Toward Alternative Routes to Access Functionalized Arenes

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Abstract

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This thesis describes the development of novel methods and processes to efficiently access complex molecules and advanced materials.

After a brief overview of the various synthetic strategies available to chemists for the construction of highly decorated aromatic rings in chapter 1, the "borrowing hydrogen" synthetic concept for the direct synthesis of functionalized arenes from phenols is presented in chapter 2. As a first step towards this goal; a direct, versatile and original approach for the synthesis of functionalized aryl ethers is introduced. This reaction, catalyzed by copper complexes, allows the oxidative condensation of aliphatic alcohols and 2-cyclohexenone derivatives to generate *in situ* the aromatic ring through aerobic aromatization. In addition, the amount of copper catalyst can be reduced and molecular oxygen used as the terminal oxidant.

Next, further exploration of the dehydrogenative aromatization of cyclohexenone derivatives to access decorated arenes is presented in chapter 3. The development of a new palladium catalyst is introduced for the atom-economic and waste-minimized selective arylation of various secondary amines from non-aromatic precursors.

In chapter 4, the recent advances in the field of dehydrogenative aromatization and its application to the synthesis of heterocycles is discussed along with the successful application of the "borrowing hydrogen" strategy for formal direct cross coupling of phenols with amines.

Finally, chapter 5 presents preliminary results on the exploration of supercritical carbon dioxide as medium for the synthesis of metal organic frameworks. In particular, the synthesis of porous and non-porous zeolitic imidazolate frameworks from metal oxide is introduced.

Résumé

Cette thèse décrit le développement de nouvelles méthodes de synthèse de molécules complexes et de matériaux avancés.

Un bref récapitulatif des diverses stratégies de synthèse à la disposition des chimistes pour la construction de cycles aromatiques hautement décorés est présenté dans le chapitre 1. Le concept de synthèse de « l'hydrogène chapardé » pour la synthèse directe d'arènes fonctionnalisées à partir de phénols est introduit dans le chapitre 2. La première étape dans la réalisation de cet objectif a mené au développement d'une nouvelle approche pour la synthèse d'éther aromatique. Cette réaction catalysée par des complexes de cuivre, permet la condensation oxydante d'alcools aliphatiques avec des dérives de la cyclohexenone pour la génération *in situ* du cycle aromatique par aromatisation aérobie. De surcroit, la quantité du catalyseur de cuivre peut être réduit et l'oxygène moléculaire utilisé comme oxydant terminal.

Le chapitre 3 présente de plus amples explorations de la déshydrogénation aromatique des dérivés de la cyclohexenones pour accéder aux arènes fonctionnalisés. Le développement d'un nouveau catalyseur au palladium est décrit pour l'arylation sélective de diverses amines secondaires à partir de précurseurs non-aromatiques.

Dans le chapitre 4, les récents développements dans le domaine de la déshydrogénation aromatique et ses applications à la synthèse d'hétérocylces seront présentés ainsi que la récente application du concept de « l'hydrogène chapardé » pour le couplage direct entre phénols et amines.

Enfin, le chapitre 5 présente les résultats préliminaires dans l'exploration du dioxyde de carbone supercritique comme milieu réactionnel pour la synthèse de squelettes organométalliques poreux cristallins. Plus particulièrement, de la synthèse de squelettes d'imidazolate zéolitique à partir d'oxydes métalliques.

"Le savant n'est pas l'homme qui fournit les vraies réponses, c'est celui qui pose les vraies questions."

"The scientist is not a person who gives the right answers, he is one who asks the right questions."

- Claude Lévi-Strauss -

For my parents

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Contributions and Publications

During my doctoral research, the following publications (consisting of literature research and original research) have resulted from my dissertation, and are therefore the basis of, or are discussed within this thesis:

1) "Catalytic Synthesis of Aromatic Ethers from Non-Aromatic Precursors" Dr. Marc-Olivier Simon, **Simon A. Girard**, Prof. Dr. Chao-Jun Li, *Angewandte Chemie International Edition*, **2012**, *51*, 30, *7537-7540*.
2) "Pd-Catalysed Synthesis of Aryl Amines via Oxidative Aromatization of Cyclic Ketones and Amines with Molecular Oxygen" **Simon A. Girard**, Xiong Hu, Thomas Knauber, Feng Zhou, Marc-Olivier Simon, Guo-Jun Deng, Chao-Jun Li, *Organic Letters,* **2012***, 14,* 21*, 5606–5609.*
3) "Catalytic Dehydrogenative Aromatization: an Alternative Route to Functionalized Arenes" **Simon A. Girard**, Huawen Huang, Feng Zhou, Guo-Jun Deng and Chao-Jun Li, *Organic Chemistry Frontiers*, **2015**, 2, *279-287*.
4) "Formal Direct Cross-Coupling of Phenols with Amines" Zhengwang Chen, Huiying Zeng, **Simon A. Girard**, Feng Wang, Ning Chen and Chao-Jun Li, *Angewandte Chemie International Edition,* **2015**, *54*, 48, *14487–14491*.

Chapter 5 of this thesis concerns work that is intended for publication at a future date, and is a collaborative project between myself (Simon A. Girard), Dr. Cristina Mottillo, Christopher Nickels, Prof. Tomislav Friščić and Prof. Chao-Jun Li. The early stage of this research led to the following patent:

5) "Method for the preparation of metal-organic compounds" Friščić, T., **Girard, S.A.,** Mottillo, C., Li, C.-J. 2015. US Patent Pending WIPO No.PCT/CA2016/050172.

Additionally, the following articles and book chapters were published during my doctoral work, but were not included in my thesis:

6) "The Cross-Dehydrogenative Coupling of C sp^3-H Bonds: A Versatile Strategy for C-C Bond Formations" **Simon A. Girard**, Thomas Knauber, Chao-Jun Li, *Angewandte Chemie International Edition,* **2014**, *53*, 1, *74–100*.
7) "The Evolution of the Concept of Cross-Dehydrogenative-Coupling Reactions**" Girard, S. A.;** Knauber, T. and Li, C.-J. (**2015**). In: LI, C.-J. ed. *From C-H to C-C Bonds: Cross-Dehydrogenative-Coupling.* Cambridge: Royal Society of Chemistry, pp 1-32.
8) "Gold-catalyzed tandem reactions of amide–aldehyde–alkyne coupling and cyclization-synthesis of 2,4,5-trisubstituted oxazoles" Pierre Querard, **Simon A. Girard**, Nick Uhlig, Chao-Jun Li, *Chemical Science*, **2015**, 6, *7332-7335*.

The final publication comprised some of the PhD work of Pierre Querard, and I contributed in the design and the optimization of reaction conditions.

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List of Schemes

List of Abbreviations

aq.	Aqueous
AMLA	Ambiphilic metal ligand activation
B_2pin_2	Bis(pinacolato)diborane
BTX	Benzene, Toluene, Xylene
C-C	Carbon-carbon
Cbz	Benzyloxy carbonyl
CDC	Cross-dehydrogenative coupling
CIPE	Complex-induced proximity effect
C-H	Carbon-hydrogen
Cl	Chloride
CMD	Concerted metalation-deprotonation
C-N	Carbon-nitrogen
C-O	Carbon-oxygen
CO_2	Carbon dioxide
COD	Crystallography open database
CSD	Cambridge structural database
Cu	Copper
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DG	Directing group
DME	Dimethyl ether
DMG	Directing metalation group
DMSO	Dimethyl sulfoxide
DMAP	4-Dimethylaminopyridine
DoM	Directed *ortho*-metalation
dppe	1,2-Bis(diphenylphosphino)ethane
dppf	1,1'-Bis(diphenylphosphino)ferrocene
dppp	1,3-Bis(diphenylphosphino)propane
DreM	Directed remote metalation
EA	Electrophilic activation
EDG	Electron-donating group
equiv.	Equivalents
ESI	Electrospray ionisation
ET	Electron transfer
EWG	Electron-withdrawing group
GC	Gas chromatography
HDDA	Hexadehydro-Diels-Alder
HMeIm	2-methylimidazole
Him	Imidazole
HRMS	High-resolution mass spectrometry
IES	Internal electrophilic substitution
ILAG	Ion- and liquid-assisted grinding
^{i}Pr	iso-Propyl ($CH(CH_3)_2$)
KEM	Kinetically enhanced metalation

LAG	Liquid-assisted grinding
L_n	Ligand
LUMO	Lowest unoccupied molecular orbital
MAF	Metal azolate framework
M^n	Metal at oxidation state n
MOF	Metal organic framework
MS	Molecular sieve
MW	Microwave radiation
NBS	N-Bromosuccinimide
NMP	N-Methyl-2-pyrrolidone
NMR	Nuclear magnetic resonance
Nu^-	Nucleophile
NHPI	*N*-hydroxyphthalimide
p	Para
Pd	Palladium
Ph	Phenyl
PINO	Phthalimido-*N*-oxyl
PLC	Prelithiation complex
PXRD	Powder X-ray diffraction
RCM	Ring closing metathesis
rt	Room temperature
SBM	σ-Bond metathesis
SBU	Secondary building units”
σ-CAM	σ-Complex-assisted metathesis
$scCO_2$	Supercritical carbon dioxide
S_EAr	Electrophilic aromatic substitution
SOD	Sodalite
S_NAr	Nucleophilic aromatic substitution
$S_{RN}1$	Substitution, radical-nucleophilic, unimolecular
TFA	Trifluoroacetic acid
TLC	Thin-layer chromatography
TsOH	p-Toluenesulfonic acid
[O]	Oxidant, or oxidizing condition
OA	Oxidative addition
OAc	Acetoxy (CH_3CO_2) or acetate ($CH_3CO_2^-$)
OATS	Oxidatively added transition state
OHM	Oxidative hydrogen migration
OTf	Triflate, trifluoromethanesulfonate ($^-OSO_2CF_3$)
[TM]	Transition Metal
X	Halide
ZIF	Zeolitic imidazolate frameworks

Introduction

This dissertation will introduce some of the most popular strategies employed for the synthesis of functionalized arenes and present a brief overview of the most important raw materials and intermediates used by the chemical industry. Accordingly, the main basic building blocks employed to access molecules of interest are currently derivatives of fossil raw materials.

Chapter 2 will subsequently present a synthetic concept, which in term would circumvent the requirement for the use of finite fossil materials as a source of building blocks for the synthesis of functionalized arenes. By applying the borrowing hydrogen strategy to the phenolic moiety, a wide variety of decorated aromatic rings could potentially be accessed from renewable sources. As a first step toward the development of such methodology, two different copper-catalyzed systems were investigated for the synthesis of aryl-alkyl ethers from cyclohexenone derivatives and aliphatic alcohols.

Chapter 3 will present the extension of such methodology to nitrogen-based nucleophile, allowing the synthesis of arly-amines from a broad scope of secondary amines and cyclohexenones using a palladium catalyst.

Chapter 4 will present the recent advances in the extension of the nucleophilic addition/dehydrogenative aromatization process between cyclohexanone derivatives and oxygen, nitrogen, sulfur and carbon-based nucleophiles to access decorated aromatic rings. In addition, this methodology has been successfully applied to the synthesis of various heterocycles. Furthermore, based on these findings, the borrowing hydrogen strategy has been effectively implemented to the direct coupling of phenols and amines using heterogeneous catalysis.

Our search for more efficient heterogeneous systems to access functionalized arenes led us to investigate metal-organic frameworks (MOFs) as a potential platform for the design of new

systems. Chapter 5, will present preliminary results on the development of a new medium for the synthesis of MOFs, more specifically of zeolitic imidazolate frameworks (ZIFs). The use of supercritical carbon dioxide ($scCO_2$) enables the large-scale manufacture of ZIFs from non-toxic metal oxides and imidazoles under relatively mild conditions.

Chapter 1 – Functionalization of Arenes

This Chapter introduces the key milestones and salient features of the different strategies currently available to synthetic chemists to access functionalized arenes. In addition, some industrial considerations will be discussed and an overview of the main raw materials and key intermediates employed by the chemical industry is presented, highlighting the current role of fossil raw materials as a source of building block for the synthesis of molecules of interest.

1.1 Introduction

Arenes are an important class of molecules present in our environment from both natural and synthetic occurrence. In nature, arenes are involved in a wide range of functions; from supporting life, providing the core structure to trees as a biopolymer (lignin), to the control of numerous biological processes, including our feelings as neurotransmitter (such as dopamine). Synthetically produced, arenes have found extensive applications, stretching from material science and energy-harvesting technologies to drug discovery and crop-protection.

Arenes are so essential to our society that it pushes mankind to incredible achievements: drilling for oil in the middle of the arctic ocean to access the starting materials needed for the synthesis of arenes, digging the earth to unconceivable scale to extract coal and the rare metals required for their functionalization.

However, the structure and functionality of arenes are very diverse, with a small change in their composition having drastic repercussion on their behaviors and applications. As a result,

synthetic chemists have continuously developed new processes to access highly decorated aromatic rings.

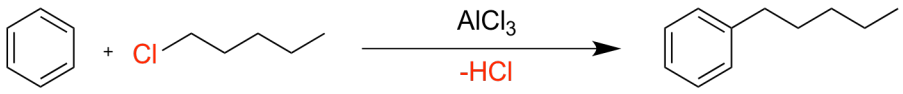
1.2 Arene functionalization: an overview

The following sections intend to give an overview of the most popular strategies available to access functionalized arenes and do not constitute an exhaustive review of arylation reactions.

1.2.1 Electrophilic aromatic substitution (S_EAr)

The early stage of arene functionalization employed substitution strategies to access molecules with new functionality, either using nucleophiles (S_NAr) or electrophiles (S_EAr) to substitute a functional group from the arene substrate.

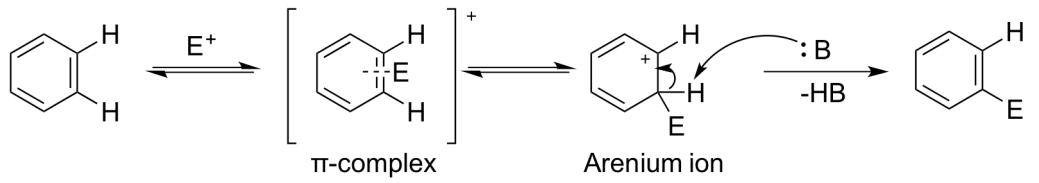
In 1877, Charles Friedel and James Crafts observed the first example of the Friedel-Crafts alkylation in the formation of amylbenzene from amyl chloride and benzene in presence of aluminum chloride ($AlCl_3$)(Scheme 1.2-1).[1–3]



Scheme 1.2-1 Amylbenzene synthesis as reported by Friedel and Crafts in 1877

Since then, the electrophilic aromatic substitution (S_EAr) reaction has one of the most thoroughly studied reaction mechanism. It is possible to summarize the different types of S_EAr in an overall mechanism (Scheme 1.2-2). The incoming electrophile interacts with the π-system from the arene to form an encounter complex or π-complex. The π-complex can then form the

arenium ion. The final step consists of the rapid abstraction of the *ipso* proton by a base to regenerate the aromatic π-system.

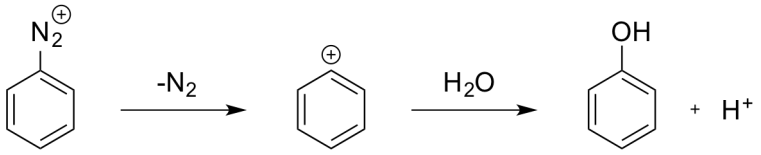


Scheme 1.2-2 Proposed general mechanism for S_EAr reaction

In most cases, the arenium ion represents the highest energy intermediate in the S_EAr process and resembles the transition state that preceded it. Electron-donating groups (EDGs) capable of stabilizing the carbocation will also stabilize the transition state and increase the relative reaction rate. Since most S_EAr reactions are kinetically controlled, the nature of the substituents present on the aromatic ring strongly influence the reactivity (activation or deactivation) and regioselectivity of the reaction.[4] This transformation can be challenging in the case of electron-deficient arenes. In addition, harsh reaction conditions caused by the use of stoichiometric or super-stoichiometric amounts of a Lewis or Brønsted acid usually required to initiate the reaction, result in a vast amount of by-products wastes.[5]

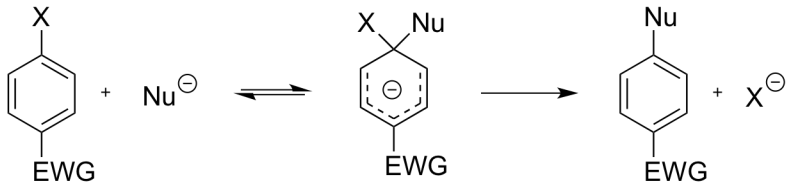
1.2.2 Nucleophilic aromatic substitution (S_NAr)

Until the 1950s, nucleophilic aromatic substitution reactions of electron-rich arenes were believed to only be possible through either the S_N1 and the unimolecular S_NAr processes.[6] The S_N1 mechanism being mostly observed with diazonium salts, and in rare occasions with aryl halides and sulfonates; only when both *ortho* positions contain bulky groups (*tert*-butyl or SiR_3)(Scheme 1.2-3).[7]



Scheme 1.2-3 Phenol synthesis from arenediazonium salts through S_N1 process

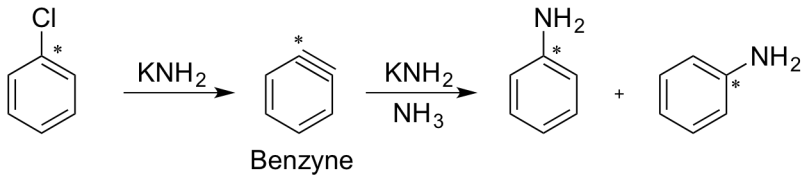
The S_NAr pathway involves an attack of an aromatic ring with an anionic nucleophile followed by elimination of the sacrificial nucleofuge. At least one strong electron-withdrawing group (EWG) on the ring is required, preferentially in position *ortho* and *para,* to dissipate the negative charge either inductively or by resonance (Scheme 1.2-4). Unlike in S_EAr where several hydrogens could serve as leaving group, the low stability of the potential leaving hydride ion, makes an attack on arene carbon bearing a hydrogen unlikely. As a result, the previously mentioned mechanisms require the presence on the aromatic ring of a sacrificial nucleofuge, usually a halogen, nitro group, sulfonates, alkoxy or phenoxy group.[8]



Scheme 1.2-4 Proposed general mechanism for S_NAr reaction

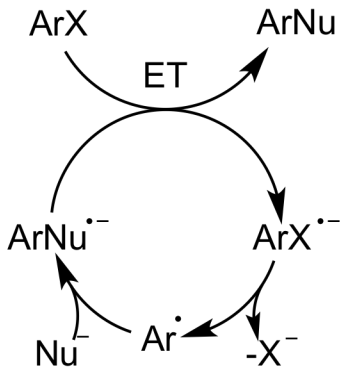
In the 1950s, Roberts *et al.* established the possibility for another mechanism pathway to take place. This pathway undergoes an elimination-addition process through a benzyne intermediate. Transforming ^{14}C labeled chlorobenzene into aniline where the ^{14}C now resides at the 1- and 2- position in a nearly 1:1 ratio corroborated a benzyne intermediate (Scheme 1.2-5).[9,10] This discovery opened a whole new area of chemistry, allowing formal nucleophilic

substitution in systems not activated by strong electron-withdrawing groups (EWGs). (See section 2.1.3)



Scheme 1.2-5 ^{14}C Labeled experiment by Roberts *et al*

In 1962, Russell *at al.* showed that aromatic nitro compounds can form radical anions in harsh alkaline solutions.[11] This was the first step toward the development of the *substitution, radical-nucleophilic, unimolecular* ($S_{RN}1$) reaction for the functionalization of arenes.[12,13] Most reactions involve a chain process, initiated by the formation of the radical anion of the aromatic substrate $ArX^{\bullet-}$ through electron transfer (ET) (Scheme 1.2-6). The following fragmentation of the radical anion $ArX^{\bullet-}$ affords the radical arene $Ar^{\bullet}$ and the X^- ion. These can react with a nucleophile Nu^- to form the radical anion $ArNu^{\bullet-}$. Another ET to the substrate yields the functionalized product ArNu and the radical anion $ArX^{\bullet-}$ which propagates the cycle. In most cases, under thermal conditions, the nucleophile serves as the electron donor to initiate the reaction. However, different methodologies are also available to induce the ET required and includes: photochemical reaction, electrochemical initiation, inorganic salts, among others.[14–16]



Scheme 1.2-6 General mechanism for $S_{RN}1$ reaction

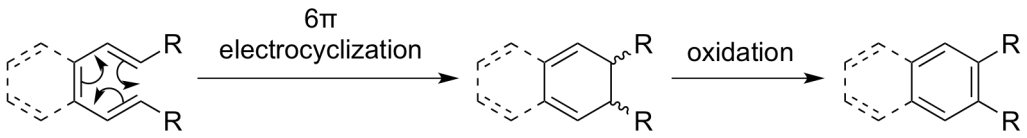
The $S_{RN}1$ reaction can involve a wide array of nucleophiles such as carbanion and heteroatoms. Interestingly, Sn derivatives (especially R_3Sn) are also suitable nucleophiles and can be involved in further reactions such as the Stille coupling. This process has the advantage of being compatible with a wide variety of substituents such as alky groups, OR, CF_3, CO_2R, NH_2, SO_2R, CN, COR, $CONH_2$ and has many synthetic applications.[16]

1.2.3 Pericyclic reactions and aromatic rearrangements

Pericyclic reactions represent an important class of processes involving π-systems and allow access to complex structures from simple and easily available starting materials. In addition, their concerted nature gives pericyclic reactions fine stereochemical control of the final product. There are five main types of pericyclic reactions: electrocyclic ring closure, cycloaddition, sigmatropic rearrangement, cheletropic conversion, and group transfer reactions.[17] However, only electrocyclic ring closure and cycloaddition reactions lead to the formation of cyclic compounds that can be further transformed into a fully aromatic product by a variety of strategies. Pericyclic reactions circumvent regio-selectivity issues inherent to arene functionalization by forming the arene backbone from pre-functionalized starting materials.

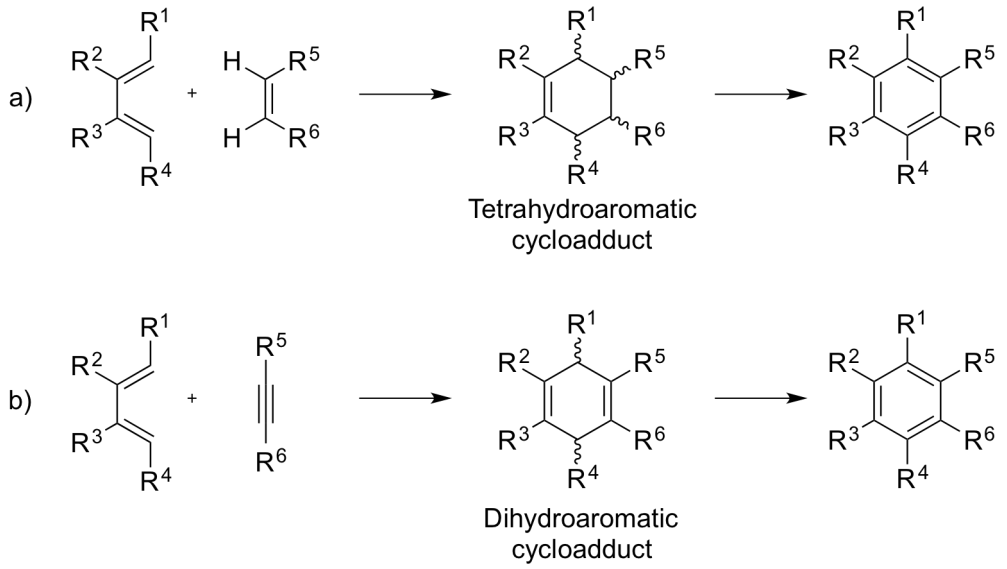
Because those processes follow the Woodward-Hoffmann rules,[18,19] it is possible to have high control on the final position of the functionality in the product by carefully choosing the precursors.

The 6π-electron cyclization of a 1,3,5-hexatriene or 1,2-divinylarene derivatives directly from functionalized cyclic dehydroaromatic compounds. These can be further oxidized into corresponding aromatic products (Scheme 1.2-7). Following Woodward-Hoffmann rules, the 6π electrocyclization can either occur in a disrotatory manner, under thermal conditions, or in a conrotatory manner, under photo-irradiation conditions. However, the synthesis of aromatic compounds eliminates the stereochemistry of the intermediate. This process is of particular interest in combination with the Heck coupling for the construction of complex polycyclic structures.[20]



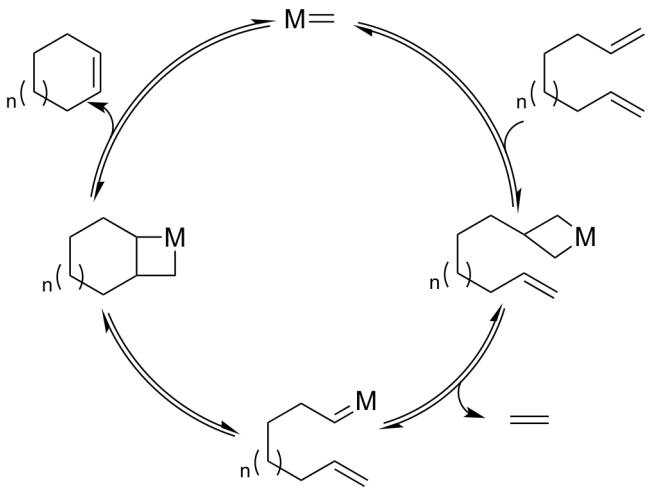
Scheme 1.2-7 6π Electrocyclization/oxidative aromatization synthesis of arene

The [4+2] cycloaddition reaction will form either tetrahydroaromatic or dihydroaromatic derivatives, depending on whether the dieneophile is an olefin (a) or alkyne (b) (Scheme 1.2-8). Dehydrogenation of the tetra- or dihydroaromatic cycloadduct affords the aromatic product.



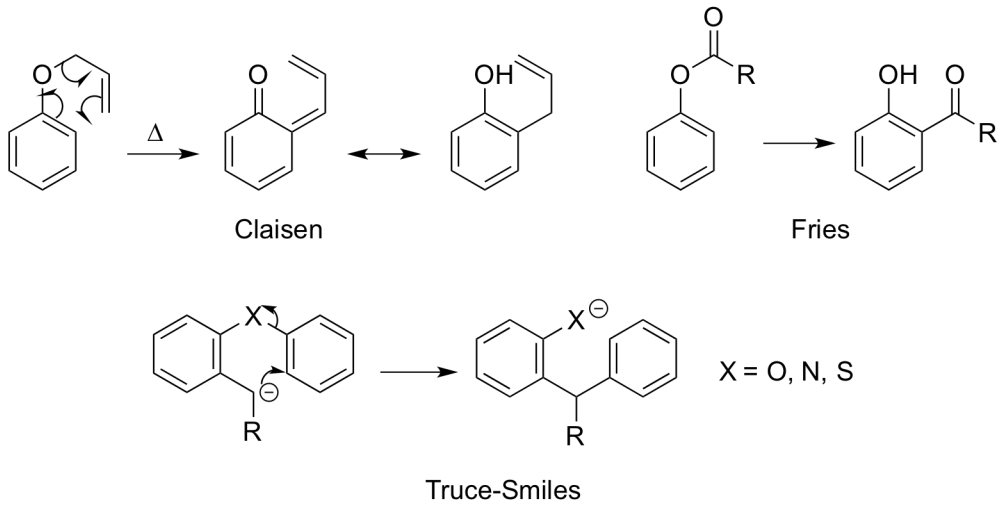
Scheme 1.2-8 General strategy for the formation of arenes with [4+2] cycloaddition

The ring closing metathesis (RCM) reaction is also a very efficient way to directly assemble functionalized aromatic ring backbone from dienes. A transition metal catalyst undergoes a series of metal-mediated [2+2] cycloadditions/cycloreversions involving metallacyclobutane intermediates to produce the cyclic product (Scheme 1.2-9). The ethylene gas often exhausted during the process is one of the driving forces of the reaction. In addition, the product of the reaction can also be involved in further transformation like the Diels-Alder reaction.



Scheme 1.2-9 Ring-closing metathesis (RCM) reaction cycle

Aromatic rearrangements in which the aromatic nucleus ends up functionalized are a powerful and atom economical way to access complexity in molecules. Examples of these are the Truce-Smiles, the Fries or the Claisen rearrangements (Scheme 1.2-10).[21] Under thermal conditions, many of these rearrangements take place under harsh reaction settings and require the protection of sensitive functional groups. However, those rearrangements are also accessible under photochemical conditions. The extra energy brought to the system can generally allow the transformations to occur under milder conditions.



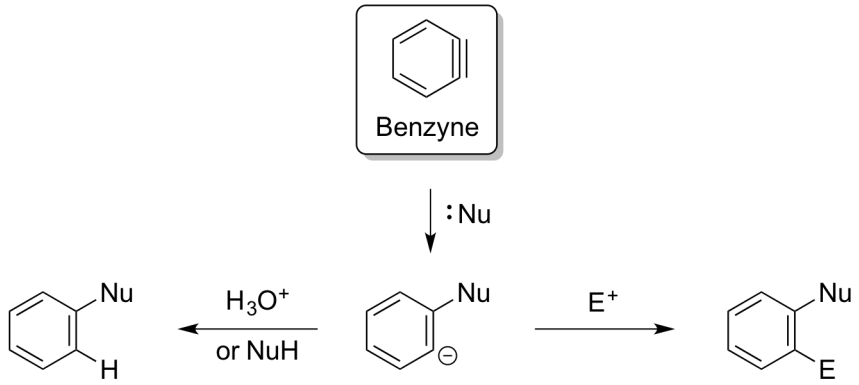
Scheme 1.2-10 Selected aromatic rearrangements

1.2.4 Aryne chemistry

Numerous syntheses of natural compounds have been successful by using the benzyne intermediate to access complex molecules.[22] The formal C-C triple bond of arynes is notably weaker compared to unstrained alkynes. This is reflected in experimental data such as its respective stretching vibration: 1846 cm^{-1} for the benzyne vs 2150 cm^{-1} for typical alkynes,[23] or the length of the C-C bond (1.24 Å).[24]

The aryne intermediate offers an alternative to nucleophilic aromatic substitution strategy, which generally required the activation of the arene substrate by strong electron-withdrawing substituents such as nitro groups. Their atypical triple bond makes arynes prone to nucleophilic attack by a variety of nucleophiles. However, the addition reaction can occur at both the C1 and C2 position leading to the formation of regioisomers. Under nucleophilic attack the

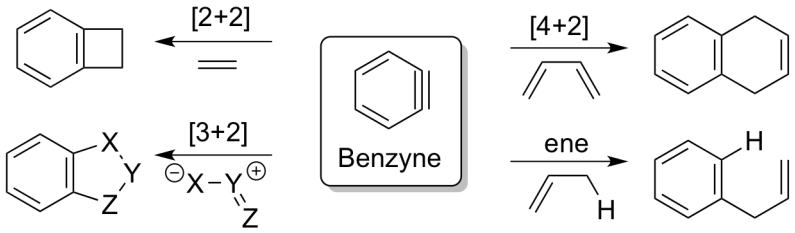
transition state is distorted to accommodate the developing negative charge, resulting in the attack being favored at the site that minimizes charge distortion.[25] As a result, the transformation of unsymmetrically substituted arynes is controlled by the electronic and steric proprieties of the substituents. A general scheme summarizing the reactivity of arynes toward nucleophilic attack is presented in Scheme 1.2-11. After the attack of the anionic nucleophile to the triple bond, the resulting aryl anion is trapped by external or internal electrophiles. Trapping of the aryl anion by a proton, or in the case of nucleophile bearing an acidic hydrogen (i.e. alcohol or amine), will yield a monosubstituted arene (Scheme 1.2-11, left). If the nucleophilic addition is followed by intermolecular quenching by an external electrophile, a disubstituted arene will be produced (Scheme 1.2-11, right).



Scheme 1.2-11 Benzyne reactivity toward nucleophilic attack

In addition, the strain imposed on the triple bond by the ring distorts the unhybridized p-orbital, resulting in reduced orbital overlap and lowering the energy of its lowest unoccupied molecular orbital (LUMO). The low-lying LUMO makes arynes a partner of choice for pericyclic processes and has been involved in [4+2],[26,27] [3+2],[28] [2+2][29,30] and ene[31,32]

reactions (Scheme 1.2-12). Arynes can also be involved in transition metal-catalyzed reactions as cyclic alkyne to access complex structures such as: cyclotrimerization,[33] cocyclization with alkynes[34] or alkenes,[35] and carbopalladation with Pd-complexes.[36,37]



Scheme 1.2-12 Pericyclic reactions with benzyne

In the last 60 years, benzyne chemistry has distinguished itself as a highly flexible alternative for arylation.[38,39] Its progress has been hindered by lack of efficient and convenient methods to generate benzynes intermediates. Most of the strategies developed involve a formal elimination under harsh conditions where the aryne precursor loses one or more substituents to form benzyne, drastically impacting the atom economy of the transformation.[40–43] Nevertheless, the number of available methods for easy generation of benzynes under softer conditions is continually increasing. The work of Hoye *et al*, illustrates this effort, introducing a highly atom-efficient strategy for the generation of arynes based on the intramolecular "hexadehydro-Diels-Alder" (HDDA) reaction of triynes.[44]

1.2.5 Light-mediated processes

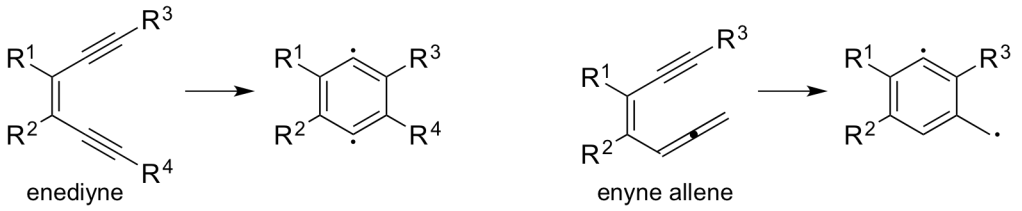
Photochemical processes involve inducing chemical reactions by exciting molecules with certain wavelengths of light and are employed in a wide range of transformations.[45,46] Absorption of a photon causes changes to the electronic configuration of the molecule which

accesses new reactivities and products otherwise difficult to obtain. The difference in spin multiplicity of the photoexcited states often results in an umpolung in reactivity, making photochemical reactions complementary with ground state reactions. A perfect illustration of this are cycloaddition and electrocyclization reactions, where orbital symmetry[18,19] predict complementary stereochemistry under thermal or photochemical conditions. Those reactions have been frequently applied to the synthesis of complex polycyclic molecules otherwise difficult to access,[47–49] such as the construction of helicenes.[50]

From a historical perspective, photochemical transformations have mostly involved the reactivity of photon-induced transition of π systems from their ground state to their excited states (π,π*). However, it is also possible to use substoichiometric amount of organic photosensitive molecules, such as eosin Y or benzophenone derivatives, to perform energy or electron transfer to a reaction partner. Similarly, using the photoredox properties of transition metal complexes to access highly reactive radical intermediates by single electron transfer has recently been the focus of intensive research and allow a wide range of arene-carbon and arene-heteroatom bonds transformations.[51] In addition, the excitation of the reagent by absorption of a photon promotes the formation of a reactive intermediate capable of undergoing transformations inaccessible to its ground state, which often circumvents the need for additional activation reagent such as acids, bases or metals, allowing transformation to take place under mild conditions and reducing the generation of waste.

Cycloaromatization reactions are interesting because of their capacity to directly provide arene compounds. Here, acyclic conjugated reactants, enediyne (Bergman reaction)[52] or enyne allene (Myers-Saito reaction), cyclize and simultaneously undergo aromatization, yielding an arene with two unstable radical centers which can be involved in further reactions (Scheme

1.2-13).[53] Under photo irradiation conditions the reaction can take place under relatively mild conditions in comparison to the high temperatures required by its thermal counterpart to overcome the high activation energy barrier of the cyclization. Varying the electronic nature of the substituents on the enediynes can stabilize the transition state and accelerate the reaction.



Scheme 1.2-13 Cycloaromatization reactions

Electronic excitation due to photon absorption changes the redox potential of molecules and facilitate electron transfer processes. This efficiently accesses highly reactive radical ion intermediates which can be synthetically exploited.[54] Photochemical activation has been intensively employed to facilitate the electron transfer involved of $S_{RN}1$ nucleophilic aromatic substitution.[16][55]

1.2.6 Directed metalation

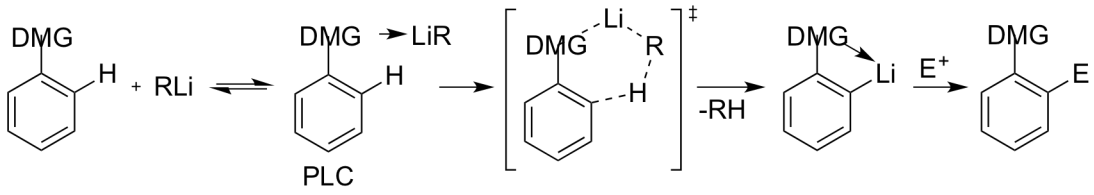
The term "metalation" was proposed by Gilman in 1934 for "reactions involving replacement of hydrogen by metal to give a true organometallic compound".[56] Organometallic compounds allow the direct functionalization of unactivated aromatic ring with a wide range of electrophiles.[57] In particular, Organolithiums, lithium amides and superbases have become powerful methods for regioselective functionalization of arenes.[58,59]

To control the position of the metalation, it is possible to employ the assistance of functional groups to guide the metalation process, named directing metalation group (DMG), resulting in *ortho* functionalization. A DMG is ideally a good coordination site and a poor electrophile to prevent nucleophilic attack to the substrate. Various functional groups are suitable DMG:

- Tertiary amide ($CONEt_2$),
- Carbamate ($OCONEt_2$),
- Secondary amides (CONHR),
- Carboxylic acids (CO_2H),
- Methylalcohols (CH_2OH),
- Secondary thioamides (CSNHR),
- Secondary amines (NHR),
- carbamates (NCO_2H),
- Alcohols (OH),
- Thiols (SH),

The directed *ortho*-metalation (DoM) mechanism is influenced by the nature of the substituents and the DMG present on the arene. In the case of DMGs bearing Lewis basic heteroatoms, generally O and N, the reaction proceeds via a *complex-induced proximity effect* (CIPE) process (Scheme 1.2-14).[60,61] The lithium of the organolithium species can act as a Lewis acid and coordinate to the lone pairs of the heteroatom from the DMG to form a prelithiation complex (PLC).[62,63] During the transition state, the basic R group abstracts hydrogen from the *ortho* position forming the ortho-lithiated species. The deprotonation is the limiting step.[64] Finally, an electrophile replaces the lithium to afford the desired functionalized arene. The driving force originates from the stabilization of the ortho-lithiated compound by

intramolecular complexation of lithium by the DMG and/or from inductive stabilization provided by the DMG.



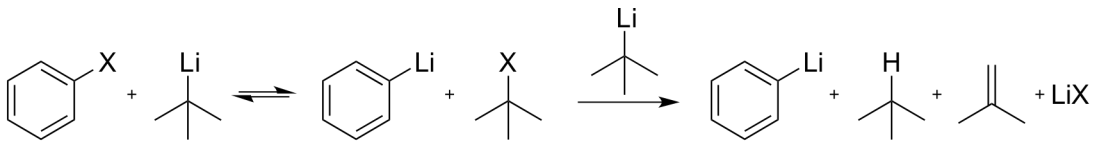
Scheme 1.2-14 Simplified general mechanism for DoM

In some cases, other factors are also postulated to take place. The group of Schleyer presented a *kinetically enhanced metalation* (KEM) model where complexation of the base and hydrogen abstraction occur simultaneously.[65] In addition, in the case of strong electronegative DMG such as halo, trifluoromethyl and cyano groups, the metalation is driven by the acidity of *ortho* hydrogen atom instead of relying on the PLC stabilization effect, named the *overriding base* mechanism. This mechanism is particularly important in the case of superbases which preferentially attack the most acidic position available.[66]

This strategy can also be employed for the peri-metalation of naphthalenes,[67] lateral metalation[68] or metalation of metal-complexed arenes (mostly chromium complexes).[69] In the case of biaryl substrates, the mechanistic concept of CIPE can also be applied to rationalize the metalation at a remote position relative to the DMG, the directed remote metalation (DreM).[70]

Another important synthetic process to access reactive organometallic intermediates is the halogen/metal exchange (Scheme 1.2-15). The bromine- or iodine-lithium permutation has been discovered by Wittig[71] and Gilman[72] in the early 1940s. Since its first report, it has become an important tool for the preparation of organometallic intermediates.[73] In addition to

the interconversion of halogens, several other elements can undergo metal exchange. This is the case of Sb, Se, Te, Sn, As, Pb, Hg, Bi, as well as sulfoxide/metal and phosphorus/metal interconversion.[74]



Scheme 1.2-15 Example of halogen/lithium exchange using *t*BuLi

In general, aryl iodides or bromides react with alkyllithium reagent very rapidly. In contrast aryl chlorides and fluorides are practically inert (ArI > ArBr >> ArCl > ArF). The halogen/metal exchange is an equilibrium-controlled process shifted toward the most stable organolithium or organomagnesium compound and therefore toward the weakest base.[75,76] As a result, when more than one halogen atom is present on an aromatic ring, different organometallic intermediates are accessible, and the reaction will take place at the most acidic position. Iodine is displaced faster than bromine and chlorine is exchange resistant.[63] Chiral ligands can be used to achieve stereoselectivity. The first enantioselective halogen exchange on an arene was reported by Kagan[77] and Alexakis.[78]

1.2.7 Transition–metal catalyzed coupling

Catalysts increase the rate of a reaction by providing an alternative route with lower activation energy and thus allow transformation to be synthetically useful. As such, catalyzed reactions allow transformation of less reactive substrates under milder conditions, and are highly efficient processes to access complex molecules. Transition metals are extremely valuable

catalysts due to the variety of transformations that can be accessed thanks to their redox proprieties. In addition to their respective characteristics, the reactivity of transition metals can be finely tuned by the addition of ancillary ligands with various electronic and structural features.

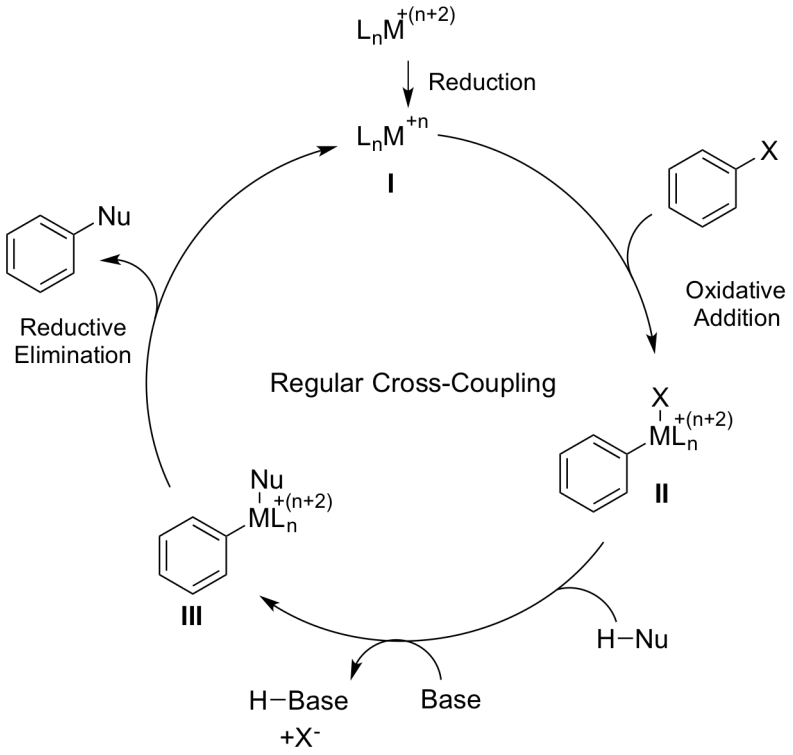
As a result, transition metal-catalyzed cross-coupling methodologies have become recognized as powerful, practical and versatile methods for carbon-carbon and carbon-heteroatom bond formation and play a crucial role in both modern drug discovery and industrial synthesis.

Cross-coupling reaction can be classified into four types of transformations based on the nature of the coupling partners (Table 1.2-1). The most common ones are regular cross-coupling involving carbon electrophile with heteroatom nucleophile and oxidative cross-coupling of carbon nucleophile with heteroatom nucleophile. Reductive cross-coupling between two electrophiles and inverse cross-coupling with carbon nucleophile and heteroatom electrophile are the least investigated.

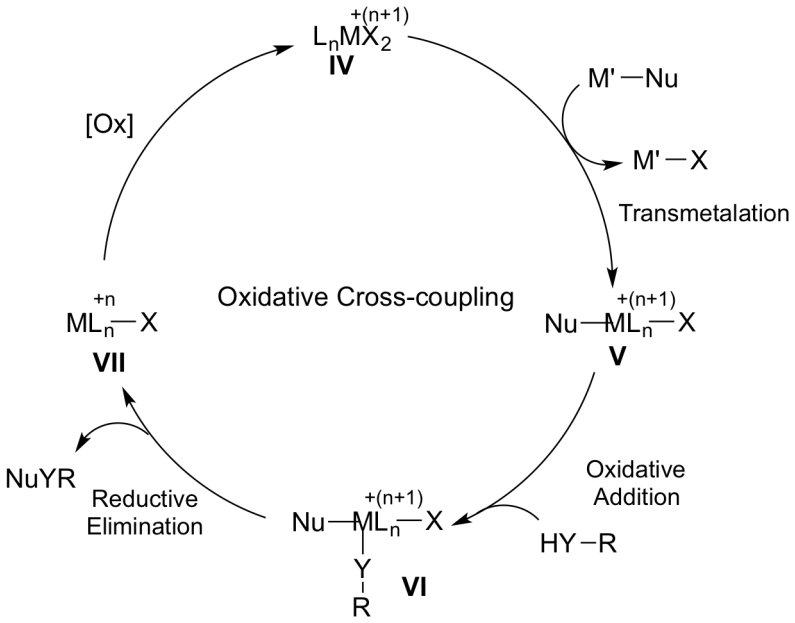
Table 1.2-1 General classification of cross-coupling reaction

Entry	Name	Coupling partners
1)	Regular Cross-coupling	Electrophile + Nucleophile
2)	Oxidative Cross-coupling	Nucleophile + Nucleophile
3)	Reductive Cross-coupling	Electrophile + Electrophile
4)	Inverse Cross-coupling	Nucleophile + Heteroatom Electrophile

Archetypal mechanism of regular transition-metal catalyzed cross-coupling begins with preactivation of the catalyst complex **I** (M^nL_n) through reduction (Scheme 1.2-16). The first step involves oxidative addition to the electrophile arene to generate the aryl-M^{n+2} complex **II.** This step is usually facilitated by the electron-rich ancillary ligands. Coordination of the nucleophile to **II**, followed by base promoted proton abstraction would form the aryl-M-nucleophile intermediate **III**. Finally, the reductive elimination step gives the coupling product and regenerates the reactive species **I**. Usually, the reductive elimination is facilitated by bulky ancillary ligands, which increase the steric strain in complex **III**.[79] Oxidative cross-coupling involves a transmetalation step, followed by oxidative addition and reductive elimination (Scheme 1.2-17).[80,81] In contrary to regular cross-coupling reaction, oxidative cross-couplings rely on high-valent transition metal complex (e.i. Pd(II)/Pd(IV) or Cu(I)/Cu(III) pairs instead of Pd(0)/Pd(II)). Reductive and inverse cross-coupling catalytic cycles go through an oxidative addition, transmetalation, and reductive elimination process (Scheme 1.2-18 and Scheme 1.2-19). The main difference between those two couplings is that reductive couplings involve electrophile arenes while inverse cross-coupling reactions involve heteroatom electrophiles.

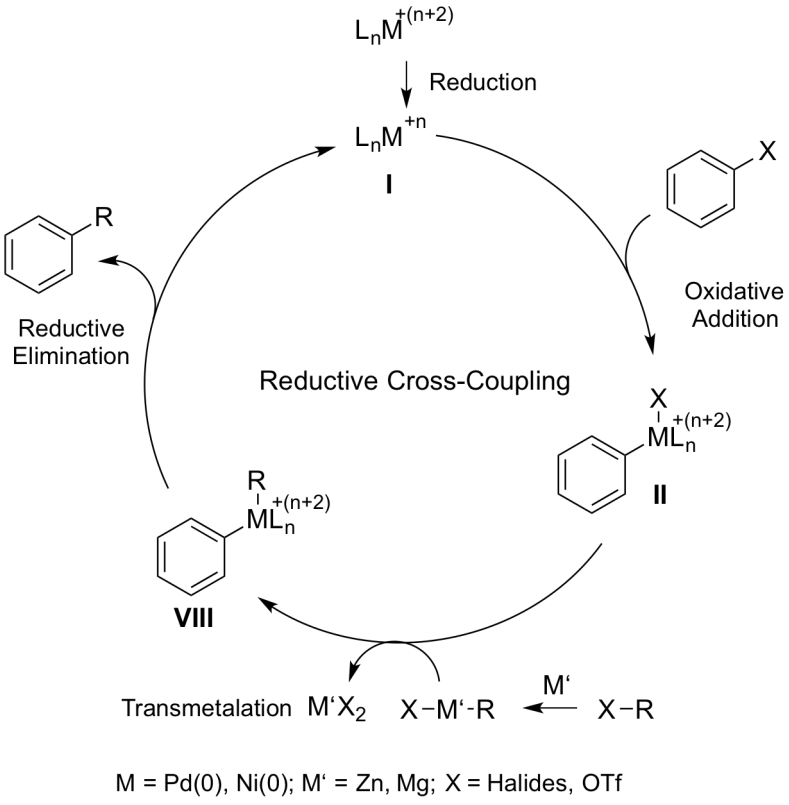


Scheme 1.2-16 Catalytic cycle for regular cross-coupling reaction

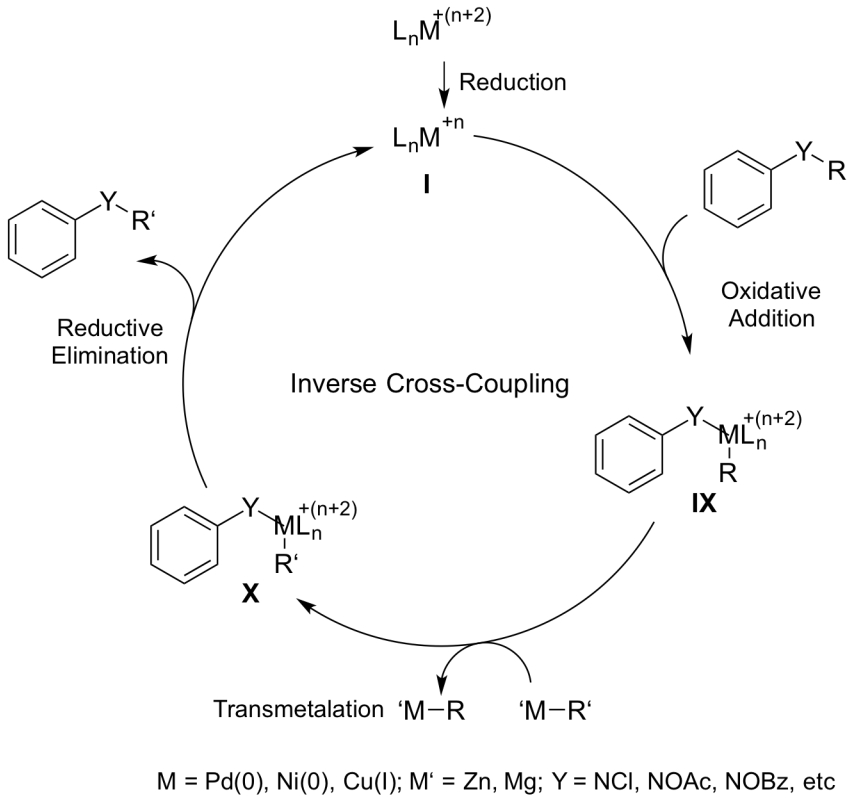


M = Pd(0), Cu(I); Y = NH, O, S, etc; M‘ = Bi^{3+}, B^{3+}, Sn^{4+}. etc

Scheme 1.2-17 Catalytic cycle for oxidative cross-coupling



Scheme 1.2-18 Catalytic cycle for reductive cross-coupling

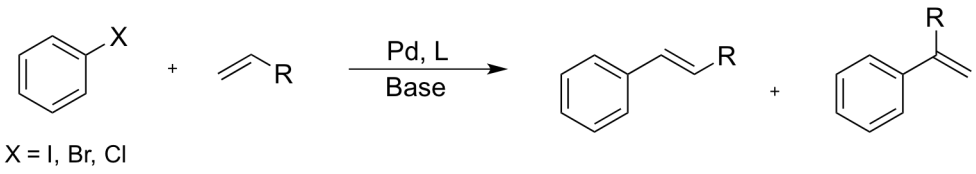


Scheme 1.2-19 Catalytic cycle for inverse cross-coupling

1.2.7.1 C-C bond formation

Until the 1970s, S_NAr reactions of aryl halides (ArX) were restricted to electron deficient haloarenes. In 1968, Fitton[82] and 1978 Kochi[83] showed the ability of elemental palladium(0) and nickel(0) to undergo oxidative addition with aryl halides (ArI >ArBr >ArCl) to form reactive $ArM^{II}XL_n$ complexes (M = Pd, Ni; X = halide; Ln = ligand). This discovery paved the way to transition metal-catalyzed reactions.

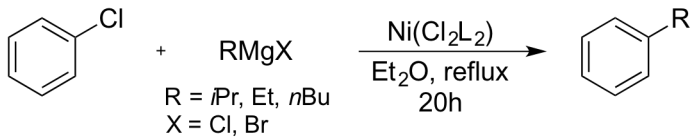
In 1968, Heck reported the first stoichiometric reaction of alkenes with [$ArPd^{II}Cl$] to form aryl alkene derivatives.[84] Mizoroki presented in 1971, the first catalytic palladium-catalyzed reaction between phenyliodines and alkenes with $PdCl_2$ in presence of KOAc as base.[85] In the following years, Heck and Mizoroki further improved what would be called the Mizoroki-Heck reaction (Scheme 1.2-20), extending the scope of the preliminary work to PhBr (with reactivity order: PhI >>PhBr) and drastically lowering the reaction temperature (75°C).[86–89] This reaction has become a particularly powerful industrial process for the synthesis of aryl vinyl compounds, due to the very large panel of functionalized alkenes available on industrial scales, flexibility toward functional group, good yield, and selectivity. In addition, intramolecular reactions are also possible (cyclization) and the use of bulky phosphines allows the use of usually cheap aryl chlorides in comparison to aryl bromide and iodine.



Scheme 1.2-20 The Mizoroki-Heck reaction (1971)

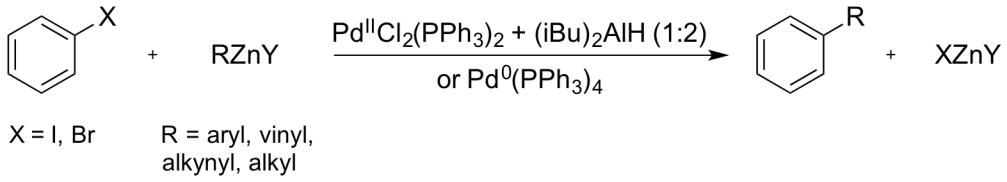
While the coupling between aliphatic halides and Grignard reagents using transition metals have been presented almost 80 years ago by Kharasch,[90] this methodology has only been successfully extended to aryl halides in 1972. The seminal works of Corriu,[91] Tamao and Kumada[92,93] presented the first nickel-catalyzed cross-coupling of PhCl with secondary Grignard reagents (Scheme 1.2-21). This discovery was the first use of an anionic carbon nucleophile in a cross-coupling reaction and showed the potential for cross-coupling reactions to

implement organometallic compounds as coupling partners. ß-hydride elimination led to isomerization of the alkyl group and the formation of by-product and ArH. By-product formation was found to be inhibited by the use of diphosphine ligand on the metal (dppe, dppp).[94,95] The original nickel-catalyzed reaction is moisture sensitive and suffers from the large quantity of magnesium salts generated during the process. Palladium with non-sophisticated ligands is also capable of catalyzing cross-coupling of aryl halides with Grignard reagents without any isomerization.[96,97]



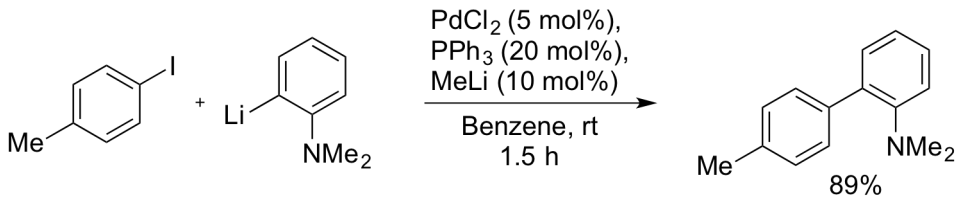
Scheme 1.2-21 The Kumada-Tamao-Corriu reaction (1972)

In 1977, Negishi and coworkers extended the scope of palladium-catalyzed cross-coupling of aryl halides with organozinc reagents (Scheme 1.2-22).[98] A large panel of organozinc derivatives is easily available and can be prepared *in situ* with a large functionality tolerance (neutral medium). However, zinc derivatives are water sensitive and generate a stoichiometric amount of waste.



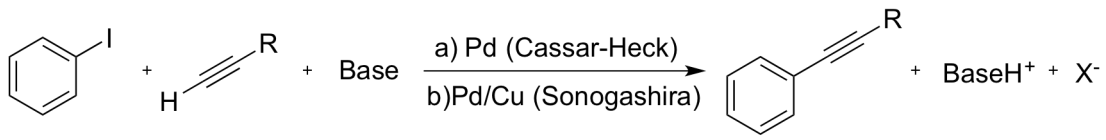
Scheme 1.2-22 The Negishi reaction (1977)

Murahashi presented in 1979 the first use of organolithium reagents as coupling partner in palladium catalyzed cross-coupling reactions with aryl iodides (Scheme 1.2-23).[99]



Scheme 1.2-23 First report of Pd-catalyzed cross-coupling of organolithium reagents (1979)

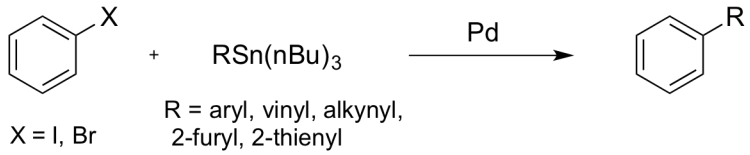
The first successful Pd-catalyzed arylation of terminal alkynes was independently reported by Cassar[100] and Heck[101] in 1975 (Scheme 1.2-24a). The reaction was improved upon by Sonogashira and coworkers with the addition of a Cu^{I} co-catalyst (CuI, CuCN). In the presence of a base, the copper co-catalyst can generate the copper acetylide which takes part in the transmetalation step (Scheme 1.2-24b).[102]



Scheme 1.2-24 The first Pd-catalyzed arylation of terminal alkynes

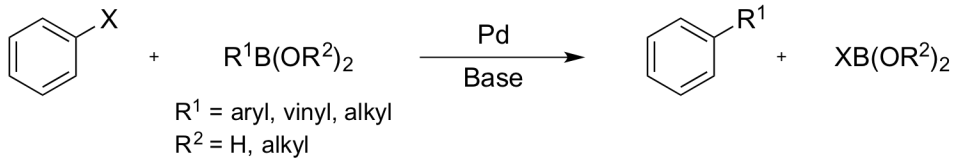
Based on the groundwork of Eaborn,[103] Migita and Kosugi,[104–106] Milstein and Stille presented in 1979 the cross-coupling of aryl halides with organotin compounds under milder reaction conditions using Me_4Sn (Scheme 1.2-25, R= Me).[107] The synthetic applications were later extended using $RSn(nBu)_3$ due to the lack of reactivity of the *n*Bu compared to other more reactive R groups. This reaction has good yield, selectivity, and functional tolerance. Yet,

organostannanes are expensive and generate large quantity of toxic waste making it unsuitable for plant production.



Scheme 1.2-25 The Stille reaction (1979)

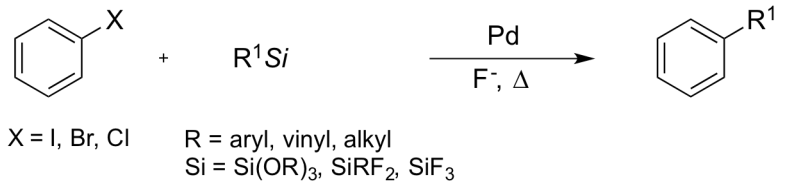
In 1979, the palladium-catalyzed Suzuki-Miyaura reaction between aryl halides and boron derivatives was presented (Scheme 1.2-26).[108,109] The oxidative cross-coupling of organoboranes with aryl halides can be performed under very mild experimental conditions (water as solvent, low temperature, low catalyst loading, etc) and has high functional group tolerance. In addition, the scope of boronic acid and ester derivatives available include a large panel of organic and inorganic functions.



Scheme 1.2-26 The Suzuki-Miyaura reaction (1979)

Later, Hiyama introduced in 1988, the palladium-catalyzed reaction between aryl halides and silanes (Scheme 1.2-27).[110,111] The reaction must be performed at high temperatures and requires a stoichiometric amount of fluoride anion in a specific reactor. More recent contributions by the Denmark's group have greatly extended the scope of cross-coupling

reactions involving organosilane compounds.[112–117] The benefits of the reaction rely on the stability of silanes derivatives, their availability, low toxicity and easy preparation.

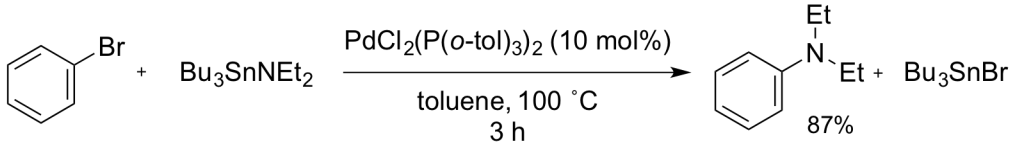


Scheme 1.2-27 The Hiyama reaction (1988)

1.2.7.2 C-Heteroatom bond formation

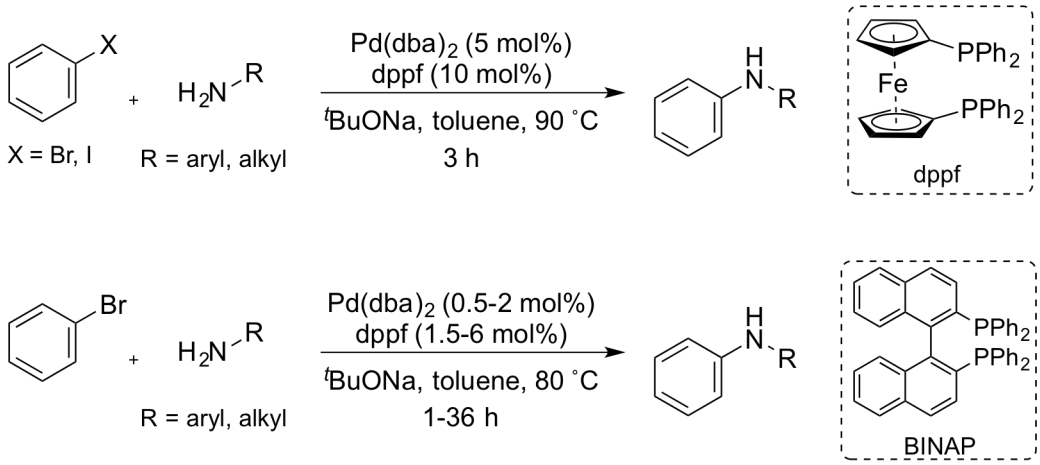
C-N

Migita presented the first Pd-catalyzed C-N coupling between aryl halide and organotin as nitrogen nucleophile (Scheme 1.2-28).[118] A labile bulky monophoshine ligand (P(*o*-tol)$_3$) was responsible for the original low yield of desired aniline product due to ß-hydride elimination process.



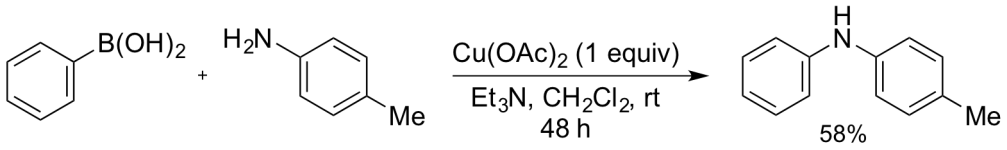
Scheme 1.2-28 The first Pd-catalyzed C-N coupling (1983)

Later, Buchwald and Hartwig groups explored the use of bidentate ligands, allowing amination of aryl bromides and iodides with aliphatic and aromatic amines (Scheme 1.2-29).[119,120]



Scheme 1.2-29 Pd-catalyzed aryl halides amination using bidentate ligands

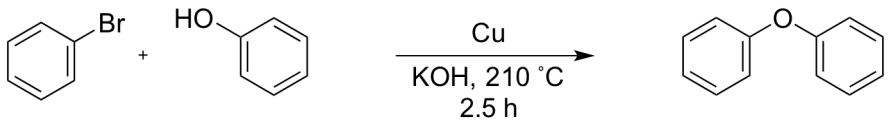
Chan and coworkers presented the oxidative cross-coupling of phenylboronic acid and anilines derivatives with stoichiometric amount of $Cu(OAc)_2$ (Scheme 1.2-30).[121]



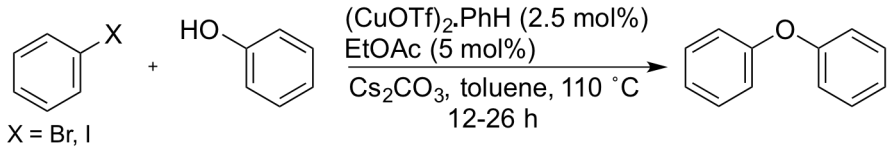
Scheme 1.2-30 Oxidative cross-coupling between phenylboronic acid and *p*-toluidine

C-O

The Ullmann ether synthesis from aryl halides and phenols was discovered over 100 years ago. However, this process requires a stoichiometric amount of copper and suffers from harsh reaction conditions (Scheme 1.2-31, top).[122,123] However the copper catalyzed cross-coupling of phenols with aryl bromides in presence of Cs_2CO_3 was only presented in 1997 by Marcoux *et al.* (Scheme 1.2-31, bottom).[124]

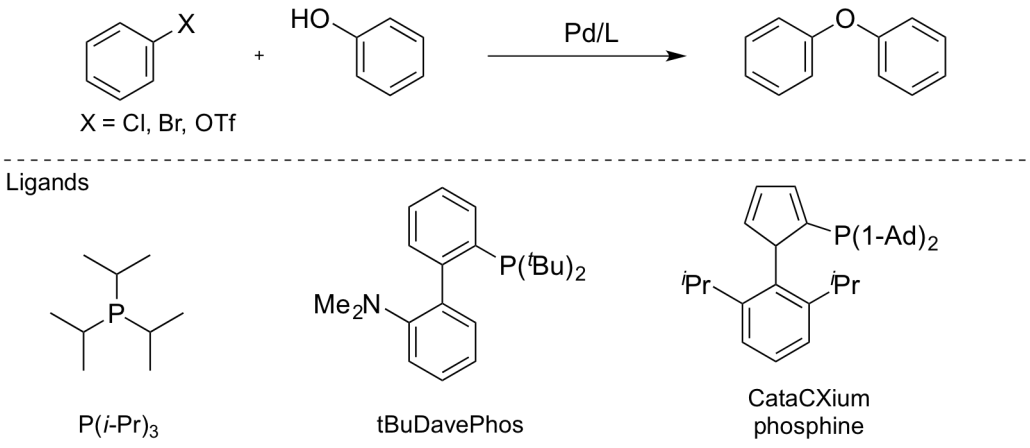


The Ullman condensation of aryl bromides and phenols (1905)



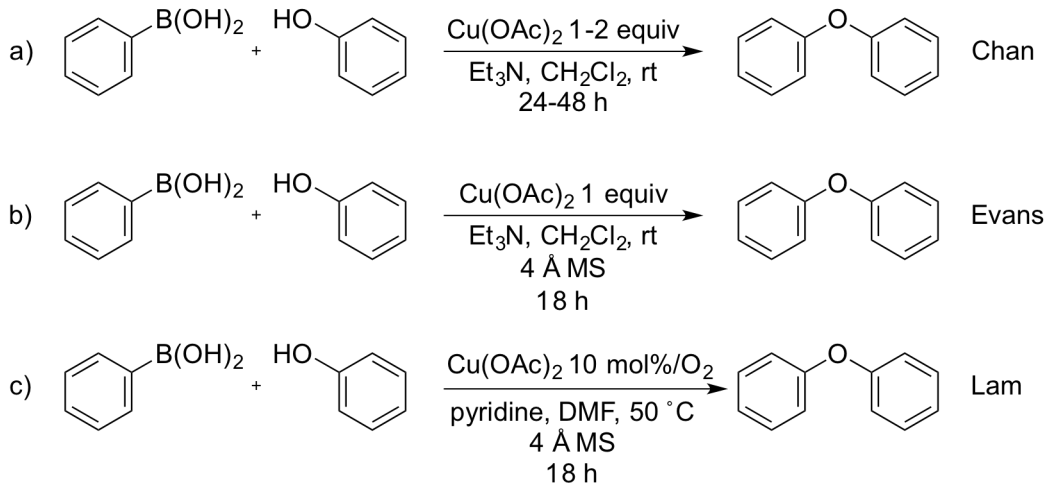
Scheme 1.2-31 Cu-catalyzed cross-coupling of aryl halides with phenols (1997)

Such transformation can also be performed using palladium catalyst for the C-O coupling of phenols with aryl halides and sulfonates, and required the use of bulky phosphorus-based ligands to facilitate the reductive elimination step. This strategy was extended by Beller and other in successive work (Scheme 1.2-32).[125,126]



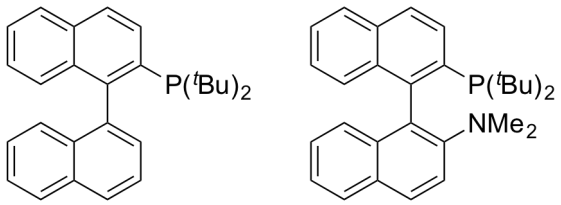
Scheme 1.2-32 Investigation of phosphine ligand in C-O cross-coupling

The coupling of phenols with boronic acids is a popular methodology for the synthesis of aryl ethers. The original work from Chan[121] (a) was subsequently improved by Evans[127] (b) and Lam (c),[128] making the process catalytic in copper by using molecular oxygen as oxidant and improving the yield of the reaction (Scheme 1.2-33).



