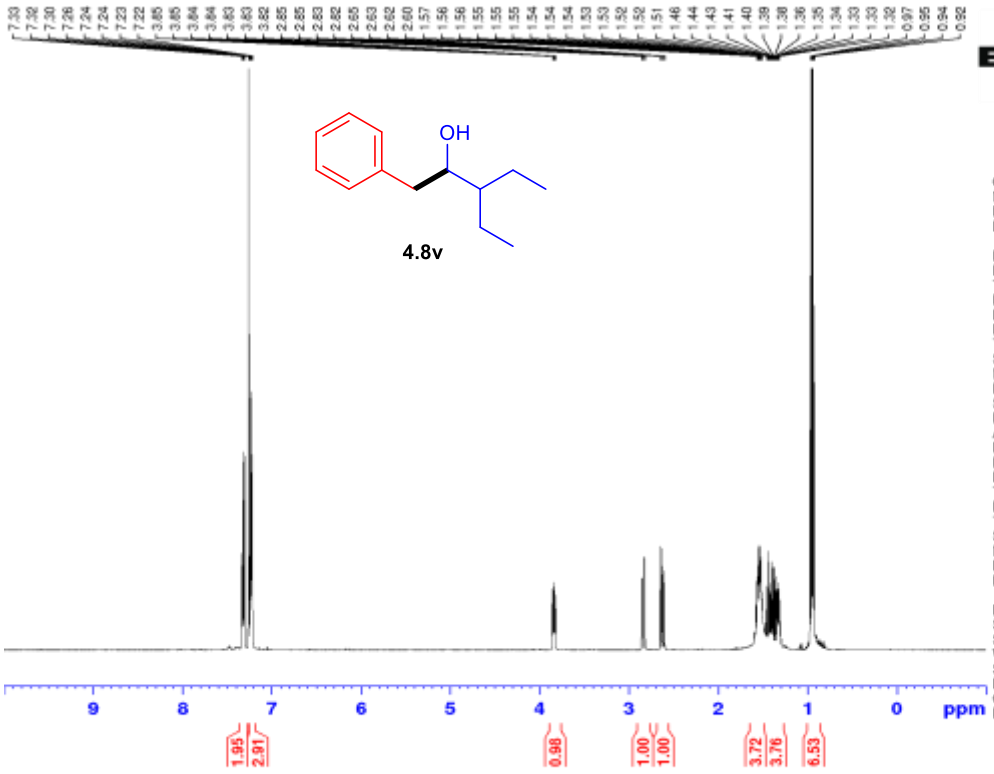

7.31
7.31
7.30
7.30
7.28
7.26
7.25
7.25
7.25
7.23
7.23
7.22
7.22
7.22
7.21
3.41
3.22
3.21
3.16
3.14
2.82
1.77
1.14
HO
Me
OMe
4.8p
BRUKER
Current Data Parameters
NAME DXJ-D2080-PTLC-3
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20160118
Time 16.50 h
INSTRUM AVIII500HD
PROBHD Z119470_0125 (
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 10000.000 Hz
FIDRES 0.305176 Hz
AQ 3.2767999 sec
RG 192.72
DW 50.000 usec
DE 13.50 usec
TE 300.0 K
D1 1.00000000 sec
TD0 1
SFO1 500.3030896 MHz
NUC1 1H
P1 10.00 usec
PLW1 21.89999962 W
F2 - Processing parameters
SI 65536
SF 500.3000122 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
9
8
7
6
5
4
3
2
1
0
ppm
1.94
2.91
2.99
1.00
1.03
2.04
1.17
3.09


137.46
130.43
128.12
126.38
78.78
77.25
77.00
76.74
72.31
59.11
45.15
23.76
BRUKER
Current Data Parameters
NAME DXJ-D2080-PTLC-3
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20160119
Time 7.57 h
INSTRUM AVIII500HD
PROBHD Z119470_0125 (
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 3000
DS 4
SWH 30000.000 Hz
FIDRES 0.915527 Hz
AQ 1.0922667 sec
RG 192.72
DW 16.667 usec
DE 7.48 usec
TE 300.0 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
SFO1 125.8131140 MHz
NUC1 13C
P1 10.00 usec
PLW1 75.00000000 W
SFO2 500.3020012 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 80.00 usec
PLW2 21.00000000 W
PLW12 0.32813001 W
PLW13 0.16504000 W
F2 - Processing parameters
SI 32768
SF 125.8006371 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
200
180
160
140
120
100
80
60
40
20
ppm


Current Data Parameters
NAME DXJ-D2072-PURE
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20160116
Time 10.40 h
INSTRUM AVIII500HD
PROBHD Z119470_0125 (
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 10000.000 Hz
FIDRES 0.305176 Hz
AQ 3.2767999 sec
RG 50.67
DW 50.000 usec
DE 13.50 usec
TE 300.0 K
D1 1.00000000 sec
TD0 1
SFO1 500.3030896 MHz
NUC1 1H
P1 10.00 usec
PLW1 21.89999962 W
F2 - Processing parameters
SI 65536
SF 500.3000122 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
ppm
2.01
2.99
2.00
1.04
1.09
30.27
10.24
3.22
2.98

4.8t

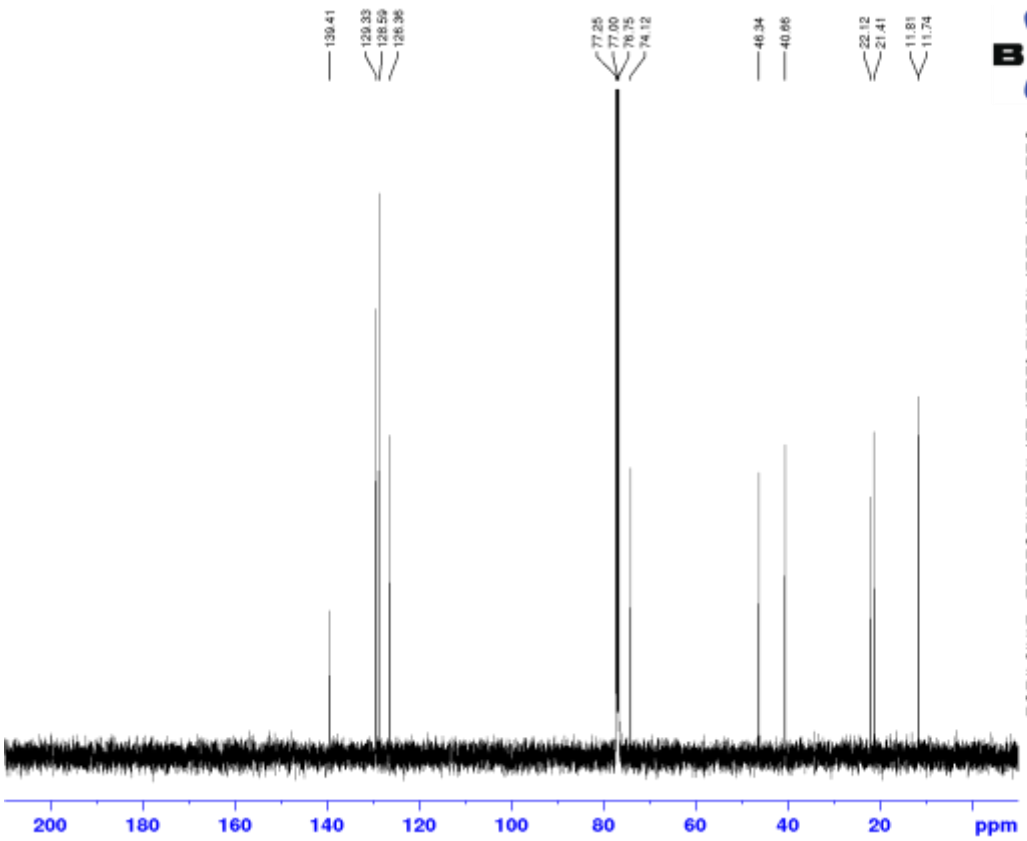

Current Data Parameters
NAME DXJ-D2072-PURE
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20160116
Time 13.04 h
INSTRUM AVIII500HD
PROBHD Z119470_0125 (
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 1500
DS 4
SWH 30000.000 Hz
FIDRES 0.915527 Hz
AQ 1.0922667 sec
RG 192.72
DW 16.667 usec
DE 7.48 usec
TE 300.0 K
D1 2.00000000 sec
d11 0.03000000 sec
DELTA 1.89999998 sec
TD0 1
SFO1 125.8131140 MHz
NUC1 13C
P1 10.00 usec
PLW1 78.00000000 W
SFO2 500.3020012 MHz
NUC2 1H
CPDPRG[2 waltz16
PLW2 21.00000000 W
PLW12 0.32813001 W
PLW13 0.16504000 W
F2 - Processing parameters
SI 32768
SF 125.8005388 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
ppm



Current Data Parameters
NAME sea-04-056
EXPNO 36
PROCNO 1

F2 - Acquisition Parameters
Date_ 20160130
Time 17.07 h
INSTRUM AVIII500HD
PROBHD Z119470_0125 (
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 10000.000 Hz
FIDRES 0.305176 Hz
AQ 3.2767999 sec
RG 106.56
DW 50.000 usec
DE 13.50 usec
TE 300.0 K
D1 1.00000000 sec
TD0 1
SFO1 500.3030896 MHz
NUC1 1H
P1 10.00 usec
PLW1 21.89999962 W

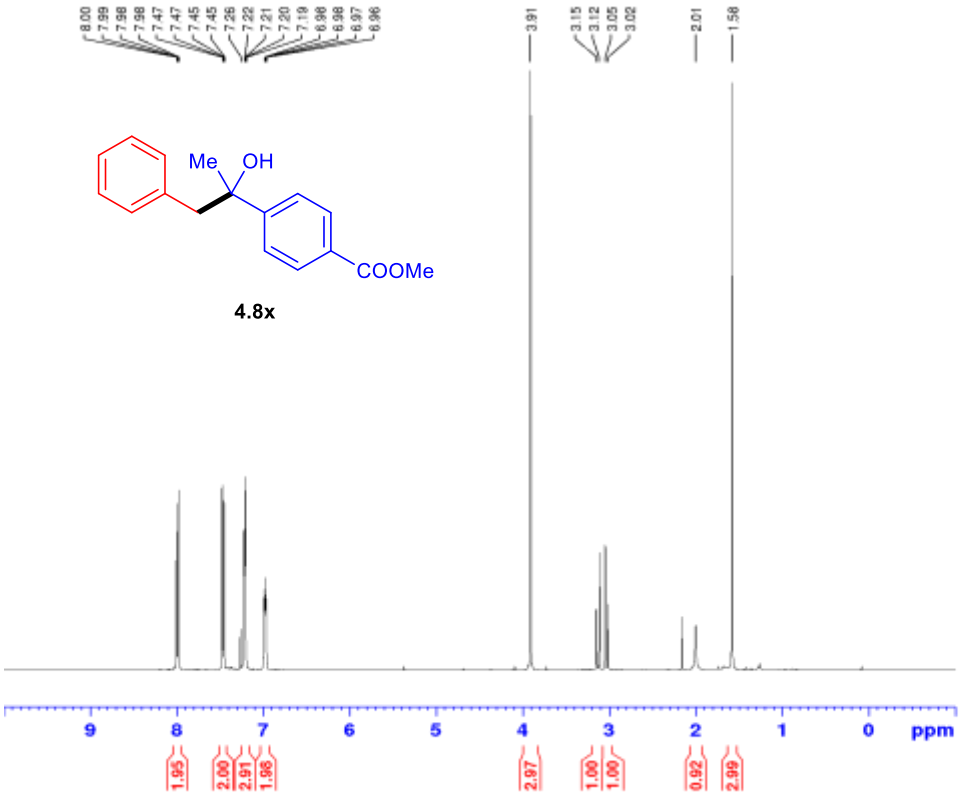
F2 - Processing parameters
SI 65536
SF 500.3000120 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00



Current Data Parameters
NAME sea-04-056
EXPNO 37
PROCNO 1

F2 - Acquisition Parameters
Date_ 20160130
Time 17.34 h
INSTRUM AVIII500HD
PROBHD Z119470_0125 (
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 400
DS 4
SWH 30000.000 Hz
FIDRES 0.915527 Hz
AQ 1.0922567 sec
RG 192.72
DW 16.667 usec
DE 7.48 usec
TE 300.0 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
SFO1 125.8131140 MHz
NUC1 13C
P1 10.00 usec
PLW1 78.00000000 W
SFO2 500.3020012 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 80.00 usec
PLW2 21.00000000 W
PLW12 0.32813001 W
PLW13 0.16504000 W

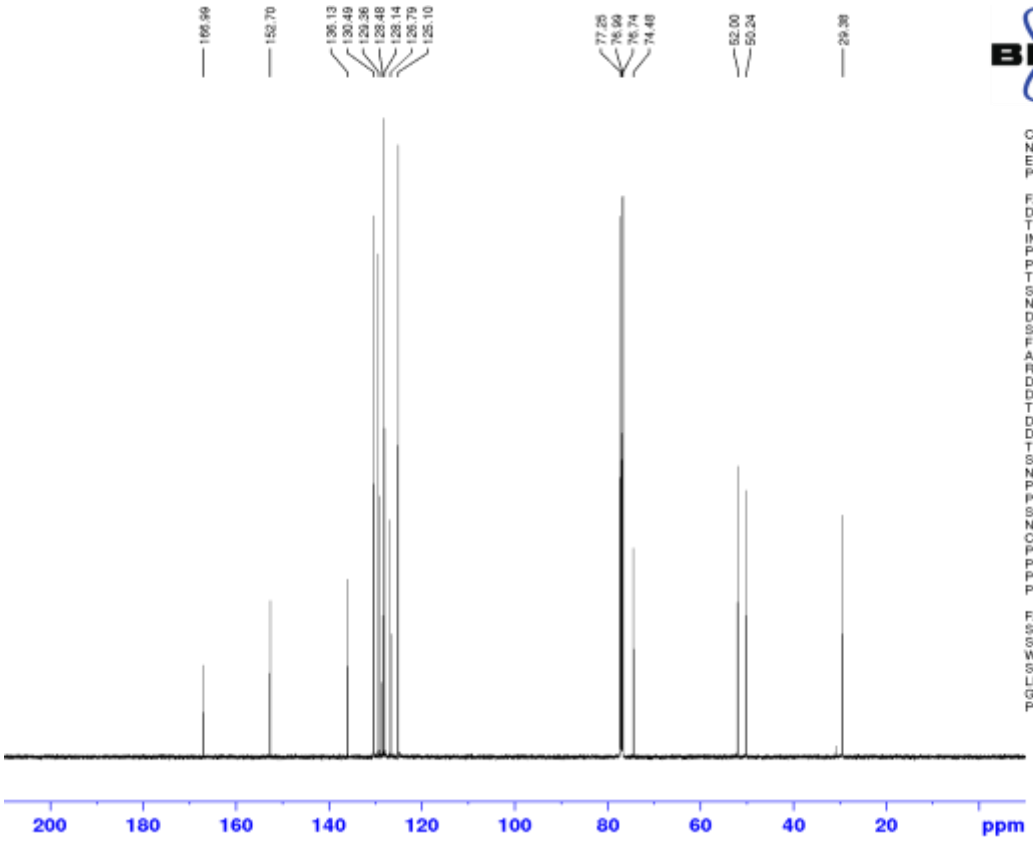
F2 - Processing parameters
SI 32768
SF 125.8006366 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40



Current Data Parameters
NAME DXJ-E2138-PURE
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date_ 20160301
Time 13.10 h
INSTRUM B400
PROBHD Z116098_0217 (
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 8012.820 Hz
FIDRES 0.244532 Hz
AQ 4.0894465 sec
RG 56.72
DW 62.400 usec
DE 17.53 usec
TE 300.0 K
D1 1.00000000 sec
TD0 1
SFO1 400.3524723 MHz
NUC1 1H
P1 9.25 usec
PLW1 17.00000000 W

