이학박사학위논문

Development of Catalytic Reactions of Imines via Isocyanide Activation and Methanol Dehydrogenation

아이소사이아나이드 활성화 및 메탄올 탈수소화를 통한 이민의 촉매 반응 개발

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Abstract

Development of Catalytic Reactions of Imines via Isocyanide Activation and Methanol Dehydrogenation

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The imine, which contains a double bond between carbon and nitrogen, is a fundamental functional group in organic chemistry. Its innate electrophilic character has been extensively studied, especially in carbon–carbon bond formation. The development of transition metal catalysis has further enriched imine chemistry. This thesis describes catalytic reactions of imines via two different strategies.

Part I introduces isocyanide chemistry and its applications to *N*-aryl/alkyl-β-enaminonitrile synthesis. A brief overview of activation strategies for isocyanides and representative examples, along with their history, characteristics, and physical properties, is presented in Chapter 1. An adaption of the transition-metal-catalyzed migratory insertion of an isocyanide in the synthesis of *N*-aryl/alkyl-β-

enaminonitrile is introduced in Chapter 2. The use of isocyanide as a nitrogen source enabled access to a broad substrate scope with good functional group tolerance. An imine-like species, the imidoyl copper intermediate, participates in the reaction.

Part II describes the synthetic application of methanol as a C1 source and the (amino)methylation of phenol derivatives with methanol. In industry, carbon monoxide plays a crucial role in raw materials synthesis, despite its toxicity and flammability. In recent decades, methanol has attracted great attention as an alternative C1 feedstock due to its safety and potential renewability. In Chapter 3, transition-metal-catalyzed methods for the dehydrogenative activation of alcohols, along with the distinct features of methanol compared to higher alcohols, are reviewed. Then, state-of-art examples of the dehydrogenative activation of methanol are summarized. Chapter 4 describes the aminomethylation and methylation of phenol derivatives with methanol and amines. Methanol is dehydrogenated by a ruthenium pincer catalyst, and the resulting formaldehyde condenses with amines to form imines. The different reactivity of this transformation with different substrates was thoroughly investigated.

Keywords: imine, isocyanide, copper, enaminonitrile, methanol, dehydrogenation, ruthenium, aminomethylation, methylation, phenol

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Table of Contents

Abstract i

Table of Contents iii

List of Tables vii

List of Schemes viii

List of Figures xi

Part I. Activation Strategies of Isocyanides and Application to *N*-Aryl-β-Enaminonitrile Synthesis

Chapter 1. Characteristics and Activation Strategies of Isocyanides for Synthetic Applications

1.1 Introduction 1

1.2 Preparation, general reactivity, and physical properties of isocyanides 2

1.3 Activation strategies for isocyanides in synthetic applications 5

1.3.1 Non-catalyzed reactions of isocyanides 5

1.3.2 Lewis-acid-catalyzed reactions of isocyanides 10

1.3.3 Transition-metal-catalyzed reactions of isocyanides 12

1.3.4 Reactivity of α-metalated isocyanides 18

1.3.5 Radical reactions of isocyanides 21

1.4 Conclusion 23

1.5 References 24

Chapter 2. Copper-Catalyzed *N*-Aryl-β-Enaminonitrile Synthesis Utilizing Isocyanides as the Nitrogen

2.1 Introduction 33

2.2 Results and discussion 36

2.2.1 Optimization for the synthesis of β-enaminonitrile from isocyanides and benzylcyanides 36

2.2.2 Substrate scope of isocyanides 39

2.2.3 Substrate scope of arylacetonitriles 41

2.2.4 Mechanistic studies 43

2.2.5 Application of β-enaminonitrile 47

2.3 Conclusion 48

2.4 Experimental section 49

2.4.1 General information 49

2.4.2 General procedure for *N*-aryl/alkyl-β-enaminonitrile synthesis 49

2.4.3 General procedure for 3-oxo-2-phenylpropanenitrile synthesis 50

2.4.4 General procedure for 4-phenyl-1*H*-pyrazol-3-amine synthesis 50

2.4.5 Characterization data 51

2.5 References 62

Part II. Synthetic Applications of Methanol as a C1 Source and (Amino)methylation of Phenol Derivatives with Methanol

Chapter 3. Utilization of Methanol as a C1 Building Block through Transition Metal Catalysis

3.1 Introduction 66

3.2 Dehydrogenative activation of alcohols 67

3.2.1 Traditional reactivity of alcohols 67

3.2.2 Basic concepts and mechanistic aspects of transition-metal-catalyzed dehydrogenation 69

3.2.3 Synthetic applications of catalytic alcohol dehydrogenation 75

3.3 Dehydrogenative activation of methanol 77

3.3.1 Methanol utilization with carbon nucleophile 77

3.3.2 Methanol utilization with nitrogen nucleophile 81

3.4 Methanol utilization via radical pathway 87

3.5 Conclusion 90

3.6 References 91

Chapter 4. Ruthenium-Catalyzed Aminomethylation and Methylation of Phenol Derivatives Utilizing Methanol as the C1 Source

4.1 Introduction 97

4.2 Results and discussion 100

4.2.1 Optimization for the *ortho*-aminomethylation of phenol 101

4.2.2 Substrate scope for the *ortho*-aminomethylation of phenol 103

4.2.3 Optimization for the methylation of naphthol 105

4.2.4 Substrate scope for the methylation of naphthol 107
4.2.5 Mechanistic studies 108
4.3 Conclusion 117
4.4 Experimental section 119
4.4.1 General information 119
4.4.2 General procedure for *ortho*-aminomethylation of phenol 119
4.4.3 General procedure for methylation of naphthol 119
4.4.4 General procedure for the capture of *ortho*-quinone methide 120
4.4.5 Characterization data 121
4.5 References 131

Appendix

Chapter 2 136
Chapter 4 163

Abstract in Korean 163

List of Tables

Chapter 2

Table 2.1 Optimization of the reaction conditions 38

Table 2.2 Substrate scope of isocyanides 40

Table 2.3 Substrate scope of arylacetonitriles 42

Table 2.4 Effect of catalyst and base 44

Chapter 4

Table 4.1 Optimization of the reaction conditions 101

Table 4.2 Scope of *ortho*-aminomethylation reaction 104

Table 4.3 Effect of base on methylation of 2-naphthol 106

Table 4.4 Scope of methylation reaction 107

Table 4.5 Reaction between phenol and formamide 110

Table 4.6 Reaction between naphthol and formamide 110

List of Schemes

Chapter 1

Scheme 1.1 Synthesis of isocyanides 3

Scheme 1.2 Physical properties of isocyanides 4

Scheme 1.3 Early examples of isocyanides: the Passerini reaction and Ugi reaction 6

Scheme 1.4 Variations of the Ugi reaction 7

Scheme 1.5 Reactions of isocyanides with nucleophiles 8

Scheme 1.6 Carbenic reactivity of isocyanides: synthesis of 1-acyl-3,4-dihydroisoquinoline from 2-ethylphenyl isocyanide 9

Scheme 1.7 Activation of electrophile by Lewis acids 11

Scheme 1.8 Lewis-acid-catalyzed insertion of isocyanides into C–heteroatom bonds 12

Scheme 1.9 General reaction pathway of transition-metal-catalyzed reactions of isocyanides 13

Scheme 1.10 Reactions involving simple binding of coupling partners 14

Scheme 1.11 Reactions beginning with the oxidative addition of an aryl halide: classification via the later isocyanide insertion step 16

Scheme 1.12 Reactions beginning with the C–H activation of the substrate: classification by the hybridization of the C–H bond 17

Scheme 1.13 Miscellaneous examples of isocyanide insertions 17

Scheme 1.14 General reactivity of α-metalated isocyanides 18

Scheme 1.15 Representative reactions of α-metalated isocyanides 19

Scheme 1.16 Examples of α-metalated isocyanides with exotic coupling partners 20

Scheme 1.17 First synthesis of heterocycle from isocyanides via a radical pathway 21

Scheme 1.18 Synthesis of phenanthridines from isocyanides via a radical pathway 22

Chapter 2

Scheme 2.1 Synthesis of diverse heterocycles from β-enaminonitrile 32

Scheme 2.2 Synthetic methods for β-enaminonitriles classified according to nitrogen sources 35

Scheme 2.3 Proposed reaction mechanism 46

Scheme 2.4 Reactions of formimidates 46

Scheme 2.5 Transformation of β-enaminonitrile **3aa** 47

Chapter 3

Scheme 3.1 Traditional reactivity of alcohols 68

Scheme 3.2 Transition-metal-catalyzed dehydrogenative alcohol activation 70

Scheme 3.3 Mechanisms of dehydrogenation reactions 71

Scheme 3.4 Differentiation between the monohydride mechanism and the dihydride mechanism through the racemization of α-deuterated phenylethanol 72

Scheme 3.5 Classification of the monohydride mechanism and metal-ligand cooperation (MLC) 74

Scheme 3.6 Catalytic amide synthesis from an alcohol and an amine 75

Scheme 3.7 α-Alkylation of a ketone with an alcohol as the alkylating reagent 76

Scheme 3.8 General reaction pathway of dehydrogenative methanol utilization with a carbon nucleophile 78

Scheme 3.9 α-Methylation of a ketone with methanol under an oxygen atmosphere 79

Scheme 3.10 β-Methylation of an alcohol with methanol 80

Scheme 3.11 Hydroxymethyl group installation of an allene with methanol 81

Scheme 3.12 General reaction pathway for dehydrogenative methanol utilization with a nitrogen nucleophile 82

Scheme 3.13 N-formylation of amines and nitriles with methanol 83

Scheme 3.14 Urea synthesis from an amine and methanol 84

Scheme 3.15 Monomethylation of aryl amines and dimethylation of aliphatic amines with methanol 85

Scheme 3.16 Monomethylation of aryl amines and dimethylation of aliphatic amines with methanol in the same catalytic system 86

Scheme 3.17 Construction of quinazolinone with methanol as a –CH– source . 86

Scheme 3.18 Utilization of methanol via a radical pathway with stoichiometric amounts of the oxidants 88

Scheme 3.19 Utilization of methanol via a radical pathway through dual catalysis with a photocatalyst and organocatalyst 89

Chapter 4

Scheme 4.1 Classical and developed synthetic methods for *ortho*-aminomethylation of phenol derivatives 98

Scheme 4.2 Deuterium labelling study 111

Scheme 4.3 Possible intermediates in *ortho*-aminomethylation of phenol 113

Scheme 4.4 Possible intermediates in methylation of naphthol 115

Scheme 4.4 Plausible mechanism 118

List of Figures

Chapter 2

Figure 2.1 Crystal structure of **3aa**. ORTEP diagram showing 50% probability thermal ellipsoids 37

Chapter 4

Figure 4.1 Kinetic profile of *ortho*-aminomethylation of **1b**. Error bars were calculated from three repetitions. 108

Chapter 1. Characteristics and Activation Strategies of Isocyanides for Synthetic Application

1.1 Introduction

Isocyanides, which are also called isonitriles, are organic compounds with the functional group –N≡C, and are isomers of nitriles. They remained unexplored for a long time due to their unpleasant odor, but have become indispensable materials due to their unique characteristics and reactivity. Isocyanides serve as strong σ-donating ligands with excellent π*-accepting properties,[1] and are thus used to remove ligands.[2] They can be used as an alternative to thiols for nanoparticle stabilization,[3] and can also be efficiently polymerized in the presence of transition metal catalysts if their steric hindrance is sufficiently low.[4] The utilization of isocyanides is most prominent in multi-component reactions (MCRs) and heterocycle synthesis.[5] Various types of activation methods have been adapted for the use of isocyanides in synthetic applications, ranging from simple nucleophilic attack to transition metal catalysis and radical addition. Asymmetric reactions have also been developed.[1,6]

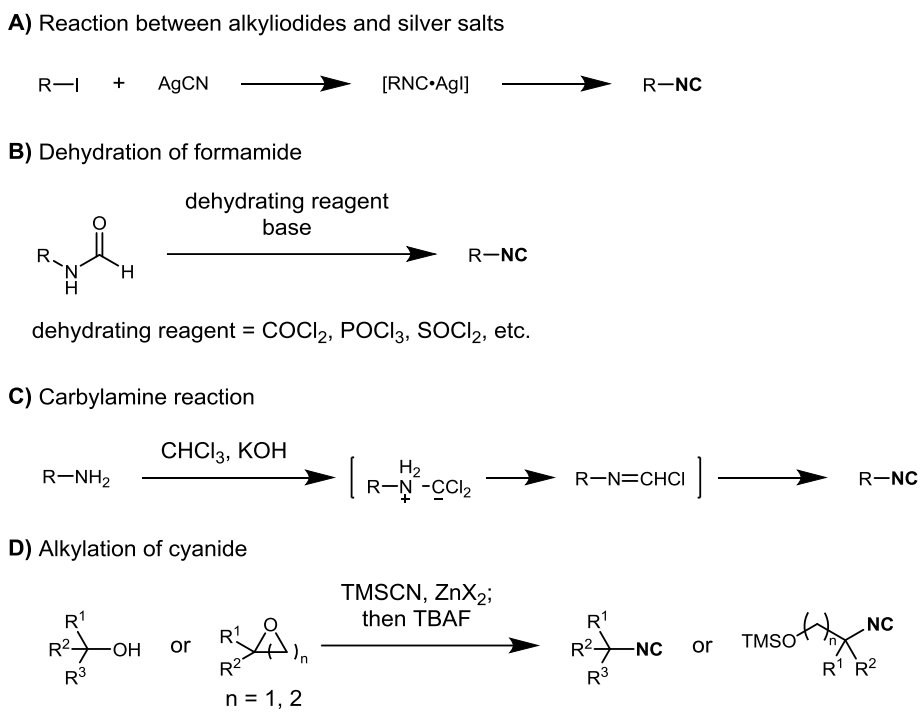
This chapter describes the history, synthetic routes, general reactivity, and physical properties of isocyanides. An overview of non-catalyzed reactions of isocyanides is provided, and the activation methods for isocyanides for synthetic applications are classified into four main categories and discussed with representative examples.

1.2 Preparation, general reactivity, and physical properties of isocyanides

The first discovery of a natural product containing an isocyanide group was reported in 1957.[7] The compound was isolated from *Penicillium notatum* and named xanthocillin. To date, several classes of isocyanide-containing natural products have been discovered, including marine isocyanides, terrestrial isocyanides, cyclopentyl isocyanides, diterpenes, sesquiterpenes, and indolalkaloids.[8]

Interestingly, the first synthesis of isocyanide in the laboratory had taken place nearly a century earlier. In 1859, W. Lieke reported that mixing allyl iodide with silver cyanide afforded a vile-smelling liquid different from the expected allyl cyanide (Scheme 1.1A).[9] Several years later, A. Gautier[10] and A. W. Hofmann[11] independently described these malodorous compounds as isomers of cyanides. The study of isocyanides began in earnest after the synthesis of isocyanides via the dehydration of formamides was discovered (Scheme 1.1B);[12] this is still the most commonly used method. The development of several other methods followed, such as the carbylamine reaction (Scheme 1.1C),[13] the alkylation of cyanides with alcohols[14] or strained oxacycles[15] (Scheme 1.1D), the deoxygenation of isocyanates,[16] and the desulfuration of isothiocyanates.[17]

The electronic properties of isocyanides can be described by their resonance structures, which consist of a zwitterionic form and a carbenic form (Scheme 1.2A). Thus, the carbon atoms of isocyanides have both anion and carbene character. As isocyanides are isoelectronic with carbon monoxide, the general reactivity and physical properties of isocyanides naturally resemble those of carbon monoxide.

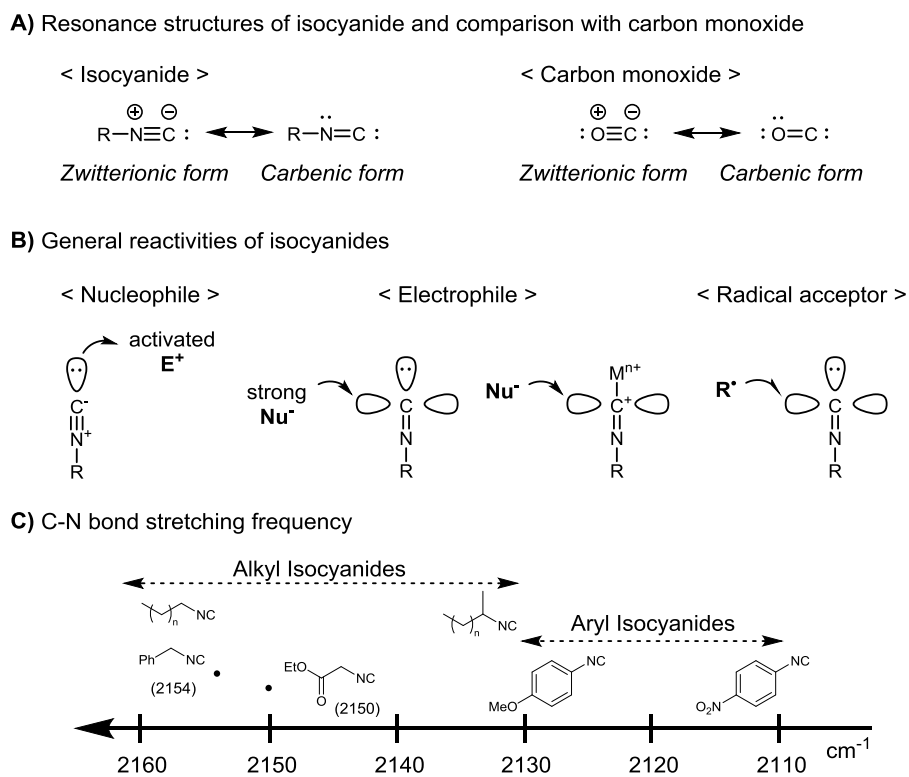


Scheme 1.1 Synthesis of isocyanides

Similarly to carbon monoxide, the carbon atoms of isocyanides act as nucleophiles, electrophiles, and radical acceptors (Scheme 1.2B). The nucleophilicity of isocyanides, which originates from their zwitterionic resonance form, was measured by the H. Mayr group and found to be comparable with that of α,β-unsaturated amides and silyl enol ethers.[18,19] Thus, attack by an isocyanide can activate electrophiles such as iminium ions. The carbenic resonance form containing an empty *p*-orbital enables isocyanides to react with strong nucleophiles. When isocyanides are activated by a Lewis acid, proton, or transition metal, the range of applicable nucleophiles becomes broader. In addition to the closed-shell reaction

pathways depicted above, open-shell intermediates can participate in the radical attack of an empty *p*-orbital. The resulting carbon-centered radicals undergo radical cascade reactions.

As would be anticipated from its resonance structures, the C–N bond stretching frequencies are found within the range 2110-2160 cm^{-1} (Scheme 1.2C), [20] i.e., they are stronger than double bonds (1600-1700 cm^{-1}) but weaker than triple bonds (2200-2300 cm^{-1}).[21] Generally, alkyl isocyanides have stronger C–N bonds owing to the stabilization of the cationic charge on the nitrogen atoms of the zwitterionic resonance form, which contains a triple bond.



Scheme 1.2 Physical properties of isocyanides

1.3 Activation strategies for isocyanides in synthetic applications

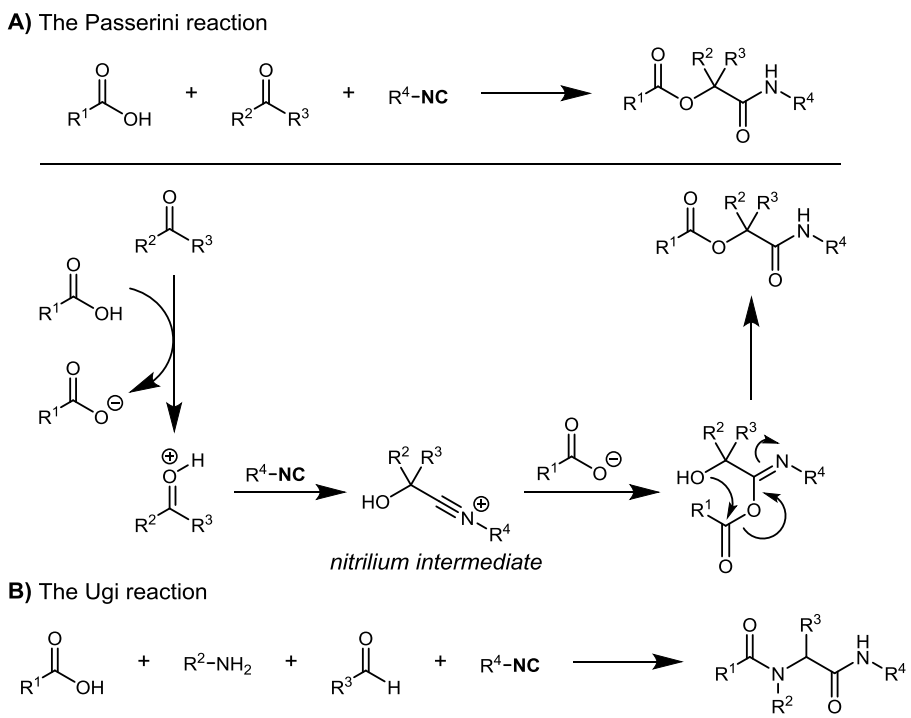
1.3.1 Non-catalyzed reactions of isocyanides

Isocyanides have innate, albeit moderate, nucleophilicity and electrophilicity. Hence, many non-catalyzed reactions of isocyanides with activated substrates have been reported. In 1921, the group of M. Passerini made a breakthough;[22] they discovered that carboxylic acids, ketones, and isocyanides undergo three component reactions (Scheme 1.3A). Initially, the carboxylic acid protonates the ketone, followed by nucleophilic attack of this activated substrate by the isocyanide. The resulting nitrilium intermediate is subsequently captured by the carboxylate. α-Hydroxy carboxamides are finally furnished via a rearrangement accompanied by C–O bond formation and cleavage. However, the above-described ionic mechanism cannot adequately explain the fast reaction rates observed in non-polar solvents. Hence, a concerted reaction pathway and ketone-carboxylic acid pair were also suggested.[22c] Approximately 40 years later, I. Ugi and co-workers accomplished four component reactions by replacing the ketones with in situ generated imines from aldehydes and amines to produce α-aminoacyl amide derivatives instead (Scheme 1.3B).[23]

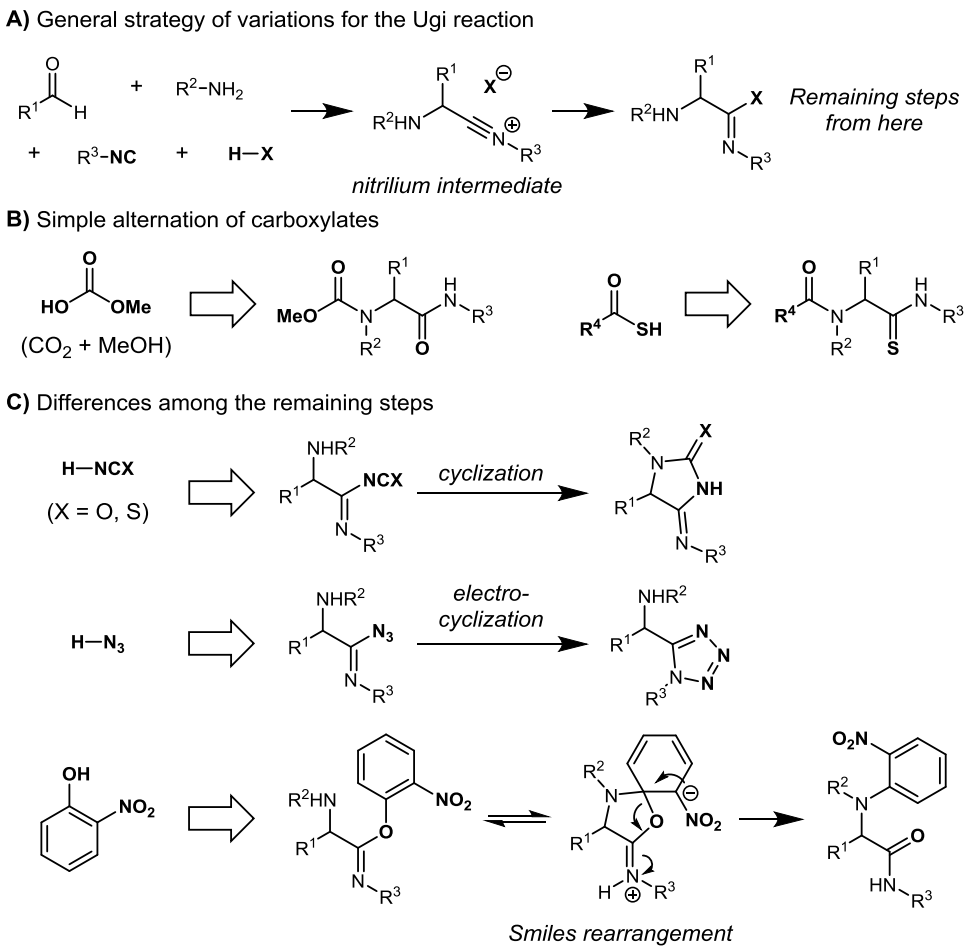
The discovery of the Ugi reaction greatly enriched organic chemistry through many subsequent studies (Scheme 1.4).[5j] The key aspect in variations of the Ugi reaction is the manner in which the nitrilium intermediates are captured (Scheme 1.4A). If in situ generated carbonic acids[24] or thiocarboxylic acids[25] take the place of the carboxylates, the corresponding analogous proudcts are furnished (Scheme 1.4B). Relying on nucleophiles, the final rearrangement step can be totally different (Scheme 1.4C). Isocyanic acid derivatives undergo cyclization via intramolecular

capture instead of the original rearrangement,[26] while hydrazoic acid participates in electrocyclization to form tetraazacycles.[27] Substrates with internal nucleophiles can be used to produce dozens of heterocycles:[5j] aminopyridines,[28] aminothiazoles,[28] dihydrothiazoles,[29] 2-aminooxazoles,[30] etc. When electronically poor phenol derivatives such as nitro-group-substituted arenes or heterocycles are used, a dearomatization-aromatization sequence known as the Smiles rearrangement[31] occurs.[32] This reaction has been named the Ugi-Smiles coupling.