Scheme 1.2-33 The Cham-Evans-Lam reaction

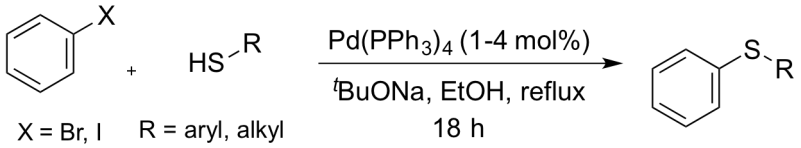
The use of tertiary alcohols as a coupling partner with an electron-deficient aryl bromide was successfully reported using Pd(0) in combination with dppf ligand in presence of *tert*-butoxide.[129] The scope of the reaction was then extended to both electron-deficient and -rich using P^tBu_3 as a ligand.[130] Due to the potential ß-hydride elimination, the cross-coupling of primary and secondary alcohols with aryl halides has been challenging. This has been overcome by Buchwald in 2000 using binaphthyl-based ligands (Scheme 1.2-34).[131,132]



Scheme 1.2-34 Buchwald ligands for alkoxylation reactions

C-S, C-Se, C-Te

The transition metal catalyzed cross-coupling of sulfur compounds remains challenging due to catalyst poisoning by sulfur. Nevertheless, Magita presented the first report of cross-coupling reaction between aryl halides and thiols using $Pd(PPh_3)_4$ (Scheme 1.2-35).[133,134] Hartwig's studies on ligand effects demonstrated that ligands with large bite angles facilitate the reductive elimination step.[135] Aryl halides have also been successfully coupled with selenols[136] and tellurolate ions.[136]

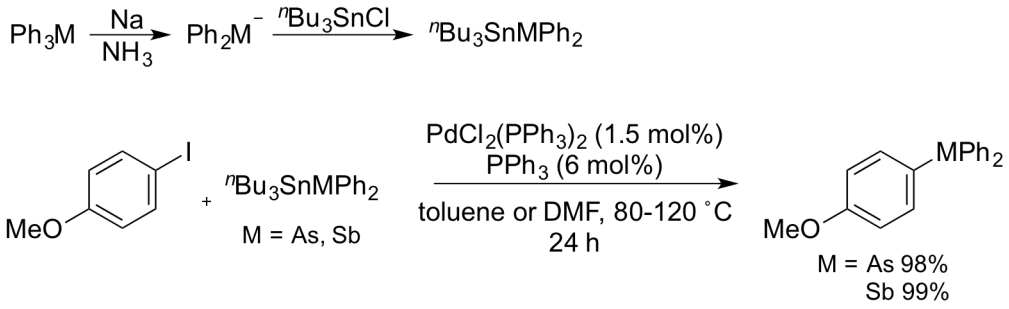


Scheme 1.2-35 Pd-catalyzed cross-coupling of aryl halides and thiols

C-P C-As, C-Sb

C-P bonds are also important for bioactive molecule synthesis and ligand design. The scope of cross-coupling reactions involving phosphorous-based nucleophiles with electrophilic arene derivatives is vast,[137] and includes but is not limited to: phosphonate ester,[138,139] phosphinate ester,[140] secondary phosphine oxides,[141] phosphinic acid[142] and phosphines.[143] There are sporadic reports of cross-coupling reactions involving triphenyl-arsines and stibines derivatives. The formal palladium-catalyzed cross-coupling of triphenyl-arsines and stibines with

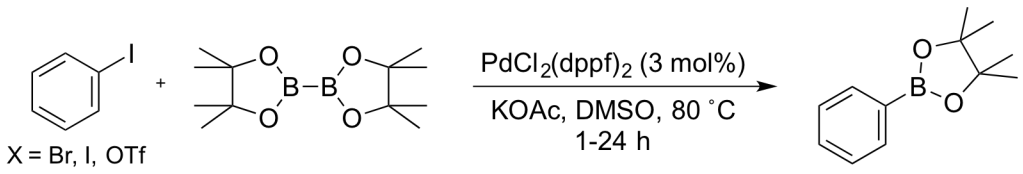
aryl iodines and aryl triflates *via* arsine- and stibine-stannanes derivatives has been reported in 2004 (Scheme 1.2-36).[144]



Scheme 1.2-36 One-pot sequential Pd-catalyzed cross-coupling of aryl iodine with triphenyl-arsines and stibines derivatives

C-B

Organoborane derivatives are extensively used as coupling partners in cross-coupling reactions.[145] Miyaura subsequently reported the first $PdCl_2$(dppf) catalyzed coupling of bis(pinacolato)diborane (B_2pin_2) with aryl halides and aryl triflates (Scheme 1.2-37).[146,147] Other transition metals capable of such coupling include Cu and Ni, with $NiCl_2$(dppp) allowing the borylation of aryl mesylates, triflate and sulfamates at room temperature.[148]



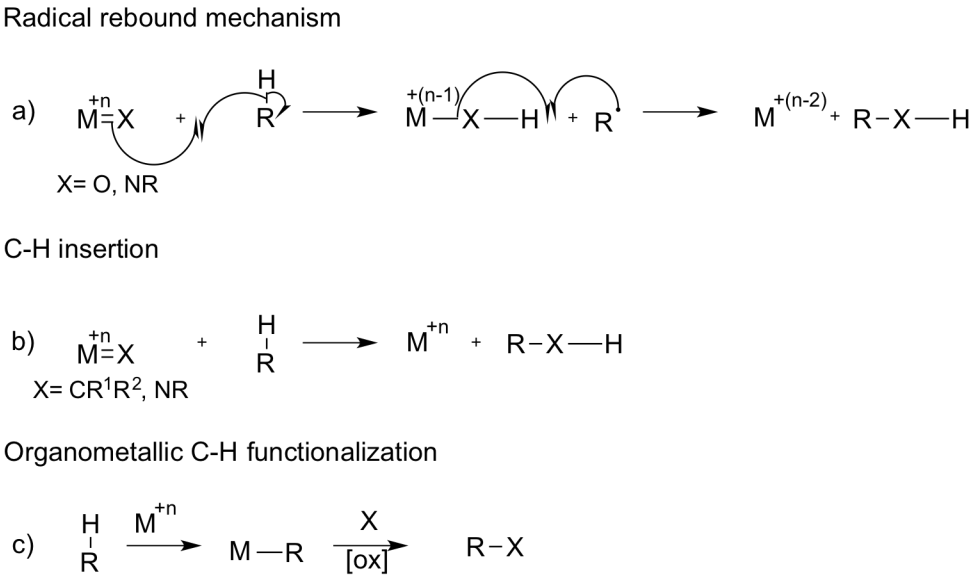
Scheme 1.2-37 Palladium-catalyzed C-B cross-coupling

The scope of coupling partner has been tremendously extended since the first reports of these transformations. For their contribution, Heck, Negishi and Suzuki would receive the Nobel Prize in 2010 *"for palladium-catalyzed cross couplings in organic synthesis"*.

1.2.8 C-H functionalization

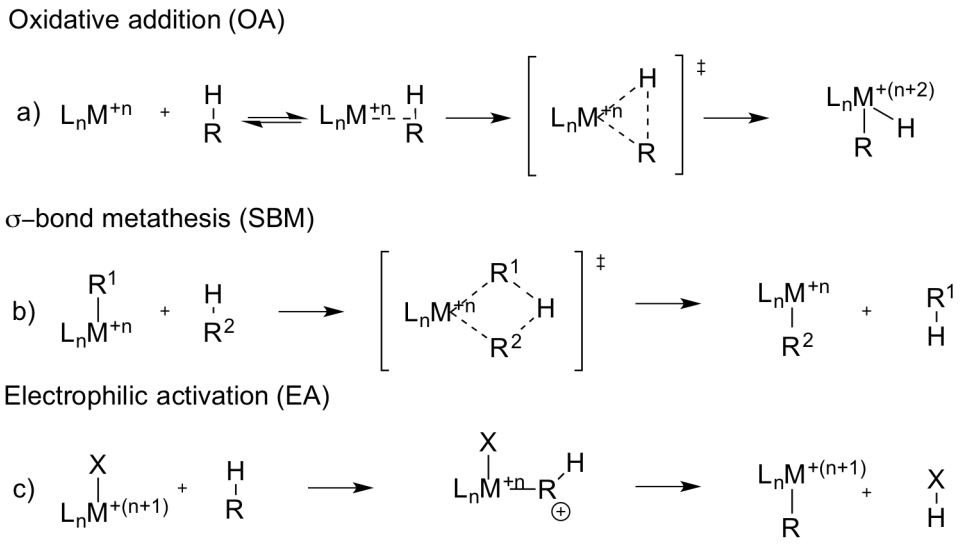
In an effort to extend the scope of coupling partners to less reactive substrates and reduce the number of synthetic steps by preventing the need to pre-functionalize the coupling partners, synthetic chemists have developed transition-metal catalyzed processes that introduce functional groups at C-H bonds that lack the activating influence of existing functional groups.[149]

C-H functionalization can generally occur through three different types of pathways: (a) *radical rebound mechanism*, typically observed with metal-oxo catalysts present in enzymes; (b) *C-H insertion,* most often observed for the functionalization of weak C-H bonds as it required the complete cleavage of the bond; (c) and through the use of *organometallic intermediates*, which is currently the most investigated mechanism (Scheme 1.2-38).



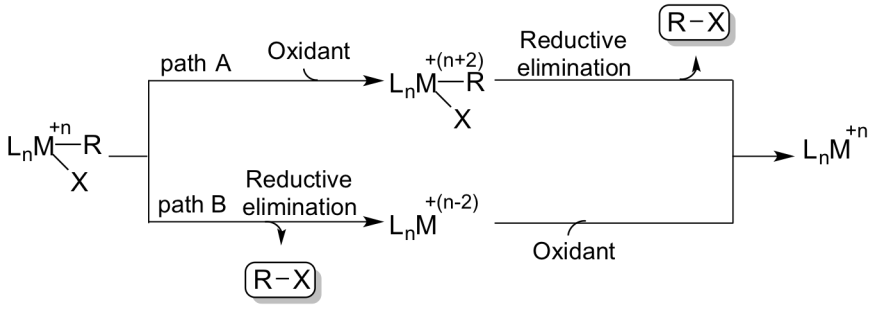
Scheme 1.2-38 General mechanisms of C-H functionalization

Until the mid-1990s, C-H activation by organometallic complexes were believed to proceed through one of three mechanisms: (a) oxidative addition (OA) at electron-rich low-valence transition metal centers (b) σ-bond metathesis (SBM) at electrophilic early transition metal centers and (c) electrophilic activation (EA) at electron-deficient late transition metal centers (Scheme 1.2-39). Thus their classification was traditionally identified with the nature of the metal center. However, the use of computational methods has shed further light onto the complexity of the C-H activation mechanism steps, unrevealing numerous key ligands/substrate interactions. As a result, to illustrate the nuances in mechanisms, several acronyms have emerged in the literature: concerted metallation-deprotonation (CMD), internal electrophilic substitution (IES), ambiphilic metal-ligand activation (AMLA), oxidative hydrogen migration (OHM), oxidatively added transition state (OATS), and σ-complex-assisted metathesis (σ-CAM) among others.



Scheme 1.2-39 Different mechanisms for C-H activation

Once the C-H activation step has occurred, two different pathways can take place that lead to C-H functionalization depending on the nature of the metal catalyst (Cu, Pd, Rh, Ir, Ru), oxidation process (one- vs. two-electron oxidants), type of the bond formed (C-C vs C-X) and reaction conditions (temperature, solvent, pH, etc)(Scheme 1.2-40). The formation of polarized bonds (e.g. C-N, C-O) generally follows pathway A, with initial oxidation of the intermediate followed by subsequent bond formation when the reductive elimination is challenging with catalyst with lower oxidation state.[150,151] In pathway B, the bond is formed first before the catalyst is regenerated by oxidation.[152]



Scheme 1.2-40 C-H Functionalization with organometallic intermediates

One of the key challenges of C-H activation processes is the selective functionalization of a specific C-H bond of the arene. In the case of electron-rich as well as electron-deficient arenes, when the electronic proprieties of the coupling partners dominate their reactivity, the regioselectivity can be controlled. However, with electronically unbiased arenes, the use of directing group (DG) circumvents regioselectivity issues (Scheme 1.2-41a). In addition, those DGs can coordinate to the catalyst and assist both the C-H cleavage and the formation of the new bond.

A wide variety of structures have been employed as directing group, with the most common coordinating atoms being O, N, S, and P. Some of the directing group reported includes: N- and O-containing heterocycles, carboxylate derivatives, oximes and imines, amines, ketones, hydroxyl and others.[153,154] Because of the strength of the coordinating bond depends on the nature of both, the transition metal catalyst and the coordinating atom, the efficiency of a DG in chelation-assisted C-H functionalization depends on the reaction conditions and the nature of the transformation.

Thanks to the variety of transition metals and directing groups available, this strategy has enabled the direct and efficient introduction of a wide variety of functional groups. The earliest

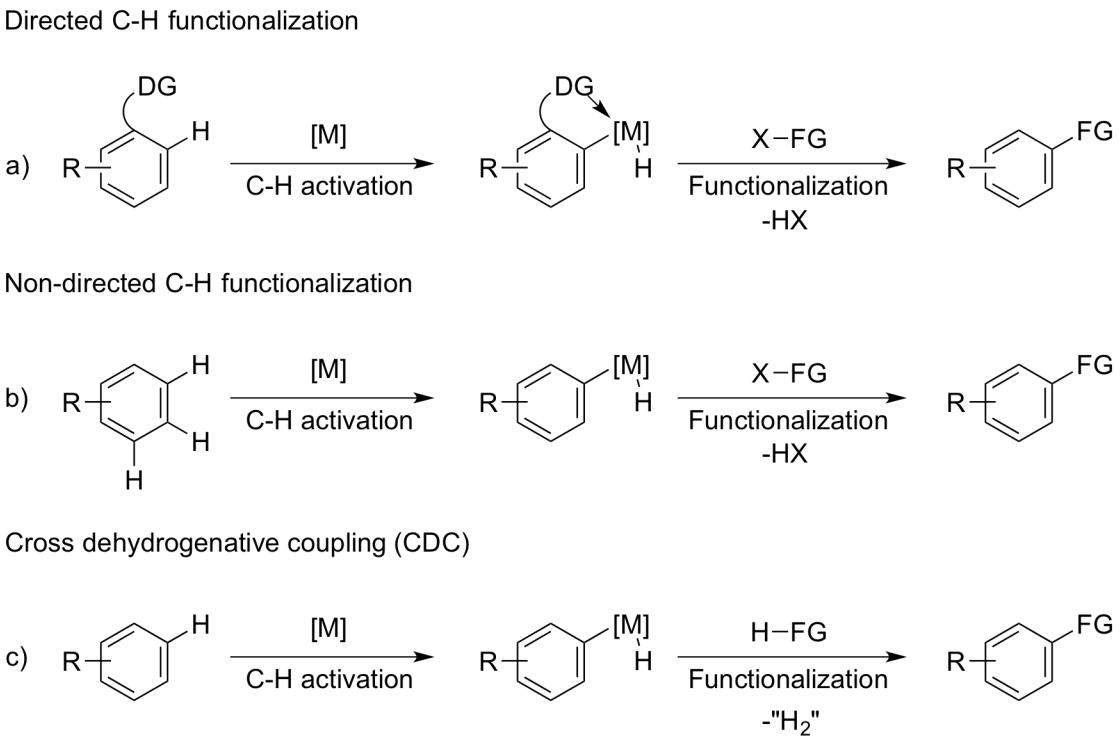
reports dated back from the 1990s involving C-C bond formation of arenes with alkenyl and aryls moieties.[155–158] In the subsequent years, the range of C-C functionalization accessible was extended to alkyl,[159] acyl,[160] CN[161] and CF_3[162] as well as C-heteroatoms bond: C-B,[163] C-Si,[164] C-O,[165] C-N,[166] C-P,[167] C-S[168] and halides.[169]

However, installation of appropriate DG at a suitable position onto the substrate might be synthetically challenging. Furthermore, in most cases the DG moiety is not part of the target molecules, leading to additional synthetic steps to remove it, thus reducing the atom economy of the overall process. In addition, these reactions proceed via a metallacycle intermediates, usually a five- or six-membered ring, restraining the transformation to takes place in proximity to the catalyst coordination site, typically in *ortho* position thus restricting the scope of accessible products.

A more appealing strategy for arene C-H functionalization involves the direct use of simpler arenes derivatives lacking DGs (Scheme 1.2-41b). While an attractive approach, with the lack of DGs on the substrate rise regioselectivity and reactivity issues. Without DG to selectively activate a distinct bond from chemically equivalent C-H bonds a mixture of products might be obtained. Nevertheless, catalyst-based control is a powerful tool to access efficient regiofunctionalization of arenes. The careful modification of the steric and electronic nature of the ancillary ligands has the potential to allow preferential functionalization of the desired C-H bond. Despite these challenges, exciting progress has been made toward the direct functionalization of C-H bonds and includes successful report of C-C, C-O, C-N, C-B and C-Si bond formation.[170,171]

The aforementioned reactions involve the coupling of an arene with a prefunctionalized partner X-FG (Scheme 1.2-41b). A more attractive strategy from an environmental perspective

involves the direct coupling of two C-H bonds (Scheme 1.2-41c). Such oxidative coupling of two different C-H bonds was termed cross-dehydrogenative coupling (CDC) by Li in 2004 and has become a growing field of interest. Benefits of this strategy include lower cost, as it reduces the number of steps to the target molecule, and less waste, as it precludes the stoichiometric formation of halogenated or organometallic by-products. The CDC reactions are particularly challenging because both the chemo- and site-selectivity of arene C-H activation and bond formation need to be controlled on both partners to avoid forming mixtures. In addition, despite being termed *cross-dehydrogenative coupling,* hydrogen gas is usually not the by-product of these reactions. Thermodynamically the formation of carbon-carbon or carbon-heteroatom bond with loss of H_2 is typically unfavorable and thus requires an external driving force, namely, an external sacrificial oxidant. Yet, efficient catalytic systems have been developed for the formation of C-C, C-O, C-N bonds.[172–178]



Scheme 1.2-41 Conceptual strategies for C-H activation

1.2.9 Biotransformation

Due to the ubiquitous presence of the arene motif in bioactive compounds, Nature has deployed a vast range of enzymes to catalyze biotransformations of aromatic substrates. Recent years have seen enzyme-catalyzed reactions of aromatics, moving from being of primary interest to biologists, to being more accessible to synthetic chemists.

Because of the complexity of the systems involved in living organisms, enzymes are usually highly substrate specific, stereo- and regioselective, and efficient under mild reaction

conditions.[179] Among them the most common ones are: arene alkylation (biocatalytic Friedel-Crafts),[180] arene deacylation, arene carboxylation (biocatalytic Kolbe-Schmitt),[181] arene halogenation (halogenase), arene oxidation (laccases),[182] arene hydroxylation,[183] and arene nitration.[182]

1.3 Industrial considerations

The following section intends to give a general overview of the current sources of starting materials and key intermediates employed by the chemical industry for the synthesis of molecules of interest and does not represent an exhaustive representation of the matter.

Currently, the chemical industry access most of its feedstock required for the production of organic compounds from - coal, oil, and natural gas – with hard coal representing over 50% of the fossil raw materials (Figure 1.3-1).[184] The most important coal-refining process involves its pyrolytic conversion into coke, gas and coal tar. Coal tar represents the main source of polynuclear aromatics such as naphthalene, phenanthrene, fluoranthene, pyrene, acenaphthene, anthracene, and heterocyclic carbazole, quinoline, and isoquinoline. While olefins are also present in tar, olefinic and aliphatic compounds are almost exclusively accessed from crude oil and natural gas. The production of olefins is performed through thermal cracking of oil, with naphtha cracking being the most important process worldwide for the manufacture of ethylene, which represents the feedstock for roughly 30% of all petrochemicals. The thermal cracking of hydrocarbon involves radical cleavage of hydrocarbons under high pressure and temperature to produces olefins. Mononuclear aromatics such as benzene, toluene, and xylene (BTX) are accessible from both crude oil and coal. The main methods employed for the production of BTX

aromatics involve thermal and catalytic processes, with the three most important sources of feedstock being:

1. Products from coking of hard coal
2. Reformate gasoline from processing of crude gasoline
3. Pyrolysis gasoline from ethylene/propene production

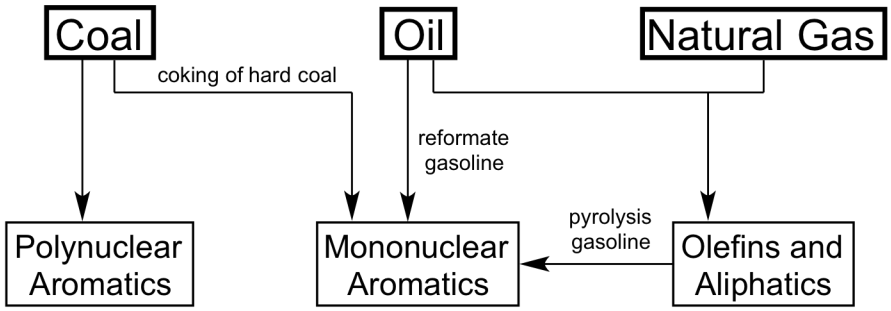


Figure 1.3-1 Principal raw materials of the chemical industry

Around 75% of the BTX are produced from reformate gasoline and is, therefore, the major source of raw material. However, due to the relatively low benzene content of reformer gasoline, part of the toluene and xylene produced are converted into benzene through disproportionation and dealkylation methods to meet the demand. The large volume of benzene consumed by the chemical industry is explained by the variety of key products accessed from it.

The most important products of benzene in term of quantity are alkylated derivatives (Figure 1.3-2).[185] Ethylbenzene is industrially manufactured by the Friedel-Crafts alkylation of benzene with ethylene, and virtually exclusively used for the production of styrene through catalytic dehydrogenation to meet the need of the polymer industry. With about 50% of the production of benzene being dedicated to the manufacture of ethylbenzene, this is by far the most important process in terms of quantity. Other uses of benzene include the manufacture of

nitrobenzene as intermediate for the production of aniline, hydrogenation to produce cyclohexane and chlorination reaction. The production of chlorobenzene from benzene and chlorine was one of the first large-scale manufacture of basic organic chemicals as it represented the basic intermediate for the manufacture of picric acid, a strategic starting material during World War I for the synthesis of explosives. Nowadays the volume produced has drastically decreased but still represent a highly versatile intermediate in the production of complex molecules.

The second most important industrial derivative of benzene after ethylbenzene is cumene. Its manufacture consumes about 20% of the total amount of benzene produced and is also accessed by alkylation with propylene, as its direct recovery from coal and petrochemical stream is uneconomical. The main driving force behind the industrial production of cumene in such large scale lays in the importance of the phenol as intermediate for the polymer industry. The oxidative conversion of cumene occurs via the formation of the cumene hydroperoxide in presence of O_2, which upon its catalytic cleavage, generate phenol and acetone. This process has proved to be an environmentally safe and economical process and thus is currently the only industrial process in operation worldwide for the manufacture of phenol. From phenol, cyclohexanone can easily be accessed through hydrogenation in order to produce adipic acid and ε-caprolactam as important intermediates of synthetic fibers such as Nylon-6,6 and Nylon-6.

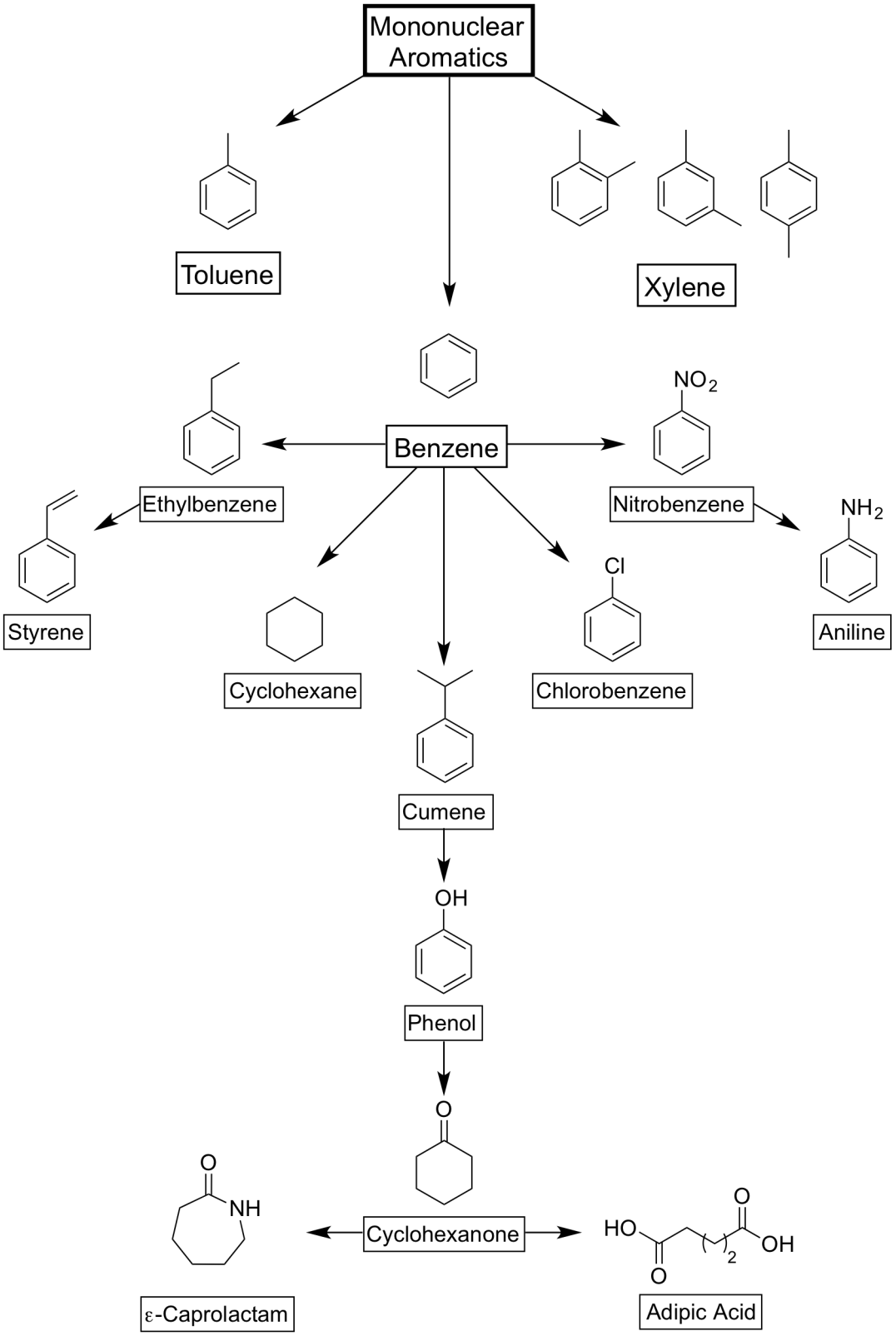


Figure 1.3-2 Key intermediates accessed from the BTX

1.4 Conclusion and outlook

The considerable variety of strategies employed to access functionalized arenes reflects the importance and ubiquity of the arene motif. With growing environmental concerns, we can notice a paradigm shift in the design of new reactions. This has been illustrated by the publication from Anastas and Warner of the 10 principles of green chemistry in the 1990s,[186] and the development of new metrics for the quantification of energy input, masses balance and life cycle environmental impact of chemical processes. In the past few decades, we moved from accessing target molecules at all cost, to the design of more efficient reactions allowing the use of simpler and easily available starting materials to access highly functionalized and complex structures. With our current society being the result of mankind accessing fossil raw materials, it is no surprise that our "easily accessible" starting materials are derivatives from oil, coal and natural gas and that the chemical industry has implemented its processes on it. With the realization that oil and coal are finite resources, it is becoming clear that mankind will need access to alternative building blocks for the construction of molecules of interest.

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Chapter 2 – Aerobic Synthesis of Aromatic Ethers from Non-Aromatic Precursors

The results reported in this chapter have been published in the journal *Angewandte Chemie International Edition* as a full paper entitled "Catalytic Synthesis of Aromatic Ethers from Non-Aromatic Precursors" co-authored by Marc-Olivier Simon, Simon A. Girard, Chao-Jun Li. Marc-Olivier Simon discovered the reaction and a considerable part of that manuscript was written by him and has thus been re-written by S.A. Girard for inclusion into this thesis. The reaction conditions for the $CuCl_2.2H_2O$ and $Cu(OTf)_2$ catalyzed oxidative condensations of alcohol with cyclohexanone derivatives were developed by me (Simon A. Girard), with supervision by Marc-Olivier Simon under the guidance of Prof. Chao-Jun Li. All reactions, isolations, and characterizations (with the exception of high-resolution mass spectrometry) were performed by me and Marc-Olivier Simon. High-resolution mass spectrometry was performed by Dr. Nadim Saadeh at the McGill University Department of Chemistry Mass Spectrometry Laboratory.

Most of the current synthetic methods available to access functionalized arenes use fossil material derivatives as building blocks and thus rely on the use of finite resources. Consequently, alternative sources of basic building block for the construction of molecules of interest are being investigated. This chapter introduces the concept of the borrowing hydrogen strategy as a potential alternative synthetic route to access functionalized arenes from renewable sources. As a first step toward the development of such methodology, this chapter presents the development

copper catalyzed systems for the synthesis of aryl-ether from non-aromatic cyclohexenone derivatives.

2.1 Introduction

Mankind accessing oil in the early 20th century has tremendously shaped our societies. With twice the energy density of coal, petroleum quickly became the most important trade commodity and its use has spread far beyond a simple energy source. The chemical industry is using petroleum derivatives as starting materials for the construction of molecules of interest. With the realization that petroleum has an environmental cost and will eventually run out, research on finding alternative building blocks for the chemical industry was initiated. Ideally, the material substituting the petroleum would be naturally abundant and can be replenished quickly. With forests covering approximately 30 % of the dry land, wood is being evaluated as a source of renewable chemical starting materials. Thus increasing efforts are being made to implement constituents of wood into valuable industrial processes. One of its constituent, lignin, is a biopolymer present in vascular plants and some seaweed,[1] responsible for their structural rigidity (Figure 2.1-1). While the structure of lignin is highly heterogeneous; it is mostly composed of phenolic moiety subunits.

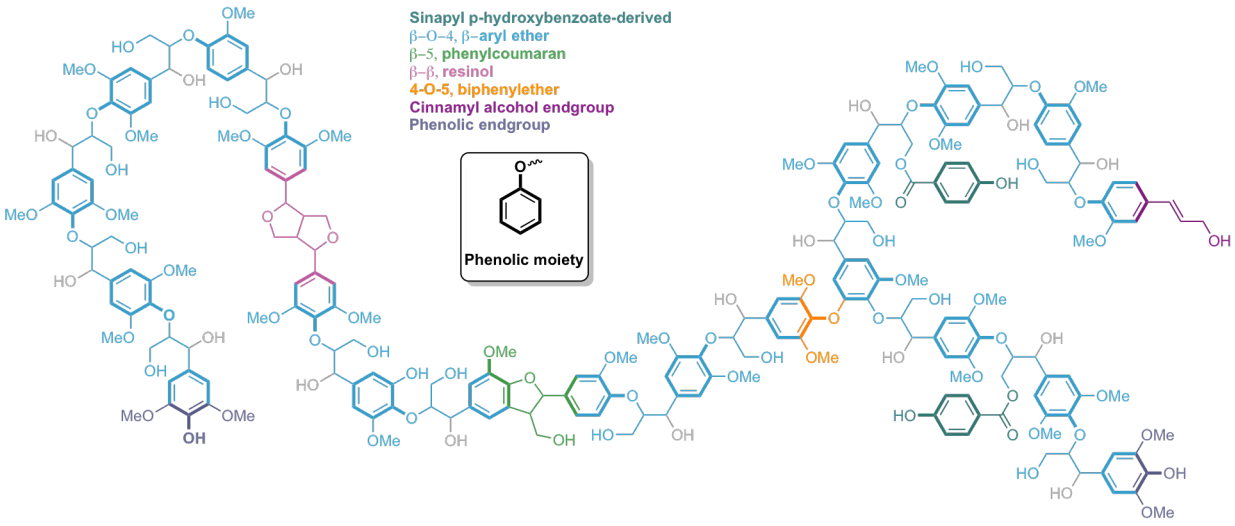
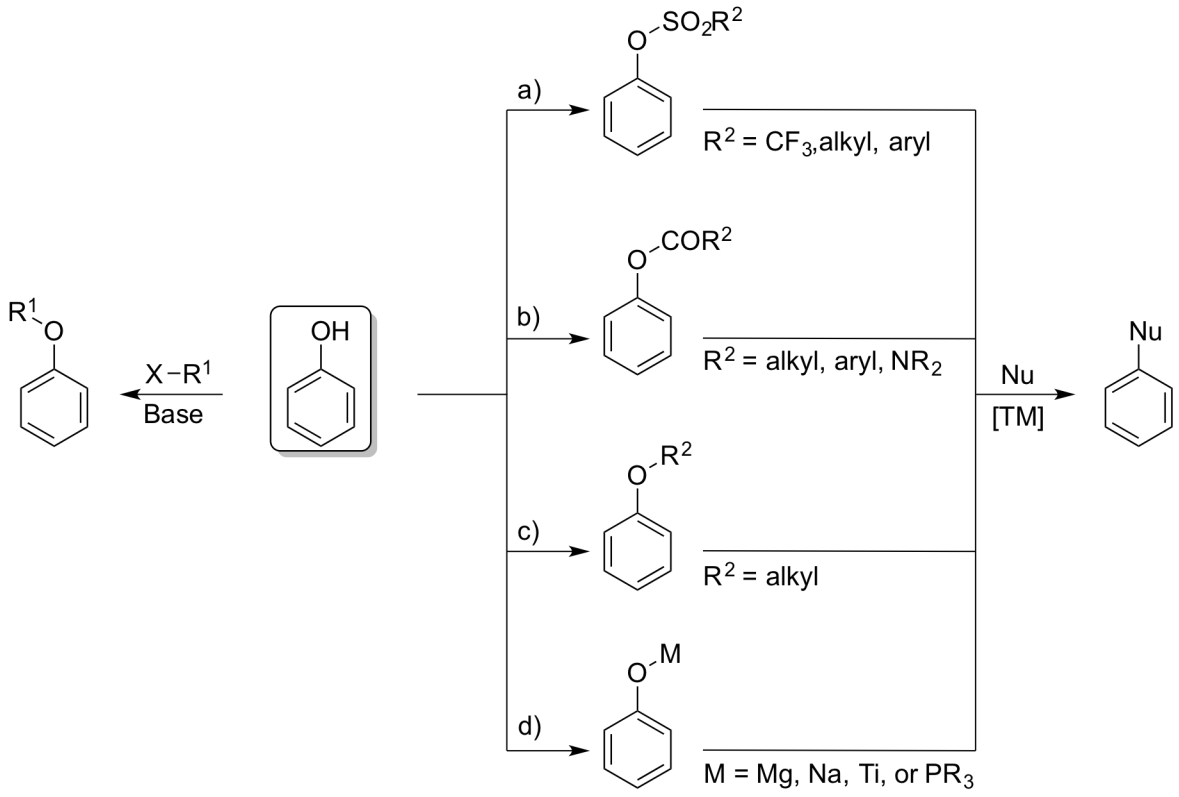


Figure 2.1-1 Structure of lignin

Substituted arenes are ubiquitous moiety. As a result, synthetic chemists have been ingenious in accessing highly decorated aromatic rings. Along with the rapid development of organometallic chemistry in the last few decades, a wide range of transition metal catalyzed arylation strategies have been explored and successfully employed on industrial scales. However, a common feature of all the strategies is the utilization of arene derivatives as a coupling partner, usually pre-activated with a functional group, typically haloarenes. Phenols found in lignin have the same oxidation state as haloarenes and their direct coupling has long been a synthetic aspiration. However, to successfully implement lignin as a suitable starting material for industrial chemical production, two parallel efforts are required: 1) efficient processes for the extraction and separation of the different constituents from wood have to be developed and 2) the scope of transformation involving phenols has to be extended as the direct use of phenols remain challenging. Our work will focus on the second of the aforementioned problems.

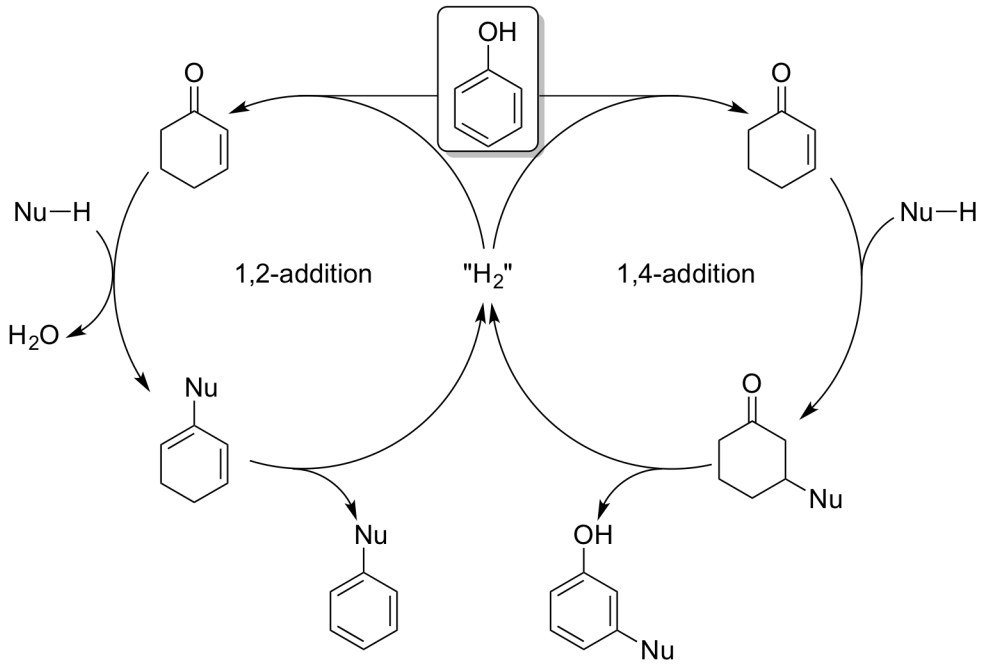
Phenol reactivity is controlled by two proprieties: 1) a very reactive hydroxyl group, and 2) a C-O bond with high dissociation energy owing to p–π conjugation. As a result, the functionalization of phenols can be divided into two main strategies: 1) taking advantage of the hydroxyl nucleophilicity to react with various electrophile as seen in Williamson type reactions[2,3] (Scheme 2.1-1 left), or 2) through activation of the C-O bond by its transformation into more reactive derivatives (Scheme 2.1-1 right). The latter has recently seen progress with the development of coupling reactions of phenols by catalytic C-O bond cleavage. In those coupling reactions, in order to activate the C-O bond the phenol is transformed into more active derivatives, such as: a) aryl sulfonates (e.g., triflates, tosylates, mesylates, and sulfamates),[4,5] b)



Scheme 2.1-1 General strategies to access functionalized arenes from phenol

aryl esters or aryl carbamate derivatives,[6–8] c) aryl alkyl ethers,[9,10] and d) phenolic salts.[11–13] As a result, the number of synthetic and purification steps increases, raising the cost of such transformations and generating stoichiometric amounts of wastes. In addition, because both strategies rely on the reactivity of the hydroxyl moiety, the regioselectivity of any functionalization is limited to take place at this position.

An alternative strategy that precludes the need for pre-activation of phenols would be highly valuable; this would shorten the number of synthetic steps and circumvent generation of stoichiometric amounts of waste. In theory, it is possible to exploit alternative reactivities underlying in the phenolic scaffold through the temporary generation of a small amount of the ketone from phenol. The partial reduction of phenol to their corresponding cyclohexenone derivatives would afford new handles for chemical transformations. Once the cyclohexenone is generated, it is conceivable that introduction of an appropriate nucleophile into the catalytic system would introduce functionalization (Scheme 2.1-2). Substituted arenes or phenols derivatives could be obtained through the selective control of nucleophilic addition or conjugate addition followed by dehydrogenation. These processes would formally only produce water and hydrogen as by-products and have the potential to go through the so-called "hydrogen-borrowing strategy",[14,15] where the hydrogen required for the partial reduction of phenol is regenerated during the dehydrogenative aromatization.

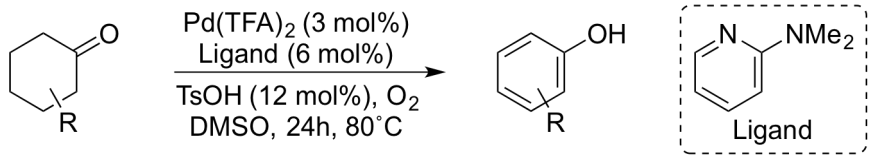


Scheme 2.1-2 Conceptual phenol transformation through 2-cyclohexenone intermediates

2.2 Plan of study

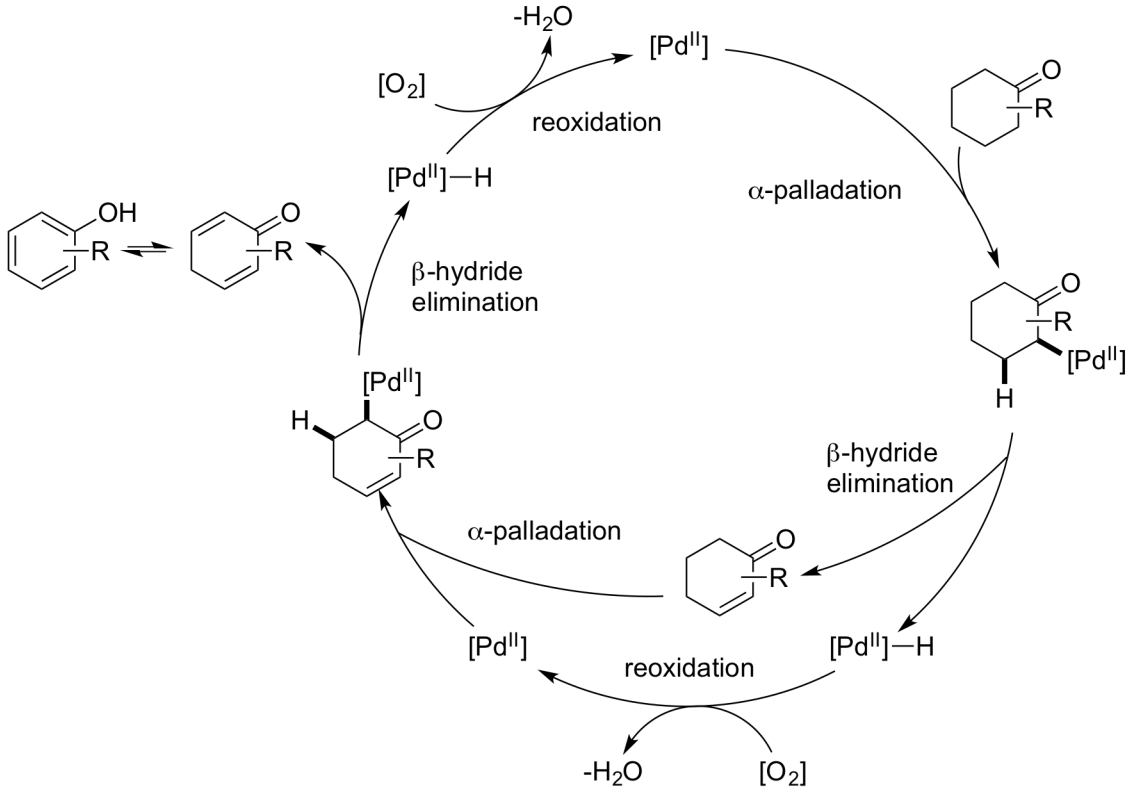
The first step toward the development of the direct functionalization of phenols through the hydrogen borrowing strategy is to demonstrate the compatibility of the nucleophilic addition and the dehydrogenative aromatization steps.

The transformation from cyclohexanone to phenol date back to the early twentieth century, when the heterogeneous nickel dehydrogenation in the gas phase was applied to produce phenol.[16–18] The reaction required elevated temperatures and produced a mixture of hydrogenated products. In 2011, the Stahl group presented the first palladium-catalyzed homogeneous aerobic dehydrogenation of substituted cyclohexanones to the corresponding phenols (Scheme 2.2-1).[19]



Scheme 2.2-1 Pd-Catalyzed phenol synthesis from cyclohexenone

This palladium-based catalytic system, via the ingenious combination of two successive α-palladation/β-H eliminations and aerobic oxidation of palladium, can successfully abstract hydrogen atoms from the six-membered ring to yield the aromatized product (Scheme 2.2-2).

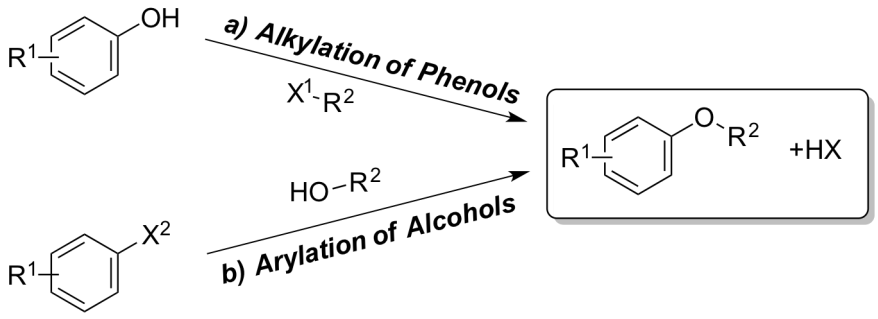


Scheme 2.2-2 Proposed mechanism for the phenol synthesis from cyclohexanone derivatives

This report demonstrates the potential of transition metals to perform catalyzed oxidative aromatization from cyclohexanone to phenols in presence of other functionality, using oxygen as

the terminal oxidant. Various cyclohexanone derivatives, including methyl ether, ester, CF_3, and halides; were successfully converted to their corresponding phenols with this methodology.

In theory, various functionalizations could be introduced to the aryl moiety through nucleophilic addition to cyclohexenone. Aryl ethers are ubiquitous compounds and intermediates used in dyes, cosmetics, materials, fragrances, plant protection agents, stabilizers for plastics, natural products synthesis, and drugs.[20,21] The ability to assemble a range of aliphatic and aromatic moieties presents a real challenge and has attracted constant interest. Nevertheless, most of the existing methods are based on the same reaction scheme and use either a preexisting oxygen atom (phenols) or a preinstalled reactive functionality (Scheme 2.2-3). For example, aryl alkyl ethers can be prepared by nucleophilic substitutions either with a phenol on an aliphatic substrate (Williamson reaction)[2,3] or with an alcohol on an aromatic precursor.[22] More recent approaches employ transition metal-catalysts to assist such transformation and include allylic *O*-alkylations of phenols[23] and electrophilic additions of phenols to alkenes.[24] Transition metals have demonstrated great efficiency in the coupling reactions between alcohols and aryl halides using palladium (Buchwald-Hartwig reaction)[25] or copper (Ullmann ether synthesis)[26,27] catalysts, as well as copper-catalyzed coupling reactions of alcohols with arylboron (Chan-Lam type coupling)[28] or arylbismuth[29] compounds. However, those transformations required pre-functionalization of at least one of the coupling partners, thus increasing the number of synthetic steps. In addition, stoichiometric amounts of waste are generated during the coupling step of most of these syntheses, which goes against the modern context of developing more environmentally friendly processes.[30,31] Thus, the development of new synthetic routes for the manufacture of aryl-ethers is attractive.

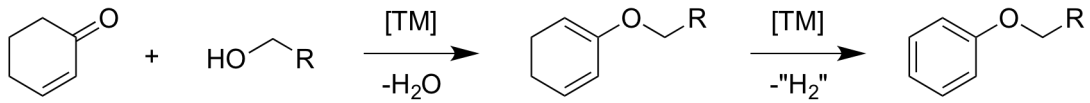


X^1 is a leaving group such as a halide, hydroxyl, carbonate, acetate, sulfate or sulfonate and X^2 is either a halide, sulfonate, organoboron or organobismuth derivative.

Scheme 2.2-3 General approaches for the preparation of aryl ethers

2.3 Results and discussions

We reasoned that the condensation of an alcohol and a 2-cyclohexenone would lead to an adduct, the oxidative aromatization of which would afford the aryl ether product (Scheme 2.3-1). This approach is very attractive since its only theoretical by-products are water and hydrogen.



Scheme 2.3-1 Conceptual pathway for the aryl-ether synthesis from cyclohexenone

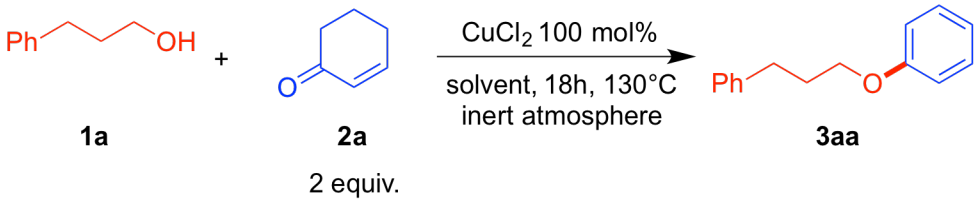
However, this transformation remains very challenging since it requires the right substance that will efficiently catalyze not only the formation of the adduct but also its selective oxidation in the presence of the alcohol and the 2-cyclohexenone, both of which can be oxidized.[19,32] Ideally, this reaction would involve a cheap and abundant metal catalyst, capable of performing the oxidative aromatization with readily available oxidants.

2.3.1 Development of the reaction conditions

Copper catalysts, in combination with molecular oxygen, are able to perform oxidation reactions.[33] In addition, their Lewis acid proprieties could potentially assist the nucleophilic attack to the carbonyl. A notable difference between copper and palladium is the ability of copper to access odd-electron states, allowing it to take part in redox single-electron processes. Thus copper appeared to us as a potential candidate to mediate such transformation.[34,35]

To begin our study, we investigated the reaction of 3-phenyl-1-propanol **1a** with 2-cyclohexenone **2a** in presence of copper chloride under an inert atmosphere at 130 ˚C. The solvent was found to be a critical parameter in this reaction (Table 2.3-1). An only trace amount of the desired aryl alkyl ether **3aa** product was detected when the reaction was performed in DMSO, previously reported by Stahl and co-workers for the dehydrogenation of cyclohexanones to phenols (entry 1). Ethers (entries 2-3) and halogenated solvent (entry 4) only afforded the product in trace amounts. Unfortunately, running the reaction under neat condition resulted in a very low yield (entry 5), and the use of water as solvent did not lead to any product (entry 6). Aromatic solvents like xylenes, chlorobenzene and toluene (entries 7-9) led to an average 40% product yield. Running the reaction with 2 equiv of $CuCl_2$ allowed for a drastic increase in yield, up to 95 % (entry10). Finally, carrying out the reaction with O_2 saturated toluene with an oxygen balloon generated the desired product in 82 % yield with only 1 equiv of copper chloride (entry 11).

Table 2.3-1 Influence of solvent in the oxidative condensation of 3-phenylpropan-1-ol **1a** with 2-cyclohexenone **2a**.



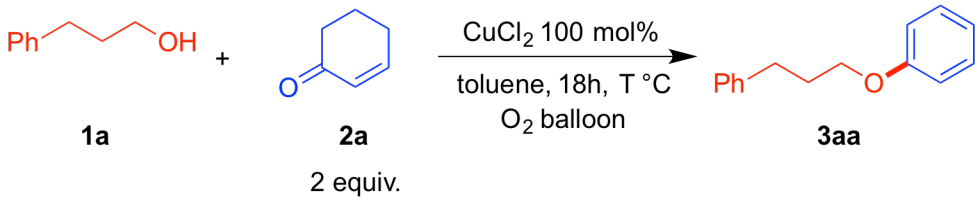
1a **2a** 2 equiv. **3aa**

Entry	Solvent	Conversion (%)[a]
1	DMSO	1
2	1,4-Dioxane	8
3	DME	4
4	1,2-Dichloroethane	0
5	Neat	15
6	Water	0
7	Xylenes	42
8	Chlorobenzene	40
9	Toluene	38
10	Toluene	95[b]
11	Toluene	82[c]

Reaction conditions: 3-phenylpropan-1-ol **1a** (0.1 mmol) with 2-cyclohexenone **2a** (2 equiv), copper salt (1 equiv), solvent (0.2 ml), argon, 130°C, 18h. [a] Conversions were determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard. [b] Reaction run with 2 equiv of $CuCl_2$. [c] Reaction run with O_2 saturated toluene with an oxygen balloon.

To investigate the potential reduction of the energy input of the transformation we evaluated the influence of the reaction temperature (Table 2.3-2). The reaction was slower at 60 and 80 ˚C (entries 1-2), while a yield of 72% was obtained at 100 ˚C (entry 3). We found that performing the reaction at 100 °C in a sealed reactor under 1 atmosphere of oxygen led to the formation of aryl alkyl ether **3aa** in 96% yield (entry 4).

Table 2.3-2 Influence of reaction temperature to the oxidative condensation of 3-phenylpropan-1-ol **1a** with 2-cyclohexenone **2a**.



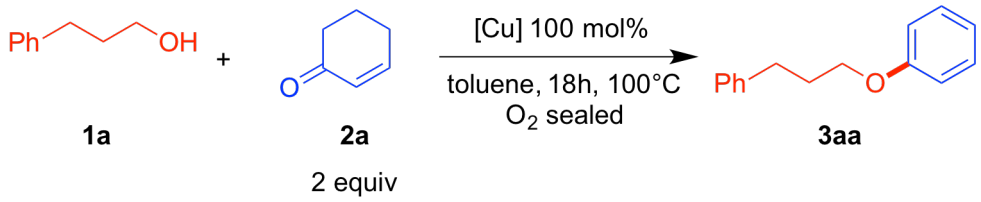
1a **2a** 2 equiv. **3aa**

Entry	Temperature (°C)	Conversion (%)[a]
1	60	40
2	80	63
3	100	72
4	100	96[b]
5	130	82

Reaction conditions: 3-phenylpropan-1-ol **1a** (0.1 mmol) with 2-cyclohexenone **2a** (2 equiv), copper salt (1 equiv), solvent (0.2 ml), argon, 130 °C, 18h. [a] Conversions were determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard. [b] O_2, sealed

Other copper sources were also evaluated (Table 2.3-3). $CuBr_2$ was less effective with a yield of 44% (entry 2), and copper(I) halide complexes showed no reactivity (entries 3-5). Copper(I) and (II) trifluoromethanesulfonate showed moderate activities (entries 6-7), yielding 24% and 21% of ether **3aa,** respectively. Other precursors such as CuO, $CuSO_4$ and $Cu(CN)_2$ did not afford any product (entries 8-10). Finally, the cheaper hydrated $CuCl_2$ turned out to be as efficient as anhydrous $CuCl_2$, leading to **3aa** with a yield of 97% (entry 11).

Table 2.3-3 Influence of copper source in the oxidative condensation of 3-phenylpropan-1-ol **1a** with 2-cyclohexenone **2a**.



1a **2a** (2 equiv) **3aa**

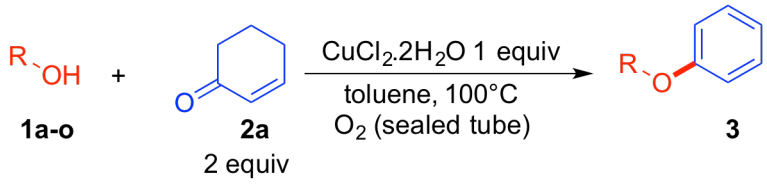
Entry	[Cu]	Conversion (%)[a]
1	$CuCl_2$	96
2	$CuBr_2$	44
3	CuCl	0
4	CuBr	9
5	CuI	0
6	$Cu(OTf)_2$	21
7	$[Cu(OTf)]_2$·toluene	24
8	CuO	0
9	$CuSO_4$	0
10	$Cu(CN)_2$	0
11	$CuCl_2.2H_2O$	97

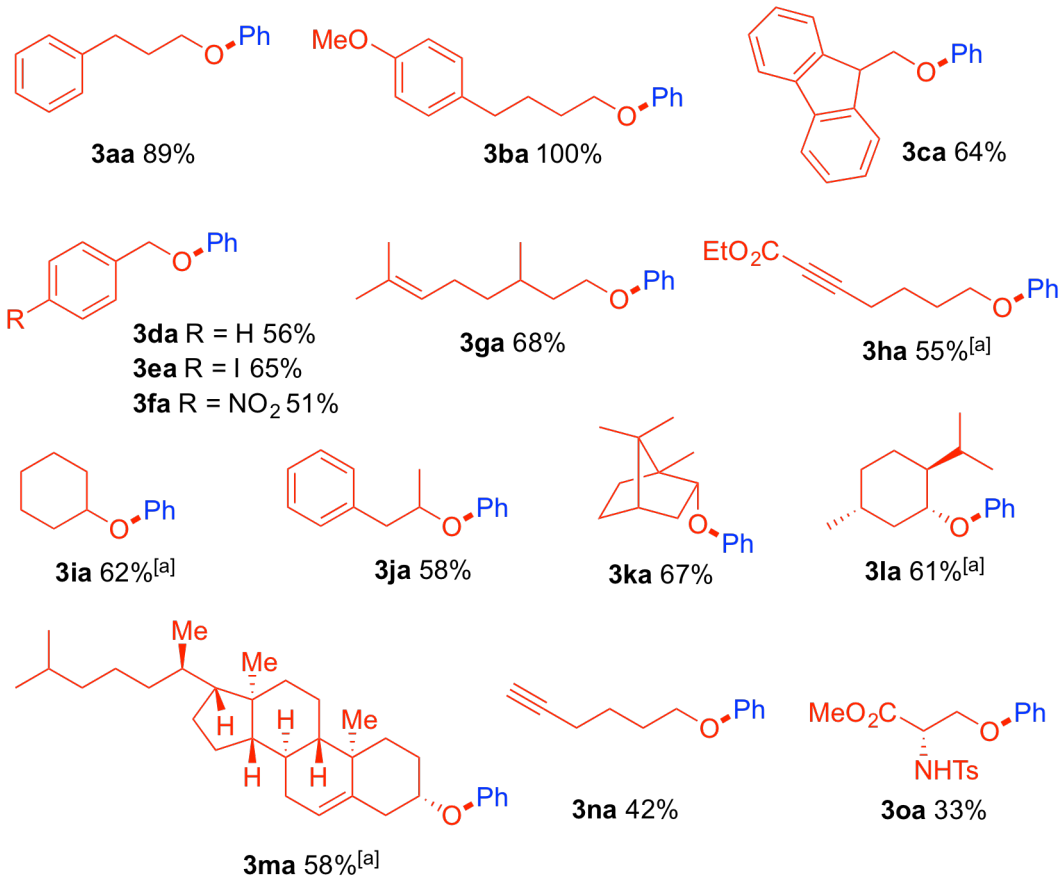
Reaction conditions: 3-phenylpropan-1-ol **1a** with 2-cyclohexenone **2a** (2 equiv), copper salt (1 equiv), toluene, O_2, 100 °C, 18h. OTf is trifluoromethanesulfonate (OSO_2CF_3). [a] Conversions were determined by ^1H NMR using 1,3,5-trimethoxybenzene as an internal standard.

2.3.2 Substrate scope

These optimized conditions were then applied to a wide range of substrates to investigate the scope of the reaction (Table 2.3-4). Phenyl alkyl ethers were obtained efficiently from the reaction of 2-cyclohexenone **2a** and various primary and secondary alcohols (**1a-o**). In particular, several functional groups such as methoxy (**3ba**), nitro (**3fa**), ester and internal alkynes (**3ha, 3ga**) were well tolerated in this reaction. In addition, the reaction proceeded readily in the presence of an iodo-aromatic derivative (**3ea**), which allows further functionalization of the product through classical coupling reactions.[36] Naturally functionalized alcohols like β-citronellol (**3ga**), (-)-borneol (**3ka**), (-)-menthol (**3la**) and cholesterol (**3ma**) were also successfully converted into the corresponding phenyl ethers with good yields. Alcohols with terminal alkyne functionality were also functionalized under these conditions (**3na**). Protected serine was also used in this reaction, however, affording the ether in a moderate 33% yield (**3oa**).

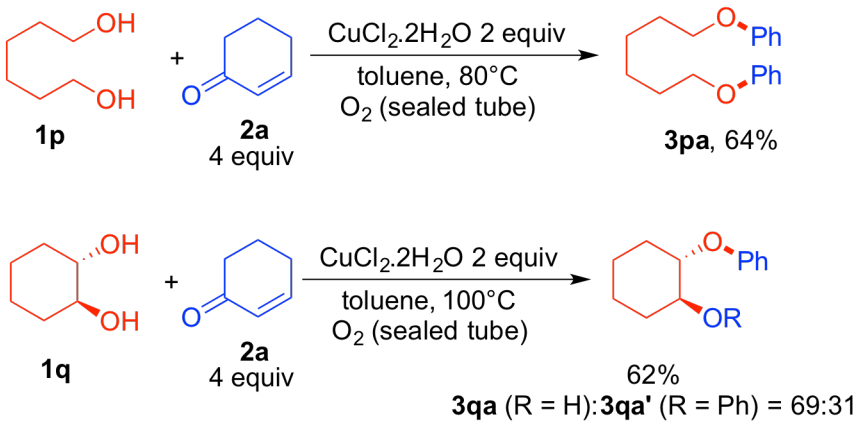
Table 2.3-4 Reaction scope of the oxidative condensation of alcohol and cyclohexenone **2a**.





Reaction conditions: Alcohol, 2-cyclohexenone (2 equiv), $CuCl_2.2H_2O$ (1 equiv), toluene, O_2, 100 °C, 18h. [a] Reaction conducted at 80 ˚C.

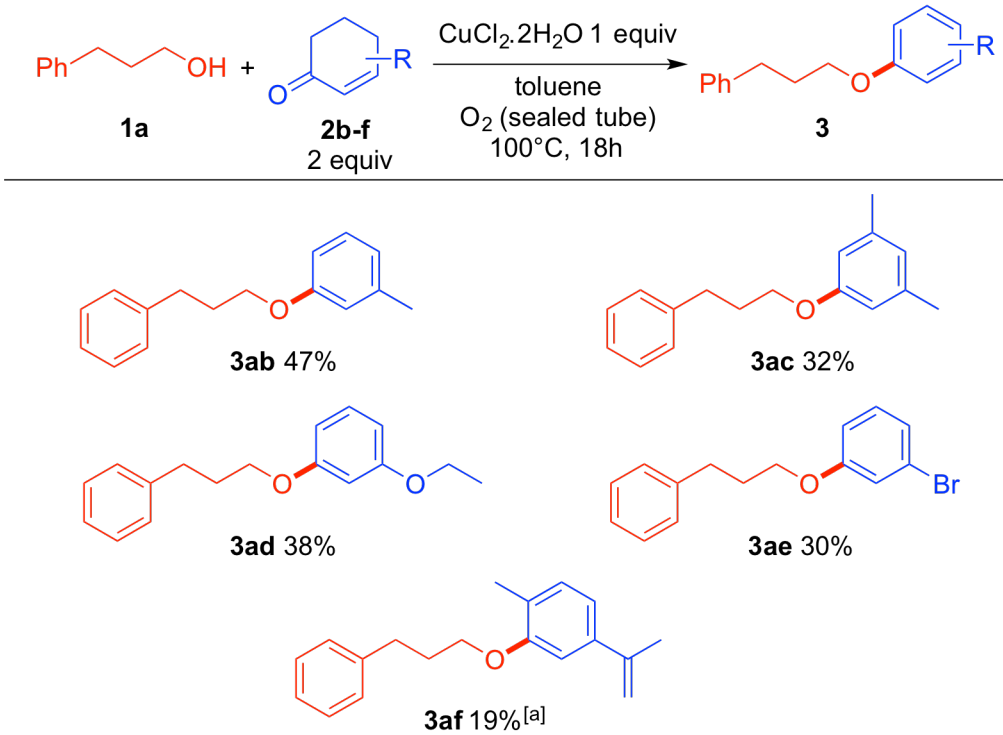
1,6-Diphenoxyhexane (**3pa**) was also prepared from 1,6-hexanediol (**1p**) affording the diether as the sole product in 64% yield (Scheme 2.3-2). In the case of a secondary diol like *trans*-1,2-cyclohexanediol, a mixture of mono- and diether was obtained with a good overall yield of 62% (**3qa, 3qa'**).



Scheme 2.3-2 Oxidative condensation of diols with 2-cyclohexenone **2a**.

To evaluate the influence of functional group of the ketone on the transformation, we also studied various 2-cyclohexenone (**2b-f**) derivatives to afford functionalized aryl ethers (Table 2.3-5). The reaction of methyl (**3ab, 3ac**), ethoxy (**3ad**) and bromo (**3ae**) substituted 2-cyclohexenone with **1a**, led to the corresponding ethers with moderate 30-47% yields. Interestingly, even *ortho*-substituted cyclohexenone such as (R)-carvone could be used as a substrate, although the desired product (**3af**) was only obtained in 19% and a lower temperature

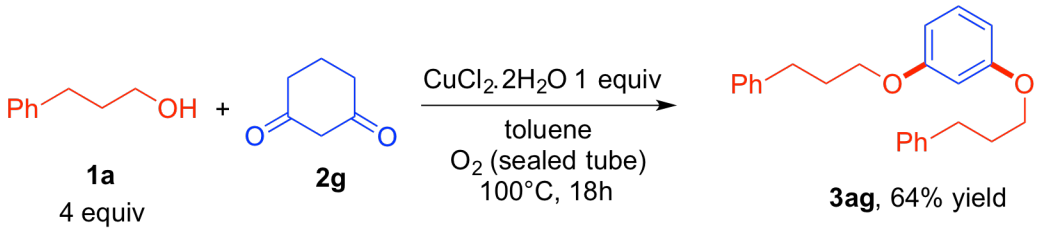
Table 2.3-5 oxidative condensations of various 2-cyclohexenone derivatives and 3-phenyl-1-propanol **1a.**



Reaction conditions: Alcohol, 2-cyclohexenone (2 equiv), $CuCl_2.2H_2O$ (1 equiv), toluene, O_2, 100 °C, 18h. [a] Reaction conducted at 80 ˚C.

was required, suggesting a strong influence of steric on the reactivity of ketone partner.

Finally, to examine the synthetic potential of more complex structures, we carried out the reaction of **1a** with 1,3-cyclohexanedione **2g**, which afforded the diether with a good 64% yield (Scheme 2.3-3).



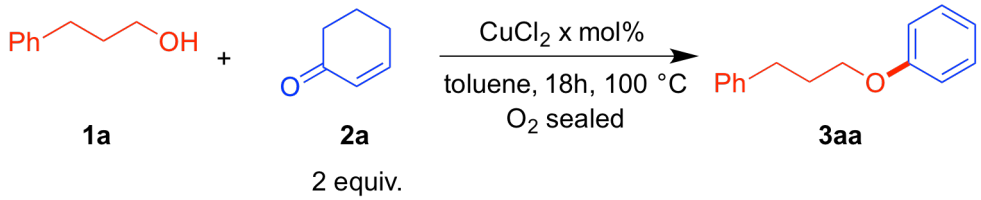
Scheme 2.3-3 Copper-catalyzed reaction of cyclohexane-1,3-dione **2g** with 3-phenyl-1-propanol **1a**.