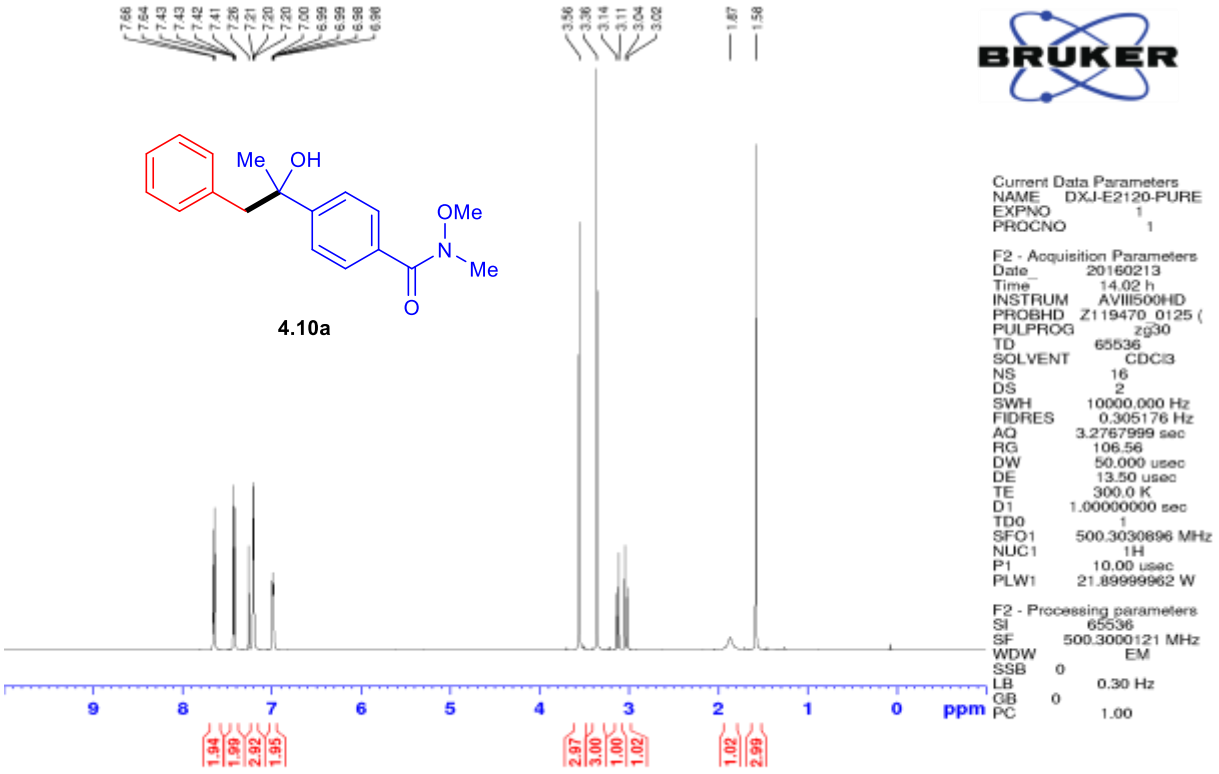
F2 - Processing parameters
SI 65536
SF 400.3500095 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00



Current Data Parameters
NAME DXJ-E2138-PURE
EXPNO 2
PROCNO 1

F2 - Acquisition Parameters
Date_ 20160301
Time 15.16 h
INSTRUM AVIII500HD
PROBHD Z119470_0125 (
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 512
DS 4
SWH 30000.000 Hz
FIDRES 0.915827 Hz
AQ 1.0922667 sec
RG 192.72
DW 16.667 usec
DE 7.48 usec
TE 300.0 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
SFO1 125.8131140 MHz
NUC1 13C
P1 10.00 usec
PLW1 78.00000000 W
SFO2 500.3020012 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 80.00 usec
PLW2 21.00000000 W
PLW12 0.32813001 W
PLW13 0.16504000 W

F2 - Processing parameters
SI 32768
SF 125.8005426 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

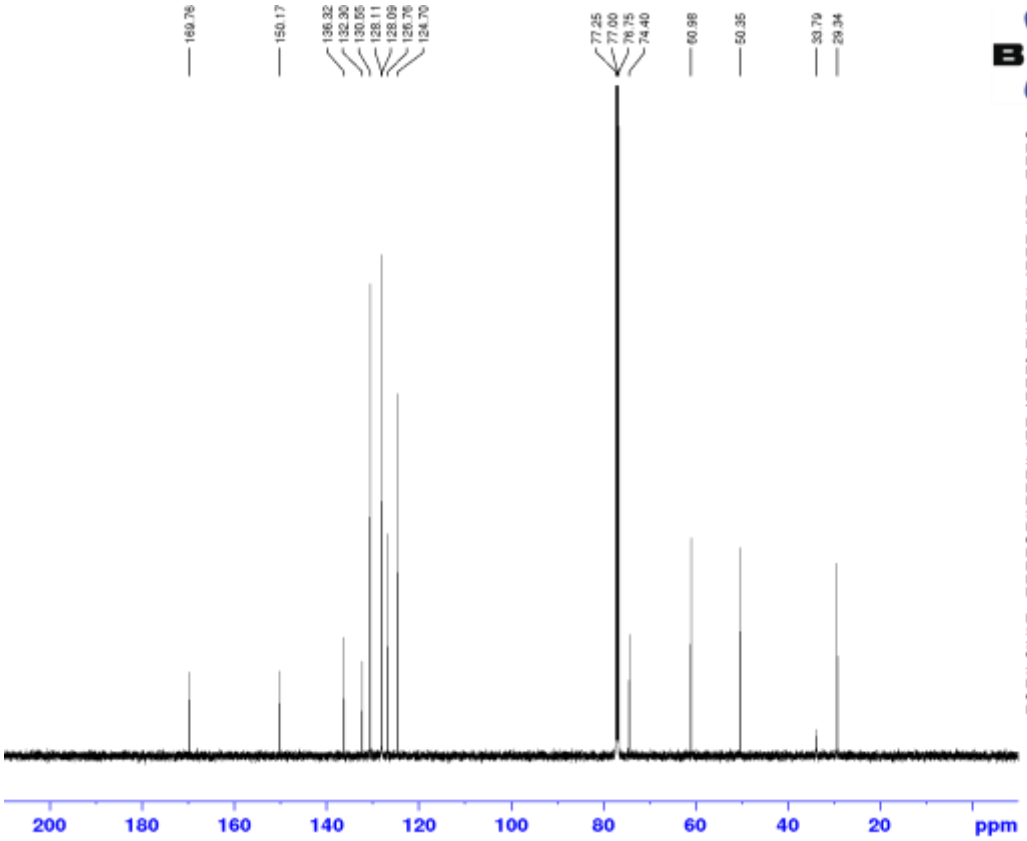


BRUKER

Current Data Parameters
NAME DXJ-E2120-PURE
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date_ 20160213
Time 14.02 h
INSTRUM AVIII500HD
PROBHD Z119470_0125 (
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 10000.000 Hz
FIDRES 0.305176 Hz
AQ 3.2767999 sec
RG 106.56
DW 50.000 usec
DE 13.50 usec
TE 300.0 K
D1 1.00000000 sec
TD0 1
SFO1 500.3030896 MHz
NUC1 1H
P1 10.00 usec
PLW1 21.89999962 W

F2 - Processing parameters
SI 65536
SF 500.3000121 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

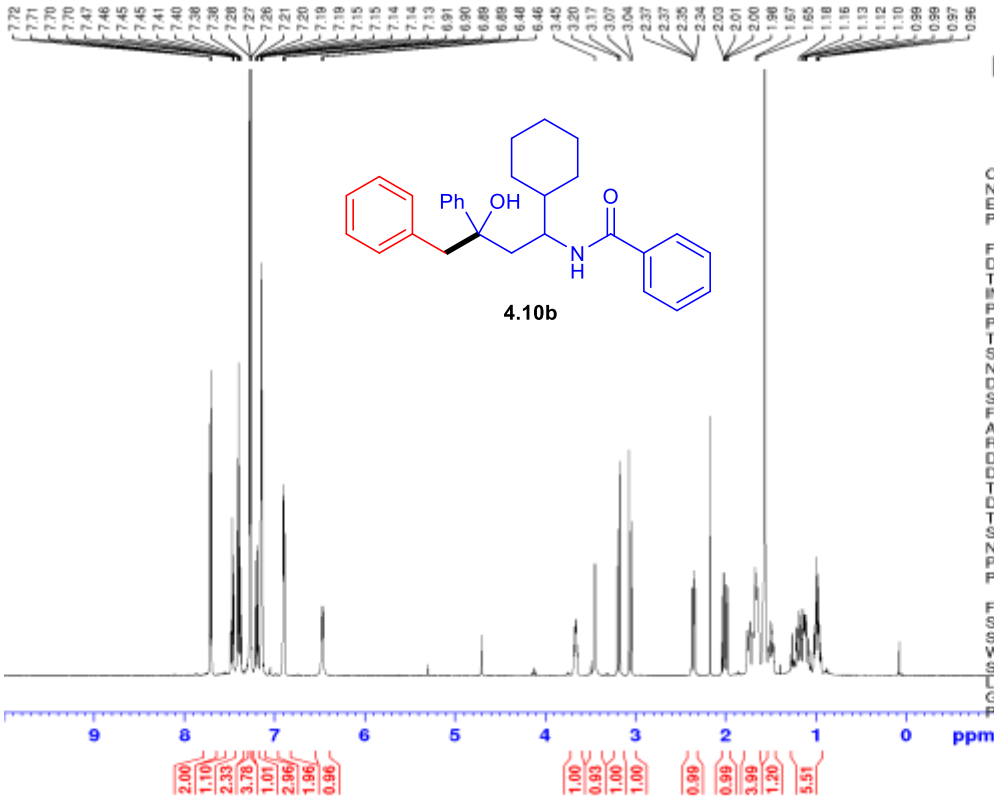


BRUKER

Current Data Parameters
NAME DXJ-E2120-PURE
EXPNO 3
PROCNO 1

F2 - Acquisition Parameters
Date_ 20160213
Time 14.30 h
INSTRUM AVIII500HD
PROBHD Z119470_0125 (
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 512
DS 4
SWH 30000.000 Hz
FIDRES 0.915527 Hz
AQ 1.0922667 sec
RG 192.72
DW 16.667 usec
DE 7.48 usec
TE 300.0 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
SFO1 125.8131140 MHz
NUC1 13C
P1 10.00 usec
PLW1 78.00000000 W
SFO2 500.3020012 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 80.00 usec
PLW2 21.00000000 W
PLW12 0.32813001 W
PLW13 0.16504000 W

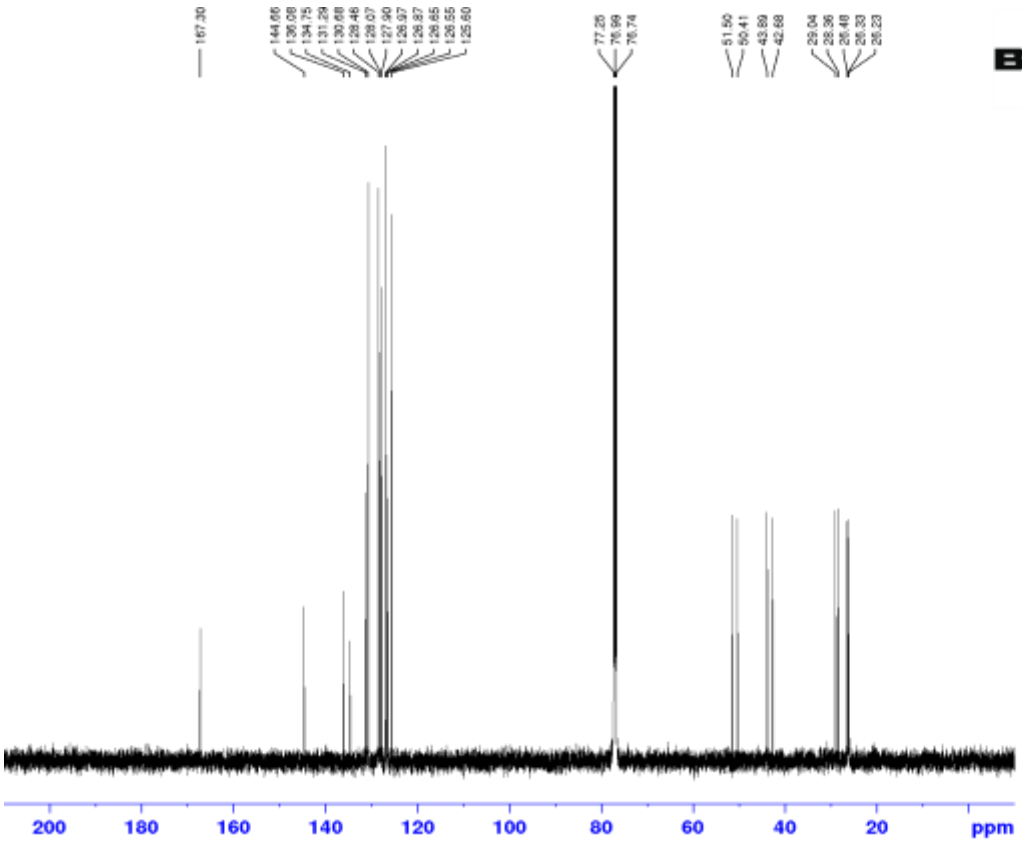
F2 - Processing parameters
SI 32768
SF 125.8005388 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40



Current Data Parameters
NAME DXJ-E2136-PURE
EXPNO 4
PROCNO 1

F2 - Acquisition Parameters
Date_ 20160302
Time 2.39 h
INSTRUM AVIII500HD
PROBHD Z119470_0125 (
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 32
DS 2
SWH 10000.000 Hz
FIDRES 0.305176 Hz
AQ 3.2767999 sec
RG 169.11
DW 50.000 usec
DE 13.50 usec
TE 300.0 K
D1 1.00000000 sec
TD0 1
SFO1 500.3030896 MHz
NUC1 1H
P1 10.00 usec
PLW1 21.89999962 W

F2 - Processing parameters
SI 65536
SF 500.3000120 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