Isocyanide-based multicomponent reactions (IMCRs) have attracted great attention in various fields of applied chemistry, including drug discovery, natural product synthesis, peptide synthesis, polymers, and bioconjugation, owing to their diversity, functional group tolerance, and chemo-, regio-, and stereoselectivity.[33]



Scheme 1.3 Early examples of isocyanides: the Passerini reaction and Ugi reaction

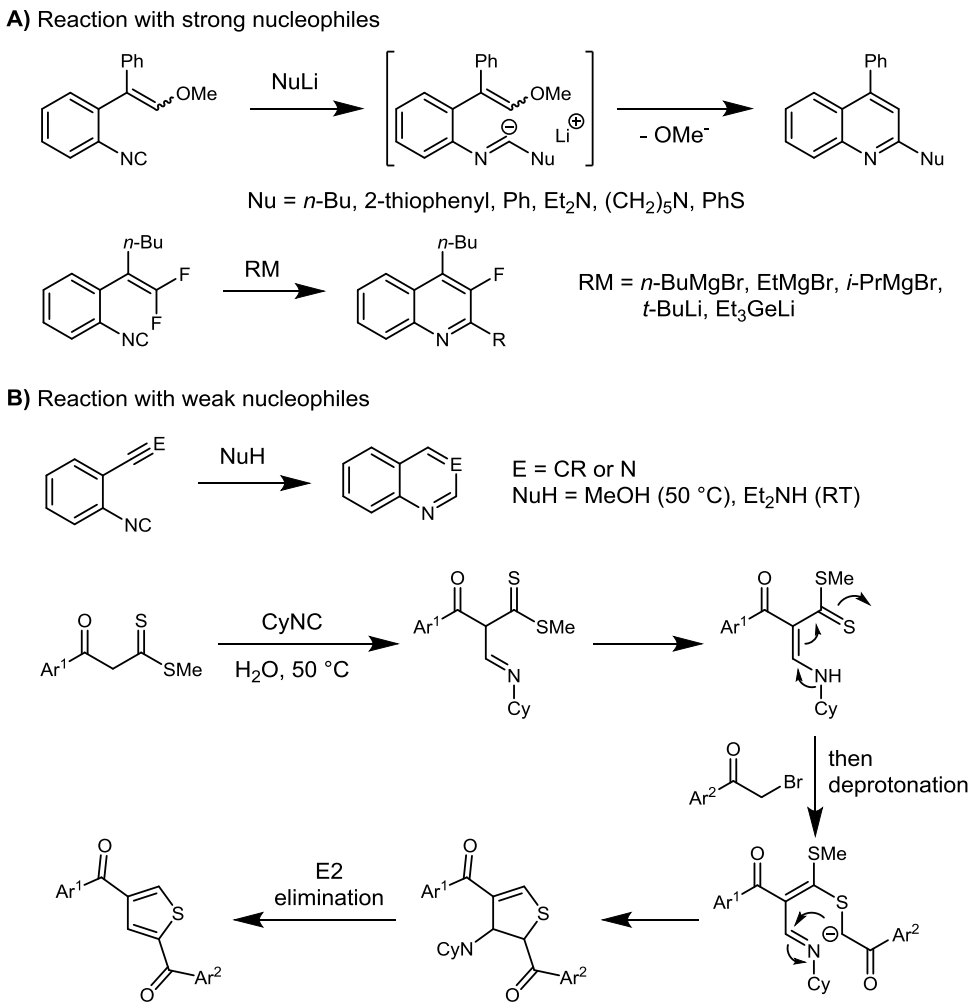


Scheme 1.4 Variations of the Ugi reaction

Isocyanides act as nucleophiles not only for carbonyl compounds and imines (the Passerini reaction and Ugi reaction), but also for activated enone,[34] dialkyl acetylenedicarboxylate,[35] and Knoevenagel intermediate.[36]

Reactions in which isocyanides act as electrophiles are mainly achieved using strong nucleophiles. When an isocyanide group and an activated olefin are located *ortho* to one another on a benzene ring, a Grignard reagent or alkyl lithium reagent

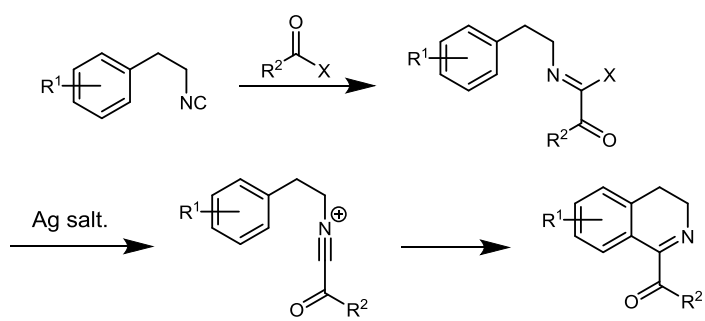
can be used to attack the isocyanide group, followed by cyclization with the olefin to form a quinoline (Scheme 1.5A).[37] Intramolecular nucleophilic attacks on isocyanides have also been developed. When the benzyl C–H bond of an *ortho*-alkylphenyl isocyanide is lithiated, it directly undergoes cyclization to produce an indole.[38] *ortho*-Lithiophenyl isocyanides react with iso(thio)cyanates,[39] carbon dioxide,[40] and ketones[40] to afford the corresponding heterocycles.



Scheme 1.5 Reactions of isocyanides with nucleophiles

The reactivity of isocyanides with weak nucleophiles such as methanol and diethylamine was first reported for *ortho*-alkynylisocyanobenzene and *ortho*-isocyanobenzonitrile, which produced quinoline and quinazoline, respectively (Scheme 1.5B).[41] F. M. Moghaddam and co-workers reported that when a cyclohexyl isocyanide is attacked by a deprotonated β-ketodithoester, a polythiophene is produced (Scheme 1.5B).[42]

The carbenic character of isocyanides can be observed in the presence of acyl halide.[43] After insertion of the isocyanide into the C–Cl bond of an acyl cyanide, an acylnitrilium intermediate can be generated with the aid of a silver salt. T. Livinghouse and co-workers employed 2-ethylphenyl isocyanide to furnish 1-acyl-3,4-dihydroisoquinolines (Scheme 1.6).[43a,43b]

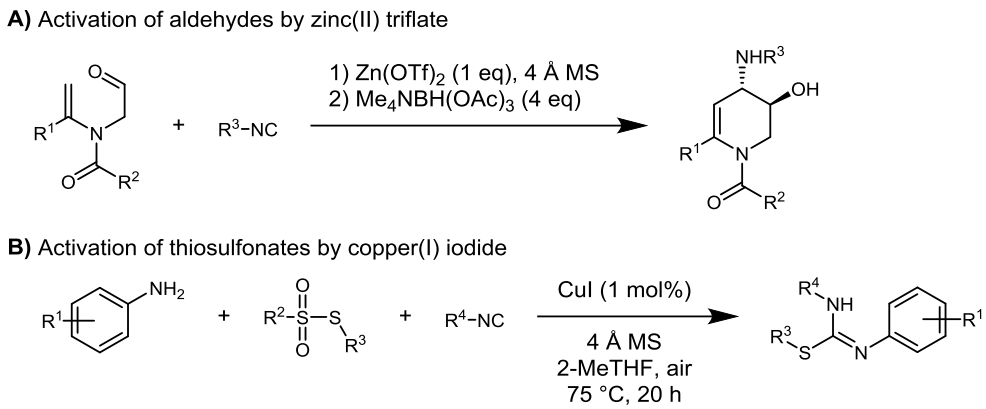


Scheme 1.6 Carbenic reactivity of isocyanides: synthesis of 1-acyl-3,4-dihydroisoquinoline from 2-ethylphenyl isocyanide

1.3.2 Lewis-acid-catalyzed reactions of isocyanides

Activation with a Lewis acid is a well-known strategy to lower the energy of the lowest unoccupied molecular orbital (LUMO) of an electrophile. The use of Lewis acids in reactions involving isocyanides has taken various forms.

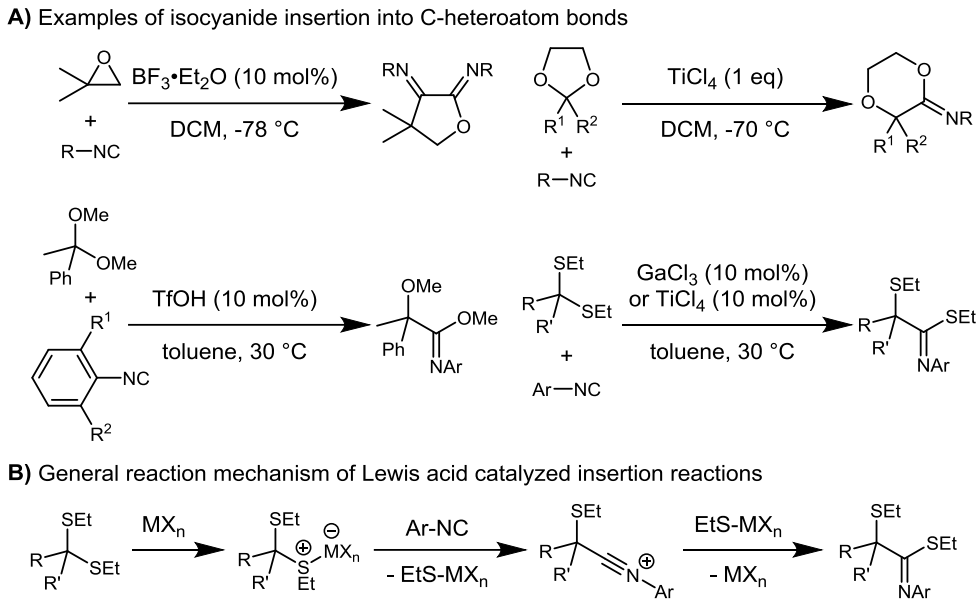
M.–X. Wang and co-workers reported the synthesis of dihydropyridin-4(1*H*)-ones from *N*-formylmethyl-substituted enamides and isocyanides (Scheme 1.7A).[44] In this reaction, an aldehyde activated by zinc(II) triflate is attacked by an isocyanide to produce a nitrilium ion. Subsequent intramolecular attack by an enamine moiety and reduction render the desired heterocycle. The activation of electrophiles can also be utilized in the three-component synthesis of isothioureas from isocyanides, thiosulfonates, and amines developed by B. U. W. Maes and co-workers (Scheme 1.7B).[45] A thiosulfonate activated by copper(I) iodide is attacked by an isocyanide. The resulting isothiocyanate intermediate is then captured by aniline to form an isothiourea. Non-metallic Lewis acids such as boron trifluoride or tris(pentafluorophenyl)boron also afforded the desired product, proving that the copper catalyst acts as a Lewis acid.



Scheme 1.7 Activation of electrophile by Lewis acids

When isocyanides are activated by Lewis acids, their enhanced electrophilicity allows them to react with nucleophiles. T. Saegusa and co-workers observed the cyclization of phenylisocyanide with an internal hydroxy group (–N≡C + HO– → –N=C–O–) in the presence of copper(I) oxide.[46] Similar reactivity was also observed with boron trifluoride, zinc(II) chloride, and tin(IV) chloride.[47]

Several Lewis-acid-catalyzed reactions for the insertion of isocyanides into C–heteroatom bonds including epoxides,[48] cyclic ketals,[49] acyclic ketals,[50] and acyclic dithioketals[51] have also been reported (Scheme 1.8A).[5f] Rather than direct insertion, these reactions proceed via carbocation generation by the Lewis acid, isocyanide attack to form the nitrilium intermediate, and re-incorporation of the leaving group (Scheme 1.8B).[51]

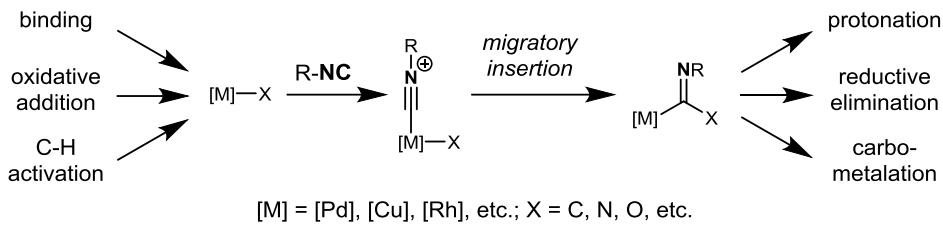


Scheme 1.8 Lewis-acid-catalyzed insertion of isocyanides into C–heteroatom bonds

1.3.3 Transition-metal-catalyzed reactions of isocyanides

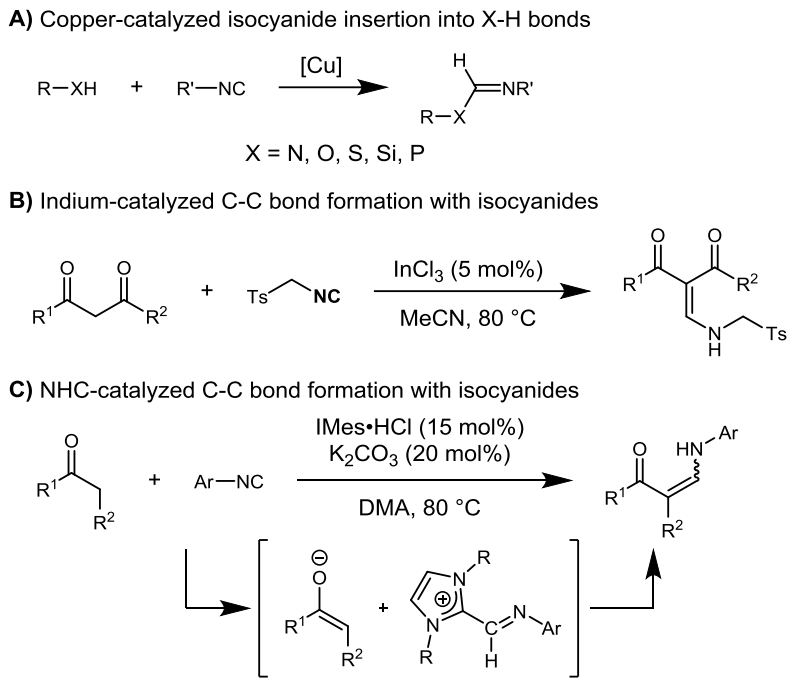
In the presence of a transition metal catalyst, isocyanides easily bind to form nitrilium-like complexes. Hence, the general pathway of reactions involving transition metals resembles that of the reaction of isocyanides with electrophiles, involving the formation of a nitrilium intermediate and subsequent attack by the nucleophile. Nevertheless, the peculiar reactivity of transition metals enriches the practical usage of isocyanides (Scheme 1.9). At the beginning of the catalytic cycle, the coupling partner can be activated in various ways, including oxidative addition or C–H activation, as well as direct binding. After the migratory insertion, the

generated imidoyl metal species can undergo not only protonation, but also reductive elimination or carbometalation of multiple bonds.



Scheme 1.9 General reaction pathway of transition-metal-catalyzed reactions of isocyanides

The simplest reactivity, the binding-protonation sequence, is well documented for nucleophiles including amines,[52] alcohols,[53] thiols,[54] silanes,[55] and phosphines[56] (Scheme 1.10A). Those reactions result in the overall insertion of an isocyanide into the X–H bond. In contrast, the C–C bond formation of isocyanides via this sequence is relatively less explored. P. R. Krishna and co-worker reported that *p*-tosylmethyl isocyanides couple with 1,3-dicarbonyl compounds in the presence of indium(III) chloride (Scheme 1.10B).[57] Palladium catalyzed reactions with indole were also reported.[58] Recently, S. H. Hong and co-worker discovered that an N-heterocyclic carbene (NHC), 1,3-bis(2,4,6-trimethylphenyl)imidazole (IMes), catalyzes the coupling reaction between isocyanides and enolates (Scheme 1.10C).[59] Unlike in transition metal catalysis, IMes attacks the isocyanide to form a reactive intermediate. Reaction between this intermediate and the enolate gives an enaminone.



Scheme 1.10 Reactions involving simple binding of coupling partners

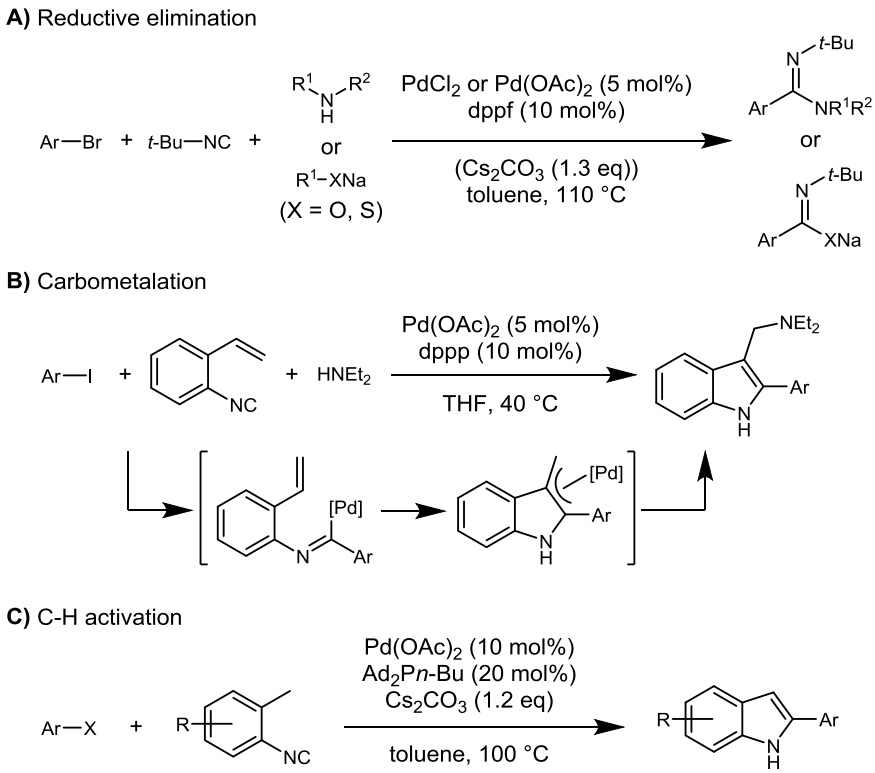
Aryl halides or alkenyl halides can be incorporated with isocyanides through oxidative addition mediated by palladium catalysts. In 1986, M. Kosugi and co-workers developed the coupling reaction of bromobenzene, isocyanides, and organotin compounds.[60] The imidoyl palladium species derived from bromobenzene and the isocyanide undergoes reductive elimination with the organotin compound. However, this reaction suffers from low yields and requires the use of toxic reagents. Subsequently, more practical reaction conditions began to be developed using more general nucleophiles, such as amines,[61] alkoxides,[62] and thiolates,[62] rather than organotin reagents (Scheme 1.11A). Alkenyl bromide participates in the reaction

with amines to afford α,β-unsaturated aldimines.[63] The use of water as the nucleophile gave an amide;[64] meanwhile, internal nucleophiles enabled the constuction of heterocycles such as cyclic aldimines,[65] 4-aminoquinazolines,[66] quinazolin-4(3*H*)-imines,[67] and 4-aminophthalazin-1(2*H*)-ones.[68]

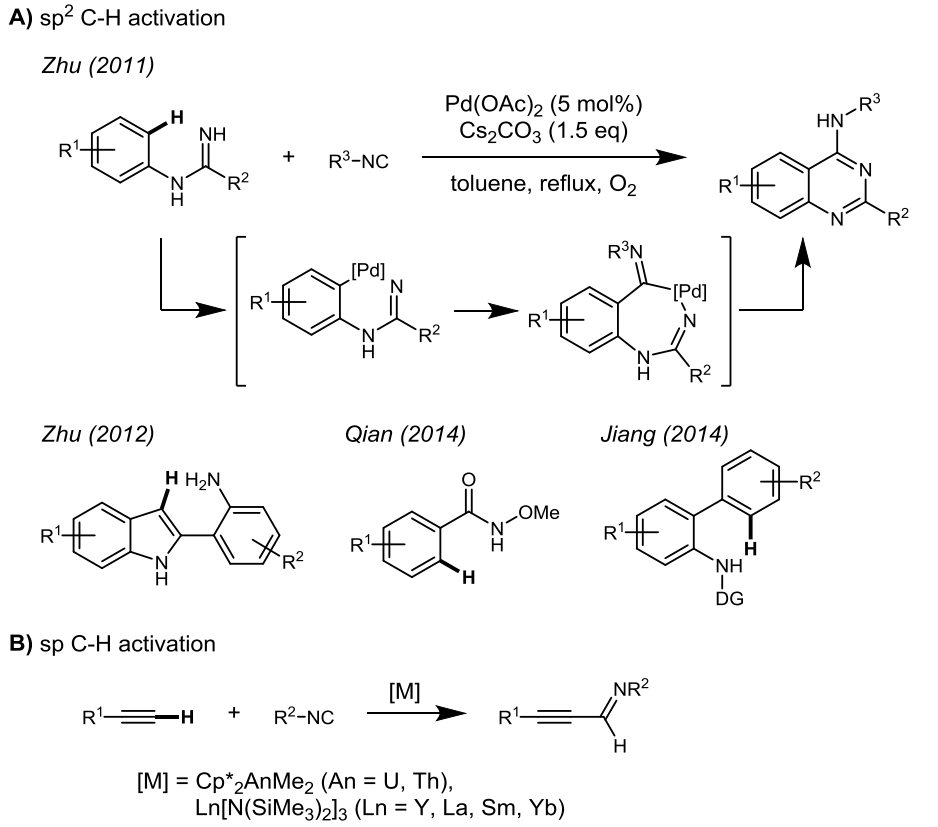
Instead of reductive elimination, the attached palladium can undergo either carbometalation or C–H activation. S. Takahashi and co-workers reported that *o*-alkenylphenyl isocyanides undergo palladium-catalyzed carbometalation and reductive elimination after migratory insertion (Scheme 1.11B).[69] A similar reaction pathway occurs with *o*-alkynylphenyl isocyanides.[70] If a C–H bond is located in the proper position with respect to the imidoyl-palladium species, further C–H activation will furnish the cyclized product (Scheme 1.11C).[70]

C–H activation can be an initial step in reactions involving isocyanides.[5h] Q. Zhu and co-workers reported that 4-aminoquianozlines can be synthesized from *N*-arylamidines via sequential sp^2 C–H activation, isocyanide insertion, and reductive elimination (Scheme 1.12A). [71] Many other substrates with different directing groups were successfully explored by Q. Zhu,[72] Y. Qian,[73] H. Jiang,[74] and others.[75] Isocyanide insertions into sp C–H bonds using rare-earth metals such as uranium, thorium, yttrium, lanthanum, samarium, and ytterbium have been studied (Scheme 1.12B).[76] The basic ligand bound to the metal center deprotonates the sp C–H bond so that the alkynyl group is ligated to the metal. After isocyanide insertion, the imidoyl metal complex deprotonates the next substrate and regenerates the original complex, producing enynes.