2.3.3 System optimization with NHPI

In our continuing efforts to develop more sustainable reactions,[37,38] we attempted to improve this reaction by reducing the amount of copper catalyst required. Indeed, an "ideal" version of this reaction (from a green chemistry point of view) would require catalytic amounts of copper complexes, using O_2 as the sole terminal oxidant, and this sequence would only form water as by-product.[30]

Unfortunately, decreasing the catalyst loading of $CuCl_2$ in this reaction dramatically decreased the yield of the desired product, and with 10 mol% of $CuCl_2$ only 15% of the product was formed (Table 2.3-6 entry 4).

Table 2.3-6 Influence of the catalyst loading on the oxidative condensation of 3-phenylpropan-1-ol **1a** with 2-cyclohexenone **2a**.

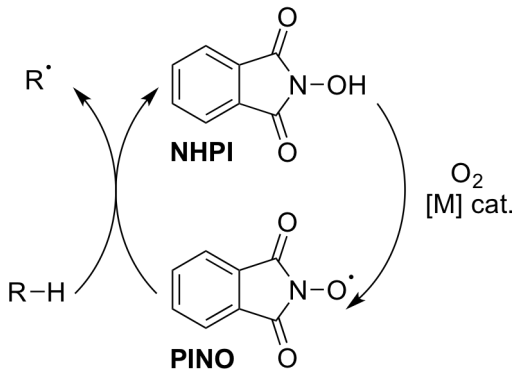


1a **2a** 2 equiv. **3aa**

Entry	Catalyst (x mol%)	Conversion (%)[a]
1	100	96
2	50	64
3	25	38
4	10	15

Reaction conditions: 3-phenylpropan-1-ol **1a** (0.1 mmol) with 2-cyclohexenone **2a** (2 equiv), copper salt (1 equiv), solvent (0.2 ml), oxygen, 100 °C, 18h. [a] Conversions were determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard.

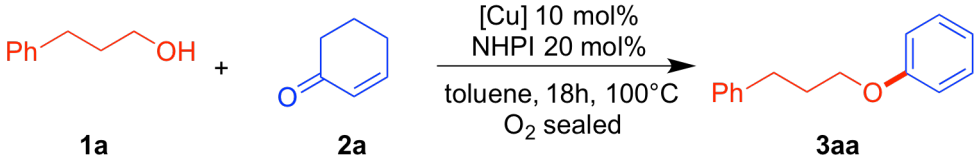
This result led us to investigate the addition of *N*-hydroxyphthalimide (NHPI) as a potential organo-cocatalyst. NHPI is a cheap and non-toxic precursor of phthalimido-*N*-oxyl (PINO) radical, which has been reported to be effective in C-H activation (Scheme 2.3-4). In combination with molecular oxygen and a transition metal (such as Cu, Co, Pb, and Fe),[39,40] a catalytic amount of NHPI is capable of efficiently performing hydrogen abstraction on a wide variety of substrates.[40–46]



Scheme 2.3-4 NHPI reactivity

To begin our study, we examined the oxidative condensation of 3-phenylpropan-1-ol **1a** with 2-cyclohexenone **2a** in the presence of 10 mol% of copper complexes and 20 mol% of NHPI (Table 2.3-7). An examination of copper sources revealed that in conjunction with NHPI, $CuCl_2$ only afford the desired product in 6% yield (entry 1) while CuCl showing no activity in the transformation (entry 2). The use of $Cu(OAc)_2$ did not provide any transformation either (entry 3). Copper (I) and (II) triflates afforded the desired product in reasonable yield (entries 4-5), with $Cu(OTf)_2$ being the most active copper complex for the regeneration of the PINO radical, allowing the formation of **3aa** with a 47% yield (entry 4). A combination of both copper (I) and (II) triflates merely provides the desired product in 36% yield (entry 6).

Table 2.3-7 Influence of copper source in combination with NHPI on the oxidative condensation of 3-phenylpropan-1-ol **1a** with 2-cyclohexenone **2a**



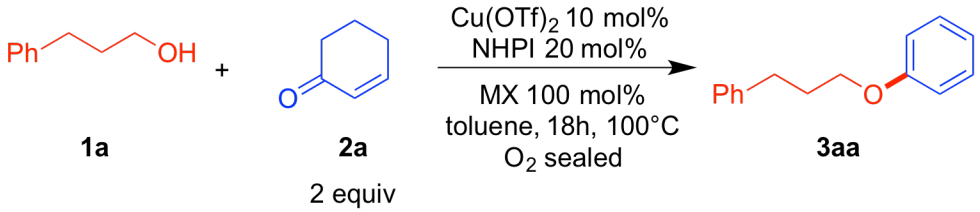
1a **2a** 2 equiv **3aa**

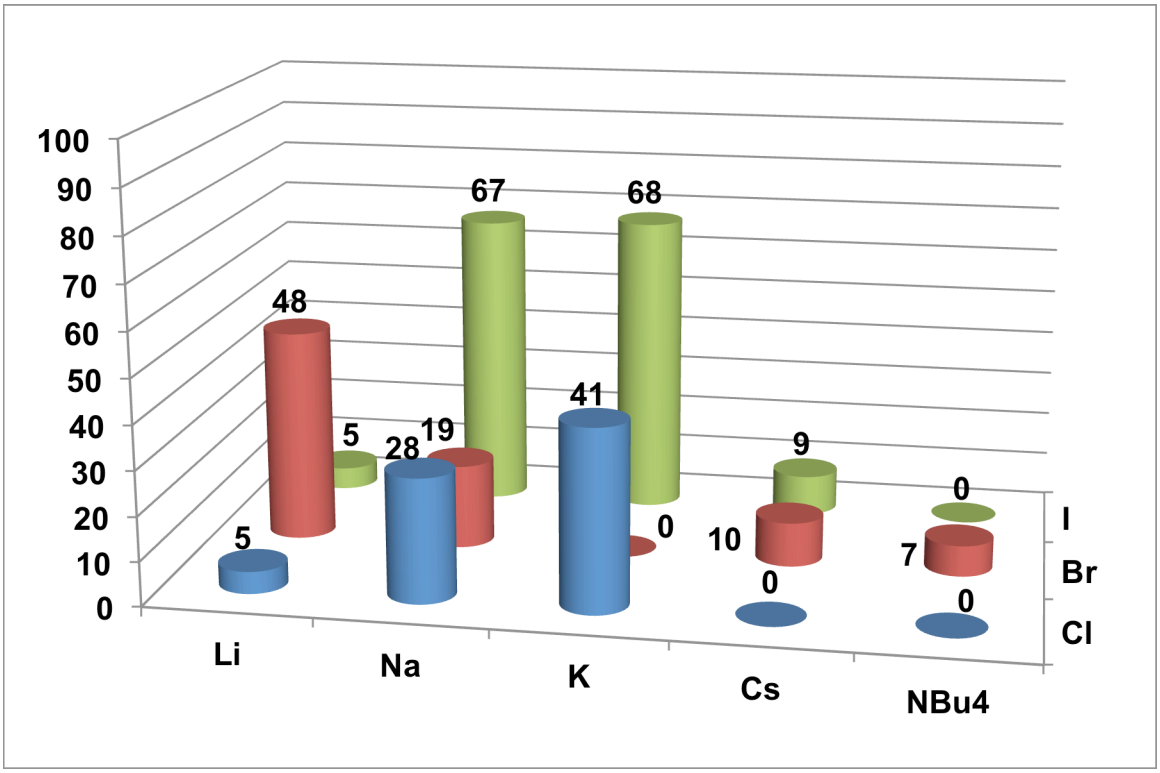
Entry	[Cu]	Conversion (%)[a]
1	$CuCl_2$	6
2	CuCl	0
3	$Cu(OAc)_2$	0
4	$Cu(OTf)_2$	47
5	$[Cu(OTf)]_2$.toluene	39
6	$Cu(OTf)_2$/$[Cu(OTf)]_2$.toluene	36

Reaction conditions: 3-phenylpropan-1-ol **1a** (0.1 mmol) with 2-cyclohexenone **2a** (2 equiv), copper salt (10 mol%), NHPI (20 mol%), solvent (0.2 ml), oxygen, 100 °C, 18h. [a] Conversions were determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard.

Subsequently, we studied the effect of MX type additives where M was Li, Na, or Cs and X was a halide: Cl, Br and I (Table 2.3-8).

Table 2.3-8 Influence of MX additive on the oxidative condensation of 3-phenylpropan-1-ol **1a** with 2-cyclohexenone **2a.**





M = Li, Na, K, Cs, NBu_4; X = Cl, Br, I. Reaction conditions: 3-phenylpropan-1-ol **1a** (0.1 mmol) with 2-cyclohexenone **2a** (2 equiv), copper salt (10 mol%), NHPI (20 mol%), MX (100 mol%), solvent (0.2 ml), oxygen, 100 °C, 18h. Conversions were determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard.

The best results were obtained with sodium and potassium iodide, which allowed the formation of about 70% of product (2nd and 3rd line, 3rd row). In the case of sodium iodide, the isolated yield of the product was 58%. Ammonium halides were also investigated in an attempt to improve solubility of the salt in the organic phase; unfortunately, no product was obtained. Interestingly, the use of NaI or KI appears to stabilize the catalyst. This is hypothesized from the formation of a black crude product without the additive after 18h; whereas the crude reaction mixture remained translucent with the addition of NaI or KI (Figure 2.3-1).

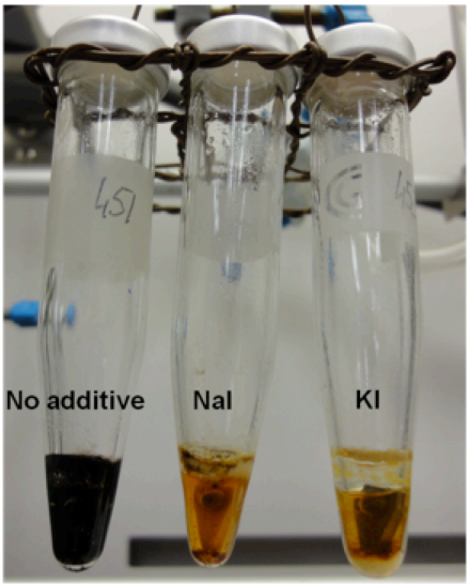


Figure 2.3-1 Influence of NaI and KI

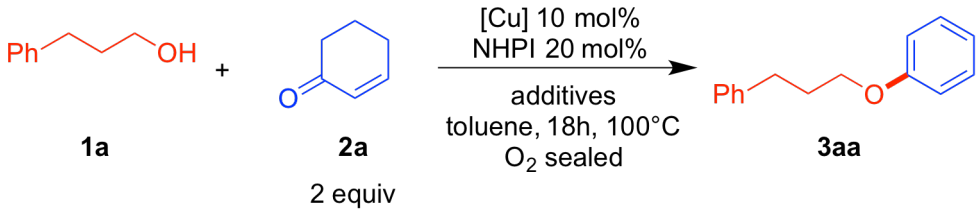
Consequently, we investigated the influence of the amount of potassium iodide (KI) (Table 2.3-9). While 1 equiv was found to significantly improve the reaction, leading to the formation of **3aa** with a yield of 68% (entry 2), a catalytic amount of KI only afforded the desired product in 40% yield (entry 3). As expected, NHPI is an essential additive in this reaction, since in its absence only 13% of product was obtained (entry 4). In order to check if the reaction was not due to the *in situ* formation of CuI_2 from KI and $Cu(OTf)_2$, which is known to then decompose

into CuI and I_2, the addition of several amounts of I_2 in combination with CuI was investigated. The use of 1 equiv of I_2 led to 14% of product (entry 5) but a catalytic amount (10 mol%) of I_2 yielded the product in 33% (entry 6). In both cases, 1-iodo-3-phenylpropane was formed as a by-product, which was not observed otherwise. No product was obtained without I_2 (entry 7).

The influence of a drying agent on the catalytic system was also investigated, with $MgSO_4$ (entry 8) and Na_2SO_4 (entry 9) affording the desired product in a moderate 30% and 27% yields, respectively. The addition of molecular sieve (MS 4Å) did not provide any product (entry10). The addition of 1 equiv of water proved to be beneficial, allowing the formation of 86% of product (entry 11), probably assisting the copper catalyst during the regeneration of the PINO radical.

Finally, to further facilitate the removal of hydrogen, the reaction was conducted under 1 bar of O_2, which further increased the yield of **3aa** to 92% (with an 83% isolated yield) (entry 12). This is comparable to the result obtained under the previous stoichiometric conditions (Table 2.3-3 entry 11).

Table 2.3-9 Optimization of the reaction conditions for the oxidative condensation of 3-phenylpropan-1-ol **1a** with 2-cyclohexenone **2a** using catalytic amounts of copper



1a **2a** 2 equiv **3aa**

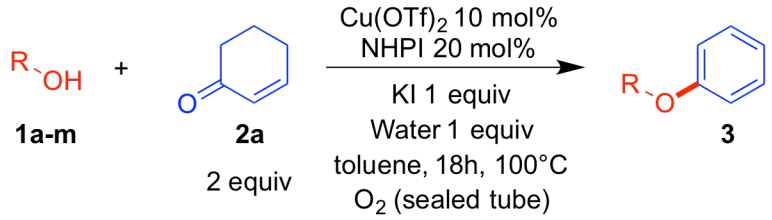
Entry	[Cu]	Additive (mol%)	Conversion (%)[a]
1	$Cu(OTf)_2$	none	47
2	$Cu(OTf)_2$	KI (100)	67
3	$Cu(OTf)_2$	KI (10)	40
4	$Cu(OTf)_2$	KI (100)	13[b]
5	CuI	I_2 (100)	14[c]
6	CuI	I_2 (10)	33[d]
7	CuI	none	0
8	$Cu(OTf)_2$	$MgSO_4$ (200)	30
9	$Cu(OTf)_2$	Na_2SO_4 (200)	27
10	$Cu(OTf)_2$	MS 4Å	0
11	$Cu(OTf)_2$	KI (100), H_2O (100)	86
12	$Cu(OTf)_2$	KI (100), H_2O (100)	92 (83)[e]

Reaction condition: 3-phenylpropan-1-ol **1a** (0.1 mmol) with 2-cyclohexenone **2a** (2 equiv), copper salt (10 mol%), NHPI (20 mol%), solvent (0.2 ml), oxygen, 100 °C, 18h. [a] Conversions were determined by 1H NMR using 1,3,5-trimethoxybenzene as an internal standard. Yield in bracket are isolated ones. [b] Reaction run without NHPI. [c] 67% of 1-iodo-3-phenylpropane detected. [d] 18% of 1-iodo-3-phenylpropane detected. [e] Reaction run under 1 bar of O_2.

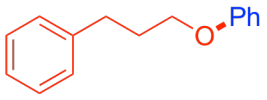
2.3.4 Substrate scope of the Cu/NHPI system

The scope of the reaction under the copper catalyzed conditions was then investigated (Table 2.3-10) and we were pleased to find that good overall reactivity was generally observed. Indeed, aryl ethers could be isolated with similar yields as under the initial conditions. In some cases, however, a higher temperature was found to be helpful to achieve higher conversions (**3da, 3ea, 3fa, 3ha, 3ja**), particularly in the case of benzylic alcohols.

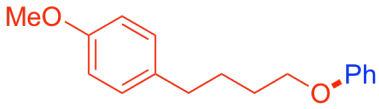
Table 2.3-10 Scope of the oxidative condensation of alcohols with 2-cyclohexenone **2a** using catalytic amounts of copper salt.



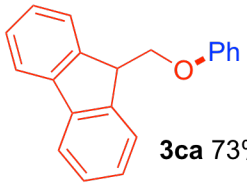
1a-m **2a** 2 equiv **3**



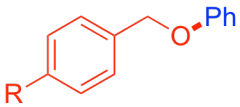
3aa 83% (89%)



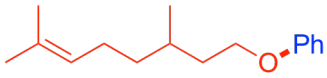
3ba 58% (100%)



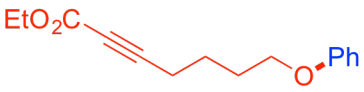
3ca 73% (64%)



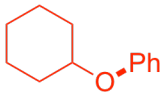
3da R = H 38%[b] (56%)
3ea R = I 59%[b] (65%)
3fa R = NO_2 60%[b] (51%)



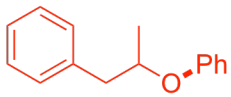
3ga 74% (68%)



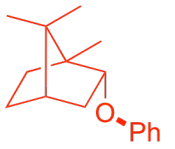
3ha 49%[b] (55%[a])



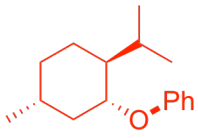
3ia 71% (62%[a])



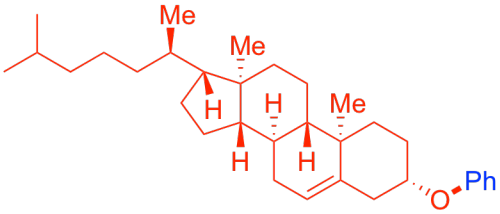
3ja 64%[b] (58%)



3ka 40% (67%)



3la 81% (61%[a])

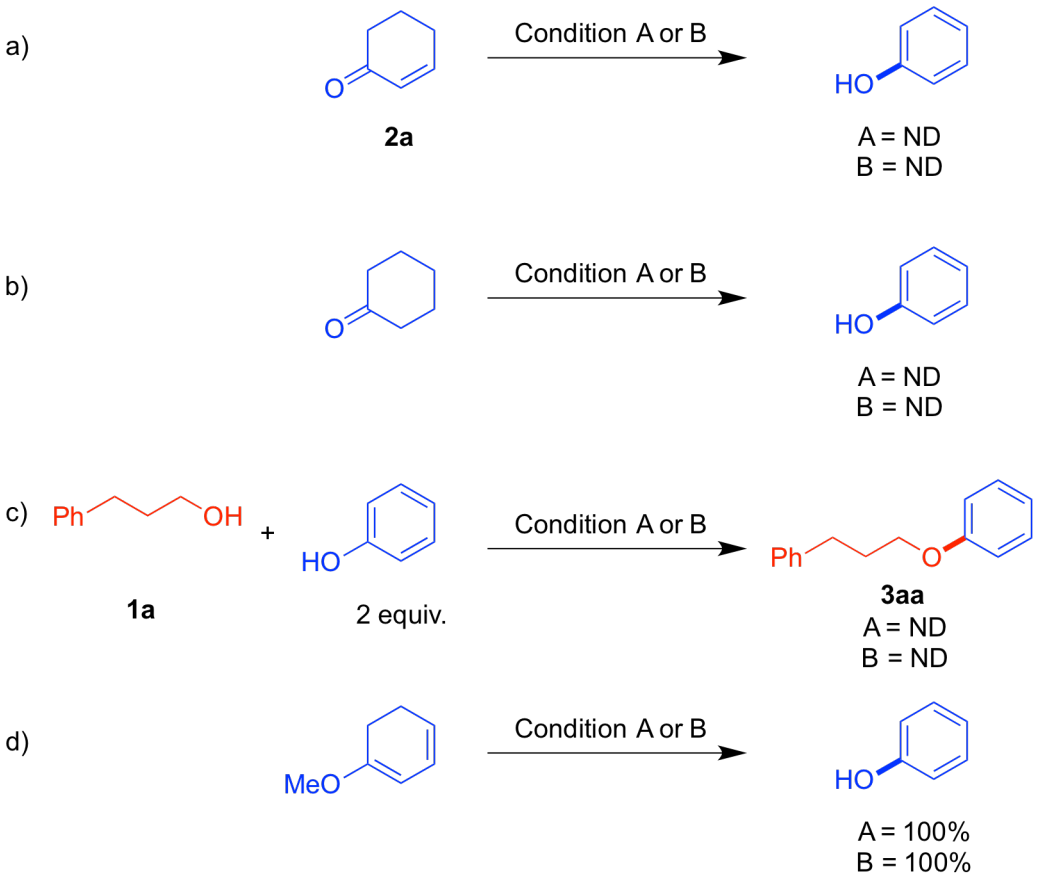


3ma 39% (58%[a])

For comparison, yields in brackets correspond to the reaction performed under stoichiometric conditions using $CuCl_2$. Catalytic reaction conditions: Alcohol, 2-cyclohexenone (2 equiv), $Cu(OTf)_2$ (10 mol %), NHPI (20 mol %), KI (1 equiv), H_2O (1 equiv), toluene, O_2 (1 bar), 100 °C, 18h. [a] Reaction conducted at 80 ˚C. [b] Reaction conducted at 120 ˚C for 24h.

2.3.5 Mechanistic discussion

To gain insights into this reaction, several control experiments were carried out to elucidate the mechanism (Scheme 2.3-5). When cyclohexenone **2a** was reacted under both optimized conditions in [d_8]toluene, no phenol was detected (Scheme 2.3-5a). Similarly, when cyclohexanone was submitted to 1 equiv of $CuCl_2$ (condition A) or to the Cu/NHPI system (condition B), no dehydrogenative aromatization reaction was observed and no phenol product was detected (Scheme 2.3-5b). The use of phenol instead of cyclohexenone **2a** with alkyl alcohol **1a** under both reaction conditions did not afford any aryl ether product **3aa** (Scheme 2.3-5c). However, when the commercially available 1-methoxy-1,3-cyclohexadiene was submitted to the optimized conditions in [d_8]toluene, anisole was formed as the sole product; suggesting that the catalytic system is only able to perform the oxidative aromatization on diene substrates (Scheme 2.3-5d). These results suggest that the catalytic system is only proficient enough to perform dehydrogenative aromatization on the alkoxydiene **II** intermediate. In addition, under the present conditions, no coupling between phenols and alkyl alcohol is achievable.



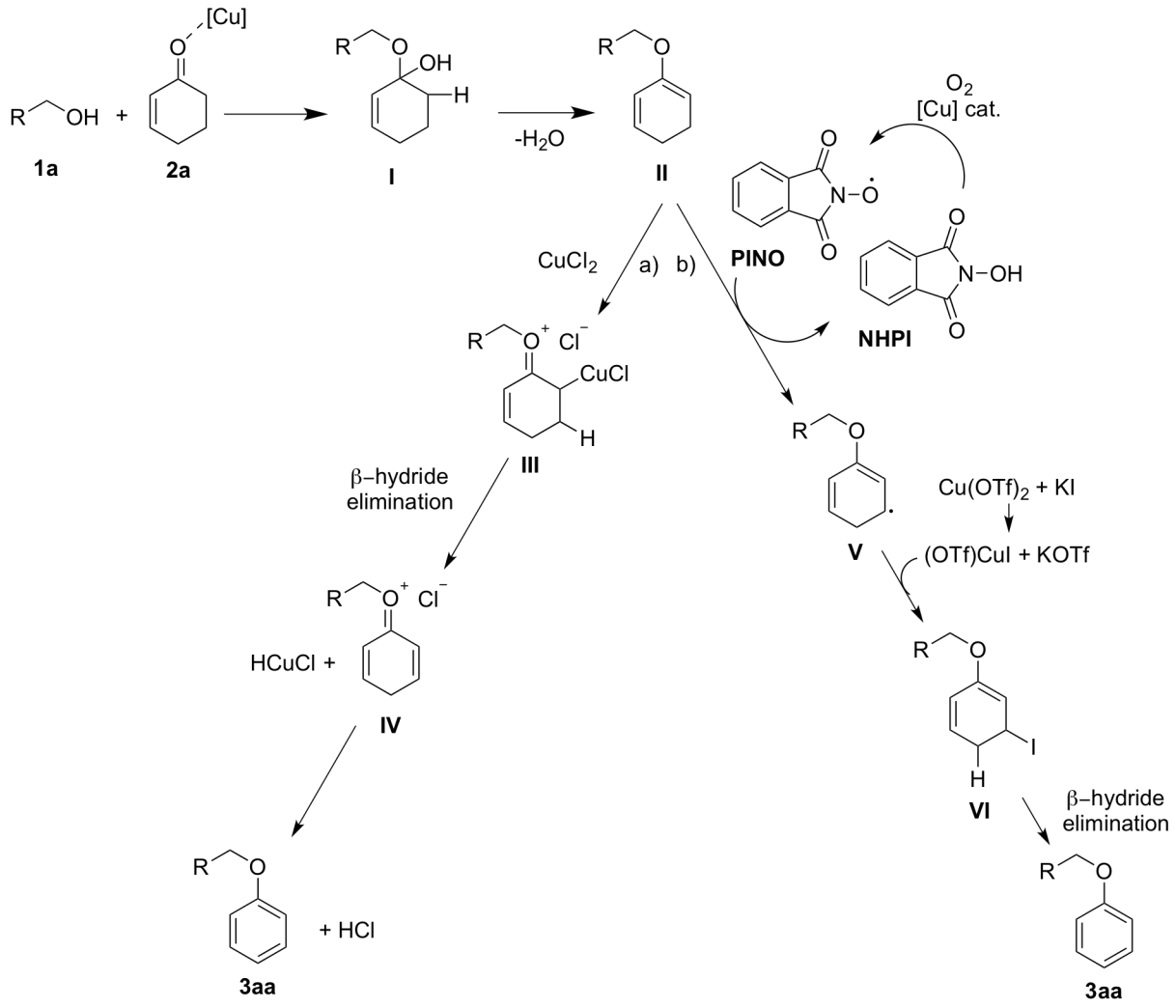
Scheme 2.3-5 Control experiments

Condition A: $CuCl_2$ (100 mol%), toluene, O_2 (1 bar), 100 °C, 18h. Condition B: $Cu(OTf)_2$ (10 mol %), NHPI (20 mol %), KI (1 equiv), H_2O (1 equiv), toluene, O_2 (1 bar), 100 °C, 18h.

Based on these results and previously reported literature the following reaction mechanisms can be proposed (Scheme 2.3-6). The hemiacetal **I** may be formed through electrophilic activation of the ketone by the copper complex, and elimination of water could lead to the alkoxydiene **II** (or an isomer).

Under the reaction conditions A (Scheme 2.3-6a), the alkoxydiene **II** could attack the electron-poor $CuCl_2$ and form the intermediate **III**, which upon β-hydride elimination followed by aromatization would yield the desired product **3aa** and the copper hydride species HCuCl.

NHPI has been described to efficiently catalyze the oxidation of many different classes of organic compounds and is capable of performing hydrogen abstraction.[40–46] Under the reaction conditions B (Scheme 2.3-6b), NHPI can form the PINO radical in presence of copper and oxygen. The abstraction of a hydrogen atom from **II** by the in situ formed N-oxyl radical would yield intermediate **V**. $Cu(OTf)_2$ in presence of KI can undergo ligand exchange to form TfOCuI and KOTf, which can then react with the alkoxydiene radical **V** to form CuOTf and the iododiene intermediate **VI** which undergoes β-hydride elimination to afford the desired product **3aa**.



Scheme 2.3-6 Proposed mechanism for the formation of aryl alkyl ether

3aa from **1a** and **2a**

a) Condition A: $CuCl_2$ (100 mol%), toluene, O_2 (1 bar), 100 °C, 18h. b) Condition B: $Cu(OTf)_2$ (10 mol%), NHPI (20 mol%), KI (1 equiv), H_2O (1 equiv), toluene, O_2 (1 bar), 100°C, 18h.

2.4 Conclusion and outlook

In summary, we have developed the first step toward an original approach for the synthesis of functionalized arenes from phenols. This was demonstrated by proving that cyclohexenones are suitable substrates to access functionalized arenes through oxidative catalysis with nucleophilic addition. This is a straightforward method to access a range of functionalized products from readily available starting materials. The copper-catalyzed reaction uses O_2 as the terminal oxidant and formally generates water as the only by-product. Considering the wide utility of ethers, these results show a simplified synthetic sequence, which will certainly pave the way for new applications and developments in both the academic and industrial fields.

2.5 Experimental section

2.5.1 General information

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 precoated plates (0.25 mm) or Sorbent Silica Gel 60 F254 plates. The developed chromatography was analyzed by UV lamp (254 nm) and potassium permanganate as visualization methods. Flash column chromatography was performed with E. Merck silica gel 60 (230–400 mesh) or SORBENT silica gel 30-60 μm. GCMS analysis was conducted on an Agilent GCMS-6890N instrument equipped with a HP-5 column (30 m × 0.25 mm, Hewlett-Packard) and Agilent 5973 Mass Selective Detector. High-resolution mass spectra (HRMS) were obtained from a JEOL JMS-700 instrument (ESI). Nuclear magnetic resonance (NMR) spectra were recorded on Varian MERCURY plus-300 spectrometer (^{1}H 300 MHz, ^{13}C 75 MHz) spectrometer or a Varian MERCURY plus-400 spectrometer (^{1}H 400 MHz, ^{13}C 100 MHz). Chemical shifts for ^{1}H NMR spectra are reported in parts per million (ppm) from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$: δ 7.26 ppm). Chemical shifts for ^{13}C NMR spectra are reported in parts per million (ppm) from tetramethylsilane with the solvent as the internal standard ($CDCl_3$: δ 77.0 ppm). Data are reported as following: chemical shift, multiplicity (s = singlet, d = doublet, dd = doublet of doublets, t = triplet, q = quartet, m = multiplet, br = broad signal) and integration. Liquid reagents were used after distillation over CaH_2 under reduced pressure. Toluene was dried over alumina column prior to use. All other commercially available compounds were purchased and used as received. Ethyl 7-hydroxy-2-heptynoate[47] **1h**, *N-p-*

toluenesulfonyl-L-serine methyl ester[48] **1o**, and 3-bromo-2-cyclohenone[49] **2e** were prepared according to procedures reported in the literature. Characterization data for the following compounds matched data reported previously: (3-phenylpropoxy)benzene[50] **3aa**, (phenoxymethyl)benzene[51] **3da**, 1-iodo-4-(phenoxymethyl)benzene[52] **3ea**, 1-nitro-4-(phenoxymethyl)benzene[53] **3fa**, ((3,7-dimethyloct-6-en-1-yl)oxy)benzene[54] **3ga**, (cyclohexyloxy)benzene[55] **3ia**, *Endo*-(1S)-1,7,7-trimethyl-2-phenoxybicyclo[2.2.1]heptane[56] **3ka,** (((1R,2S,5R)-2-Isopropyl-5-methylcyclohexyl)oxy)benzene[57] **3la,** phenyl cholesteryl ether[58] **3ma**, 1,6-diphenoxyhexane[59] **3pa**, *trans*-2-phenoxycyclohexanol[60] **3qa**.

2.5.2 General procedures

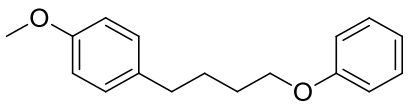
2.5.2.1 Typical procedure for the $CuCl_2$-catalyzed formation of aryl ethers

Copper(II) chloride dihydrate (0.3 mmol, 1 equiv) was charged in a septum capped vial. The vial was placed under vacuum for 10 minutes then under an O_2 atmosphere (due to the low solubility of oxygen in toluene, saturation of the solvent with oxygen before use is a crucial parameter). Toluene was treated by 5 cycles of vacuum/O_2 atmosphere, followed by bubbling of O_2 for 1 hour, and then added into the vial (0.6 mL). The alcohol (0.3 mmol) and the 2-cyclohexenone derivative (0.6 mmol, 2 equiv) were successively added under an O_2 atmosphere, and the septum was replaced by a cap, which was sealed. The reaction mixture was stirred for 18h at 80 or 100 °C. The mixture was then allowed to cool down to room temperature and then flushed through a short column of silica gel with dichloromethane. After rotary evaporation, the compound was isolated by flash chromatography on silica gel.

2.5.2.2 Typical procedure for the $Cu(OTf)_2$-catalyzed formation of aryl ethers

Copper(II) triflate (0.03 mmol, 10 mol%), NHPI (0.06 mmol, 20 mol%) and KI (0.3 mmol, 1 equiv) were charged in a septum capped vial. The vial was placed under vacuum for 10 minutes then under an O_2 atmosphere. Toluene was treated by 5 cycles of vacuum/O_2 atmosphere, followed by bubbling of O_2 for 1 hour, and then added into the vial (0.6 mL). The alcohol (0.3 mmol), water (0.3 mmol, 1 equiv) and the 2-cyclohexenone derivative (0.6 mmol, 2 equiv) were successively added under an O_2 atmosphere, and the septum was replaced by a cap. The reaction mixture was placed in a carousel under 1 bar of O_2 and stirred for 18h at 100 °C or for 24h at 120 °C. The mixture was then allowed to cool down to room temperature and then flushed through a short column of silica gel with dichloromethane. After rotary evaporation, the compound was isolated by flash chromatography on silica gel.

2.5.3 Characterization data of new compounds



1-methoxy-4-(4-phenoxybutyl)benzene, **3ba**

Prepared according to the general procedure in section 2.5.2.1 typical procedure for the $CuCl_2$-catalyzed formation of aryl ethers from alcohol **1b** and cyclohexanone **2a**.

Yield: 100%

Prepared according to the general procedure in section 2.5.2.2 typical procedure for the $Cu(OTf)_2$-catalyzed formation of aryl ethers from alcohol **1b** and cyclohexanone **2a**.

Yield: 83%

Appearance: yellow oil.

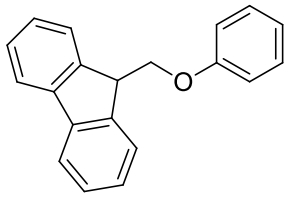
Rf: 0.56 (hexane/ethyl acetate 9:1).

^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.25-7.32 (2H, m, Ar*H*), 7.13 (2H, d, *J* = 6.4 Hz, Ar*H*), 6.82-6.98 (5H, m, Ar*H*), 3.98 (2H, t, *J* = 5.0 Hz, CH_2CH_2OPh), 3.80 (3H, s, CH_3O), 2.65 (2H, t, *J* = 5.2 Hz, $ArCH_2CH_2$), 1.74-1.88 (4H, m, $ArCH_2CH_2CH_2$).

^{13}C NMR (75 MHz, $CDCl_3$, δ): 159.0, 157.8, 134.3, 129.4, 129.3, 120.5, 114.5, 113.7, 67.6, 55.3, 34.7, 28.8, 28.1.

MS (EI, m/z): 256 (M^+ 31%), 163 (47%), 134 (13%), 121 (100%).

HRMS: calculated for $C_{17}H_{20}NaO_2$ $(M+Na)^+$: 279.13555; found: 279.13447.



9-(phenoxymethyl)-9*H*-fluorene, **3ca**

Prepared according to the general procedure in section 2.5.2.1 typical procedure for the $CuCl_2$-catalyzed formation of aryl ethers from alcohol **1c** and cyclohexanone **2a**.

Yield: 64%

Prepared according to the general procedure in section 2.5.2.2 typical procedure for the $Cu(OTf)_2$-catalyzed formation of aryl ethers from alcohol **1c** and cyclohexanone **2a**.

Yield: 73%

Appearance: white solid.

Mp: 91°C.

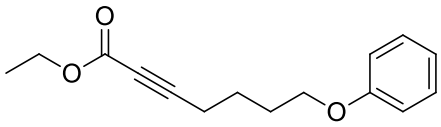
Rf: 0.40 (hexane/dichloromethane 3:1).

^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.80 (2H, d, *J* = 7.4 Hz, Ar*H*), 7.74 (2H, d, *J* = 7.5 Hz, Ar*H*), 7.42 (2H, t, *J* = 6.9 Hz, Ar*H*), 7.27-7.39 (4H, m, Ar*H*), 6.93-7.04 (3H, m, Ar*H*), 4.43 (1H, t, *J* = 7.4 Hz, C*H*CH_2OPh), 4.22 (2H, d, *J* = 7.5 Hz, CHC*H*$_2$OPh).

^{13}C NMR (75 MHz, $CDCl_3$, δ): 158.8, 144.3, 141.3, 129.5, 127.7, 127.1, 125.4, 120.9, 120.0, 114.5, 70.5, 47.4.

MS (EI, m/z): 272 (M^+ 21%), 179 (80%), 178 (100%), 165 (38%).

HRMS: calculated for $C_{20}H_{16}NaO$ $(M+Na)^+$: 295.10934; found: 295.10948.



Ethyl-7-phenoxyhept-2-ynoate, **3ha**

Prepared according to the general procedure in section 2.5.2.1 typical procedure for the $CuCl_2$-catalyzed formation of aryl ethers from alcohol **1h** and cyclohexanone **2a**.

Yield: 55%

Prepared according to the general procedure in section 2.5.2.2 typical procedure for the $Cu(OTf)_2$-catalyzed formation of aryl ethers from alcohol **1h** and cyclohexanone **2a**.

Yield: 49%

Appearance: orange oil.

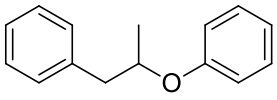
Rf: 0.45 (hexane/ethyl acetate 4:1).

^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.24-7.33 (2H, m, Ar*H*), 6.85-6.98 (3H, m, Ar*H*), 4.22 (2H, q, *J* = 7.1 Hz, COOC*H*$_2$CH$_3$), 3.98 (2H, t, *J* = 6.1 Hz, PhO C*H*$_2$CH$_2$), 2.43 (2H, t, *J* = 6.8 Hz, CH$_2$C*H*$_2$CC), 1.85-1.97 (2H, m, CH$_2$C*H*$_2$CH$_2$), 1.73-1.85 (2H, m, CH$_2$C*H*$_2$CH$_2$), 1.31 (3H, t, *J* = 7.1 Hz, CH$_2$C*H*$_3$).

^{13}C NMR (75 MHz, $CDCl_3$, δ): 158.8, 153.8, 129.4, 120.7, 114.4, 88.7, 73.5, 66.9, 61.8, 28.4, 24.3, 18.4, 14.0.

MS (EI, m/z): 246 (M^+ 14%), 207 (32%), 171 (10%), 144 (11%), 125 (28%), 107 (31%), 94 (100%), 79 (55%).

HRMS: calculated for $C_{15}H_{19}O_3$ $(M+H)^+$: 247.13287; found: 247.1329.



2-Phenoxy-1-phenylpropane, **3ja**

Prepared according to the general procedure in section 2.5.2.1 typical procedure for the CuCl2-catalyzed formation of aryl ethers from alcohol **1j** and cyclohexanone **2a**.

Yield: 58%

Prepared according to the general procedure in section 2.5.2.2 typical procedure for the $Cu(OTf)_2$-catalyzed formation of aryl ethers from alcohol **1j** and cyclohexanone **2a**.

Yield: 64%

Appearance: yellow oil.

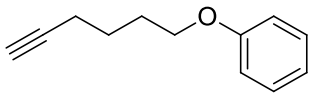
Rf: 0.63 (hexane/ethyl acetate 9:1).

^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.18-7.33 (7H, m, Ar*H*), 6.86-6.96 (3H, m, Ar*H*), 4.52-4.64 (1H, m, $PhCH_2CHOPh$), 3.11 (1H, dd, J = 13.6 Hz and J = 5.8 Hz, $PhCH_2CH$), 2.82 (1H, dd, J = 13.6 Hz and J = 6.7 Hz, $PhCH_2CH$), 1.30 (3H, d, J = 6.1 Hz, $CHCH_3$).

^{13}C NMR (75 MHz, $CDCl_3$, δ): 157.8, 138.2, 129.5, 129.4, 128.3, 120.7, 116.0, 74.6, 42.6, 19.4.

MS (EI, m/z): 212 (M^+ 28%), 121 (40%), 118 (37%), 94 (31%), 91 (100%), 77 (21%).

HRMS: calculated for $C_{15}H_{16}AgO$ $(M+Ag)^+$: 319.02466; found: 319.02445.



(Hex-5-yn-1-yloxy)benzene, **3na**

Prepared according to the general procedure in section 2.5.2.1 typical procedure for the $CuCl_2$-catalyzed formation of aryl ethers from alcohol **1n** and cyclohexanone **2a**.

Yield: 42%

Appearance: pale yellow oil.

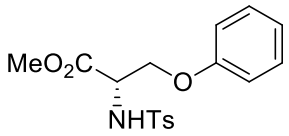
Rf: 0.78 (hexane/ethyl acetate 9:1).

^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.24-7.32 (2H, m, Ar*H*), 6.86-6.97 (3H, m, Ar*H*), 3.99 (2H, t, *J* = 6.2 Hz, C*H*$_2$OPh), 2.78 (2H, td, *J* = 7.0 Hz and *J* = 2.6 Hz, C*H*$_2$CCH), 1.97 (1H, t, *J* = 2.6 Hz, CH_2CC*H*), 1.86-1.95 (2H, m), 1.66-1.78 (2H, m).

^{13}C NMR (75 MHz, $CDCl_3$, δ): 158.9, 129.4, 120.6, 114.4, 84.1, 68.6, 67.1, 28.3, 25.1, 18.2.

MS (EI, m/z): 174 (M^+ 13%), 145 (7%), 131 (6%), 94 (100%), 79 (24%).

HRMS: calculated for $C_{12}H_{15}O$ $(M+H)^+$: 175.11174; found: 175.1112.



(S)-Methyl 2-(4-methylphenylsulfonamido)-3-phenoxypropanoate, **3oa**

Prepared according to the general procedure in section 2.5.2.1 typical procedure for the $CuCl_2$-catalyzed formation of aryl ethers from alcohol **1o** and cyclohexanone **2a**.

Yield: 33%

Appearance: brown solid.

Mp: 101°C.

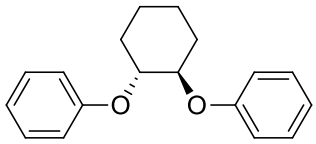
Rf: 0.19 (hexane/ethyl acetate/dichloromethane 7:2:1).

^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.21-7.31 (4H, m, Ar*H*), 7.75 (2H, d, *J* = 8.3 Hz, Ar*H*), 6.97 (1H, t, *J* = 7.3 Hz, Ar*H*), 6.79 (2H, d, *J* = 7.8 Hz, Ar*H*), 5.55 (1H, d, *J* = 9.5 Hz, O_2CHNH), 4.27-4.35 (2H, m, CH_2OPh), 4.11-4.18 (1H, m, $CH_3OCOCHNH$), 3.60 (3H, s, CH_3O), 2.40 (3H, s, $SO_2C_6H_4CH_3$).

^{13}C NMR (75 MHz, $CDCl_3$, δ): 169.4, 157.8, 143.8, 136.9, 129.5, 127.7, 127.1, 121.6, 114.6, 68.7, 55.5, 52.9, 21.5.

MS (EI, m/z): 349 (M^+ 23%), 256 (67%), 155 (93%), 91 (100%).

HRMS: calculated for $C_{17}H_{20}NO_5S$ $(M+H)^+$: 350.10567; found: 350.10494.



Trans-1,2-diphenoxycyclohexane, **3qa'**

Prepared with two equivalent of Copper salt according to the general procedure in section 2.5.2.1 typical procedure for the $CuCl_2$-catalyzed formation of aryl ethers from alcohol **1q** and 2 equiv of cyclohexanone **2a**.

Yield: 62%

Appearance: pale yellow oil.

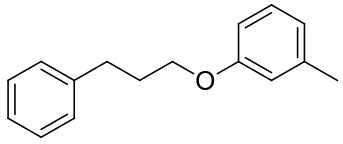
Rf: 0.63 (hexane/dichloromethane, 1:1).

^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.20-7.31 (4H, m, Ar*H*), 6.89-6.98 (6H, m, Ar*H*), 4.33-4.44 (2H, m, CH_2CHOPh), 2.10-2.44 (2H, m), 1.70-1.84 (2H, m), 1.52-1.70 (2H, m), 1.34-1.48 (2H, m).

^{13}C NMR (75 MHz, $CDCl_3$, δ): 158.2, 129.4, 120.9, 116.5, 78.0, 29.1, 22.7.

MS (EI, m/z): 268 (M^+ 49%), 175 (64%), 145 (1.3%), 133 (6%), 107 (41%), 94 (24%), 81 (100%).

HRMS: calculated for $C_{18}H_{20}NaO_2$ $(M+Na)^+$: 291.13555; found: 291.13474.



1-Methyl-3-(3-phenylpropoxy)benzene, **3ab**

Prepared according to the general procedure in section 2.5.2.1 typical procedure for the $CuCl_2$-catalyzed formation of aryl ethers from alcohol **1a** and cyclohexanone **2b**.

Yield: 47%

Appearance: pale yellow oil.

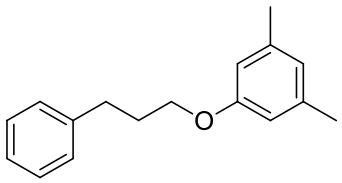
Rf: 0.81 (hexane/ethyl acetate 4:1).

^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.11-7.38 (6H, m, Ar*H*), 6.68-6.83 (3H, m, Ar*H*), 3.96 (2H, t, *J* = 6.3 Hz, CH_2CH_2OAr), 2.83 (2H, t, *J* = 7.3 Hz, $PhCH_2CH_2$), 2.34 (3H, s, CH_3), 2.04-2.20 (2H, $CH_2CH_2CH_2Ph$).

^{13}C NMR (75 MHz, $CDCl_3$, δ): 159.0, 141.6, 139.4, 129.2, 128.5, 128.4, 125.9, 121.4, 115.4, 111.4, 66.7, 32.2, 30.9, 21.5.

MS (EI, m/z): 226 (67%), 118 (42%), 108 (41%), 91 (100%).

HRMS: calculated for $C_{16}H_{18}NaO$ $(M+Na)^+$: 249.12499; found: 249.12493.



1,3-Dimethyl-5-(3-phenylpropoxy)benzene, **3ac**

Prepared according to the general procedure in section 2.5.2.1 typical procedure for the $CuCl_2$-catalyzed formation of aryl ethers from alcohol **1a** and cyclohexanone **2c**.

Yield: 32%

Appearance: Pale yellow oil.

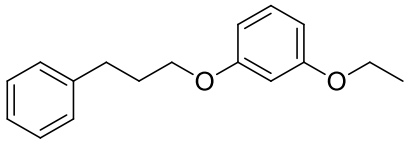
Rf: 0.83 (hexane/ethyl acetate 4:1).

^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.13-7.35 (5H, m, Ar*H*), 6.59 (1H, s, Ar*H*), 6.53 (2H, s, Ar*H*), 3.94 (2H, t, *J* = 6.5 Hz, CH_2CH_2OAr), 2.81 (2H, t, *J* = 7.6 Hz, $PhCH_2CH_2$), 2.29 (6H, s, CH_3Ar), 2.00-2.15 (2H, m, $CH_2CH_2CH_2OAr$).

^{13}C NMR (75 MHz, $CDCl_3$, δ): 159.0, 141.6, 139.1, 128.5, 128.4, 125.9, 122.4, 112.3, 66.6, 32.2, 30.9, 21.4.

MS (EI, m/z): 240 (M^+ 84%), 149 (4%), 122 (85%), 107 (15%), 91 (100%).

HRMS: calculated for $C_{17}H_{21}O$ $(M+H)^+$: 241.15869; found: 241.15844.



1-Ethoxy-3-(3-phenylpropoxy)benzene, **3ad**

Prepared according to the general procedure in section 2.5.2.1 typical procedure for the $CuCl_2$-catalyzed formation of aryl ethers from alcohol **1a** and cyclohexanone **2d**.

Yield: 38%

Appearance: pale yellow oil.

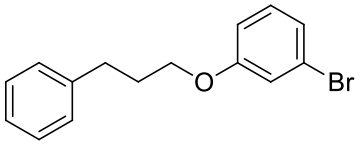
Rf: 0.53 (hexane/ethyl acetate 9:1).

^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.12-7.35 (6H, m, Ar*H*), 6.42-6.55 (3H, m, Ar*H*), 3.96 (2H, q, *J* = 7.0 Hz, C*H*$_2$CH$_3$), 3.95 (2H, t, *J* = 6.3 Hz, ArOC*H*$_2$CH$_3$), 2.81 (2H, t, *J* = 7.5 Hz, CH$_2$C*H*$_2$Ph), 2.06-2.14 (2H, m, CH$_2$C*H*$_2$CH$_2$), 1.41 (3H, t, *J* = 7.0 Hz, CH$_2$C*H*$_3$).

^{13}C NMR (75 MHz, $CDCl_3$, δ): 160.2, 160.1, 141.5, 129.8, 128.5, 128.4, 125.9, 106.7, 106.6, 101.4, 66.8, 63.4, 32.2, 30.8, 14.8.

MS (EI, m/z): 256 (M^+ 73%), 207 (25%), 138 (55%), 110 (44%), 91 (100%).

HRMS: calculated for $C_{17}H_{20}NaO_2$ $(M+Na)^+$: 279.13555; found: 279.13636.



1-Bromo-3-(3-phenylpropoxy)benzene, **3ae**

Prepared according to the general procedure in section 2.5.2.1 typical procedure for the $CuCl_2$-catalyzed formation of aryl ethers from alcohol **1a** and cyclohexanone **2e**.

Yield: 30%

Appearance: brown oil.

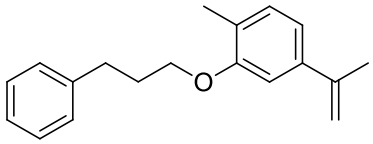
Rf: 0.29 (hexane/dichloromethane 4:1).

^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.16-7.33 (6H, m, Ar*H*), 6.88-6.95 (2H, m, Ar*H*), 6.76-6.81 (1H, m, Ar*H*), 3.94 (2H, t, *J* = 6.2 Hz, CH_2CH_2OAr), 2.81 (2H, t, *J* = 7.4 Hz, $PhCH_2CH_2$), 2.07-2.15 (2H, m, $CH_2CH_2CH_2$).

^{13}C NMR (75 MHz, $CDCl_3$, δ): 159.8, 141.3, 134.8, 130.2, 128.5, 128.4, 126.0, 120.8, 114.8, 113.0, 67.1, 32.1, 30.7.

MS (EI, m/z): 292 (M^+ 21%), 290 (M^+, 21%), 207 (8), 118 (42%), 91 (100%).

HRMS: calculated for $C_{15}H_{16}BrO$ $(M+H)^+$: 291.03845; found: 291.03849.



1-Methyl-2-(3-phenylpropoxy)-4-(prop-1-en-2-yl)benzene, **3af**

Prepared according to the general procedure in section 2.5.2.1 typical procedure for the $CuCl_2$-catalyzed formation of aryl ethers from alcohol **1a** and cyclohexanone **2f** at 80 ˚C.

Yield: 19%

Appearance: pale yellow oil.

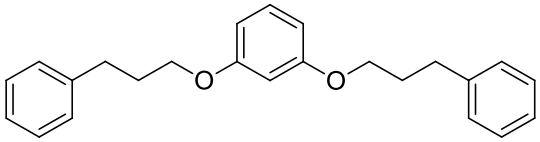
Rf: 0.45 (hexane/ethyl acetate 4:1).

^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.16-7.35 (5H, m, Ar*H*), 7.10 (1H, d, *J* = 7.7 Hz, Ar*H*), 6.96 (1H, d, *J* = 7.7 Hz, Ar*H*), 6.89 (1H, s, Ar*H*), 5.30 (1H, s, CH_2CCH_3), 5.03 (1H, s, CH_2CCH_3), 4.00 (2H, t, *J* = 6.1 Hz $ArOCH_2CH_2$), 2.85 (2H, t, *J* = 7.6 Hz, $PhCH_2CH_2$), 2.25 (3H, s, $C_6H_3CH_3$), 2.13 (3H, s, CH_3CCH_2), 2.06-2.20 (2H, m, $CH_2CH_2CH_2$),

^{13}C NMR (75 MHz, $CDCl_3$, δ): 156.9, 143.4, 141.7, 140.2, 130.2, 128.5, 128.4, 126.3, 125.9, 117.5, 111.7, 108.3, 66.7, 32.3, 31.1, 22.0, 16.0.

MS (EI, m/z): 266 (M^+ 100%), 148 (82%), 133 (11%), 119 (10%), 108 (5%), 91 (90%).

HRMS: calculated for $C_{19}H_{23}O$ $(M+H)^+$: 267.17434; found: 267.17446.



1,3-Bis(3-phenylpropoxy)benzene, **3ag**

Prepared according to the general procedure in section 2.5.2.1 typical procedure for the $CuCl_2$-catalyzed formation of aryl ethers from alcohol **1a** and cyclohexanone **2g**.

Yield: 47%

Appearance: yellow oil.

Rf: 0.84 (hexane/ethyl acetate 2:1).

^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.09-7.34 (11H, m, Ar*H*), 6.46-6.53 (3H, m, Ar*H*), 3.96 (4H, t, *J* = 6.3 Hz, CH_2CH_2OAr), 2.82 (4H, t, *J* = 7.9 Hz, $PhCH_2CH_2$), 2.05-2.16 (4H, m, $CH_2CH_2CH_2OAr$).

^{13}C NMR (75 MHz, $CDCl_3$, δ): 160.3, 141.5, 129.8, 128.5, 128.4, 125.9, 106.8, 101.5, 66.9, 32.2, 30.8.

MS (EI, m/z): 346 (M^+ 52%), 207 (32%), 118 (70%), 91 (100%).

HRMS: calculated for $C_{24}H_{26}NaO_2$ $(M+Na)^+$: 369.1825; found: 369.18303.

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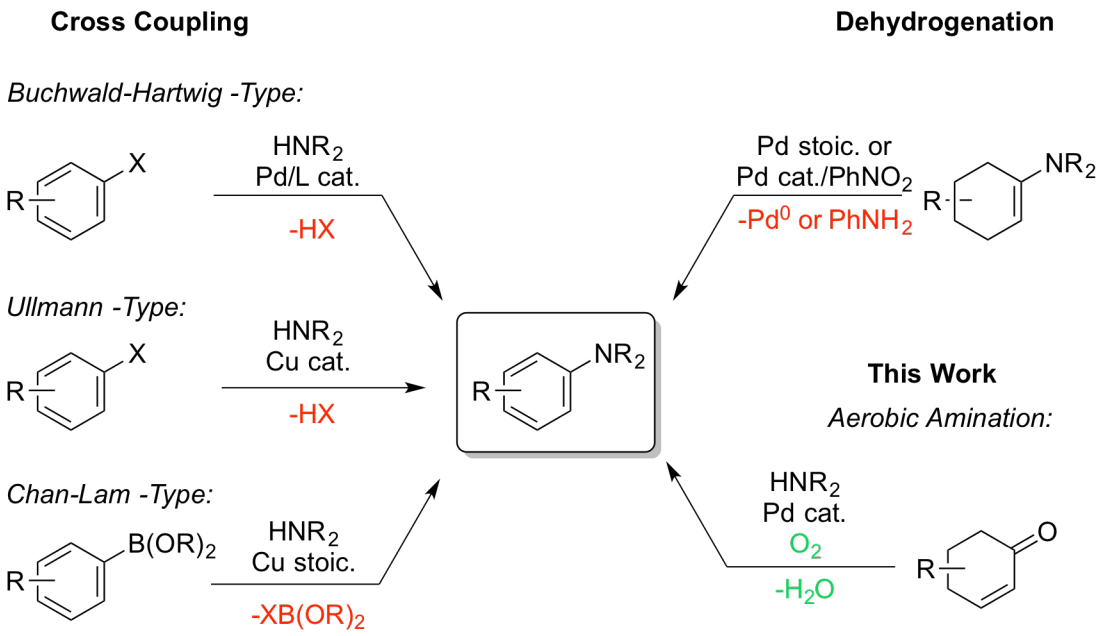
Chapter 3 - Pd-Catalyzed Synthesis of Aryl Amines via Oxidative Aromatization of Cyclic Ketones and Amines with Molecular Oxygen

The results reported in this chapter have been published in the journal *Organic Letters* as a full paper entitled "Pd-Catalysed Synthesis of Aryl Amines via Oxidative Aromatization of Cyclic Ketones and Amines with Molecular Oxygen" co-authored by Simon A. Girard, Xiong Hu, Thomas Knauber, Feng Zhou, Marc-Olivier Simon, Guo-Jun Deng, Chao-Jun Li. This paper was the result of a joint publication between the Li and the Deng research groups. Xiong Hu and Guo-Jun Deng developed a palladium-catalyzed system for the arylation of aromatic amines from cyclohexanones while Simon A. Girard, Thomas Knauber, Feng Zhou, Marc-Olivier Simon and Chao-Jun Li presented the synthesis of aryl amines from secondary aliphatic amines and cyclohexenone derivatives. The reaction was discovered by me, Simon A. Girard and the optimization of the reaction conditions were developed by me, Dr. Thomas Knauber and Dr. Feng Zhou with supervision by Prof. Dr. Chao-Jun Li. All reactions, isolations, and characterizations (with the exception of high-resolution mass spectrometry) were performed by me, Dr. Thomas Knauber and Dr. Feng Zhou. High-resolution mass spectrometry was performed by Dr. Nadim Saadeh and Dr. Alexander Wahba at the McGill University, Department of Chemistry Mass Spectrometry Laboratory. The manuscript upon which this chapter is based was prepared by me and Dr. Thomas Knauber, with proofreading and editing by Prof. Dr. Chao-Jun Li and Dr. Feng Zhou and has therefore been re-written by me for inclusion into this thesis.

Through the successful development of copper-catalyzed systems for the aerobic synthesis of aryl ethers from cyclohexenone derivatives, we had demonstrated the potential of the nucleophilic addition/dehydrogenative aromatization procedure to access functionalized arenes. We thus decided to further investigate the scope of nucleophiles amenable to this methodology to validate the synthetic potential of the hydrogen borrowing strategy to access various functionalized arenes.

3.1 Introduction

Over the last few decades, transition metal catalysis has become a powerful tool for the regioselective synthesis of complex molecules. Due to the aryl amines' important roles in pharmaceuticals, agrochemicals, and organic materials, powerful methodologies for their production have been developed.[1,2] Some important examples of these reactions include the Buchwald-Hartwig-couplings,[3–6] the Ullmann-type reactions[7–9] and the Chan-Lam-type aminations (Scheme 3.1-1, left).[10–12] However, their overall atom-economy[13,14] is limited by the requirement of pre-functionalized aryl starting materials, which lead to the generation of stoichiometric quantities of chemical waste from the coupling step. Moreover, the leaving groups necessitate pre-installation on the substrates in multi-step procedures and involve the use of highly reactive and hazardous reagents.[15,16]



Scheme 3.1-1 Strategies for the synthesis of aryl amines

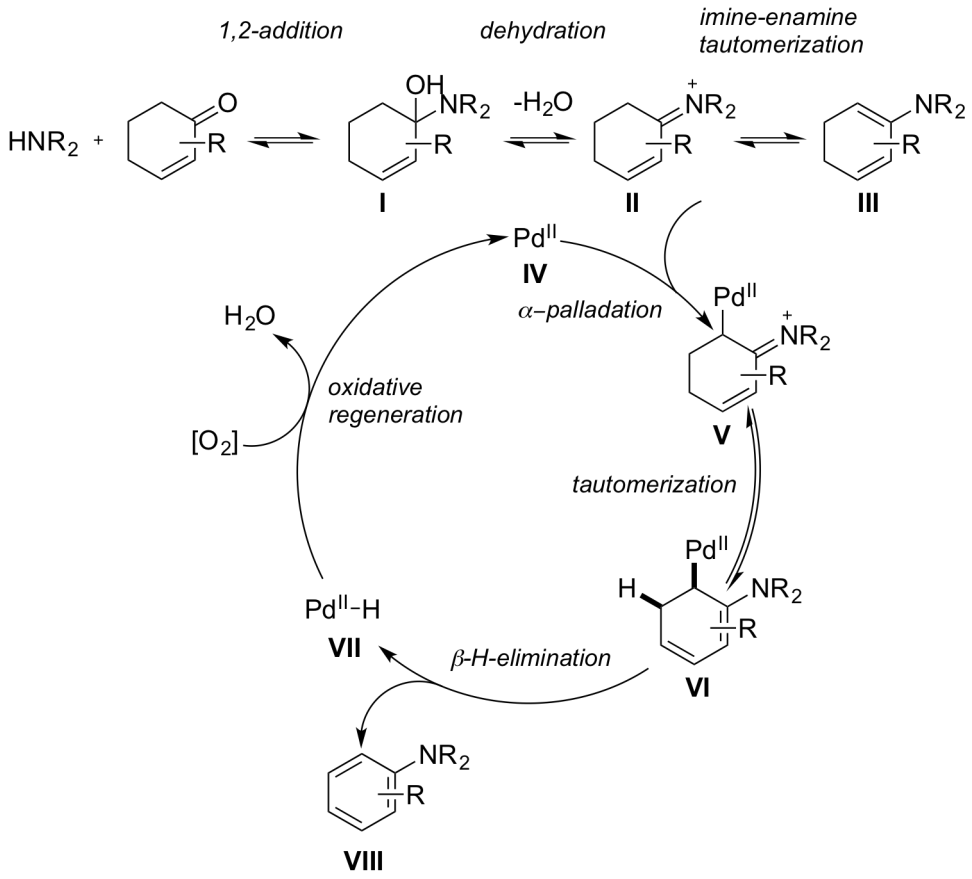
In addition to the cross-coupling methodologies, several seminal dehydrogenative aromatization[17,18] procedures have been developed for the synthesis of aryl amines from nonaromatic enamines and imines (Scheme 3.1-1, top-right). The group of Semikolenov developed a gas-phase procedure for the synthesis of 2,6-dimethylaniline that involves a Pd-catalyzed cross-dehydrogenative aromatization step.[19] In 2001, the group of Ishikawa and Saito demonstrated that pre-formed enamines can be transformed into the corresponding aryl amines in the presence of stoichiometric quantities of a Pd(II) complex.[20] The first Pd-catalyzed protocols were independently developed by Cossy[21] and Beller[22] using nitrobenzene and benzyloxy carbonyl protecting groups (Cbz) as hydrogen acceptors, respectively. More recently, the group of Yoshikai encountered an oxidative aromatization in the development of a Pd-catalyzed aerobic indole synthesis.[23] In addition to the Pd-catalyzed procedures, a few aromatizations with stoichiometric quantities of $SnCl_4$, $Hg(OAc)_2$, and $TiCl_4$ have been reported.[24–26] Inspired by

the pioneering work of Horning,[17,27] Muzart[28,29] and Wenzel,[30] on Pd-catalyzed oxidative aromatizations, the group of Stahl succeeded in developing broadly applicable, aerobic phenol-syntheses[31] as well as chemo-selective syntheses of cyclic enones from cyclohexanone derivatives.[28]

3.2 Plan of study

After successfully demonstrating that intermolecular nucleophilic addition and catalytic dehydrogenative aromatization protocols are compatible via a Cu-catalyzed arylation of aliphatic alcohols with 2-cyclohexen-1-ones,[32] we attempted to extend the methodology to amine nucleophiles. We envisaged that an aerobic aromatization of various cyclohexanone derivatives with secondary amines would introduce a synthetic method that was both atom-economic and selective to access various aryl amines.

Unfortunately, the transformation of piperidine with cyclohexenone in presence of the NHPI/Cu system, which mediates the aerobic synthesis of aryl ethers, only afford the desired N-phenylpiperidine in trace amount.[32] Inspired by the previous work of Stahl[31] we reasoned that the transformation of amine with cyclohexenone might be possible through the mechanism concept outlined in Scheme 3.2-1. This reaction starts with a classical textbook enamine condensation.[15] Subsequently, the enamine species **III** reacts with the Pd-catalyst **IV** to form **V**.[33,34] Tautomerization and β-hydride-elimination will liberate the aryl amine **VIII** and a metal-hydride species **VII**. The latter could regenerate the initial catalyst **IV** in the presence of oxygen.[35–40]



Scheme 3.2-1 Postulated oxidative arylamine formation from cyclohexenone

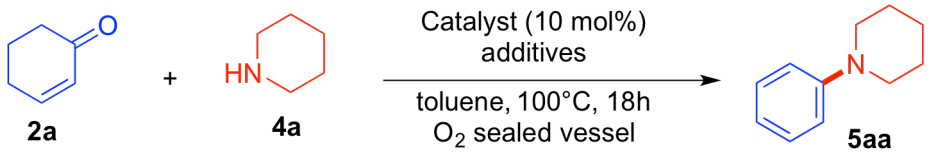
3.3 Results and discussion

3.3.1 Development of the reaction conditions

We chose piperidine and 2-cyclohexen-1-one as our test substrates for the arylation. The results are outlined in Table 3.3-1.

Encourage by the successful development of copper-catalyzed systems for the synthesis of aryl ethers from cyclohexenone and aliphatic alcohols, we began our investigation using copper catalyst. However, exposure of piperidine and 2-cyclohexen-1-one in presence of 10 mol% of $Cu(OTf)_2$ with 1 equiv of H_2O and KI to 1 bar of oxygen in toluene only affords the desired N-phenylpiperidine **5aa** in 8% yield (Table 3.3-1 entry 1). Subsequently, we decided to investigate previously reported palladium salts and were pleased to obtain the desired product in moderate yields (entries 2-6). Among the pre-catalysts tested, yields of 56% and 59%, were

Table 3.3-1 Evaluation of palladium catalysts for the aerobic amination of 2-cyclohexen-1-one **2a** with piperidine **4a**



2a + **4a** → **5aa**

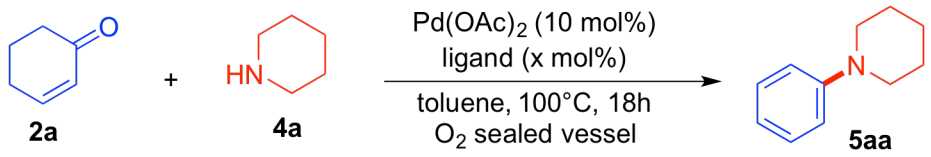
Entry	Catalyst	Additives	Conversion (%)
1	$Cu(OTf)_2$	NHPI/H_2O/KI[a]	8
2	$Pd(OAc)_2$	-	56
3	$[(PPh_2Me)_2PdCl_2]$	-	59
4	$Pd(TFA)_2$	-	52
5	$Pd(acac)_2$	-	30
6	$PdCl_2$	-	17

Reaction conditions: **2a** (0.2 mmol), **4a** (0.1 mmol), catalyst (10 mol%), additive, toluene (0.2 mL), O_2, 100 ˚C, 18 h. Conversions were determined by ^1H NMR analysis with 1,3,5-trimethoxy benzene as internal standard. [a] NHPI (20 mol%), H_2O (1.0 equiv), KI (1.0 equiv).

obtained with $Pd(OAc)_2$ and $[(PPh_2Me)_2PdCl_2]$ respectively (entries 2-3). Changing to the more acidic trifluoroacetic ligand (TFA, entry 4) or to the acetylacetonate (acac, entry 5) resulted in yields of 52% and 30% respectively. Unfortunately, the cheaper palladium (II) chloride salts lowered the **5aa** yield to 17% (entry 6), with the formation of undefined decomposition products.[41]

Subsequently, we investigate the effect of the addition of P-ligands in combination with $Pd(OAc)_2$ to improve the reaction outcome (Table 3.3-2). A small decrease in yield was observed upon addition of 20 mol% of PPh_3 (entry 2). Phosphines with similar electronic properties but a larger cone angle afford the desired product in 46% yield (entry 3).[42] Highly basic phosphine (pKa = 9.70), with large cone angle (170˚) gave similar results (entry 4). Addition of a phosphine with a reduced electron-donating ability and smaller cone angle in comparison to PPh_3, (P(2-furyl)$_3$, entry 5) provided the desired product in 50% yield. These results seem to suggest very little influence of the electronic and steric proprieties of phosphine ligand on the outcome of the reaction. Nitrogen based ligand such as DMAP previously reported by Stahl[31] for the palladium-catalyzed dehydrogenation of cyclic ketones did not improve the performance of the catalytic system (entries 6-7).

Table 3.3-2 Investigation of ligand effect on the palladium-catalyzed aerobic amination of 2-cyclohexen-1-one **2a** with piperidine **4a**



2a + **4a** → **5aa**

Entry	Ligand (mol%)	Conversion (%)
1	PCy_3 (20)	48
2	PPh_3 (20)	52
3	P(*p*-tolyl.)$_3$ (20)	46
4	PCy_3 (20)	48
5	P(2-furyl.)$_3$ (20)	50
6	Pyridine (20)	49
7	2-DMAP (20)	47
8	1,10-phen. (10)	34

Reaction conditions: **2a** (0.2 mmol), **4a** (0.1 mmol), $Pd(OAc)_2$ (10 mol%), ligand (x mol%), O_2, toluene (0.2 mL), 100 ˚C, 18 h. Conversions were determined by ^{1}H NMR analysis with 1,3,5-trimethoxy benzene as internal standard.

To gain a better understanding of the mechanism, the reaction progress was monitored by in situ ^{1}H-NMR experiments using $[(PPh_2Me)_2PdCl_2]$ as the catalyst. A reaction vial was charged with $[(PPh_2Me)_2PdCl_2]$, evacuated and refilled with molecular oxygen. Deuterated benzene *d*-6 (0.2 mL), which was bubbled with oxygen, was added. 2-Cyclohexen-1-one and piperidine were then added. The reaction vessel was sealed, placed in an oil bath and heated to 100 °C under vigorous stirring. At the indicated time, the mixture was cooled to room temperature, a known

quantity of the internal standard 1,3,5-trimethoxy benzene was added and the mixture was analyzed by ^{1}H-NMR. (Figure 3.3-1).