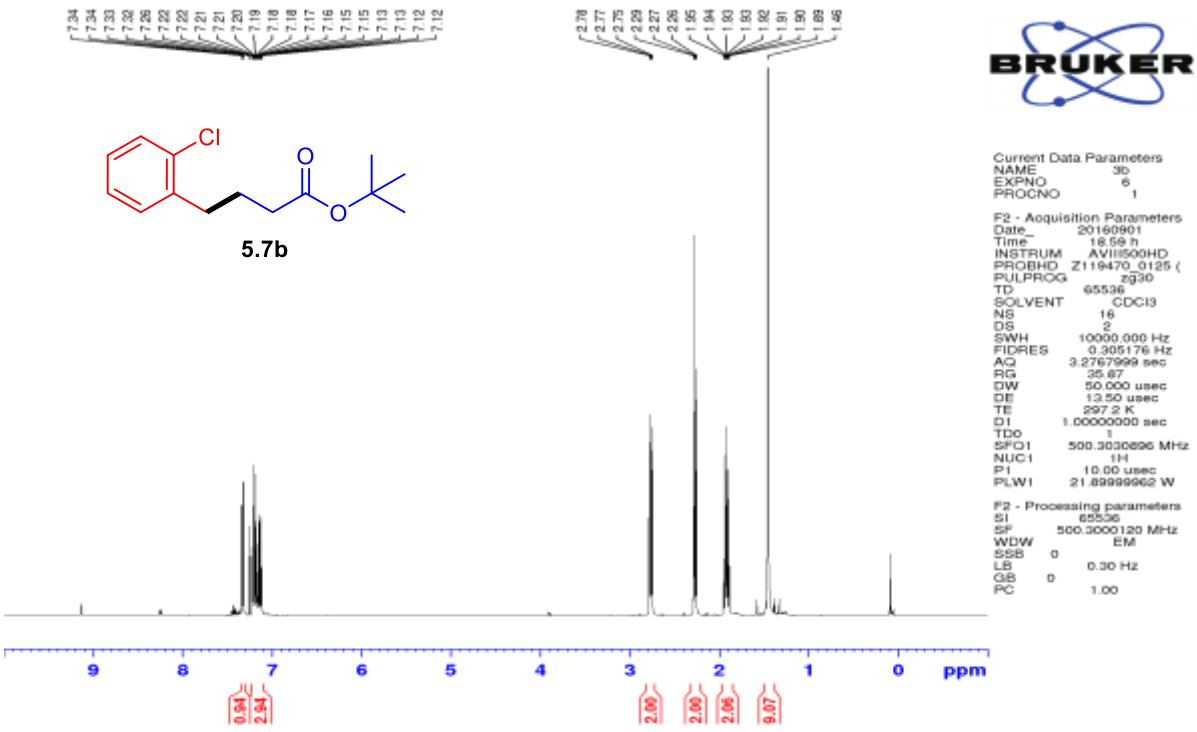


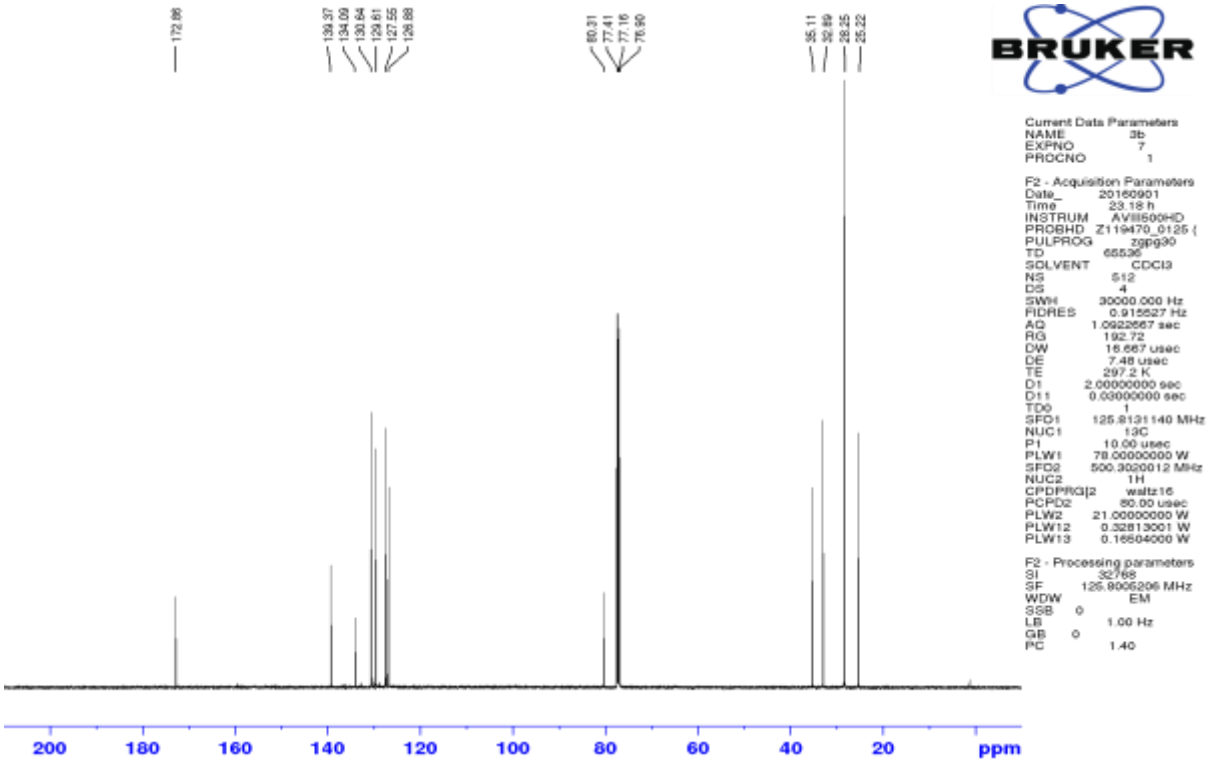
Current Data Parameters
NAME DXJ-E2136-PURE
EXPNO 5
PROCNO 1

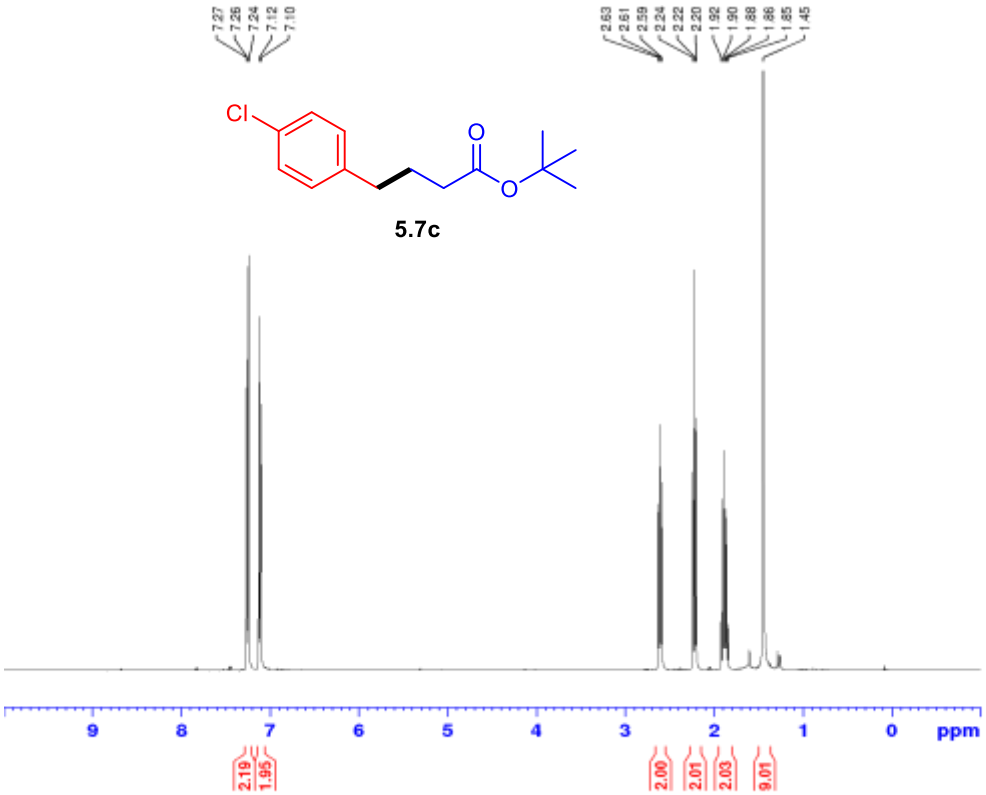
F2 - Acquisition Parameters
Date_ 20160302
Time 5.34 h
INSTRUM AVIII500HD
PROBHD Z119470_0125 (
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 3300
DS 4
SWH 30000.000 Hz
FIDRES 0.915527 Hz
AQ 1.0922667 sec
RG 192.72
DW 16.667 usec
DE 7.48 usec
TE 300.0 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
SFO1 125.8131140 MHz
NUC1 13C
P1 10.00 usec
PLW1 78.00000000 W
SFO2 500.3020012 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 90.00 usec
PLW2 21.00000000 W
PLW12 0.32813001 W
PLW13 0.16504000 W

F2 - Processing parameters
SI 32768
SF 125.8005379 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

Appendix 3: NMR Data for Unknown Compounds in Chapter 5





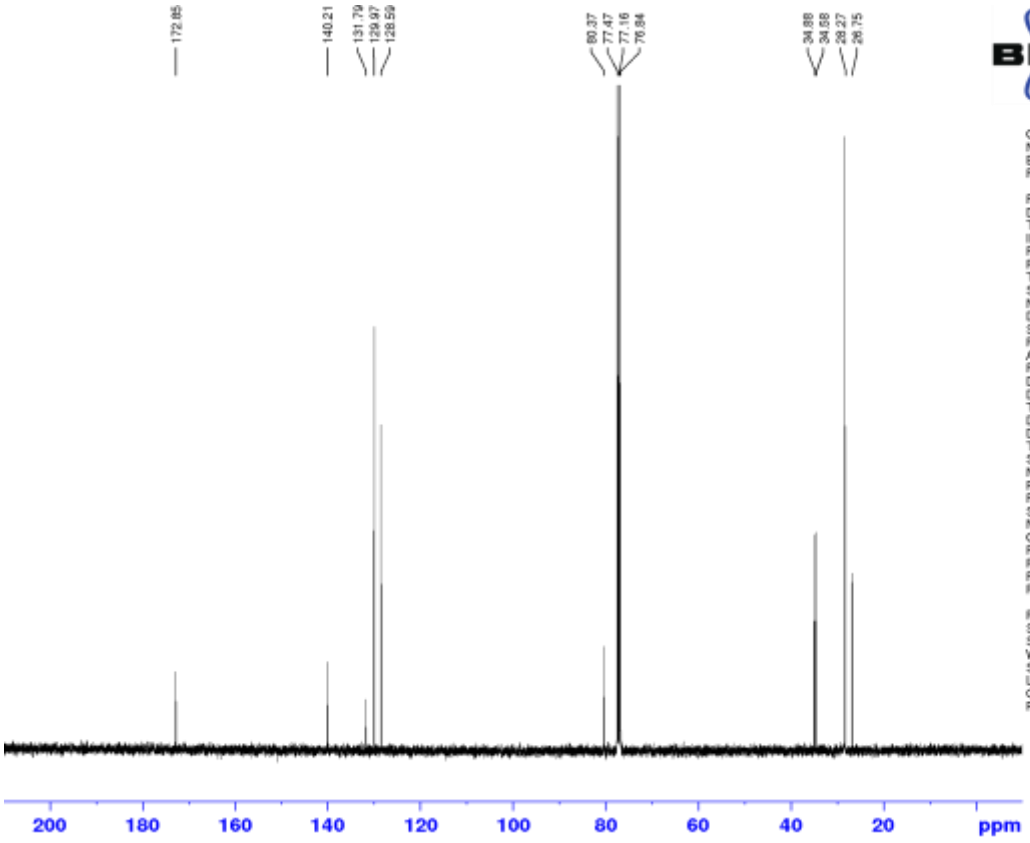


5.7c

Current Data Parameters
NAME Haining
EXPNO 11
PROCNO 1

F2 - Acquisition Parameters
Date_ 20160516
Time 23.56 h
INSTRUM B400
PROBHD Z116098_0217 (
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 8012.820 Hz
FIDRES 0.244532 Hz
AQ 4.0894465 sec
RG 117.63
DW 62.400 usec
DE 17.53 usec
TE 302.3 K
D1 1.00000000 sec
TD0 1
SFO1 400.3524723 MHz
NUC1 1H
P1 9.25 usec
PLW1 17.00000000 W

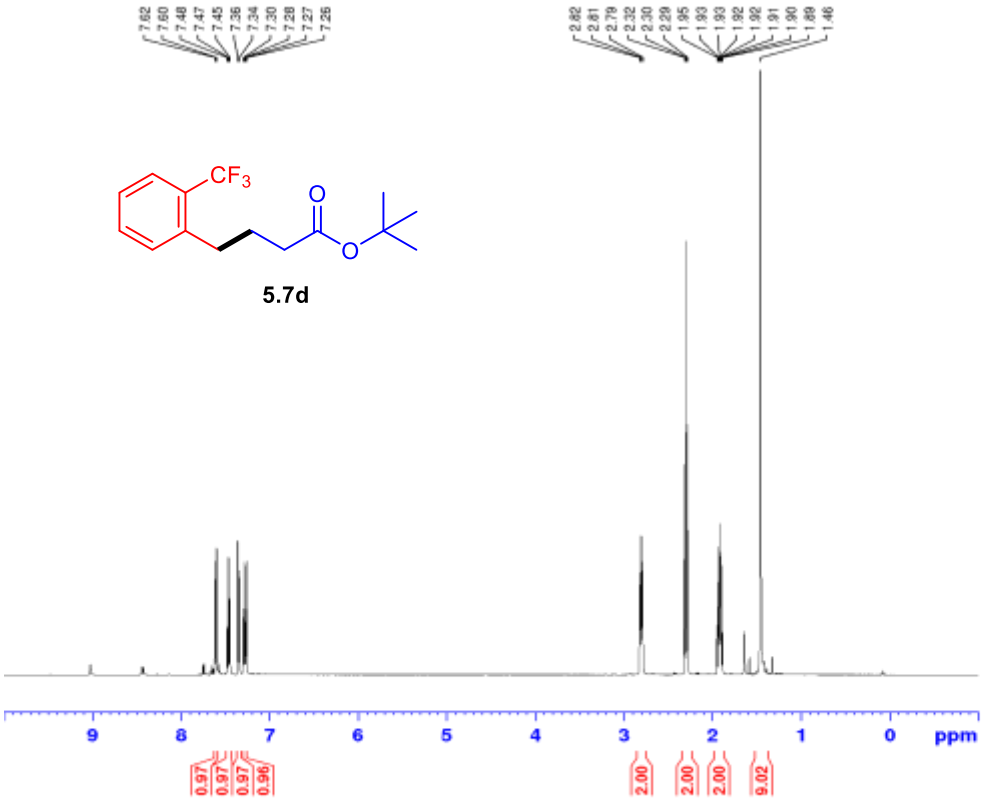
F2 - Processing parameters
SI 65536
SF 400.3500076 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00



Current Data Parameters
NAME Haining
EXPNO 12
PROCNO 1

F2 - Acquisition Parameters
Date_ 20160517
Time 18.22 h
INSTRUM B400
PROBHD Z116098_0217 (
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 298
DS 4
SWH 24038.461 Hz
FIDRES 0.733696 Hz
AQ 1.3631488 sec
RG 202.76
DW 20.800 usec
DE 9.57 usec
TE 303.3 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
SFO1 100.6781539 MHz
NUC1 13C
P1 10.00 usec
PLW1 67.00000000 W
SFO2 400.3516014 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 90.00 usec
PLW2 25.00000000 W
PLW12 0.21416000 W
PLW13 0.10772000 W

F2 - Processing parameters
SI 32768
SF 100.6680740 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

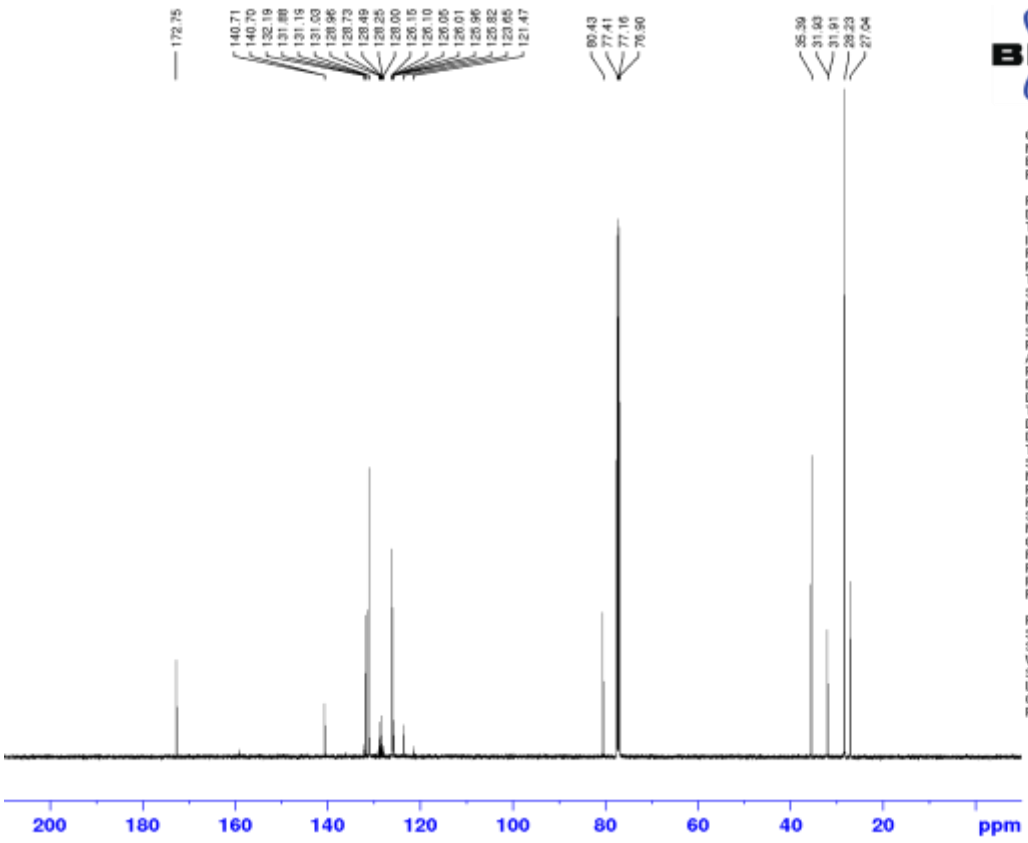


5.7d

Current Data Parameters
NAME 3d
EXPNO 5
PROCNO 1

F2 - Acquisition Parameters
Date_ 20160902
Time 16.07 h
INSTRUM AVIII500HD
PROBHD Z119470_0125 (
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 10000.000 Hz
FIDRES 0.305176 Hz
AQ 3.2767999 sec
RG 63.07
DW 50.000 usec
DE 13.50 usec
TE 297.2 K
D1 1.00000000 sec
TD0 1
SFO1 500.3030896 MHz
NUC1 1H
P1 10.00 usec
PLW1 21.89999962 W