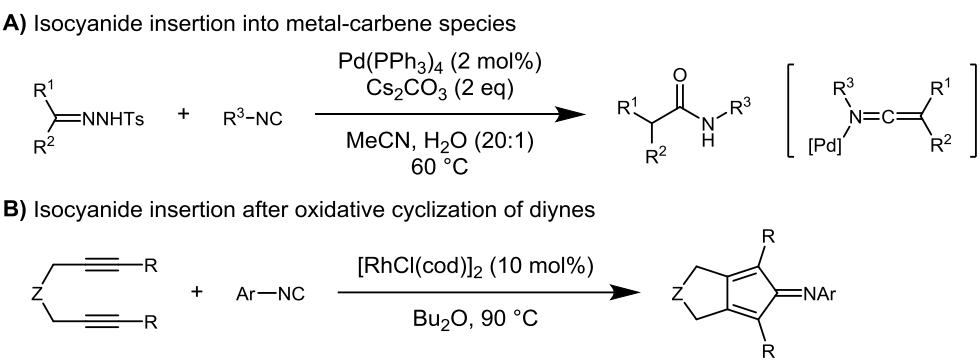
Additionally, the insertion of isocyanides into palladium carbene species (Scheme 1.13A)[77] or palladacycles derived from the oxidative cyclization of a diyne (Scheme 1.13B)[78] has also been reported.



Scheme 1.11 Reactions beginning with the oxidative addition of an aryl halide: classification via the later isocyanide insertion step



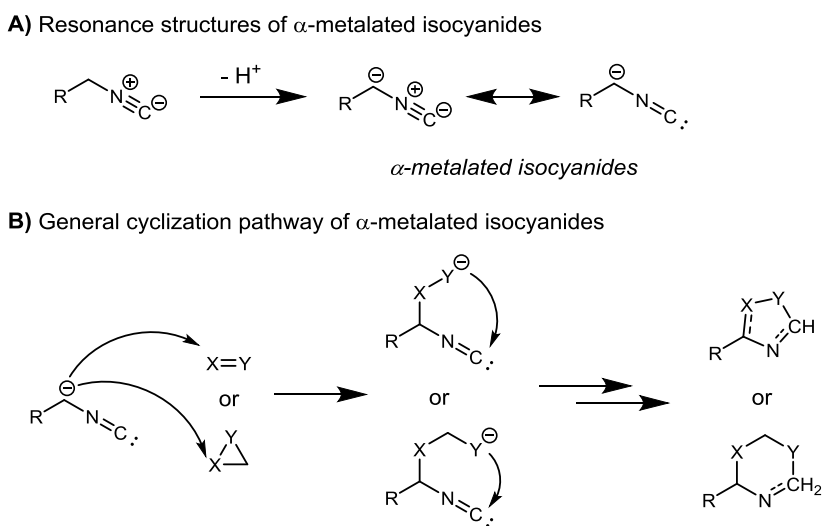
Scheme 1.12 Reactions beginning with the C–H activation of the substrate: classification by the hybridization of the C–H bond



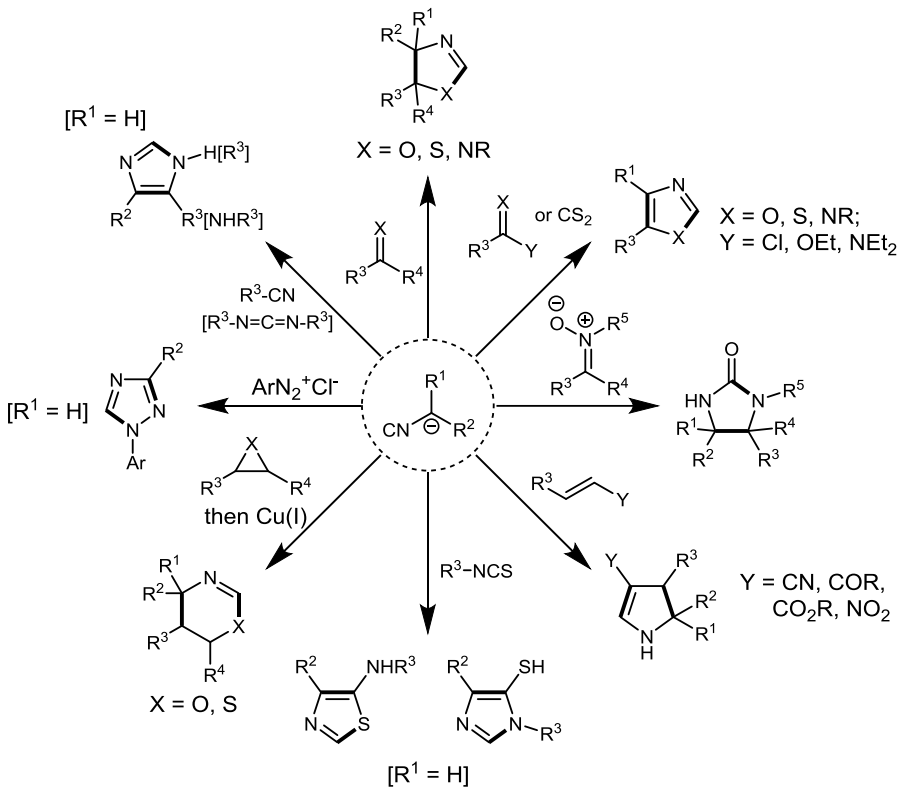
Scheme 1.13 Miscellaneous examples of isocyanide insertions

1.3.4 Reactivity of α-metalated isocyanides

As demonstrated by their resonance structures (Scheme 1.2A), the nitrogen atoms of isocyanides are electron-poor, and thus act as strong electron withdrawing groups. Hence, the α-C–H bonds of isocyanides can easily be deprotonated to form a 1,3-dipole-like structure (Scheme 1.14A). Naturally, α-metalated isocyanides participate in the syntheses of various heterocycles.[5a,79] Initially, the α-carbanion of the isocyanide attacks an unsaturated compound (atom X is attacked in the scheme; Scheme 1.14B). The resulting anion (atom Y) then attacks the carbon atom of the isocyanide. Subsequent steps, which vary depending on the substrate, finally render the cyclic compound. A. de Meijere and co-worker summarized representative examples in their review paper (Scheme 1.15).[5a]



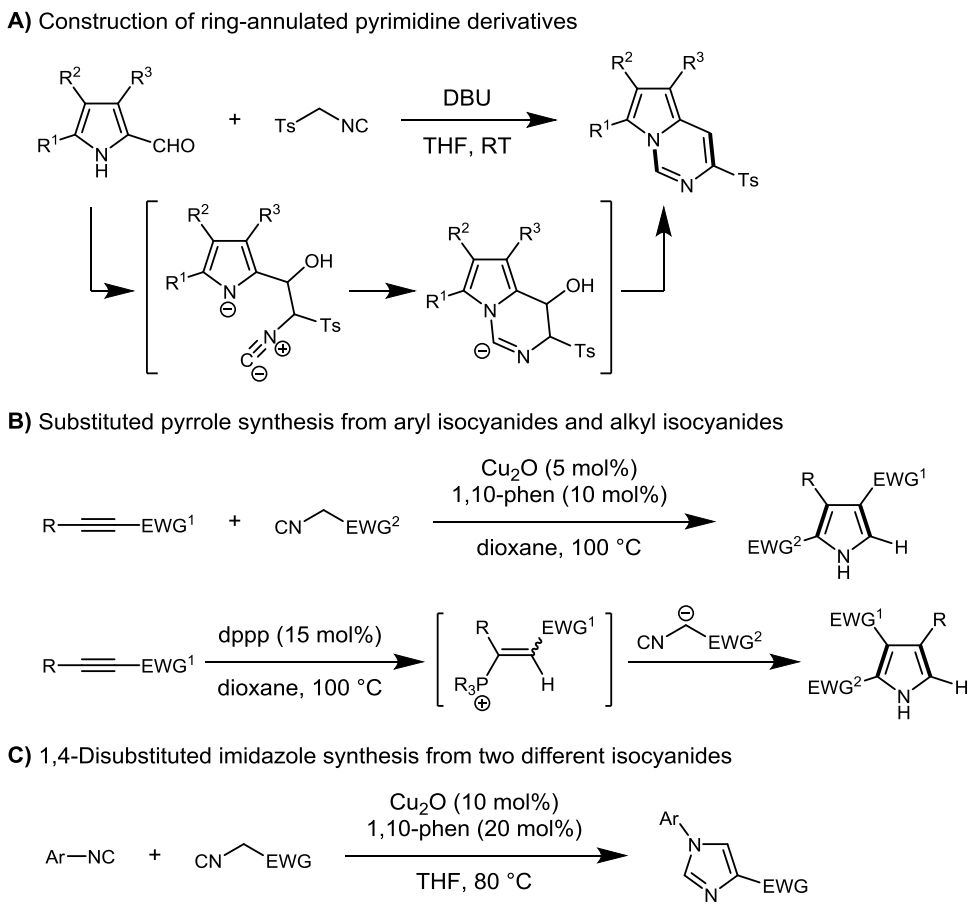
Scheme 1.14 General reactivity of α-metalated isocyanides



Scheme 1.15 Representative reactions of α-metalated isocyanides[5a]

Syntheses of heterocycles with exotic coupling partners via the pathway described above are depicted in Scheme 1.16. J. Alvarez-Builla and co-workers reported the construction of a ring-annulated pyrimidine derivative from pyrrole-2-carboxaldehyde (Scheme 1.16A).[80] After the addition of an α-metalated isocyanide, proton transfer, intramolecular nucleophilic attack, and dehydration gave a fused ring system. Similar reactivity was reported by J. J. Vaquero and co-workers for N-protected bromomethylazoles.[81] Y. Yamamoto and co-workers discovered that activated alkynes are coupled with α-metalated isocyanides to form pyrrole in the

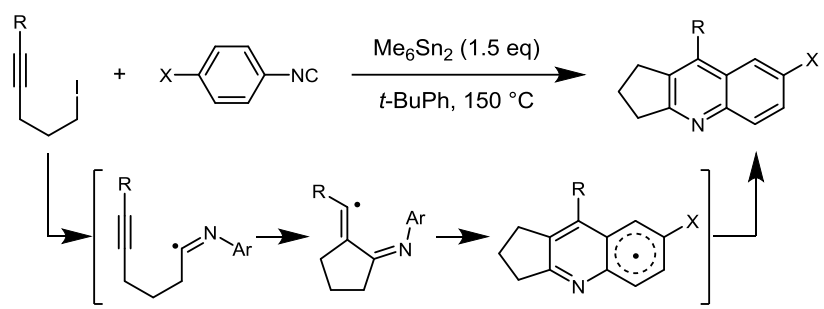
presence of copper(I) oxide and 1,10-phenanthroline (Scheme 1.16B).[82] Surprisingly, the use of a catalytic amount of 1,3-bis(diphenylphosphino)propane (dppp) gave inverse regioselectivity due to the generation of a cationic intermediate from the activated alkyne and phosphine. Under copper-catalyzed reaction conditions, a 1,4-disubstituted imidazole was synthesized when another isocyanide molecule was employed as a coupling partner (Scheme 1.16C).[83]



Scheme 1.16 Examples of α-metalated isocyanides with exotic coupling partners

1.3.5 Radical reactions of isocyanides

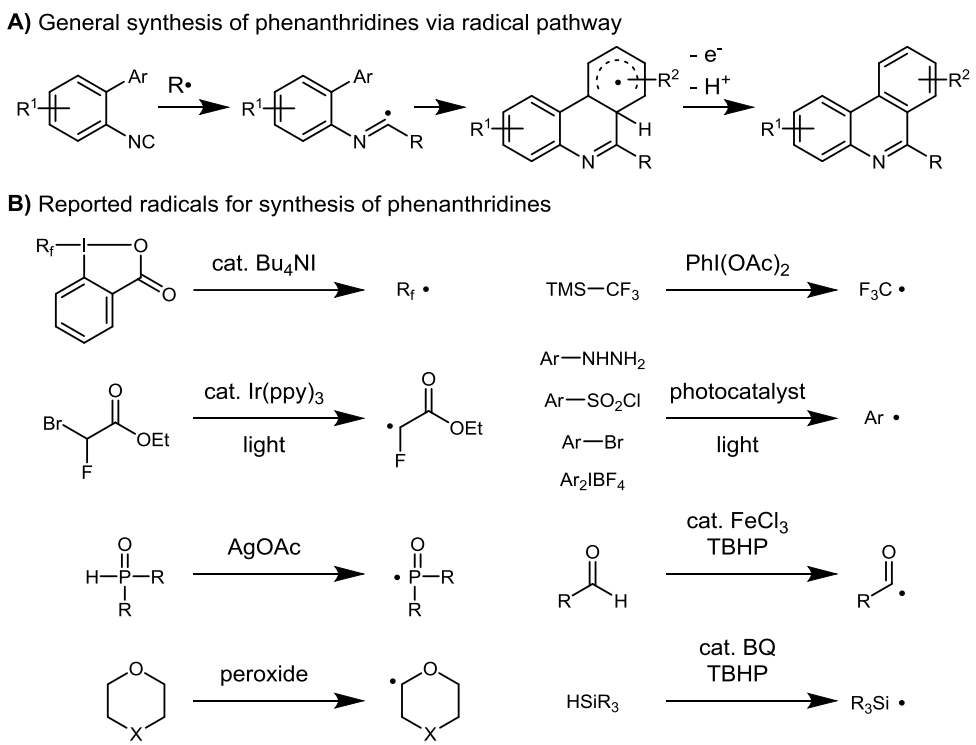
Compared to other strategies for the activation of isocyanides, the development of radical pathways has been relatively slow. In 1968, the first observation of radical addition to isocyanides was made by T. Saegusa and co-workers with a tin radical.[84] In 1991, D. P. Curran and co-worker reported the first example of heterocycle synthesis via a radical pathway (Scheme 1.17).[85] In this pathway, a primary alkyl radical generated by hexamethylditin attacks the carbon atom of the isocyanide group, and a carbon-centered radical is formed at the same atom. A radical cascade reaction through alkyne and arene rings produces cyclopenta-fused quinolones.



Scheme 1.17 First synthesis of heterocycle from isocyanides via a radical pathway

Radical reactions of isocyanides have mainly focused on the synthesis of phenanthridine derivatives from 2-isocyanobiphenyls following the general reaction pathway illustrated in Scheme 1.18A. The imidoyl radical generated from radical addition to the isocyanide undergoes addition to the neighboring arene ring. Successive one-electron oxidation and deprotonation afford the phenanthridine. Versatile derivatives can be produced by changing the radical added; examples include the perfluoroalkyl radical, trifluoromethyl radical, ethyl fluoroacetyl radical, aryl radical, phosphoryl radical, acyl radical, α-oxyalkyl radical, and silyl radical

(Scheme 1.18B).[5g] One-electron oxidants or peroxides for hydrogen atom transfer (HAT) have been used for radical generation, but recently, photocatalytic methods have become widely used to avoid the use of a stoichiometric amount of the radical initiator.



Scheme 1.18 Synthesis of phenanthridines from isocyanides via a radical pathway

When the starting material is changed from a 2-isocyanobiphenyl to a 2-alkenyl/alkynyl aryl isocyanide, β-isocyanostyrenes and arylisocyanides with γ-bromonitrile, indoles,[86] isoquinolines,[87] and quinoxalines[88] can be furnished, respectively.

1.4 Conclusion

Despite their unpleasant odor, isocyanides have become irreplaceable organic building blocks due to their unique reactivity as electrophiles, nucleophiles, and carbenes. By combining activated substrates with isocyanides, highly efficient and robust IMCRs have been developed without further activating reagents. Owing to their ability to construct diverse and complex structures, they have attracted great attention in applied chemistry. Other activation strategies, such as Lewis acid catalysts, transition metal catalysts, α-metalation of isocyanides, and radical pathways, have further widened the applicability of isocyanides. In particular, the synthesis of heterocycles from isocyanides has been extensively studied.

Activation strategies other than non-catalyzed IMCRs have mainly been used for the construction of heterocycles. The insertion of isocyanides into C–heteroatom bonds to afford acyclic compounds has been widely studied, but synthetically useful reactions of this type have been less explored. In particular, reactions with soft carbon nucleophiles (stabilized carbanions) are quite limited[57-59] compared to other nucleophiles. Thus, the development of synthetic methods for acyclic compounds from isocyanides still requires further exploration. Most known radical reactions with isocyanides utilize two reaction components. Hence, the development of IMCRs via a radical pathway with three or more components is also a remaining challenge.[5g]

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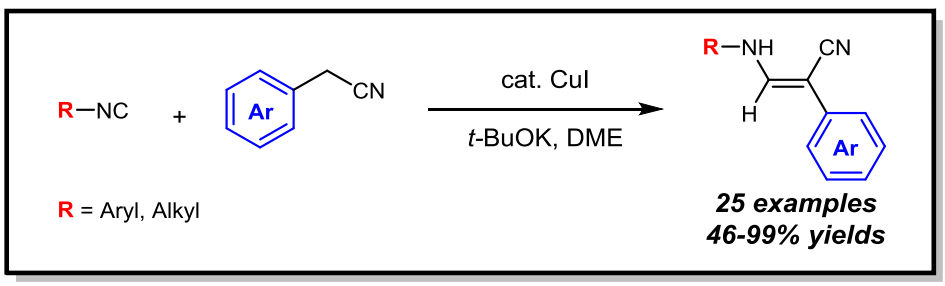
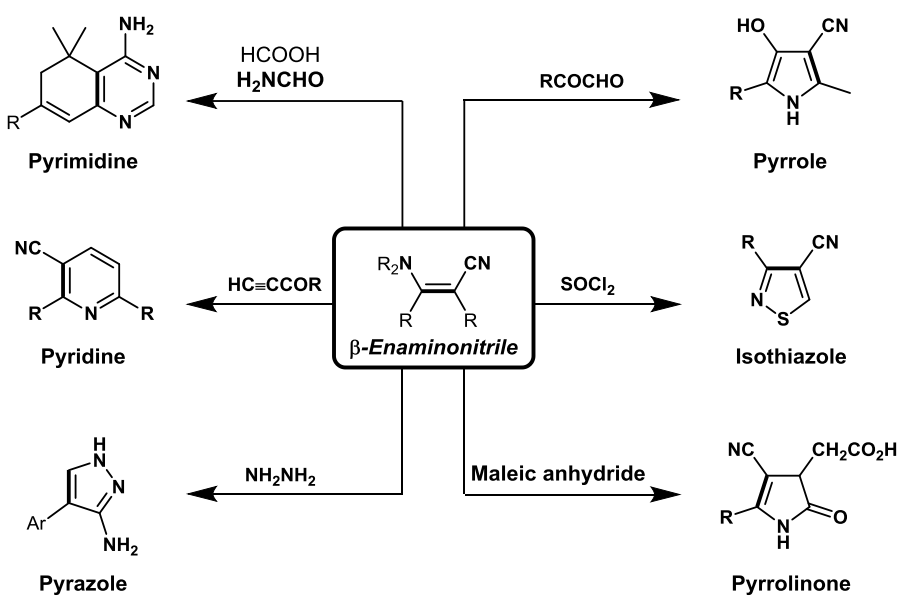
Chapter 2. Copper-Catalyzed *N*-Aryl-β-Enaminonitrile Synthesis Utilizing Isocyanides as the Nitrogen Source*



* The majority of this work has been published: Seoksun Kim and Soon Hyeok Hong*, *Adv. Synth. Catal.* **2015**, *357*, 1004-1012.

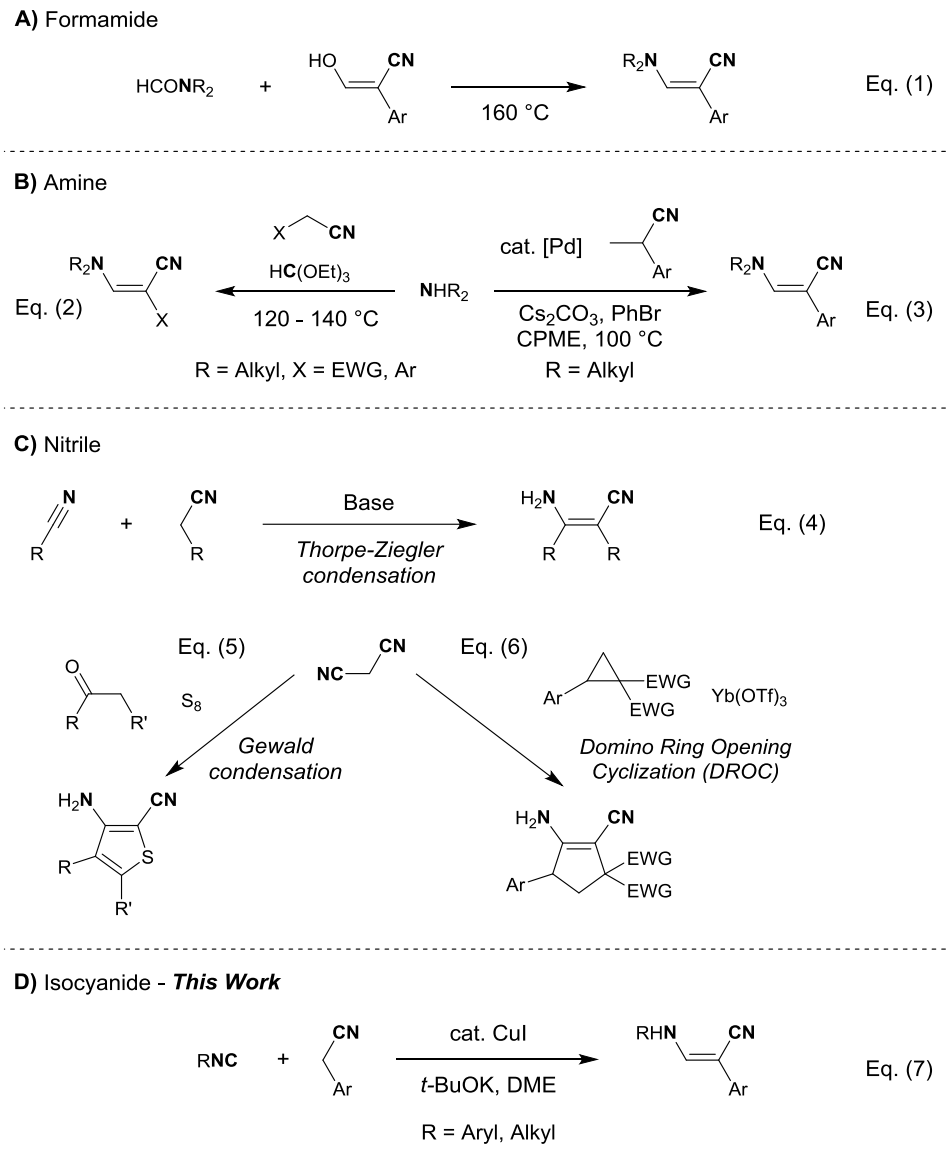
2.1 Introduction

For several decades, the β-enaminonitrile group has been highlighted as a useful building block for the synthesis of heterocycles[1] such as pyrimidine,[2] pyridine,[3] pyrazole,[4] pyrrole,[5] isothiazole,[6] and pyrrolinone[7] (Scheme 2.1). This building block has also been applied to the synthesis of polymers such as thermally stable poly(enaminonitrile)s[8] and pharmaceutical chemistry.[9] Because of its importance, diverse aspects of β-enaminonitrile have been studied, such as tautomerization,[10] isomerization,[11] and photochemical reactions.[12]



Scheme 2.1 Synthesis of diverse heterocycles from β-enaminonitrile

Despite the importance of the β-enaminonitriles, limited methods have been reported for their synthesis. Traditionally, β-enaminonitriles have been synthesized by the condensation of formamide with arylformylacetonitriles [Scheme 2.2, eq 1],[13] or ammonia with cyanoacetophenone.[14] Moreover, amines and activated acetonitriles can serve as starting materials for the synthesis of β-enaminonitriles in the presence of triethyl orthoformate [Scheme 2.2, eq 2].[1b] However, the abovementhioned methods usually require harsh conditions. Thorpe–Ziegler condensation [Scheme 2.2, eq 4][15] and Gewald condensation [Scheme 2.2, eq 5],[16] which use nitriles as the nitrogen source, require mild conditions; however, the substrate scope is limited to *N*-unsubstituted-β-enaminonitriles and thiophene derivatives. To broaden the substrate scope of β-enaminonitriles, Pd-catalyzed tandem reactions [Scheme 2.2, eq 3][17] and domino ring-opening cyclization reactions [Scheme 2.2, eq 6][18] have been recently reported. Although various synthetic methods are available, the substrate scope of β-enaminonitriles is still poor, and nitrogen sources were limited to formamides, amines, and nitriles. In particular, examples of aryl-substituted enaminonitrile synthesis are quite rare with a narrow substrate scope and harsh reaction conditions.[10b,19]



Scheme 2.2 Synthetic methods for β-enaminonitriles classified according to nitrogen sources

To develop an efficient synthetic method for *N*-aryl-β-enaminonitriles, we turned our attention to isocyanides. Since the Ugi reaction was reported,[20] extensive studies have been carried out to utilize isocyanides in organic synthesis, such as heterocycle synthesis.[21] Recently we developed a method for 1,4-diarylimidazole synthesis[22] based on Cu-catalyzed formimidate formation from isocyanides.[23] Thus, we envisioned a novel strategy for the synthesis of β-enaminonitriles from isocyanides as the nitrogen source [Scheme 2.2, eq 7]. To the best of our knowledge, this is the first example of *N*-aryl-β-enaminonitrile synthesis using isocyanides as the nitrogen source.