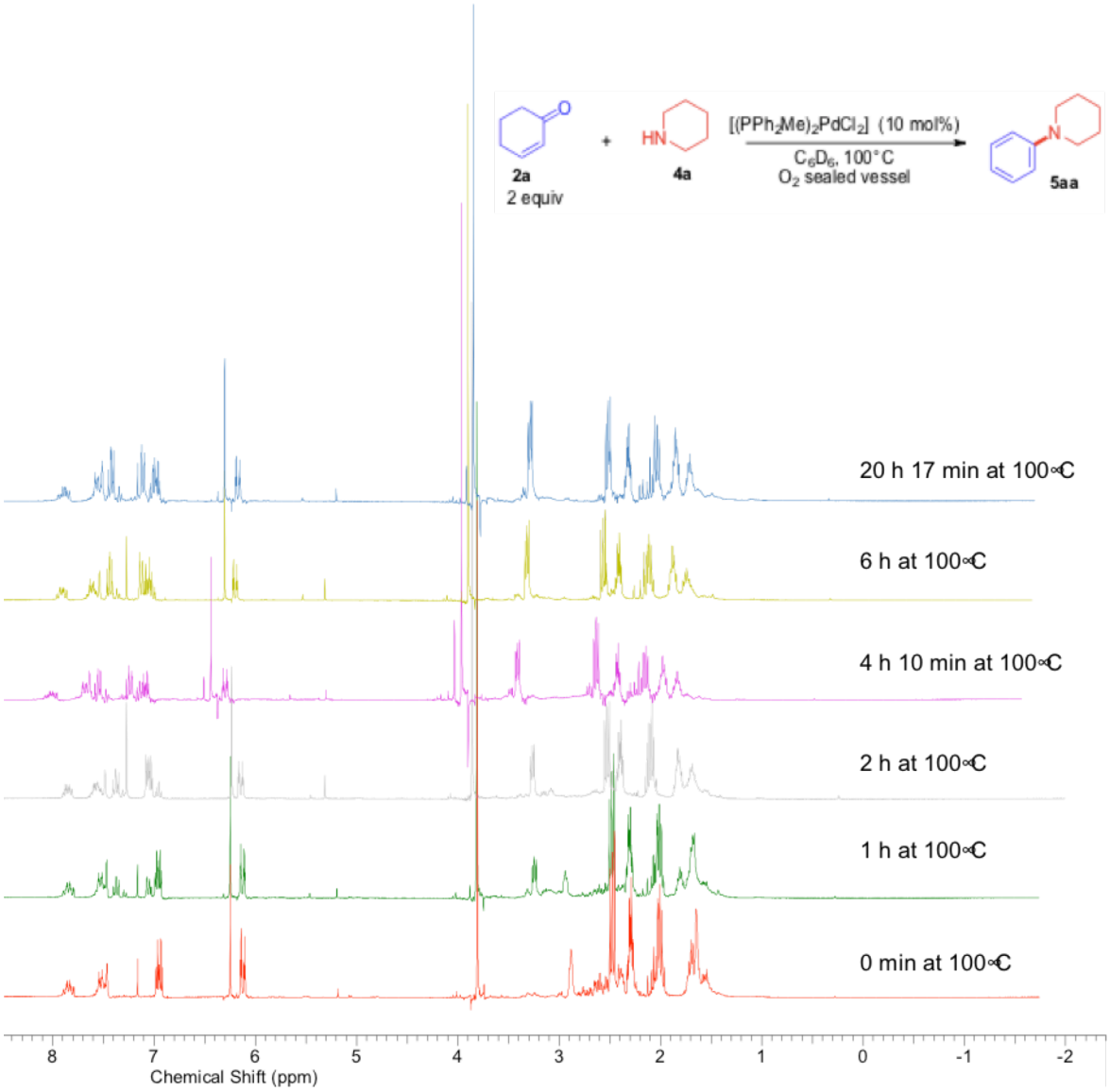


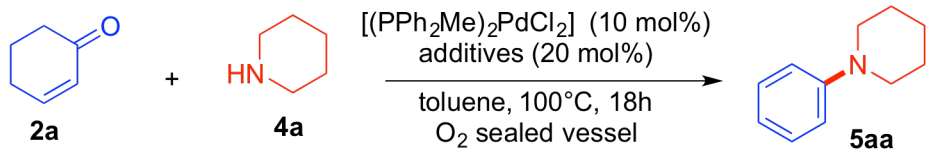
Figure 3.3-1 ^{1}H-NMR profile over time of the palladium catalyzed aerobic amination of 2-cyclohexen-1-one **2a** with piperidine **4a**

The Pd-catalyzed oxidative aromatization of 2-cyclohexen-1-one and piperidine was monitored to gain a more detailed insight into the reaction progress. The reactions were performed following the above-mentioned general procedure. Samples were taken after the indicated reaction times. As illustrated in Figure 3.3-2, piperidine was fully consumed after 2-3 h at 100 ˚C along with an equimolar amount of 2-cyclohexen-1-one. At this point, N-phenylpiperidine was formed in 52% yield. A thorough interpretation of the recorded spectra revealed the formation of an intermediate that is structurally related to both substrates and the product. This intermediate accumulated in the reaction mixture and was converted into N-phenylpiperidine during the remaining reaction time. At the end of the reaction (after 20 h) the intermediate was fully converted and the ^{1}H-NMR of the crude reaction mixture showed only resonances of the product, excess of 2-cyclohexen-1-one and the phosphine ligand. However, the characterization of the intermediate and the quantification by NMR spectroscopic analyses was complicated by overlap of the signals. Nevertheless, the absence of proton resonances in the range of 4.5-5.0 ppm (characteristic for enamines[43]) allowed us to exclude the corresponding enamine as intermediate, and suggest the imine instead.

Figure 3.3-2 Yield over time of the palladium catalyzed aerobic amination of 2-cyclohexen-1-one **2a** with piperidine **4a**

Based on those observations we investigated the influence of various additives to the efficiency of the system (Table 3.3-3). The hemiaminal **I** was readily formed and was accumulated in the reaction mixture. The rate of the dehydration step, releasing the enamine **III,** could be controlled by the addition of catalytic quantities of moderately strong ($pK_a \approx 4$) Brønsted acids (entries 4-7). The best results were obtained with anisic and benzoic acids, which gave the desired product **5aa** in 78% yield (entries 6-7). In contrast, the addition of strong acids (entries 8-10) resulted in a rapid conversion of the enamine, which was decomposed[44–46] before it could be efficiently converted by the catalyst. Investigation of the amount of benzoic acid shows no strong correlation with the outcome of the reaction; with the addition of 40 mol% and 1 equiv of acid affording the desired product in 75% and 81% yield respectively (entry11-12). The yield was further improved by lowering the catalyst loading (entry 13) and, under optimized conditions (entry 14), N-phenyl piperidine was detected in 93% yield with only 1.2 equiv of cyclohexenone.

Table 3.3-3 Optimization of the palladium catalyzed aerobic amination of 2-cyclohexen-1-one **2a** with piperidine **4a**



2a + **4a** → **5aa**

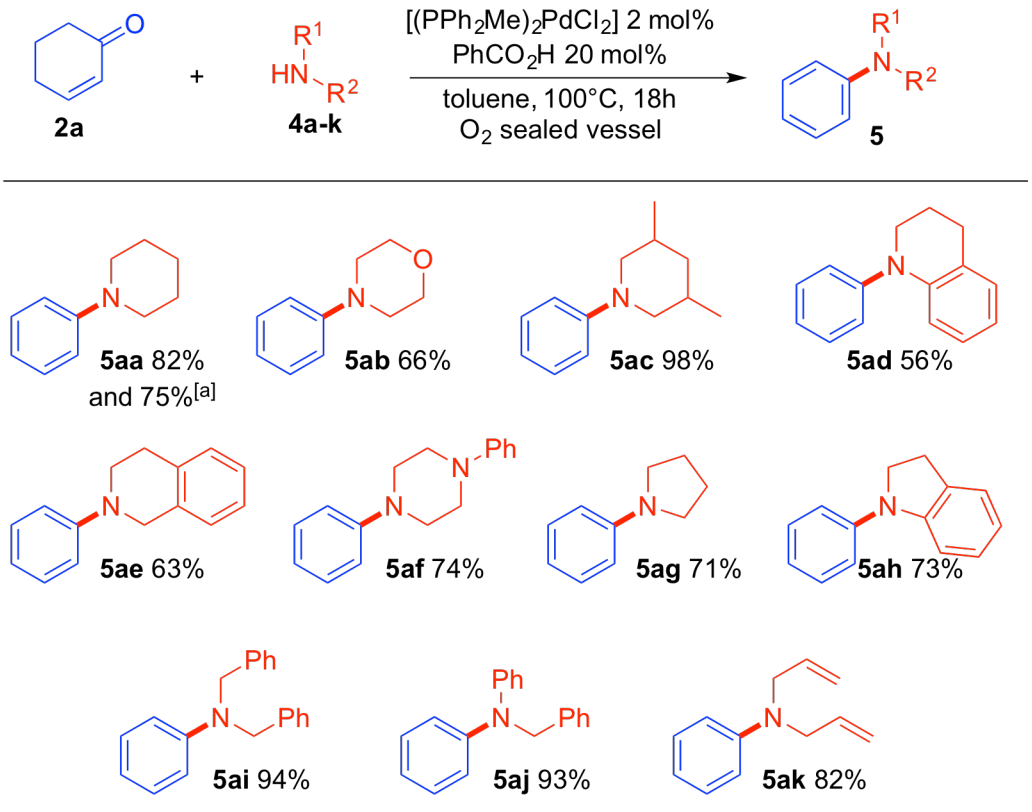
Entry	Additives	Conversion (%)
1	-	59[a]
2	-	66
3	aq. HCl	57
4	AcOH	74
5	$^{t}BuCO_2H$	75
6	$4\text{-}MeOC_6H_4CO_2H$	78
7	$PhCO_2H$	78
8	$4\text{-}NO_2C_6H_4CO_2H$	6
9	TsOH/MS 4 Å	44
10	CF_3CO_2H	61
11	$PhCO_2H$ (40 mol%)	75
12	$PhCO_2H$ (100 mol%)	81
13	$PhCO_2H$	93[b]
14	$PhCO_2H$	93 (82) [c]

Reaction conditions: **2a** (0.2 mmol), **4a** (0.1 mmol), Pd-source, additive (20 mol%), O_2 saturated toluene (0.2 mL), 100 ˚C, 18 h. Conversions were determined by ^{1}H NMR analysis with 1,3,5-trimethoxy benzene as internal standard. Isolated yields in brackets. [a] Degased toluene [b] 2 mol% of palladium salt was used [c] 2 mol% Pd-source and **2a** (1.2 equiv) were used.

3.3.2 Substrate scope

Having determined the optimized reaction conditions, we moved on to explore the scope of the procedure (Table 3.3-4). These conditions allow various heterocyclic and aliphatic secondary amines to be arylated with 2-cyclohexen-1-one **2a** in good to high yields. Amines containing β-hydrogen atoms such as **4i** or **4j** were arylated in excellent yields. The reaction conditions are mild enough to even be tolerated by delicate amines. Oxidation-sensitive compounds prone to oxidation such as **4d**, **4h**, and diallylamine **4k** were smoothly converted into the corresponding aryl amines.

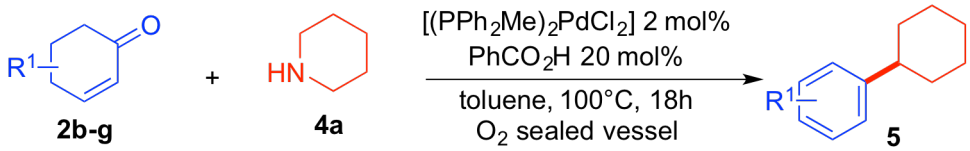
Table 3.3-4 Scope of the aerobic amination of 2-cyclohexen-1-one **2a.**

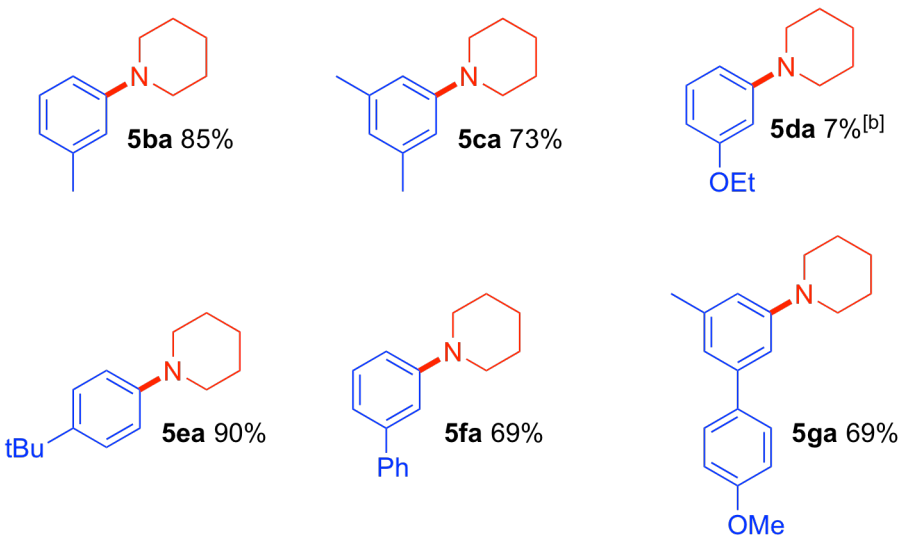


Reaction conditions: **2a** (0.39 mmol, 1.3 equiv), **4a-k** (0.3 mmol, 1.0 equiv), $[(PPh_2Me)_2PdCl_2]$ (2 mol%), $PhCO_2H$ (20 mol%), O_2 saturated toluene (0.6 mL), 100 ˚C, 18 h. Isolated yields are based on **4**. [a] Reaction on 2.0 mmol scale.

Various moderately electron rich 2-cyclohexenone derivatives **2b-g** are converted into the corresponding aryl amines in good yields. However, the reaction between piperidine and less electrophilic cyclohexenone derivatives such as **2d** resulted in low yields.

Table 3.3-5 Scope of the aerobic amination with various cyclohexenone derivatives **2a-g.**





Reaction conditions: **2a** (0.39 mmol, 1.3 equiv), **4a-k** (0.3 mmol, 1.0 equiv), $[(PPh_2Me)_2PdCl_2]$ (2 mol%), $PhCO_2H$ (20 mol%), O_2 saturated toluene (0.6 mL), 100 ˚C, 18 h. Isolated yields are based on **4**. [b] Yield determined by ^1H NMR.

3.4 Conclusion and outlook

In conclusion, Pd-catalyzed aerobic arylation reactions of various primary and secondary amines with cyclohexanone derivatives have been successfully developed. Since molecular oxygen serves as a formal hydrogen acceptor, the only by-product is water. Thus, the new procedure minimizes waste and allows a “greener” approach to access aryl amines. Moreover, this procedure complements the existing amination protocols of pre-functionalized arenes. The oxidative amination reactions discussed herein set the basis for the development of a complete class of related aerobic arylation reactions by utilizing further nucleophiles, which react with the cyclic ketones.

3.5 Experimental section

3.5.1 General information

Liquid reagents were distilled prior to use. Solid commercial starting materials were used as received. Solvents were dried following literature known procedures[47] and stored over molecular sieves. Analytical thin layer chromatography (TLC) was performed using Merck silica gel 60 F254 precoated plates (0.25 mm). The developed chromatography was analyzed by UV lamp (254 nm) and potassium permanganate as visualization methods. Flash column chromatography was performed with E. Merck silica gel 60 (230–400 mesh) or SORBENT silica gel 30-60 μm. Eluents are indicated in the experimental sections. Gas chromatography (GC) analyses were recorded an a Agilent 5975 gas chromatograph equipped with a HP 5 column using a temperature gradient starting at 80 °C. Yields were determined with 1,3,5-trimethoxy benzene or mesitylene as internal standard and were corrected with response factors of known quantities of the corresponding compounds. GCMS were recorded on an Agilent 5975 GC-MS instrument (EI) and an Agilent GCMS-6890N instrument equipped with HP-5 columns (30 m × 0.25 mm). High-resolution mass spectra (HRMS) were obtained from a JEOL JMS-700 instrument (ESI) and a Bruker Apex IV FTMS. Nuclear magnetic resonance (NMR) spectra were recorded on Varian Mercury plus-300 spectrometer, Varian MERCURY plus-400 spectrometer, Varian VNMRS 500 spectrometer and Bruker-AV 400 with proton resonances at 300/400/500 MHz and carbon resonances at 75/100/126 MHz, respectively. Chemical shifts are reported in parts per million (ppm). The solvent residual peaks, e.g., of chloroform ($CDCl_3$: δ 7.26 ppm and δ 77.0 ppm), were used as reference. Data are reported as following: chemical

shift, multiplicity (s = singlet, d = doublet, dd = doublet of doublets, t = triplet, q = quartet, m = multiplet, br = broad signal) and integration.

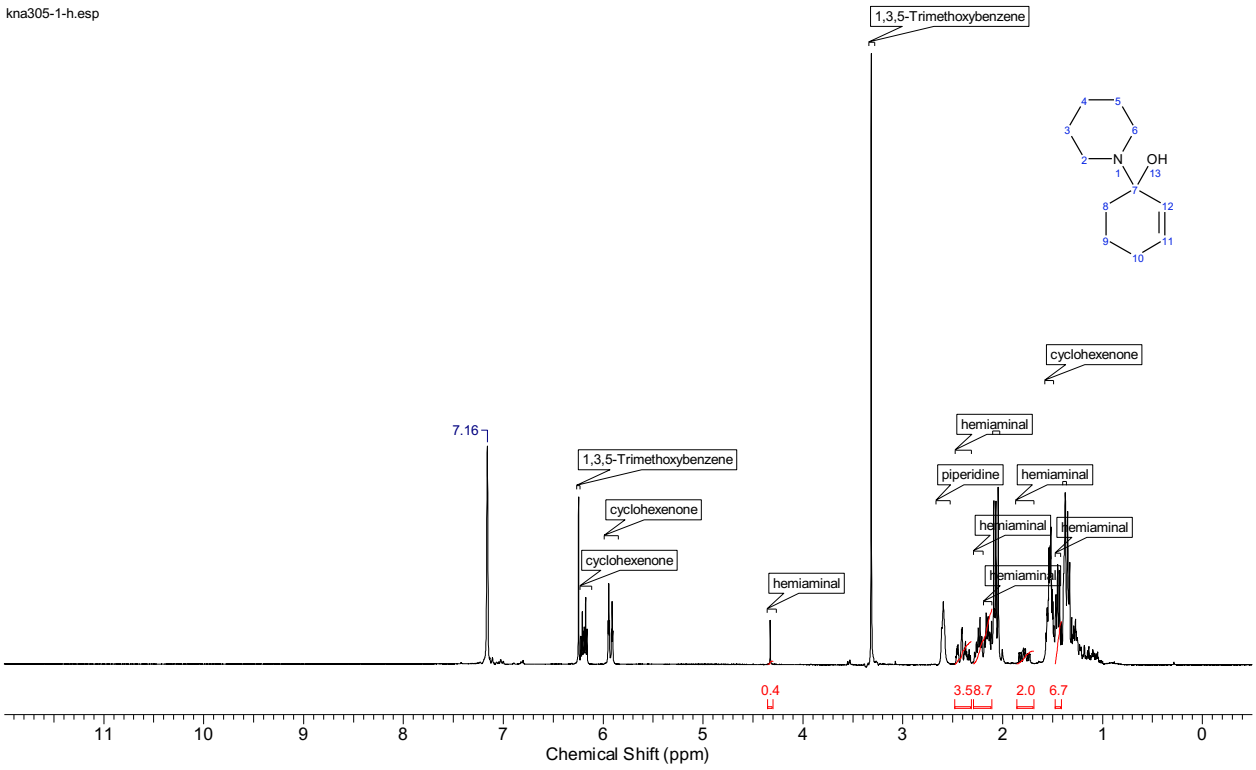
3.5.2 General procedure

A V-shaped 10 mL Biotage reaction vial was charged with $[(Ph_2Me)_2PdCl_2]$ (6.0 μmol, 3.46 mg), benzoic acid (60 μmol, 7.30 mg) and solid starting materials, where applicable. The reaction vessel was evacuated and refilled with molecular oxygen three times. Toluene (0.6 mL) was added which was freshly saturated with oxygen by passing molecular oxygen trough the vigorously stirred solvent for 3 h. Liquid starting materials were added, and the reaction vessel was sealed and placed in an oil bath. The reaction mixture was heated from room temperature to 100 °C with a rate of 4°C/min under vigorous stirring (approx. 1400 rpm) and hold for 18 h unless otherwise noted. The reaction vessel was cooled to room temperature, diluted with CH_2Cl_2 (2 mL), filtered through a plug of basic Al_2O_3 and rinsed with CH_2Cl_2 (4 × 3 mL). The combined rinsing was concentrated and purified by column chromatography or preparative thin layer chromatography to yield the corresponding tertiary amines **3aa**-**3ga**.

3.5.3 Procedure for the hemiaminal preformation

A V-shaped 10 mL Biotage reaction vial was evacuated and refilled with argon. Deoxygenated deuterated benzene *D-6* (0.2 mL), 2-cyclohexen-1-one (0.2 mmol, 19.2 mg, 19.5 μL) and piperidine (0.1 mmol, 8.52 mg, 9.9 μL) were added. The reaction vessel was sealed, and the reaction mixture was stirred for 1 h at room temperature. A known quantity of 1,3,5-trimethoxy benzene was added as internal standard and the mixture was analyzed by ^{1}H-NMR.

Acquisition Time (sec)	2.9981	***Comment***	Std Proton parameters			***Date***	Jun 9 2012
Date Stamp	Jun 9 2012			***File Name***	D:\NMR\kna305-1-h.fid\fid	***Frequency (MHz)***	300.06
Nucleus	1H	***Number of Transients***	8	***Original Points Count***	14393	***Points Count***	16384	***Pulse Sequence***	s2pul
Receiver Gain	20.00	***Solvent***	BENZENE-d6			***Spectrum Offset (Hz)***	1813.0299	***Spectrum Type***	STANDARD
Sweep Width (Hz)	4800.77	***Temperature (degree C)***	21.000						

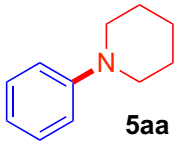


3.5.4 General procedure for *in situ* ^{1}H-NMR experiments

A V-shaped 10 mL Biotage reaction vial was charged with [$(Ph_2Me)_2PdCl_2$] (10 µmol, 5.78 mg), evacuated and refilled with molecular oxygen three times. Deuterated benzene *d-6* (0.2 mL) was added which was freshly saturated with oxygen by passing molecular oxygen trough the heavily stirred solvent for 3 h. 2-Cyclohexen-1-one (0.2 mmol, 19.2 mg, 19.5 µL) and piperidine (0.1 mmol, 8.52 mg, 9.9 µL) were added. The reaction vessel was sealed, placed in an oil bath and heated from room temperature to 100 °C with a rate of 4°C/min under vigorous stirring (approx. 1400 rpm) and held for 18 h for the indicated reaction time. The mixture was cooled to room temperature, a known quantity of 1,3,5-trimethoxy benzene was added as internal standard, and the mixture was analyzed by ^{1}H-NMR.

3.5.5 Characterization data of new compounds

N-phenyl piperidine (5aa) [CAS: 4096-20-20]:[48]



5aa

Compound **5aa** was prepared from 2-cyclohexen-1-one (**2a**, 0.39 mmol, 37.5 mg, 37.8 μL) and piperidine (**4a**, 0.3 mmol, 25.5 mg, 29.7 μL), following the general procedure. The title compound was isolated (66.5 mg, 82%) as a colorless liquid after flash column chromatography (SiO_2, hexanes/ethyl acetate 5:1).

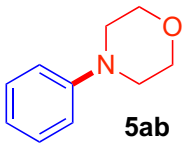
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28-7.24 (m, 2 H), 6.96 (d, J = 7.6 Hz, 2 H), 6.85-6.81 (m, 1 H), 3.16 (t, J = 5.6 Hz, 4 H), 1.75-1.69 (m, 4 H), 1.61-1.57 (m, 2 H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) δ 160.2, 129.0, 119.2, 116.5, 50.7, 25.8, 24.3 ppm.

MS (70 eV, EI) m/z (%): 161 [M^+], 160 [M^+-H] (100), 146, 132, 120, 105, 77.

IR (neat) ν (cm^{-1}) 3022, 2930, 2851, 2791, 1596, 1492, 1149, 1383, 1235, 1130, 1024, 916, 753, 690.

N-phenyl morpholine (5ab) [CAS: 92-53-5]:[49]



5ab

Compound **5ab** was prepared from 2-cyclohexen-1-one (**2a**, 0.39 mmol, 37.5 mg, 37.8 μL) and morpholine (**4b**, 0.3 mmol, 26.1 mg, 26.1 μL), following the general procedure. The title

compound was isolated (32,2 mg, 66%) as a colorless solid after preparative thin layer chromatography (SiO_2, hexanes/ethyl acetate 5:1).

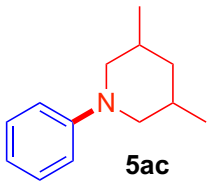
^{1}H NMR (300 MHz, $CDCl_3$) □7.32-7.27 (m, 2 H), 6.95-6.87 (m, 3 H), 3.88 (t, *J* = 4.8 Hz, 4 H), 3.17 (t, *J* = 4.8 Hz, 4 H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) □151.2, 129.2, 120.1, 115.7, 66.9, 49.4 ppm.

MS (70 eV, EI) m/z (%): 163 [M^+], 132, 105 (100), 77, 51.

IR (neat) □(cm^{-1}) 2853, 2823, 1596, 1493, 1447, 1223, 1117, 923, 769, 698.

(rac) N-phenyl-3,5-dimethyl piperidine (5ac) [CAS: (*S*,*R*) 19819-05-5 and (*R*,*R*) 19812-06-6]:



5ac

Compounds **5ac** were prepared from 2-cyclohexen-1-one (**2a**, 0.39 mmol, 37.5 mg, 37.8 µL) and (rac) 3,5-dimethyl piperidine (**4c**, 0.3 mmol, 34.0 mg, 40 µL), following the general procedure. The title compounds were isolated (55.7 mg, 98%) as colorless liquid in a 6:1 isomeric mixture after flash column chromatography (SiO_2, hexanes/ethyl acetate 5:1).

^{1}H NMR (major isomer, 500 MHz, $CDCl_3$) □7.28-7.32 (m, 2 H), 7.00 (d, *J* = 8.1 Hz, 2 H), 6.84-6.88 (m, 1 H), 3.58-3.74 (m, 2 H), 2.26 (t, *J* = 11.4 Hz, 2 H), 1.77-1.94 (m, 3 H), 0.99 (d, *J* = 6.4 Hz, 6 H), 0.68-0.80 (m, 1 H) ppm.

^{13}C NMR (major isomer, 126 MHz, $CDCl_3$) □129.0, 119.0, 118.6, 116.4, 57.3, 42.1, 30.8, 19.4 ppm.

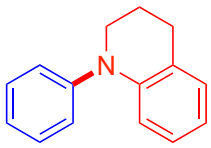
^{1}H NMR (minor isomer, 500 MHz, $CDCl_3$) □7.27-7.33 (m, 2 H), 6.96 (dd, *J* = 8.8 Hz, 1.0 Hz, 2 H), 6.81-6.89 (m, 1 H), 3.20 (d, *J* = 3.7 Hz, 2 H), 2.87 (d, *J* = 6.6 Hz, 2 H), 2.03-2.12 (m, 2 H), 1.47 (t, *J* = 5.7 Hz, 2 H), 1.08 (d, *J* = 6.8 Hz, 6 H) ppm.

^{13}C NMR (minor isomer, 126 MHz, $CDCl_3$) □128.9, 118.9, 118.6, 116.4, 56.7, 39.0, 27.3, 18.8 ppm.

MS (70 eV, EI) m/z (%): 189 [M^+] (100), 187, 160, 146, 120, 105, 77.

IR (neat) □ (cm^{-1}) 3058, 2950, 2913, 2869, 2786, 1596, 1494, 1458, 1382, 1239, 1180, 1146, 1031, 959, 856, 751, 690.

N-phenyl-1,2,3,4-tetrahydroquinoline (5ad) [CAS: 3297-76-5]:[50]



5ad

Compound **5ad** was prepared from 2-cyclohexen-1-one (**2a**, 0.39 mmol, 37.5 mg, 37.8 μL) and 1,2,3,4-tetrahydroquinoline (**4d**, 0.3 mmol, 39.9 mg, 37.7 μL), following the general procedure. The reaction mixture was stirred 36 h at 100 °C. The title compound was isolated (35.1 mg, 56%) as colorless liquid after flash column chromatography (SiO_2, hexanes/ethyl acetate 5:1).

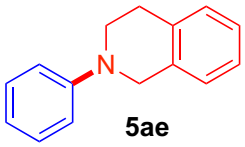
^{1}H NMR (500 MHz, $CDCl_3$) □7.37-7.33 (m, 2 H), 7.26-7.24 (m, 2 H), 7.10 (tt, *J* = 7.5 Hz, 1.0 Hz, 1 H), 7.07-7.05 (m, 1 H), 6.95-6.92 (m, 1 H), 6.76 (dd, *J* = 8.0 Hz, 1.0 Hz, 1 H), 6.71 (td, *J* = 7.5 Hz, 1.0 Hz, 1 H), 3.65-3.63 (m, 2 H), 2.86 (t, *J* = 6.5 Hz, 2 H), 2.08 (m, 2 H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) □148.3,) 144.3, 141.1, 129.3, 126.3, 124.6, 124.5, 123.5, 118.2, 115.7, 50.8, 27.7, 22.7 ppm.

MS (70 eV, EI) m/z (%): 209 [M^+] (100), 208, 193, 180, 152, 130, 115, 104, 91, 77;

IR (neat): $\tilde{\nu}$(cm^{-1}) 2927, 2840, 1591, 1573, 1490, 1308, 1200, 743, 693.

N-phenyl-1,2,3,4-tetrahydroisoquinoline (5ae) [CAS: 3340-78-1]:[51]



5ae

Compound **5ae** was prepared from 2-cyclohexen-1-one (**2a**, 0.39 mmol, 37.5 mg, 37.8 µL) and 1,2,3,4-tetrahydroisoquinoline (4**e**, 0.3 mmol, 40.0 mg, 39.7 µL), following the general procedure. The title compound was isolated (39.5 mg, 63%) as colorless liquid after preparative thin layer chromatography (SiO_2, hexanes/ethyl acetate 5:1).

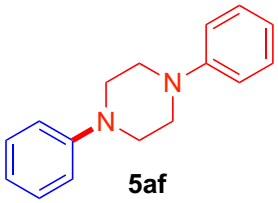
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31-7.15 (m, 6 H), 6.99 (d, J = 8.0 Hz, 2 H), 6.83 (t, J = 7.2 Hz, 1 H), 4.42 (s, 2 H), 3.57 (t, J = 6.0 Hz, 2 H), 2.99 (t, J = 6.0 Hz, 2 H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) δ 150.5, 134.9, 134.5, 129.2, 128.5, 126.5, 126.3, 126.0, 118.7, 115.1, 50.7, 46.5, 29.1 ppm.

MS (70 eV, EI) m/z (%): 209 [M^+], 208 (100), 193, 181, 165, 130, 115, 104, 91, 77, 65, 51;

IR (neat) $\tilde{\nu}$(cm^{-1}) 2919, 2812, 1597, 1499, 1386, 1215, 929, 742, 689.

N,N-diphenyl piperazine (5af) [CAS: 613-39-8]:[48]



5af

Compound **5af** was prepared from 2-cyclohexen-1-one (**2a**, 0.39 mmol, 37.5 mg, 37.8 µL) and N-phenyl piperazine (**4f**, 0.3 mmol, 48.7 mg, 45.5 µL), following the general procedure. The title

compound was isolated (53.1 mg, 74%) as colorless solid after flash column chromatography (SiO_2, hexanes/ethyl acetate 5:1).

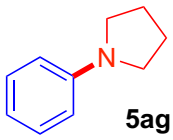
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (t, J = 7.8 Hz, 4 H), 7.01 (d, J = 8.4 Hz, 4 H), 6.91 (t, J = 7.2 Hz, 2 H), 3.36 (s, 8 H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ 151.2, 129.2, 120.1, 116.3, 49.4 ppm.

MS (70 eV, EI) m/z (%): 238 [M^+] (100), 223, 196, 132, 105, 91, 77.

IR (neat) ν (cm^{-1}) 2830, 1596, 1494, 1226, 1155, 1030, 939, 763, 693.

N-phenyl pyrrolidine (5ag) [CAS: 4096-21-3]:[52]



5ag

Compound **5ag** was prepared from 2-cyclohexen-1-one (**2a**, 0.39 mmol, 37.5 mg, 37.8 μL) and pyrrolidine (**4g**, 0.3 mmol, 44.2 mg, 43,2 μL), following the general procedure. The title compound was isolated (31.4 mg, 71%) as colorless liquid after preparative thin layer chromatography (SiO_2, hexanes/ethyl acetate 5:1).

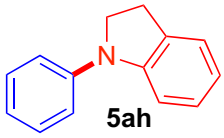
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28-7.21 (m, 2 H), 6.67 (t, J = 7.5 Hz, 1 H), 6.58 (d, J = 7.8 Hz, 2 H), 3.32-3.27 (m, 4 H), 2.03-1.99 (m, 4 H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) δ 147.9, 129.1, 115.3, 111.6, 47.6, 25.4 ppm.

MS (70 eV, EI) m/z (%): 147 [M^+], 148 [M^++1$^+$] (100), 119, 104, 91, 77.

IR (neat) ν (cm^{-1}) 2968, 2830, 1607, 1594, 1505, 1369, 1237, 1044, 910, 745, 731, 690.

N-phenyl-2,3-dihydroindole (5ah) [CAS: 25083-1-8]:[50]



5ah

Compound **5ah** was prepared from 2-cyclohexen-1-one (2**a**, 0.39 mmol, 37.5 mg, 37.8 μL) and 2,3-dihydroindole (**4h**, 0.3 mmol, 35.7 mg, 34.4 μL), following the general procedure. The reaction mixture was stirred 36 h at 100 °C. The title compound was isolated (42.8 mg, 73%) as colorless solid after flash column chromatography (SiO_2, hexanes/ethyl acetate 5:1).

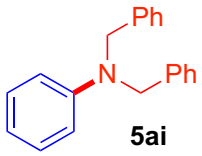
^{1}H NMR (300 MHz, $CDCl_3$) □ 7.32-7.44 (m, 2 H), 7.27 (s, 2 H), 7.15-7.22 (m, 2 H), 6.94-7.14 (m, 2 H),6.77 (t, *J* = 7.2 Hz, 1 H), 3.86-4.06 (m, 2 H), 3.15 (t, *J* = 8.4 Hz, 2 H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) □ 147.0, 144.1, 131.2, 129.1, 127.0, 125.0, 120.8, 118.8, 117.6, 108.0, 52.0 28.1 ppm.

MS (70 eV, EI) m/z (%): 195 [M+], 193 (100), 165, 139, 116, 89.

IR (neat) □ (cm^{-1}) 3035, 2923, 2855, 1590, 1498, 1481, 1469, 1452, 1376, 1331, 1264, 1220, 1167, 1101, 1088, 1023, 874, 756, 738, 696.

N,N-dibenzyl aniline (5ai) [CAS: 91-73-6]:[53]



5ai

Compound **5ai** was prepared from 2-cyclohexen-1-one (**2a**, 0.39 mmol, 37.5 mg, 37.8 μL) and N,N-dibenzylamine (**4i**, 0.3 mmol, 59.18 mg, 57.6 μL), following the general procedure. The

title compound was isolated (77 mg, 94%) as colorless liquid after flash column chromatography (SiO_2, hexanes/ethyl acetate 5:1).

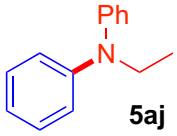
^{1}H NMR (500 MHz, $CDCl_3$) □7.39-7.35 (m, 4 H), 7.31-7.28 (m, 6 H), 7.23-7.20 (m, 2 H), 6.80-6.73 (m, 3 H), 4.70 (s, 4 H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) □149.1, 138.6, 129.2, 128.6, 126.8, 126.6, 116.7, 112.4, 54.1 ppm.

MS (70 eV, EI) m/z (%): 273 [M^+], 196, 182, 104, 91 (100), 77, 65.

IR (neat) □(cm^{-1}) 2966, 2867, 1597, 1504, 1450, 1361, 1229, 957, 730.

N,N-ethyl phenyl aniline (5aj) [CAS: 606-99-5]:[54]



5aj

Compound **5aj** was prepared from 2-cyclohexen-1-one (**2a**, 0.39 mmol, 37.5 mg, 37.8 μL) and N-ethylaniline (**4j**, 0.3 mmol, 36.4 mg, 38.5 μL), following the general procedure. The reaction mixture was stirred 30 h at 100 °C. The title compound was isolated (53.7 mg, 93%) as colorless liquid after preparative thin layer chromatography (SiO_2, hexanes/ethyl acetate 5:1).

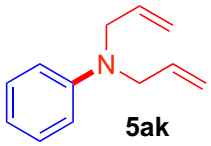
^{1}H NMR (500 MHz, $CDCl_3$) □7.29-7.26 (m, 4 H), 7.02-7.01 (m, 2 H), 7.00-6.99 (m, 2 H), 6.95 (tt, J = 7.5 Hz, 1.0 Hz, 2 H), 3.79 (q, J = 7.5 Hz, 2 H), 1.23 (t, J = 7.5 Hz, 3 H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) □147.7, 129.2, 121.1, 120.9, 46.4, 12.6 ppm.

MS (70 eV, EI) m/z (%): 197 [M^+], 182 (100), 167, 139, 104, 77.

IR (neat) □(cm^{-1}) 2970, 1586, 1492, 1369, 1259, 1240, 1130, 746, 692.

N,N-diallyl aniline (5ak) [CAS:6247-00-3]:[55]



5ak

Compound **5ak** was prepared from 2-cyclohexen-1-one (**2a**, 0.39 mmol, 37.5 mg, 37.8 µL) and N,N-diallylamine (**4k**, 0.3 mmol, 29.2 mg, 36.9 µL), following the general procedure. The title compound was isolated (42.4 mg, 82%) as colorless liquid after flash column chromatography (SiO_2, hexanes/ethyl acetate 5:1).

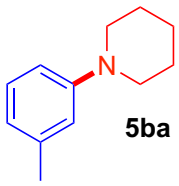
^{1}H NMR (300 MHz, $CDCl_3$) □7.27 (s, 3 H), 6.65-6.87 (m, 3 H), 5.71-6.04 (m, 2 H), 5.10-5.27 (m, 4 H), 3.89-3.99 (m, 4 H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) □ 148.6, 134.0, 129.0, 116.2, 115.9, 112.3, 52.7 ppm.

MS (70 eV, EI) m/z (%): 173 [M^+], 158, 146 (100), 130, 117, 104, 77.

IR (neat) □(cm^{-1}) 2922, 2852, 1598, 1504, 1457, 1358, 1258, 1231, 1181, 1014, 917, 799, 745, 690.

N-(3-toluyl) piperidine (5ba) [CAS: 71982-24-6]:[56]



5ba

Compound **5ba** was prepared from 3-methyl-2-cyclohexen-1-one (**2b**, 0.39 mmol, 43 mg, 44.6 µL) and piperidine (**4a**, 0.3 mmol, 25.6 mg, 29.7 µL), following the general procedure. The reaction mixture was stirred 36 h at 100 °C. The title compound was isolated (44.7 mg, 85%) as colorless liquid after preparative thin layer chromatography (SiO_2, hexanes/ethyl acetate 5:1).

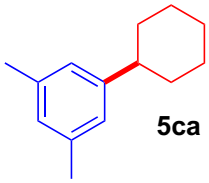
^{1}H NMR (500 MHz, $CDCl_3$) □7.15 (t, *J* = 7.5 Hz, 1 H), 6.79-6.77 (m, 2 H), 6.67 (d, *J* = 7.5 Hz, 1 H), 3.16 (t, *J* = 5.5 Hz, 4 H), 2.33 (s, 3 H), 1.75-1.70 (m, 4 H), 1.61-1.58 (m, 2 H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) □152.3, 138.6, 128.8, 120.1, 117.4, 113.7, 50.8, 25.9, 24.3, 21.7 ppm.

MS (70 eV, EI) m/z (%): 175 [M^+] (100), 160, 146, 134, 119, 105, 91, 77, 65.

IR (neat) □(cm^{-1}) 2930, 2852, 2790, 1600, 1492, 1449, 1382, 1246, 1184, 1129, 947, 769, 693.

N-(3,5-dimethylphenyl) piperidine (5ca) [CAS: 16800-74-1]:



Compound **5ca** was prepared from 3,5-dimethyl-2-cyclohexen-1-one (**2c**, 0.39 mmol, 48.4 mg, 52.4 μL) and piperidine (**4a**, 0.3 mmol, 25.6 mg, 29.7 μL), following the general procedure. The reaction mixture was stirred 36 h at 100 °C. The title compound was isolated (33.5 mg, 59%) as colorless liquid after preparative thin layer chromatography (SiO_2, hexanes/ethyl acetate 5:1).

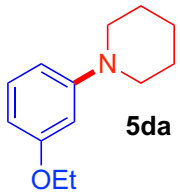
^{1}H NMR (500 MHz, $CDCl_3$) □6.61 (s, 2 H), 6.52 (s, 1 H), 3.14 (t, *J* = 5.5 Hz, 4 H), 2.29 (s, 6 H), 1.74-1.70 (m, 4 H), 1.60-1.56 (m, 2 H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) □152.3, 138.4, 121.3, 114.6, 51.0, 25.9, 24.3, 21.6 ppm.

MS (70 eV, EI) m/z (%): 189 [M^+] (100), 174, 160, 148, 133, 105, 91, 77.

IR (neat) n (cm^{-1}) 2930, 2851, 2787, 1593, 1464, 1450, 1382, 1344, 1190, 825, 694.

N-(3-ethoxyphenyl) piperidine (5da) [CAS: 81242-13-9]:[57]

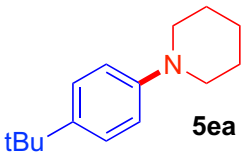


5da

Compound **5da** was prepared from 3-ethoxy-2-cyclohexen-1-one (**2d**, 0.13 mmol, 18.2 mg, 17.5 μL) and piperidine (**4a**, 0.1 mmol, 8.52 mg, 9.9 μL), following the general procedure. The reaction mixture was stirred 36 h at 100 °C. The title compound was detected in 7% yield by ^{1}H NMR using a known quantity of 1,3,5-trimethoxybenzene as internal standard.

^{1}H NMR (300 MHz, $CDCl_3$) 7.84-7.92 (s, 1 H), 7.55-7.67 (m, 1 H), 7.30-7.45 (m, 2 H), 3.18-3.26 (m, 4 H), 1.95 (q, *J* = 6.7 Hz, 3 H), 1.56 (m, 4 H), 1.46 (m, 2 H), 1.34 (t, *J* = 6.71, 3 H) ppm.

N-(4-*tert*-butylphenyl) piperidine (5ea) [CAS: 185259-34-1]:



5ea

Compound **5ea** was prepared from 4-*tert*-butyl-2-cyclohexen-1-one (**2e**, 0.39 mmol, 59.4 mg, 63.4 μL) and piperidine (**4a**, 0.3 mmol, 25.6 mg, 29.7 μL), following the general procedure. The reaction mixture was stirred 36 h at 100 °C. The title compound was isolated (58.9 mg, 90%) as colorless liquid after preparative thin layer chromatography (SiO_2, hexanes/ethyl acetate 5:1).

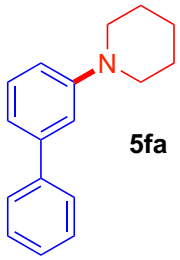
^{1}H NMR (500 MHz, $CDCl_3$) 7.31-7.28 (m, 2 H), 6.93-6.90 (m, 2 H), 3.14 (t, *J* = 5.5 Hz, 4 H), 1.75-1.71 (m, 4 H), 1.60-1.55 (m, 2 H), 1.31 (s, 9 H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) 149.9, 141.9, 125.7, 116.2, 50.9, 33.9, 31.4, 26.0, 24.3 ppm.

MS (70 eV, EI) m/z (%): 217 [M^+], 202 (100), 187, 174, 160, 146, 130, 118, 91, 77.

IR (neat) $\tilde{\nu}$ (cm^{-1}) 2932, 2855, 2790, 1609, 1516, 1233, 1131, 821.

N-(3-biphenyl)-piperidine (5fa):



5fa

Compound **5fa** was prepared from 3-phenyl-2-cyclohexen-1-one (**2f**, 0.39 mmol, 59.4 mg, 63.4 μL) and piperidine (**4a**, 0.3 mmol, 25.6 mg, 29.7 μL), following the general procedure. The reaction mixture was stirred 36 h at 100 °C. The title compound was isolated (48.8 mg, 69%) as colorless liquid after preparative thin layer chromatography (SiO_2, hexanes/ethyl acetate 5:1).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62-7.59 (m, 2 H), 7.46-7.42 (m, 2 H), 7.37-7.32 (m, 2 H), 7.18 (t, *J* = 2.0 Hz, 1 H), 7.08 (ddd, *J* = 7.5 Hz, 1.5 Hz, 1.0 Hz, 1 H), 6.97 (dd, *J* = 8.5 Hz, 2.0 Hz, 1 H), 3.24 (t, *J* = 5.5 Hz, 4 H), 1.78-1.74 (m, 4 H), 1.64-1.59 (m, 2 H) ppm.

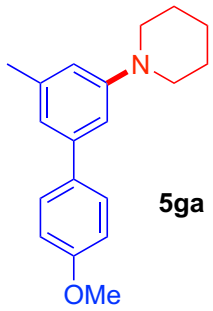
^{13}C NMR (125 Mz, $CDCl_3$) δ 152.5, 142.1, 141.9, 129.3, 128.6, 127.2, 127.1, 118.3, 115.6, 115.5, 50.8, 25.8, 24.3 ppm.

MS (70 eV, EI) m/z (%): 237 [M^+] (100), 208, 196, 181, 152, 115, 77.

IR (neat) $\tilde{\nu}$ (cm^{-1}) 2931, 2851, 2791, 1594, 1568, 1480, 1221, 754, 696.

HRMS calcd. for $C_{17}H_{19}N$ $[M+H]^+$:238.15903, found: 238.15880.

N-(4'-methoxy-5-methyl biphenyl-3-yl) piperidine (5ag):



5ga

Compound **5ga** was prepared from 3-(*p*-anisyl)-5-methyl-2-cyclohexen-1-one (**2g**, 0.39 mmol, 84.3 mg) and piperidine (**4a**, 0.3 mmol, 25.6 mg, 29.7 μL), following the general procedure. The title compound was isolated (58.2 mg, 69%) as colorless liquid after preparative thin layer chromatography (SiO_2, hexanes/ethyl acetate 5:1).

^{1}H NMR (500 MHz, $CDCl_3$) □ 7.53-7.50 (m, 2 H), 6.98-6.95 (m, 2 H), 6.94 (s, 1 H), 6.86 (s, 1 H), 6.74 (s, 1 H), 3.85 (s, 3 H), 3.21 (t, J = 5.5 Hz, 4 H), 2.37 (s, 3 H), 1.76-1.72 (m, 4 H), 1.62-1.57 (m, 2 H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) □ 159.0, 152.7, 141.6, 138.9, 134.6, 128.2, 119.1, 115.9, 114.0, 112.6, 55.3, 50.9, 25.9, 24.3, 21.9 ppm.

MS (70 eV, EI) m/z (%): 281 [M^+] (100), 265, 249, 207, 133, 88, 70. ;

IR (neat) □(cm^{-1}) 2930, 2850, 1591, 1512, 1462, 1450, 1244, 1222, 1176, 1032, 823, 699.

HRMS calcd. for $C_{19}H_{23}N$ [M+H]$^+$:282.18524, found: 282.18546.

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Chapter 4 – Update to the Field of Dehydrogenative Aromatisation

Some of the content of this chapter have been published in the journal *Organic Chemistry Frontiers* as a mini-review entitled "Catalytic Dehydrogenative Aromatization: an Alternative Route to Functionalized Arenes" co-authored by Simon A. Girard, Huawen Huang, Feng Zhou, Guo-Jun Deng and Chao-Jun Li. The original paper was written by S.A. Girard and F. Zhou based on preliminary bibliographic work performed by H. Huang and G.-J. Deng and has thus been re-written and updated by S.A. Girard for inclusion into this thesis.

This chapter will summarize the up-to-date advance on the development of efficient systems for the direct C-O, C-N, C-S and C-C bond formations through tandem nucleophilic addition and oxidative aromatization as well as the extension of these methodologies to the construction of heterocycles. First, the formation of aryl-ethers from cyclohexanones and alcohols will be discussed. Then effective procedures for the synthesis of aromatic amines will be presented, which will be followed by the subsequent use of carbon and sulfur based nucleophiles. Finally, we will illustrate some of the synthetic applications of theses methodologies to the synthesis of heterocycles.

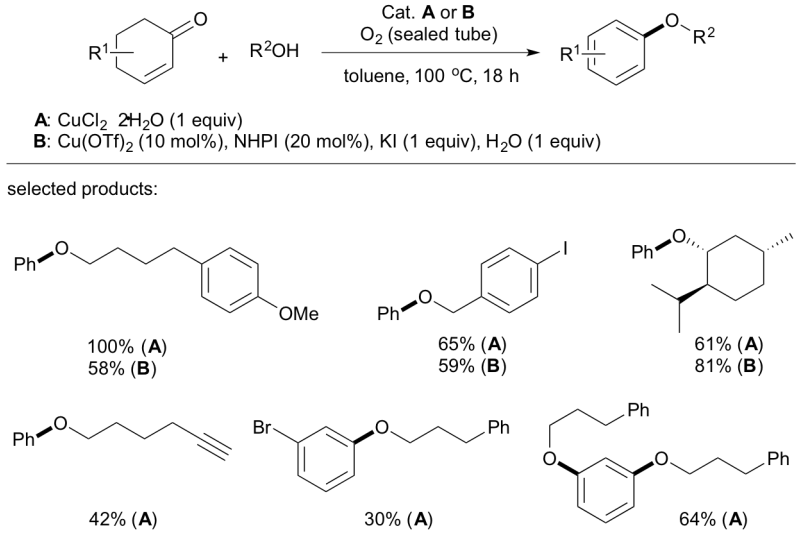
4.1 Introduction

Catalytic dehydrogenative aromatization has emerged as an efficient and environmentally friendly way to access functionalized arenes in recent years.[1–4] Typically, the compounds bearing aliphatic six-membered ring, such as cyclohexanones, are used as arylation sources. The transformation process commonly involves a sequential nucleophilic addition, dehydration, and

catalytically oxidative dehydrogenation, providing convenient entries to carbon-carbon and carbon-heteroatom bond formations. Compared to previous arylation methods, this strategy eliminates the use of harsh reaction conditions and generation of halide wastes, circumvents the issues of chemo- and regioselectivities, and offers a milder means for the synthesis of functionalized arenes.[5–9] It is worth mentioning that this approach distinguishes itself from other methods by either frequently using oxygen as the sole oxidant or applying the hydrogen-transfer strategy. In addition, an obvious advantage in terms of sustainable chemical process is that water is generated as the only by-product in most cases. Furthermore, this concept has successfully been implemented using the borrowing hydrogen strategy for the direct coupling of phenol with amines using heterogeneous catalysis.

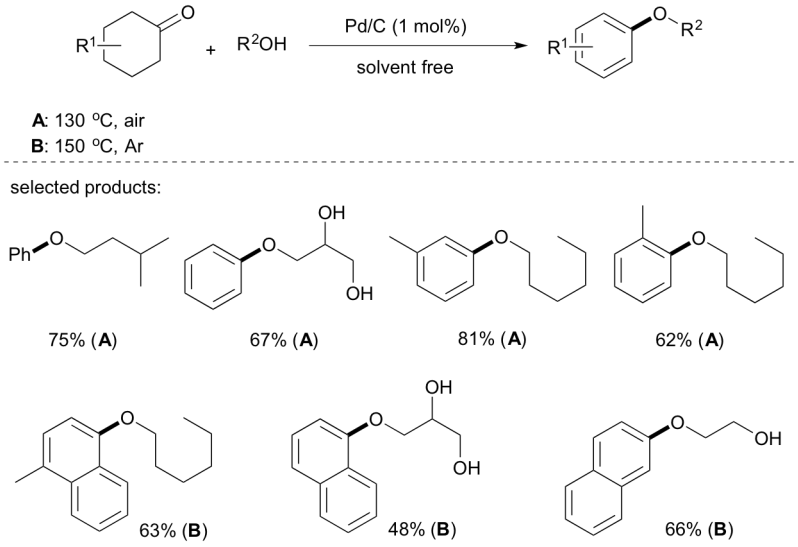
4.2 C-O bond formation

In 2012, Li's group described a copper-catalyzed aerobic synthesis of aromatic ethers, in which the aromatic moiety stemmed from the substituted cyclohexenone via an oxidative aromatization (Scheme 4.2-1).[4] While a stoichiometric amount of $CuCl_2$ afforded the dehydrogenative coupling under very handy reaction conditions, with the use of a co-catalyst *N*-hydroxyphthalimide (NHPI, 20 mol%) in the presence of potassium iodide (KI, 1 equiv), water (1 equiv), and catalytic amount of copper triflate [$Cu(OTf)_2$, 10 mol%] provided the desired aryl-ethers product. This reaction tolerated a broad range of alkyl alcohols with various functionalities, including iodo-, nitro-, alkenyl-, and alkynyl- (terminal and internal) groups. As well, natural alcohols such as *β*-citronellol, (−)-borneol, (−)-menthol, cholesterol and protected serine were successfully functionalized. Diols and diketones were also suitable reactants, and afforded the corresponding diethers in good yields.



Scheme 4.2-1 Aryl ethers from phenols/alcohols and cyclohexenones

Shortly afterward, Sutter *et al.* presented a palladium supported system for the synthesis of aryl ethers (Scheme 4.2-2).[10,11] Interestingly, cyclohexanones have a higher level of activity than cyclohexenones under the present system; and, although requiring an elevated temperature

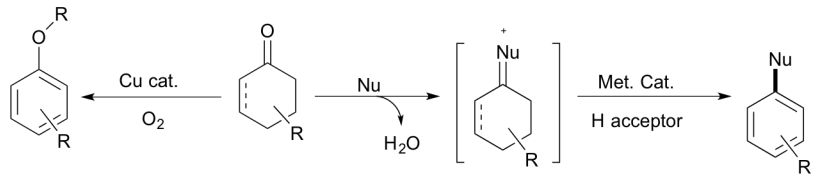


Scheme 4.2-2 Pd/C catalyzed aryl ether formation

to achieve complete conversion, tetralones were also suitable partners. It is also worth noting that this process was also efficient with 2-methyltetrahydrothiophen-3-one to give the corresponding aryl ether in good yield. Various alkyl alcohols were suitable for this transformation including polyols.

4.3 C-N bond formation

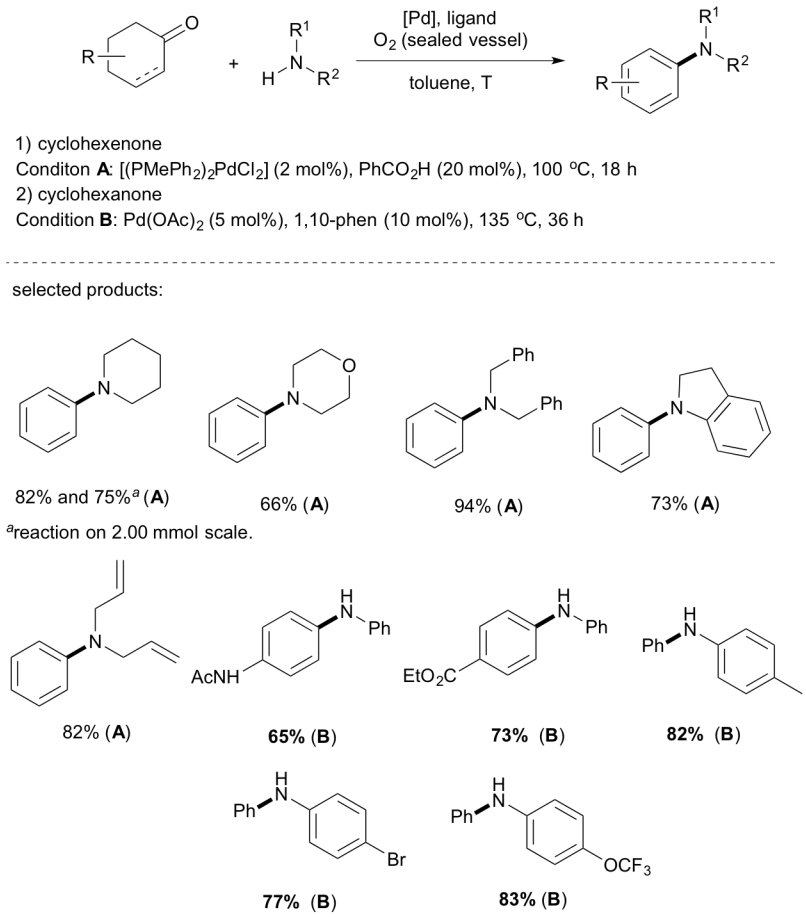
As exemplified by the formation of aromatic ethers via a copper-catalyzed process, it is thus conceivable that other nucleophiles such as amines would also undergo analogous nucleophilic addition-dehydrogenative aromatization to readily deliver the final aromatic products (Scheme 4.3-1).



Scheme 4.3-1 Aromatics via nucleophilic addition-dehydrogenative aromatization

Indeed, the groups of Li and Deng conjointly reported efficient methods for the preparation of aromatic amines. In these reactions, palladium was used as metal catalyst and O_2 as the sole terminal oxidant, generating water as the only by-product (Scheme 4.3-2).[3] Various alkylamines such as piperidine, morpholine, dibenzylamine, indoline and even diallylamine reacted smoothly to afford *N*-arylated tertiary amines. The reaction of aniline derivatives and cyclohexanones were achieved as well, in the presence of $Pd(OAc)_2$ at 135 °C. To prevent premature catalyst deactivation by precipitation of Pd-black, the reaction required the addition of 1,10-phenanthroline (Scheme 4.3-2, condition B). Aromatic rings, linear or branched alkyl chains, amido- and ester groups were well tolerated on the cyclohexanone partner. Electron rich

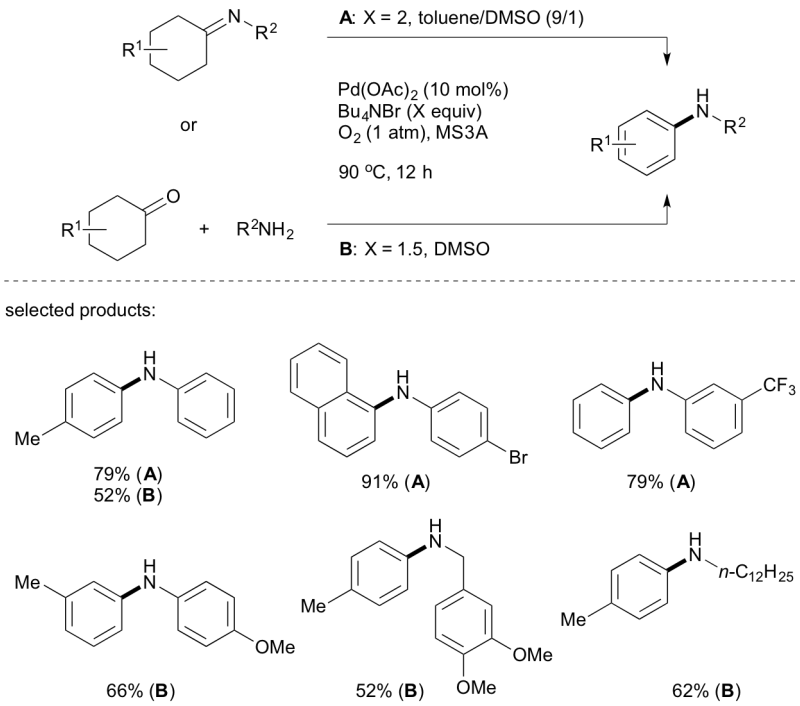
and electron deficient anilines were arylated in good yield. However, nitro- and cyano-groups underwent undesired hydrogen transfer reduction and only small quantities of the corresponding diaryl amines were obtained. In all examples, the mono-arylation product was obtained exclusively.



Scheme 4.3-2 Arylation of amines

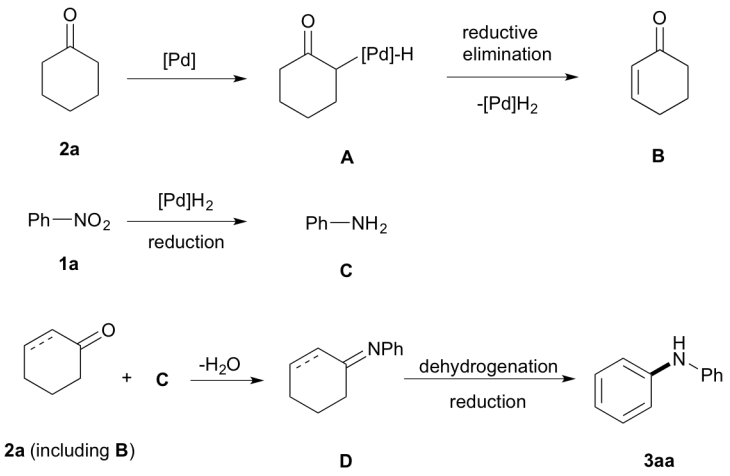
Almost at the same time, Yoshikai's group described an aerobic $Pd(OAc)_2/Bu_4NBr/DMSO$ catalytic system for the formation of aromatic amines through a palladium-catalyzed dehydrogenation from imines, which were prepared from the corresponding cyclohexnones and amines (Scheme 4.3-3).[2] The one-pot fashion of the dehydrogenative

aromatization from cyclohexanones and amines was then realized under slightly varied reaction conditions. Both alkyl amines and aromatic amines proved to be efficient coupling partner for this transformation.



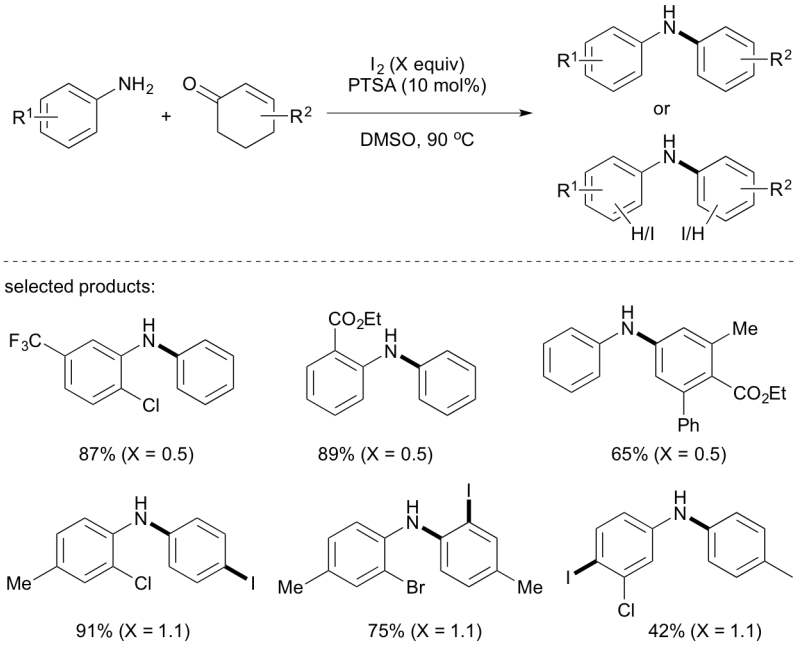
Scheme 4.3-3 Alternative procedure for the palladium-catalyzed arylation of amines

It should be noted that prior to these arylations of amines, Deng's group presented a palladium-catalyzed one-pot diarylamine formation from nitroarenes and cyclohexanones based on borrowing hydrogen strategy (Scheme 4.3-4).[12] First, the nitroarene is reduced to aniline by the hydride borrowed from the cyclohexanone via Pd-based β-hydride elimination. Then the ensuing condensation of the aniline and cyclohexanone or cyclohexenone furnishes the imine intermediate, which is followed by further Pd-catalyzed aerobic dehydrogenation to deliver the diarylamine product.



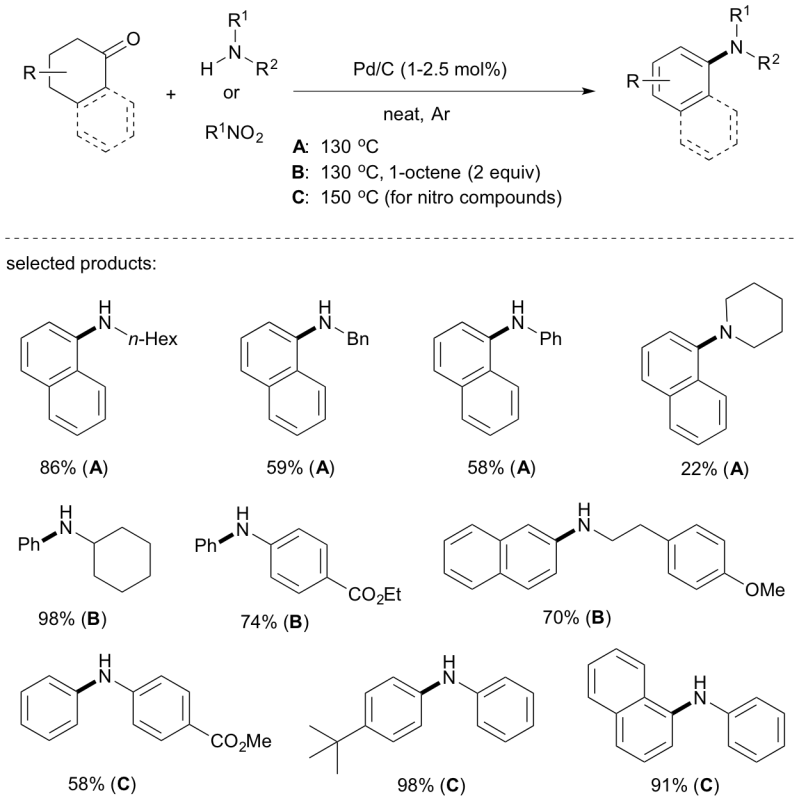
Scheme 4.3-4 Arylamine formation from nitroarenes by the hydrogen borrowing strategy

Later a metal-free reaction system containing I_2/TsOH/DMSO for the preparation of aromatic amines was described by Maycock and co-workers (Scheme 4.3-5).[8] When 0.5 equiv of I_2 was employed, the reaction proceeded smoothly to afforded diarylamine products with ester and halogen (I, Br, and Cl) being tolerated. Interestingly, the electrophilic iodination could occur on the relatively electron-rich benzene ring, giving rise to the *para*- or *ortho*-iodoanilines when 1.1 equiv of I_2 was used.



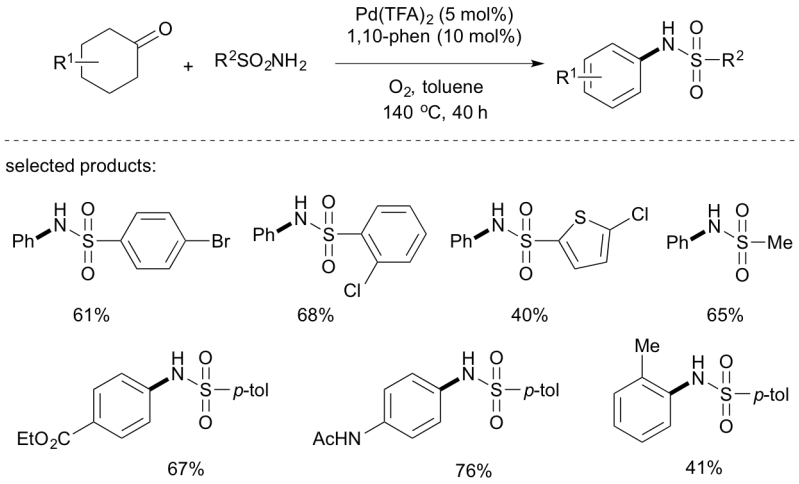
Scheme 4.3-5 Iodine-catalyzed arylation of amines

In 2013, Sutter *et al.* developed a palladium-catalyzed method for *N*-arylation of amines using cyclohexanones and tetralones (Scheme 4.3-6).[13] The reaction proceeded very efficiently by using only 1-2.5 mol% of Pd/C as the catalyst and 1-octene or nitro compounds as hydrogen acceptors. In the case of cyclohexanone or *β*-tetralone, 2 equiv of 1-octene was required to achieve high yield. A chemoselective and highly efficient condensation between cyclohexanones and nitroarenes by means of borrowing hydrogen strategy has also been accomplished under this versatile Pd/C system, albeit using large excess of cyclohexanones (10 equiv) and at an elevated reaction temperature (150 °C).