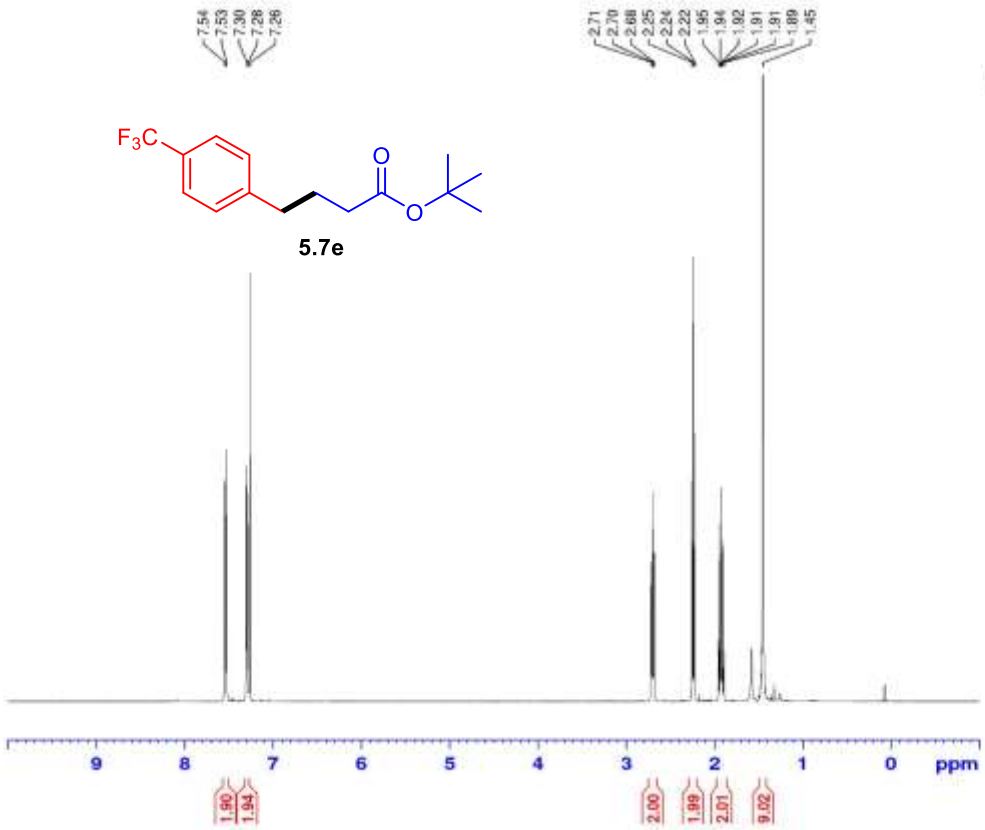
F2 - Processing parameters
SI 65536
SF 500.3000123 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00



Current Data Parameters
NAME 3d
EXPNO 6
PROCNO 1

F2 - Acquisition Parameters
Date_ 20160902
Time 17.48 h
INSTRUM AVIII500HD
PROBHD Z119470_0125 (
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 512
DS 4
SWH 30000.000 Hz
FIDRES 0.915527 Hz
AQ 1.0922667 sec
RG 192.72
DW 16.667 usec
DE 7.48 usec
TE 297.2 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
SFO1 125.8131140 MHz
NUC1 13C
P1 10.00 usec
PLW1 78.00000000 W
SFO2 500.3020012 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 80.00 usec
PLW2 21.00000000 W
PLW12 0.32813001 W
PLW13 0.16504000 W

F2 - Processing parameters
SI 32768
SF 125.8005187 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

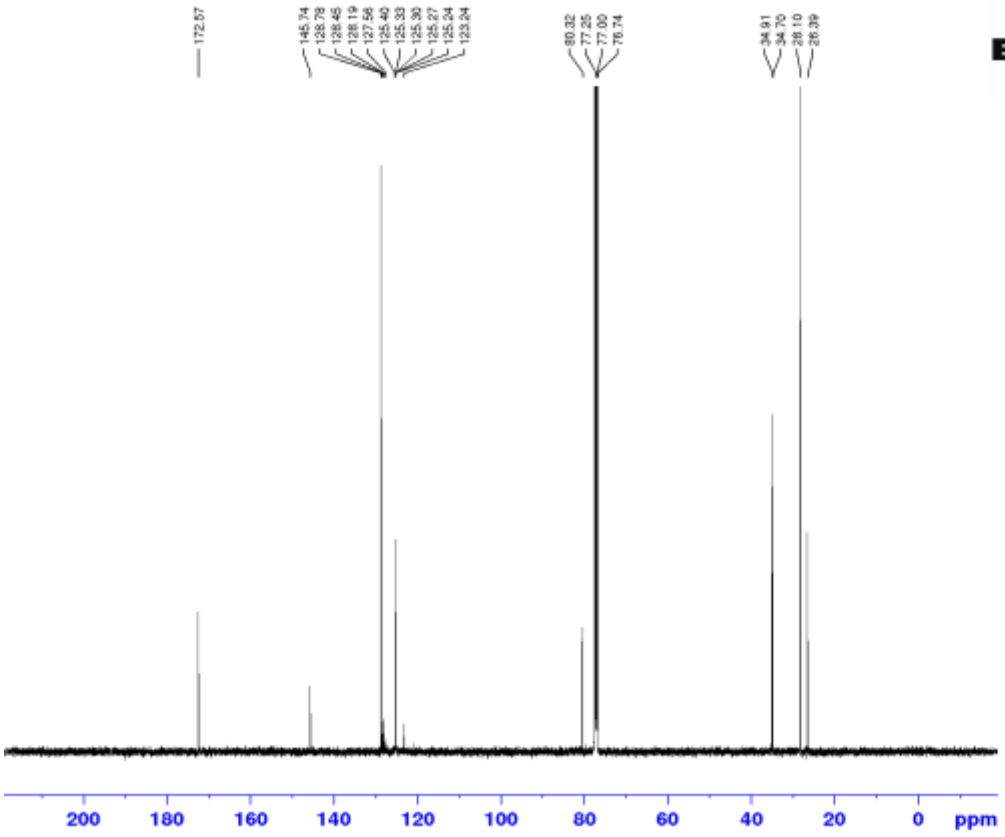


BRUKER

Current Data Parameters
NAME DXJ-E2300-PURE
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date_ 20160525
Time 13.11 h
INSTRUM AVIII500HD
PROBHD Z119470_0125 (
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 10000.000 Hz
FIDRES 0.305176 Hz
AQ 3.2767999 sec
RG 108.58
DW 50.000 usec
DE 13.50 usec
TE 297.2 K
D1 1.00000000 sec
TD0 1
SFO1 500.3030898 MHz
NUC1 1H
P1 10.00 usec
PLW1 21.89999962 W

F2 - Processing parameters
SI 65536
SF 500.3000123 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

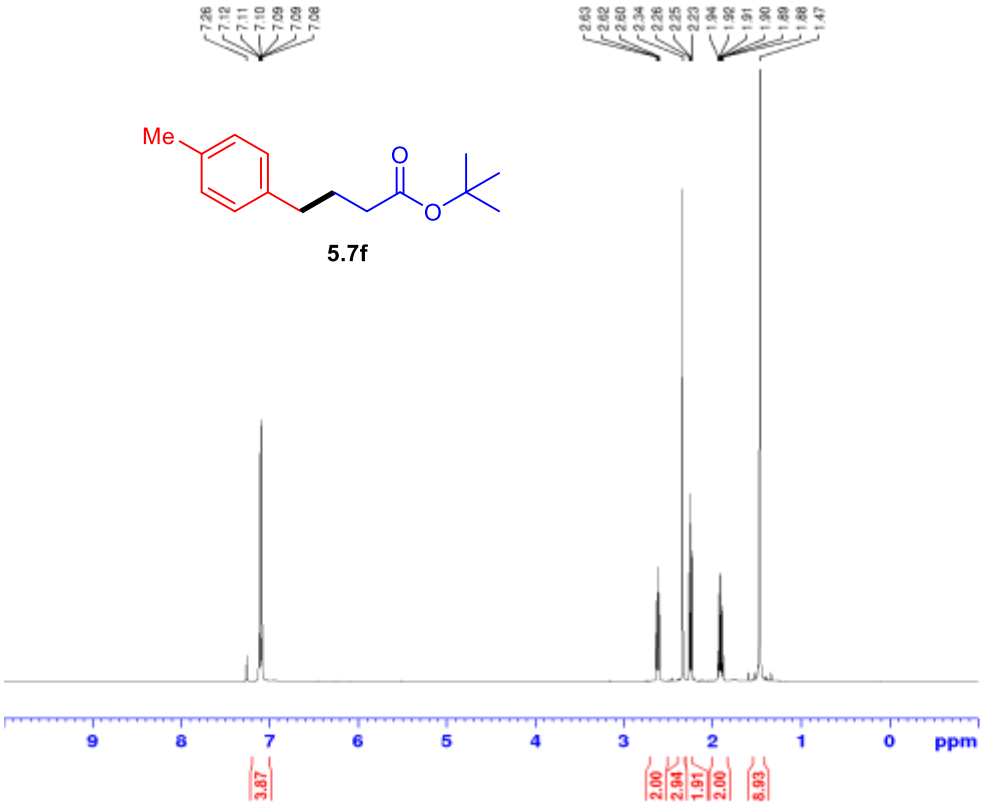


BRUKER

Current Data Parameters
NAME DXJ-E2300-PURE
EXPNO 2
PROCNO 1

F2 - Acquisition Parameters
Date_ 20160525
Time 20.23 h
INSTRUM AVIII500HD
PROBHD Z119470_0125 (
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 1500
DS 4
SWH 30000.000 Hz
FIDRES 0.915527 Hz
AQ 1.0922667 sec
RG 192.72
DW 16.667 usec
DE 7.48 usec
TE 297.2 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
SFO1 125.8131140 MHz
NUC1 13C
P1 10.00 usec
PLW1 78.00000000 W
SFO2 500.3020012 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 80.00 usec
PLW2 21.00000000 W
PLW12 0.32813001 W
PLW13 0.16504000 W

F2 - Processing parameters
SI 32768
SF 125.8005379 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

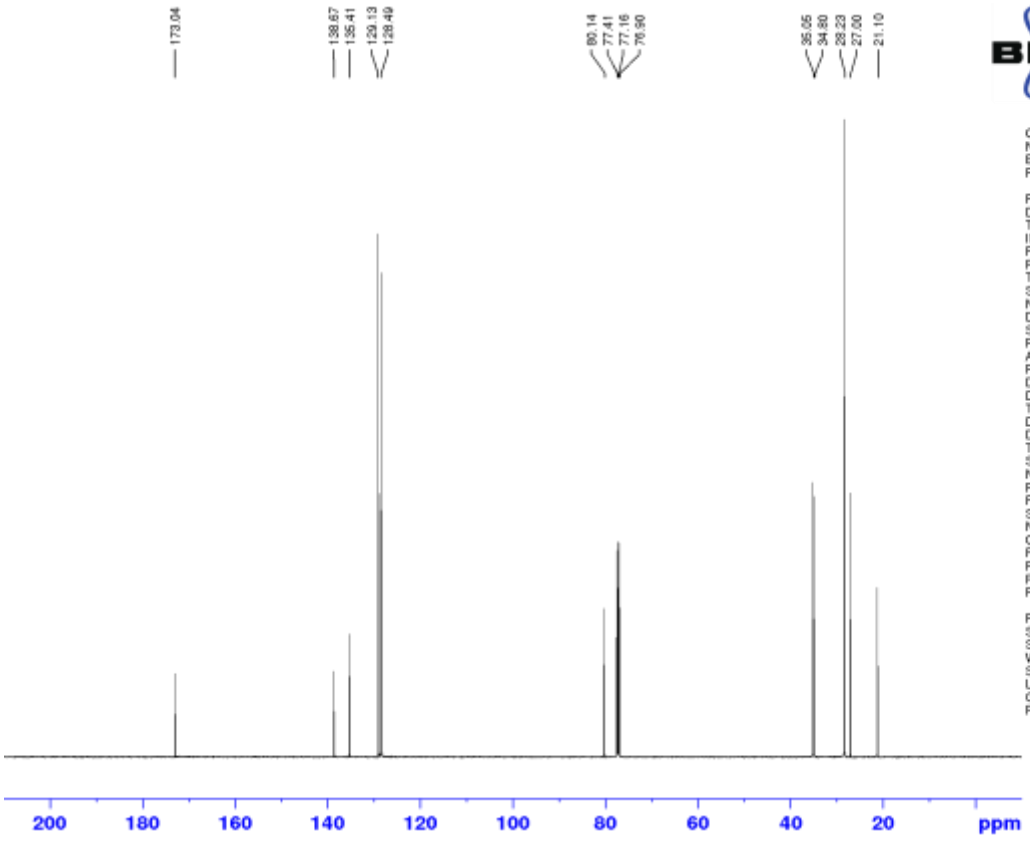


5.7f

Current Data Parameters
NAME 3f
EXPNO 7
PROCNO 1

F2 - Acquisition Parameters
Date_ 20160927
Time 20.03 h
INSTRUM AVIII500HD
PROBHD Z119470_0125 (
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 10000.000 Hz
FIDRES 0.305176 Hz
AQ 3.2767999 sec
RG 22.42
DW 50.000 usec
DE 13.50 usec
TE 297.2 K
D1 1.00000000 sec
TD0 1
SFO1 500.3030896 MHz
NUC1 1H
P1 10.00 usec
PLW1 21.69999962 W

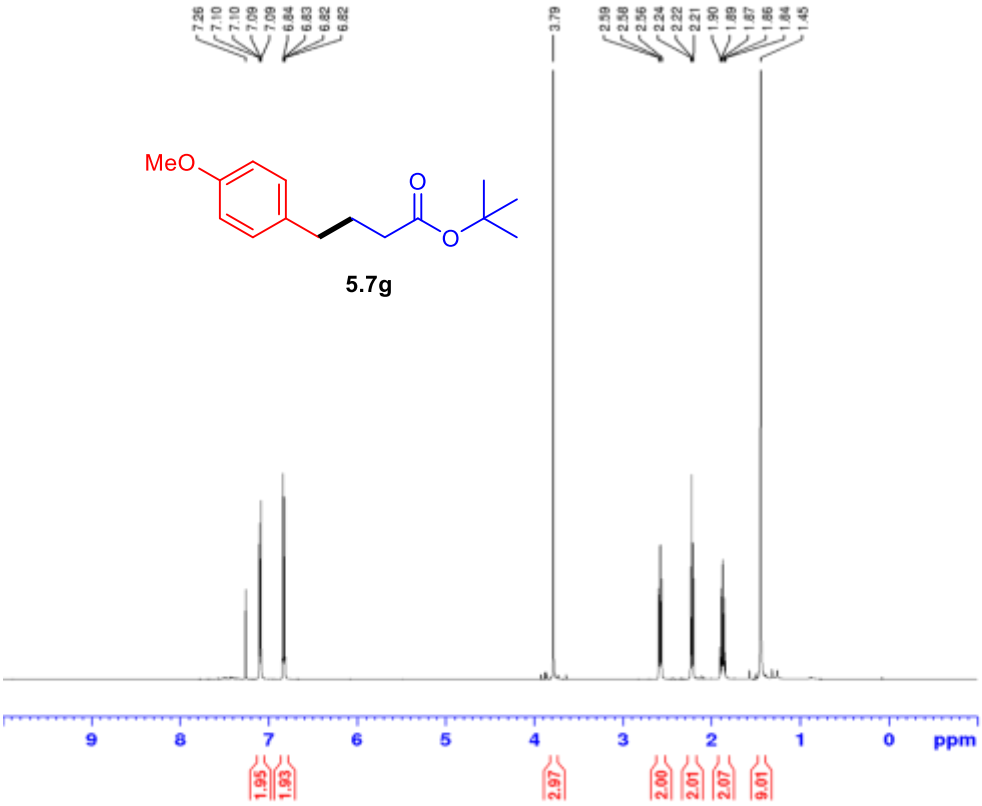
F2 - Processing parameters
SI 65536
SF 500.3000120 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00



Current Data Parameters
NAME 3f
EXPNO 10
PROCNO 1

F2 - Acquisition Parameters
Date_ 20160928
Time 0.18 h
INSTRUM AVIII500HD
PROBHD Z119470_0125 (
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 1000
DS 4
SWH 30000.000 Hz
FIDRES 0.915527 Hz
AQ 1.0922667 sec
RG 192.72
DW 16.667 usec
DE 7.48 usec
TE 297.2 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
SFO1 125.8131140 MHz
NUC1 13C
P1 10.00 usec
PLW1 78.00000000 W
SFO2 500.3020012 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 80.00 usec
PLW2 21.00000000 W
PLW12 0.32813001 W
PLW13 0.16504000 W

F2 - Processing parameters
SI 32768
SF 125.8006259 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40