2.2 Results and discussion

2.2.1 Optimization for the synthesis of β-enaminonitrile from isocyanides and benzylcyanides

We started our investigation by adapting the reaction conditions involving the N-heterocyclic carbene (NHC)-based Cu(I) species developed for 1,4-diarylimidazole synthesis.[22] To our delight, the target compound was obtained in 49% yield (Table 2.1, entry 1). The absolute configuration of the alkene was determined by X-ray crystallography (Figure 2.1).[24] Among the solvents investigated, dimethoxyethane (DME) resulted in the best yield (Table 2.1, entries 1–4). The reaction worked well in the absence of the NHC ligand and was optimized further without any additional

ligand (Table 2.1, entry 5). A strong base such as *t*-BuOK was essential for the reaction (Table 2.1, entries 6 and 7). When Cu(I) halides were screened with 1.2 equiv of *t*-BuOK, CuI resulted in quantitative yield (Table 2.1, entries 7–9). The reaction without Cu catalyst also gave the desired product, but it exhibited the much decreased yield (Table 2.1, entry 10). In this case, a dimer of benzylcyanide, (*Z*)-3-amino-2,4-diphenylbut-2-enenitrile, from Thorpe-Ziegler condensation was observed as the major by-product in 31% yield.[25]

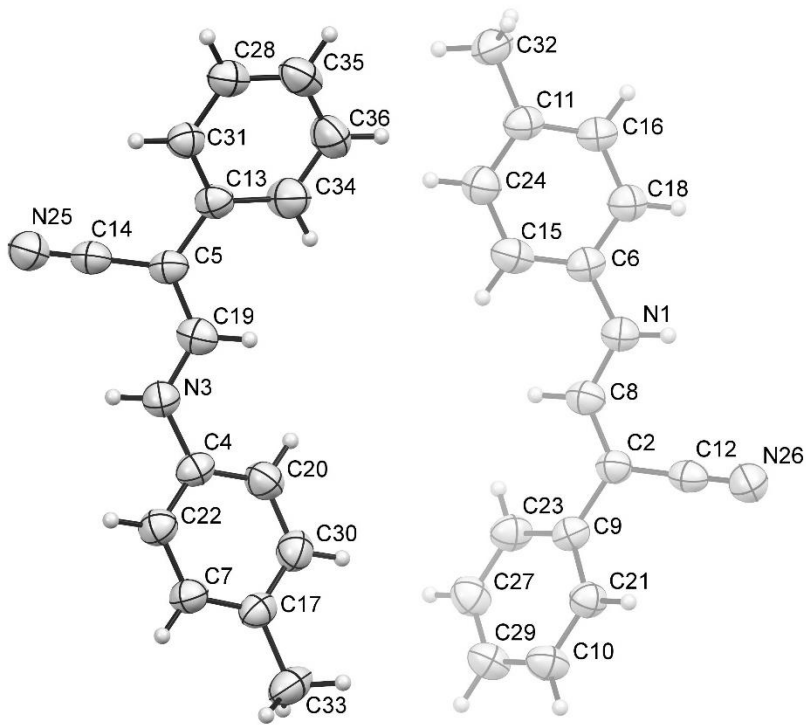
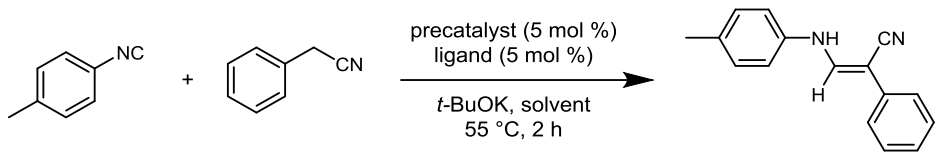


Figure 2.1 Crystal structure of **3aa**. ORTEP diagram showing 50% probability thermal ellipsoids.

Table 2.1 Optimization of the reaction conditions[a]



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

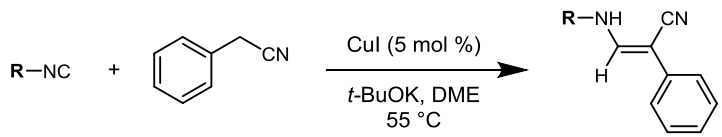
Entry	Catalyst	Ligand	Base (equiv)	Solvent	Yield (%)[b]
1	CuCl	IPr·HCl	0.5	THF	44
2	CuCl	IPr·HCl	0.5	DCM	0
3	CuCl	IPr·HCl	0.5	Benzene	29
4	CuCl	IPr·HCl	0.5	DME	55
5	CuCl	-	0.5	DME	40
6	CuCl	-	0	DME	0
7	CuCl	-	1.2	DME	93
8	CuBr	-	1.2	DME	98
9[c]	CuI	-	1.2	DME	>99
10	-	-	1.2	DME	60

[a] *Reaction conditions:* **1a** (0.2 mmol, 1.0 equiv), **2a** (0.28 mmol, 1.4 equiv), catalyst (0.01 mmol), ligand (0.01 mmol), *t*-BuOK (x equiv) in solvent (0.4 mL). IPr·HCl = 1,3-bis(2,6-diisopropylphenyl)imidazolium chloride.
[b] Yields were determined by HPLC using 2,6-diisopropylaniline as the internal standard.
[c] Reaction time: 8 h.

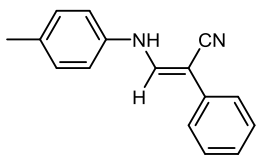
2.2.2 Substrate scope of isocyanides

With the optimized reaction conditions in hand, we investigated the substrate scope of the reaction. First, the isocyanides used in the reaction were varied (Table 2.2). In most of the cases, *N*-aryl-β-enaminonitriles were obtained in good-to-excellent yields. The reaction worked well even with sterically hindered isocyanides (**3ca**–**3fa** and **3oa**). Even stronger electron-withdrawing group substituted isocyanides worked smoothly (**3ga**–**3ka**). The reaction showed good functional group tolerance to aryl–halogen bonds (**3ga**, **3ha**, and **3ma**), ester group (**3ia**), nitrile group (**3ja**), pyridine (**3ka**), and ether group (**3la**). 3-Pyridylisocyanide resulted in only a moderate yield, probably because of its coordinating ability. Gratifyingly, alkylisocyanides also participated in the reaction (**3oa**–**3qa**).

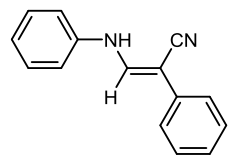
Table 2.2 Substrate scope of isocyanides[a]



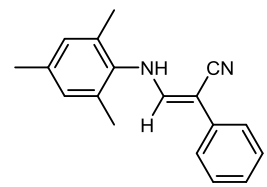
1 **2a** **3**



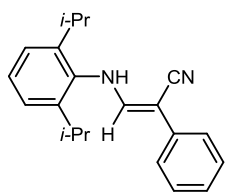
3aa
8 h, 94%



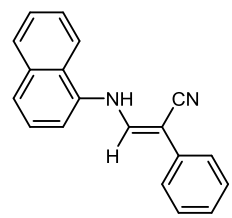
3ba
8 h, 94%



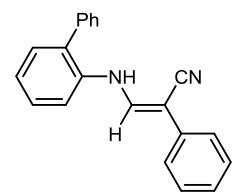
3ca
8 h, 88%



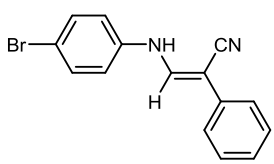
3da
8 h, 85%



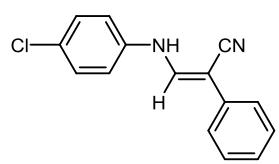
3ea
8 h, 85%



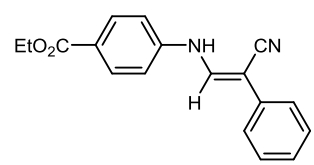
3fa
16 h, 70%



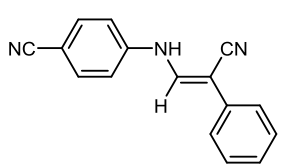
3ga
16 h, 97%



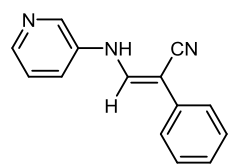
3ha
8 h, 86%



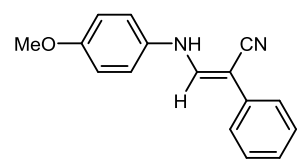
3ia
16 h, 77%



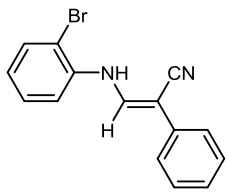
3ja
8 h, 76%



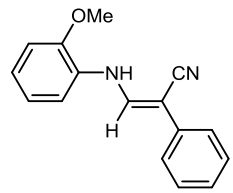
3ka
8 h, 46%



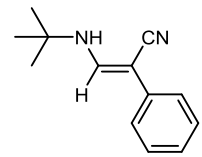
3la
8 h, 82%



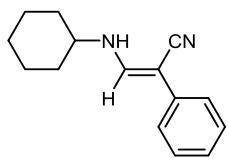
3ma
16 h, 69%



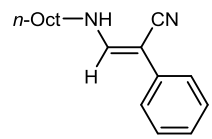
3na
8 h, 90%



3oa
16 h, 73%



3pa
16 h, 66%



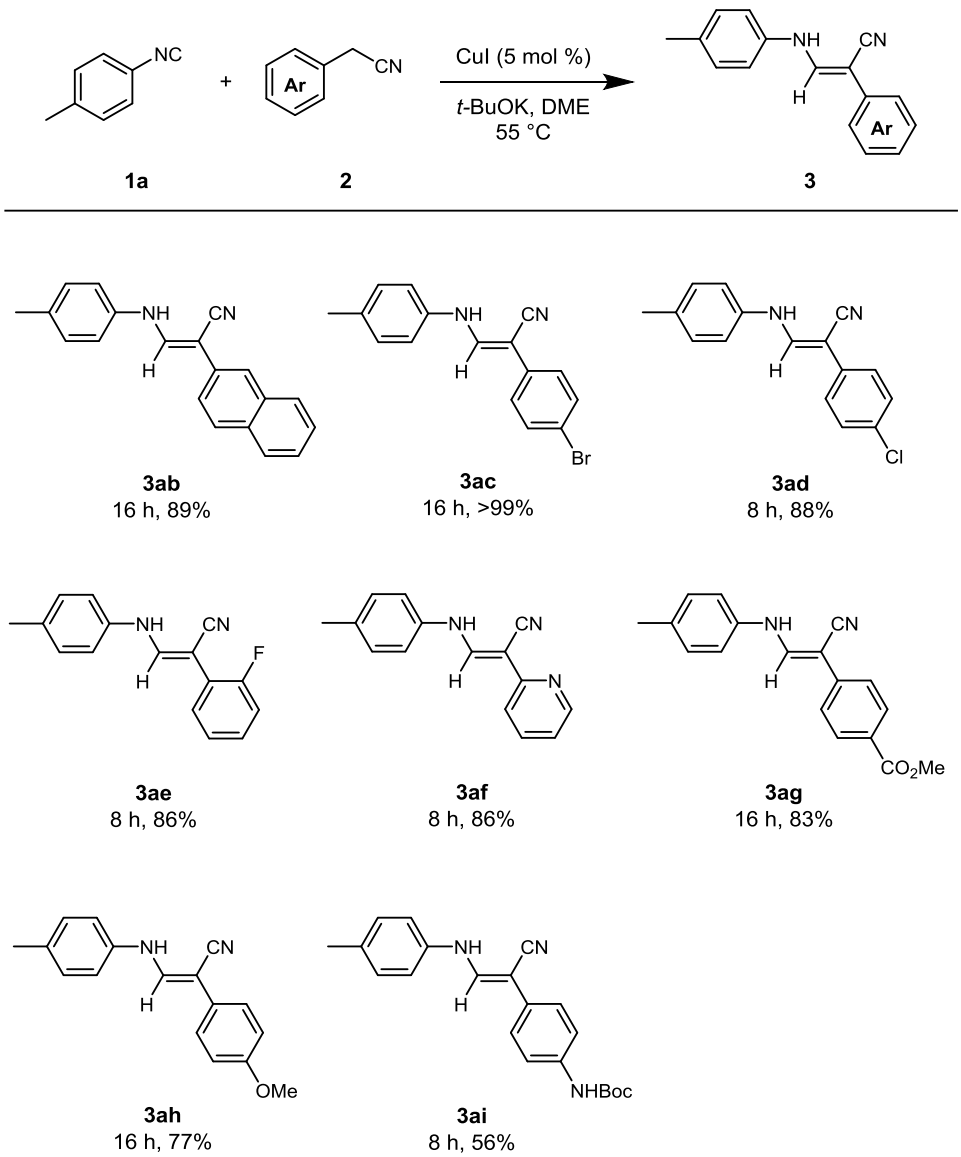
3qa
16 h, 60%

[a] *Reaction conditions:* **1** (0.40 mmol), **2a** (0.56 mmol), CuI (0.02 mmol), *t*-BuOK (0.48 mmol) in DME (0.8 mL) at 55 ℃.

2.2.3 Substrate scope of arylacetonitriles

Next, the scope of arylacetonitriles was investigated (Table 2.3). Similar to isocyanides, arylacetonitriles showed a broad substrate scope with good-to-excellent yields. 2-Naphthylacetonitrile afforded the corresponding product (**3ab**) in a very good yield. Electron-withdrawing substituents on the aryl group showed negligible effect on the yields (**3ac**–**3ag**), while electron-donating substituents on the aryl group resulted in reduced yields, probably because of the destabilization of the arylacetonitrile anion (**3ah** and **3ai**). As shown in Table 2.3, functional groups such as aryl–halogen bonds (**3ac**–**3ae**), ester group (**3ag**), and boc-protected amine group (**3ai**) were well tolerated. Interestingly, 2-pyridylacetonitrile resulted in an excellent yield, while 3-pyridylisocyanide resulted in a moderate yield (**3af** and **3ka**).

Table 2.3 Substrate scope of arylacetonitriles[a]

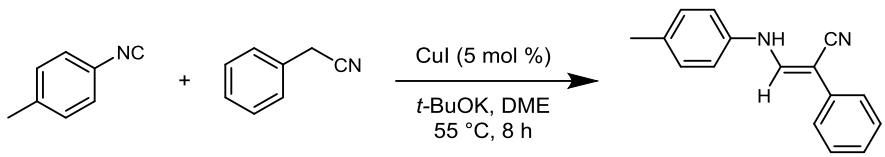


[a] *Reaction conditions:* **1a** (0.40 mmol), **2** (0.56 mmol), CuI (0.02 mmol), *t*-BuOK (0.48 mmol) in DME (0.8 mL) at 55 ℃.

2.2.4 Mechanistic studies

Effect of the Cu catalyst and the base was further examined in order to obtain mechanistic insight for the reaction (Table 2.4). Several Lewis acids were tested, and none of them exhibited enhanced reactivity even compared to the base-only reaction conditions (Table 2.4, entries 2–5). The results suggest that CuI do not act as a simple Lewis acid in this reaction.[26] Various kinds of bases were also screened. Cesium carbonate, which is not strong enough to deprotonate the benzylic proton of benzylcyanide, gave the product in a poor yield of 14% (Table 2.4, entry 7). Other strong bases exhibited only moderate yields, even with CuI (Table 2.4, entries 8–10). These results indicated that *t*-BuOK has another role aside from simple deprotonation of benzylcyanides.

Table 2.4 Effect of catalyst and base[a]



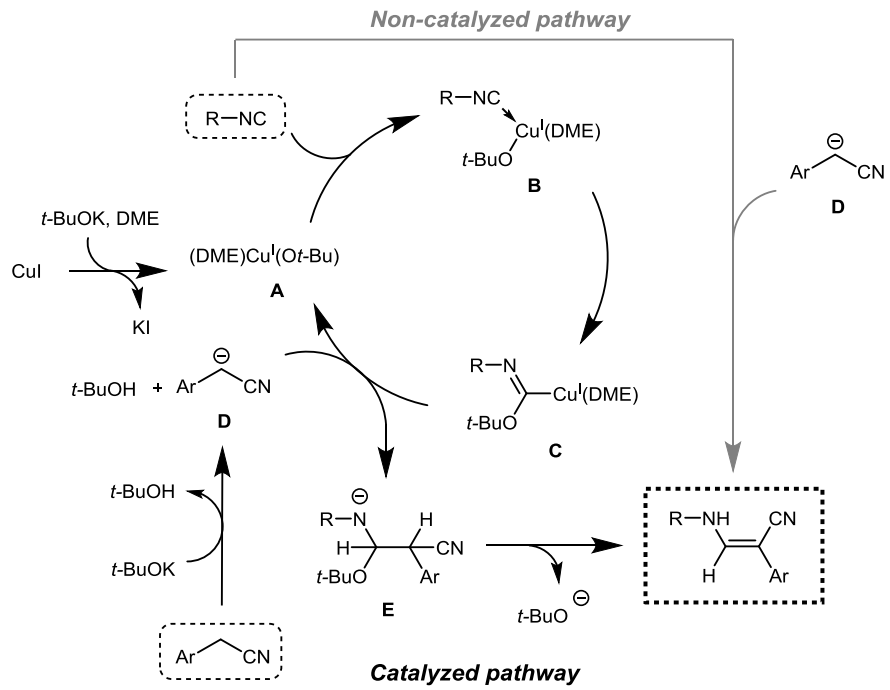
1a **2a** **3aa**

Entry	Variation from standard conditions	Yield (%)[b],[c]
1	None	>99
2	Without catalyst	60
3	$Sc(OTf)_3$ instead of CuI	45
4	AgOTf instead of CuI	61
5	$BF_3 \cdot OEt_2$ instead of CuI	53
6	$FeBr_2$ instead of CuI	56
7	Cs_2CO_3 instead of *t*-BuOK	14
8	NaH instead of *t*-BuOK	59
9	KHMDS instead of *t*-BuOK	55
10	NaOMe instead of *t*-BuOK	57

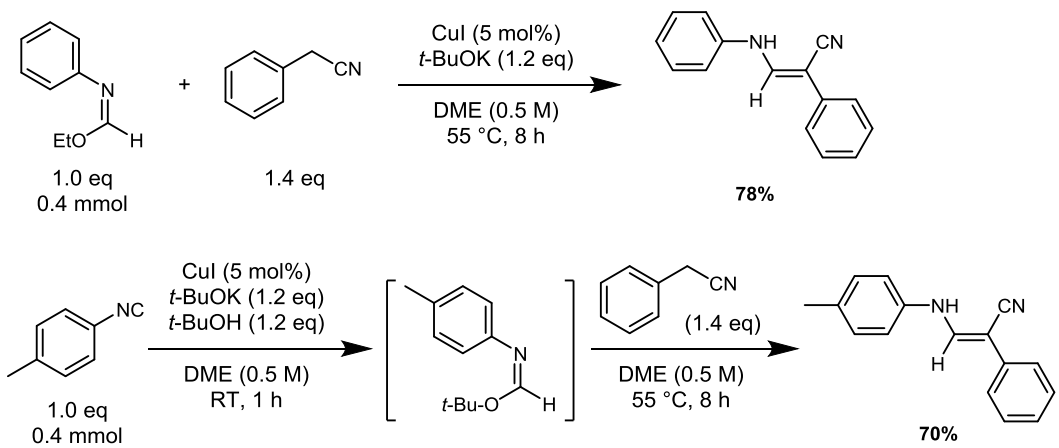
[a] *Reaction conditions:* **1a** (0.20 mmol, 1.0 equiv), **2a** (0.28 mmol, 1.4 equiv), CuI (0.01 mmol), *t*-BuOK (0.24 mmol, 1.2 equiv) in solvent (0.4 mL). [b] Yields of entries 1–6 were determined by HPLC using 2,6-diisopropylaniline as the internal standard. [c] Yields of entries 7–10 were determined by NMR using mesitylene as the internal standard.

Based on the experimental results and our previous study,[22] a possible mechanism is suggested (Scheme 2.3). Because of the enhancement in yields when coordinating solvents, such as THF and DME, were used (Table 2.1) and the fact that the (DME)Cu^{I} complex has been reported as a long-lived stable complex,[27] (DME)Cu^{I}(O*t*-Bu) (**A**) is proposed as the active catalytic species in this reaction. An isocyanide can coordinate to this species to form the 18-electron Cu(I) complex (**B**). Because of the innate electrophilic character of an isocyanide–metal complex,[21b] *tert*-butoxide ligand can attack the carbon atom of the isocyanide group of **B** to generate imidoyl-Cu complex, **C**. Deprotonated benzylcyanide (**D**), *t*-BuOH, and **C** react to afford intermediate **E** with the regeneration of (DME)Cu^{I}(O*t*-Bu) (**A**), thus completing the catalytic cycle. Finally, successive *tert*-butoxide elimination and tautomerization afford the desired *N*-substituted β-enaminonitrile.

To confirm the mechanism further, readily available ethyl formimidate and in situ generated *tert*-butyl formimidate were subjected to the reaction conditions. The desired products were afforded in good yields, supporting the proposed mechanism (Scheme 2.4). The slightly reduced yields than starting from isocyanides is presumably due to the reactivity difference between the in situ generated formimidate intermediates that stay coordinated to Cu and free formimidates. Direct reaction between an isocyanide and **D** could work, especially under base only conditions. However, in our Cu-catalyzed conditions, we believed that the proposed formimidate mechanism is more reasonable judging from the observation of special effect of *t*-BuOK in Table 2.4.



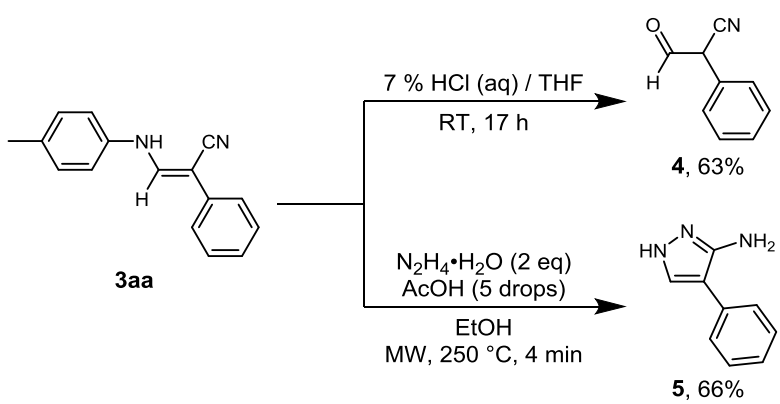
Scheme 2.3 Proposed reaction mechanism



Scheme 2.4 Reactions of formimidates

2.2.5 Application of β-enaminonitrile

The synthesized β-enaminonitrile **3aa** could be transformed to other synthetically useful products under simple reaction conditions (Scheme 2.5).[17] *p*-Toluidine group of **3aa** could be hydrolysed to form a β-keto nitrile **4**.[28] In addition, 3-aminopyrazole (**5**) could be synthesized from **3aa** through an acid-catalyzed reaction with hydrazine.[19a]



Scheme 2.5 Transformation of β-enaminonitrile **3aa**

2.3 Conclusion

In conclusion, we report a novel Cu-catalyzed *N*-aryl-β-enaminonitrile synthesis from isocyanides and nitriles. A broad scope of *N*-aryl-β-enaminonitriles, which were not easily accessible with previously reported synthetic methods utilizing other nitrogen sources, were obtained in good-to-excellent yields under mild conditions. The optimized conditions were also applicable to the synthesis of *N*-alkyl-β-enaminonitriles. This efficient, atom-economical, and operatically simple synthetic protocol for *N*-alkyl/aryl substituted β-enaminonitriles can be applied to the synthesis of diverse of heterocycles.

2.4 Experimental section

2.4.1 General information

Unless otherwise noted, all reactions were carried out using standard Schlenk techniques or in an argon-filled glove box. All anhydrous solvents were purchased from commercial suppliers and degassed with dry argon before usage. *tert*-Butyl isocyanide and cyclohexyl isocyanide were purchased from commercial suppliers and used as received without further purification, and other arylisocyanides were synthesized from the corresponding amines following the literature procedures.[29] Compounds **1q**,[22] **2b**,[30] **2g**,[30] and **2i**[31] were prepared by the methods reported in literatures, and all other arylacetonitriles were purchased from commercial suppliers. HRMS analyses were performed at the National Center for Inter-university Research Facilities (NCIRF) at Seoul National University and at the Daegu Center of the Korea Basic Science Institute (KBSI). Absolute configuration of the product **3aa** was determined by X-ray crystallography performed at the Western Seoul Center of the KBSI.