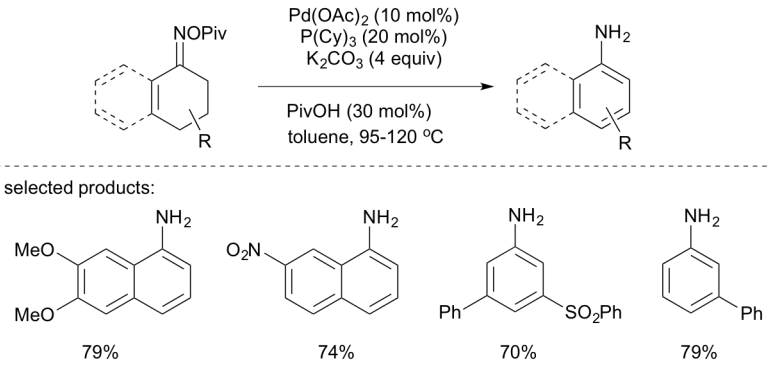
Scheme 4.3-6 Pd catalyzed N-arylation of amines

More recently, the use of arylsulfonamide in the nucleophile addition to cyclohexanone and ensuing palladium-catalyzed dehydrogenation has been realized by Deng's group.[14] Under the optimal catalytic conditions ($Pd(TFA)_2$/1,10-phen/toluene/O_2), a range of *N*-aryl sulfonamides was obtained with a broad functional group tolerance (Scheme 4.3-7). This palladium-catalyzed aerobic synthesis provides an atom-economical, low-cost, and environmentally friendly method for the synthesis of *N*-aryl sulphonamides; molecules of great importance as building blocks in pharmaceuticals and bioactive compounds.



Scheme 4.3-7 Forming *N*-aryl sulfonamides from cyclohexanone and sulphonamides

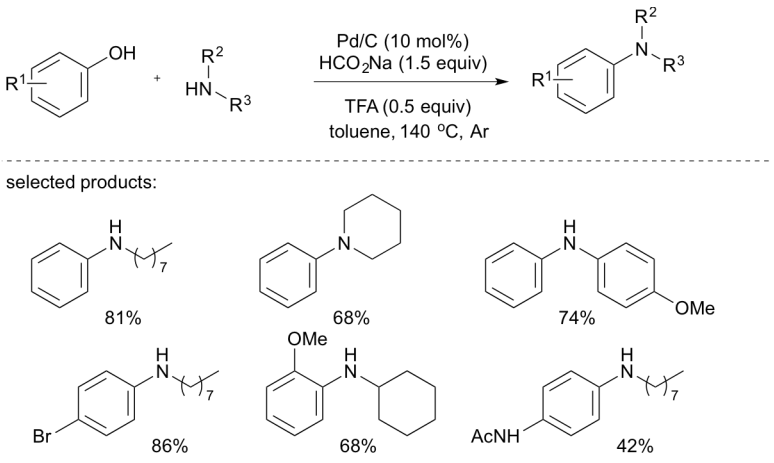
In 2013, the group of Stahl reported a protocol for the preparation of primary anilines from tetralones and cyclohexenones on the basis of Pd-catalyzed aerobic dehydrogenation routes to substituted phenols.[15] In this catalytic system, a broad range of primary aniline and 1-aminonaphthalene derivatives were generated in moderate to excellent yields (Scheme 4.3-8). The reaction of oxime with a stoichiometric amount of Pd(0) via an oxidative addition to the N-O bond was confirmed by the successful isolation of an imino-Pd(II) intermediate. Based on this observation and previous studies on cyclohexanone dehydrogenation, the following Pd-based *β*-hydride elimination and subsequent tautomerization account for the formation of the desired 1-aminonaphthalenes.



Scheme 4.3-8 Formation of primary anilines from oxime derivatives

In 2015, the Li group successfully presented the palladium-catalyzed reductive coupling of phenols with anilines and amines for the efficient synthesis of cyclohexylamines derivatives, demonstrating as such that phenols are a suitable precursor for the *in situ* generation of cyclohexanone as intermediate for further transformation.[16] Based on this result and their previous works on oxidative aromatization of cyclohexenone derivatives to access functionalized arenes, [3,4] they successfully described the same year, the first formal direct cross-coupling of phenols with amines through a tandem reduction/condensation/dehydrogenation process.[18]

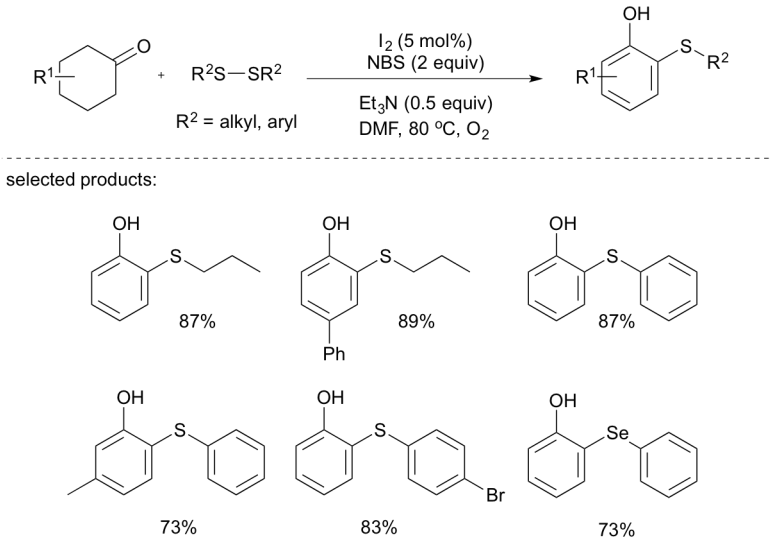
Using a combination of sodium formate (HCO_2Na) and trifluoroacetic acid (TFA) in presence of Pd/C a wide range of functionalized aryl amines were efficiently synthesized (Scheme 4.3-9). Their proposed mechanism involves the generation of the $HPd^{II}H$ species from the reaction of sodium formate and the palladium catalyst. The palladium hydride species can then reduce the phenol into the reactive cyclohexenone and cyclohexanone intermediates, which can undergo fast condensation with the amines in presence of catalytic amount of acid. This system was efficient for the coupling of phenol with various primary and secondary amines as well as aniline derivatives, with anilines bearing electron-donating groups affording the desired product in higher yields. The opposite trend was observed on the phenol partner, where phenol bearing electron-withdrawing group afford the desired product in moderate to good yield.



Scheme 4.3-9 Formal cross-coupling of phenols with amines

4.4 C-S bond formation

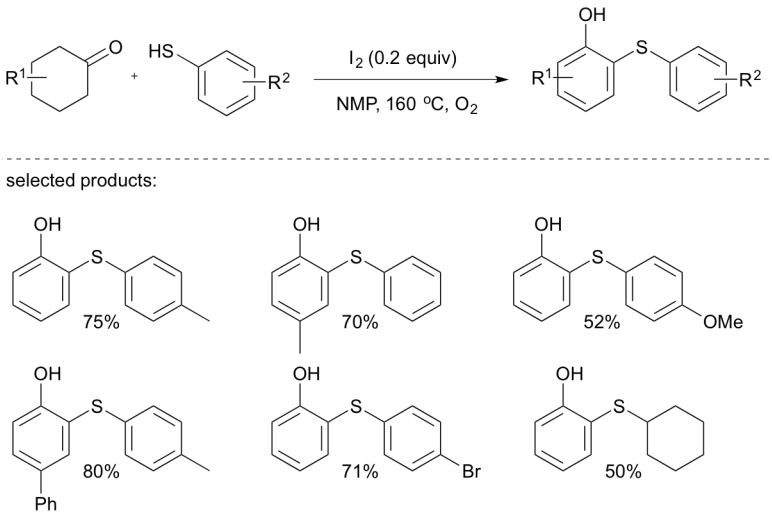
In 2013, the Wei group introduced the iodine-catalyzed synthesis of aryl and alkyl 2-sulfanylphenols via oxidative aromatization of cyclohexanones and disulfides.[19] Using a combination of NBS and I_2, various aryl and alkyl disulfides underwent transformation to afford the corresponding 2-sulfanylphenols in high yield (Scheme 4.4-1). Cyclohexanones with aryl



Scheme 4.4-1 Iodine-catalyzed synthesis of 2-sulfanylphenols

group react smoothly under the optimized conditions. It is worth noting that this transformation was also amenable to diphenyl diselenide substrate to give the (phenylselanyl)phenol product in 73%.

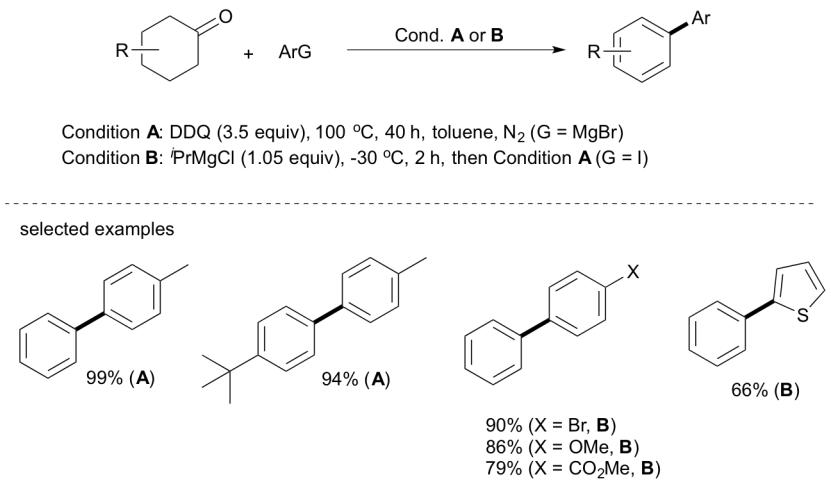
The same year, Liao *et al.* presented another system for the synthesis of 2-arylsulfanylphenol synthesis.[20] Under aerobic conditions using a catalytic amount of iodine the desired 2-arylsulfanylphenol product could be obtained from cyclohexanone and thiophenol derivatives at elevated temperature (Scheme 4.4-2). They proposed the formation of the aryldisulfide species under oxygen atmosphere. The disulfide can then form the electrophilic PhSI compound *in situ* in presence of iodine, and react with the cyclohexanone to form the 2-thio cyclohexanone. Subsequent dehydrogenation promoted by iodine and tautomerization provides the targeted molecule. Cyclohexanones bearing *para* substituents react smoothly with 4-methylbenzenethiol to afford the desired product. While tolerant to acetamido, hydroxyl, fluoro, chloro and bromo groups; thiophenol derivatives bearing electron-donating functionality afford the targeted compound in higher yield. Interestingly, aliphatic cyclohexanethiol could also undergo such transformation without aromatization of the cyclohexanethiol moiety in a moderate 50 % yield.



Scheme 4.4-2 Iodine-catalyzed synthesis of 2-arylsulfanylphenols

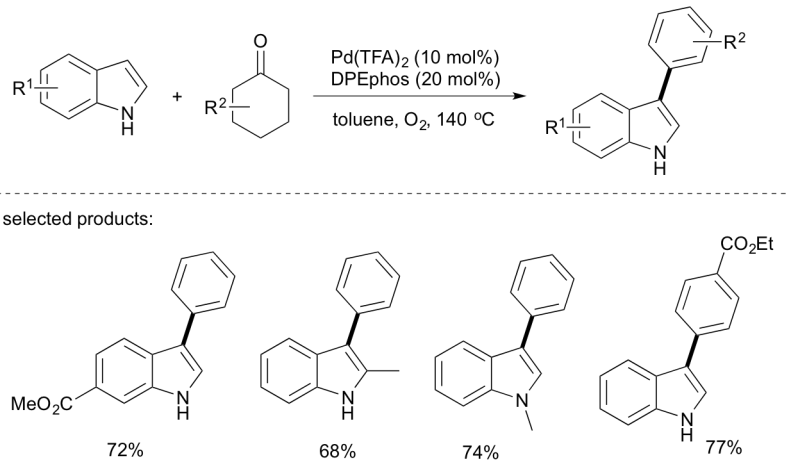
4.5 C-C bond formation

The same arylation strategy as oxygen, nitrogen and sulfur-based nucleophiles described above can be expanded to carbon-based nucleophiles. In 2013, the Li's group reported a transition-metal-free one-pot synthesis of biaryls from Grignard reagents and substituted cyclohexanones, in which the DDQ functions as hydrogen acceptor.[21] In this one-pot process, the Grignard reagent can be conveniently generated *in situ* from the corresponding aryl iodides, followed by sequentially nucleophilic addition, dehydration and dehydrogenation to afford the desired products in up to 99% yield (Scheme 4.5-1). Gratifyingly, various functionalities such as halogen, ester, and others can be well tolerated in this catalytic system. The heterocycle, 2-iodothiophene under the optimal conditions afforded the 2-phenylthiophene in good yield. This simple system eliminated the use of transition metals and no additional reagents were required.



Scheme 4.5-1 Arylation with C-nucleophiles with Grignard-reagents

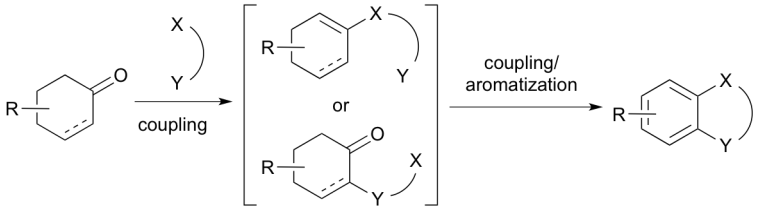
More recently, Deng's group reported a palladium-catalyzed approach to access 3-arylindoles from indoles and cyclohexanones, in which the molecular oxygen was used as the sole oxidant (Scheme 4.5-2).[22] This method is applied to the synthesis various of cyclohexanones and shows good regioselectivity as well. Since cyclohexanones are readily available starting materials, this method represents an environmentally benign approach for the preparation of biaryls and arylated heteroarenes.



Scheme 4.5-2 Arylation of indole derivatives

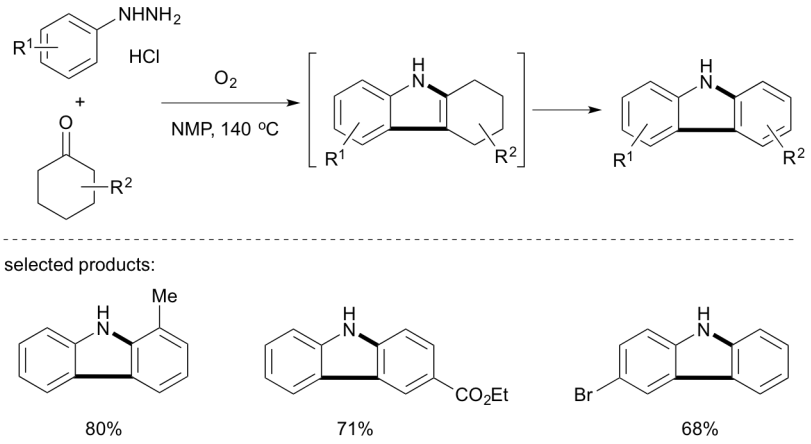
4.6 Application to the synthesis of heterocycles

A combination of two couplings at the C1 and C2 position of cyclohexanone with subsequent aromatization would provide new synthetic routes for the construction of heterocycles (Scheme 4.6-1).



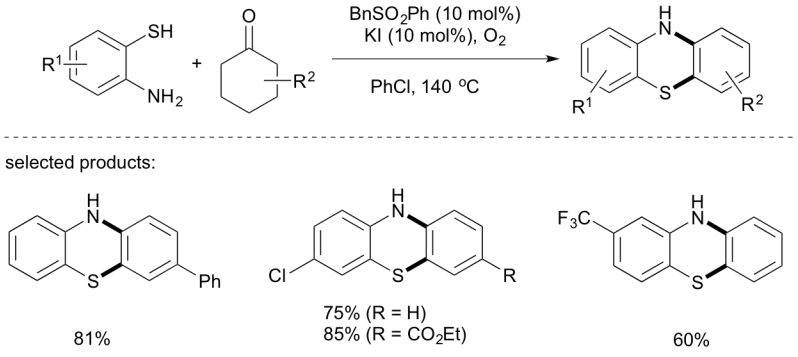
Scheme 4.6-1 Tandem C1 and C2 couplings of cyclohexanones

Deng and co-workers presented in 2012, a one-pot synthesis of carbazoles from cyclohexanones and arylhydrazine hydrochlorides (Scheme 4.6-2).[23] Unlike the widely used Fischer–Borsche reaction, this method could be achieved in a one-pot fashion in absence of a metal-catalyst by using molecular oxygen as oxidant. Heating the two substrates in NMP for 24h under oxygen atmosphere at 140 ºC gave the corresponding carbazole products in moderate to good yields. The use of hydrochloride hydrazines was crucial in this method since it generated *in situ* the stoichiometric amount of acid required for this transformation.



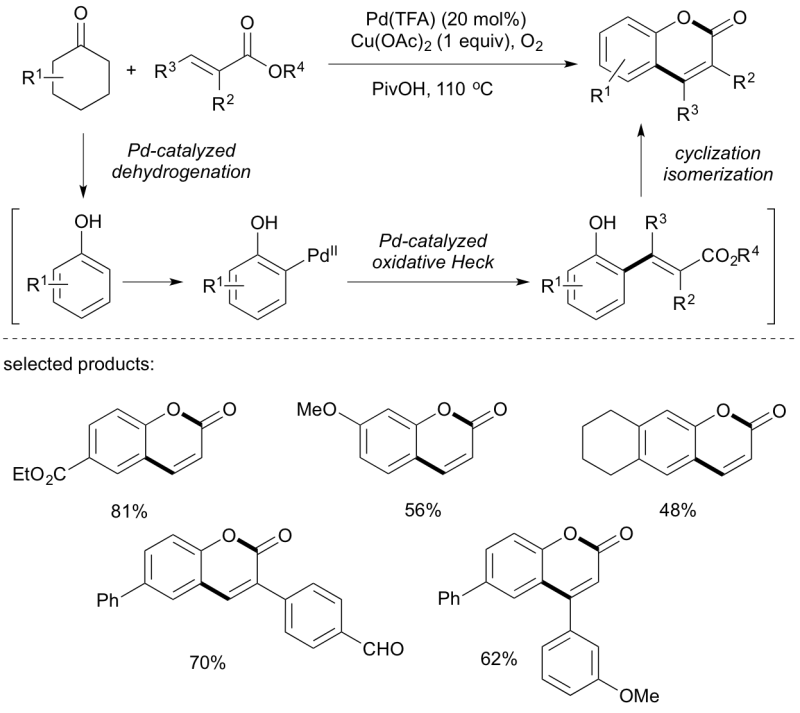
Scheme 4.6-2 One-pot synthesis of carbazoles from cyclohexanones and arylhydrazine hydrochlorides

One year later, the same group employed 2-aminobenzenethiols as the double-site coupling reagent, for the metal-free synthesis of phenothiazines (Scheme 4.6-3).[24] Various functionalized phenothiazines were successfully synthesized using a combination of benzyl aryl sulfone and potassium iodide under oxygen atmosphere. Cyclohexanones bearing electron-donating groups at the *para* position yielded the corresponding phenothiazines in good yield with several 2- aminobenzenethiols. However, the reaction is strongly influenced by steric effects.



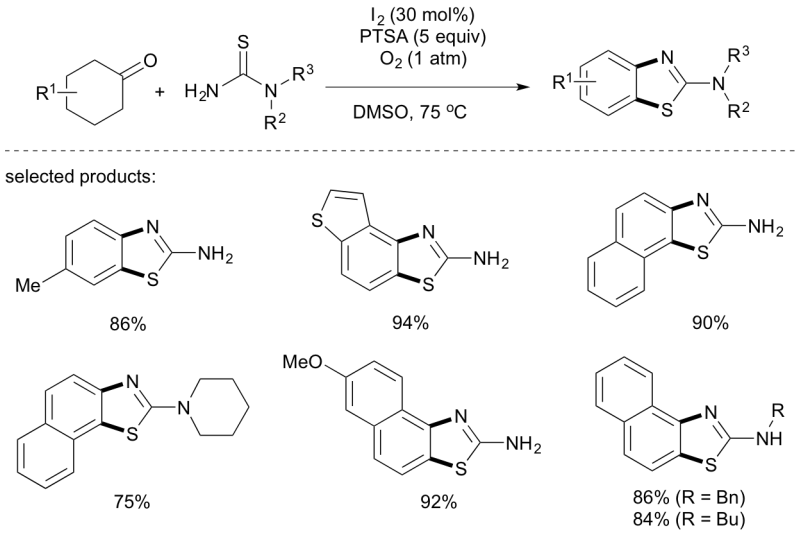
Scheme 4.6-3 Metal-free one-pot synthesis of phenothiazines from cyclohexanones and 2-aminobenzenethiols

The group of Hong described in 2013 an interesting approach to the synthesis of coumarins (Scheme 4.6-4).[25] The reaction proceeded via a Pd(II)-catalyzed dehydrogenation–oxidative Heck–cyclization. Using $Pd(TFA)_2$ in combination with copper salt and molecular oxygen as oxidant in pivalic acid, a broad range of highly functionalized coumarins were prepared in moderate to good yields. Based on the proposed mechanism, further functionalization of the coumarins was possible.



Scheme 4.6-4 Synthesis of coumarins

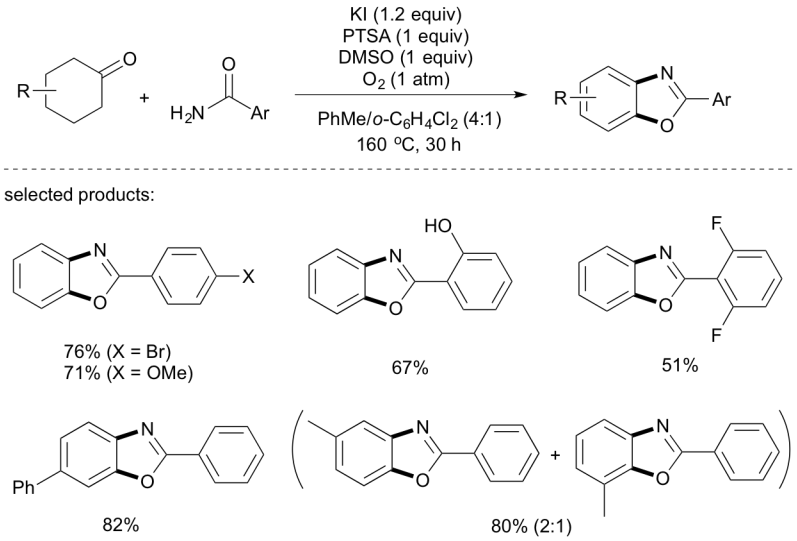
Jiang and co-workers introduced the catalytic I_2/TsOH/O_2 system for the construction of 2-aminobenzothiazoles from thioureas and cyclohexanones through a sulfanylphenol intermediate via the generation of α-C-S bond.[26] This reaction was performed at a relatively low temperature (75 ˚C) compared to previous dehydrogenations, albeit a strong sulfonic acid, TsOH, was required. While substituted cyclohexanones afforded 2-aminobenzothiazoles with generally moderate yields, the treatment of α- or β-tetralones with thioureas delivered naphtho[2,1-*d*]thiazoles in excellent yields. Notably, apart from free thiourea, *N*-alkyl and *N*-aryl, even disubstituted thioureas show high reactivities (Scheme 4.6-5).



Scheme 4.6-5 Iodine-catalyzed synthesis of 2-aminobenzothiazoles from thioureas and cyclohexanones

In addition to benzothiazole synthesis, Deng and co-workers effectively utilized aryl amides as coupling partner for the preparation of benzoxazoles.[27] Elevated temperature (160 °C) was essential for the success of this metal-free transformation, and a stoichiometric amount of DMSO was employed as a co-oxidant. A series of substituted 2-arylbenzoxazoles with alkyl, halogen, hydroxyl, and ester were prepared in moderate to good yields (Scheme 4.6-6).

Remarkably, the non-dehydrogenated intermediate product (i.e. tetrahydrobenzoxazole) could be successfully isolated in 66% yield by shortening the reaction time to 2 h.



Scheme 4.6-6 Preparation of benzoxazoles from cyclohexanone and aryl amides

4.7 Conclusion and outlook

In the past few years, the catalytic dehydrogenative aromatization has evolved into an area of intense investigation. In this context, many impressive, synthetically useful reactions have been reported via this non-cross-coupling strategy. As an efficient route to functionalized arenes in organic synthesis, the direct formation of C-O, C-N, C-S and C-C bonds has been successfully realized. Some representative synthetic applications to the construction of heterocycles have also been incorporated. Throughout all these catalytic oxidative processes, the distinctive feature is that the molecular oxygen is usually used as a terminal oxidant, thus delivering water as the main by-product in most cases. Low-cost and easily available starting materials, highly efficient atom economy and product diversity make this strategy particularly practical and fascinating. For further prospect in this field, a broader range of coupling partners and more synthetic application under simpler and milder conditions will be expected. On the other hand, the even more challenging aspect is to develop a general method for the synthesis of functionalized arenes via modified non-cross-coupling strategy, specifically, through temporarily dearomatization-introduction of coupling partners-rearomatization sequences, as exemplify by the formation of aryl amines from phenol through the hydrogen borrowing strategy.

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Chapter 5 - Supercritical CO_2 as a Medium for the Direct Synthesis of Metal-Organic Frameworks

The results described in this chapter were obtained by me (Simon A. Girard), under the guidance of Prof. Chao-Jun Li and Prof. Tomislav Friščić. All reactions were performed by me, with the assistance of Cristina Mottillo for characterizations. These investigations have not yet been submitted for publication, but are intended to be published, with additional experiments performed by Dr. Cristina Mottillo and Christopher Nickels. This is a collaborative project between myself (Simon A. Girard), Dr. Cristina Mottillo, Christopher Nickels, Prof. Tomislav Friščić and Prof. Chao-Jun Li. The early stage of this research led to the following patent: "Method for the preparation of metal-organic compounds" Friščić, T., Girard, S.A., Mottillo, C., Nickels, C., Li, C.-J. 2015. US Patent Pending WIPO No.PCT/CA2016/050172.

Our research on the development of heterogeneous catalytic systems for the direct transformation of phenols into functionalized arenes led us to consider a wide variety of original approach to perform heterogeneous catalysis. During our investigation, we became interested in a fairly new class of materials, the metal-organic frameworks (MOFs). MOFs seem particularly attractive due to their high potential for structural tunability and their possible post-synthetic modification. More specifically, the subclass of zeolitic imidazolate frameworks (ZIFs) has shown good stability toward various reaction conditions and has relatively high surface area, making ZIFs a viable platform for the design of new heterogeneous catalytic systems. However,

current synthesis of MOFs usually takes place under relatively harsh reaction conditions, which hindered their design and use as catalysts. This chapter present preliminary results on the use of supercritical carbon dioxide ($scCO_2$) as a potential milder medium for the large-scale synthesis of ZIFs from non-toxic zinc oxide and imidazoles.

5.1 Introduction

Metal-organic frameworks (MOFs) are infinite crystalline networks composed of metal centers or inorganic clusters connected with organic linkers through metal-ligand coordination bonds, and as such, are also known as coordination polymers (Figure 5.1-1).[1] Due to their extremely tunable nature combined with their microporosity, MOFs have found a large number of applications, including but not limited to: gas storage (hydrogen, methane, acetylene),[2,3] CO_2 capture,[4,5] separation of chemicals,[6] air purification of toxic chemicals,[7] and catalysis.[8–12]

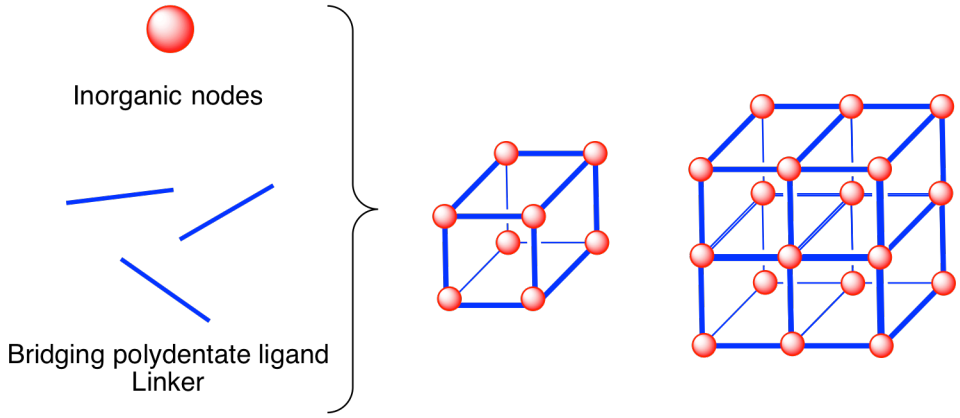


Figure 5.1-1 The node and spacer approach applied to MOFs

In order to further improve existing applications and develop new ones, it is crucial to enlarge the scope of structure and functionality available in MOFs. In that context, a subclass of MOFs belonging to the family of metal azolate framework (MAF) materials, zeolitic imidazolate frameworks (ZIFs) have shown great potential. Particularly, their relatively large microporosity[13] and stability toward moisture[14,15] makes ZIF good candidate for carbon dioxide sequestration[16,17] and molecular separation.[18,19]

5.1.1 Design of MOFs

The fundamental characteristics and proprieties of a MOF ensue from both the nature of its building blocs and the way that they are connected. Some critical parameters include the number and orientation of Lewis-basic sites on the organic linker (or ligand) as well as its length, the number of free-coordination sites on the metal center or inorganic cluster, and the mode of coordination of these sites.

As a result, in order to predict how the diverse building blocks would assemble to form the crystalline lattice, various design concepts have been developed for the synthesis of MOFs. Inspired by the methodology employed for the interpretation of zeolite structures, Robson introduced the “node and spacer” approach for the design of porous coordination polymer.[20,21] Using this concept, it has been possible to predict the structure resulting from the assembly between metal ions of known binding geometry and organic linkers.[22]

Yaghi and O’Keeffe proposed a more recent approach, named *reticular synthesis,* for the design of MOFs.[23] Simple organic ligands and metal ions were considered as primary building units in the “node and spacer” approach, where in this design concept, larger aggregate formed

by metal clusters or rigid molecular complex are represented as polygons and coined “secondary building units” (SBUs).[24,25] Thus, the simplified representation of the SBU assists the prediction of the structure that might exist between these building blocks and polytopic organic linkers. The use of SBUs for the construction of porous MOFs offers distinct advantages over simple metal ions as nodes and enables to greatly expand the range of structures accessible. Because of the greater relative size and higher rigidity of SBUs, MOFs with larger pores have become accessible. In addition, the use of a cluster of metal ions bridged by multiple linkers tends to enhance the overall robustness of the MOF.

5.1.2 Synthesis of MOFs

Traditionally the synthesis of MOFs employs solution-based methods, using pure or adequate mixture of solvents. The formation of the MOF takes place through self-assembly of the building blocks constructing the ordered lattice of metal organic coordination bonds. Typically, this is performed by mixing two solutions containing the metal node and the organic linker with or without the assistance of additives; with precipitation of the product from the solution of precursors. Classically, nitrate and chloride metal salts are selected as metal source but a broad variety of metal atoms have been successfully employed for the synthesis of MOFs and they encompass: alkaline-earth, transition metals, main group metals and rare-earth elements.[26,27] One of the main parameters in this process is the reaction temperature. It usually takes place under solvothermal or nonsolvothermal conditions, ranging from room temperature to 250 ˚C. Rabenau defined solvothermal reactions as taking place in closed autoclave under autogenous pressure above the boiling point of the solvent.[28] Consequently, nonsolvothermal

reactions take place at room temperature or below the boiling point of the solvent and at atmospheric pressure. While less energy intensive, nonsolvothermal conditions can face solubility issues with some building blocks.

Whereas solution based syntheses have historically been the conventional choice for the synthesis of MOFs, providing single crystal samples suitable for structural characterization, more recently the focus has been shifted towards milder methodologies that avoid the requirement for elevated temperature and decrease reaction time for the synthesis of metal-organic materials. In this context, microwave radiation (MW) has been explored as an alternative to conventional heating and has been shown to greatly reduce the reaction times needed for MOF synthesis.[29] Several metal carboxylate-based MOFs (M = Cu, Zn, Co, Ni, Fe, Al, Cr, V, Ce, Mn) have been prepared by MW-assisted synthesis route.[26] Cr-MIL-100 was the first reported MW synthesis of MOFs.[30] The compound was synthesized in 4 h at 220 ˚C under MW irradiation in 44% yield, which is comparable to the result of 45% obtained after 4 days under conventional heating conditions. While MW synthesis of MOFs is faster in comparison to the conventional heating counterpart, it generally yields smaller crystals which might be problematic for the characterization of new compounds.

About 10 years ago, researchers at BASF reported the first electrochemical formation of MOFs.[31] In this process, instead of using metal salts, metal ions (Zn, Cu, Mg, Co) are introduced by anode dissolution into the reaction solution containing the organic linker and a conducting salt. Whereas the electrochemical synthesis of MOFs offers the possibility of a continuous process, which is particularly attractive in an industrial setting, later reports demonstrated the inferior quality of the electrochemically synthesized products, which was

rationalized by incorporation of organic linker molecules and conducting salts in the pores during the product formation.[32]

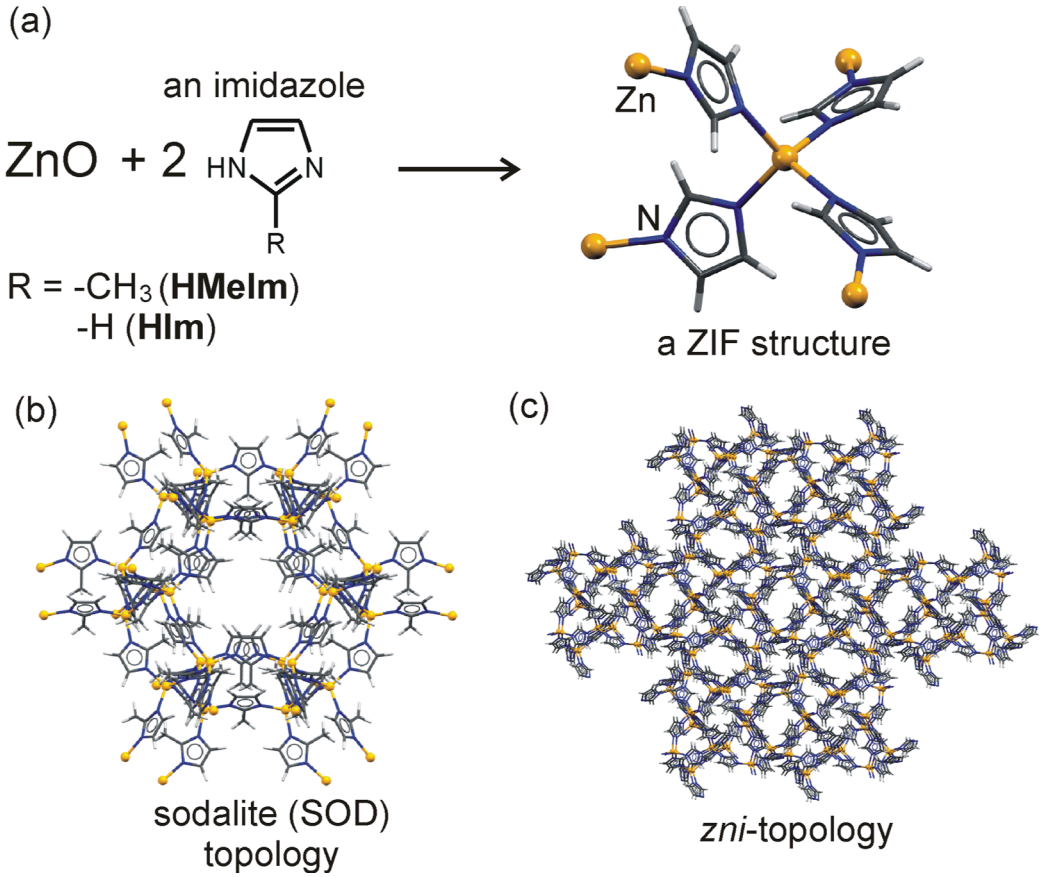
Although the effect of ultrasounds has been effectively applied to numerous synthesis of organic molecules[33] and nanomaterials,[34,35] sonochemical synthesis of MOFs remains mostly unmapped and has only been explored for the synthesis of known structures such as MOF-5,[36,37] MOF-177,[38] HKUST-1[39,40] and others.[41,42] Nevertheless, their syntheses under sonochemical conditions offer a milder and less energy consuming alternative to solvothermal synthesis and have shorter reaction time with generally higher yields.

Mechanochemistry processes offer many advantages to the synthesis of MOFs.[43] The reaction can be performed at room temperature and under solvent-free conditions, which drastically reduce the energy impact and the amount of solvent waste generated with conventional syntheses.[44,45] In addition, MOFs synthesized under mechanochemical conditions can be obtained in quantitative yield with a reaction time less than 1 h. Furthermore, in some cases metal oxides, difficult to employ in solvent-based methodologies due to their low solubility, were shown to be a source of suitable metal ions for the mechanically activated construction of MOFs, generating only water as by-product in the process.[46–48] Moreover, the addition of catalytic amount of solvent has been shown to accelerate mechanochemical reactions, so-called liquid-assisted grinding (LAG), possibly due to an increase in mobility of the reactants.[46,49] It has been suggested that similar processes might be taking place in neat grinding procedures that introduce metal ions from hydrated or acetate metal salts and release liquid *in situ* during the reaction (such as water or acetic acid).[50] More recently, this method has been

extended to ion- and liquid-assisted grinding (ILAG), where both the ion and the solvent influence the topology of the material produced.[43,51]

5.2 Plan of study

Traditionally, the synthesis of MOFs was conducted using corrosive metal chlorides and nitrates as a source of inorganic nodes. Recently, however, solvent-reduced or solvent-free methods have enabled the synthesis of metal-organic frameworks directly from basic metal oxide precursors.[48,51] In particular, previous reports of zinc oxide conversion at low temperatures into ZIF-8 with sodalite (SOD) topology (Figure 5.2-1) involved mechanochemistry (at room temperature)[57] or accelerated aging (synthesis at 40 ^{o}C-45 ^{o}C).[58] Both techniques require the presence of catalytic amounts of protic ammonium salt to enhance the reaction.



(a) Transformation of zinc oxide into zeolitic imidazolate frameworks (ZIFs); (b) fragment of a porous SOD-topology structure found in ZIF-8 and (c) fragment of the non-porous *zni*-topology structure, found in *zni*-Zn(**Im**)$_2$.

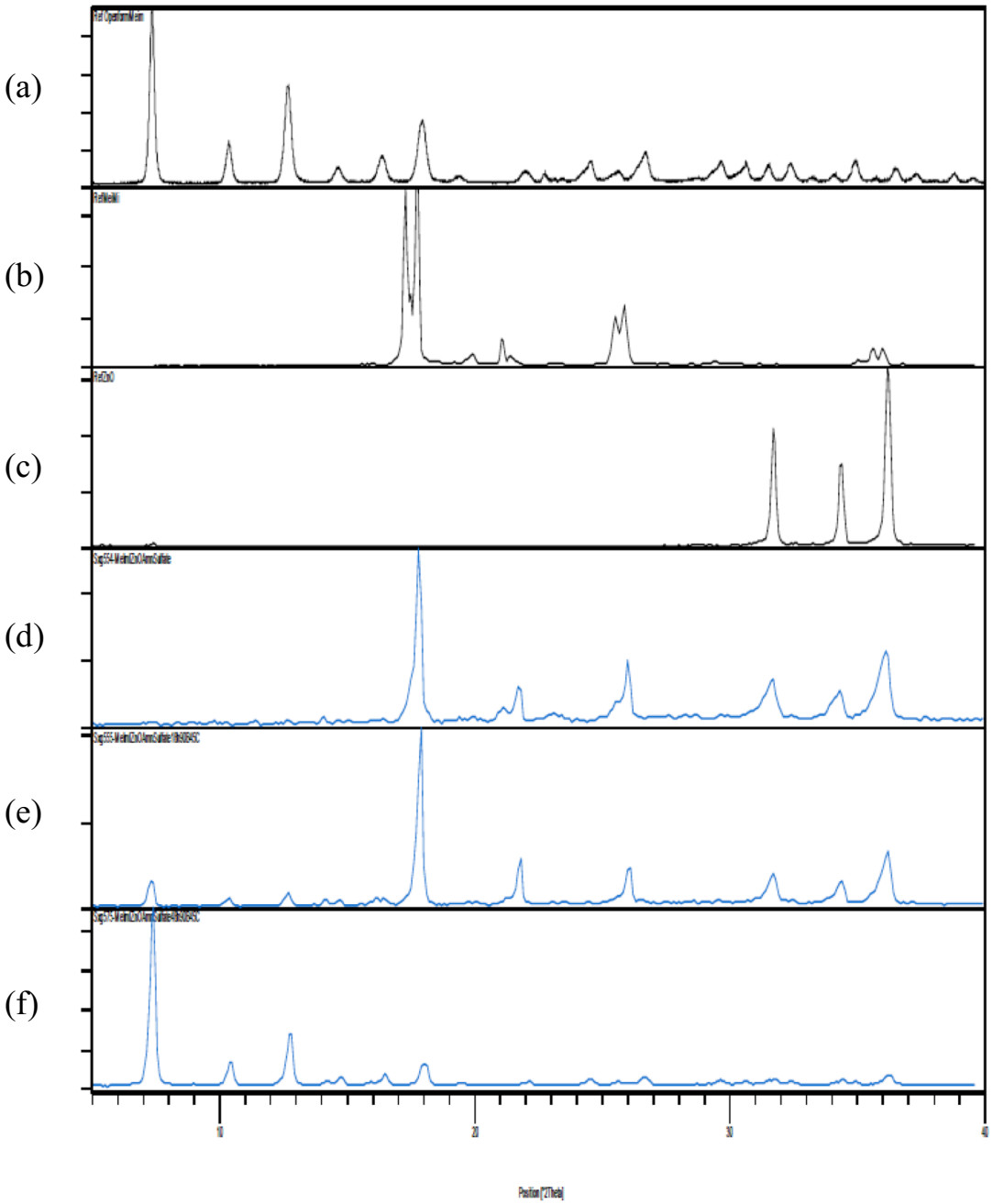
Figure 5.2-1 Formation of ZIF from ZnO

Whereas the use of supercritical CO_2 ($scCO_2$) in the context of Green Chemistry is well established, its applications have largely focused on the use of $scCO_2$ as a solvent for conducting organic synthesis or industrial extraction.[52,53] However, in the context of inorganic and metal-organic material chemistry, the potential benefits of $scCO_2$ have remained almost completely unexplored. Recently, $scCO_2$ processes have been used as a clean alternative for structural expansion and washing activation of microporous metal-organic frameworks.[54–56]

5.3 Results and discussion

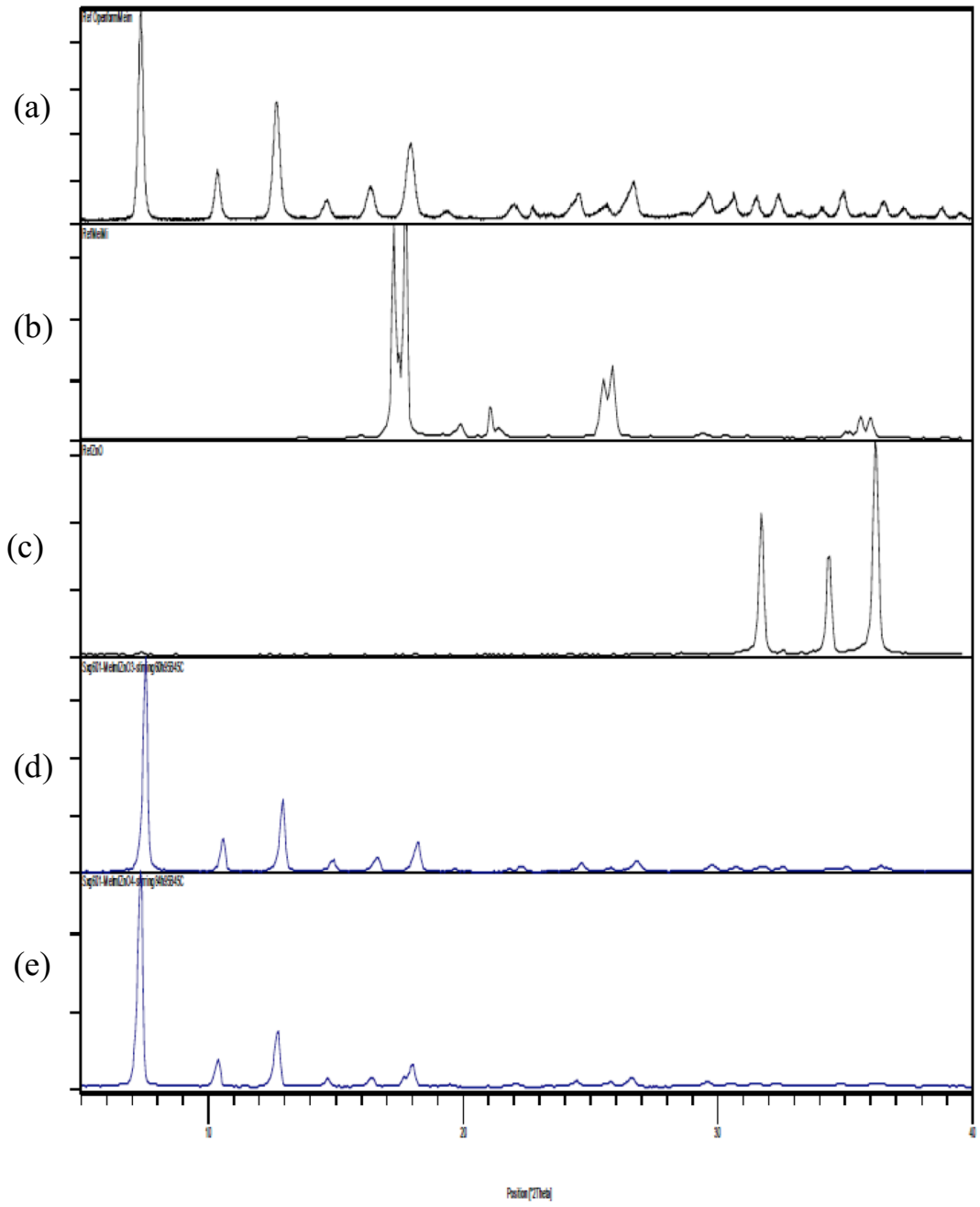
Inspired by these recent findings, we decided to investigate the use of $scCO_2$ as a medium for the direct synthesis of ZIF-8 using catalytic amount ammonium salt. We placed a 1:2 mixture of ZnO and 2-methylimidazole (**HMeIm**, Figure 5.3-1a) with 5 mol% of ammonium sulphate under $scCO_2$ conditions (90 bars, 45˚C). After 12 hours of exposure (Figure 5.3-1d), powder X-ray diffraction (PXRD) pattern showed signs of the formation of ZIF-8. Extending the reaction time to 18 hours was beneficial for the formation of ZIF-8 structure, with PXRD pattern clearly demonstrating the characteristic reflexions of the ZIF-8 structure at 2Θ diffraction angles 7.4^o, 10.4^o and 12.8^o, with the strong reflexion of remaining unreacted **HMeIm** and ZnO reactants (Figure 5.3-1e). Further extension of the reaction time to 48 hours was beneficial, as the reaction mixture consisted of almost pure ZIF-8 with only weak reflection of ZnO reactant (Figure 5.3-1f).

Encouraged by these results, we decided to investigate the influence of the ammonium sulfate on the reaction and were pleased to observe the formation of ZIF-8 even without the presence of $(NH_4)_2SO_4$ additive (Figure 5.3-2). While the reaction is slower than in presence of $(NH_4)_2SO_4$, the PXRD pattern of the reaction mixture only exhibited weak reflexions of ZnO after exposure of a 1:2 mixture of ZnO and **HMeIm** to $scCO_2$ for 60 hours (Figure 5.3-2d), and was almost undetectable after 84 hours (Figure 5.3-2e). This result is in clear contrast to the reactivity observed in mechanochemical and accelerated aging processes. More importantly, this demonstrates that $scCO_2$ is a suitable medium for the direct and additive-free synthesis of ZIF-8 from cheap and easily available ZnO.



(a) Simulated for the crystal structure of ZIF-8 (CSD code OFERUN); (b) **HMeIm** reagent; (c) reagent ZnO; (d) reaction mixture after 12 hours; (e) reaction mixture after 18 hours; (f) reaction mixture after 48 hours

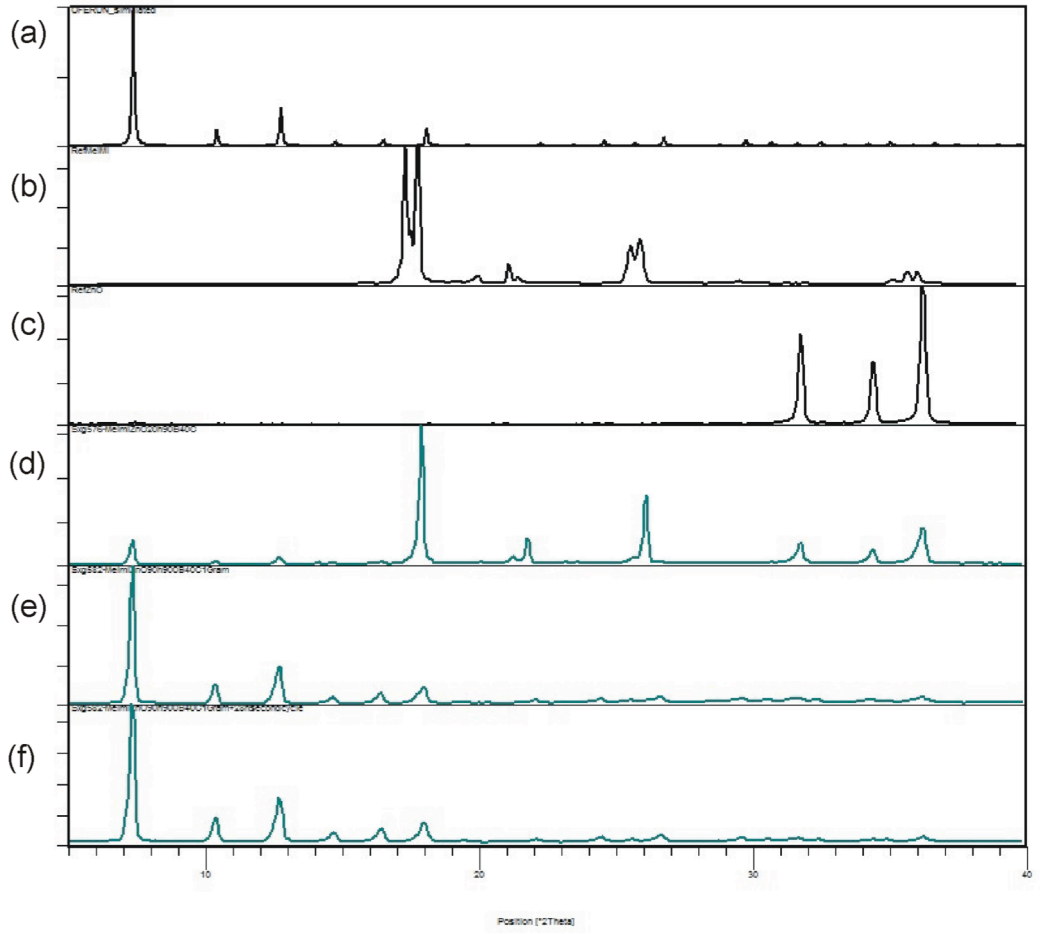
Figure 5.3-1 PXRD patterns for the synthesis of the metal-organic framework ZIF-8 with $(NH_4)_2SO_4$ from supercritical CO_2 (90 bar, 45 ^oC)



(a) Simulated for the crystal structure of ZIF-8 (CSD code OFERUN); (b) **HMeIm** reagent; (c) reagent ZnO; (d) reaction mixture after 60 hours; (e) reaction mixture after 84 hours;

Figure 5.3-2 PXRD patterns for the synthesis of the metal-organic framework ZIF-8 from supercritical CO_2 (95 bar, 45 ^{o}C)

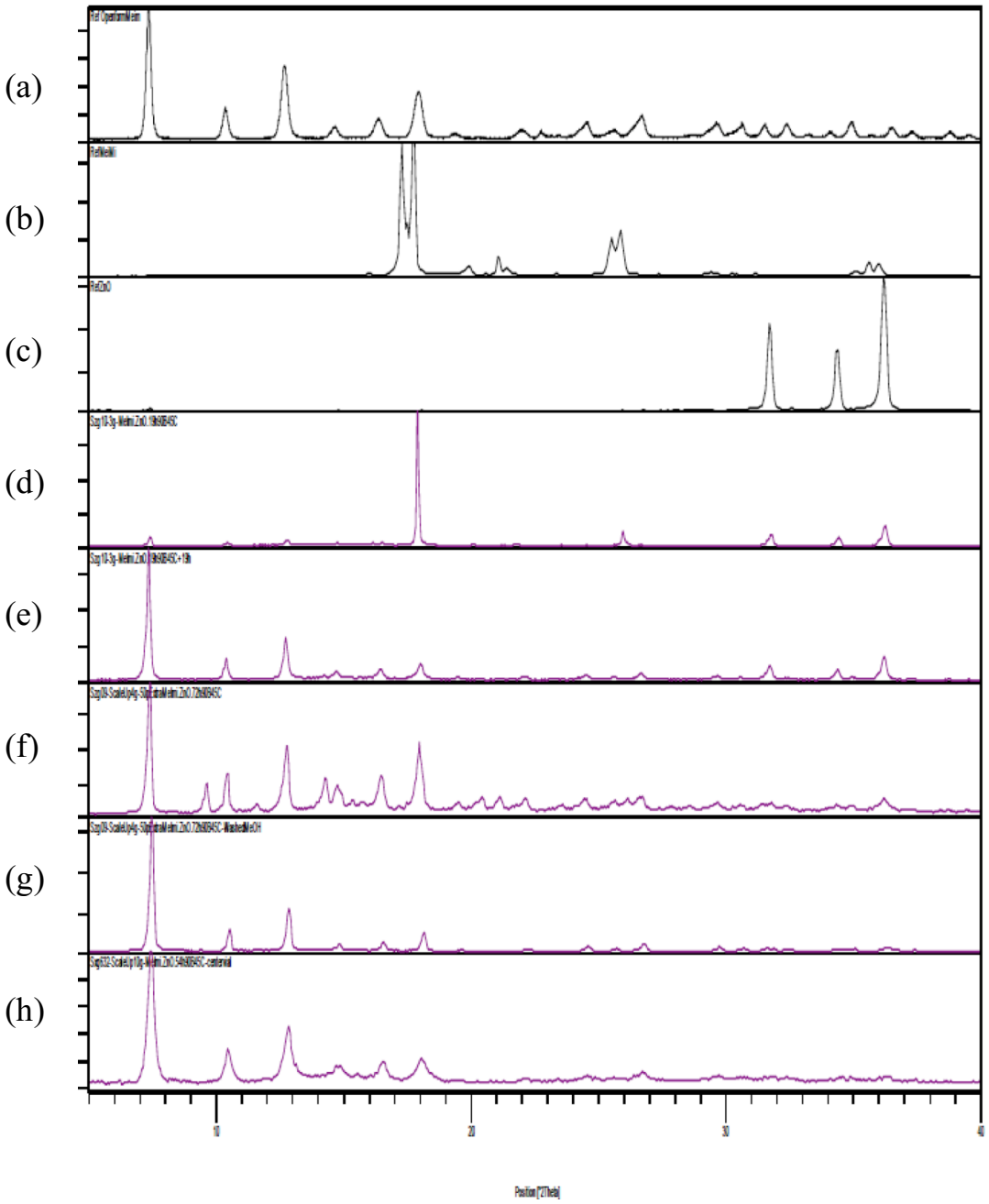
Notably, the reaction could also be easily scaled up without a loss in conversion, and one gram of ZIF-8 was obtained after 5 days of exposure to $scCO_2$ (Figure 5.3-3).



(a) Simulated for the crystal structure of ZIF-8 (CSD code OFERUN); (b) **HMeIm** reagent; (c) reagent ZnO; (d) reaction mixture after 20 hours; (e) reaction mixture after 90 hours and (f) reaction mixture after 118 hours.

Figure 5.3-3 PXRD patterns for the synthesis of the metal-organic framework ZIF-8 from supercritical CO_2 at one gram scale (90 bar, 45 ^{o}C)

Attempts to perform the conversion on larger scales were also successful. However, after running the reaction on a 3 g scale for 19 hours, the typical reflection pattern of ZnO was still observed, and visible even after extending the reaction time to 38 hours (Figure 5.3-4d and e). This observation led us to repeat the experiment for 72 hours with 50% extra amount of **HMeIm** (1:3 ZnO/**HMeIm)**, in hope to obtain complete conversion of ZnO into ZIF-8 (Figure 5.3-4f). Indeed, after washing the sample with methanol, the PXRD pattern of the reaction mixture only displays the characteristic pattern of ZIF-8 (Figure 5.3-4g). Finally, a 10 g scale reaction was investigated, leading to the almost complete disappearance of the ZnO reactant within 54 hours (Figure 5.3-4h).

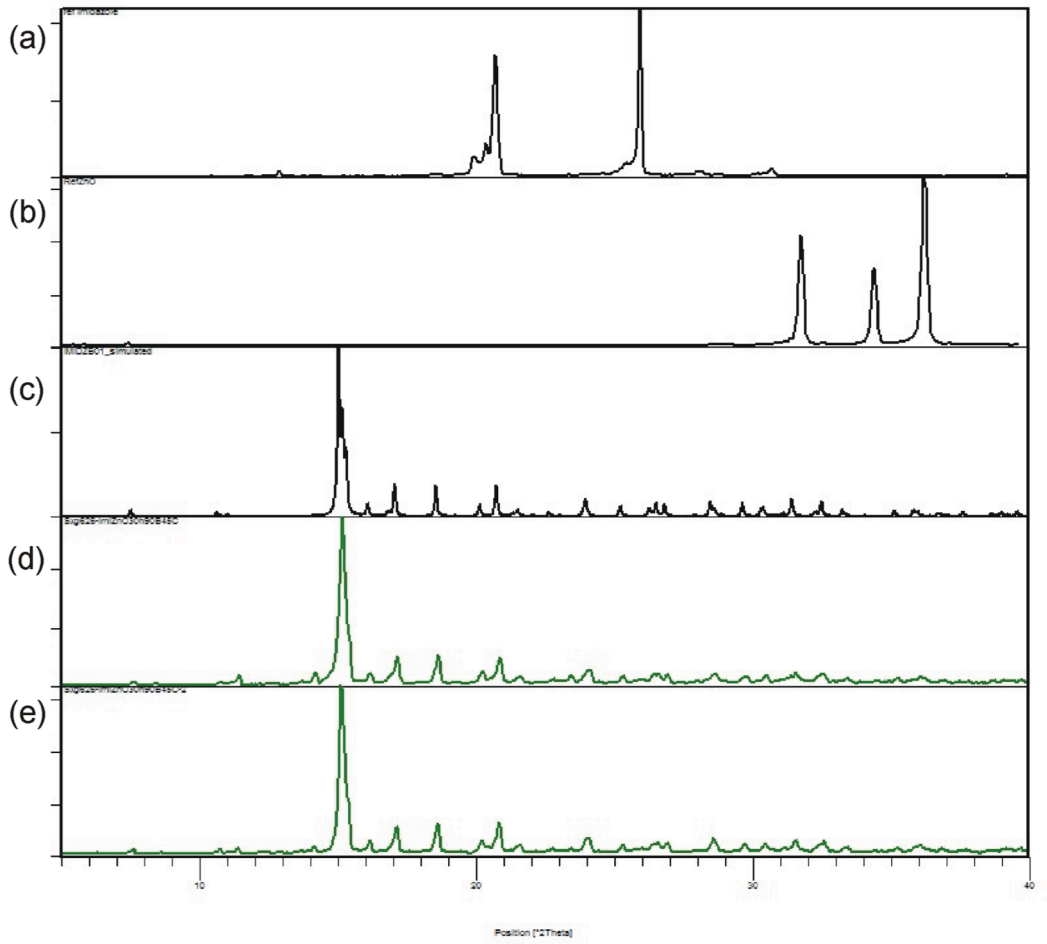


(a) Simulated for the crystal structure of ZIF-8 (CSD code OFERUN); (b) **HMeIm** reagent; (c) reagent ZnO; (d) three gram reaction mixture after 19 hours and (e) 38 hours exposure to $scCO_2$ (f) reaction at 4 gram scale, using 50 mol% excess **HMeIm** after 72 hours exposure to $scCO_2$; (g) the sample after washing with methanol, demonstrating the absence of ZnO reactant; (h) 10 gram reaction mixture after 54 hours exposure to $scCO_2$;

Figure 5.3-4 PXRD patterns for the synthesis of the metal-organic framework ZIF-8 from supercritical CO_2 on large scale (90 bar, 45 ^{o}C)

In order to get a better understanding of the reactivity of ZnO and **HMeIm** in $scCO_2$, we explored the synthesis of ZIFs using different reagents. We originally made the hypothesis that the spontaneous conversion of ZnO and **HMeIm** into ZIF-8 could be mediated by the formation of a carbonate phase. However, to our surprise, the exposure of zinc oxide to $scCO_2$ over prolonged periods of time showed no evidence of new crystalline phases besides ZnO. Moreover, attempts to conduct ZIF-8 synthesis directly from commercially available basic zinc carbonate also failed. This highlights the unexpected difference in reactivity of ZnO and basic zinc carbonate in $scCO_2$ for the synthesis ZIFs and the result is in contrast to previous reports using mechanochemical processes, where carbonates were usually more reactive than the corresponding oxides. We then explored zinc acetate, a more commonly used reagent as a precursor for the ZIF-8 synthesis. In contrast to our expectations, exposure to $scCO_2$ yielded an amorphous material.

Next, we investigated the reactivity of unsubstituted imidazole (**HIm**) with ZnO. After 30 hours exposure to $scCO_2$, the stoichiometric 1:2 ratio mixture of ZnO and **HIm** was fully transformed into the non-porous framework with *zni*-topology, *zni*-Zn(**Im**)$_2$ (Figure 5.3-5c).



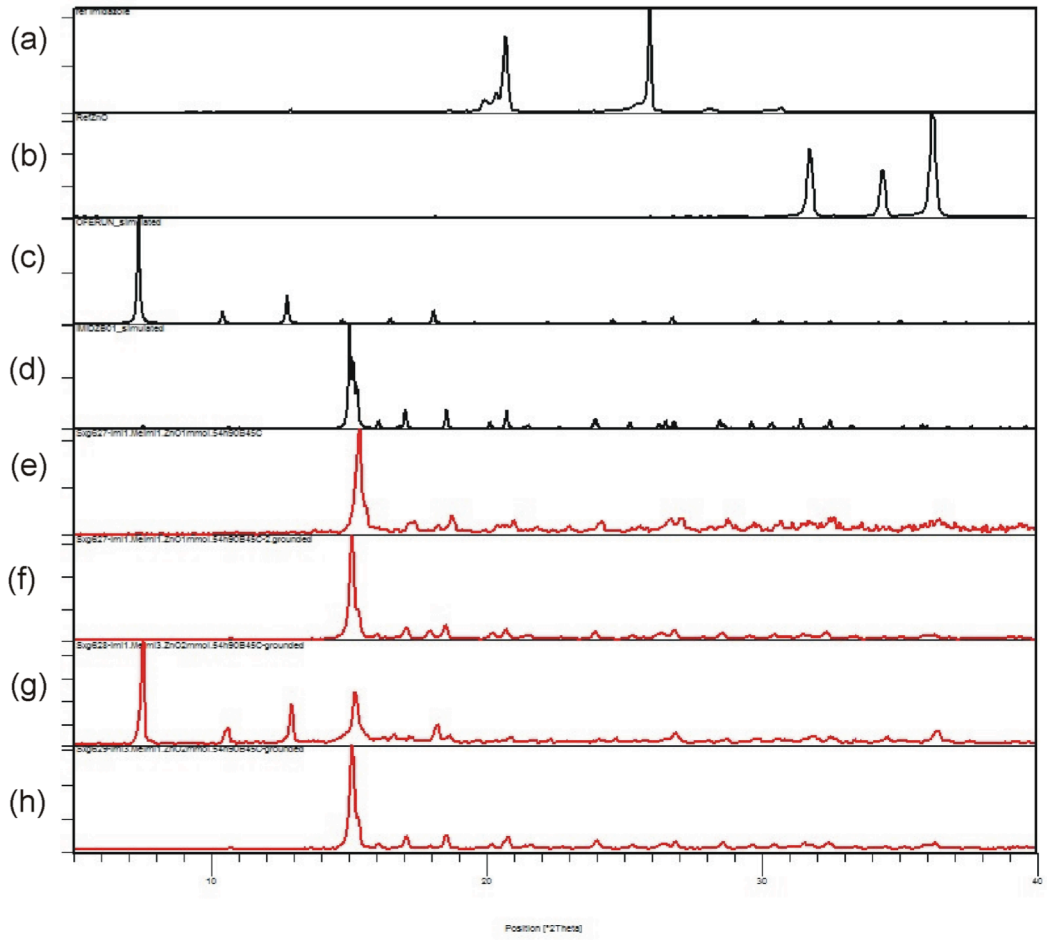
(a) **HIm** reagent; (b) reagent ZnO; (c) simulated for *zni*-Zn(**Im**)$_2$ (CSD code IMIDZB01); (d) and (e) samples of two repeated experiments after 30 hours.

Figure 5.3-5 PXRD patterns for the synthesis of the metal-organic framework *zni*-Zn(**Im**)$_2$ from supercritical CO_2 (90 bar, 45 ^oC)

We thus have successfully demonstrated the reactivity of ZnO with **HIm** and **HMeIm** under supercritical CO_2 conditions. This suggested the opportunity to investigate the synthesis of ZIFs from a mixture of ligands.

Subsequently, we explored the possibility to synthesize mixed-ligand frameworks in $scCO_2$ by exposing a reaction mixture containing one equivalent of ZnO and two equivalents of a 1:1 stoichiometric mixture of **HMeIm** and **HIm** to a supercritical carbon dioxide environment at

90 bar and 45°C (Figure 5.3-6). After 54 hours exposure, PXRD analysis revealed the complete formation of a material isostructural with *zni*-topology Zn(**Im**)$_2$ and disappearance of reflections from both reactants, imidazoles and ZnO (Figure 5.3-6e and f). Repeating the same experiment but with a different ratio in the mixture of **HIm** and **HMeIm** (3:1), yielded the same result (Figure 5.3-6g). However, if the respective stoichiometric ratio of **HIm** and **HMeIm** was reversed (1:3), the PXRD pattern was consistent with a mixture of ZIFs with *zni*- and SOD-topology (Figure 5.3-6h). Consequently, these experiments reveal that the reaction of ZnO with a mixture of **HIm** and **HMeim** leads to a *zni*-topology material as long as the ratio of **HIm**:**HMeIm** is equal to or greater than 1. If **HMeIm** is the dominant component in the mixture of the two imidazoles, the system produces a mixture of SOD- and *zni*-topology materials.



a) **HIm** reagent; (b) reagent ZnO; (c) simulated for SOD-topology Zn(**MeIm**)$_2$ (CSD code OFERUN); (d) simulated for *zni*-topology Zn(**Im**)$_2$ (CSD code IMIDZB01); (e) and (f) two samples of reactions conducted for 54 hours using a 1:1 ratio of **HIm** and **HMeim**; (g) sample of the reaction conducted for 54 hours using a 1:3 stoichiometric ratio of **HIm** and **HMeIm** and (h) sample of the reaction involving a 3:1 ratio of **HIm** and **HMeIm** after 54 hours in the scCO_2 environment.

Figure 5.3-6 PXRD patterns for the synthesis of metal-organic frameworks from ZnO and mixtures of **HIm** and **HMeim** in supercritical CO_2 (90 bar, 45 ^{o}C)

5.4 Conclusion and outlook

In conclusion, we discovered a novel alternative for the synthesis of porous and non-porous metal-organic frameworks, using supercritical carbon dioxide as a previously unexplored medium. In addition, we have demonstrated that this methodology is not only suitable for the synthesis of ZIF-8 but has the potential to be extended to other structures and can directly produce materials without extra solvents in contrast to alternative syntheses. Outstandingly, the reactivity observed in this medium does not follow previously reported reactivity patterns observed in related reactions, which represents an attractive opportunity to access new topologies and potentially new materials. Additionally, this methodology circumvents one of the key challenge in the synthesis of high porosity materials, which is the removal of guest molecules (solvents, excess of organic linker, etc.) from the framework while still maintaining its structural integrity (i.e., “activation”). Moreover, this technology represents an attractive synthetic methodology for the direct, clean and large-scale manufacture of MOFs from simple starting materials with only little energy input.

5.5 Experimental section

5.5.1 General information

All commercially available compounds were purchased and used as received. High purity liquid carbon dioxide was used (99.9%). All supercritical experiments were run using a Waters Prep SFE system. Powder X-ray diffraction (PXRD) patterns were collected using a Bruker D2 powder diffractometer equipped with a Cu-Kα (λ=1.54060 Å) source and Lynxeye detector set at a discriminant range of 0.110 V to 0.250 V. The patterns were collected in the range of 3° to 40°. Analysis of PXRD patterns was conducted using Panalytical X'Pert Highscore Plus software. Experimental patterns were compared to simulated patterns calculated from published crystal structures using Mercury crystal structure viewing software. Crystallographic Information Files containing published crystal structures were obtained from the Cambridge Structural Database (CSD) and Crystallography Open Database (COD).