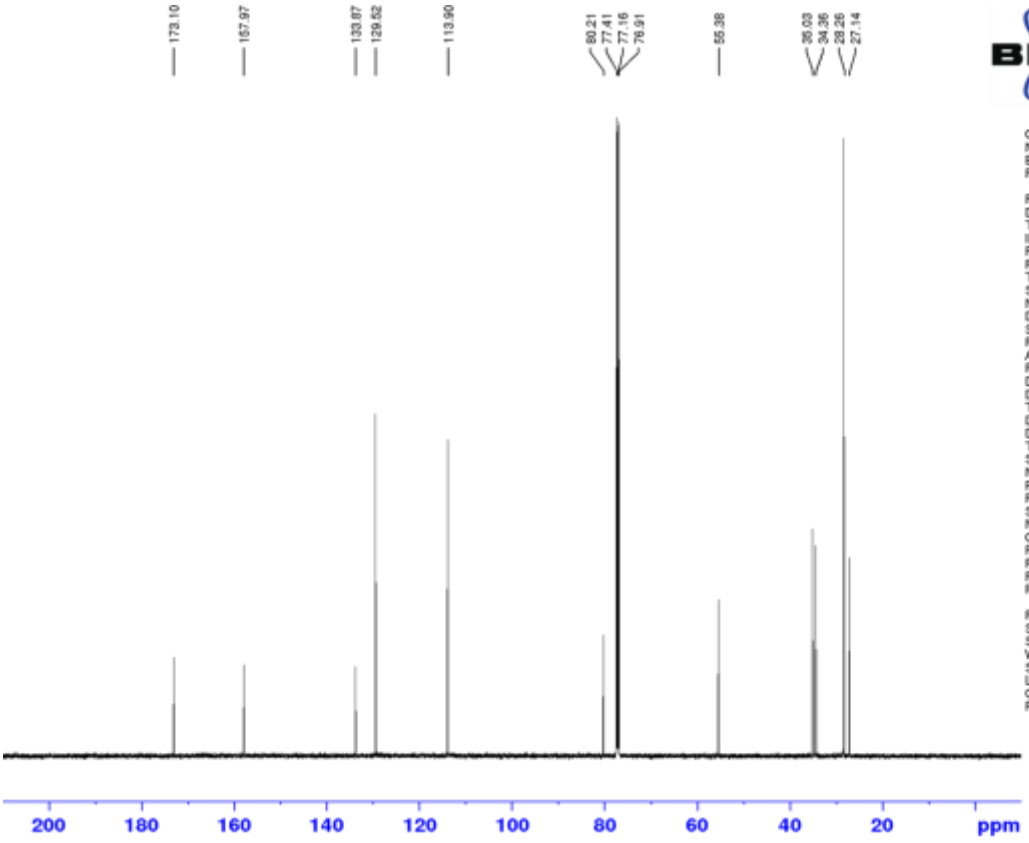
5.7g

BRUKER

Current Data Parameters
NAME sea-04-108
EXPNO 22
PROCNO 1

F2 - Acquisition Parameters
Date_ 20160515
Time 23.52 h
INSTRUM AVIII500HD
PROBHD Z119470_0125 (
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 10000.000 Hz
FIDRES 0.305176 Hz
AQ 3.2767999 sec
RG 77.88
DW 50.000 usec
DE 13.50 usec
TE 297.2 K
D1 1.00000000 sec
TD0 1
SFO1 500.3030896 MHz
NUC1 1H
P1 10.00 usec
PLW1 21.89999962 W

F2 - Processing parameters
SI 65536
SF 500.3000121 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

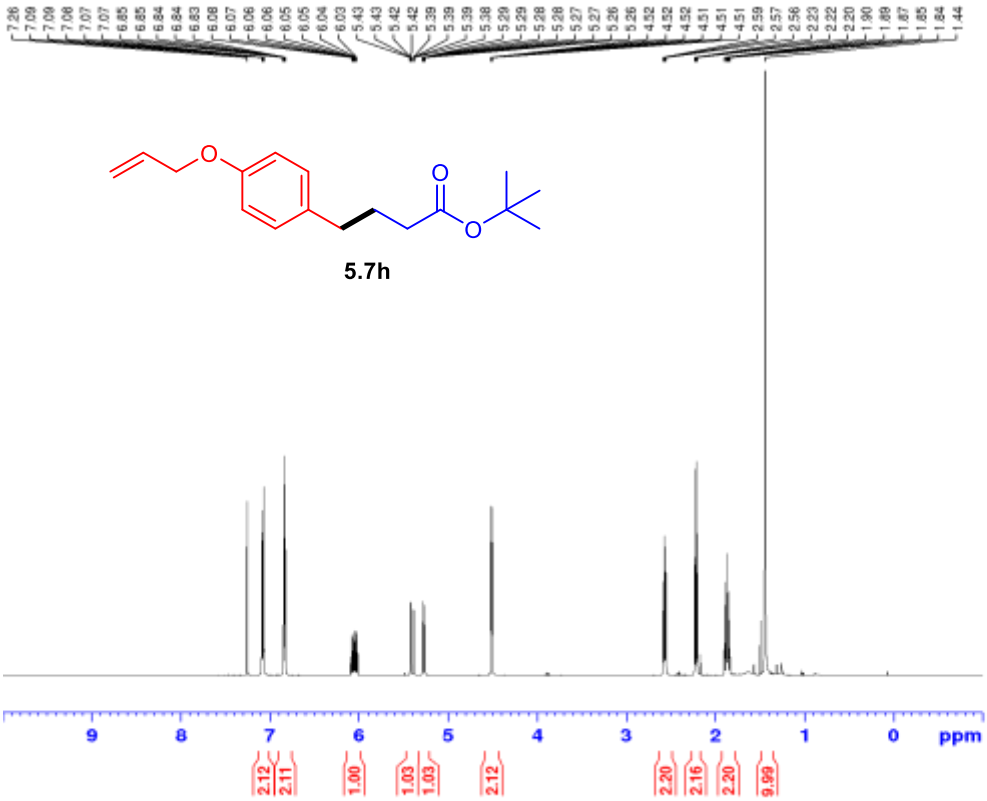


BRUKER

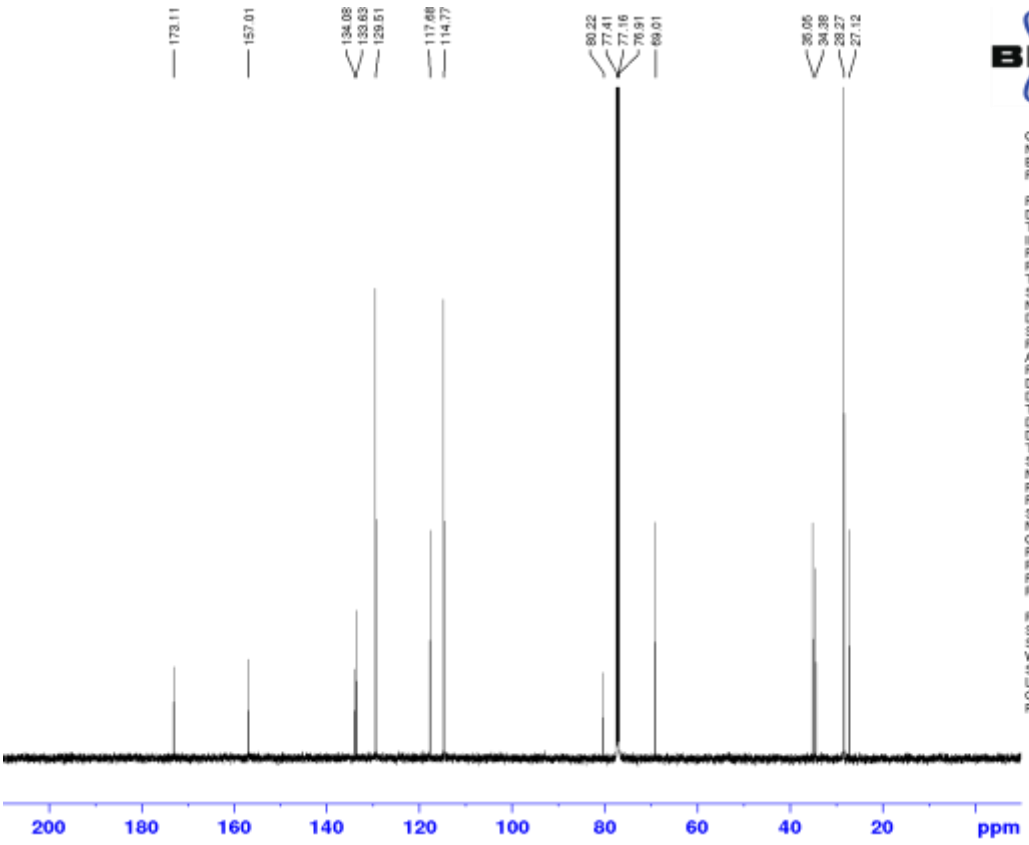
Current Data Parameters
NAME Haining
EXPNO 6
PROCNO 1

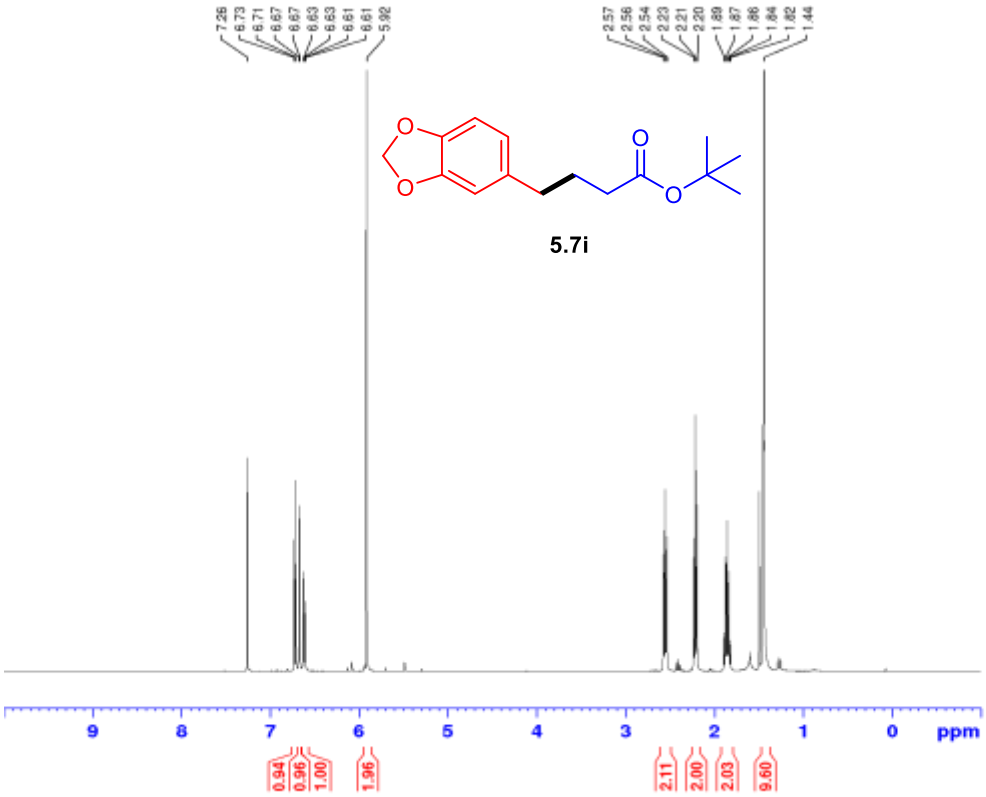
F2 - Acquisition Parameters
Date_ 20160516
Time 0.20 h
INSTRUM AVIII500HD
PROBHD Z119470_0125 (
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 512
DS 4
SWH 30000.000 Hz
FIDRES 0.915527 Hz
AQ 1.0922667 sec
RG 192.72
DW 16.667 usec
DE 7.48 usec
TE 297.1 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
SFO1 125.8131140 MHz
NUC1 13C
P1 10.00 usec
PLW1 78.00000000 W
SFO2 500.3020012 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 80.00 usec
PLW2 21.00000000 W
PLW12 0.32813001 W
PLW13 0.16504000 W

F2 - Processing parameters
SI 32768
SF 125.8005196 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40



5.7h



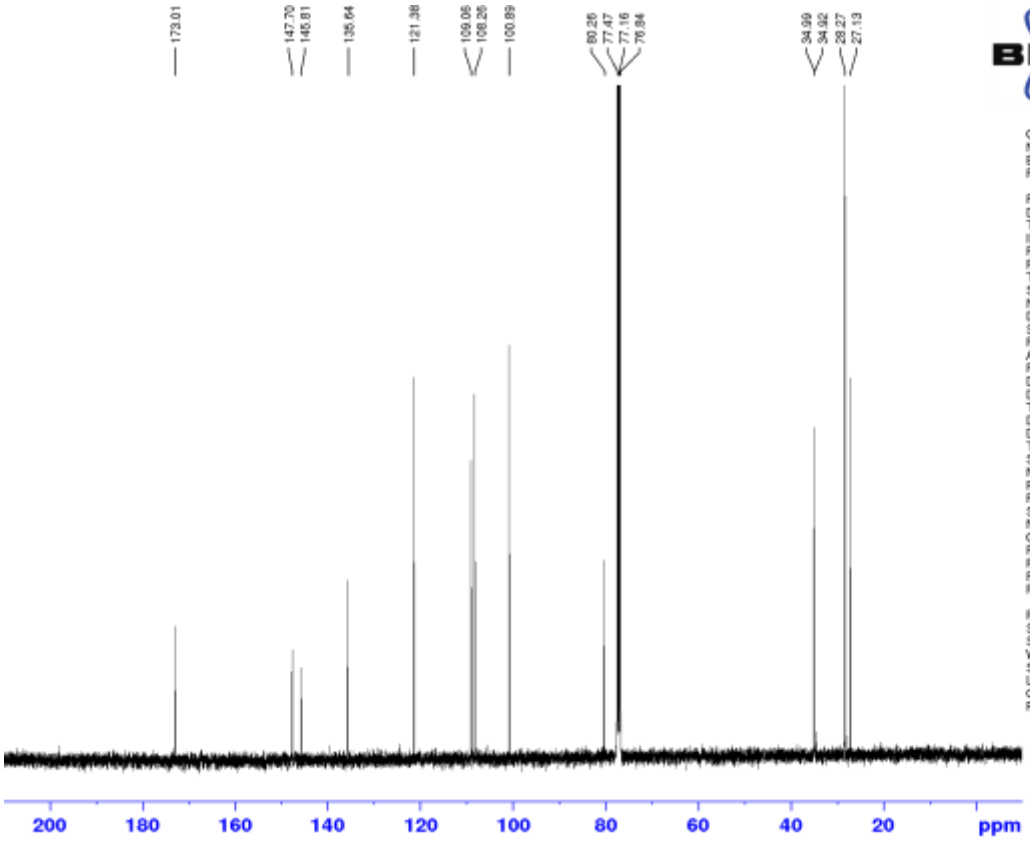


BRUKER

Current Data Parameters
NAME Haining
EXPNO 9
PROCNO 1

F2 - Acquisition Parameters
Date_ 20160517
Time 0.16 h
INSTRUM B400
PROBHD Z116098_0217 (
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 8012.820 Hz
FIDRES 0.244532 Hz
AQ 4.0894465 sec
RG 117.63
DW 62.400 usec
DE 17.53 usec
TE 302.3 K
D1 1.00000000 sec
TD0 1
SFO1 400.3524723 MHz
NUC1 1H
P1 9.25 usec
PLW1 17.00000000 W

F2 - Processing parameters
SI 65536
SF 400.3500096 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