2.4.2 General procedure for *N*-aryl/alkyl-β-enaminonitrile synthesis

To an oven-dried 4 mL-vial equipped with a stirring bar, CuI (3.8 mg, 0.02 mmol) and potassium *tert*-butoxide (53.9 mg, 0.48 mmol) were added inside a glove box. Then, the vial was sealed with a septum screw cap and taken out of the box. Anhydrous DME (0.8 mL), **2** (0.56 mmol), and **1** (0.40 mmol) were added successively to the vial. If solid **1** or **2** was used, solutions of each substrate in DME were prepared under inert condition, and then added to the vial. In those cases,

overall volume of solvent was maintained to the original procedure. Resulting reaction mixture was stirred for 8-16 h at 55 ℃. Crude products were purified via silica gel column chromatography.

2.4.3 General procedure for 3-oxo-2-phenylpropanenitrile (4) synthesis

To a solution of **3aa** (46.9 mg, 0.20 mmol) of THF (2 mL) was added 7% HCl aqueous solution (3 mL). After cooling to room temperature, the reaction mixture was stirred for 17 h at 40 ℃. The reaction mixture was extracted with EtOAc. The organic layer was separated and dried over with anhydrous $MgSO_4$ and concentrated under reduced pressure. Crude products were purified via silica gel column chromatography.

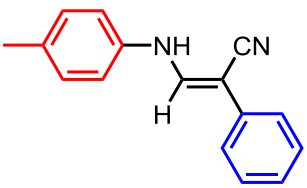
2.4.4 General procedure for 4-phenyl-1*H*-pyrazol-3-amine (5) synthesis

3aa (93.7 mg, 0.40 mmol) was treated with N_2H_4•H_2O (38.8 μL, 0.80 mmol) and five drops of acetic acid in ethanol (0.5 mL) was heated under the microwave irradiation for 4 min at 250 ℃. After cooling to room temperature, the resulting mixture was diluted by EtOAc and saturated solution of $NaHCO_3$ was added. The reaction mixture was extracted with EtOAc. The organic layer was separated and dried over with anhydrous $MgSO_4$ and concentrated under reduced pressure. Crude products were purified via silica gel column chromatography.

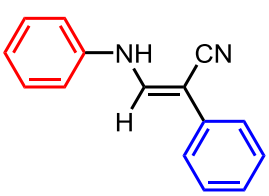
2.4.5 Characterization data

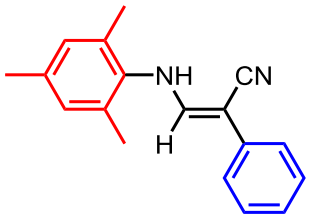
Reactions for β-enaminoniriles were performed in 0.40 mmol scale. All compounds were identified by ^{1}H, ^{13}C NMR. All new compounds were further identified by HR-MS. All reported compounds, **3ba**,[19b] **3ha**,[19b] **3la**,[19b] **4**,[32] and **5**[19a] were also identified by spectral comparison with literature data.

(*Z*)-2-Phenyl-3-(*p*-tolylamino)acrylonitrile (3aa): Light yellow solid (88 mg, 94%); ^{1}H NMR (300 MHz, DMSO-d_6) δ = 9.64 (d, *J* = 12.8 Hz, 1 H), 8.05 (d, *J* = 13.0 Hz, 1 H), 7.51 (d, *J* = 7.5 Hz, 2 H), 7.35 (t, *J* = 7.7 Hz, 2 H), 7.28 (d, *J* = 8.5 Hz, 2 H), 7.20-7.16 (m, 1 H), 7.11 (d, *J* = 8.3 Hz, 2 H), 2.25 (s, 3 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ = 142.4, 138.8, 134.4, 131.4, 129.7, 128.8, 125.4, 123.6, 118.5, 116.4, 82.1, 20.3; HRMS-FAB (m/z) $[M-H]^-$ calcd for $C_{16}H_{13}N_2$, 233.1084; found: 233.1077.

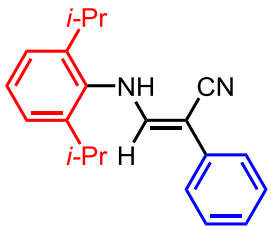


(*Z*)-2-Phenyl-3-(phenylamino)acrylonitrile (3ba):[19b] Light yellow solid (83 mg, 94%); ^{1}H NMR (300 MHz, DMSO-d_6) δ = 9.70 (d, *J* = 10.4 Hz, 1 H), 8.10 (d, *J* = 11.3 Hz, 1 H), 7.52 (d, *J* = 7.3 Hz, 2 H), 7.43-7.34 (m, 4 H), 7.32 (t, *J* = 8.5 Hz, 2 H), 7.19 (t, *J* = 7.2 Hz, 1 H), 7.01 (t, *J* = 7.2 Hz, 1 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ = 142.2, 141.2, 134.2, 129.3, 128.8, 125.6, 123.7, 122.4, 118.4, 116.4, 82.8; HRMS-FAB (m/z) $[M-H]^-$ calcd for $C_{15}H_{11}N_2$, 219.0928; found: 219.0919.

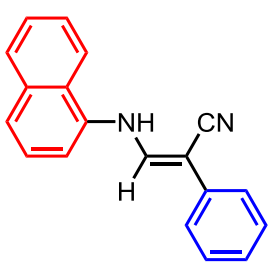


(*Z*)-3-(Mesitylamino)-2-phenylacrylonitrile (3ca): Light orange solid (93 mg, 

88%); ^{1}H NMR (300 MHz, Acetone-d_6) δ = 7.77 (d, *J* = 12.8 Hz, 1 H), 7.55 (d, *J* = 13.0 Hz, 1 H), 7.42 (d, *J* = 7.3 Hz, 2 H), 7.30 (t, *J* = 7.8 Hz, 2 H), 7.11 (tt, *J* = 7.2, 1.3 Hz, 1 H), 6.95 (s, 2 H), 2.31 (s, 6 H), 2.27 (s, 3 H); ^{13}C NMR (75 MHz, Acetone-d_6) δ = 149.5, 137.2, 136.9, 135.9, 135.5, 130.0, 129.7, 125.9, 124.0, 118.7, 81.4, 21.0, 18.6; HRMS-FAB (m/z) [M-H]$^-$ calcd for $C_{18}H_{17}N_2$, 261.1397; found: 261.1393.

(*Z*)-3-((2,6-Diisopropylphenyl)amino)-2-phenylacrylonitrile (3da): Light green 

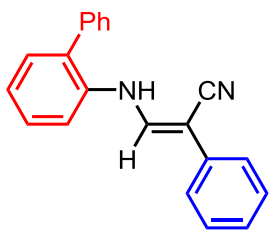
solid (104 mg, 85%); ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.95 (d, *J* = 12.1 Hz, 1 H), 7.57 (br. s., 1 H), 7.36 (d, *J* = 7.4 Hz, 2 H), 7.34-7.24 (m, 3 H), 7.19 (d, *J* = 7.4 Hz, 2 H), 7.07 (t, *J* = 7.0 Hz, 1 H), 3.21 (spt, *J* = 5.9 Hz, 2 H), 1.19 (d, *J* = 6.7 Hz, 12 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ = 150.3 (br. s), 146.1, 136.5 (br. s), 134.7 (br. s), 128.8, 128.0 (br. s), 124.5, 123.3, 122.7, 118.7 (br. s), 77.9 (br. s), 27.8, 23.4; HRMS-FAB (m/z) [M-H]$^-$ calcd for $C_{21}H_{23}N_2$, 303.1867; found: 303.1859.

(*Z*)-3-(Naphthalen-1-ylamino)-2-phenylacrylonitrile (3ea): Light yellow solid 

(92 mg, 85%); ^{1}H NMR (300 MHz, DMSO-d_6) δ = 9.67 (d, *J* = 10.2 Hz, 1 H), 8.21 (d, *J* = 8.1 Hz, 1 H), 8.06 (d, *J* = 10.0 Hz, 1 H), 7.95 (d, *J* = 7.5 Hz, 1 H), 7.73 (d, *J* = 7.7 Hz, 1 H), 7.63-7.55 (m, 2 H), 7.54-7.43 (m, 4 H), 7.36 (t, *J* =

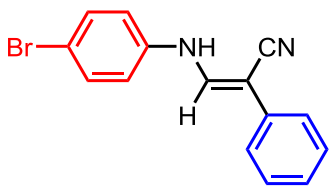
7.6 Hz, 2 H), 7.18 (t, *J* = 7.2 Hz, 1 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ = 145.5, 137.5, 134.4, 133.9, 128.9, 128.1, 126.5, 126.3, 126.0, 125.9, 125.6, 124.4, 123.6, 122.7, 118.4, 116.6, 83.6; HRMS-FAB (m/z) [M-H]$^-$ calcd for $C_{19}H_{13}N_2$, 269.1084; found: 269.1076.

(*Z*)-3-([1,1'-Biphenyl]-2-ylamino)-2-phenylacrylonitrile (3fa): Light green solid



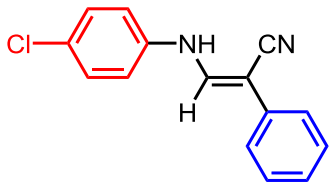
(83 mg, 70%); ^{1}H NMR (300 MHz, DMSO-d_6) δ = 8.27 (d, *J* = 13.0 Hz, 1 H), 8.00 (d, *J* = 13.2 Hz, 1 H), 7.58 (t, *J* = 7.5 Hz, 2 H), 7.55-7.38 (m, 6 H), 7.34-7.29 (m, 4 H), 7.22 (d, *J* = 7.3 Hz, 1 H), 7.19-7.11 (m, 1 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ = 143.8, 137.9, 137.4, 133.6, 131.6, 130.8, 129.1, 129.0, 128.8, 128.7, 127.7, 125.6, 123.8, 123.4, 118.7, 117.8, 82.8; HRMS-FAB (m/z) [M-H]$^-$ calcd for $C_{21}H_{15}N_2$, 295.1241; found: 295.1235.

(*Z*)-3-((4-Bromophenyl)amino)-2-phenylacrylonitrile (3ga): Light yellow solid



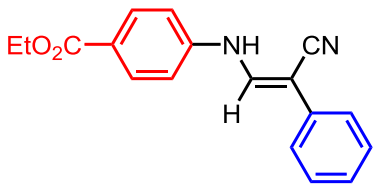
(116 mg, 97%); ^{1}H NMR (300 MHz, DMSO-d_6) δ = 9.77 (d, *J* = 12.6 Hz, 1 H), 8.07 (d, *J* = 12.6 Hz, 1 H), 7.53 (d, *J* = 8.5 Hz, 2 H), 7.46 (d, *J* = 9.0 Hz, 2 H), 7.42-7.32 (m, 4 H), 7.19 (t, *J* = 7.5 Hz, 1 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ = 141.8, 140.6, 134.0, 131.9, 128.8, 125.8, 123.8, 118.4, 118.1, 114.0, 83.8; HRMS-FAB (m/z) [M-H]$^-$ calcd for $C_{15}H_{10}BrN_2$, 297.0033; found: 297.0021.

(*Z*)-3-((4-Chlorophenyl)amino)-2-phenylacrylonitrile (3ha):[19b] Light brown solid



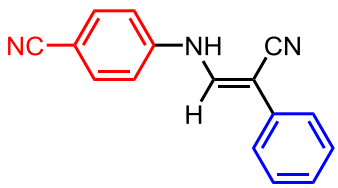
(88 mg, 86%); ^{1}H NMR (300 MHz, DMSO-d_6) δ = 9.79 (d, *J* = 12.6 Hz, 1 H), 8.08 (d, *J* = 12.8 Hz, 1 H), 7.53 (d, *J* = 7.3 Hz, 2 H), 7.43 (d, *J* = 9.0 Hz, 2 H), 7.39-7.30 (m, 4 H), 7.18 (t, *J* = 7.2 Hz, 1 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ = 141.9, 140.2, 134.0, 129.0, 128.8, 126.1, 125.7, 123.8, 118.1, 117.9, 83.7; HRMS-FAB (m/z) $[M-H]^-$ calcd for $C_{15}H_{10}ClN_2$, 253.0538; found: 253.0535.

Ethyl (*Z*)-4-((2-cyano-2-phenylvinyl)amino)benzoate (3ia): Light yellow solid



(90 mg, 77%); ^{1}H NMR (300 MHz, DMSO-d_6) δ = 10.03 (d, *J* = 12.4 Hz, 1 H), 8.16 (d, *J* = 12.4 Hz, 1 H), 7.88 (d, *J* = 8.9 Hz, 2 H), 7.58-7.48 (m, 4 H), 7.38 (t, *J* = 7.7 Hz, 2 H), 7.22 (t, *J* = 7.2 Hz, 1 H), 4.28 (q, *J* = 7.1 Hz, 2 H), 1.31 (t, *J* = 7.1 Hz, 3 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ = 165.4, 145.3, 140.9, 133.7, 130.6, 128.8, 126.2, 124.1, 123.0, 117.8, 115.6, 85.7, 60.3, 14.2; HRMS-FAB (m/z) $[M-H]^-$ calcd for $C_{18}H_{15}N_2O_2$, 291.1139; found: 291.1139.

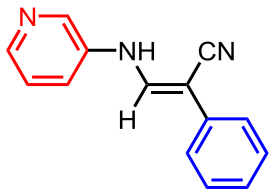
(*Z*)-4-((2-Cyano-2-phenylvinyl)amino)benzonitrile (3ja): Light yellow solid (74



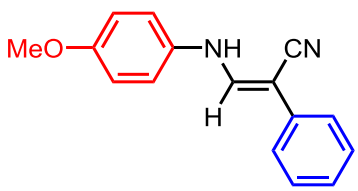
mg, 76%); ^{1}H NMR (300 MHz, DMSO-d_6) δ = 10.07 (d, *J* = 12.4 Hz, 1 H), 8.18 (d, *J* = 12.2 Hz, 1 H), 7.74 (d, *J* = 8.7 Hz, 2 H), 7.62-7.52 (m, 4 H), 7.39 (t, *J* = 7.7 Hz, 2 H), 7.23 (t, *J* = 7.2 Hz, 1 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ = 145.1,

140.7, 133.6, 133.4, 128.9, 126.4, 124.2, 119.3, 117.6, 116.4, 103.4, 86.5; HRMS-FAB (m/z) $[M-H]^-$ calcd for $C_{16}H_{10}N_3$, 244.0880; found: 244.0879.

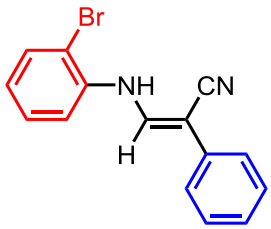
(*Z*)-2-Phenyl-3-(pyridin-3-ylamino)acrylonitrile (3ka): Light yellow solid (40 mg, 46%); ^{1}H NMR (300 MHz, DMSO-d_6) δ = 9.79 (br. s., 1 H), 8.67 (br. s., 1 H), 8.21 (dd, *J* = 4.7, 1.3 Hz, 1 H), 8.15 (s, 1 H), 7.80 (dd, *J* = 7.9, 2.1 Hz, 1 H), 7.54 (d, *J* = 7.9 Hz, 2 H), 7.41-7.28 (m, 3 H), 7.20 (t, *J* = 7.2 Hz, 1 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ = 143.2, 141.9, 138.8, 137.8, 133.8, 128.8, 125.9, 123.9, 123.8, 122.9, 118.0, 84.4; HRMS-FAB (m/z) $[M-H]^-$ calcd for $C_{14}H_{11}N_3$, 220.0880; found: 220.0876.



(*Z*)-3-((4-Methoxyphenyl)amino)-2-phenylacrylonitrile (3la):[19b] Light yellow solid (82 mg, 82%); ^{1}H NMR (499 MHz, DMSO-d_6) δ = 9.56 (br. s., 1 H), 8.00 (s, 1 H), 7.48 (d, *J* = 7.8 Hz, 2 H), 7.36-7.29 (m, 4 H), 7.15 (t, *J* = 7.7 Hz, 1 H), 6.90 (d, *J* = 9.3 Hz, 2 H), 3.73 (s, 3 H); ^{13}C NMR (75 MHz, Acetone-d_6) δ = 156.7, 143.0, 135.4, 135.3, 129.6, 126.3, 124.4, 118.7, 118.6, 115.5, 83.7, 55.7; HRMS-FAB (m/z) $[M-H]^-$ calcd for $C_{16}H_{13}N_2O$, 249.1033; found: 249.1029.

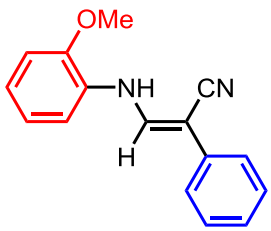


(*Z*)-3-((2-Bromophenyl)amino)-2-phenylacrylonitrile (3ma): Light green solid



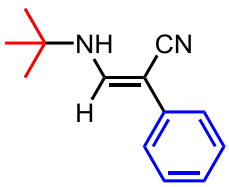
(83 mg, 69%); ^{1}H NMR (300 MHz, Acetone-d_6) δ = 8.29 (d, J = 13.0 Hz, 1 H), 7.72 (d, J = 12.4 Hz, 1 H), 7.63 (td, J = 8.5, 1.4 Hz, 2 H), 7.57 (d, J = 8.3 Hz, 2 H), 7.45-7.34 (m, 3 H), 7.24 (tt, J = 7.5, 1.9 Hz, 1 H), 7.00 (td, J = 7.7, 1.5 Hz, 1 H); ^{13}C NMR (75 MHz, Acetone-d_6) δ = 140.8, 138.6, 133.9, 133.8, 130.0, 129.8, 127.4, 125.0, 124.7, 117.7, 116.8, 112.4, 88.5; HRMS-FAB (m/z) [M-H]$^-$ calcd for $C_{15}H_{10}BrN_2$, 297.0033; found: 297.0019.

(*Z*)-3-((2-Methoxyphenyl)amino)-2-phenylacrylonitrile (3na): Light yellow solid



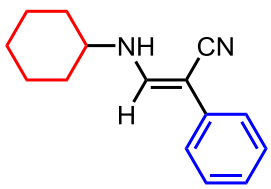
(91 mg, 90%); ^{1}H NMR (300 MHz, DMSO-d_6) δ = 8.34 (d, J = 13.4 Hz, 1 H), 7.96 (d, J = 13.4 Hz, 1 H), 7.58-7.49 (m, 3 H), 7.36 (t, J = 7.8 Hz, 2 H), 7.18 (t, J = 7.2 Hz, 1 H), 7.10-6.92 (m, 3 H), 3.89 (s, 3 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ = 147.6, 141.5, 133.3, 129.0, 128.9, 125.7, 123.5, 123.1, 121.0, 117.9, 115.2, 111.4, 83.8, 56.0; HRMS-FAB (m/z) [M-H]$^-$ calcd for $C_{16}H_{13}N_2O$, 249.1033; found: 249.1029.

(*Z*)-3-(*tert*-Butylamino)-2-phenylacrylonitrile (3oa): Light yellow solid (58 mg, 73%); ^{1}H NMR (300 MHz, DMSO-d_6) δ = 7.65 (d, J = 14.1 Hz, 1 H), 7.33 (d, J = 7.3 Hz, 2 H), 7.27 (t, J = 8.1 Hz, 2 H), 7.09-6.98 (m, 2 H), 1.30 (s, 9 H); ^{13}C NMR (75 MHz, DMSO-



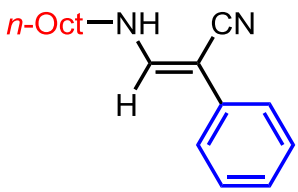
d_6) δ = 146.4, 135.4, 128.7, 124.1, 122.5, 119.4, 75.9, 52.9, 29.6; HRMS-FAB (m/z) $[M+Na]^+$ calcd for $C_{13}H_{16}N_2Na$, 223.1206; found: 223.1210.

(*Z*)-3-(Cyclohexylamino)-2-phenylacrylonitrile (3pa): White solid (60 mg, 66%);



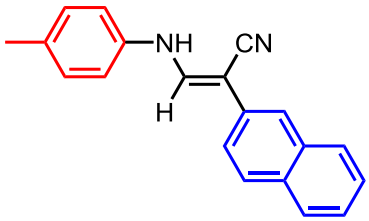
^{1}H NMR (300 MHz, Acetone-d_6) δ = 7.69 (d, *J* = 13.6 Hz, 1 H), 7.38-7.19 (m, 4 H), 7.05 (tt, *J* = 7.2, 1.3 Hz, 1 H), 6.27 (br. s., 1 H), 3.43-3.27 (m, 1 H), 2.03-1.94 (m, 2 H), 1.84-1.72 (m, 2 H), 1.68-1.57 (m, 1 H), 1.56-1.39 (m, 2 H), 1.39-1.26 (m, 2 H), 1.25-1.13 (m, 1 H); ^{13}C NMR (75 MHz, Acetone-d_6) δ = 149.1, 136.4, 129.5, 125.1, 123.4, 119.5, 78.2, 58.1, 34.7, 25.9, 25.8; HRMS-FAB (m/z) $[M-H]^-$ calcd for $C_{15}H_{17}N_2$, 225.1397; found: 225.1392.

(*Z*)-3-(octylamino)-2-phenylacrylonitrile (3qa): White solid (62 mg, 60%); ^{1}H



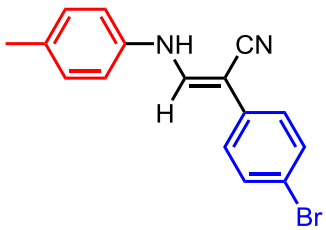
NMR (300 MHz, Acetone-d_6) δ = 7.64 (d, *J* = 13.6 Hz, 1 H), 7.33 (d, *J* = 7.2 Hz, 2 H), 7.26 (t, *J* = 7.2 Hz, 2 H), 7.05 (tt, *J* = 1.0, 7.2 Hz, 1 H), 6.47 (s, 1 H), 3.40 (q, *J* = 6.8 Hz, 2 H), 1.65 (quin, *J* = 7.1 Hz, 2 H), 1.47-1.21 (m, 10 H), 0.98-0.81 (m, 3 H); ^{13}C NMR (75 MHz, Acetone-d_6) δ = 150.9, 136.4, 129.6, 125.1, 123.4, 119.6, 78.0, 49.0, 32.6, 32.1, 30.0, 30.0, 27.2, 23.3, 14.4; HRMS-FAB (m/z) $[M+Na]^+$ calcd for $C_{17}H_{24}N_2Na$, 279.1837; found: 279.1831.

(*Z*)-2-(Naphthalen-2-yl)-3-(*p*-tolylamino)acrylonitrile (3ab): Light orange solid



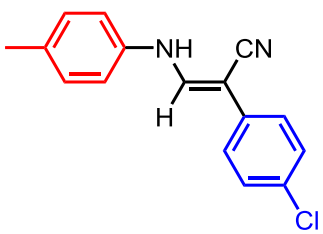
(101 mg, 89%); ^{1}H NMR (499 MHz, DMSO-d_6) δ = 9.73 (d, *J* = 13.2 Hz, 1 H), 8.24 (d, *J* = 12.7 Hz, 1 H), 7.91 (s, 1 H), 7.90-7.84 (m, 3 H), 7.79 (dd, *J* = 8.8, 2.0 Hz, 1 H), 7.49 (t, *J* = 7.6 Hz, 1 H), 7.42 (t, *J* = 7.6 Hz, 1 H), 7.34 (d, *J* = 8.3 Hz, 2 H), 7.14 (d, *J* = 8.3 Hz, 2 H), 2.26 (s, 3 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ = 142.7, 138.8, 133.4, 132.0, 131.5, 131.2, 129.7, 128.3, 127.5, 127.3, 126.5, 125.1, 122.4, 121.0, 118.5, 116.5, 82.2, 20.3; HRMS-FAB (m/z) $[M-H]^-$ calcd for $C_{20}H_{15}N_2$, 283.1241; found: 283.1241.

(*Z*)-2-(4-Bromophenyl)-3-(*p*-tolylamino)acrylonitrile (3ac): Yellow solid (125



mg, >99%); ^{1}H NMR (499 MHz, DMSO-d_6) δ = 9.72 (d, *J* = 12.7 Hz, 1 H), 8.11 (d, *J* = 13.2 Hz, 1 H), 7.51 (d, *J* = 7.8 Hz, 2 H), 7.46 (d, *J* = 8.8 Hz, 2 H), 7.29 (d, *J* = 8.3 Hz, 2 H), 7.12 (d, *J* = 8.3 Hz, 2 H), 2.25 (s, 3 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ = 143.0, 138.6, 133.9, 131.6, 131.5, 129.6, 125.4, 118.1, 117.8, 116.6, 80.8, 20.3; HRMS-FAB (m/z) $[M-H]^-$ calcd for $C_{16}H_{12}BrN_2$, 311.0189; found: 311.0180.