5.5.2 General procedures

In a typical experiment, a 1:2 stoichiometric mixture of ZnO (1 mmol, 81.4 mg) and 2-methylimidazole (**HMeIm**, 2 mmol, 164.2 mg) along with 5 mol% (with respect to ZnO) of ammonium sulphate $(NH_4)_2SO_4$ were manually grinded in a mortar for 2 minutes, and placed in a 1 dram glass vial. The open vial was then placed in the 500 mL extraction chamber of the Waters Prep SFE system. Once sealed, the extraction chamber was then flushed with gaseous CO_2 for 2 minutes using the CO_2 pump at a 5 g/minutes flow rate. The heaters were then turned on and set

to the appropriate temperature (heat exchanger: 45 ˚C, vessel: 45 ˚C) before setting up the backpressure regulator to 90 bars. The CO_2 pump was then activated, and liquid CO_2 was pumped at a 20 g/minute flow rate into the extraction chamber, until the desired pressure and temperature were reached. The extraction chamber was then sealed by manually closing the valves and let sit for the set amount of time. After completion of the experiment, the extraction chamber was then brought to atmospheric pressure over a 10 minutes period. The vial was then capped and PXRD patterns were collected.

5.6 References

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Chapter 6 – Summary, Conclusion and Prospects

6.1 Summary and contribution to knowledge

Substituted arenes are a ubiquitous substructure of both, naturally occurring and synthetically produced organic compounds. While synthetic chemists have shown great ingenuity in the development of methodologies and processes to access functionalized arenes, most of the popular strategies employed for their manufacture rely on the use of petroleum derivatives as starting materials. More recently, with the realization that the exploitation of fossil materials has an environmental impact and that we will eventually run out, it is becoming clear that mankind will need to find renewable alternatives to access the building blocks required for the manufacture of molecules of interest. Consequently, with about 30% of the land covered by forest, the different constituents of wood are currently being investigated as a potential source of basic building blocks for the chemical industry. In particular, lignin, which is mostly composed of phenol moiety subunits, seems especially attractive as it could represent a convenient source of building blocks for the construction of functionalized arenes. Thus, in pursuit of new approaches for the simple and environmental synthesis of functionalized arenes directly from phenols we successfully introduced new strategies to generate decorated aromatic rings from cyclohexenone derivatives.

As the first step toward the direct functionalization of phenols, we successfully developed copper catalyzed systems for synthesis of aryl ether from cyclohexenones derivatives.[1] The

copper-catalyzed aerobic system was found to be compatible with a wide range of aliphatic alcohols and cyclohexenone derivatives, affording a direct, versatile and original approach for the synthesis of functionalized aryl ethers through dehydrogenative aromatization. As such we demonstrated the compatibility between the nucleophilic addition and dehydrogenative aromatization steps. In addition, the amount of copper was successfully reduced to sub-stoichiometric quantity with the assistance of a co-catalyst, NHPI. This system conveniently uses molecular oxygen as the terminal oxidant, hence only formally producing water and hydrogen as the sole by-products. This reaction not only represents an original alternative to existing methodologies but was also the first step towards the successful application of the "borrowing hydrogen" strategy to the synthesis of functionalized arenes directly from phenols. In addition, this system could potentially be further improved by addition of various substituents on NHPI in order to enhance the efficiency of the dehydrogenative aromatization process, thus potentially enabling the use of cyclohexanone derivatives as suitable substrates and allowing the use of air instead of pure molecular oxygen.

With this proof of concept at hand, we then challenged the viability of this methodology to the atom-economic and waste-minimized aerobic synthesis of aryl amines. We designed a palladium-catalyzed system for the selective arylation of various secondary aliphatic amines with cyclohexanone derivatives under aerobic condition.[2] As such we demonstrated that the condensation/dehydrogenative aromatization processes could be successfully extended to other nucleophiles. The positive influence of the addition of catalytic amount of acid on the efficiency of such transformation suggests further investigation on the impact of pH on the reaction outcome. The use of a buffer such as $PhCO_2H/PhCO_2Na$ or a more soluble ammonium salt might

further improve the efficacy of such transformation. In addition, the successful use of air instead of pure oxygen would represent an attractive improvement, as it would greatly facilitate the implementation of such methodology to industrial processes.

This research represents the groundwork for the direct transformation of phenols to functionalized arenes and has led to the successful development of a catalytic system for the direct coupling of phenol with amines through the borrowing hydrogen strategy.[3] In addition, we have efficiently demonstrated that the cyclohexenone moiety is a suitable substrate to access decorated aromatic ring and this synthetic concept has since been extended by us and other to other nucleophiles and to the synthesis of various heterocycles. Furthermore, in theory, cyclohexenone derivatives could potentially be involved in other class of transformation before the dehydrogenative aromatization step. One could imagine performing the conjugated addition instead of the 1,2 nucleophilic addition to the carbonyl or involve the conjugated ketone in Diels-Alder transformations before the dehydrogenative aromatization process which would greatly extend the scope of structure and functionality accessible.

Finally, preliminary results on the use of supercritical carbon dioxide as a medium for the direct and simple synthesis of activated zeolitic imidazolate frameworks were also discussed. Exciting new reactivity patterns were observed with metal oxides and showed great potential for the large-scale manufacture of metal-organic frameworks in a clean and efficient fashion.[4] The scope of topology accessible has yet to be explored and the detailed mechanism must be elucidated.

The reactions described here represent our contribution to the development of new chemical tools for the efficient and atom-economical synthesis of important molecules and

advanced materials. We believe these studies not only represent an improvement to the existing methodology for synthesis, but also unravel new pathways that will lead to the discovery of new and interesting compounds with potential application in medicinal chemistry and materials design.

6.2 References

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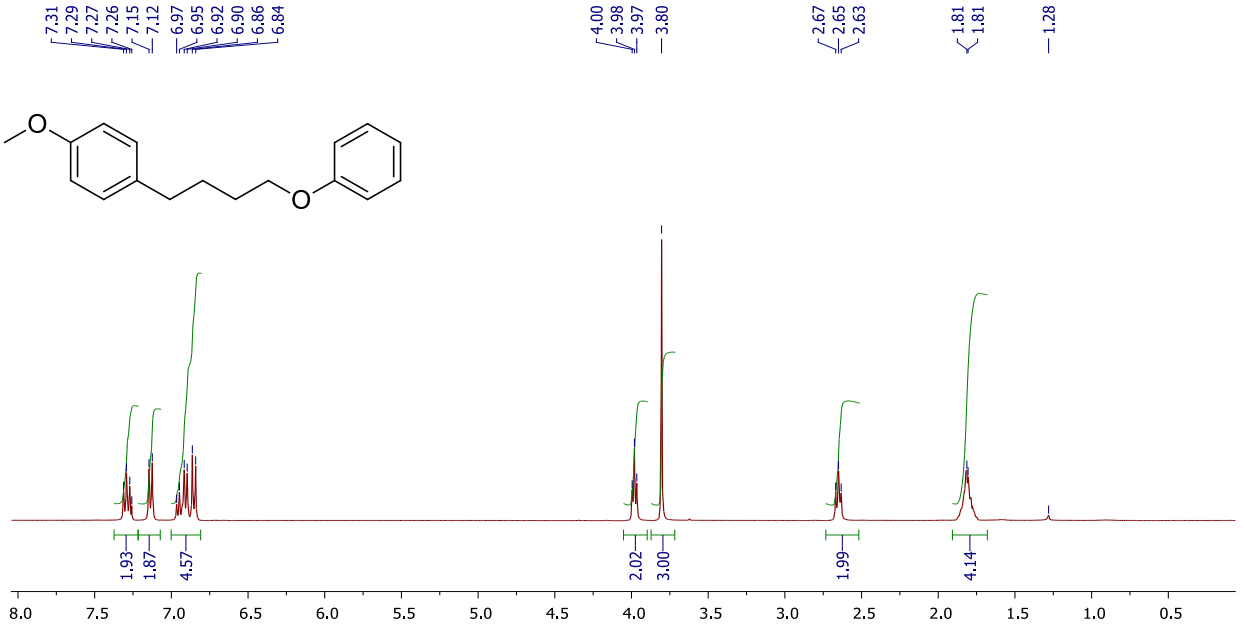
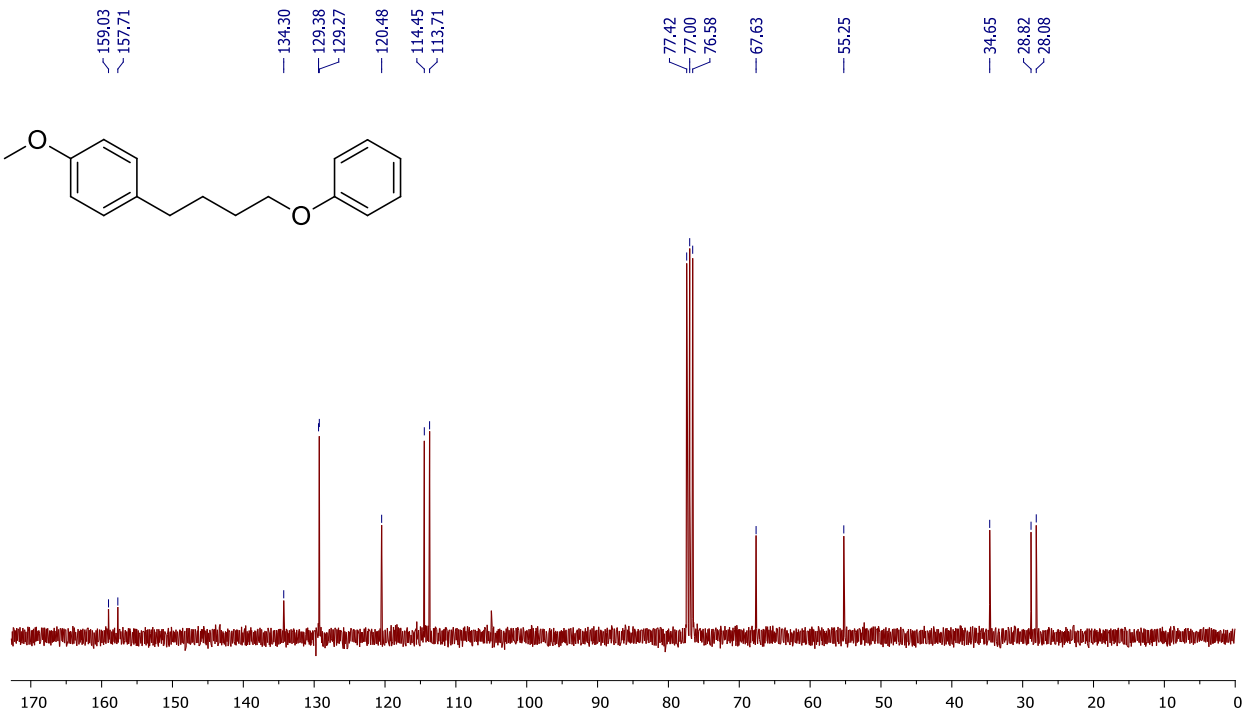
Supporting Information

Spectra for previously unknown compounds in chapter 2

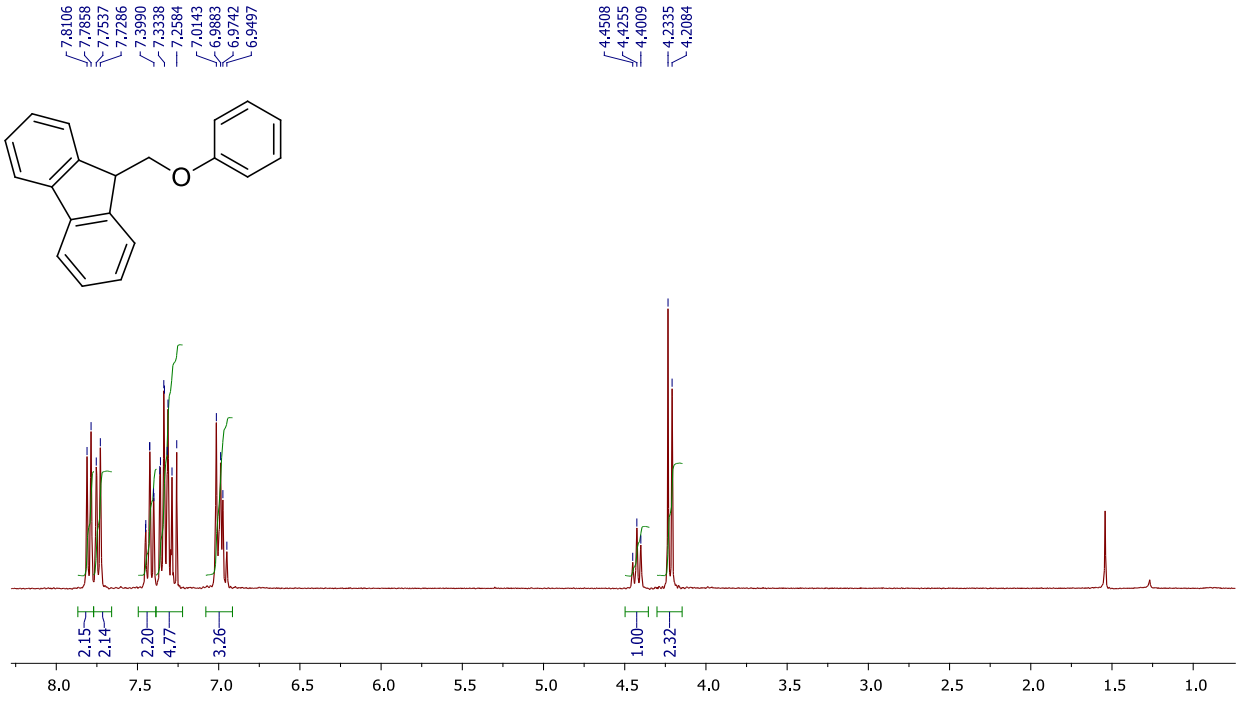
7. ^{1}H and ^{13}C NMR spectra of new compounds

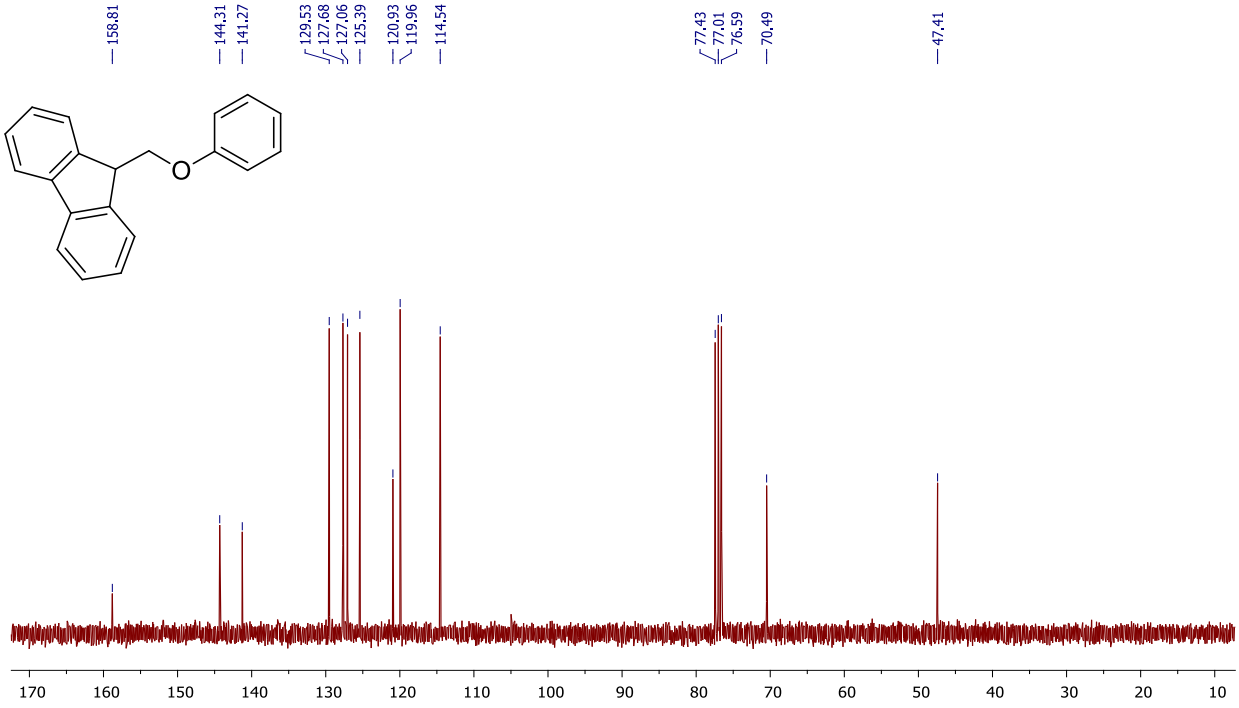
7.1. ^{1}H and ^{13}C NMR spectra of 3ba in $CDCl_3$



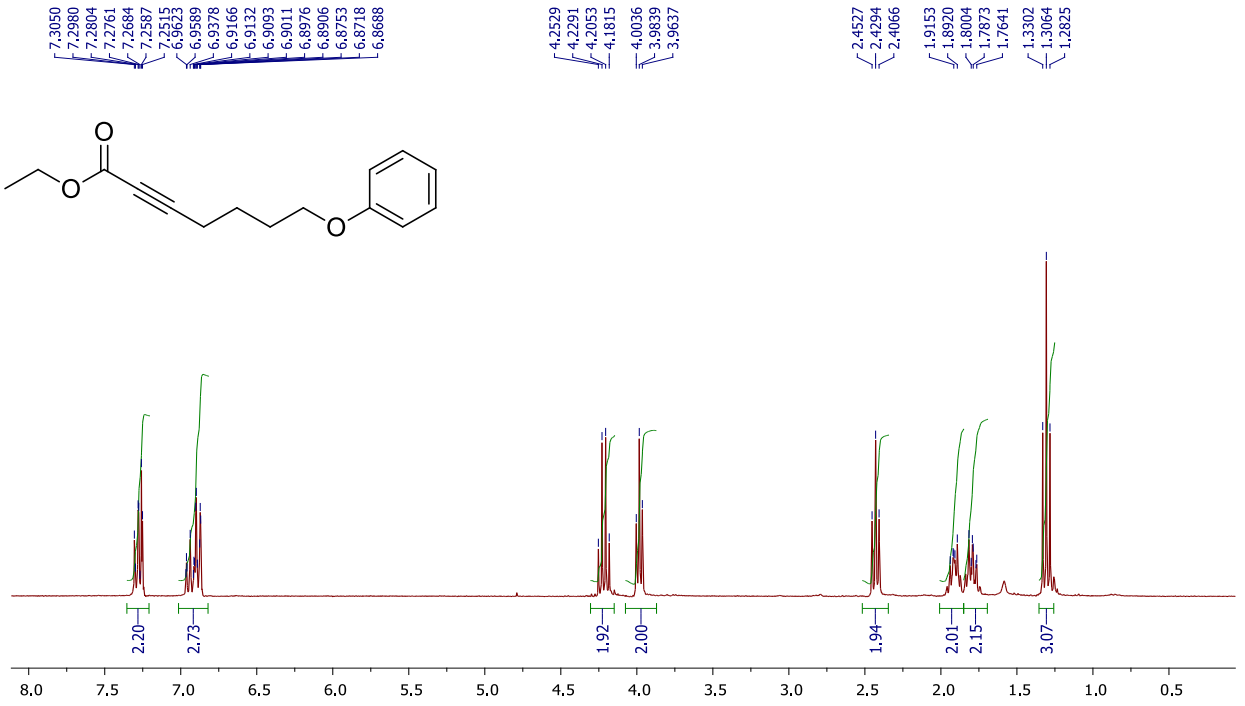


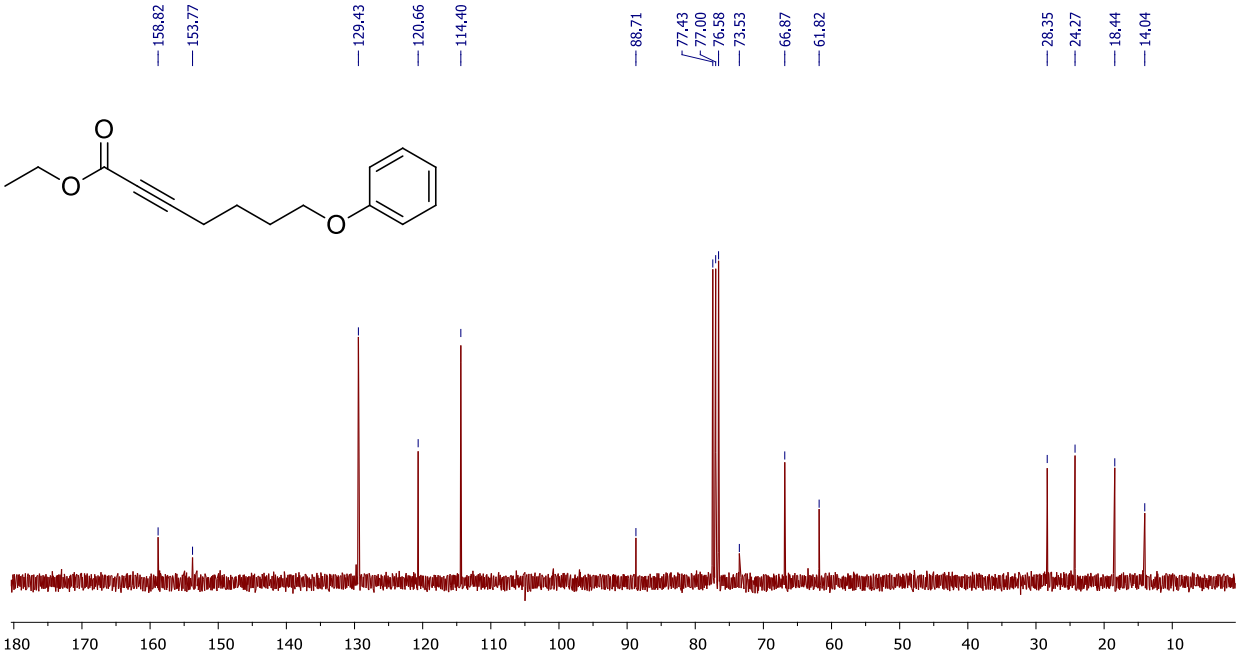
7.2. ^{1}H and ^{13}C NMR spectra of 3ca in $CDCl_3$



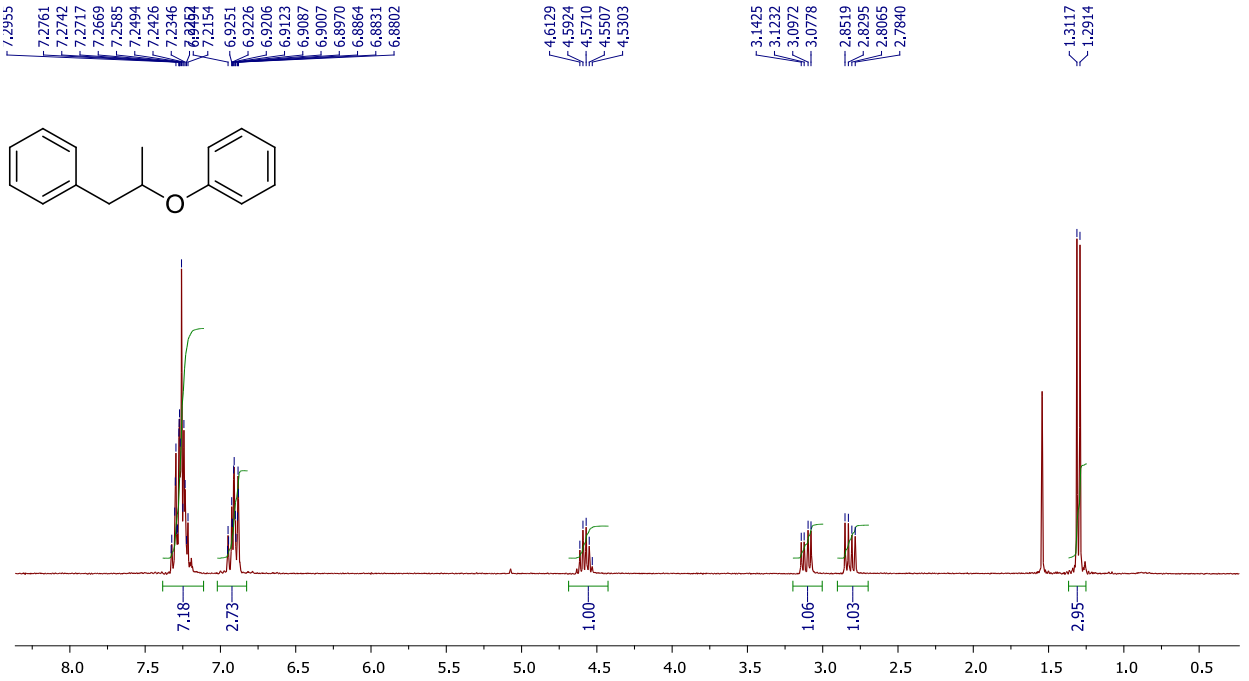


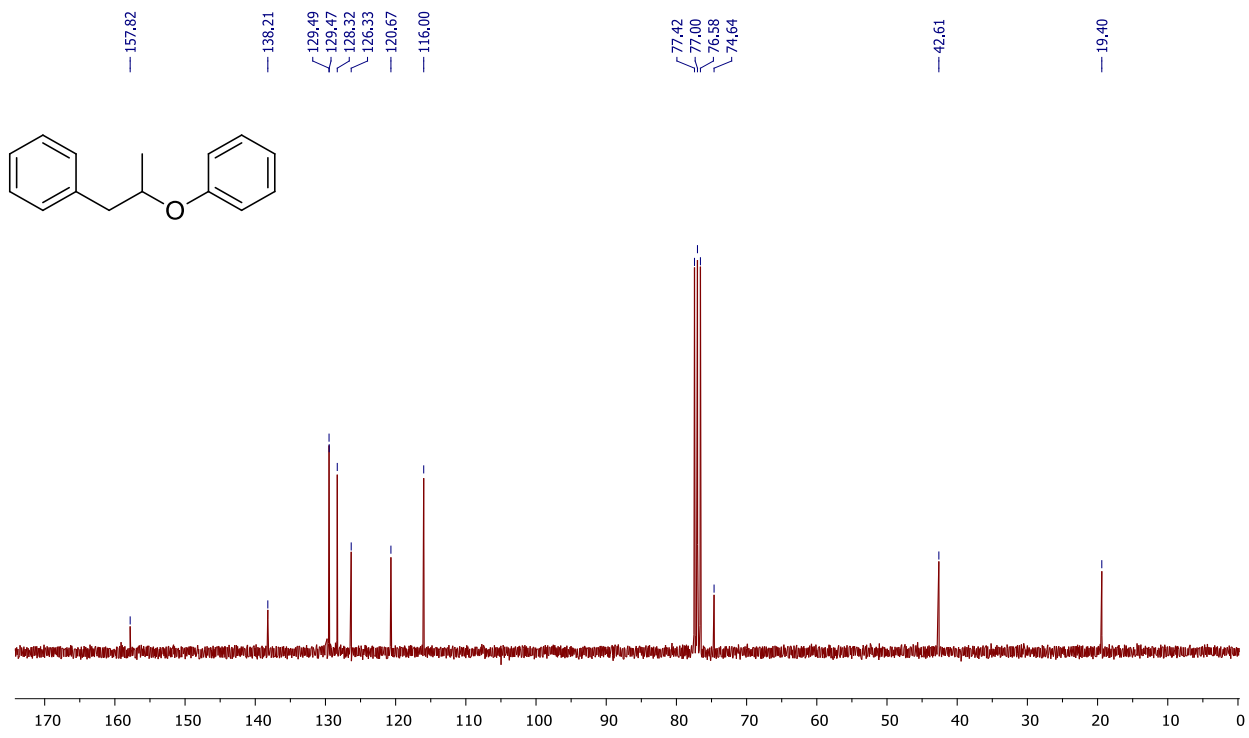
7.3. ^{1}H and ^{13}C NMR spectra of 3ha in $CDCl_3$





7.4. ^{1}H and ^{13}C NMR spectra of 3ja in $CDCl_3$





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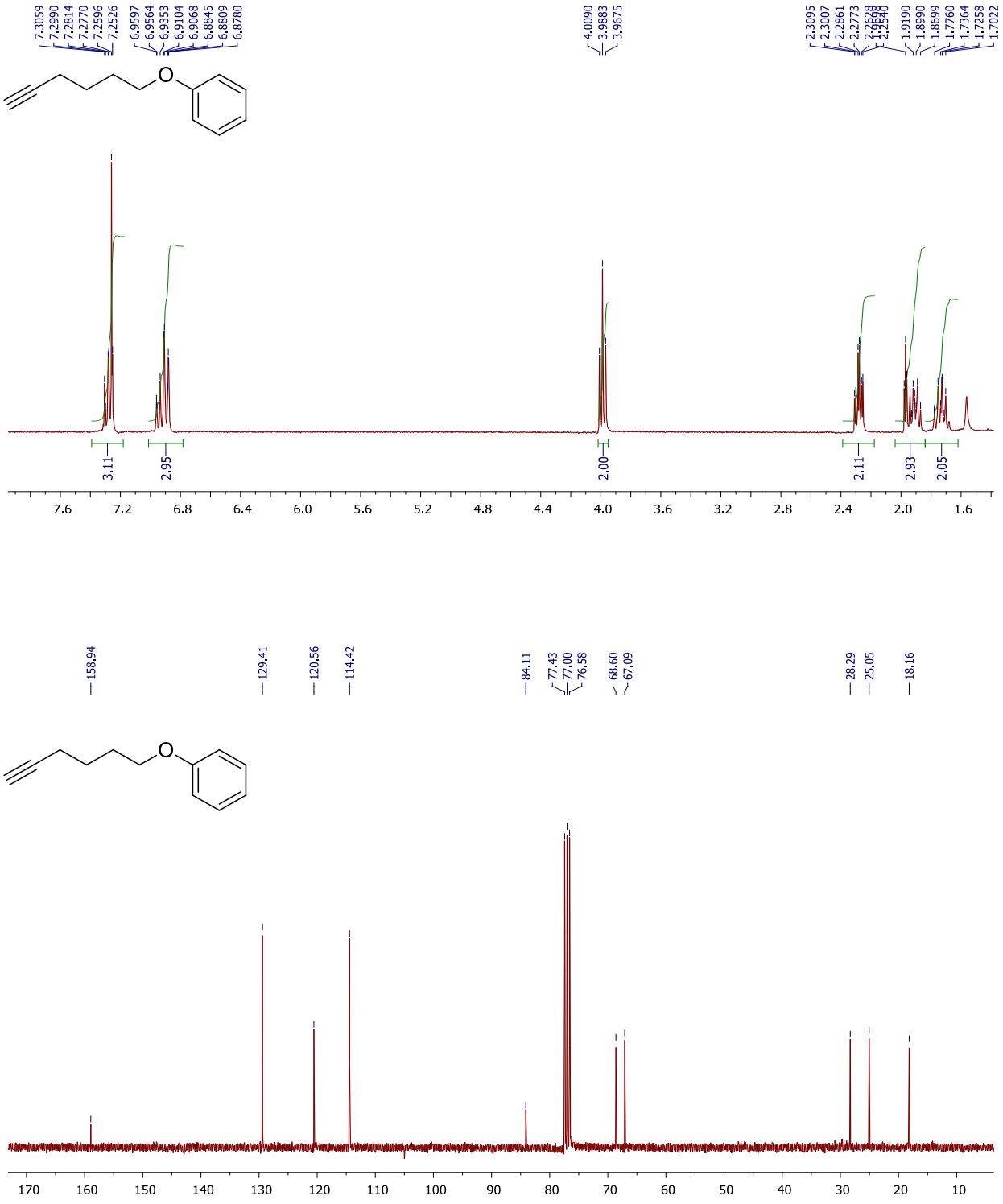
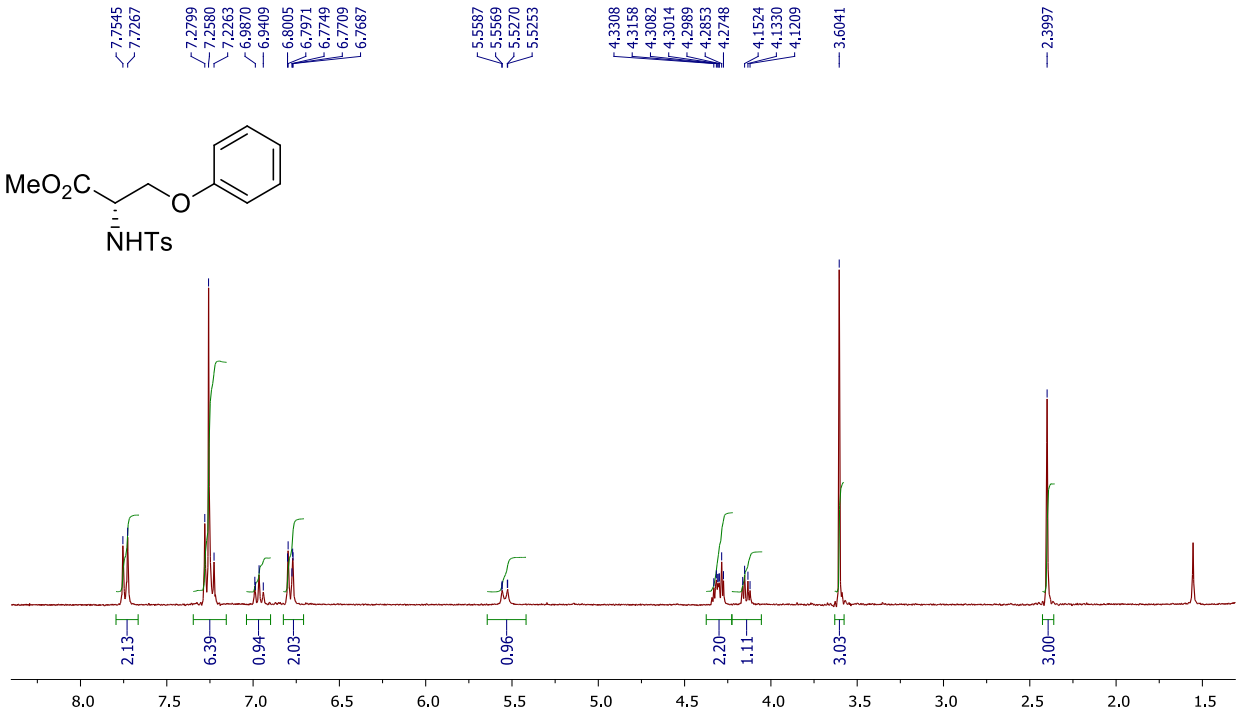
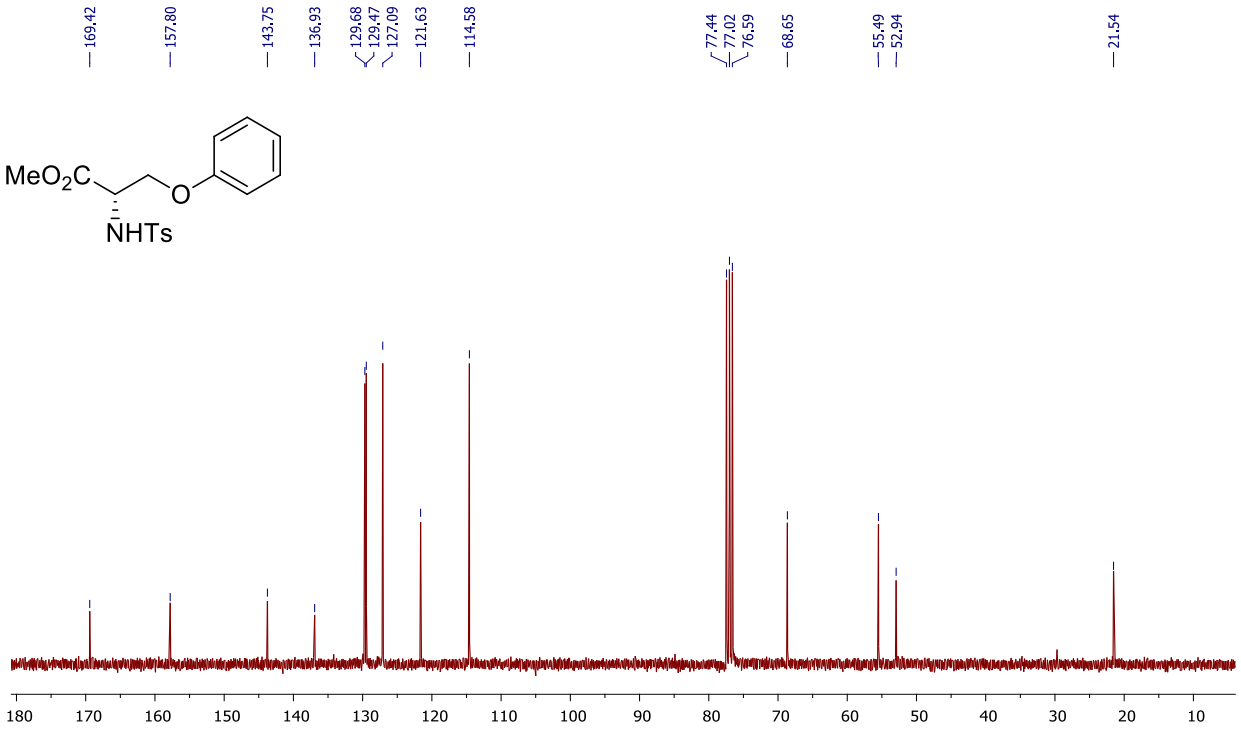
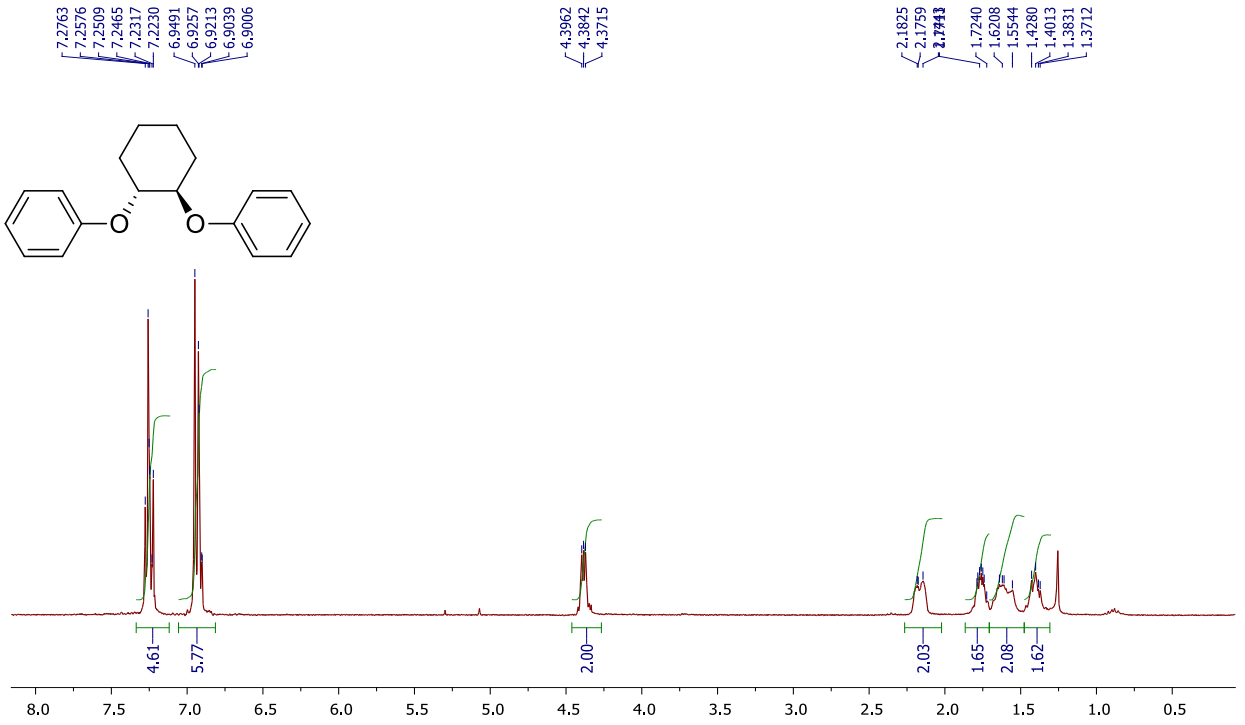


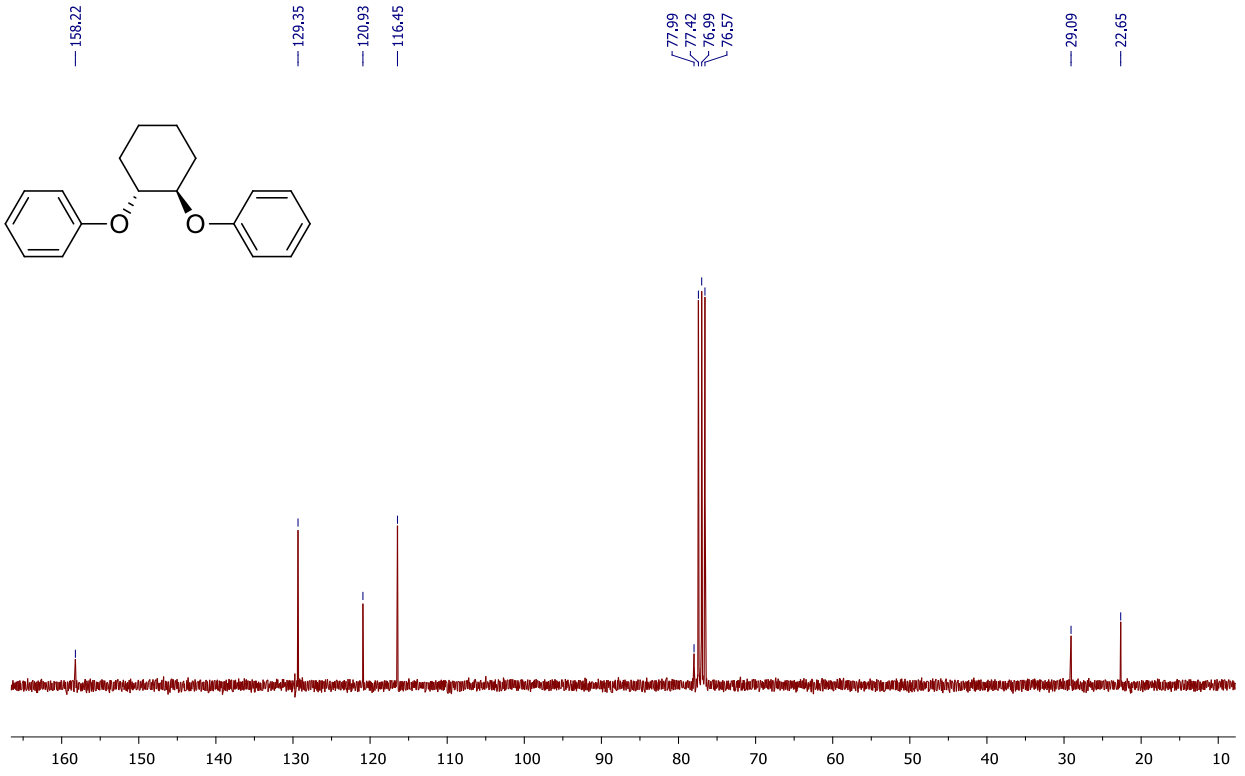
7.6. ^{1}H and ^{13}C NMR spectra of 3oa in $CDCl_3$



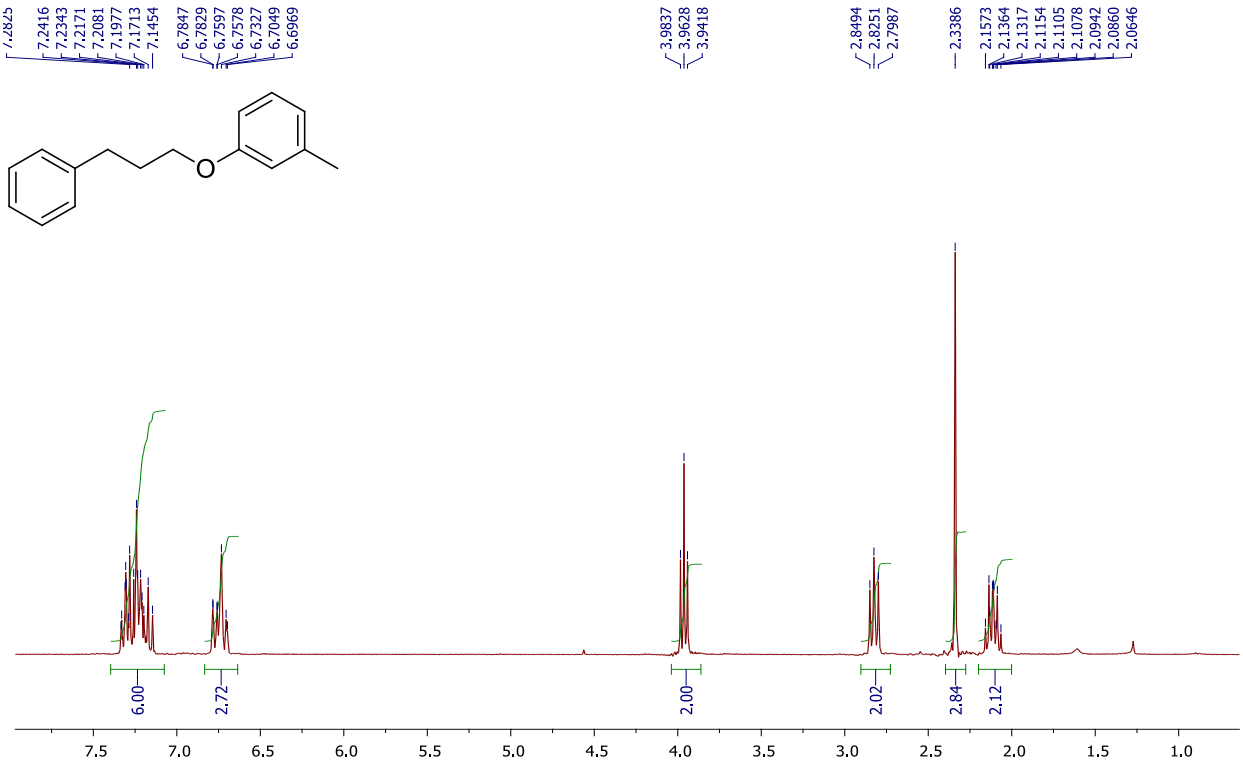


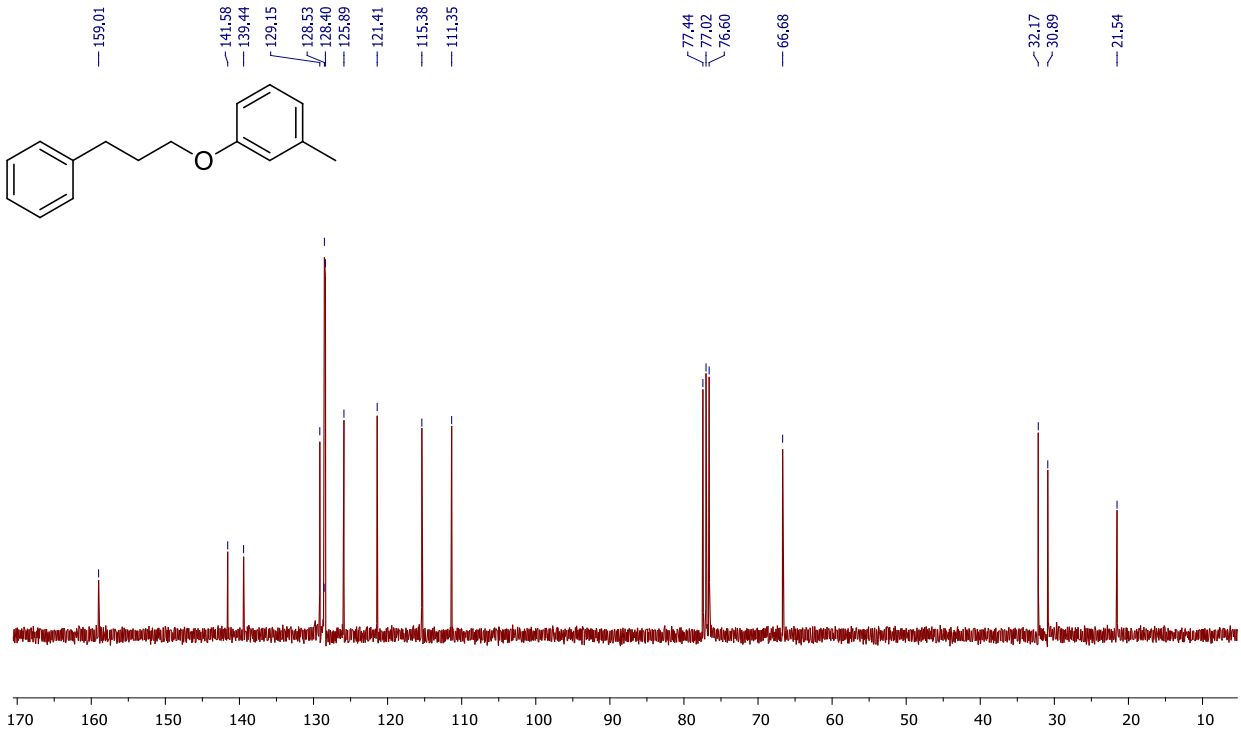
7.7. ^{1}H and ^{13}C NMR spectra of 3qa' in $CDCl_3$



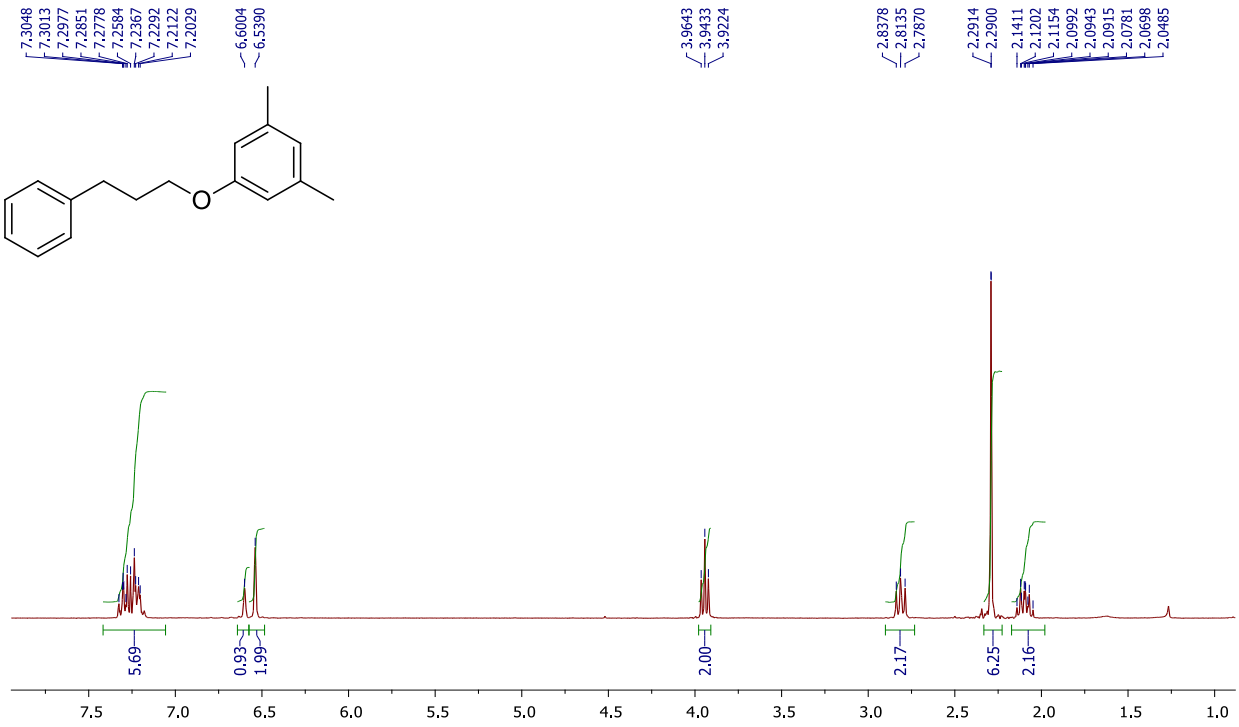


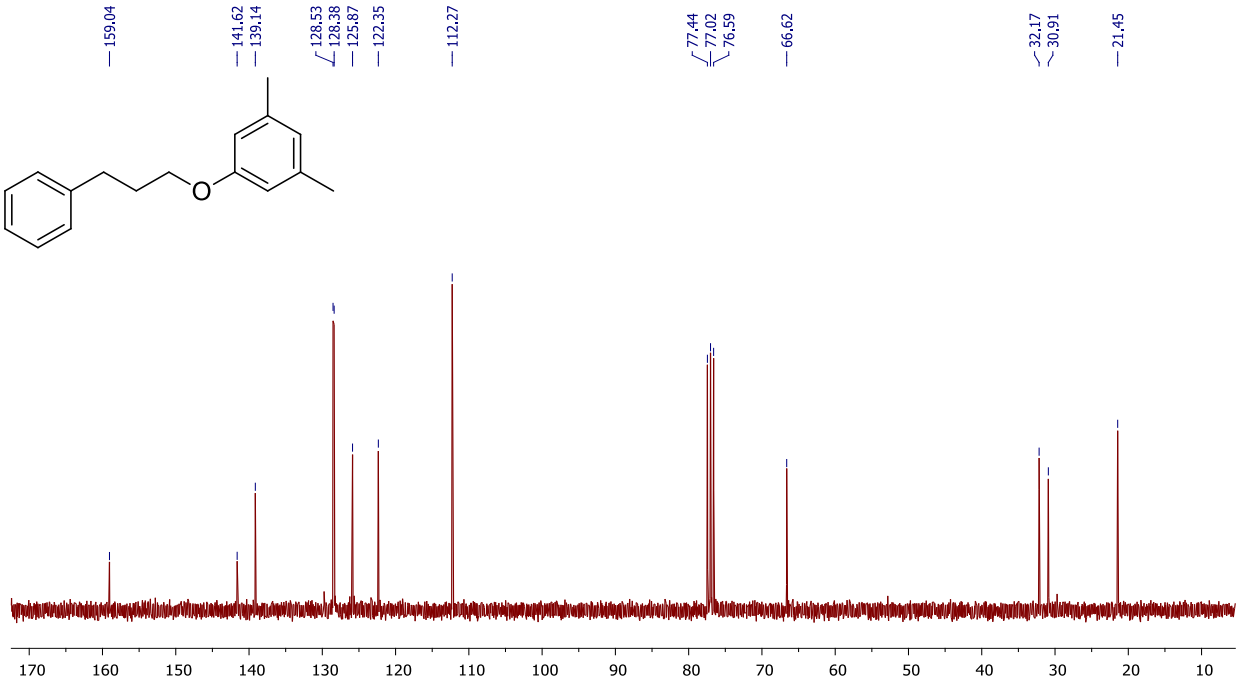
7.8. ^{1}H and ^{13}C NMR spectra of 3ab in $CDCl_3$



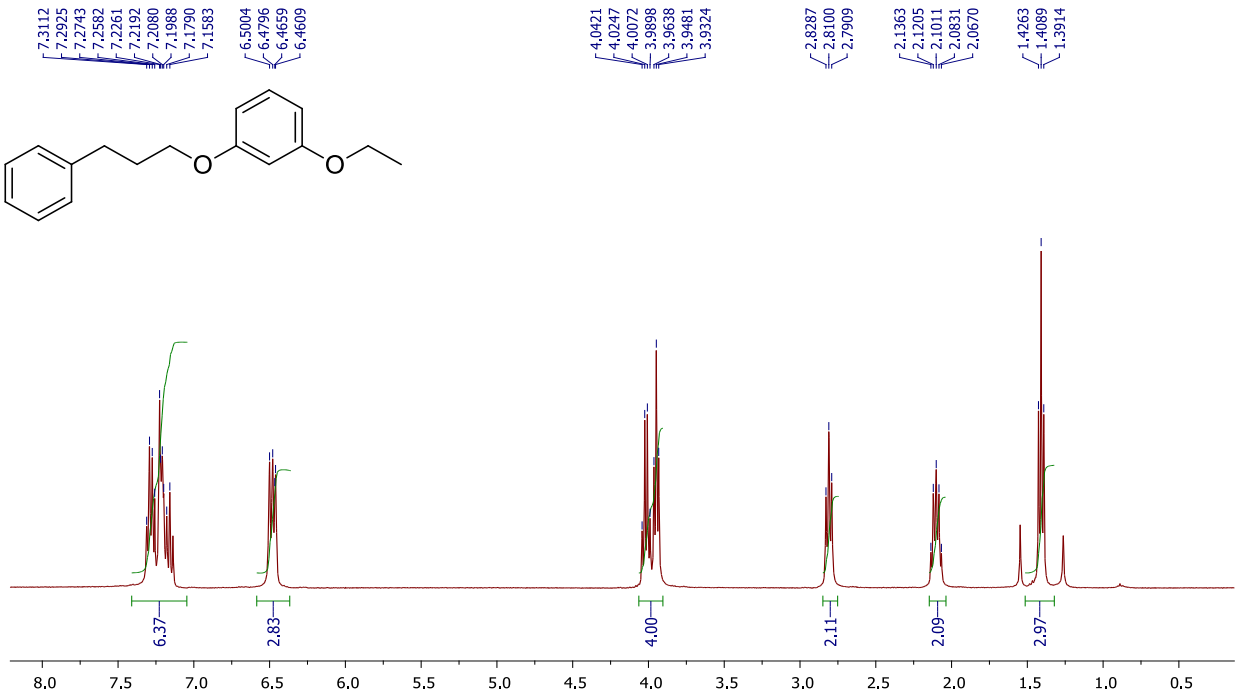


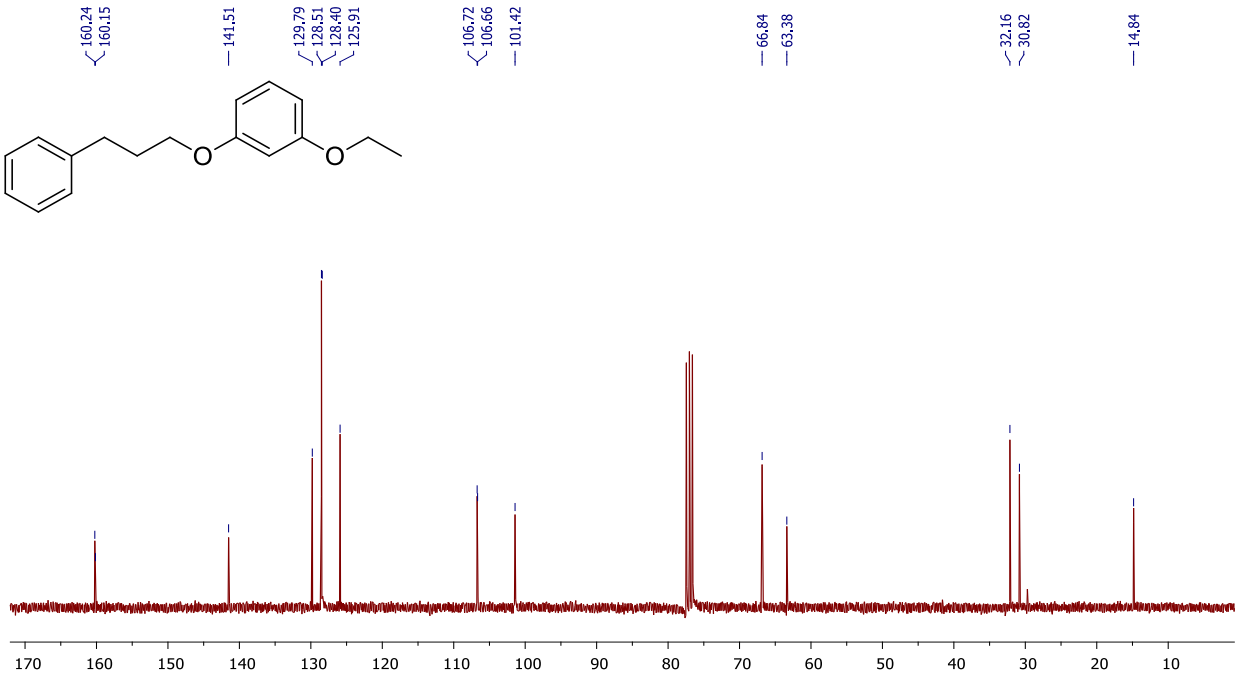
7.9. ^{1}H and ^{13}C NMR spectra of 3ac in $CDCl_3$



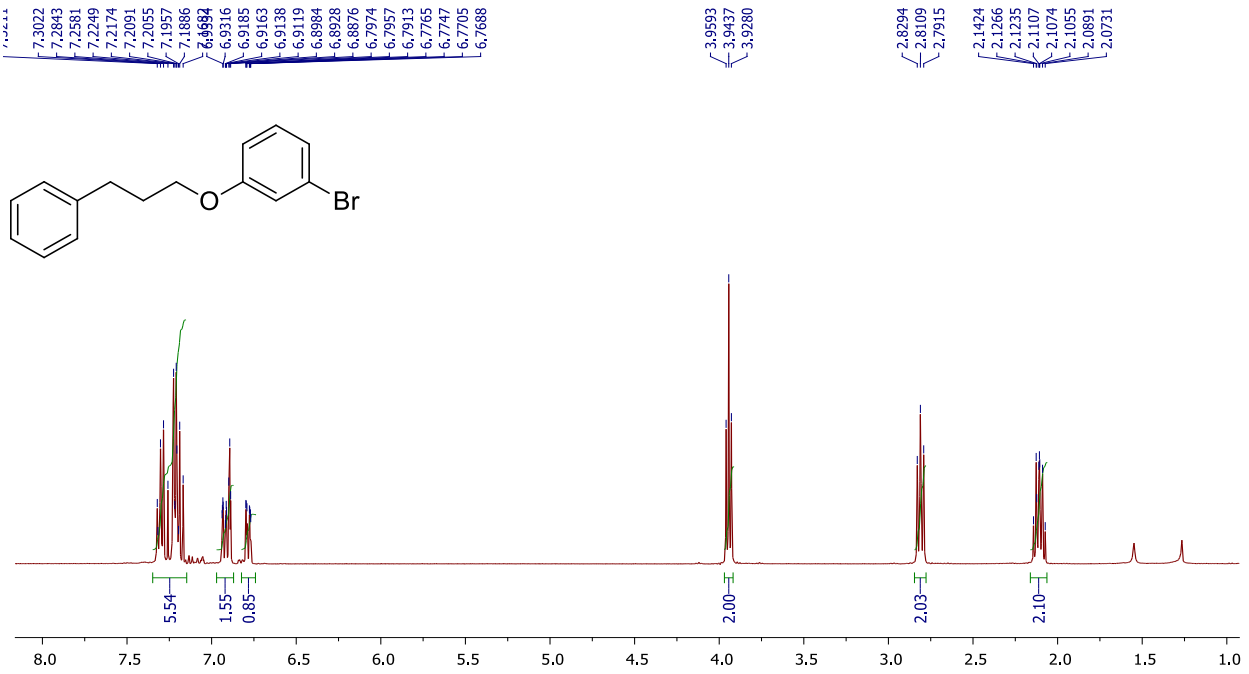


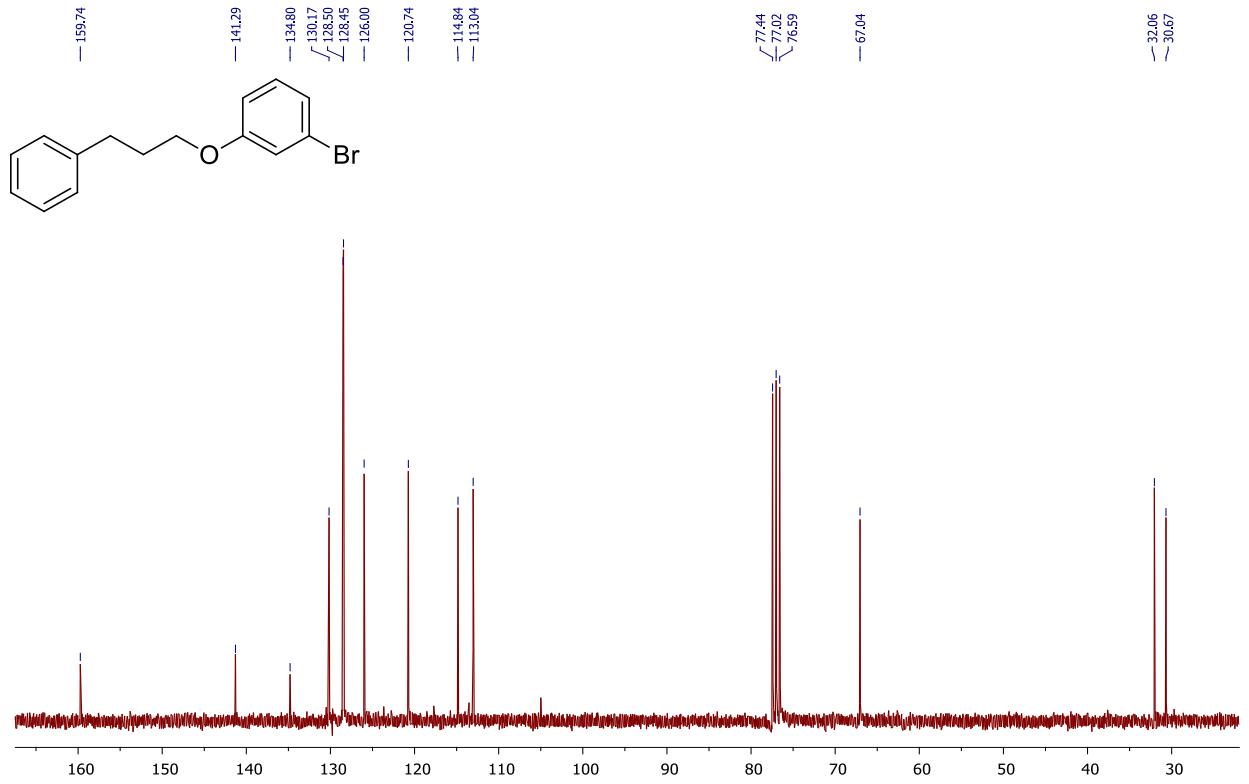
7.10. ^{1}H and ^{13}C NMR spectra of 3ad in $CDCl_3$