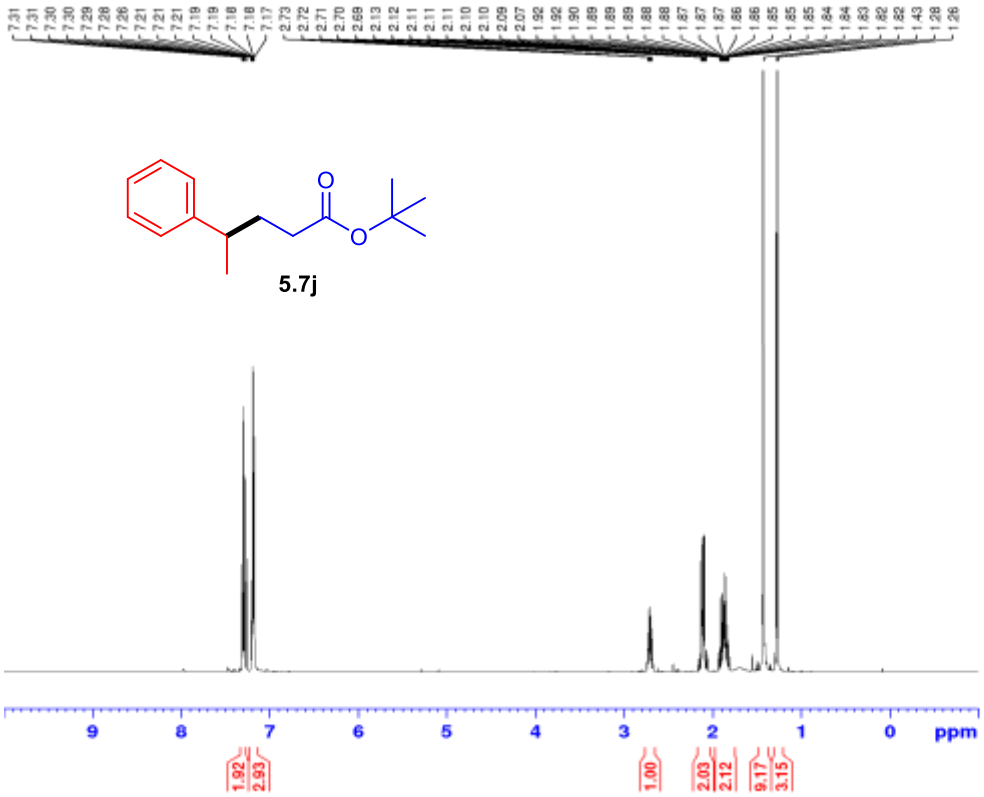


BRUKER

Current Data Parameters
NAME Haining
EXPNO 10
PROCNO 1

F2 - Acquisition Parameters
Date_ 20160517
Time 1.15 h
INSTRUM B400
PROBHD Z116098_0217 (
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 1024
DS 4
SWH 24038.461 Hz
FIDRES 0.733696 Hz
AQ 1.3631488 sec
RG 202.76
DW 20.800 usec
DE 9.57 usec
TE 303.1 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
SFO1 100.6781539 MHz
NUC1 13C
P1 10.00 usec
PLW1 67.00000000 W
SFO2 400.3516014 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 90.00 usec
PLW2 25.00000000 W
PLW12 0.21416000 W
PLW13 0.10772000 W

F2 - Processing parameters
SI 32768
SF 100.6680740 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

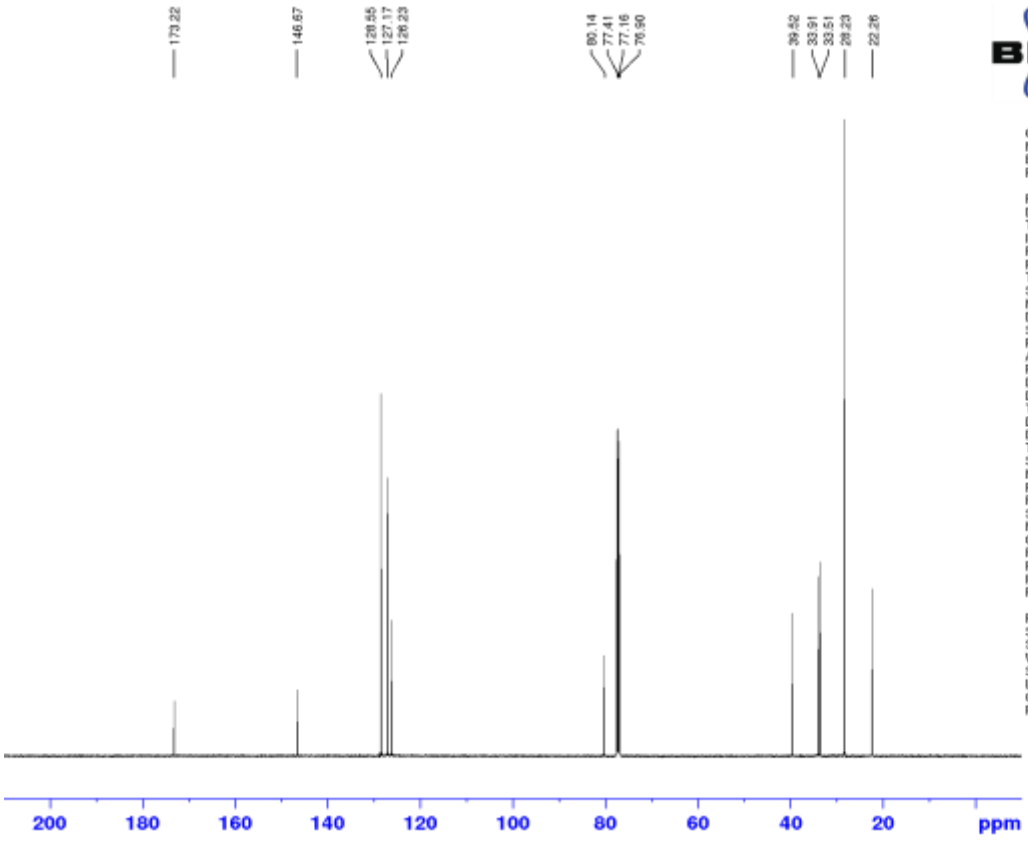


BRUKER

Current Data Parameters
NAME 3j
EXPNO 3
PROCNO 1

F2 - Acquisition Parameters
Date_ 20160922
Time 16.02 h
INSTRUM AVIII500HD
PROBHD Z119470_0125 (
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 10000.000 Hz
FIDRES 0.305176 Hz
AQ 3.2767999 sec
RG 56.3
DW 50.000 usec
DE 13.50 usec
TE 297.2 K
D1 1.00000000 sec
TD0 1
SFO1 500.3030896 MHz
NUC1 1H
P1 10.00 usec
PLW1 21.89999962 W

F2 - Processing parameters
SI 65536
SF 500.3000120 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

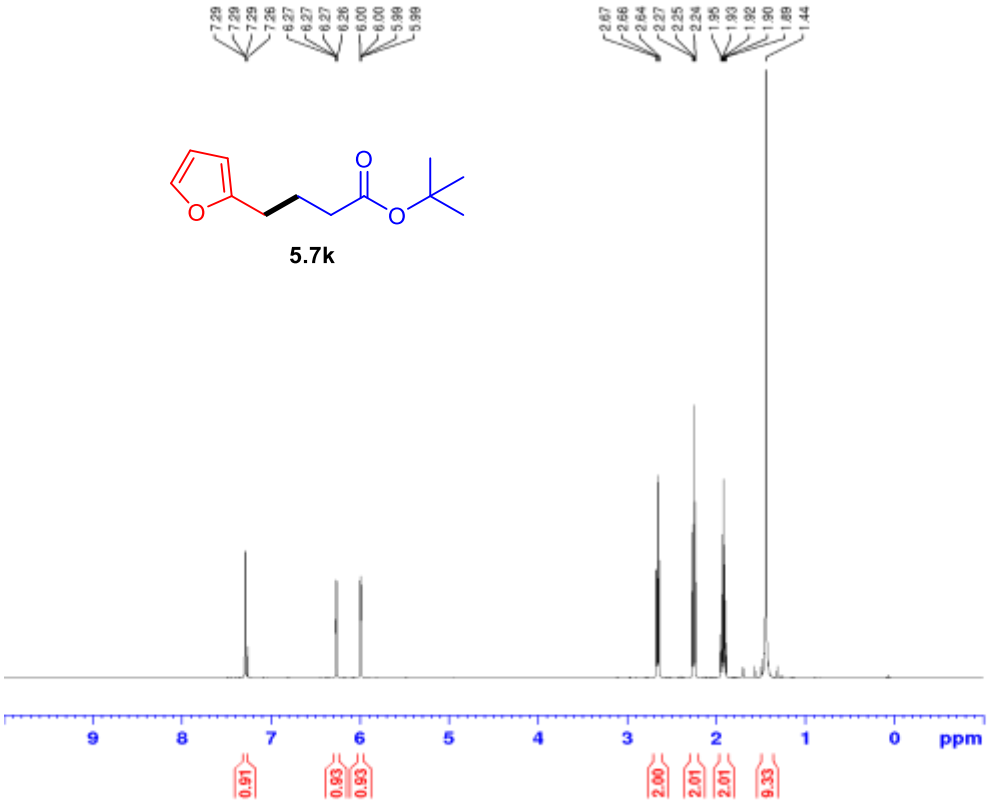


BRUKER

Current Data Parameters
NAME 3j
EXPNO 6
PROCNO 1

F2 - Acquisition Parameters
Date_ 20160923
Time 2.32 h
INSTRUM AVIII500HD
PROBHD Z119470_0125 (
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 1000
DS 4
SWH 30000.000 Hz
FIDRES 0.915527 Hz
AQ 1.0922667 sec
RG 192.72
DW 16.667 usec
DE 7.48 usec
TE 297.2 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
SFO1 125.8131140 MHz
NUC1 13C
P1 10.00 usec
PLW1 78.00000000 W
SFO2 500.3020012 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 80.00 usec
PLW2 21.00000000 W
PLW12 0.32813001 W
PLW13 0.16504000 W

F2 - Processing parameters
SI 32768
SF 125.8006206 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

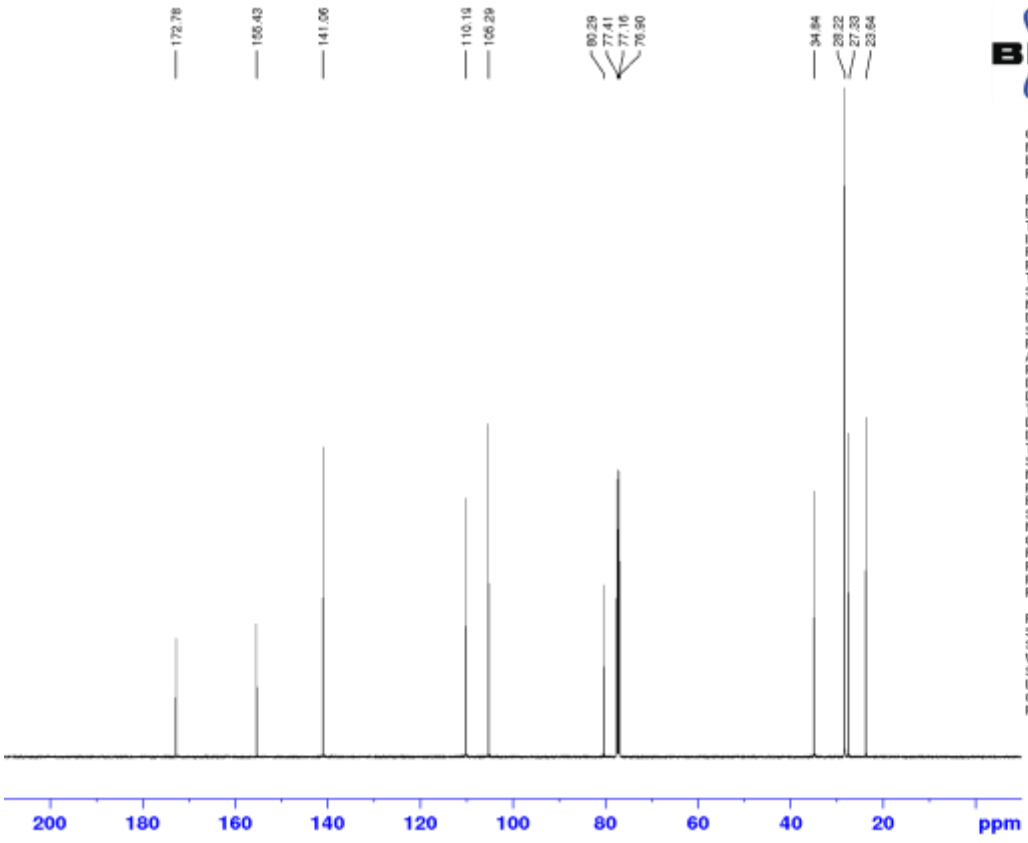


5.7k

Current Data Parameters
NAME sea-04-145
EXPNO 8
PROCNO 1

F2 - Acquisition Parameters
Date_ 20160908
Time 20.40 h
INSTRUM AVIII500HD
PROBHD Z119470_0125 (
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 10000.000 Hz
FIDRES 0.305176 Hz
AQ 3.2767999 sec
RG 25.23
DW 50.000 usec
DE 13.50 usec
TE 297.2 K
D1 1.00000000 sec
TD0 1
SFO1 500.3030896 MHz
NUC1 1H
P1 10.00 usec
PLW1 21.89999962 W

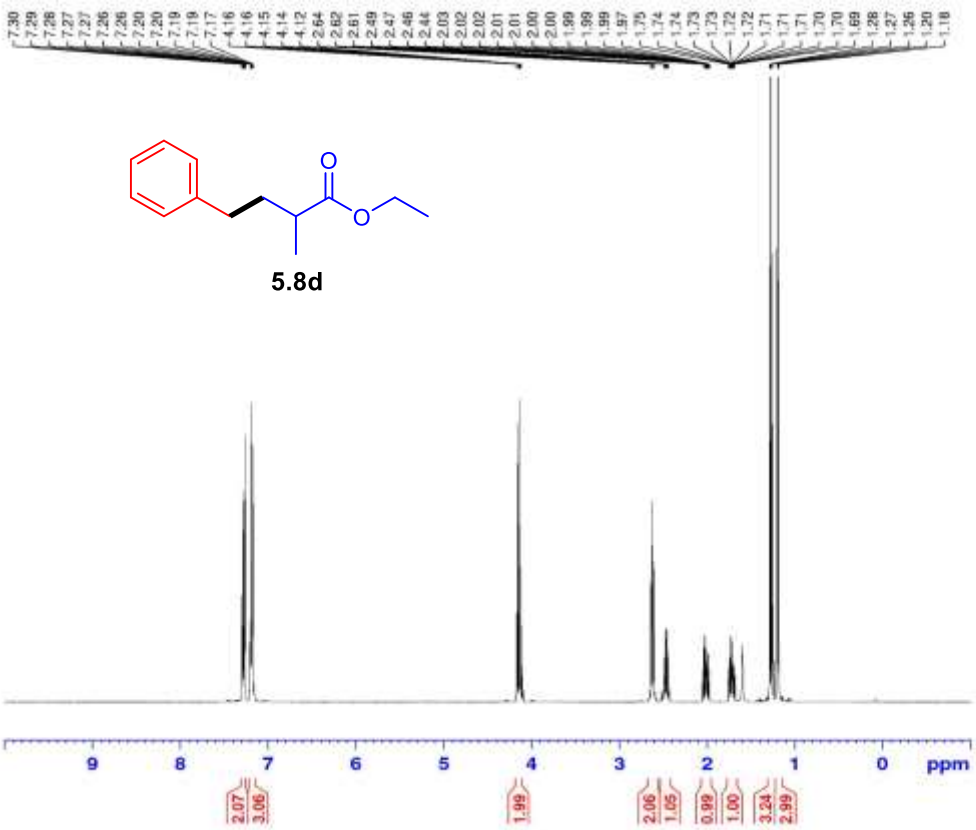
F2 - Processing parameters
SI 65536
SF 500.3000121 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00



Current Data Parameters
NAME sea-04-145
EXPNO 9
PROCNO 1

F2 - Acquisition Parameters
Date_ 20160908
Time 21.35 h
INSTRUM AVIII500HD
PROBHD Z119470_0125 (
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 512
DS 4
SWH 30000.000 Hz
FIDRES 0.915527 Hz
AQ 1.0922667 sec
RG 192.72
DW 16.667 usec
DE 7.48 usec
TE 297.2 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
SFO1 125.8131140 MHz
NUC1 13C
P1 10.00 usec
PLW1 78.00000000 W
SFO2 500.3020012 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 80.00 usec
PLW2 21.00000000 W
PLW12 0.32813001 W
PLW13 0.16504000 W

F2 - Processing parameters
SI 32768
SF 125.8005215 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