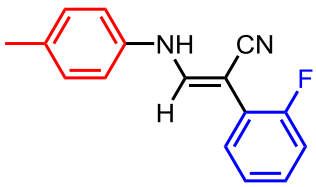
(*Z*)-2-(4-Chlorophenyl)-3-(*p*-tolylamino)acrylonitrile (3ad): Light yellow solid



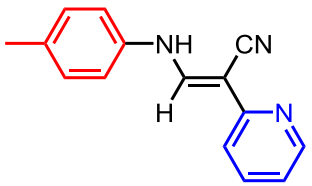
(95 mg, 88%); ^{1}H NMR (499 MHz, DMSO-d_6) δ = 9.71 (d, *J* = 13.2 Hz, 1 H), 8.10 (d, *J* = 13.2 Hz, 1 H), 7.52 (d, *J* = 8.8 Hz, 2 H), 7.38 (d, *J* = 8.8 Hz, 2 H), 7.29 (d, *J* = 8.8 Hz, 2 H), 7.12 (d, *J* = 8.3 Hz, 2 H), 2.25 (s, 3 H); ^{13}C NMR (75 MHz, DMSO-

d_6) δ = 143.0, 138.6, 133.4, 131.6, 129.6, 129.5, 128.6, 125.0, 118.2, 116.6, 80.8, 20.3; HRMS-FAB (m/z) $[M-H]^-$ calcd for $C_{16}H_{12}ClN_2$, 267.0694; found: 267.0689.

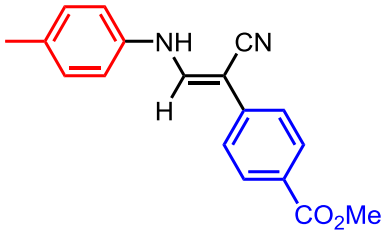
(*Z*)-2-(2-Fluorophenyl)-3-(*p*-tolylamino)acrylonitrile (3ae): White solid (86 mg, 86%); ^{1}H NMR (300 MHz, DMSO-d_6) δ = 9.74 (d, *J* = 13.0 Hz, 1 H), 7.89 (d, *J* = 13.0 Hz, 1 H), 7.54-7.43 (m, 1 H), 7.32-7.16 (m, 5 H), 7.11 (d, *J* = 8.7 Hz, 2 H), 2.24 (s, 3 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ = 158.5 (d, *J* = 245.4 Hz), 145.8 (d, *J* = 6.5 Hz), 138.6, 131.7, 129.7, 128.4 (d, *J* = 2.4 Hz), 127.6 (d, *J* = 8.1 Hz), 124.8 (d, *J* = 3.2 Hz), 122.4 (d, *J* = 11.3 Hz), 118.0, 116.5, 115.9 (d, *J* = 21.8 Hz), 75.8, 20.2; HRMS-FAB (m/z) $[M-H]^-$ calcd for $C_{16}H_{12}FN_2$, 251.0990; found: 251.0989.



(*Z*)-2-(Pyridin-2-yl)-3-(*p*-tolylamino)acrylonitrile (3af): Light yellow solid (77 mg, 86%); ^{1}H NMR (300 MHz, DMSO-d_6) Major isomer: δ = 12.51 (d, *J* = 12.6 Hz, 1 H), 8.62 (d, *J* = 4.1 Hz, 1 H), 8.28 (d, *J* = 12.4 Hz, 1 H), 7.87 (td, *J* = 7.8, 1.7 Hz, 1 H), 7.39 (d, *J* = 8.3 Hz, 1 H), 7.30 (d, *J* = 8.3 Hz, 2 H), 7.22 (t, *J* = 6.2 Hz, 1 H), 7.17 (d, *J* = 8.1 Hz, 2 H), 2.27 (s, 3 H); Minor isomer: δ = 10.03 (d, *J* = 13.6 Hz, 1 H), 8.57 (d, *J* = 13.8 Hz, 1 H), 8.45 (d, *J* = 4.7 Hz, 1 H), 7.73 (td, *J* = 8.5, 1.9 Hz, 1 H), 7.43-7.36 (m, 1 H), 7.27-7.07 (m, 5 H), 2.27 (s, 3 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ = 155.0, 147.8, 145.1, 137.6, 137.2, 132.7, 130.0, 120.7, 119.9, 119.3, 116.4, 79.7, 20.3; HRMS-FAB (m/z) $[M+H]^+$ calcd for $C_{15}H_{14}N_3$, 236.1182; found: 236.1187.

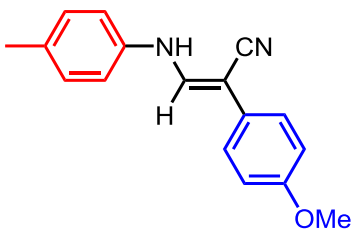


Methyl (*Z*)-4-(1-cyano-2-(*p*-tolylamino)vinyl)benzoate (3ag): Light yellow solid



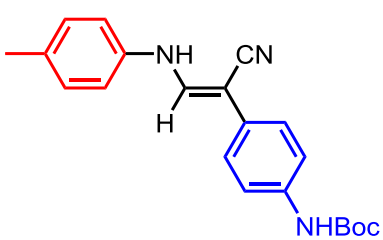
(98 mg, 83%); ^{1}H NMR (300 MHz, DMSO-d_6) δ = 9.92 (d, *J* = 11.7 Hz, 1 H), 8.27 (d, *J* = 11.7 Hz, 1 H), 7.90 (d, *J* = 8.7 Hz, 2 H), 7.63 (d, *J* = 8.5 Hz, 2 H), 7.33 (d, *J* = 8.7 Hz, 2 H), 7.14 (d, *J* = 8.3 Hz, 2 H), 3.83 (s, 3 H), 2.26 (s, 3 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ = 166.0, 144.2, 139.7, 138.4, 132.1, 129.7, 129.7, 125.7, 123.0, 118.0, 117.0, 81.0, 51.9, 20.3; HRMS-FAB (m/z) $[M-H]^-$ calcd for $C_{18}H_{15}N_2O_2$, 291.1139; found: 291.1130.

(*Z*)-2-(4-Methoxyphenyl)-3-(*p*-tolylamino)acrylonitrile (3ah): Light yellow solid



(82 mg, 77%); ^{1}H NMR (300 MHz, DMSO-d_6) δ = 9.45 (d, *J* = 12.8 Hz, 1 H), 7.90 (d, *J* = 12.8 Hz, 1 H), 7.41 (d, *J* = 8.9 Hz, 2 H), 7.24 (d, *J* = 8.5 Hz, 2 H), 7.10 (d, *J* = 8.3 Hz, 2 H), 6.93 (d, *J* = 8.9 Hz, 2 H), 3.75 (s, 3 H), 2.24 (s, 3 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ = 157.5, 141.1, 139.0, 130.9, 129.6, 126.6, 125.0, 118.7, 116.1, 114.3, 82.0, 55.1, 20.2; HRMS-FAB (m/z) $[M]^+$ calcd for $C_{17}H_{16}N_2O$, 264.1263; found: 264.1263.

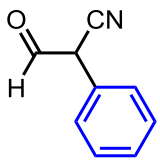
***tert*-Butyl (*Z*)-(4-(1-cyano-2-(*p*-tolylamino)vinyl)phenyl)carbamate (3ai):** Light



yellow solid (78 mg, 56%); ^{1}H NMR (300 MHz, DMSO-d_6) δ = 9.48 (d, *J* = 12.8 Hz, 1 H), 9.32 (s, 1 H), 7.92 (d, *J* = 12.8 Hz, 1 H), 7.43 (d, *J* = 9.0 Hz, 2 H), 7.37 (d, *J* = 9.0 Hz, 2 H), 7.24 (d, *J* =

8.7 Hz, 2 H), 7.10 (d, *J* = 8.3 Hz, 2 H), 2.25 (s, 3 H), 1.47 (s, 9 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ = 152.7, 141.2, 138.9, 137.3, 131.0, 129.6, 127.9, 123.9, 118.5, 116.2, 82.1, 79.0, 28.1, 20.2; HRMS-FAB (m/z) $[M-H]^-$ calcd for $C_{21}H_{22}N_3O_2$, 348.1718; found: 348.1716.

3-Oxo-2-phenylpropanenitrile (4):[32] Light yellow solid (18 mg, 63%); ^{1}H NMR



(300 MHz, DMSO-d_6) δ = 12.12 (br. s., 1 H), 8.02 (s, 0.6 H), 7.72-7.63 (m, 1.3 H), 7.46-7.30 (m, 3.1 H), 7.24 (q, *J* = 7.2 Hz, 1 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ = 159.5, 158.0, 132.2, 131.6, 128.9, 128.6, 126.8, 126.6, 126.5, 124.1, 120.2, 116.8, 89.8, 89.5.

4-Phenyl-1*H*-pyrazol-3-amine (5):[19a] White solid (42 mg, 66%); ^{1}H NMR (300

MHz, DMSO-d_6) δ = 11.71 (br. s., 1 H), 7.67 (s, 1 H), 7.51 (d, *J* = 7.5 Hz, 2 H), 7.32 (t, *J* = 7.6 Hz, 2 H), 7.12 (t, *J* = 7.3 Hz, 1 H), 4.80 (br. s., 2 H).

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Chapter 3. Utilization of Methanol as a C1 Building Block through Transition Metal Catalysis

3.1 Introduction

Fossil fuels such as petroleum, coal, and natural gas play vital roles in industry as energy sources as well as raw materials. As the global depletion of fossil fuels approaches, the search for nontoxic, inexpensive, and renewable feedstocks has become a significant issue for green and sustainable chemistry.

Methanol, which is the simplest alcohol and a commonly used organic solvent, is emerging as a potentially renewable resource.[1] Methanol is already used not only as an energy source in applications such as gasoline blending, propane replacement by dimethyl ether (DME) in liquid petroleum gas (LPG), and biodiesel, but also as a chemical feedstock for formaldehyde, methanol-to-olefin (MTO) routes, and acetic acid.[2] The use of methanol as a hydrogen storage medium has also been suggested.[3] Although methanol is currently produced mainly from syngas in industry,[4] the development of methods to produce methanol via the reduction of carbon dioxide[5] and biomass conversion[6] is expected to result in a "methanol economy".[7] Due to the increasing applications of methanol, global methanol demand reached 75 million metric tons in 2015 and continues to grow.[2]

As importance of methanol increases, the direct utilization of methanol has been extensively investigated.[8] In particular, the dehydrogenative activation of methanol has attracted great attention based on its green nature and economic advantages over

traditional methods. In this chapter, the concept of alcohol dehydrogenation in homogeneous catalytic systems and its development are briefly reviewed. Then, its application to methanol is illustrated and discussed; a number of seminal examples of methanol dehydrogenation are categorized according to the nucleophile used. The utilization of methanol via radical pathways is also discussed.

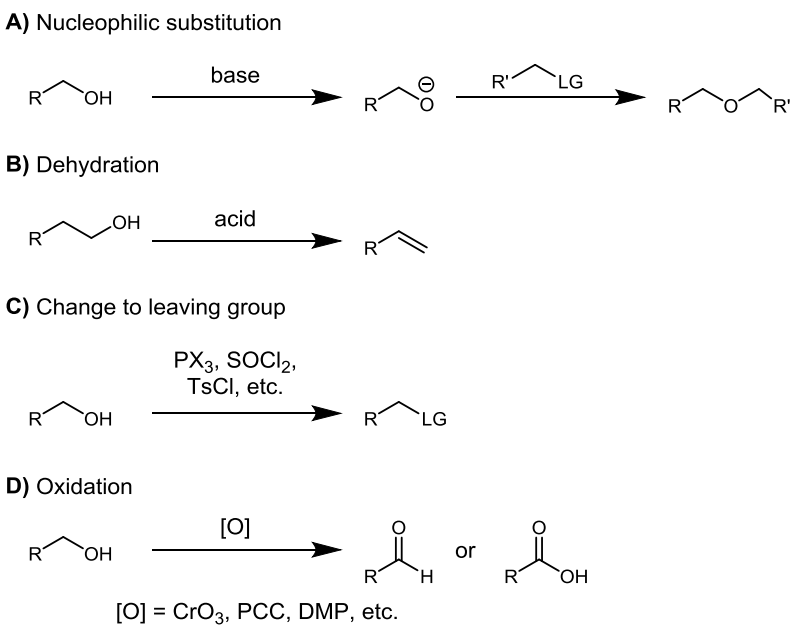
3.2 Dehydrogenative activation of alcohols

3.2.1 Traditional reactivity of alcohols

Alcohols are one of the most abundant and fundamental building blocks in organic chemistry. They are widely found in nature, and the hydroxyl group can be easily introduced synthetically via the oxidation or hydration of substrates. Thus, the utilization of alcohols in the synthesis of complex molecules and the transformation of the hydroxyl group into other functional groups have been extensively studied.

Understandably, the traditional reactivity of alcohols originates from the electron rich oxygen atom. The alcohol itself or its deprotonated form reacts with an electrophile to assemble an ether with a new C–O bond (Scheme 3.1A). When a strong acid is treated with an alcohol, the protonated hydroxyl group acts as a leaving group, thereby generating an olefin via elimination (Scheme 3.1B). The attack of an alcohol on reagents such as phosphorous trihalide (PX_3; X = Cl, Br, and I), thionyl chloride ($SOCl_2$), and tosyl chloride (TsCl) results in an alkyl (pseudo)halide (Scheme 3.1C). When an alcohol instead attacks an oxidant such as chromium(VI) trioxide (CrO_3), pyridinium chlorochromate (PCC), or Dess-Martin periodinane

(DMP), an aldehyde, ketone, or carboxylic acid is generated (Scheme 3.1D). After functional group conversion, the resulting olefins, alkyl (pseudo)halides, and carbonyl compounds can also take part in the construction of new C–C bonds or C–heteroatom bonds via additional steps.



Scheme 3.1 Traditional reactivity of alcohols

These traditional methods are quite efficient, and are extensively utilized in contemporary organic synthesis. However, they usually require harsh reaction conditions (strong acid or base, high temperature) or a stoichiometric amount of the reagents, which results in the generation of large quantities of toxic chemical wastes. In recent decades, green chemistry has become an important issue for a sustainable

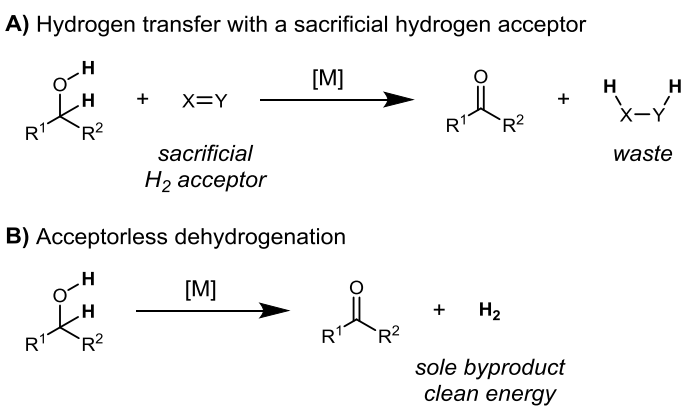
future.[9] The term "green chemistry" was defined in a 1988 book by P. T. Anastas and J. C. Warner as "the utilization of a set of principles that reduces or eliminates the use or generation of hazardous substances in the design, manufacture, and application of chemical products."[10] Naturally, the development of catalytic reactions for alcohol activation is highly desirable in order to develop atom- and step-economic reactions that prevent the generation of equivalents of toxic wastes.

3.2.2 Basic concepts and mechanistic aspects of transition-metal-catalyzed dehydrogenation

The transition-metal-catalyzed dehydrogenation of alcohol has been extensively studied as a greener approach.[11] Owing to energetically uphill character of alcohol dehydrogenation,[12] sacrificial hydrogen acceptors were required to alleviate the thermodynamic demand in early examples of these reactions (Scheme 3.2A). In 1937, R. V. Oppenauer first presented this concept using a catalytic amount of aluminum *tert*-butoxide in the presence of acetone; this is the so-called Oppenauer oxidation.[13] Acetone could be replaced by other ketones or the internal carbonyl functional group of a reactant.[14] Although the resulting 2-propanol has low toxicity, the use of a sacrificial hydrogen acceptor still produces a stoichiometric amount of the byproduct. In contrast, acceptorless dehydrogenation produces molecular hydrogen as the sole byproduct, thereby achieving the maximum theoretical atom-economy (Scheme 3.2B). Additionally, hydrogen is an environmentally-friendly, efficient, and safe energy source. Acceptorless dehydrogenation technology can be further utilized in

hydrogen gas storage. Despite these benefits, an efficient catalytic system for acceptorless dehydrogenation was not developed until the 1960s due to the thermodynamic hurdle. The first example was reported by H. B. Charman in 1970.[15] In the presence of rhodium-tin chloride complexes, isopropanol could be oxidized to acetone, accompanied by the production of hydrogen gas.

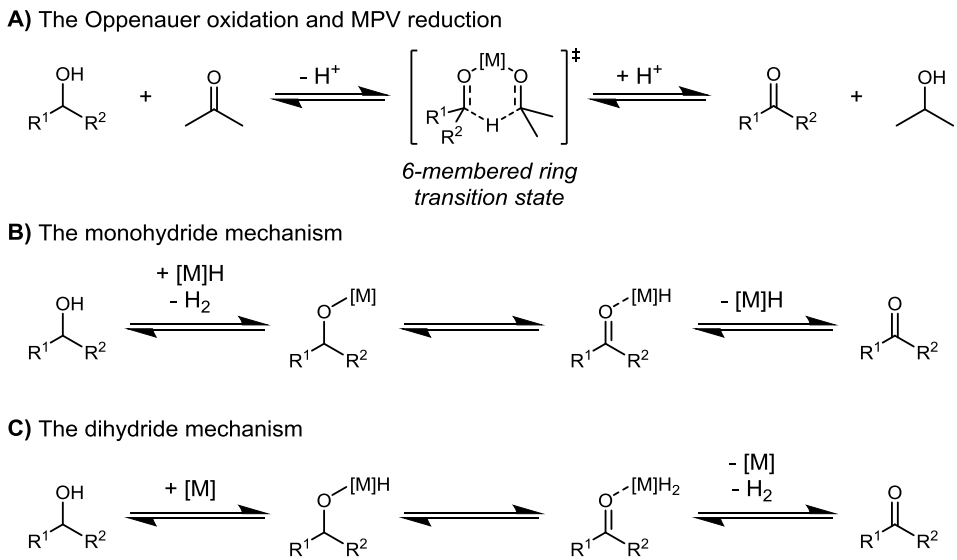
Currently, dehydrogenative alcohol activation can be performed by the inexpensive and abundant first-row transition metals manganese, iron, and cobalt,[11c-e] as well as by the precious transition metals ruthenium, rhodium, and iridium.[11a,11b]



Scheme 3.2 Transition-metal-catalyzed dehydrogenative alcohol activation

The Oppenauer oxidation and its reverse reaction, the Meerwein-Ponndorf-Verley (MPV) reduction, were proposed to involve a six-membered ring transition state (Scheme 3.3A).[16] However, mechanistic studies suggested that hydridic metal

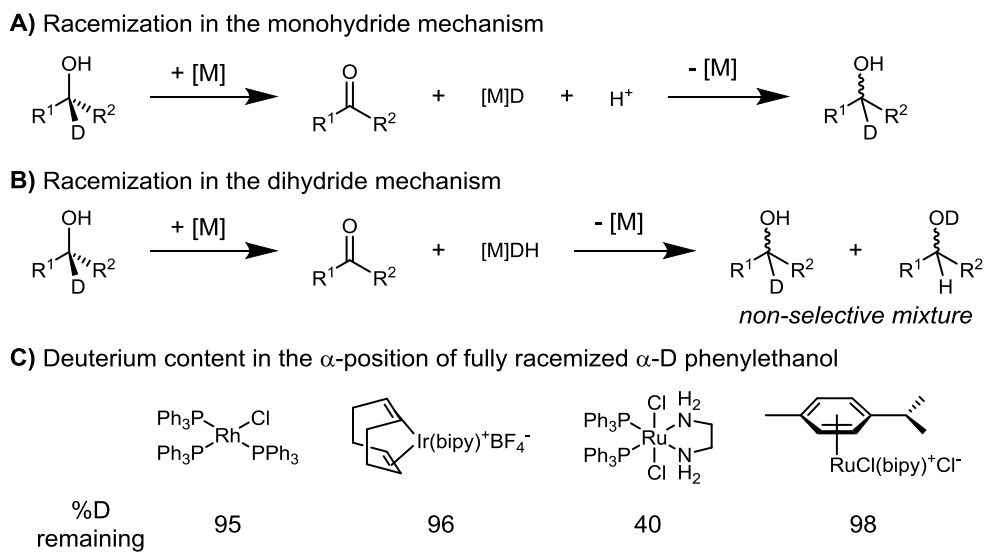
complexes were involved in transition-metal-catalyzed dehydrogenation and its reverse reaction, hydrogenation.[17] The suggested metal hydride complexes were directly isolated, and the effect of the base in promoting the catalysis was observed. Mechanisms involving hydridic complexes can be grouped into two main categories: 1) the monohydride mechanism (Scheme 3.3B; although the inner-sphere mechanism is depicted here, an outer-sphere mechanism is also possible) and 2) the dihydride mechanism (Scheme 3.3C).



Scheme 3.3 Mechanisms of dehydrogenation reactions

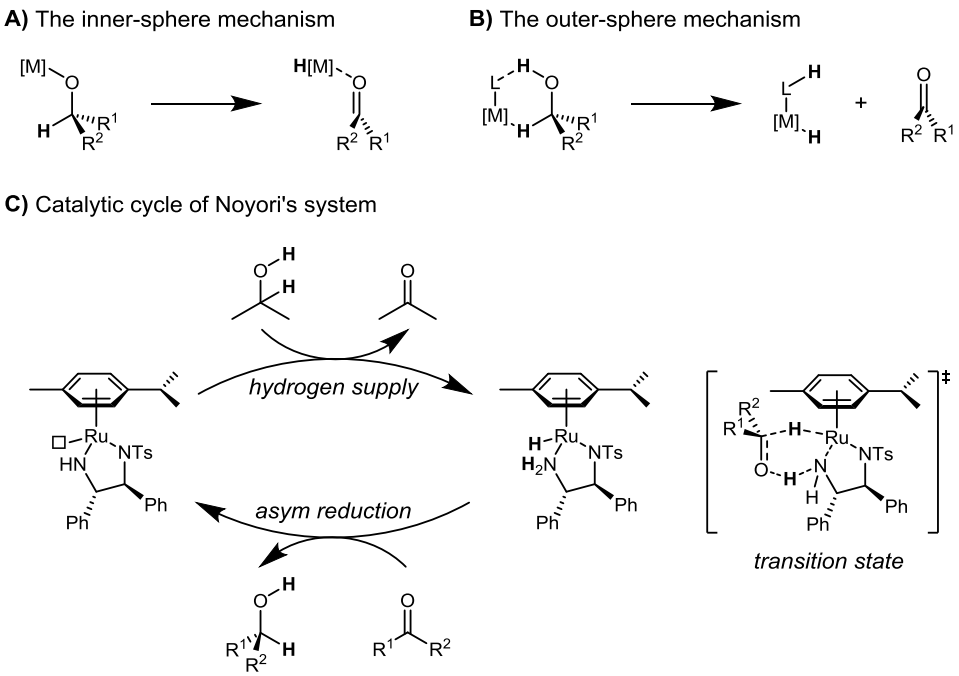
Differentiation between the monohydride mechanism and the dihydride mechanism can be achieved via the racemization of an α-deuterated chiral alcohol (Scheme 3.4).[18] Unlike in the monohydride system, which discriminates between the the hydride and the proton during the racemization process (Scheme 3.4A), the

identities of the hydride and the proton are not retained during the generation of dihydride metal complexes in the dihydride system (Scheme 3.4B). Hence, deuterium content approximately 50% of the initial value should be observed after the full racemization of an α-deuterated chiral alcohol if the dihydride mechanism is involved. J.–E. Bäckvall and co-workers carried out racemization reactions of an α-deuterated phenylethanol using various catalysts (Scheme 3.4C; selected examples are shown). As a result, they found that rhodium and iridium catalysts follow the monohydride mechanism, while the mechanism of the ruthenium catalysts depends on the ligand system of the specific ruthenium complex.