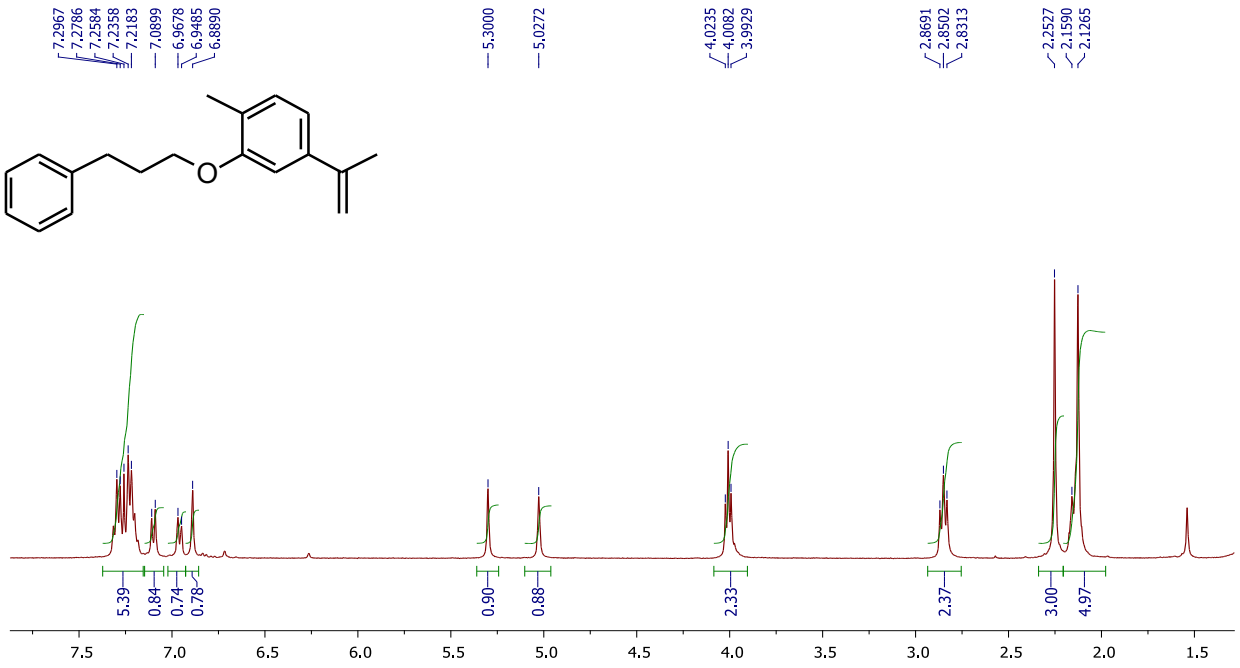


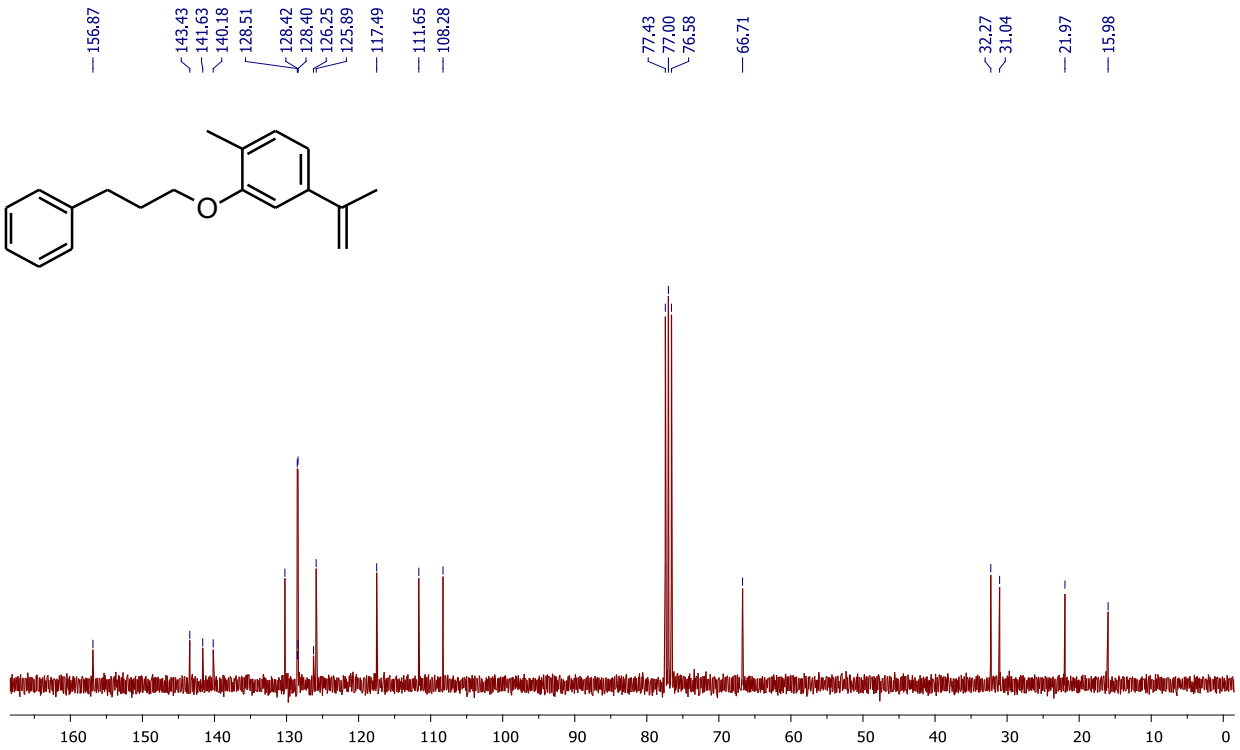
7.11. ^{1}H and ^{13}C NMR spectra of 3ae in $CDCl_3$



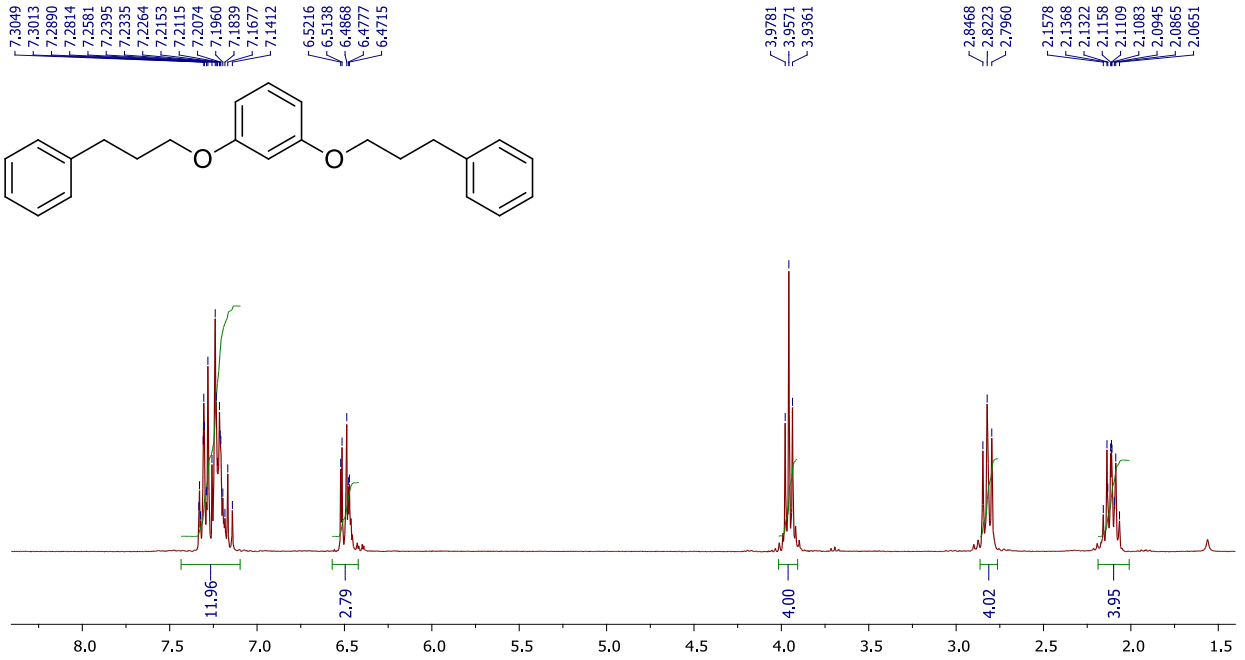


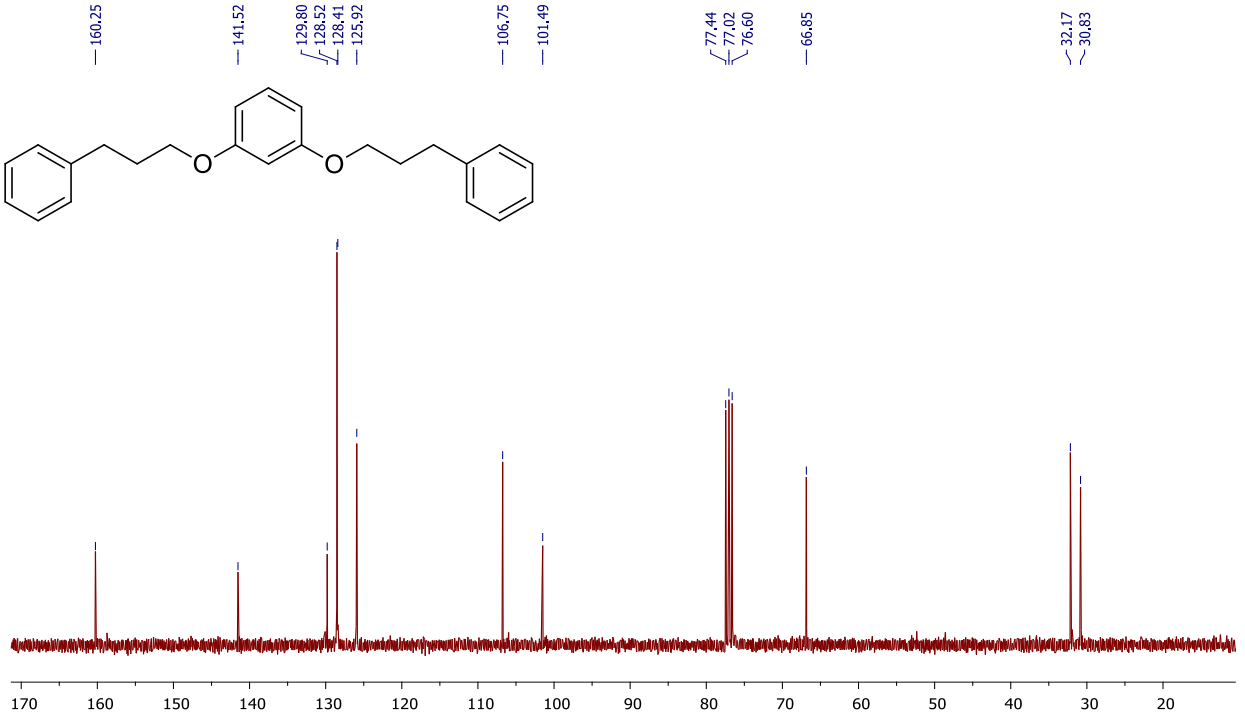
7.12. ^{1}H and ^{13}C NMR spectra of 3af in $CDCl_3$





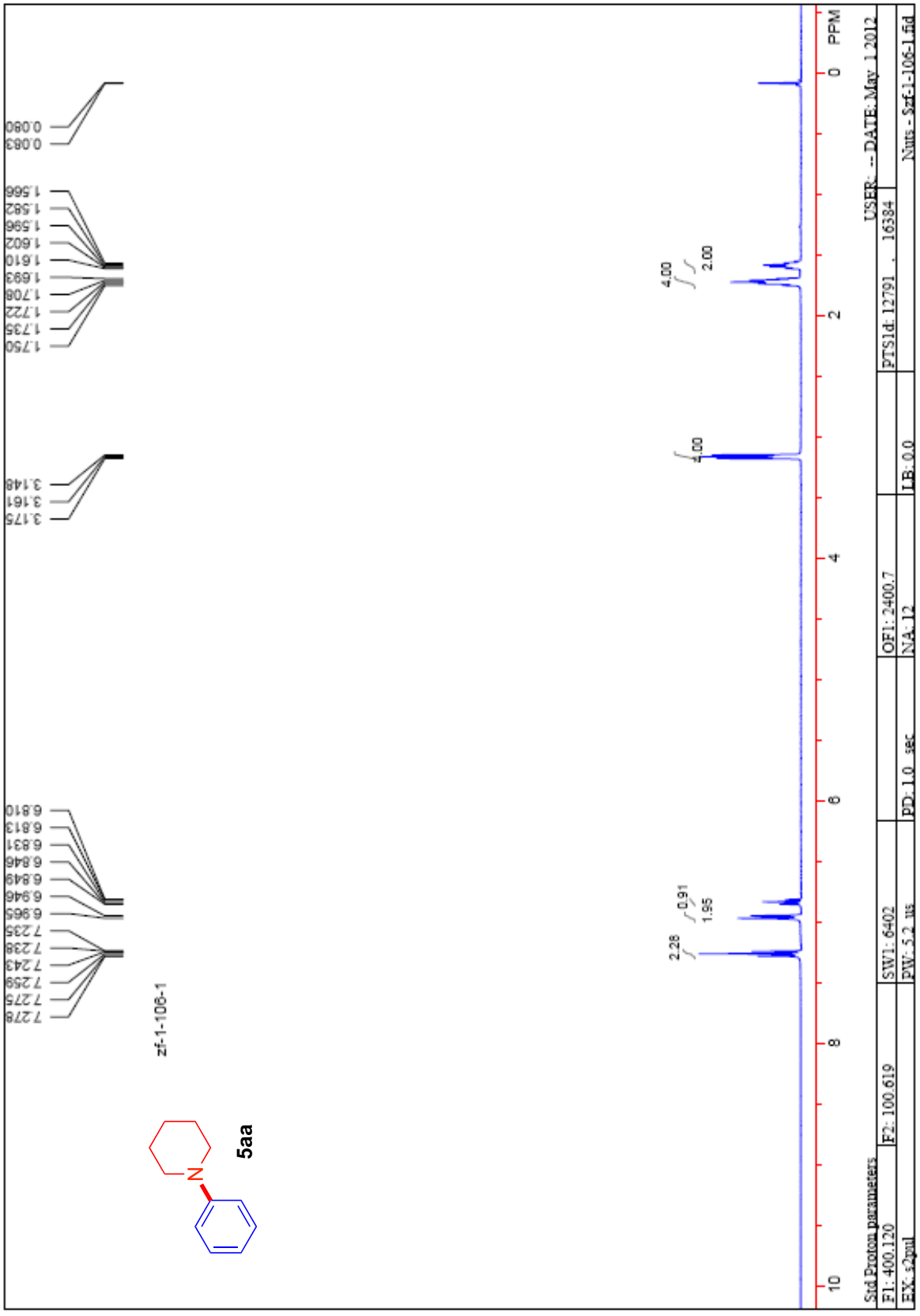
7.13. ^{1}H and ^{13}C NMR spectra of 3ag in $CDCl_3$

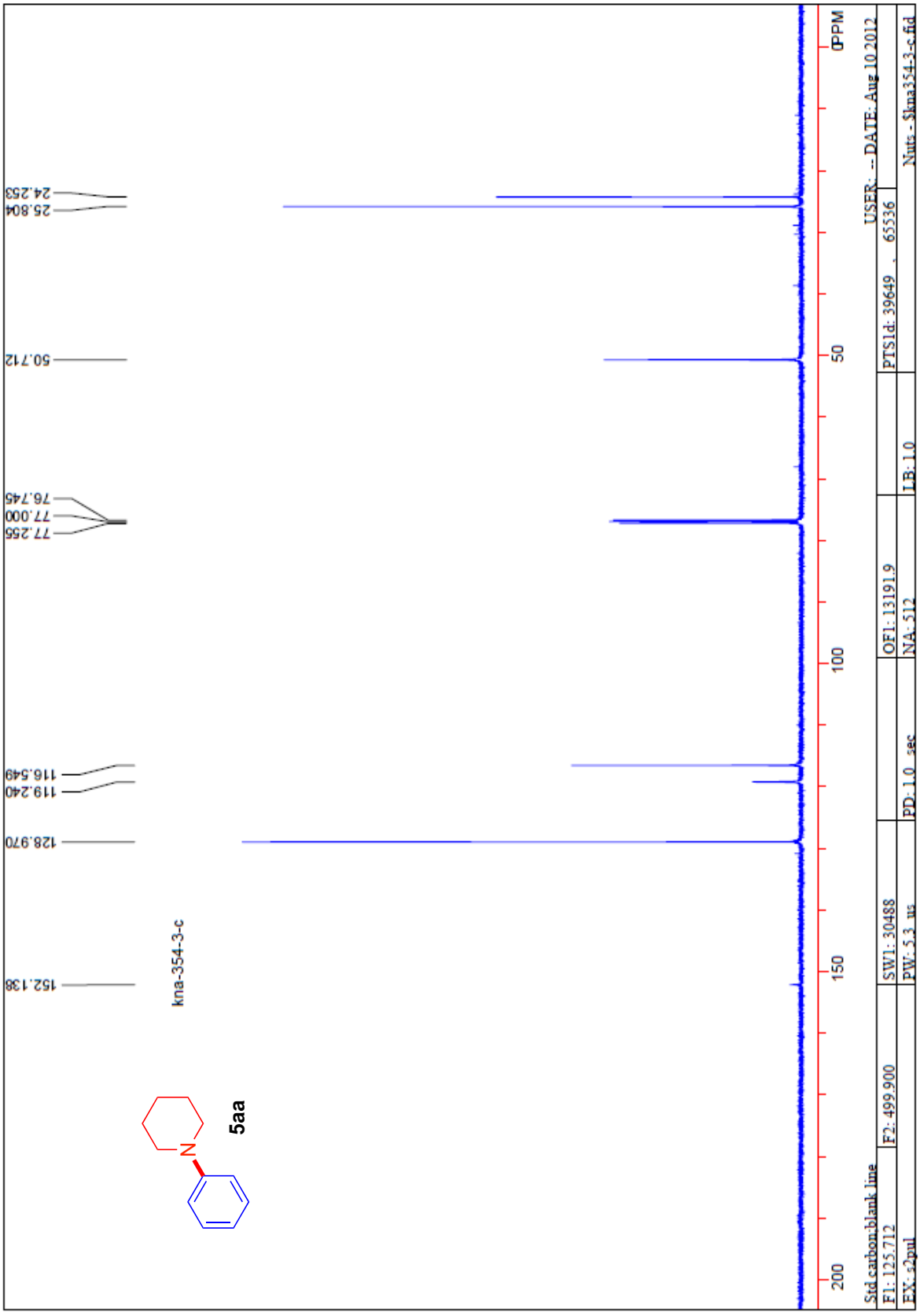




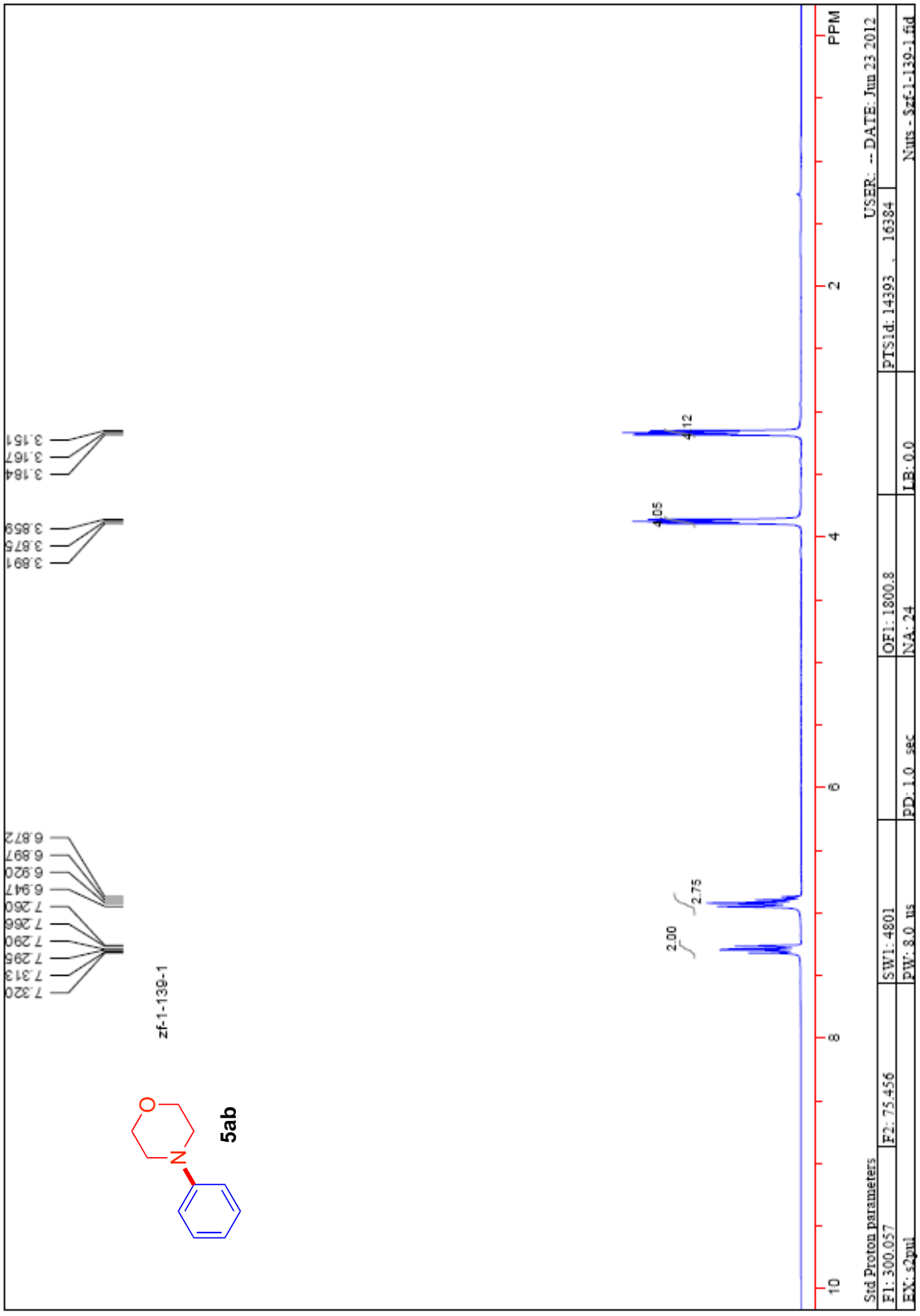
Spectra for previously unknown compounds in chapter 3

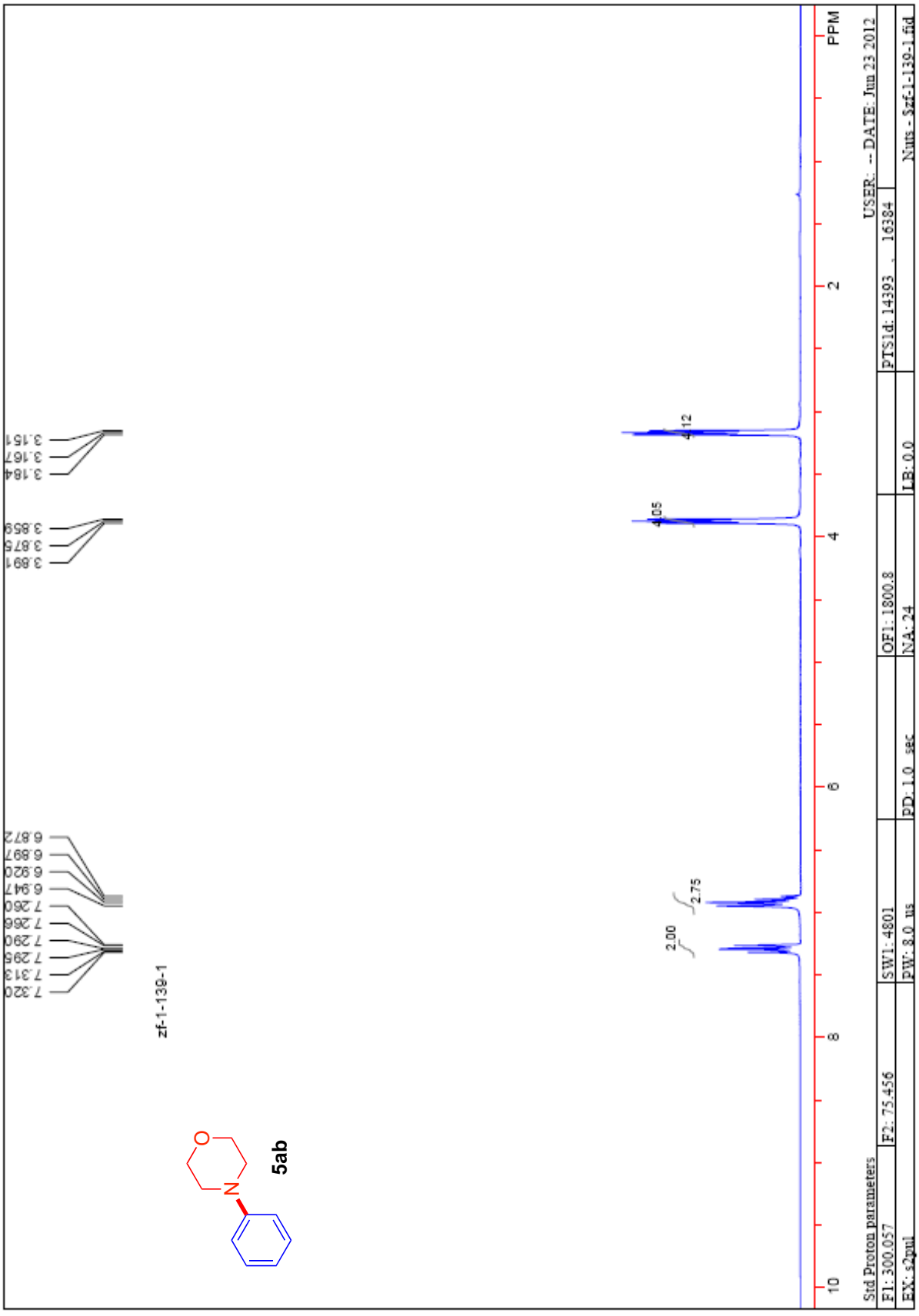
7.14. ^{1}H and ^{13}C NMR spectra of 5aa in $CDCl_3$



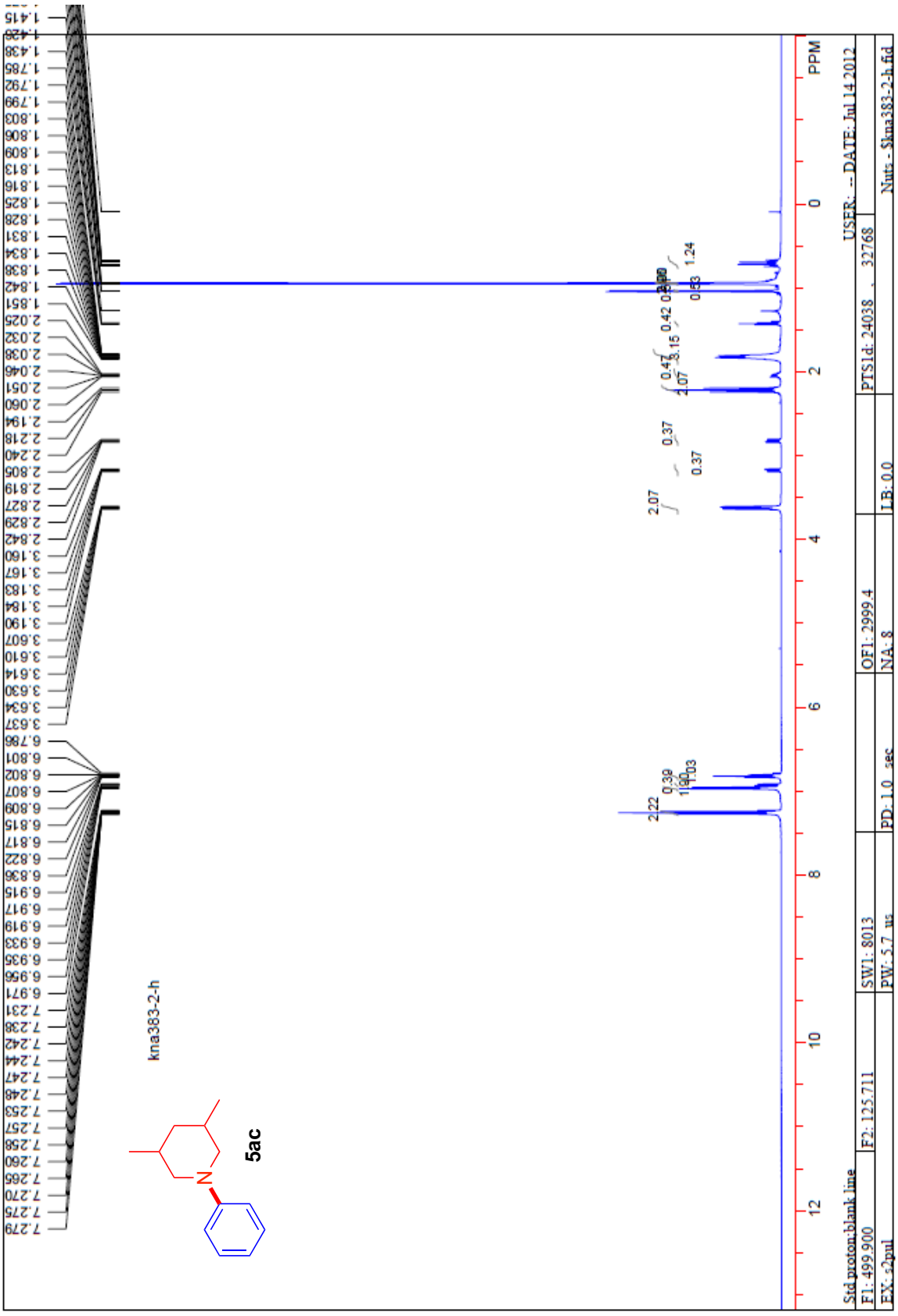

24.253
25.804
50.712
76.745
77.000
77.255
119.240
116.549
128.970
152.138
kna-354-3-c
5aa
N
200
150
100
50
0
PPM
Std carbon:blank line
F1: 125.712
F2: 499.900
SW1: 30488
PW: 5.3 us
PD: 1.0 sec
OF1: 13191.9
NA: 512
PTS1d: 39649 . 65536
LB: 1.0
USER: -- DATE: Aug 10 2012
EX: s2pul
Nuts - $kna354-3-c.fid

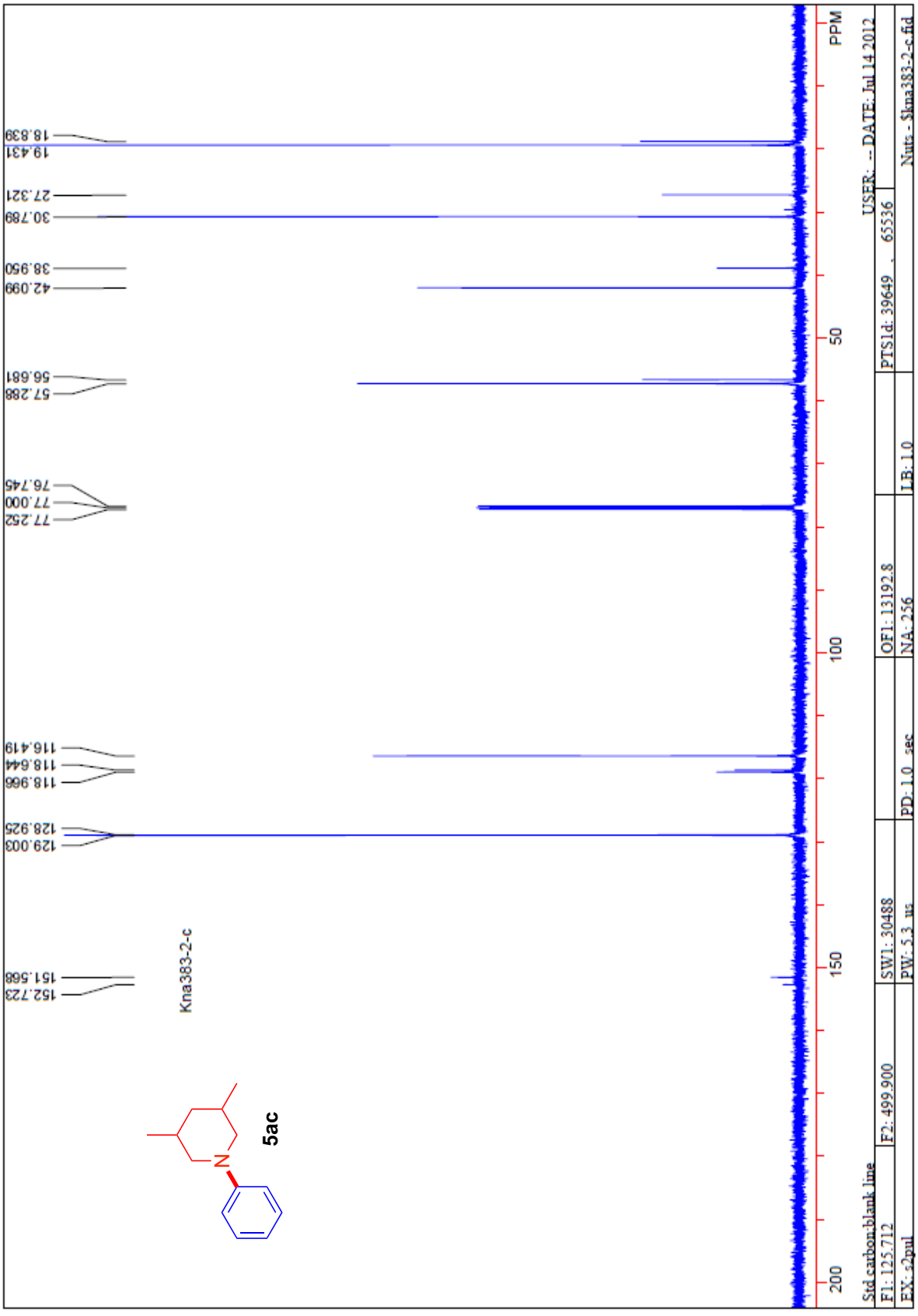
7.15. ^{1}H and ^{13}C NMR spectra of 5ab in $CDCl_3$



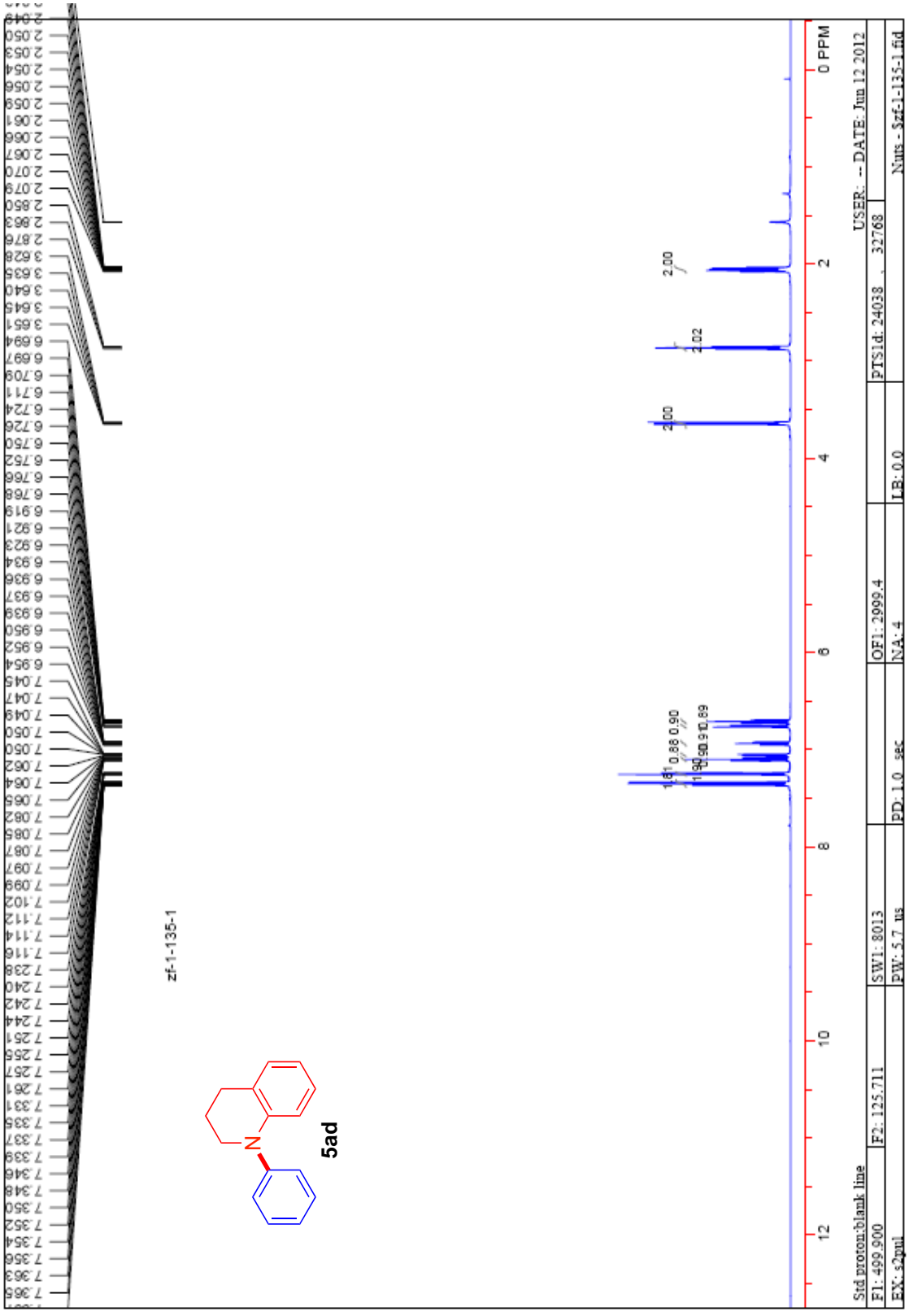

5ab
zf-1-139-1
7.320
7.313
7.295
7.290
7.266
7.260
6.947
6.920
6.897
6.872
3.891
3.875
3.859
3.184
3.167
3.151
4.12
4.05
2.75
2.00
PPM
Std Proton parameters
F1: 300.057
F2: 75.456
SW1: 4801
OF1: 1800.8
PTS1d: 14393 , 16384
EX: s2pul
PW: 8.0 us
PD: 1.0 sec
NA: 24
LB: 0.0
USER: -- DATE: Jun 23 2012
Nms - Szf-1-139-1.fid

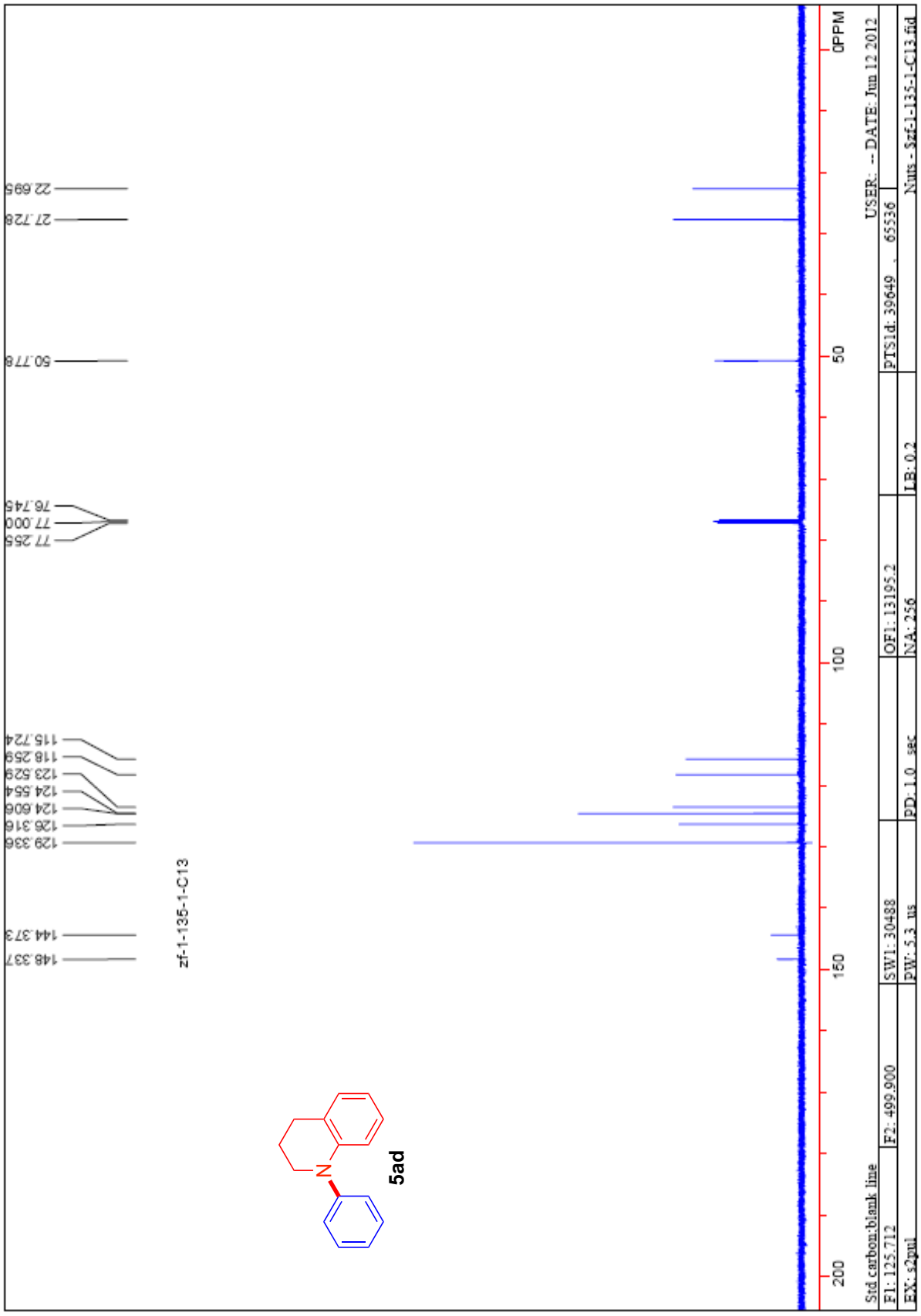
7.16. ^{1}H and ^{13}C NMR spectra of 5ac in $CDCl_3$



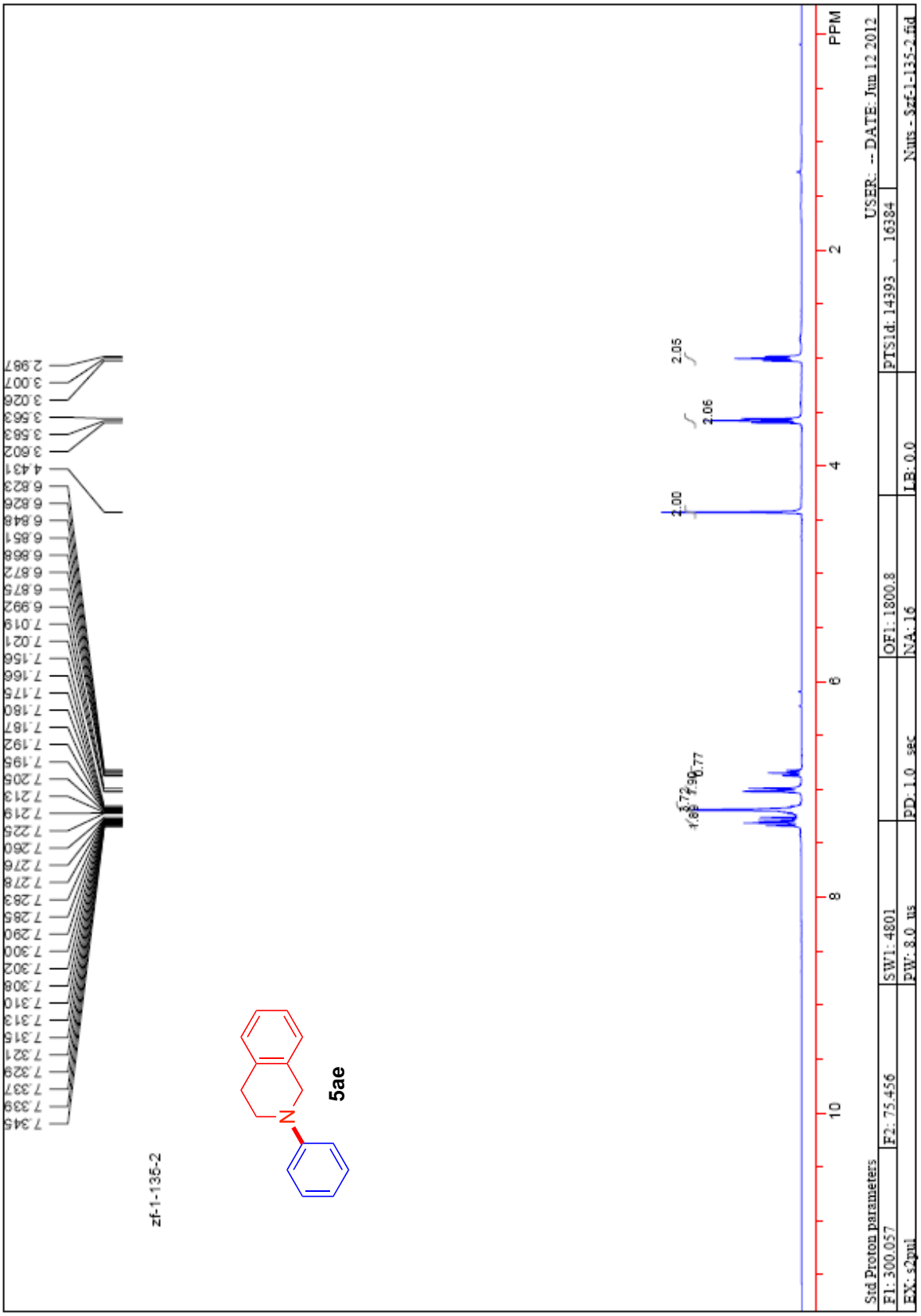

18.839
19.431
27.321
30.789
38.950
42.099
56.681
57.288
76.745
77.000
77.252
116.419
118.644
118.966
128.925
129.003
151.568
152.723
Kna383-2-c
5ac
N
PPM
200
150
100
50
Std carbon:blank lme
F1: 125.712
F2: 499.900
SW1: 30488
OF1: 13192.8
PTS1d: 39649 , 65536
USER: -- DATE: Jul 14 2012
EX: s2pul
PW: 5.3 us
PD: 1.0 sec
NA: 256
LB: 1.0
Nuts - $kna383-2-c.fid

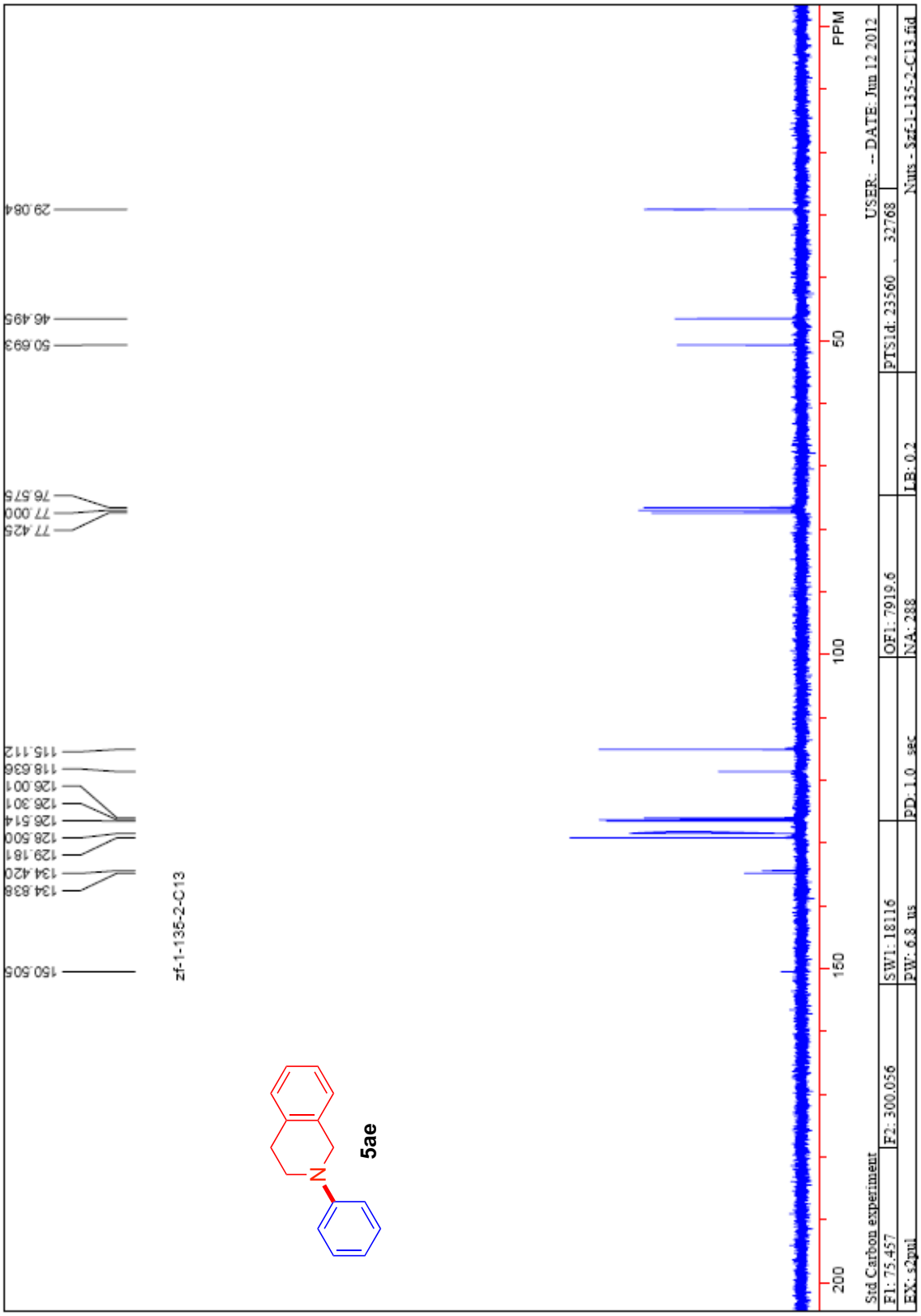
7.17. ^{1}H and ^{13}C NMR spectra of 5ad in $CDCl_3$



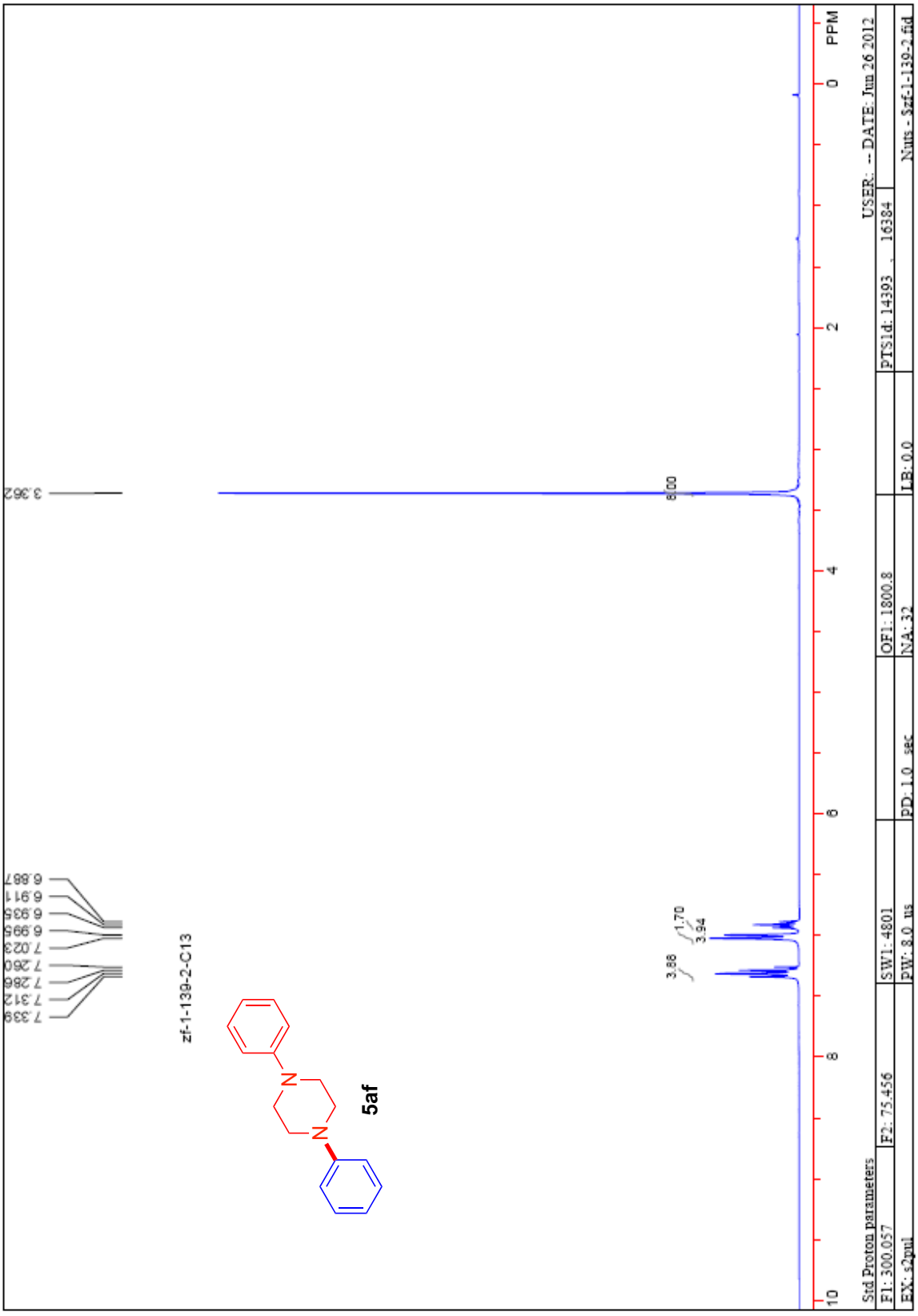

22.695
27.728
50.778
76.745
77.000
77.255
115.724
118.259
123.529
124.554
124.606
126.316
129.336
144.373
148.337
zf-1-135-1-C13
5ad
200
150
100
50
0PPM
Std carbon:blank line
F1: 125.712
F2: 499.900
SW1: 30488
OF1: 13195.2
PTS1d: 39649
65536
EX: s2pul
PW: 5.3 us
PD: 1.0 sec
NA: 256
LB: 0.2
USER: -- DATE: Jun 12 2012
Nuns - Szf-1-135-1-C13.fid

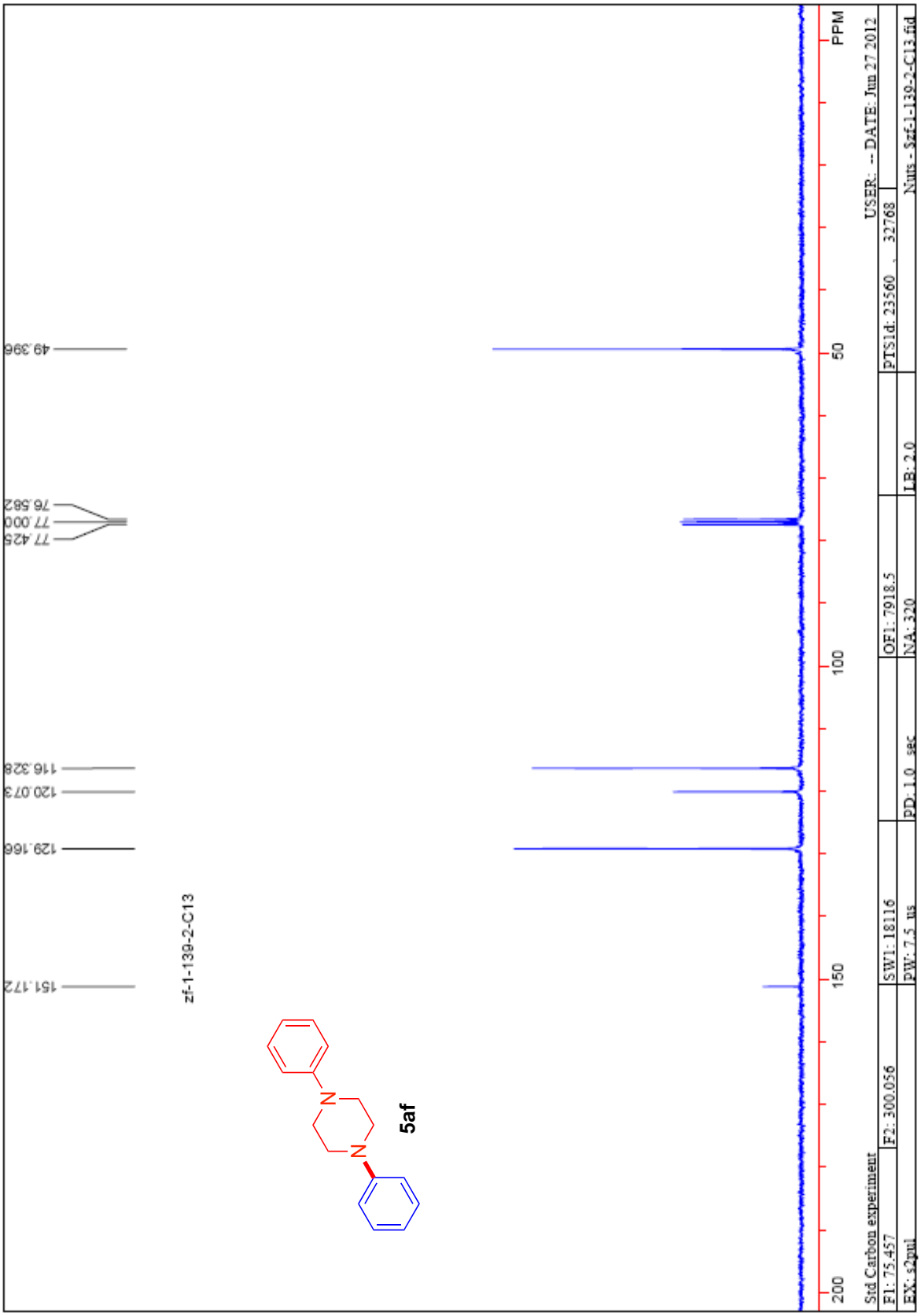
7.18. ^{1}H and ^{13}C NMR spectra of 5ae in $CDCl_3$



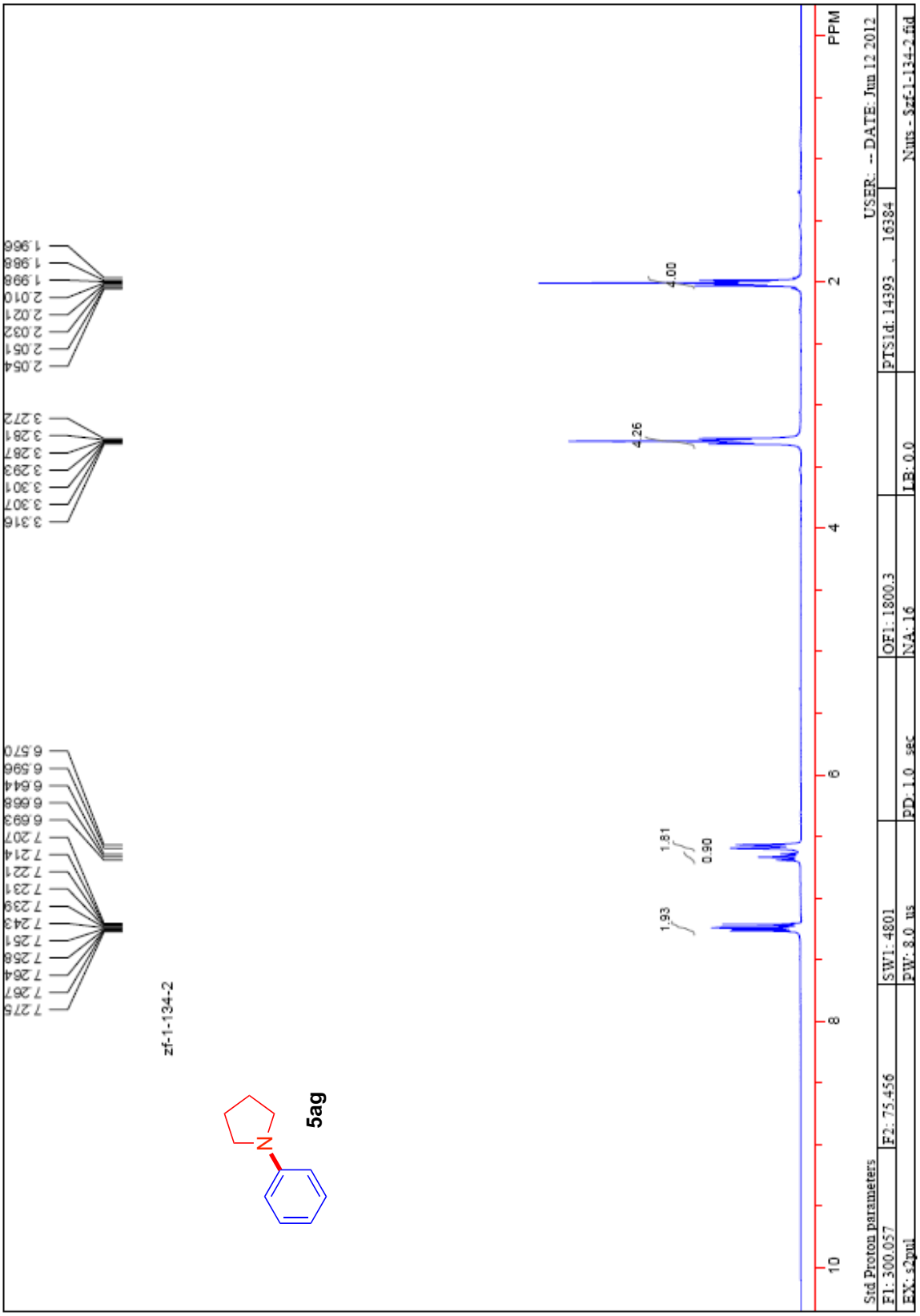

29.084
46.495
50.693
76.575
77.000
77.425
115.112
118.636
126.001
126.301
126.514
128.500
129.181
134.420
134.838
150.505
zf-1-135-2-C13
5ae
N
200
150
100
50
PPM
Std Carbon experiment
F1: 75.457
F2: 300.056
SW1: 18116
PW: 6.8 us
PD: 1.0 sec
OF1: 7919.6
NA: 288
LB: 0.2
PTS1d: 23560 . 32768
USER: -- DATE: Jun 12 2012
EX: s2pul
Nuns - $zf-1-135-2-C13.fid

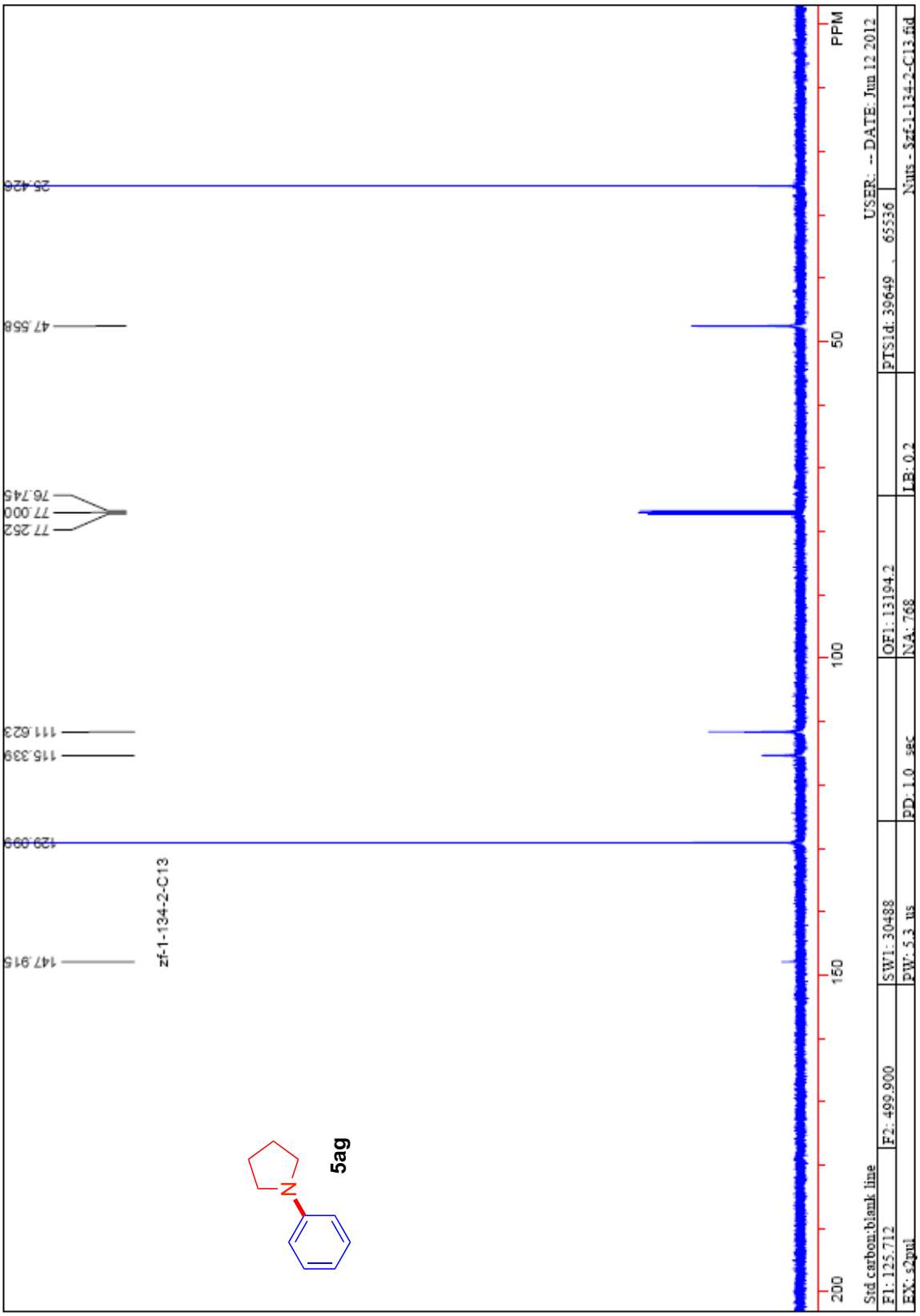
7.19. ^{1}H and ^{13}C NMR spectra of 5af in $CDCl_3$



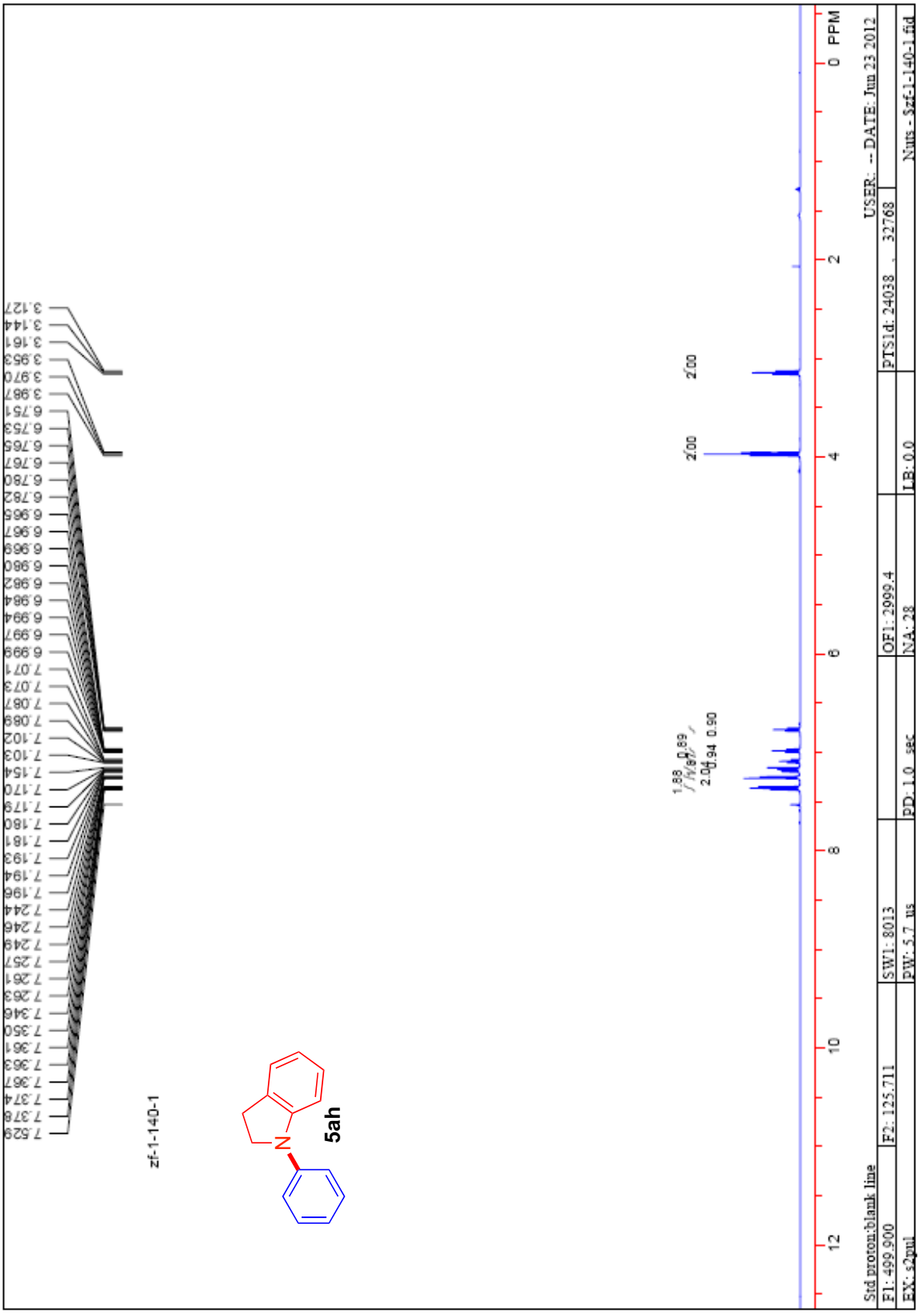

49.396
77.425
77.000
76.582
129.166
120.073
116.328
151.172
zf-1-139-2-C13
5af
200
150
100
50
PPM
Std Carbon experiment
F1: 75.457
F2: 300.056
SW1: 18116
PW: 7.5 us
PD: 1.0 sec
OF1: 7918.5
NA: 320
LB: 2.0
PTS1d: 23560 , 32768
USER: -- DATE: Jun 27 2012
EX: s2pul
Nuts - $zf-1-139-2-C13.fid