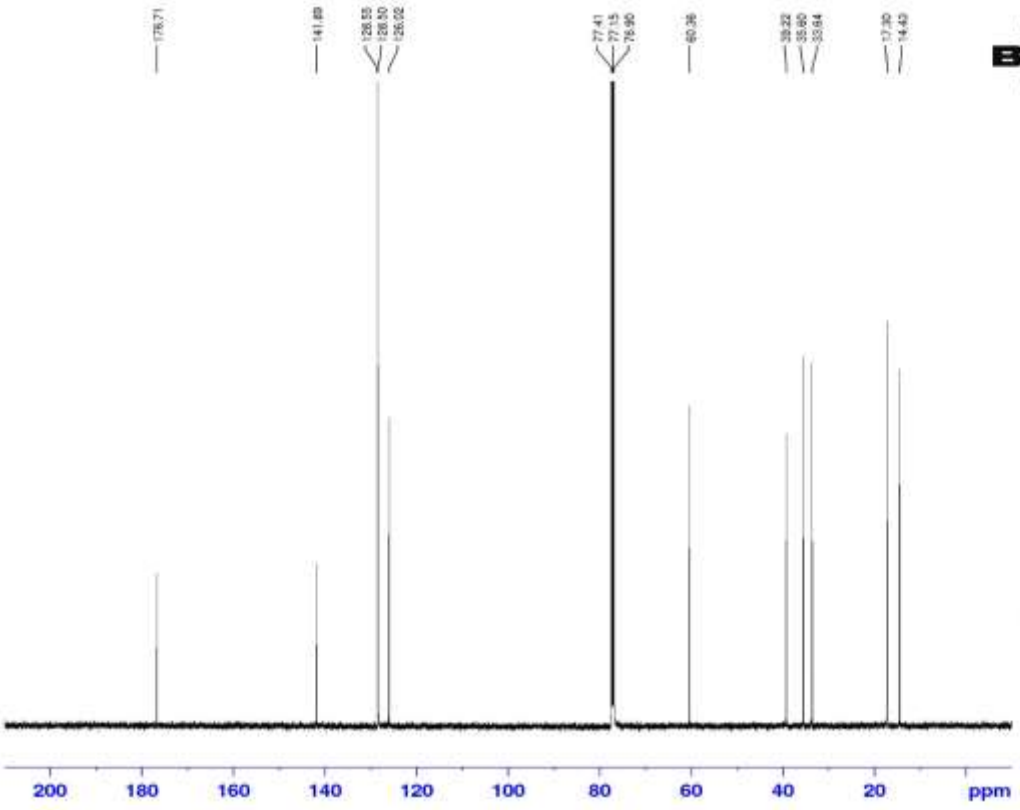


5.8d

Current Data Parameters
NAME DXJ-E2363-PURE
EXPNO 2
PROCNO 1

F2 - Acquisition Parameters
Date_ 20160705
Time 3.09 h
INSTRUM AVIII500HD
PROBHD Z119470_0125 (
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 10000.000 Hz
FIDRES 0.305176 Hz
AQ 3.2767988 sec
RG 106.56
DW 50.000 usec
DE 13.50 usec
TE 297.2 K
D1 1.00000000 sec
TD0 1
SFO1 500.3030896 MHz
NUC1 1H
P1 10.00 usec
PLW1 21.89999962 W

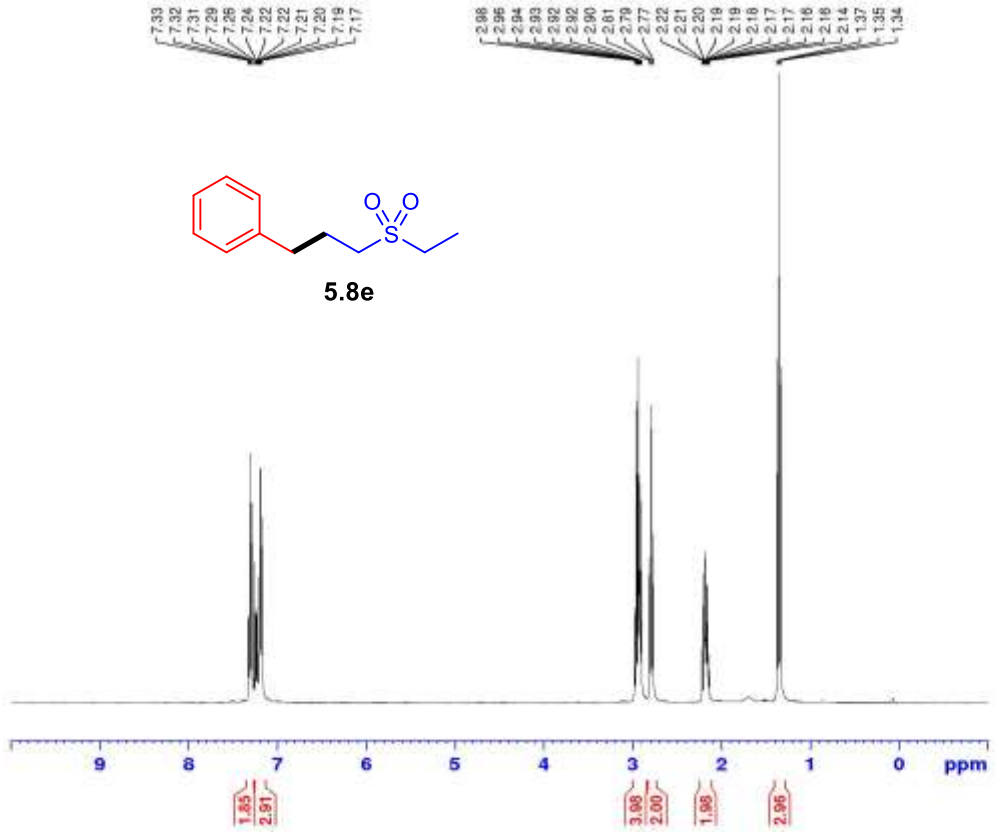
F2 - Processing parameters
SI 65536
SF 500.3000122 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00



Current Data Parameters
NAME DXJ-E2363-PURE
EXPNO 3
PROCNO 1

F2 - Acquisition Parameters
Date_ 20160705
Time 6.26 h
INSTRUM AVIII500HD
PROBHD Z119470_0125 (
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 1700
DS 4
SWH 30000.000 Hz
FIDRES 0.915527 Hz
AQ 1.0922667 sec
RG 199.72
DW 16.667 usec
DE 7.48 usec
TE 297.2 K
D1 2.00000000 sec
d11 0.03000000 sec
DELTA 1.89999998 sec
TD0 1
SFO1 125.8131140 MHz
NUC1 13C
P1 10.00 usec
PLW1 78.00000000 W
SFO2 500.3020012 MHz
NUC2 1H
CPDPRG[2 waltz16
PLW2 21.00000000 W
PLW12 0.32813001 W
PLW13 0.16504000 W

F2 - Processing parameters
SI 32768
SF 125.8005196 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40



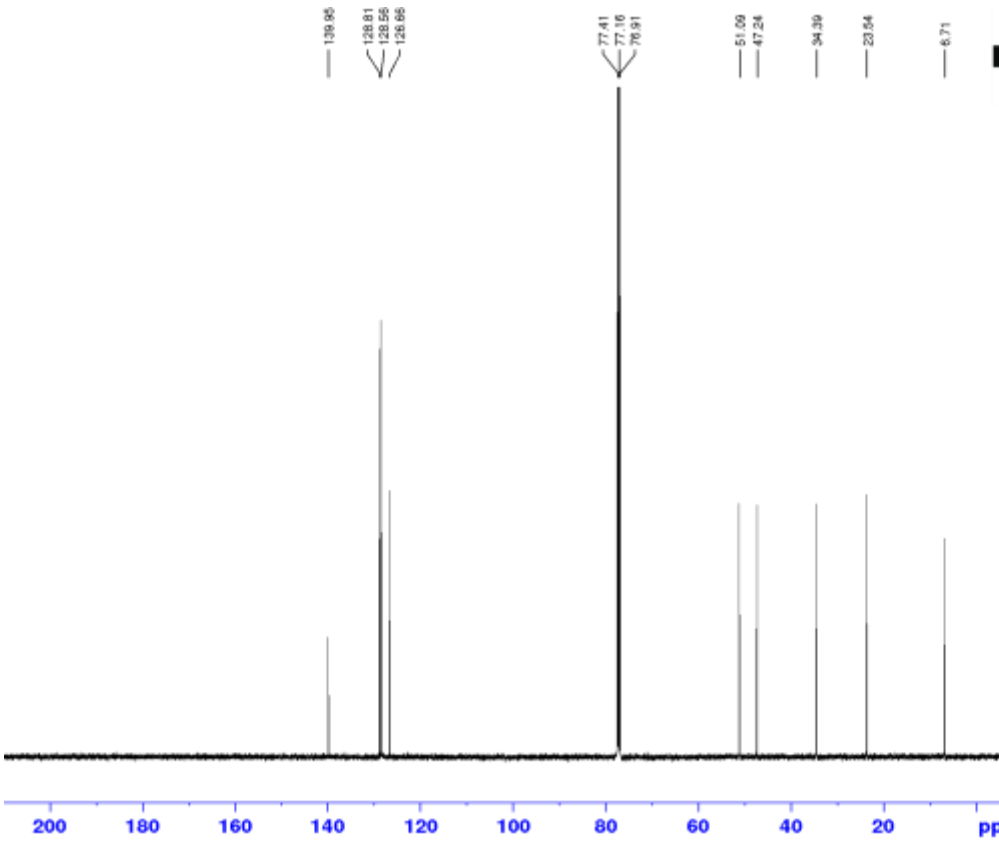
5.8e

BRUKER

Current Data Parameters
NAME DXJ-E2335-PURE
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date_ 20160622
Time 21.55 h
INSTRUM B400
PROBHD Z116098_0217 (
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 8012.820 Hz
FIDRES 0.244532 Hz
AQ 4.0894465 sec
RG 117.63
DW 62.400 usec
DE 17.53 usec
TE 300.0 K
D1 1.00000000 sec
TD0 1
SFO1 400.3524723 MHz
NUC1 1H
P1 9.25 usec
PLW1 17.00000000 W

F2 - Processing parameters
SI 65536
SF 400.3500094 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

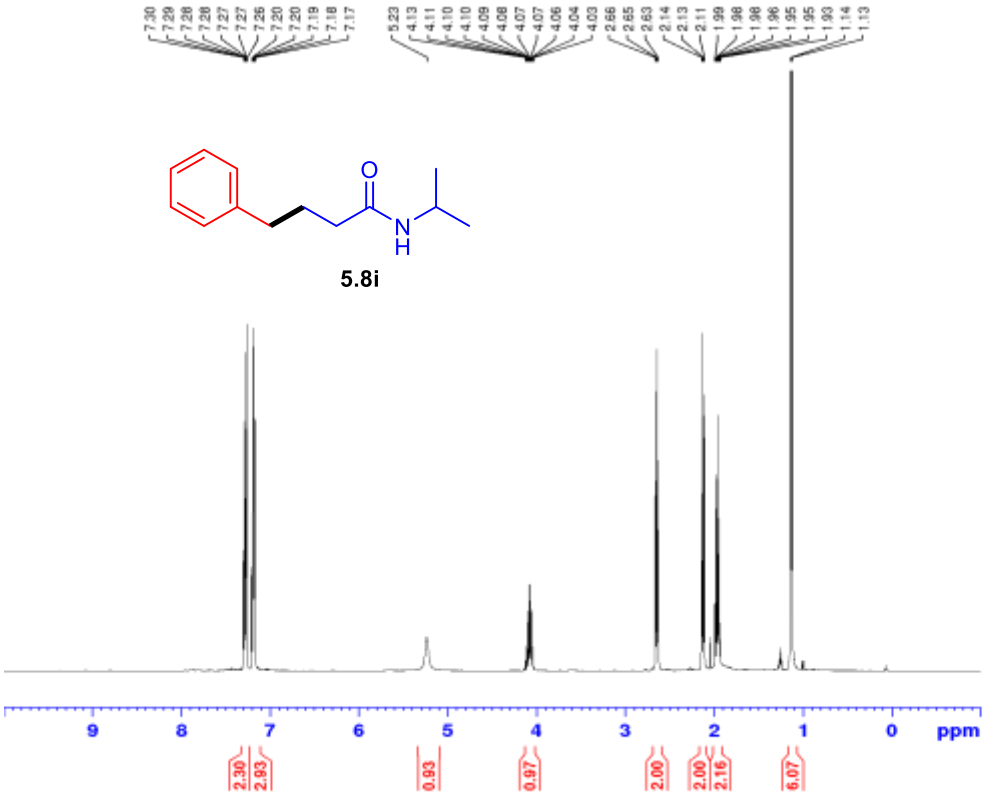


BRUKER

Current Data Parameters
NAME DXJ-E2335-PURE
EXPNO 3
PROCNO 1

F2 - Acquisition Parameters
Date_ 20160624
Time 2.34 h
INSTRUM AVIII500HD
PROBHD Z119470_0125 (
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 512
DS 4
SWH 30000.000 Hz
FIDRES 0.915527 Hz
AQ 1.0922667 sec
RG 192.72
DW 16.667 usec
DE 7.48 usec
TE 297.2 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
SFO1 125.8131140 MHz
NUC1 13C
P1 10.00 usec
PLW1 78.00000000 W
SFO2 500.3020012 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 80.00 usec
PLW2 21.00000000 W
PLW12 0.32813001 W
PLW13 0.16504000 W

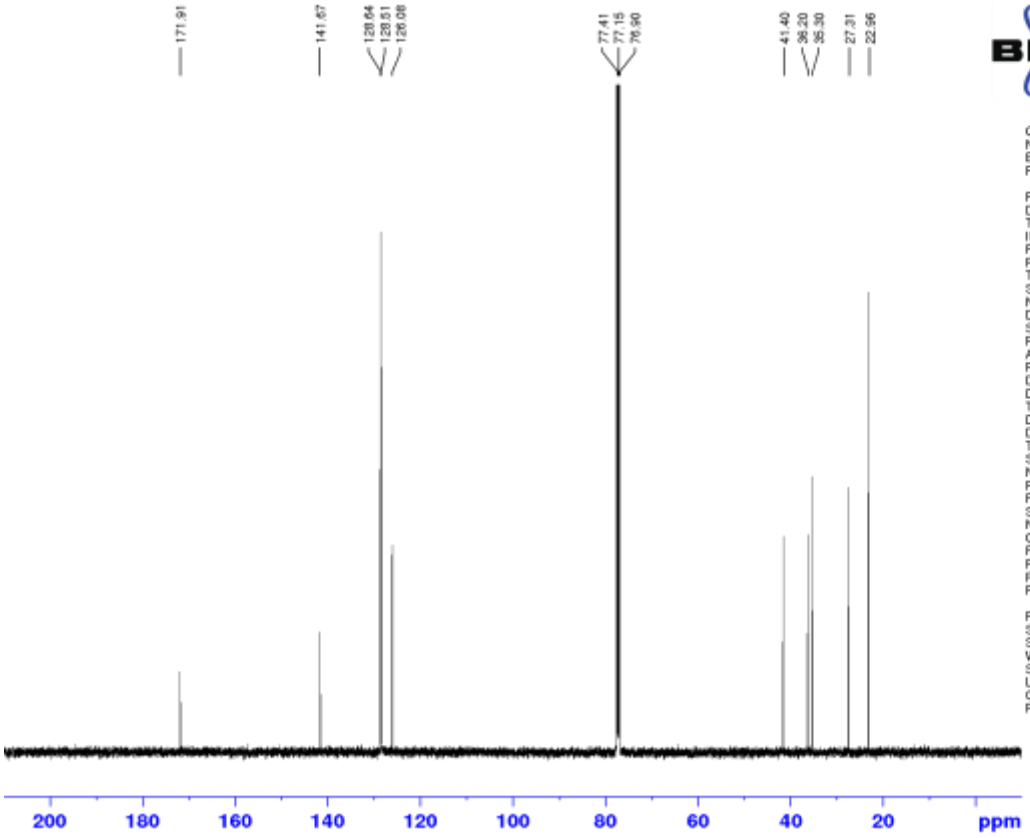
F2 - Processing parameters
SI 32768
SF 125.8005215 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40



Current Data Parameters
NAME DXJ-E2346-PURE
EXPNO 2
PROCNO 1

F2 - Acquisition Parameters
Date_ 20160705
Time 14.41 h
INSTRUM AVIII500HD
PROBHD Z119470_0125 (
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 10000.000 Hz
FIDRES 0.305176 Hz
AQ 3.2767999 sec
RG 106.56
DW 50.000 usec
DE 13.50 usec
TE 297.2 K
D1 1.00000000 sec
TD0 1
SFO1 500.3030896 MHz
NUC1 1H
P1 10.00 usec
PLW1 21.89999962 W