Scheme 3.4 Differentiation between the monohydride mechanism and the dihydride mechanism through the racemization of α-deuterated phenylethanol

The monohydride mechanism can occur in two ways: 1) via an inner-sphere mechanism consisting of sequential alkoxide binding and β-hydride elimination (Scheme 3.5A) and 2) via an outer-sphere mechanism with the aid of the ligands (Scheme 3.5B).[17] The latter was neatly discovered and described by R. Noyori and co-workers during their pioneering work in asymmetric hydrogenation (Scheme 3.5C).[19] They found that complexes of the type [(η^6-*p*-cymene)Ru(chiral diamine)] are quite efficient for the enantioselective hydrogenation of aryl alkyl ketones with (1*S*,2*S*)-*N*-tosyl-1,2-diphenylethylenediamine [(S,S)-Ts-DPEN]. When [(S,S)-Ts-DPEN] was replaced by ligands bearing NH_2 such as 2-aminoethanol, the catalysts were still active for hydrogenation and dehydrogenation. However, ruthenium complexes derived from *N*,*N*-dimethylated diamine were totally inactive for the reaction.[20] Furthermore, (η^6-arene)RuH(diamine) was shown to be active for the hydrogenation, even though it has no vacant site for ketone binding. Hence, they suggested that the NH bond of the bound diamine ligand forms a hydrogen bond with the oxygen atom of ketone in the outer-sphere type six-membered ring transition state. Based on this observation, they coined the term "bifunctional metal/ligand catalyst". Today, this is a well-accepted concept, and is also known as metal-ligand cooperation (MLC).[21] Several representative dehydrogenation/hydrogenation catalysts, such as the Milstein catalyst,[21a] Ru-MACHO,[21b] and the Shvo catalyst[17,22] are known to operate via MLC (Scheme 3.5D; active forms are shown).

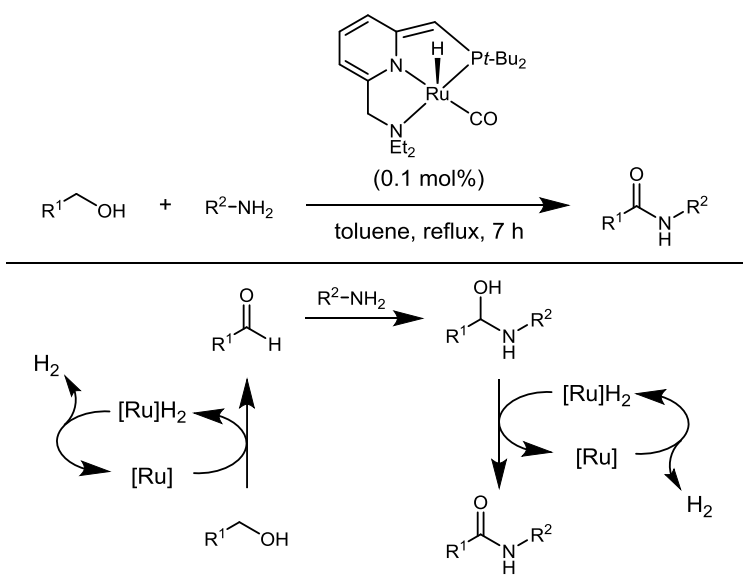


Scheme 3.5 Classification of the monohydride mechanism and metal-ligand cooperation (MLC)

3.2.3 Synthetic applications of catalytic alcohol dehydrogenation

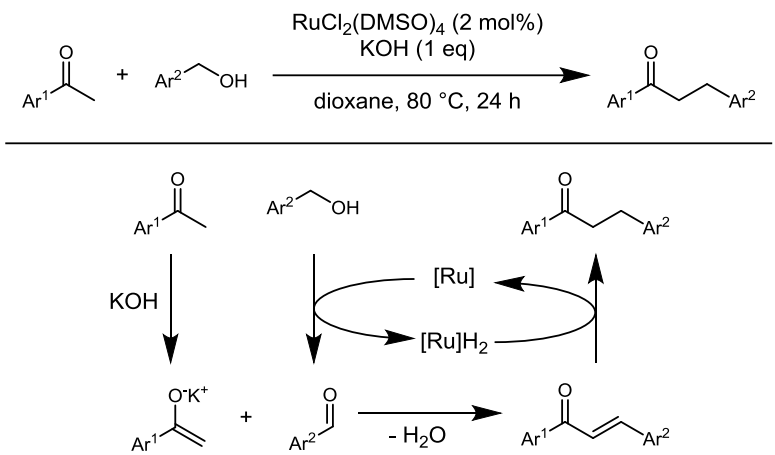
Based on the alcohol dehydrogenation strategy described above, extremely versatile reaction methods have been developed by changing the reaction components, i.e., the alcohol, catalyst, and coupling partner. However, all of these reactions were designed using the combination of hydrogen transfer and acceptorless dehydrogenation (Scheme 3.2). Two representative examples are discussed below.

In 2007, D. Milstein and co-workers reported a groundbreaking work in the intermolecular synthesis of an amide from an alcohol and an amine (Scheme 3.6).[23] They utilized 0.1 mol% of a pyridine-based pincer ruthenium catalyst, which follows a MLC mechanism involving aromatization-dearomatization of the pyridine ring (Scheme 3.5D); no additional base or hydrogen acceptor was required. The acceptorless dehydrogenation of the primary alcohol occurs to produce an aldehyde. After the formation of a hemiaminal from the aldehyde and amine, additional dehydrogenation furnishes the amide.



Scheme 3.6 Catalytic amide synthesis from an alcohol and an amine

The α-alkylation of a ketone with an alcohol as the alkylating reagent was reported by M. Yus and co-workers in 2006 (Scheme 3.7).[24] Although the substrate scope was limited to acetophenone and benzylalcohol, a simple ruthenium complex, $[RuCl_2(DMSO)_4]$ was successfully applied in borrowing hydrogen strategy without additional ligands. The benzyl alcohol is oxidized to a benzaldehyde, while the acetophenone is converted to an enolate under basic conditions. The enone generated from the benzaldehyde and the enolate is finally reduced to form an α-alkylated ketone. During this process, the hydrogen removed from the benzyl alcohol is transferred to the enone by the ruthenium catalyst.



Scheme 3.7 α-Alkylation of a ketone with an alcohol as the alkylating reagent

In addition to the examples described above, there are diverse examples of adaptations of transition-metal-catalyzed dehydrogenative alcohol activation:[11] the synthesis of amides from an alcohol and an azide[25] or from an alcohol and a nitrile,[26] lactone synthesis,[27] lactam synthesis,[28] imide synthesis,[29] imine synthesis,[30] N-alkylation of amine,[31] C-α-alkylation of ketones,[32] and others.

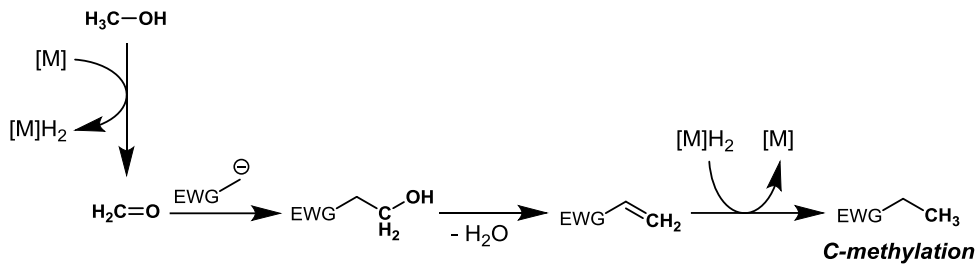
3.3 Dehydrogenative activation of methanol

Although methanol is also an alcohol, only limited examples of its dehydrogenation have been reported, in striking contrast to higher alcohols.[8,33] This is due to its higher thermodynamic requirements for dehydrogenation compared to higher alcohols (dehydrogenation of ethanol: ΔH = +68 kJ mol^{-1} vs ΔH = +84 kJ mol^{-1} for methanol)[33a] and catalyst deactivation by the carbon monoxide generated from methanol dehydrogenation.[34] Synthetic applications of the dehydrogenative activation of methanol up to the present time are discussed in this section.

3.3.1 Methanol utilization with carbon nucleophile

The construction of C–C bonds is always important issue in organic chemistry. Not surprisingly, there are several Nobel Prize winning reactions for the formation of C–C bonds, such as the Grignard reaction and Suzuki coupling. In particular, C-methylation is not only helpful for building organic molecules, but is also effective in some bioactive molecules owing to the "the magic methyl effect" originating from hydrophobic interactions.[35] The general reaction pathway for dehydrogenative methanol utilization with a carbon nucleophile is outlined in Scheme 3.8. Initially, methanol is transformed to formaldehyde via dehydrogenation, followed by the addition of a soft carbon nucleophile (stabilized carbanion). The resulting primary alcohol usually undergoes dehydration due to the stabilization of the resulting olefin intermediate by an electron withdrawing group. Subsequent hydrogenation produces the α-methylated product. When the β-position of the primary alcohol intermediate

is a quaternary center, dehydration is impossible, and the hydroxymethylated product is afforded. If the olefin intermediate from dehydration is captured by another nucleophile, the methanol can serve as a methylene group.



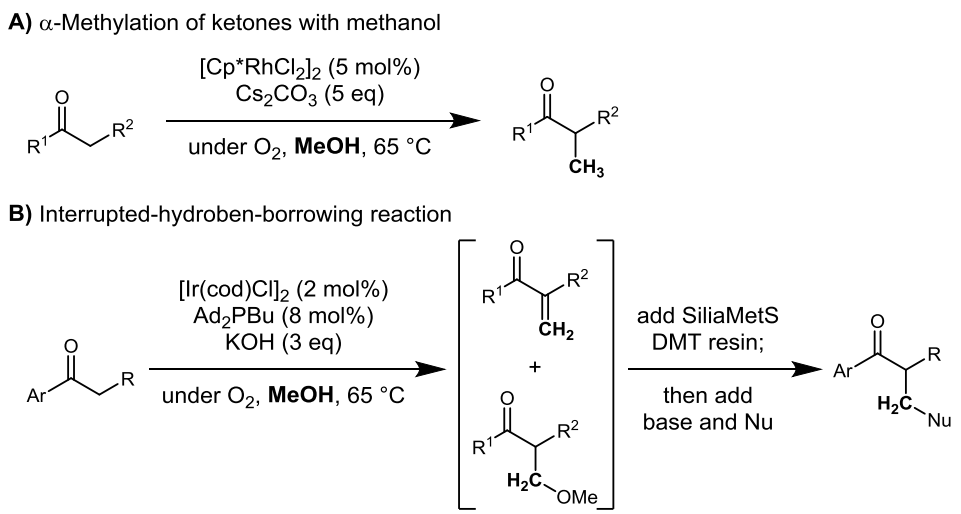
Scheme 3.8 General reaction pathway of dehydrogenative methanol utilization with a carbon nucleophile

Traditionally, the α-methylation of ketones was performed with diazomethane or iodomethane, which are explosive or toxic. Hence, the development of economical and non-toxic reaction conditions for α-methylation of ketone was required. A dehydrogenative approach was first achieved by T. J. Donohoe and co-workers in 2014 (Scheme 3.9A).[33c] $[Cp^*RhCl_2]_2$ was used in the presence of 5 equivalents of cesium carbonate for the enolization of the ketone. By utilizing an oxygen atmosphere as the hydrogen acceptor, the reaction proceeds at a mild temperature (65 ℃).

A year later, the same group found that the olefin intermediate can be captured by a second nucleophile under similar reaction conditions (Scheme 3.9B).[33d] The use of an iridium catalyst, $[Ir(cod)Cl]_2$, with a lower catalyst loading and a sterically

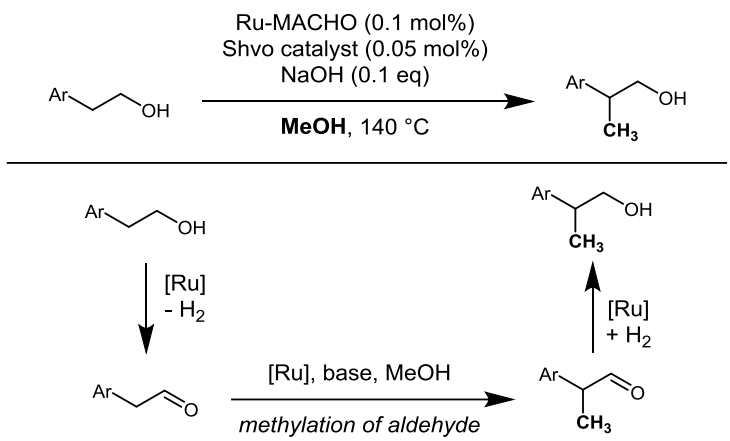
bulky ligand (Ad_2PBu; cataCXium A) enabled the reaction to be stopped at the intermediate mixture consisting of olefin and its methoxylated compound. After the addition of a metal scavenger resin (SiliaMetS DMT), the intermediate mixture can be captured by several nucleophiles, such as nitroalkane and ketone, in the presence of a base. Epoxidation with *tert*-butyl hydroperoxide (*t*-BuOOH) and benzylation with a boron reagent were also reported.

P. G. Anderson and co-workers found that an iridium complex with an N-heterocyclic carbene (Ir-NHC) can catalyze the α-methylation of ketone in the absence of a hydrogen acceptor.[36] The A. M. Seayad group[37] and Y. Obora group[38] reported catalytic system using a substoichiometric amount of a base with ruthenium and iridium complexes, respectively. Applying a similar strategy using a ketone, C. Cai and co-workers developed a $[Cp^*IrCl_2]_2$ catalyzed 3-methylation of indole with methanol.[39]



Scheme 3.9 α-Methylation of a ketone with methanol under an oxygen atmosphere

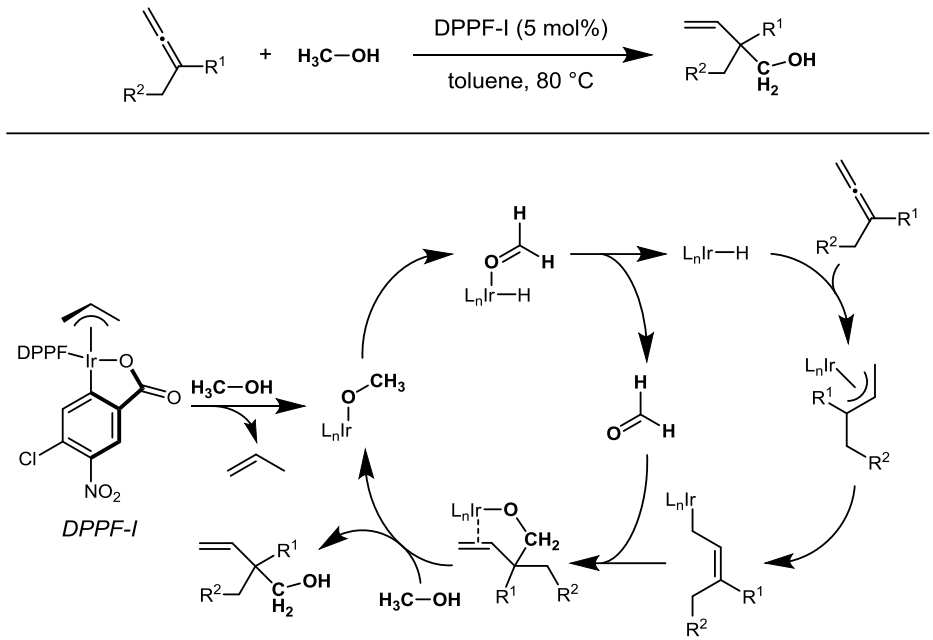
M. Beller and co-workers reported the β-methylation of alcohol with methanol (Scheme 3.10).[33h] Although 2-arylethanol does not contain an acidic C–H bond, the aldehyde generated in situ from the alcohol participates in the reaction. The α-methylated aldehyde is then reduced to a β-methylated alcohol. Interestingly, two kinds of ruthenium catalyst, Ru-MACHO and the Shvo catalyst, should be used for better activity, even though the reaction proceeds with only one of these catalysts.



Scheme 3.10 β-Methylation of an alcohol with methanol

The hydroxymethylation of an aliphatic carbon center via dehydrogenative methanol activation had not been reported due to the facile dehydration step (see Scheme 3.8). M. J. Krische and co-workers solved this problem through the hydrofunctionalization of a 1,1-disubstituted allene (Scheme 3.11).[40] At the beginning of the reaction, the complex DPPF-I dehydrogenates methanol to form formaldehyde and iridium hydride. The subsequent hydrometalation of the allene affords the allyl iridium complex. The allyl ligand of the iridium complex attacks formaldehyde, and an alcohol with a β-quaternary carbon center, which cannot

undergo dehydration, is obtained. They also achieved an enantioselective version of this reaction with a 1,1-disubstituted CF_3-allene by using an iridium precursor and chiral diphosphine ligand.[41]

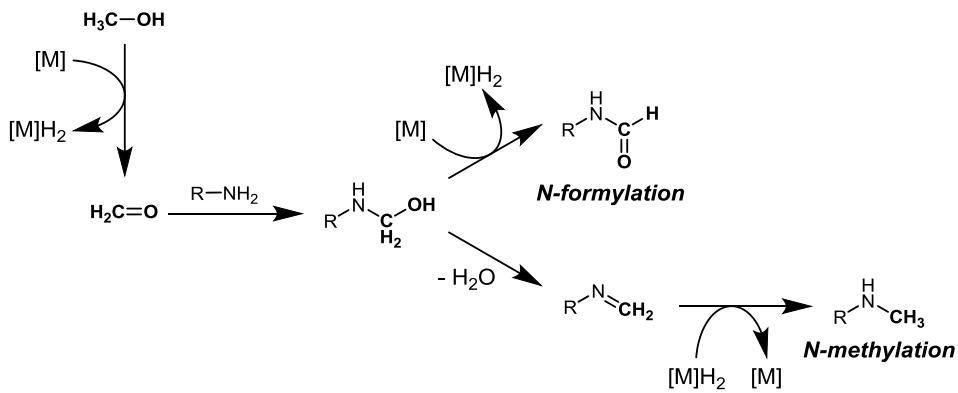


Scheme 3.11 Hydroxymethyl group installation of an allene with methanol

3.3.2 Methanol utilization with nitrogen nucleophile

Amines are one of the most easily accessible classes of nucleophiles in organic chemistry. Accordingly, many reactions between amines and methanol have been developed. They are largely divided into N-methylation and N-formylation reactions (Scheme 3.12). First, methanol is transformed into formaldehyde by the dehydrogenation catalyst. When the amine attacks the formaldehyde, a hemiaminal intermediate is generated. This intermediate is common to both transformations, and

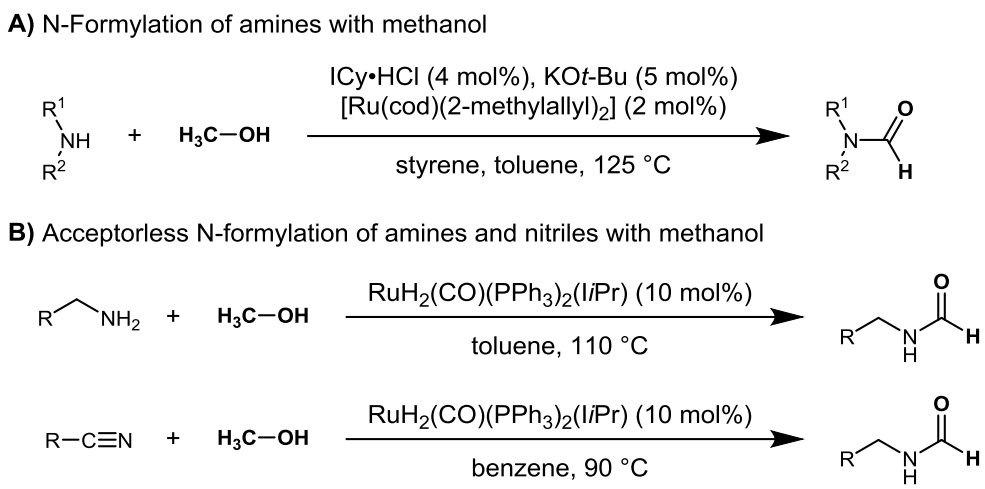
can undergo either dehydrogenation or dehydration. If further dehydrogenation is facilitated, N-formylation occurs, while dehydrogenation affords the imine, which is reduced to the N-methylated product. Depending on the reaction conditions, the N-formylated product, formamide, can act as an electrophile, whereas the N-methylated product can take part in a second N-methylation or N-formylation.



Scheme 3.12 General reaction pathway for dehydrogenative methanol utilization with a nitrogen nucleophile

N-formylation is a basic transformation, and is also known to play an important role in post-translational regulation steps and protein biosynthesis.[42] In traditional methods, a stoichiometric amount of the formylating reagent (ethyl formate, formic acid, or formamide) is used, which produces the corresponding number of equivalents of the byproducts. F. Glorius and co-workers utilized methanol as an N-formylating reagent for amines (Scheme 3.13A).[33f] The use of the bis-NHC ruthenium complex generated in situ from *N*,*N*′-dicyclohexylimidazolium chloride (ICy•HCl), potassium *tert*-butoxide (KO*t*-Bu), and [Ru(cod)(2-methylallyl)$_2$] as the active catalyst was suggested. The use of methanol in solvent quantity was not

required, but styrene was required as a hydrogen acceptor, resulting in equivalents of ethylbenzene being produced as a byproduct. S. H. Hong and co-worker solved this problem by using a mono-NHC ruthenium complex, $[RuH_2(CO)(PPh_3)_2(I\textit{i}Pr)]$ (Scheme 3.13B).[33m] In addition, nitriles can be N-formylated under similar reaction conditions after in situ reduction to an amine.

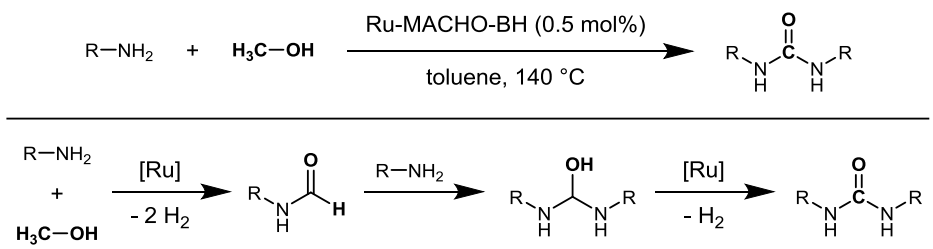


Scheme 3.13 N-formylation of amines and nitriles with methanol

Non-precious transition-metal-catalyzed N-formylation reactions have recently been reported. The D. W. C. Milstein group[43] and the W. Bernskoetter group[44] developed manganese- and iron-catalyzed N-formylation of amines, respectively.

The further reaction of in situ produced formamide was explored by the S. H. Hong group. They demonstrated the synthesis of urea from an amine and methanol (Scheme 3.14).[33n] The formamide synthesized from the amine and methanol is attacked by another molecule of the amine to form the hemiaminal analogue, followed by dehydrogenation to give urea. Classical urea synthesis employs toxic

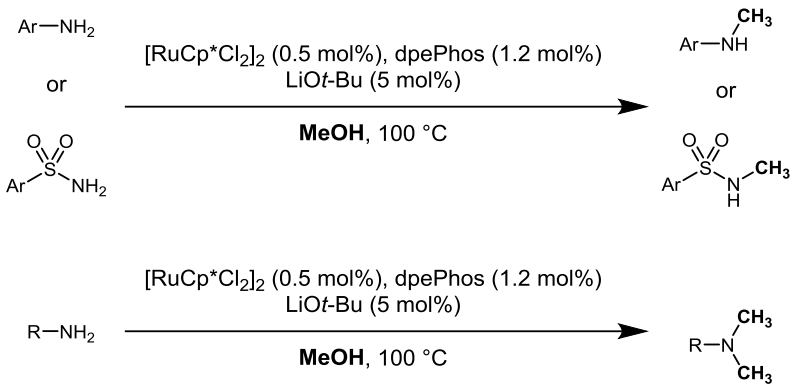
reagents such as phosgene or carbon monoxide. Alternatively, an isocyanate intermediate can be utilized, but this requires the use of expensive dehydrating reagents such as di-*tert*-butyl azodicarboxylate (DBAD) in stoichiometric amounts, limiting the utility of these methods. The developed reaction proceeds with Ru-MACHO-BH catalyst in the absence of bases or additives, and hydrogen gas is the only byproduct. Asymmetric urea can also be synthesized via a one-pot two-step strategy.