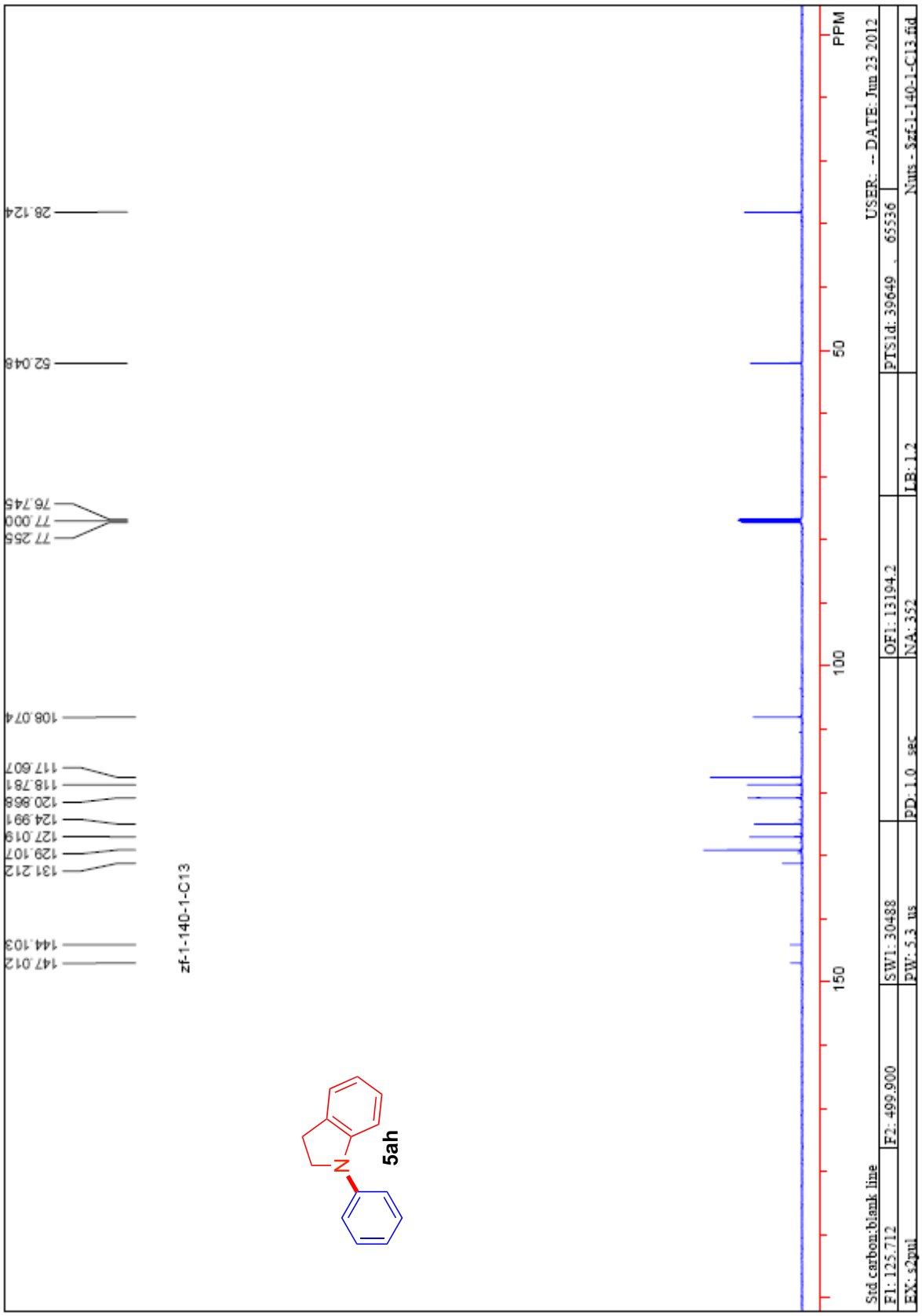
7.20. ^{1}H and ^{13}C NMR spectra of 5ag in $CDCl_3$



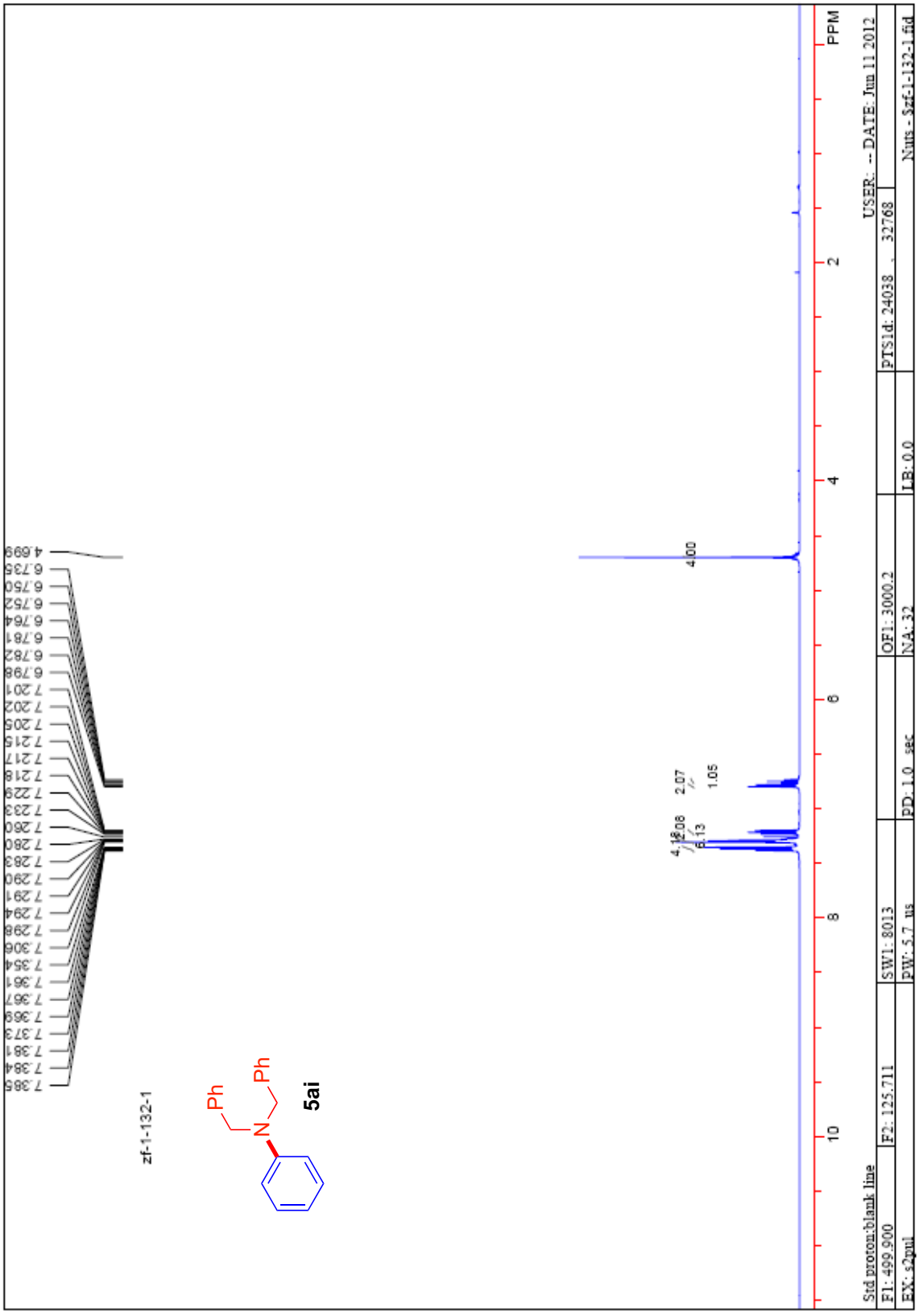

25.426
47.558
76.745
77.000
77.252
111.623
115.339
129.099
147.915
zf-1-134-2-C13
5ag
N
200
150
100
50
PPM
Std carbon:blank line
F1: 125.712
F2: 499.900
SW1: 30488
OF1: 13194.2
PTS1d: 39649
65536
EX: s2pul
PW: 5.3 us
PD: 1.0 sec
NA: 768
LB: 0.2
USER: -- DATE: Jun 12 2012
Nuts - $zf-1-134-2-C13.fid

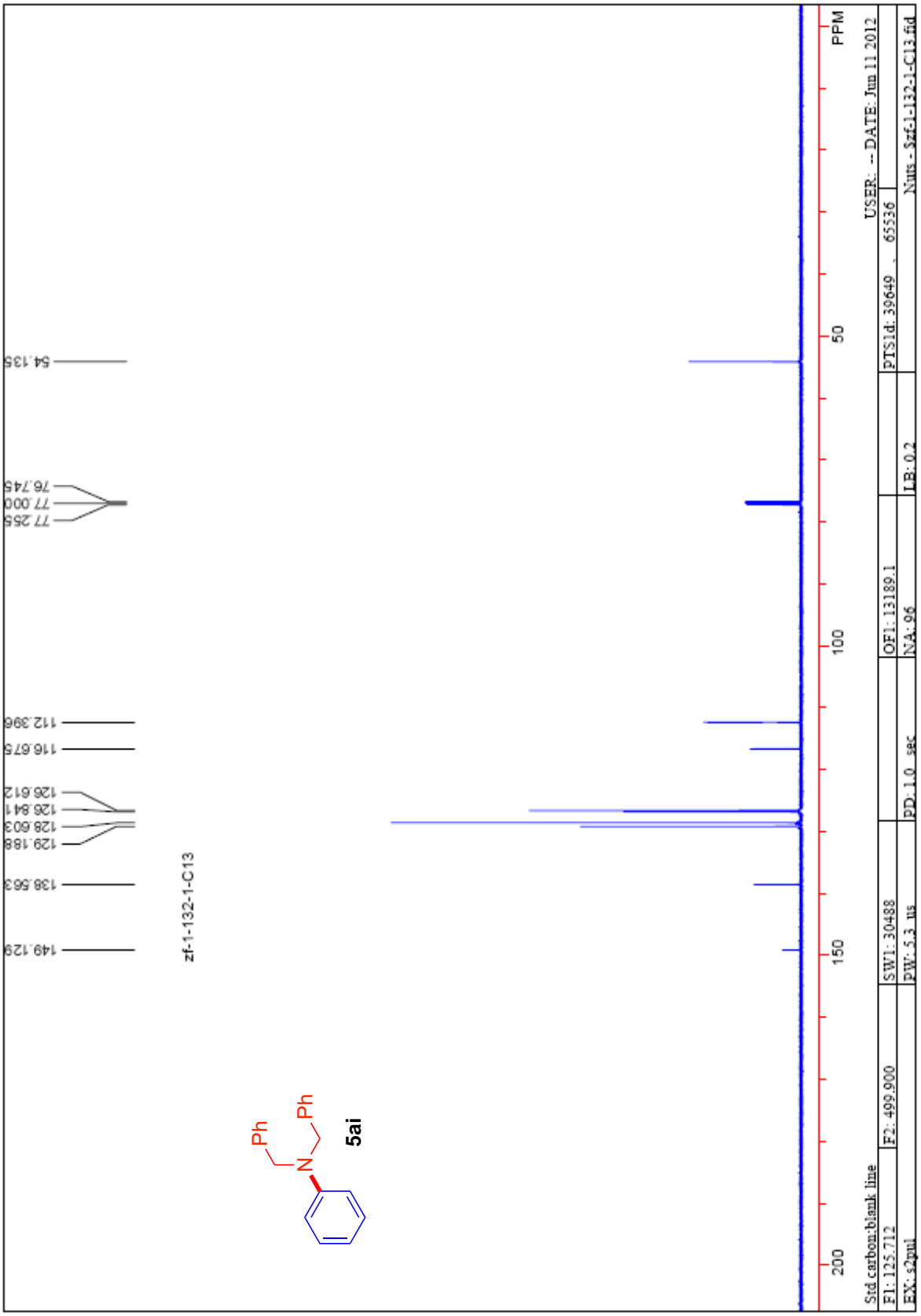
7.21. ^{1}H and ^{13}C NMR spectra of 5ah in $CDCl_3$



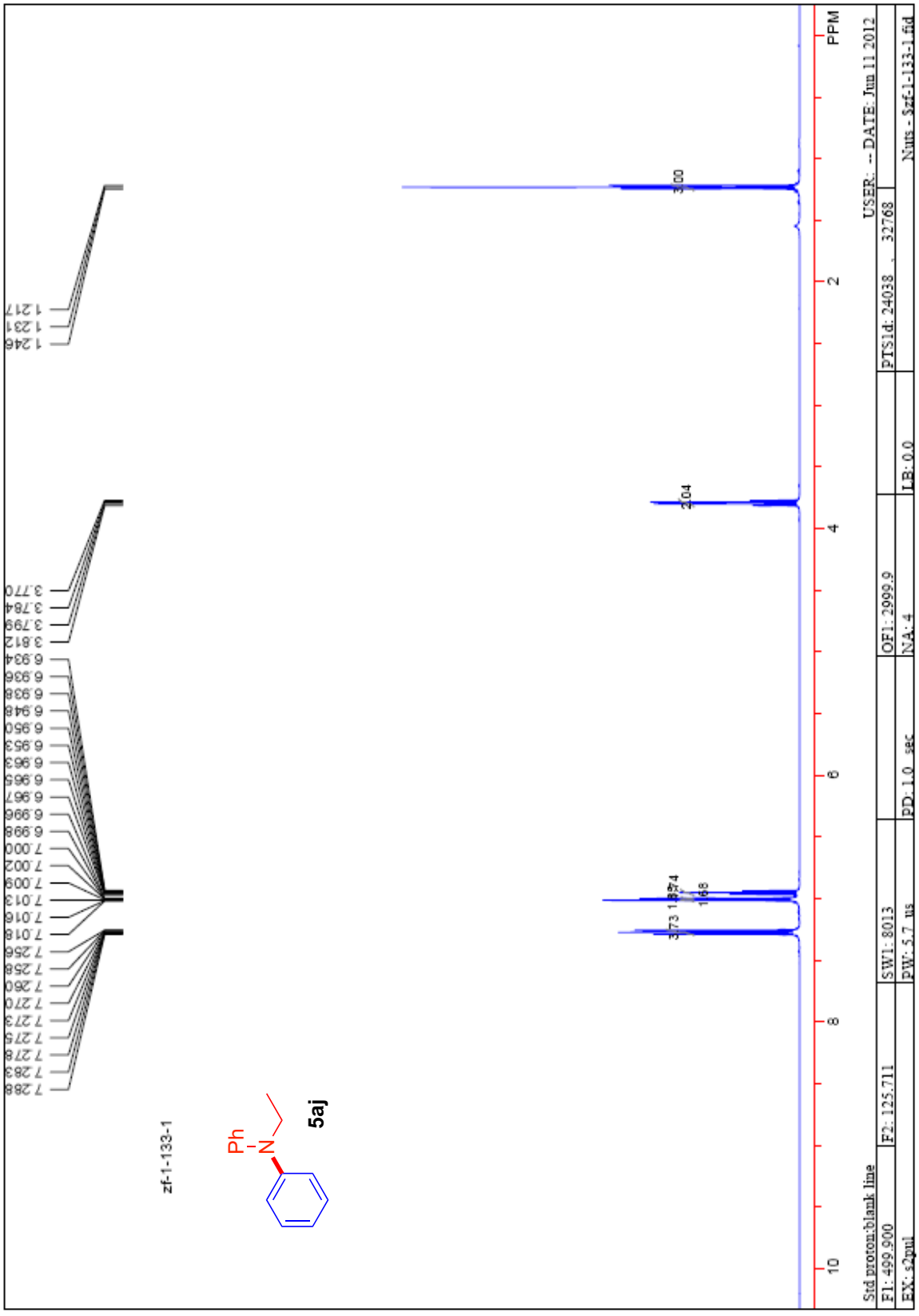

28.124
52.048
76.745
77.000
77.255
108.074
117.607
118.781
120.868
124.991
127.019
129.107
131.212
144.103
147.012
zf-1-140-1-C13
5ah
N
PPM
150
100
50
Std carbon:blank line
F1: 125.712
F2: 499.900
SW1: 30488
OF1: 13194.2
PTSid: 39649 , 65536
USER: -- DATE: Jun 23 2012
EX: s2pul
PW: 5.3 us
PD: 1.0 sec
NA: 352
LB: 1.2
Nuts - $zf-1-140-1-C13.fid

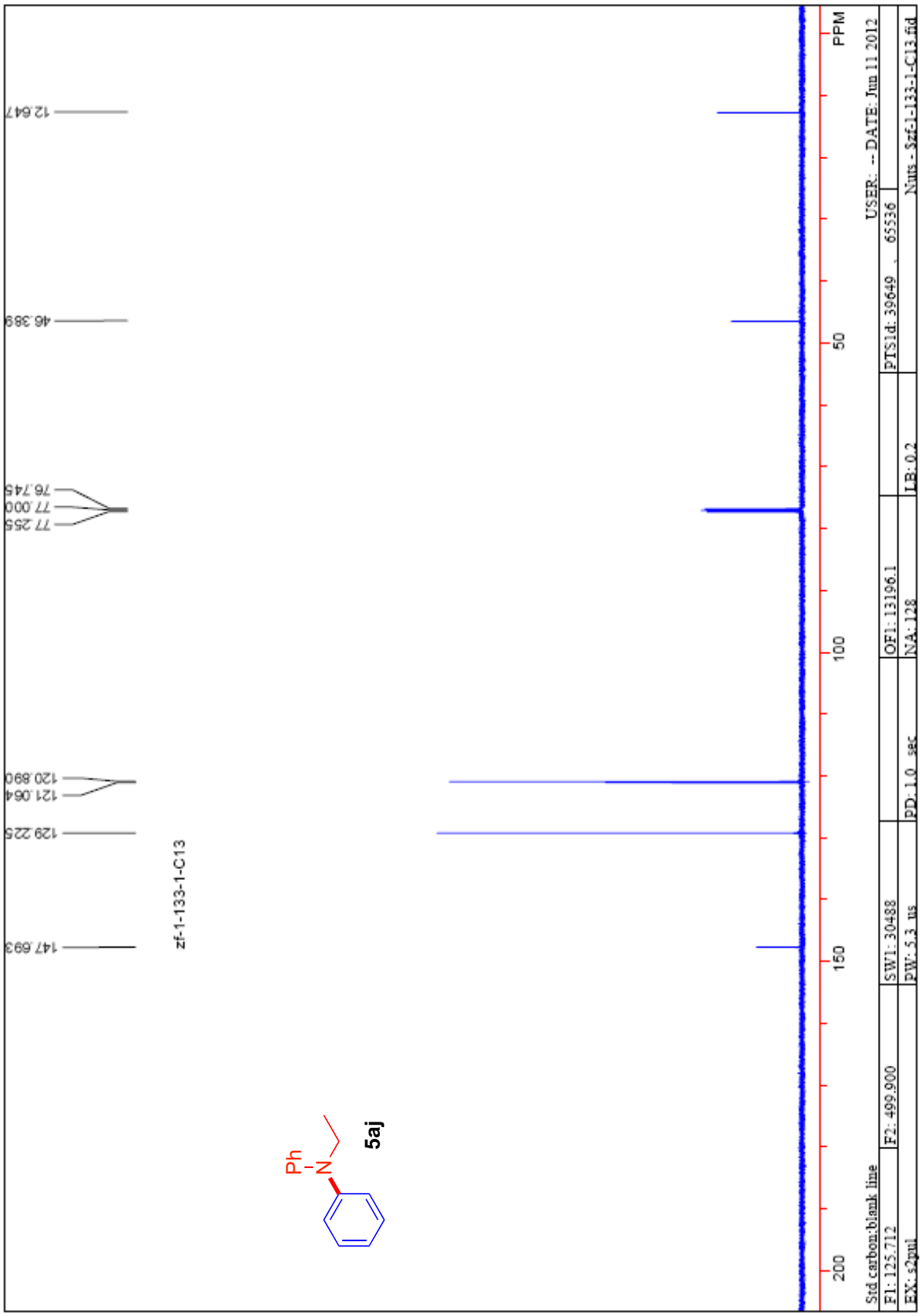
7.22. ^{1}H and ^{13}C NMR spectra of 5ai in $CDCl_3$



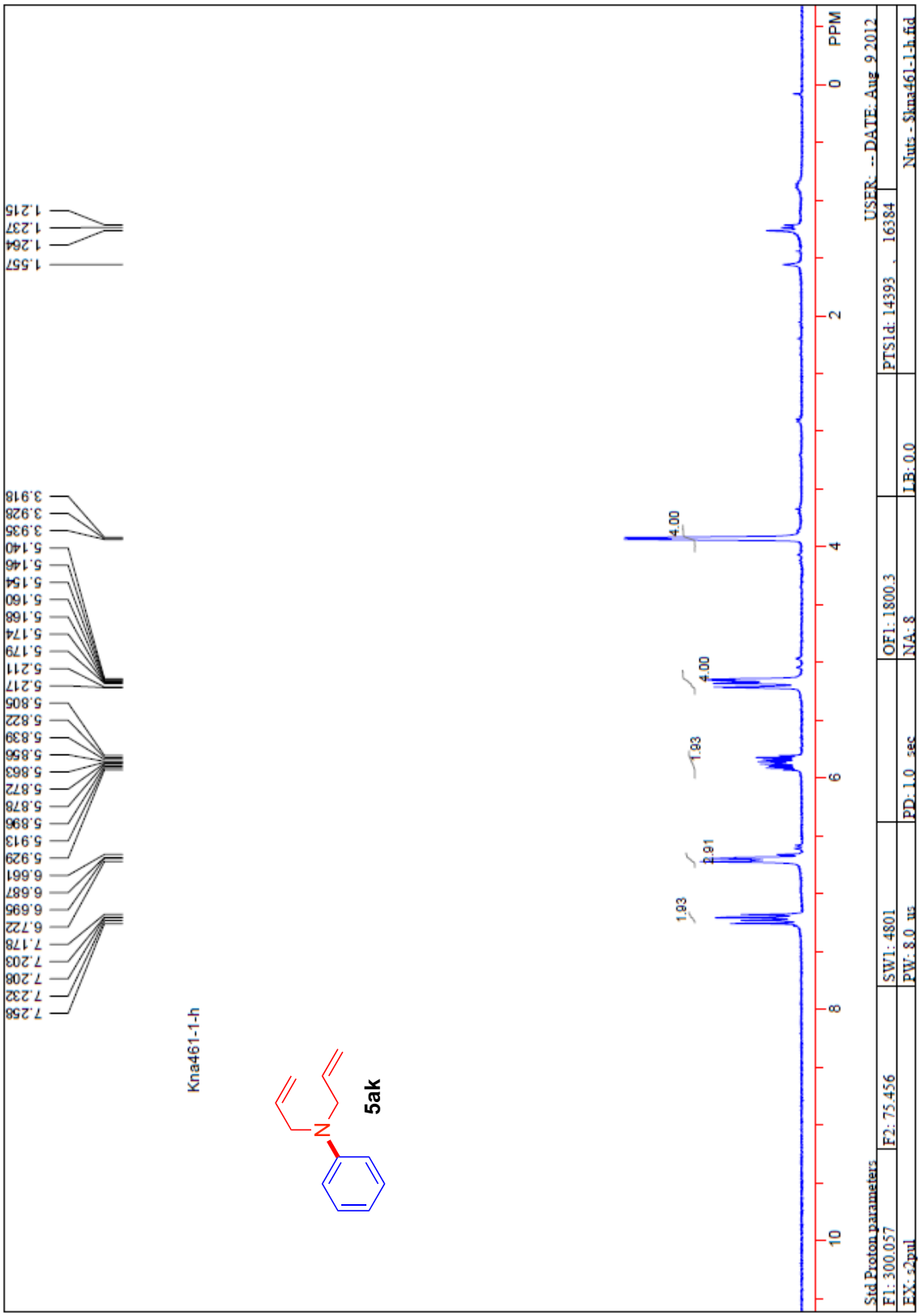

5ai
zf-1-132-1-C13
54.135
76.745
77.000
77.255
112.396
116.675
126.612
126.841
128.603
129.188
136.563
149.129
Std carbon:blank line
F1: 125.712
F2: 499.900
SW1: 30488
OF1: 13189.1
PTS1d: 39649
65536
EX: s2pul
PW: 5.3 us
PD: 1.0 sec
NA: 96
LB: 0.2
USER: -- DATE: Jun 11 2012
Nuts - $zf-1-132-1-C13.fid
PPM
200
150
100
50

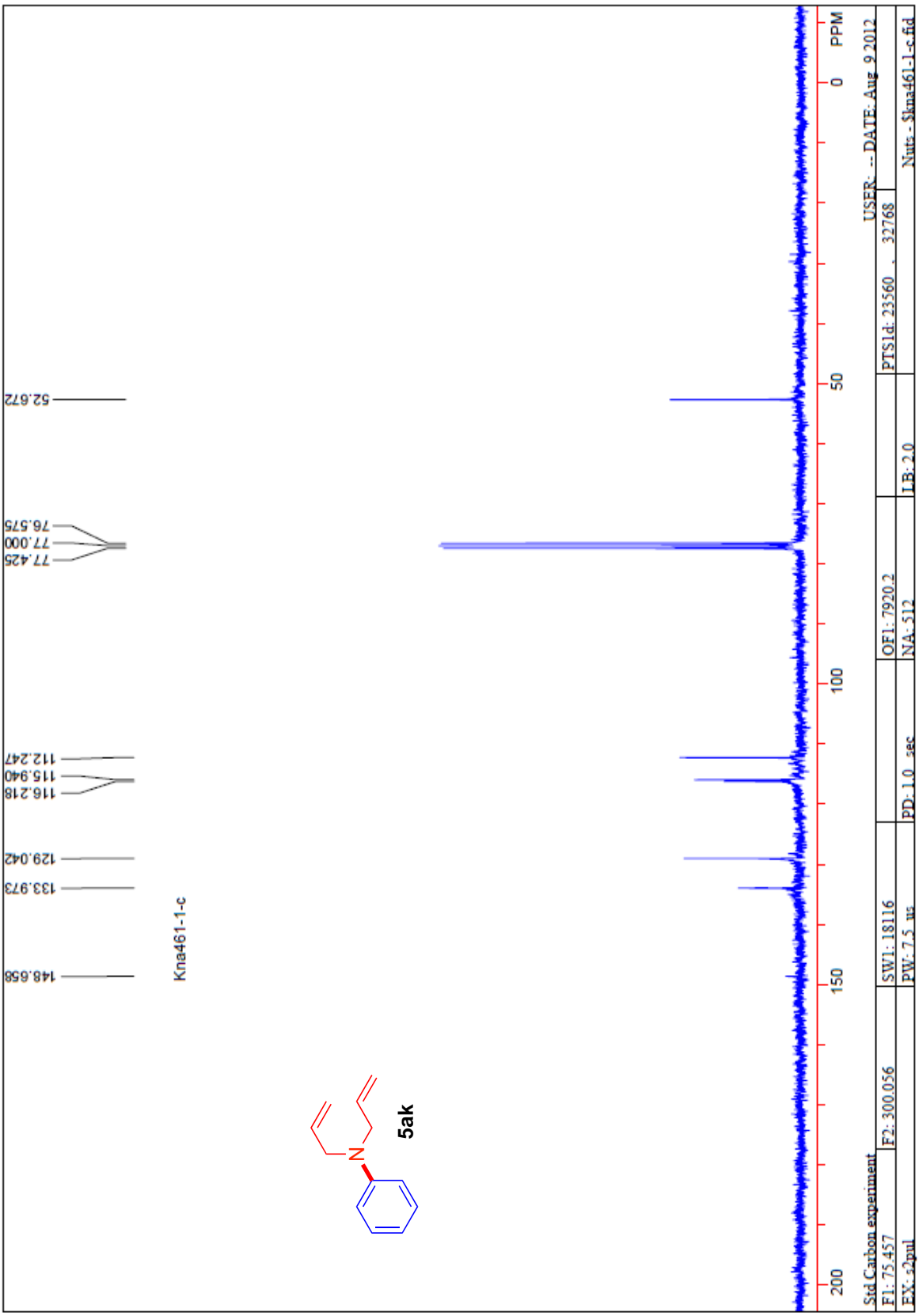
7.23. ^{1}H and ^{13}C NMR spectra of 5aj in $CDCl_3$



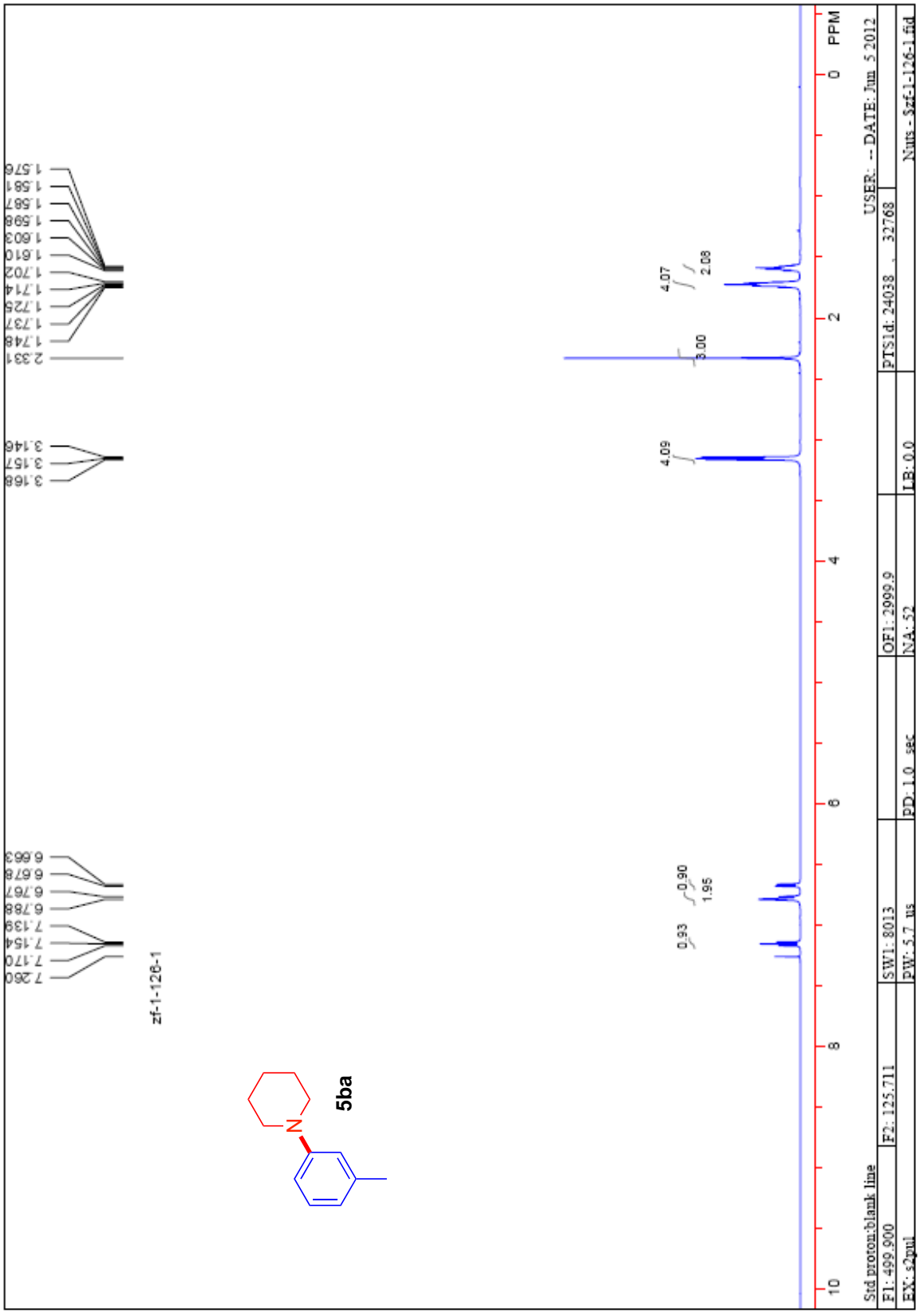

12.647
46.389
76.745
77.000
77.255
120.890
121.064
129.225
147.693
zf-1-133-1-C13
5aj
Ph
N
200
150
100
50
PPM
Std carbon:blank line
F1: 125.712
F2: 499.900
SW1: 30488
OF1: 13196.1
PTS1d: 39649
65536
EX: s2pul
PW: 5.3 us
PD: 1.0 sec
NA: 128
LB: 0.2
USER: -- DATE: Jun 11 2012
Nuts - $zf-1-133-1-C13.fid

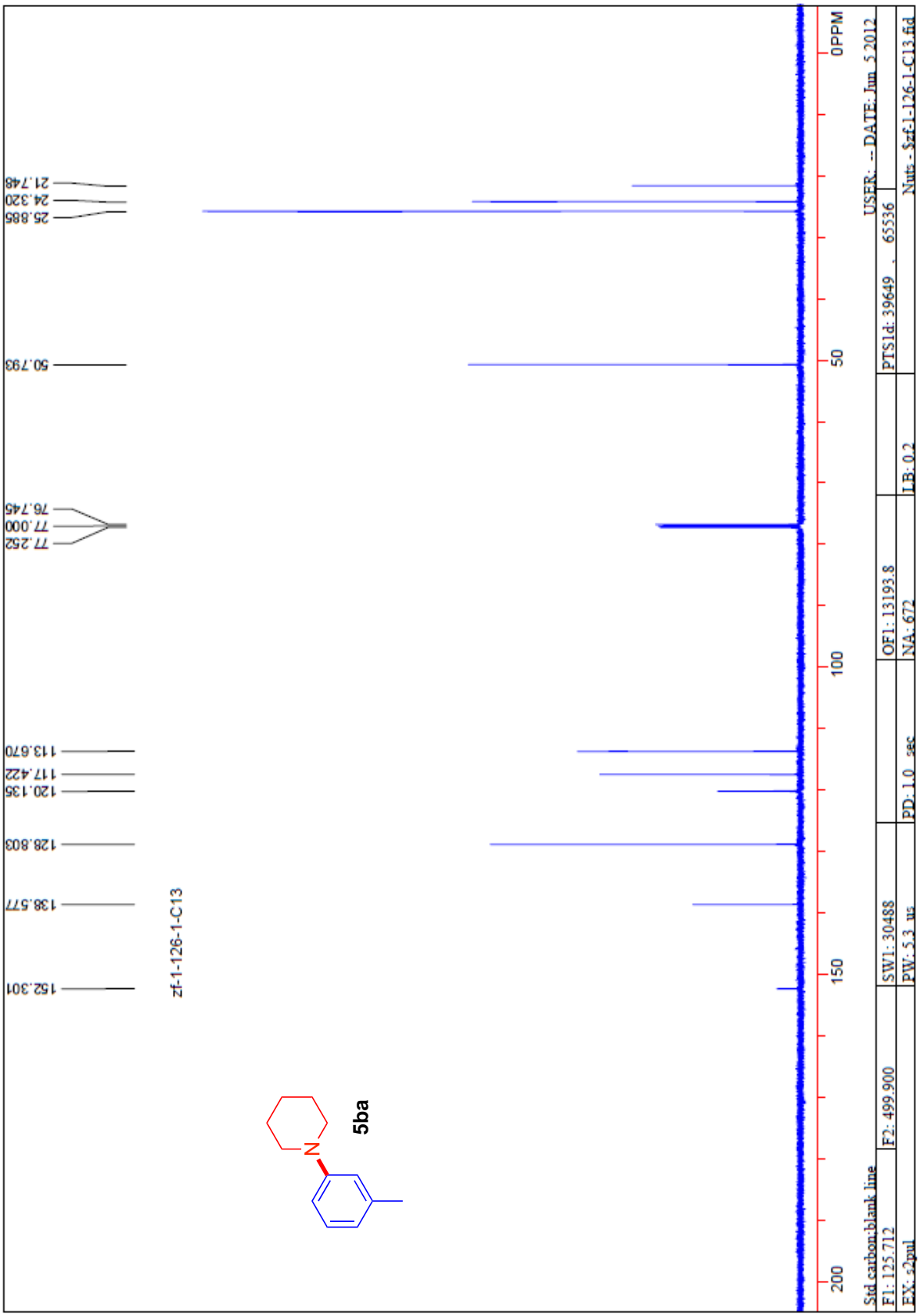
7.24. ^{1}H and ^{13}C NMR spectra of 5ak in $CDCl_3$



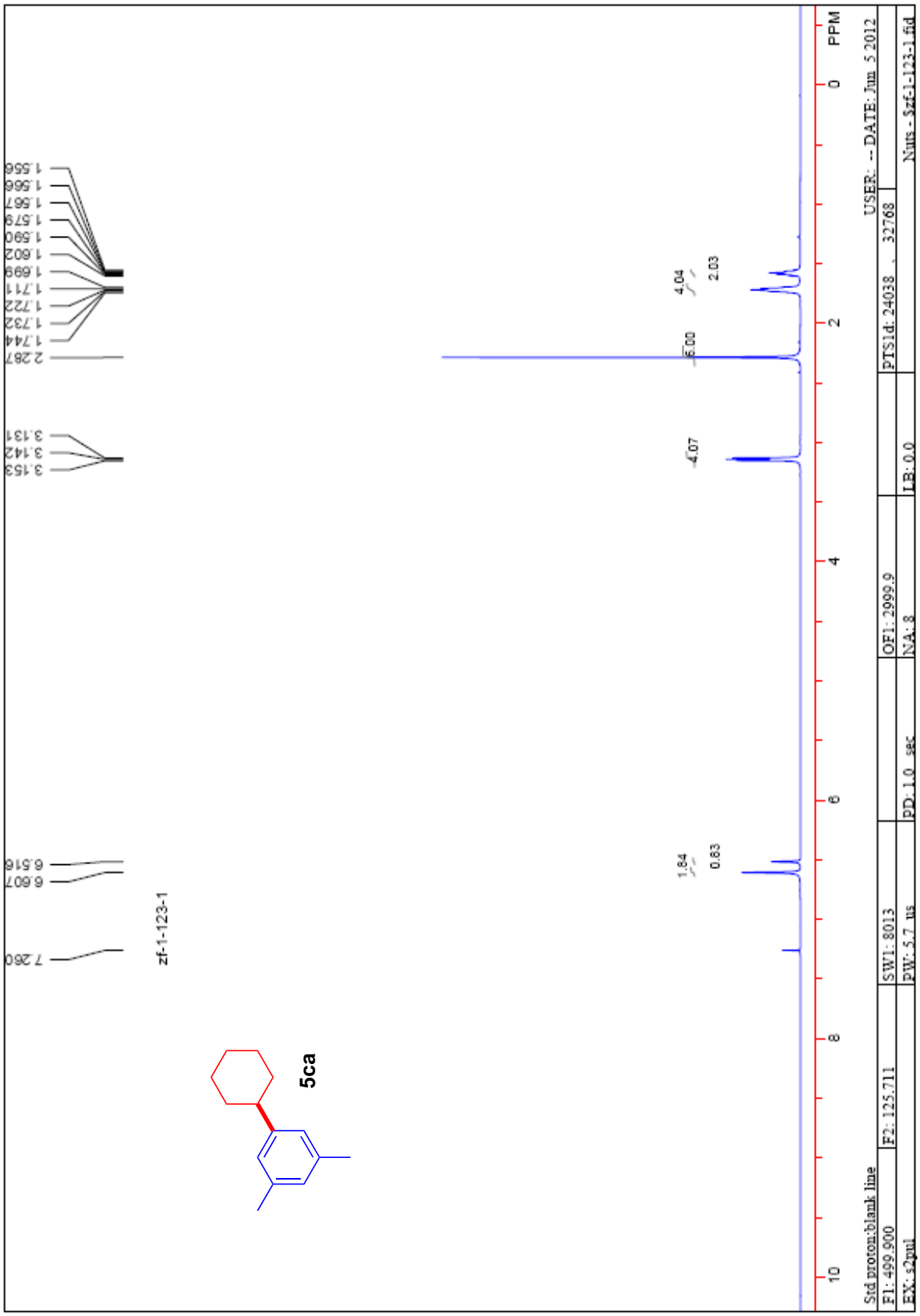

52.672
76.575
77.000
77.425
112.247
115.940
116.218
129.042
133.973
148.658
Kna461-1-c
5ak
N
Std Carbon experiment
F1: 75.457
F2: 300.056
SW1: 18116
PW: 7.5 us
PD: 1.0 sec
OF1: 7920.2
NA: 512
PTS1d: 23560 . 32768
LB: 2.0
USER: -- DATE: Aug 9 2012
EX: s2pul
Nuts - $kna461-1-c.fid
200
150
100
50
0
PPM

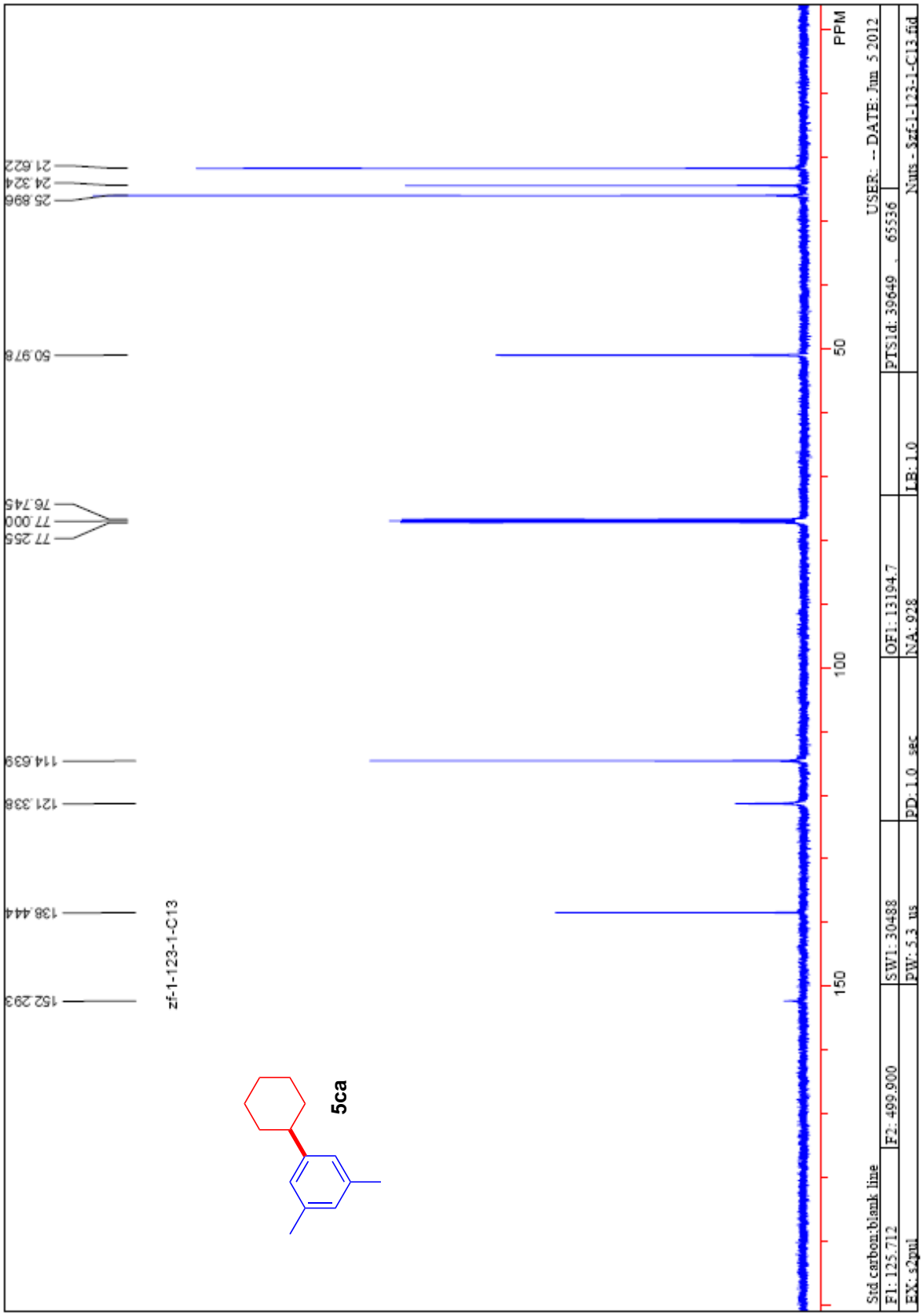
7.25. ^{1}H and ^{13}C NMR spectra of 5ba in $CDCl_3$



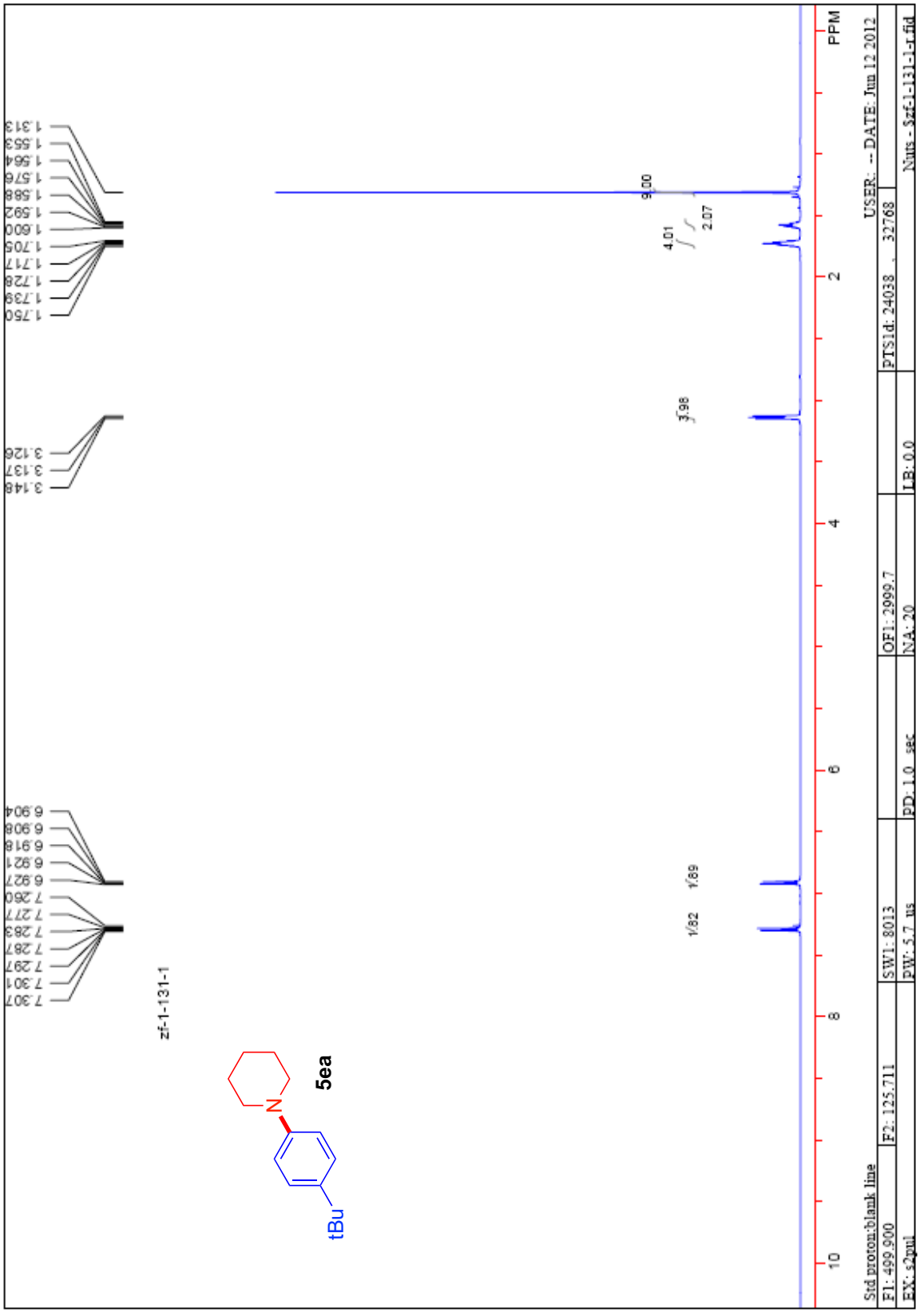

21.748
24.320
25.885
50.793
76.745
77.000
77.252
113.670
117.422
120.135
128.803
138.577
152.301
zf-1-126-1-C13
5ba
Std carbon:blank line
F1: 125.712
F2: 499.900
SW1: 30488
OF1: 13193.8
PTS1d: 39649 , 65536
USER: -- DATE: Jun 5 2012
EX: s2pul
PW: 5.3 us
PD: 1.0 sec
NA: 672
LB: 0.2
Nuts - $zf-1-126-1-C13.fid
200
150
100
50
0PPM

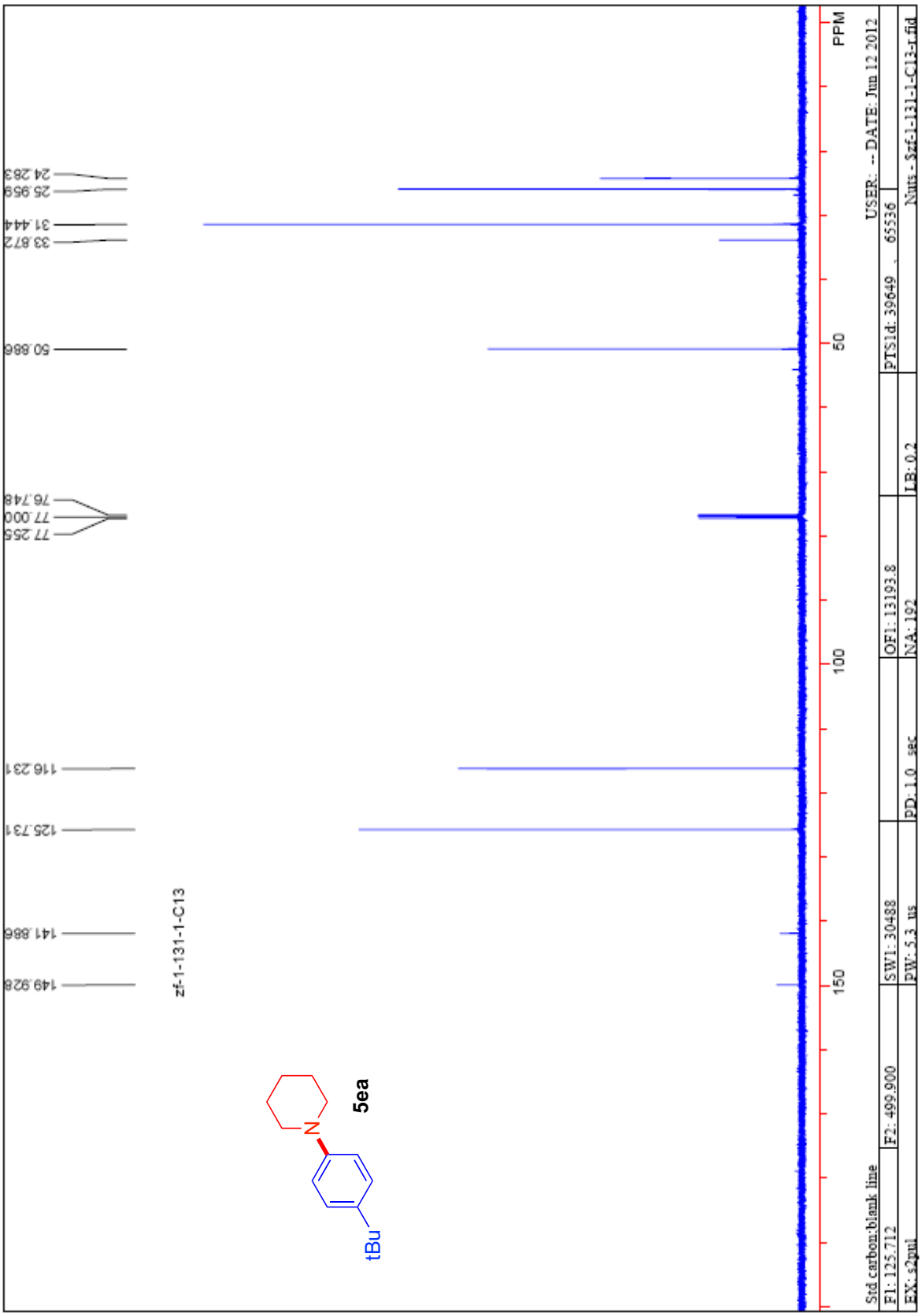
7.26. ^{1}H and ^{13}C NMR spectra of 5ca in $CDCl_3$



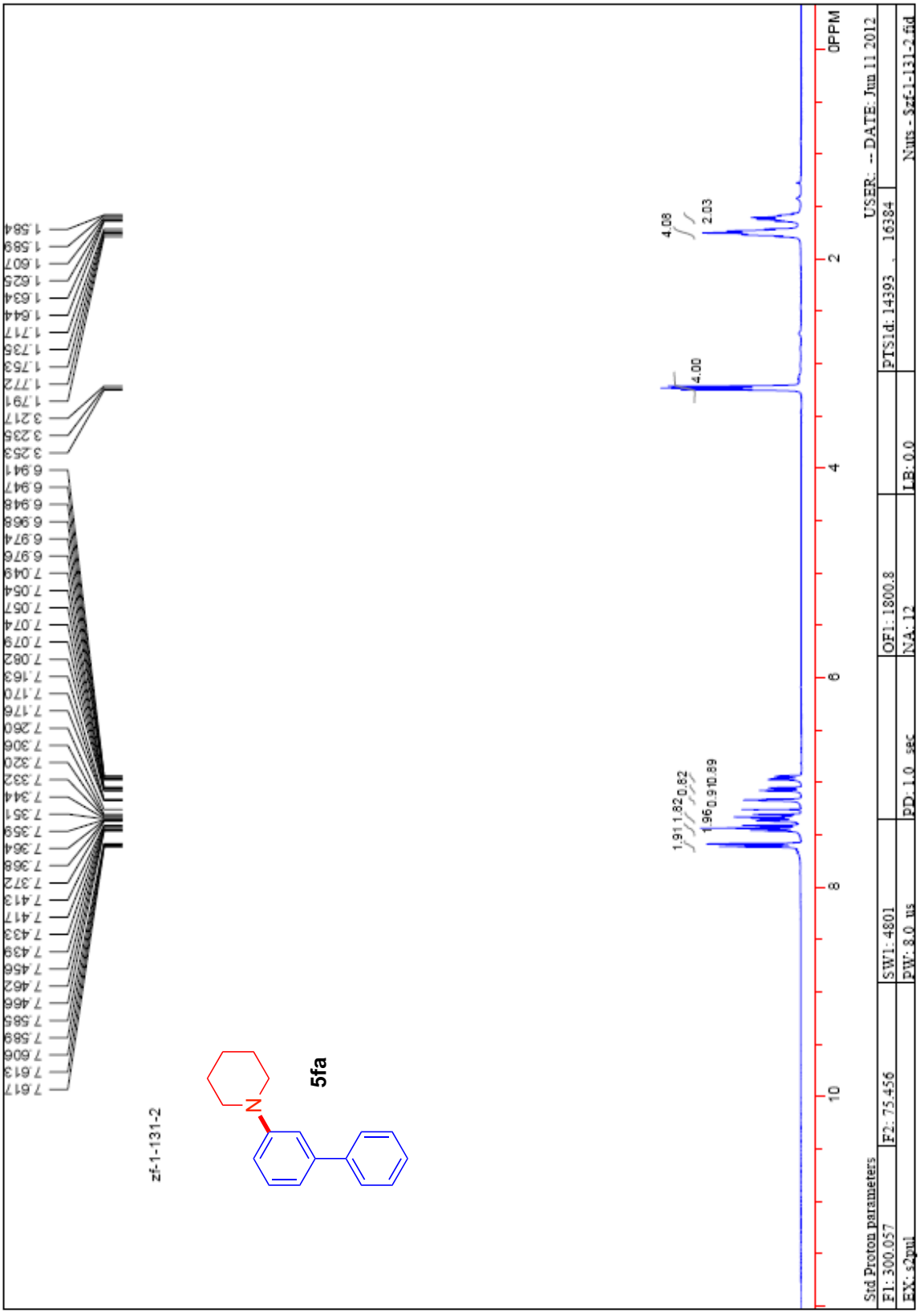

21.622
24.324
25.896
50.978
76.745
77.000
77.255
114.639
121.338
138.444
152.293
zf-1-123-1-C13
5ca
PPM
150
100
50
USER: -- DATE: Jun 5 2012
Std carbon:blank line
F1: 125.712
F2: 499.900
SW1: 30488
OF1: 13194.7
PTS1d: 39649 . 65536
EX: s2pul
PW: 5.3 us
PD: 1.0 sec
NA: 928
LB: 1.0
Nuts - $zf-1-123-1-C13.fid

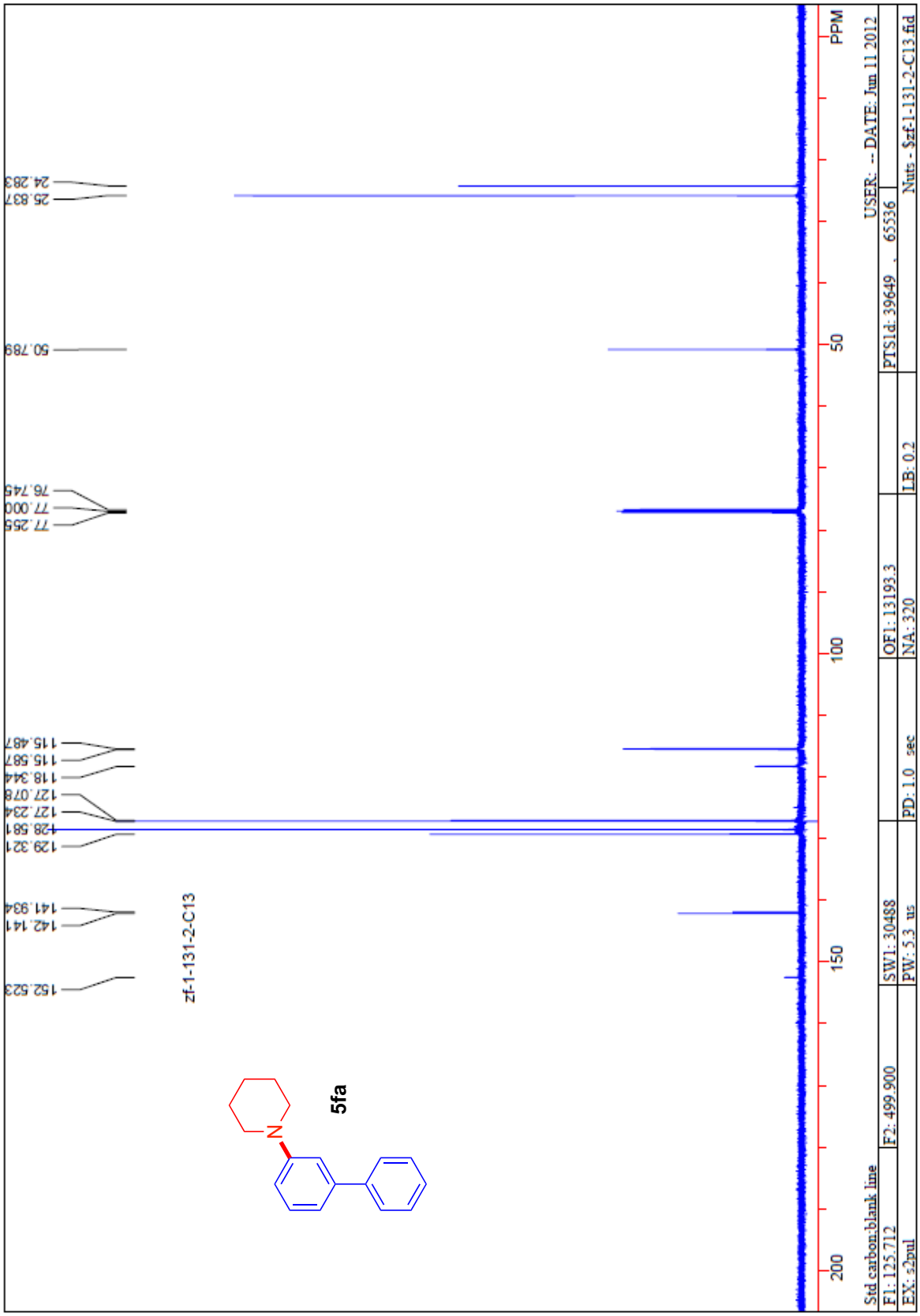
7.27. ^{1}H and ^{13}C NMR spectra of 5ea in $CDCl_3$



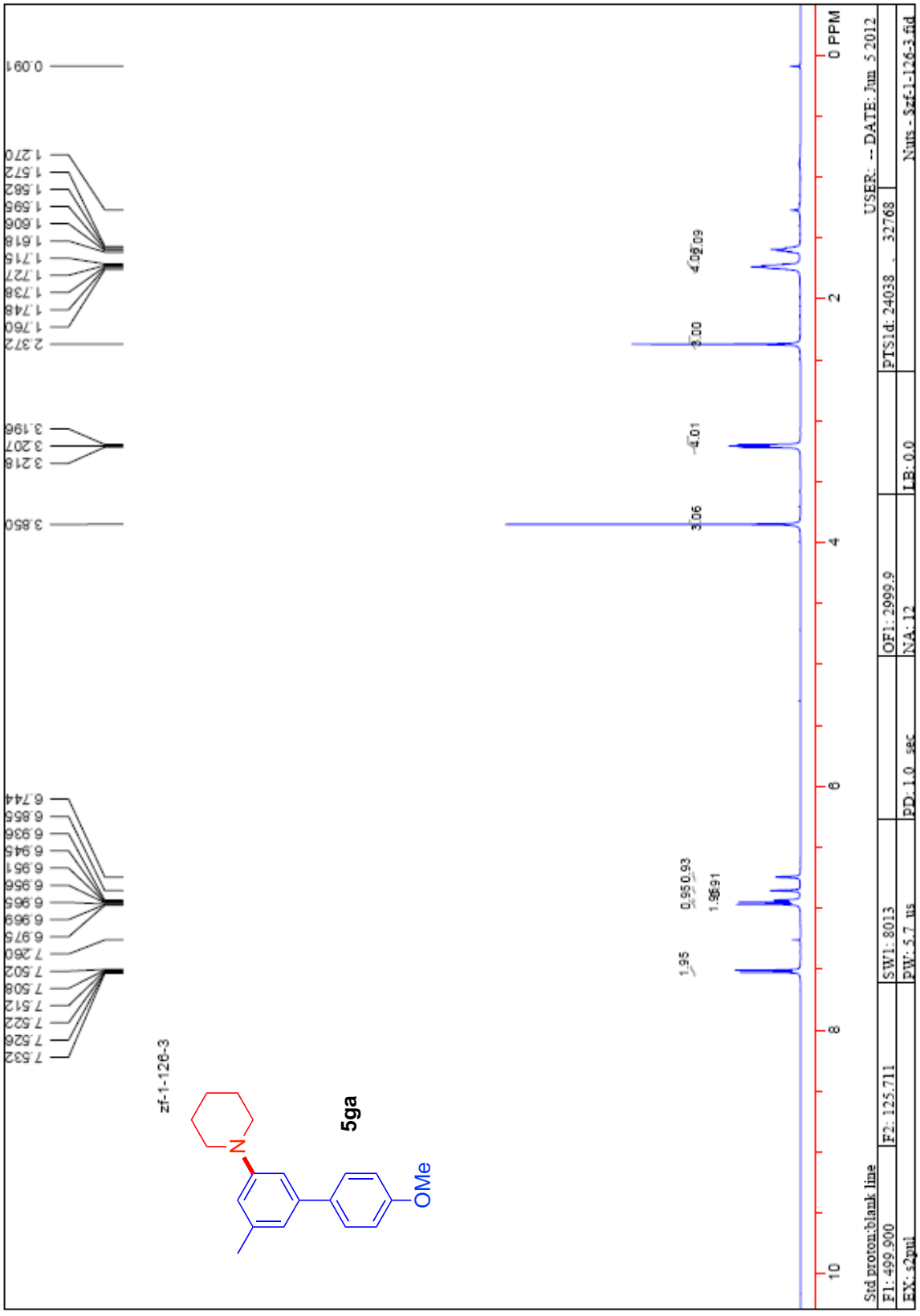

24.283
25.959
31.444
33.872
50.886
76.748
77.000
77.255
116.231
125.731
141.886
149.928
zf-1-131-1-C13
5ea
tBu
N
PPM
150
100
50
Std carbon:blank line
F1: 125.712
F2: 499.900
SW1: 30488
OF1: 13193.8
PTS1d: 39649
65536
EX: s2pul
PW: 5.3 us
PD: 1.0 sec
NA: 192
LB: 0.2
USER: -- DATE: Jun 12 2012
Nuts - $zf-1-131-1-C13-r.fid

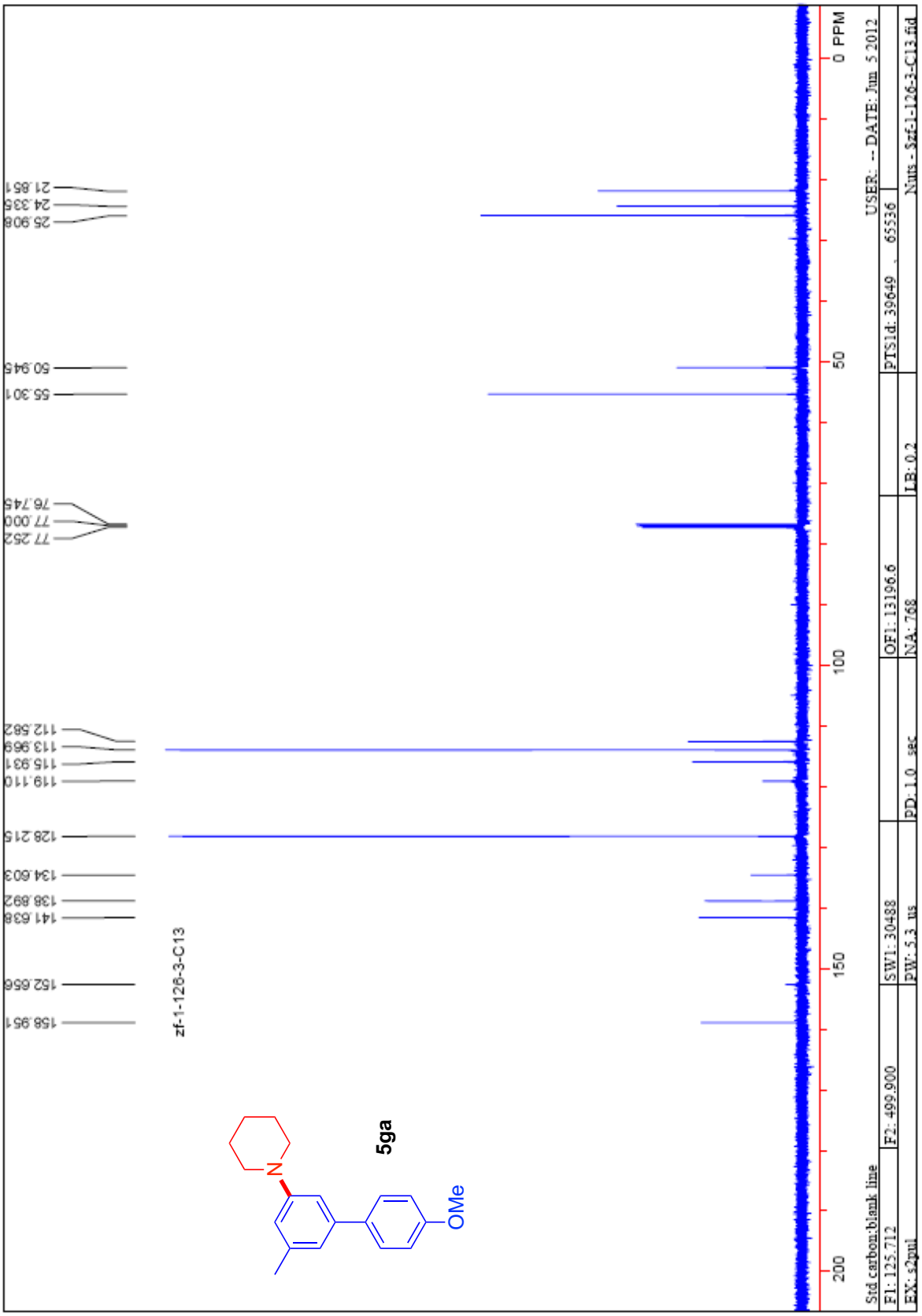
7.28. ^{1}H and ^{13}C NMR spectra of 5fa in $CDCl_3$




24.283
25.837
50.789
76.745
77.000
77.255
115.487
115.587
118.344
127.078
127.234
128.581
129.321
141.934
142.141
152.523
zf-1-131-2-C13
5fa
N
PPM
50
100
150
200
USER: -- DATE: Jun 11 2012
Std carbon:blank line
F1: 125.712
F2: 499.900
SW1: 30488
OF1: 13193.3
PTS1d: 39649 , 65536
EX: s2pul
PW: 5.3 us
PD: 1.0 sec
NA: 320
LB: 0.2
Nuts - $zf-1-131-2-C13.fid

7.29. ^{1}H and ^{13}C NMR spectra of 5ga in $CDCl_3$




21.851
24.335
25.908
50.945
55.301
76.745
77.000
77.252
112.582
113.969
115.931
119.110
128.215
134.603
138.892
141.638
152.656
158.951
zf-1-126-3-C13
5ga
N
OMe
200
150
100
50
0 PPM
Std carbon:blank line
F1: 125.712
F2: 499.900
SW1: 30488
OF1: 13196.6
PTS1d: 39649
65536
EX: s2pul
PW: 5.3 us
PD: 1.0 sec
NA: 768
LB: 0.2
USER: -- DATE: Jun 5 2012
Nuns - $zf-1-126-3-C13.fid