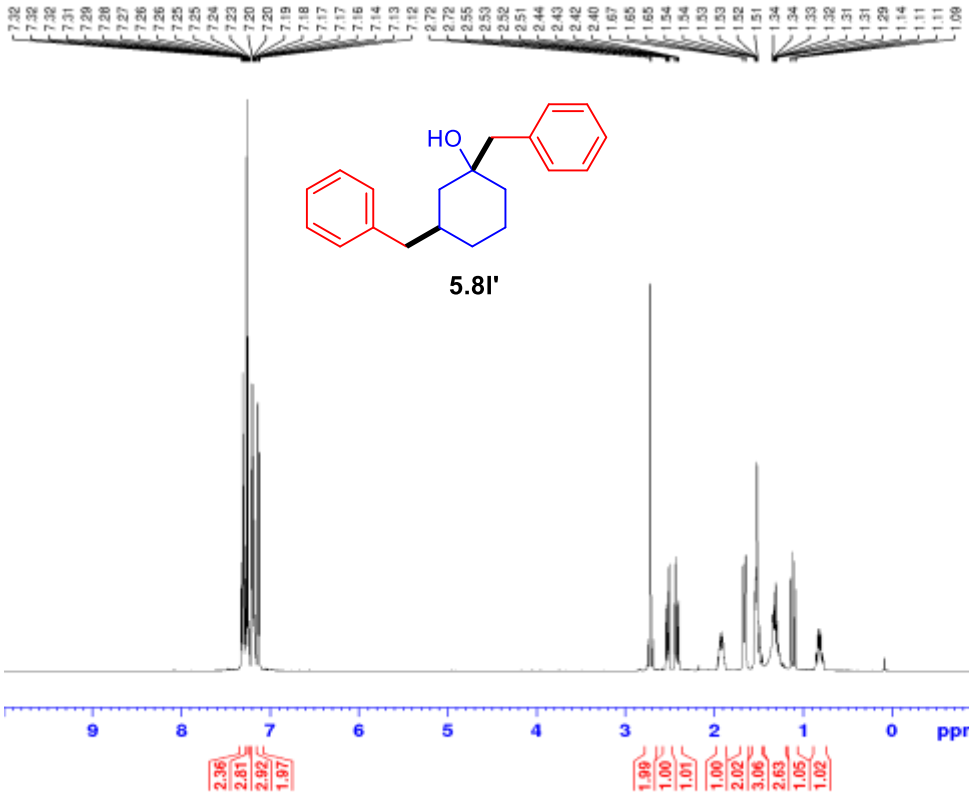
F2 - Processing parameters
SI 65536
SF 500.3000122 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00



Current Data Parameters
NAME DXJ-E2346-PURE
EXPNO 3
PROCNO 1

F2 - Acquisition Parameters
Date_ 20160706
Time 15.48 h
INSTRUM AVIII500HD
PROBHD Z119470_0125 (
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 512
DS 4
SWH 30000.000 Hz
FIDRES 0.915527 Hz
AQ 1.0922667 sec
RG 192.72
DW 16.667 usec
DE 7.48 usec
TE 297.2 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
SFO1 125.8131140 MHz
NUC1 13C
P1 10.00 usec
PLW1 78.00000000 W
SFO2 500.3020012 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 80.00 usec
PLW2 21.00000000 W
PLW12 0.32813001 W
PLW13 0.16504000 W

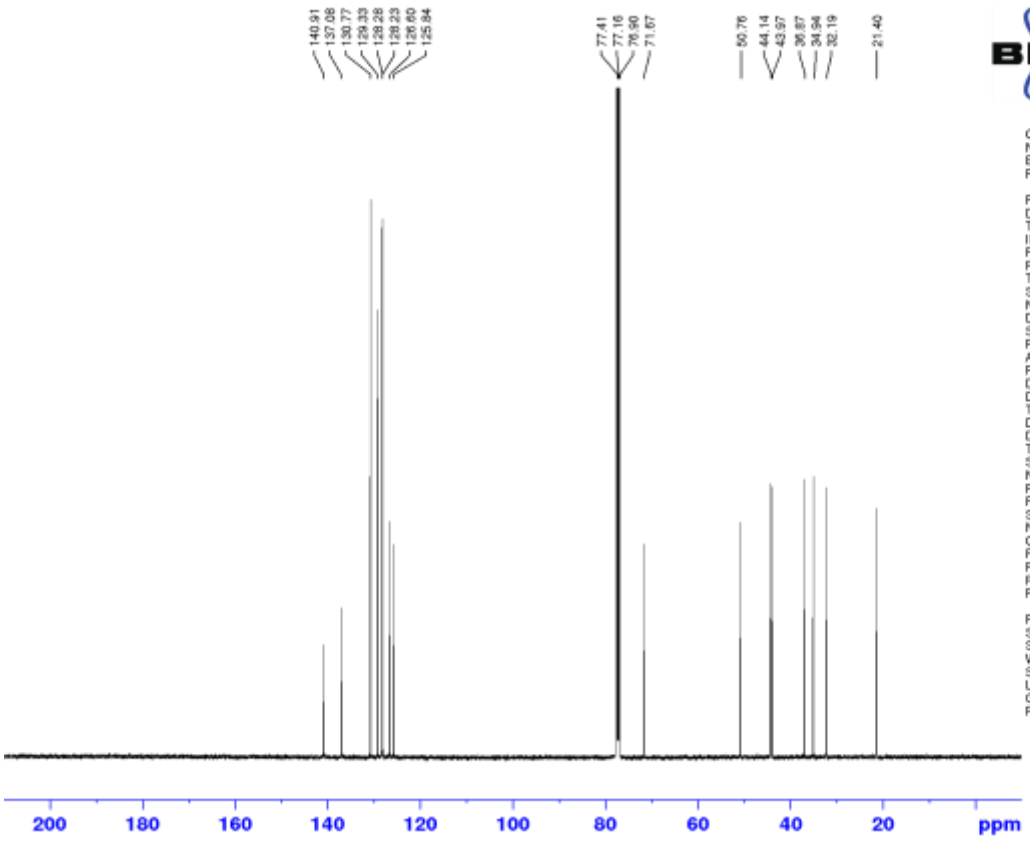
F2 - Processing parameters
SI 32768
SF 125.8005206 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40



Current Data Parameters
NAME DXJ-E2355-PURE
EXPNO 2
PROCNO 1

F2 - Acquisition Parameters
Date_ 20160703
Time 23.59 h
INSTRUM AVIII500HD
PROBHD Z119470_0125 (
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 10000.000 Hz
FIDRES 0.305176 Hz
AQ 3.2767999 sec
RG 106.56
DW 50.000 usec
DE 13.50 usec
TE 297.1 K
D1 1.00000000 sec
TD0 1
SFO1 500.3030896 MHz
NUC1 1H
P1 10.00 usec
PLW1 21.89999962 W

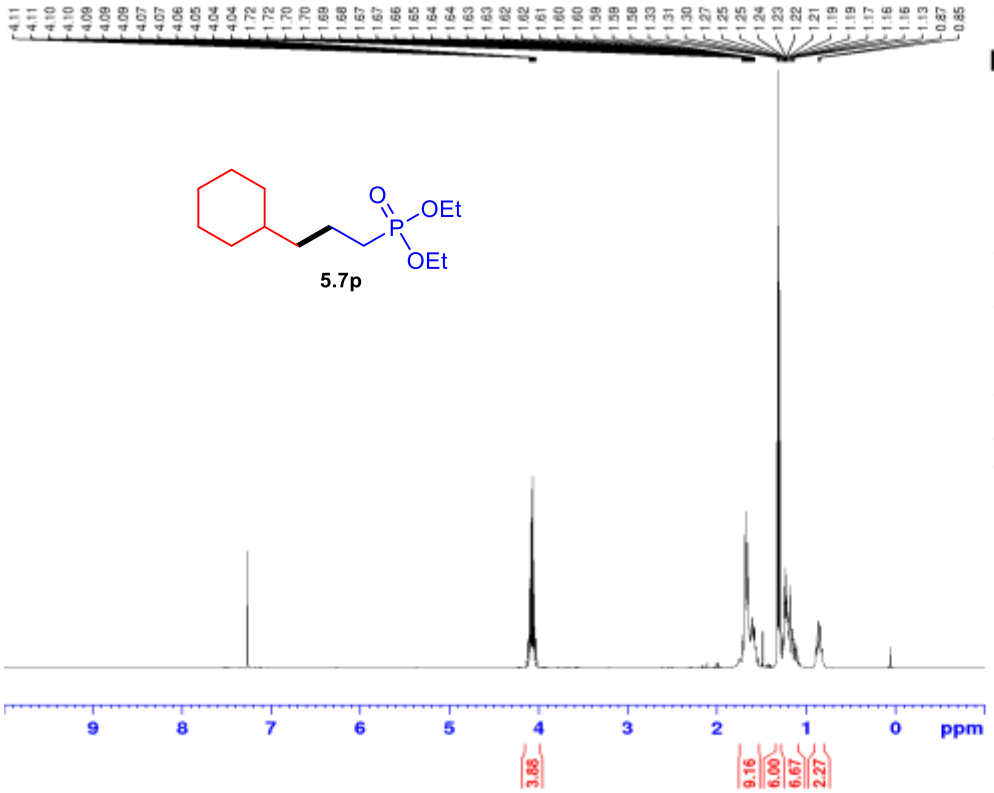
F2 - Processing parameters
SI 65536
SF 500.3000122 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00



Current Data Parameters
NAME DXJ-E2355-PURE
EXPNO 3
PROCNO 1

F2 - Acquisition Parameters
Date_ 20160704
Time 5.58 h
INSTRUM AVIII500HD
PROBHD Z119470_0125 (
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 3500
DS 4
SWH 34965.035 Hz
FIDRES 1.067048 Hz
AQ 0.9371648 sec
RG 192.72
DW 14.300 usec
DE 8.07 usec
TE 297.2 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
SFO1 125.8131140 MHz
NUC1 13C
P1 10.00 usec
PLW1 78.00000000 W
SFO2 500.3020012 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 80.00 usec
PLW2 21.00000000 W
PLW12 0.32813001 W
PLW13 0.16504000 W

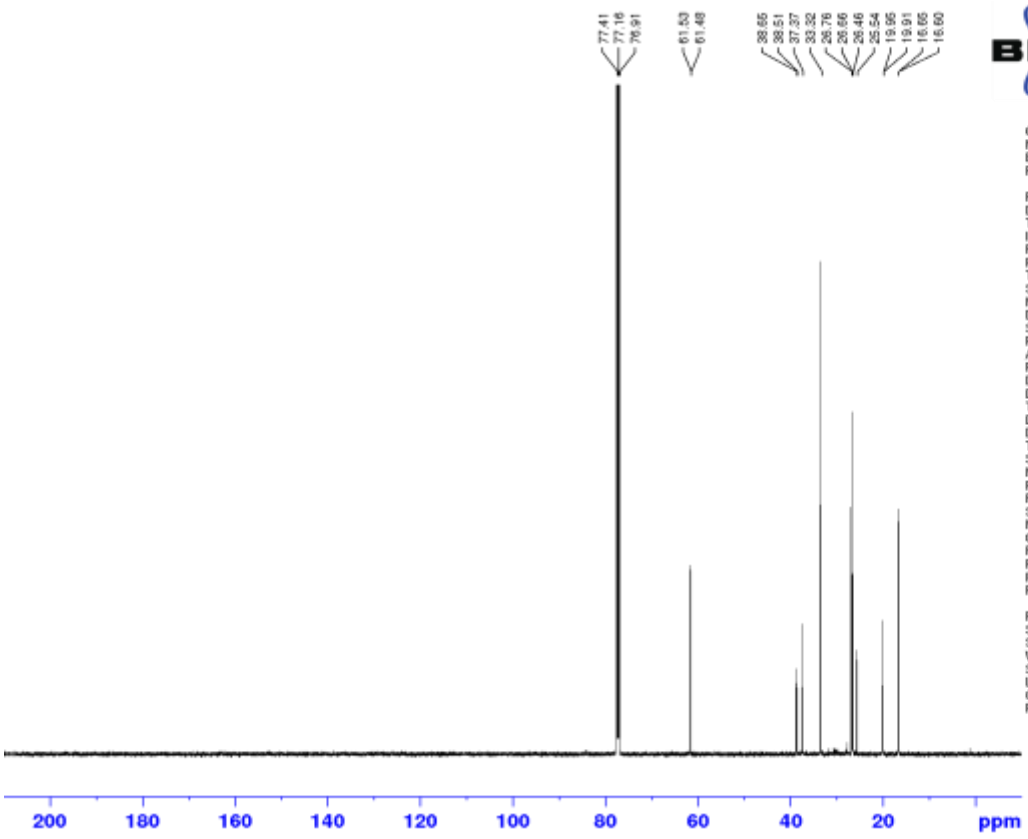
F2 - Processing parameters
SI 32768
SF 125.8005198 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40



Current Data Parameters
NAME DXJ-E2467-PURE
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date_ 20161122
Time 2.42 h
INSTRUM AVIII500HD
PROBHD Z119470_0125 (
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 10000.000 Hz
FIDRES 0.305176 Hz
AQ 3.2767999 sec
RG 106.56
DW 50.000 usec
DE 13.50 usec
TE 297.2 K
D1 1.00000000 sec
TD0 1
SFO1 500.3030896 MHz
NUC1 1H
P1 10.00 usec
PLW1 21.89999962 W

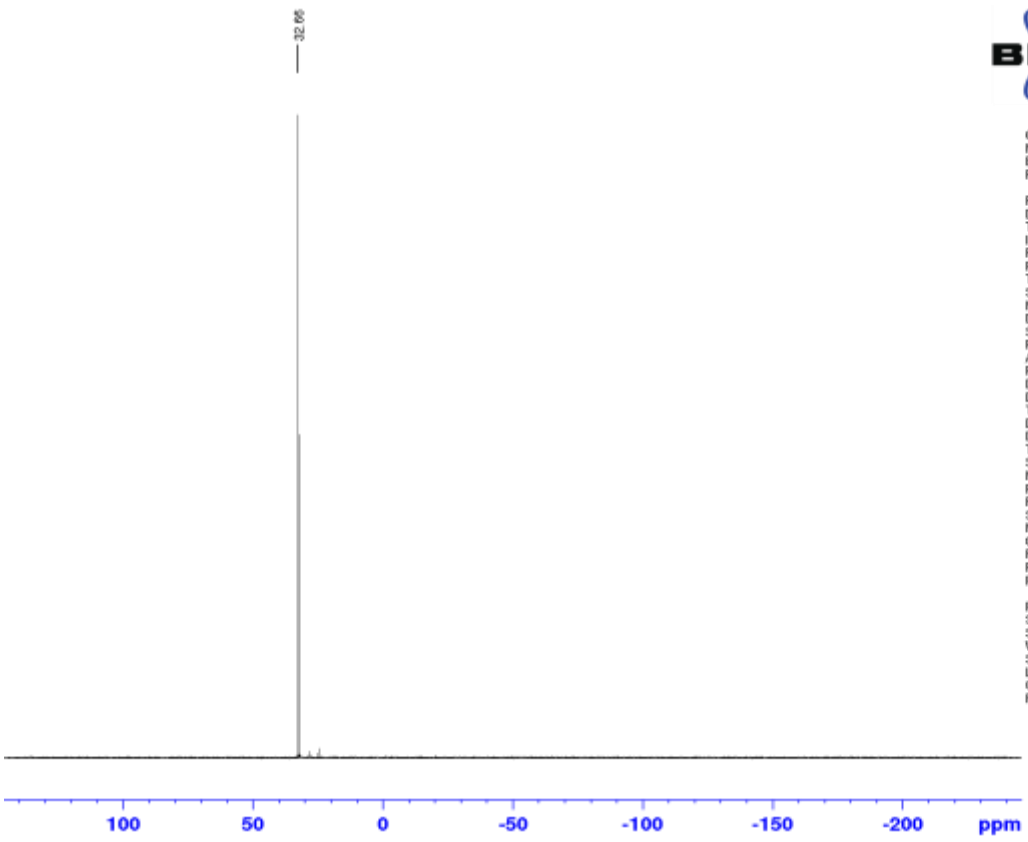
F2 - Processing parameters
SI 65536
SF 500.3000122 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00



Current Data Parameters
NAME DXJ-E2467-PURE
EXPNO 2
PROCNO 1

F2 - Acquisition Parameters
Date_ 20161122
Time 5.21 h
INSTRUM AVIII500HD
PROBHD Z119470_0125 (
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 3000
DS 4
SWH 30000.000 Hz
FIDRES 0.915527 Hz
AQ 1.0922667 sec
RG 192.72
DW 16.667 usec
DE 7.48 usec
TE 297.2 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
SFO1 125.8131140 MHz
NUC1 13C
P1 10.00 usec
PLW1 78.00000000 W
SFO2 500.3020012 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 80.00 usec
PLW2 21.00000000 W
PLW12 0.32813001 W
PLW13 0.16504000 W

F2 - Processing parameters
SI 32768
SF 125.8006187 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40



Current Data Parameters
NAME DXJ-E2467-PURE
EXPNO 3
PROCNO 1

F2 - Acquisition Parameters
Date_ 20161122
Time 9.10 h
INSTRUM AVIII500HD
PROBHD Z119470_0125 (
PULPROG zgig30
TD 131072
SOLVENT CDCl3
NS 32
DS 4
SWH 79365.078 Hz
FIDRES 1.211015 Hz
AQ 0.8257536 sec
RG 192.72
DW 6.300 usec
DE 7.12 usec
TE 297.2 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
SFO1 202.5150255 MHz
NUC1 31P
P1 14.00 usec
PLW1 44.70000076 W
SFO2 500.3015854 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 80.00 usec
PLW2 21.00000000 W
PLW12 0.32813001 W

F2 - Processing parameters
SI 262144
SF 202.5251522 MHz
WDW EM
SSB 0
LB 1.50 Hz
GB 0
PC 1.40