Scheme 3.14 Urea synthesis from an amine and methanol

In addition to C-methylation, the N-methylation of amines also has great biological significance. N-methylation not only plays a crucial role in epigenetics, being involved in DNA methylation and protein modification,[45] but also results in a dramatic change in the biological activity of medicinal compounds.[46] The first example of the N-methylation of an amine with methanol was reported by R. Grigg and co-workers.[47] Although only few amines were tested at long reaction times, methanol can be used as a methyl source in the presence of the catalyst $RhH(PPh_3)_4$. A practical homogenous catalytic system was developed by the A. M. Seayad group (Scheme 3.15).[48] With the aid of the $[RuCp^*Cl_2]_2$ complex and the diphosphine ligand dpePhos, methanol was transformed into a methyl group bonded to a nitrogen

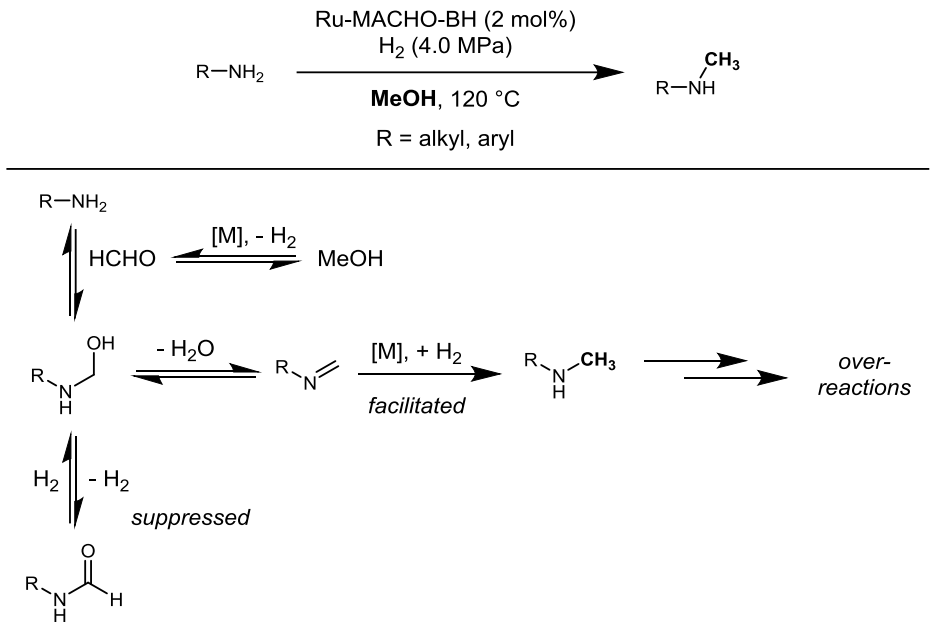
atom. It is noteworthy that aryl amines and sulfonamides undergo monomethylation, whereas aliphatic amines undergo dimethylation. This trend can be explained by their nucleophilicity and sterics. In contrast to secondary aryl amines, secondary aliphatic amines are more strongly nucleophilic. Their strong nucleophilicity can overcome the steric hindrance to allow the further second methylation reaction.



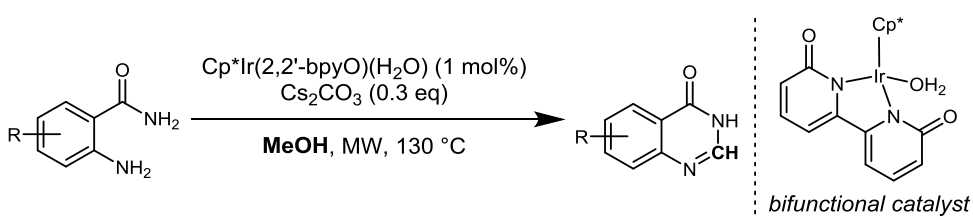
Scheme 3.15 Monomethylation of aryl amines and dimethylation of aliphatic amines with methanol

This trend was repeatedly observed in other catalytic systems.[49] Recently, S. H. Hong and co-worker accomplished the monomethylation of an aliphatic amine through the addition of hydrogen gas and careful adjustment of the reaction conditions (Scheme 3.16).[50] The additional hydrogen pressure suppressed the undesired N-formylation reaction and facilitated the desired N-methylation reaction. Further reaction could be prevented by lowering the temperature and modulating the reaction time. The developed reaction conditions were applicable to biologically relevant compounds.

Methanol can serve as a –CH– source when an imine intermediate is captured by another nucleophile during the N-methylation mechanism. F. Li and co-workers realized this concept with *o*-aminobenzamides by using the metal-ligand bifunctional catalyst [Cp*Ir(2,2′-bpyO)(H_2O)] (Scheme 3.17).[51] The reaction proceeded well regardless of the electronic properties of the starting material, and higher alcohols could also be incorporated in the molecule.



Scheme 3.16 Monomethylation of aryl amines and dimethylation of aliphatic amines with methanol in the same catalytic system



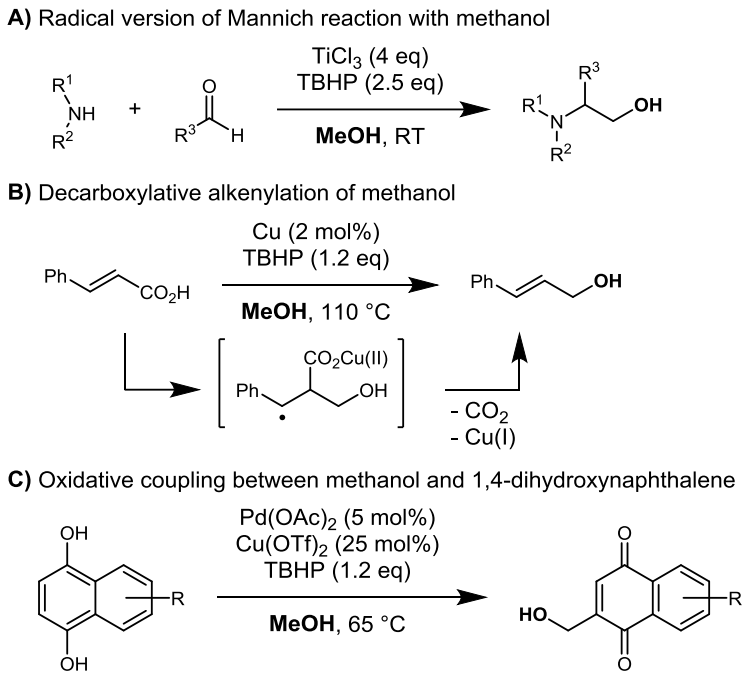
Scheme 3.17 Construction of quinazolinone with methanol as a –CH– source

3.4 Methanol utilization via radical pathway

Dehydrogenative activation essentially allows methanol act as an electrophilic carbon source. Hence, its coupling partners are limited to nucleophiles such as stabilized carbanions and amines. Open-shell systems have expanded the range of coupling partners for methanol. Unfortunately, the bond dissociation energy (BDE) of the α-C–H bond of methanol (96 kcal/mol)[52] is far higher than those of activated C–H bonds, such as the α-C–H bonds of ketones, allylic C–H bonds, acyl C–H bonds, and benzyl C–H bonds (~88 kcal/mol).[53] Thus, there are only limited examples of the utilization of methanol via radical pathways;[53-54] more examples can be found for higher alcohols,[53,54b-d,55] which have a BDE of 92 kcal/mol for the α-C–H bond.[53]

In 2008, O. Porta and co-workers developed a radical version of the Mannich reaction (Scheme 3.18A).[54a] Unlike in the typical Mannich reaction, which employs a nucleophile, a hydroxymethyl radical is added to the in situ generated iminium cation. The *tert*-butoxy radical, which is produced from a Ti(III) species and *tert*-butyl hydroperoxide (TBHP), abstracts the α-C–H bond of methanol to form a hydroxymethyl radical. In the decarboxylative alkenylation of methanol reported by Z.–Q. Liu and co-workers, the hydroxymethyl radicals undergo addition to a copper(II) cinnamate intermediate (Scheme 3.18B).[54b] After liberating carbon dioxide and a copper(I) species, the desired compound is obtained. Y. R. Lee and co-workers proposed that formaldehyde might be generated from methanol through double oxidation in their oxidative coupling reaction between methanol and 1,4-dihydroxynaphthalene (Scheme 3.18C).[54c] These examples successfully utilized methanol via a radical pathway, affording products that are difficult to access via dehydrogenative activation due to the necessity for an electrophilic coupling partner.

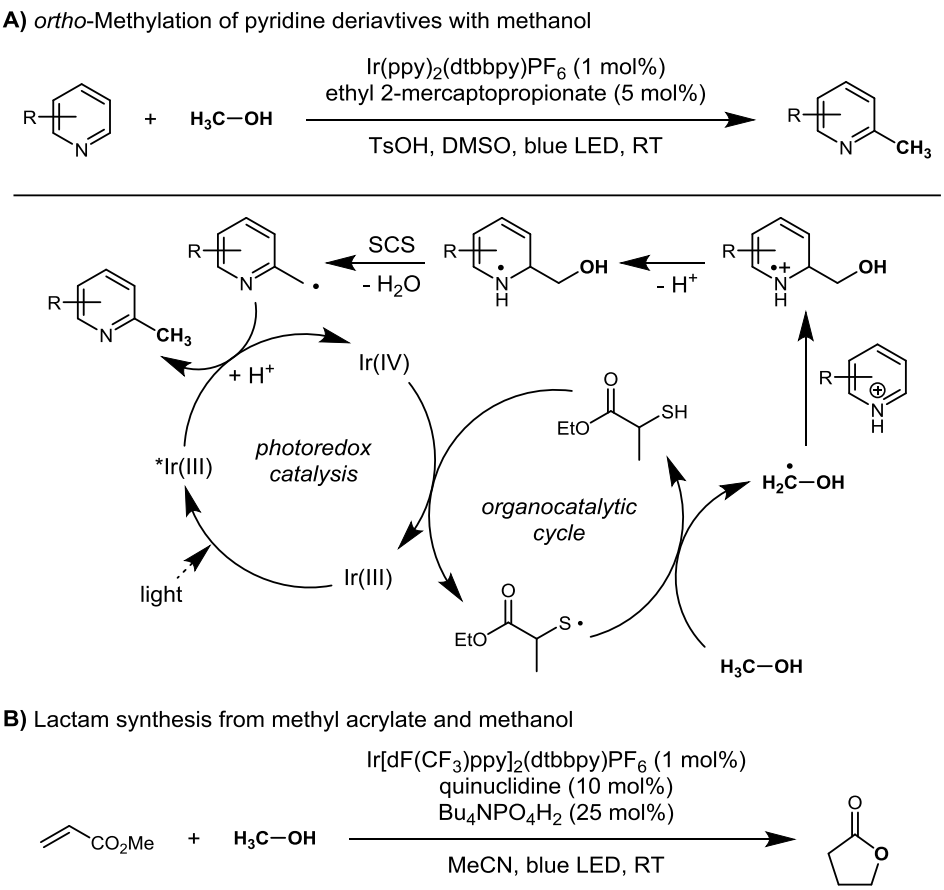
However, these methods required a stoichiometric amount of peroxide and a solvent amount of methanol.



Scheme 3.18 Utilization of methanol via a radical pathway with stoichiometric amounts of the oxidants

In 2005, D. W. C. MacMillan and co-workers neatly solved this problem through dual catalysis using a photocatalyst and an organocatalyst (Scheme 3.19A).[54d] The organocatalyst, ethyl-2-mercaptopropionate, is oxidized by the photocatalyst to form a thiyl radical. Polarity-reversal catalysis (PRC) enables facile hydrogen abstraction from the α-position of methanol by the thiyl radical.[56] The resulting hydroxymethyl radical undergoes Minisci-type addition to the pyridinium

ion. Through successive deprotonation, spin-center shift (SCS),[57] and reduction by the photocatalyst, *ortho*-methylated pyridine derivatives are obtained. In the same year, methanol activation was further developed by the addition of quinuclidine as an organocatalyst and ammonium phosphate salt (Scheme 3.19B).[53] Hydrogen bonding between the salt and methanol weakens the α-C–H bond of methanol, allowing it to be more easily and selectively activated by the quinuclidine radical cation. Using this strategy, lactam was synthesized from methyl acrylate and methanol.



Scheme 3.19 Utilization of methanol via a radical pathway through dual catalysis with a photocatalyst and organocatalyst

3.5 Conclusion

Over the past decades, the dehydrogenation of alcohols has been extensively studied and applied in many synthetic methods. Several mechanistic issues, including mono/dihydride species, inner/outer-sphere mechanisms, and metal-ligand cooperation, have been addressed and utilized in the catalyst design. The basic principles of the dehydrogenative activation of higher alcohols can be adapted well to methanol, despite its challenging thermodynamic requirements.

However, considerable scope still remains for the further use of methanol dehydrogenation chemistry in synthetic applications. For example, few selective multi-component reactions in the presence of different nucleophiles have been studied. The development of efficient, robust, selective, tolerant, and inexpensive catalysts and reaction conditions is still highly desirable.

Approaches involving the generation of open shell intermediates from methanol have allowed non-nucleophilic coupling partners to be employed; however, only a handful examples have been reported. Thus, the application of radical methods to more diverse coupling partners is another remaining challenge.

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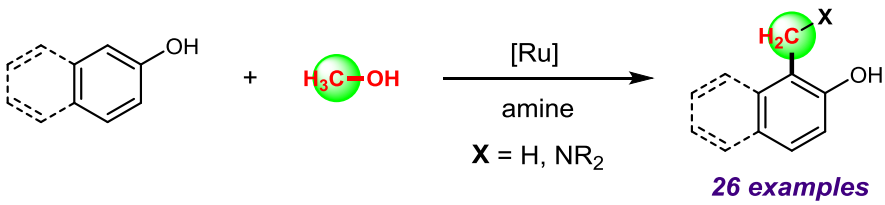
Chapter 4. Ruthenium-Catalyzed Aminomethylation and Methylation of Phenol Derivatives Utilizing Methanol as the C1 Source*



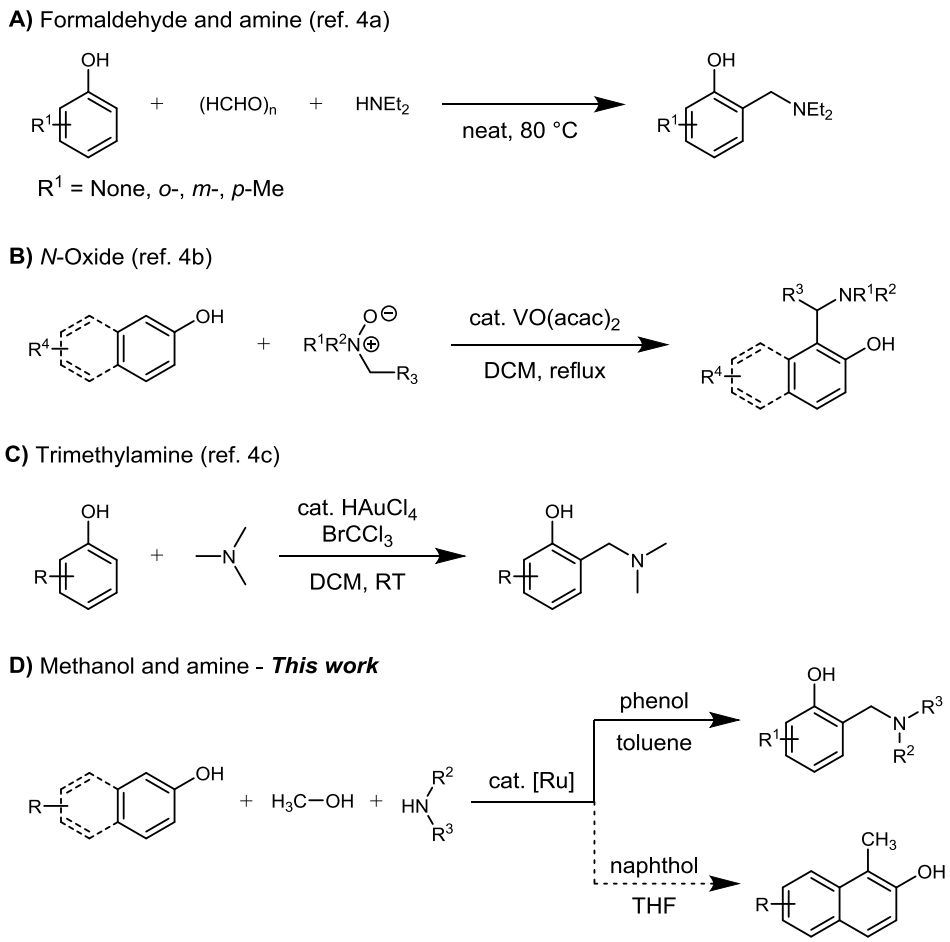
Utilization of Methanol as an Electrophilic C1 Source

* The majority of this work has been published: Seoksun Kim and Soon Hyeok Hong*, *Adv. Synth. Catal.* **2017**, *359*, 798-810.

4.1 Introduction

Since the Fridel-Crafts reactions were discovered,[1] a number of phenol functionalization methods have been extensively developed. Among those transformations, preparation of *ortho*-aminomethylated phenol structure, which can be found in various compounds such as pharmaceuticals[2] and ligands for transition metals,[3] is one of the most important types of phenol functionalization. Classically, this structure could be obtained by utilizing Eschenmoser's salt as a common intermediate,[4] but unfortunately, stoichiometric amounts of reactive species such as pre-generated salt itself, *N*-oxide, or $BrCCl_3$ are required for the reaction to proceed (Scheme 4.1).

In pursuit of environmentally benign synthesis[5] without pre-activation of substrates,[6] we designed a catalytic *ortho*-aminomethylation of phenol utilizing methanol as the methylation source. Methanol has emerged as a potential renewable resource[7] as the development of CO_2 reduction[8] and biomass conversion chemistry.[9] In the utilization of methanol as a C1 source, a commonly used strategy is *in situ* generation of formaldehyde via dehydrogenative activation of methanol. The formaldehyde intermediate generated, which acts as an electrophile, can be transformed to a hydroxymethyl group through nucleophilic attack.[10] Further dehydrogenation could afford compounds containing carbonyl groups.[11] If dehydration is facilitated rather than dehydrogenation, an $X{=}CH_2$ (X = CR_2, NR, NR_2^+) type intermediate is formed, which could be further converted to a methyl [12] or methylene group.[13]



Scheme 4.1 Classical and developed synthetic methods for *ortho*-aminomethylation of phenol derivatives

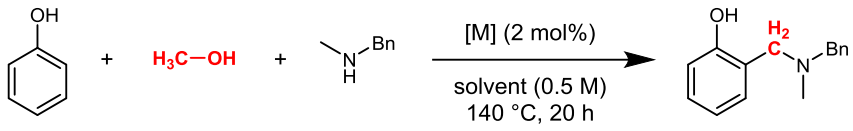
In this context, we envisioned that *ortho*-aminomethylation of phenol can be achieved by using methanol and an amine through an activated intermediate such as an iminium cation formed by successive dehydrogenation and dehydration reactions.[14] Formaldehyde generated *in situ* from methanol can be captured by two nucleophiles, phenol and the amine. Reactions between nucleophiles and formaldehyde often suffer from unwanted side reactions such as dimerization or oligomerization through bridging methylene groups.[13b,15] In this case, the desired 3-component reaction was successfully controlled without significant formation of possible side products such as 2,2'-methylenediphenol. Recently developed hydroaminomethylation and dehydrogenation sequence can also be considered as a possible reaction pathway for this transformation.[16] In the case of naphthol, we observed methylation instead of aminomethylation. Only a few methods were reported for catalytic methylation of naphthol with methanol using heterogeneous catalyst under harsh reaction conditions ($\geq$ 200 ºC).[17] Plausible intermediates and reaction pathways were proposed for each reaction on the basis of the mechanistic studies.

4.2 Results and discussion

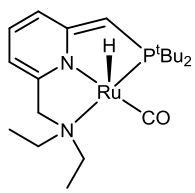
4.2.1 Optimization for the *ortho*-aminomethylation of phenol

We began our study on the *ortho*-aminomethylation of phenol with *in situ* generated (I*i*Pr)$RuH_2(CO)(PPh_3)_2$, which was used as a dehydrogenation catalyst in our previous report.[18] In the initial attempt, **4a** was obtained in 8% yield (Table 4.1, entry 1). *N*-methyl-*N*-benzylformamide (**7**) was observed as the major byproduct. Various dehydrogenation catalysts were then tested (Table 4.1, entries 2–9). The iridium complex, which is highly active for the dehydrogenation of alcohols, did not afford the desired product,[19] while Milstein catalyst[14f] and Shvo's catalyst[20] did not catalyze the reaction at all (Table 4.1, entries 2–4). $Ru(acac)_3$ catalyst with triphos ligand system[21] gave 49% yield (Table 4.1, entry 8). Among the catalyst tested, Ru-MACHO-BH exhibited the highest efficiency (Table 4.1, entry 9). When increased equivalents of the amine and elevated temperature were used, 78% of **4a** could be obtained (Table 4.1, entry 10). The developed reaction showed exclusive *ortho*-selectivity, no other regioisomer being formed. Other tested solvents did not show better reactivity than toluene (Table 4.1, entries 11–14). We also confirmed that the reaction was tolerant to moisture (Table 4.1, entry 15). Lowered temperature gave a moderate yield of **4a** (Table 4.1, entry 16). The reaction under air exhibited lower efficiency (Table 4.1, entry 17).

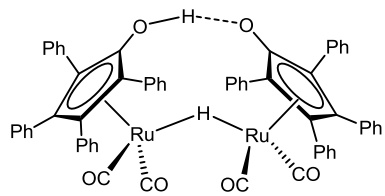
Table 4.1 Optimization of the reaction conditions[a]



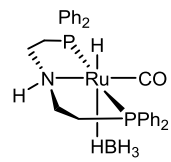
1a **2** **3a** **4a**



Milstein catalyst



Shvo's catalyst



Ru-MACHO-BH

Entry	[M]	Base	Solvent	Yield[b]
1	$RuH_2(CO)(PPh_3)_3$ / I*i*Pr·HBr	2 NaH	Toluene	8
2	$[Cp^*IrCl_2]_2$	NaOAc	Toluene	0
3	Milstein catalyst	-	Toluene	0
4	Shvo's catalyst	-	Toluene	0
5	$[Ru(p\text{-cymene})Cl]_2$ / 2 dppb	KO*t*-Bu	Toluene	5
6	$RuH_2(PPh_3)_4$	-	Toluene	5
7	$RuHCl(CO)(PPh_3)_4$	KO*t*-Bu	Toluene	10
8	$Ru(acac)_3$ / 2 triphos	-	THF	49
9	Ru-MACHO-BH	-	Toluene	61
10[c]	Ru-MACHO-BH	-	Toluene	78
11[c]	Ru-MACHO-BH	-	THF	65
12[c]	Ru-MACHO-BH	-	DCE	0

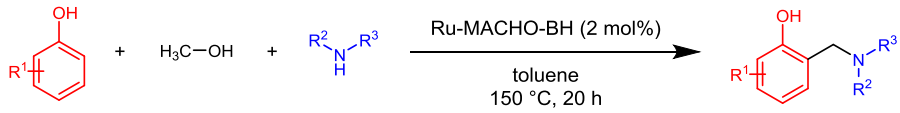
13[c]	Ru-MACHO-BH	-	MeCN	0
14[c]	Ru-MACHO-BH	-	neat	46
15[c],[d]	Ru-MACHO-BH	-	Toluene	72
16[e]	Ru-MACHO-BH	-	Toluene	56
17[c],[f]	Ru-MACHO-BH	-	Toluene	37

[a] *Reaction conditions:* **1a** (0.50 mmol, 1.0 equiv.), **2** (2.50 mmol, 5.0 equiv.), **3a** (0.50 mmol, 1.0 equiv.), [M] (0.01 mmol per metal center, 2 mol%), base (0.01 mmol, 2 mol%), 140 °C, 20 h in toluene (1.0 mL, 0.5 M), in a sealed tube. I*i*Pr·HBr = 1,3-diisopropylimidazolium bromide. [b] Yields were determined by ^{1}H NMR with CH_3NO_2 as an internal standard. [c] 2.0 equiv. of **3a** were used. 150 °C. [d] 1.0 equiv. of H_2O was added. [e] 2.0 equiv. of **3a** were used. 130 °C. [f] Under air.

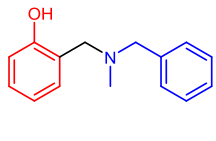
4.2.2 Substrate scope for the *ortho*-aminomethylation of phenol

The substrate scope was subsequently explored (Table 4.2). Electron-rich phenols as well as a conjugated phenol smoothly participate in the developed reaction (**4b**–**4e**). The reaction efficiency was not significantly affected by halide substituents on phenol (**4f**–**4h**). The *ortho*-aminomethylated product of *ortho*-substituted phenol could also be obtained in a moderate yield (**4i**). When anisole was employed as a substrate, the desired transformation was not observed, indicating that deprotonation of the acidic proton by the amine is an important step in the reaction. The reactions involving various acyclic secondary amines were also efficient (**4j**–**4l**). Unfortunately, when the steric hindrance of the amine was increased, the desired product was not observed (**4m**). Diverse cyclic secondary amines were tested from 5- to 7-membered rings (**4n**–**4t**). Regardless of the ring size, good yields of the desired products were obtained. When a primary amine was employed, poor reactivity was observed (**4u**). The formation of the imine rather than the iminium cation might be the reason for this observation, which could be attributed to the low electrophilicity of the former (Scheme 4.5). In low yielding cases such as **4h**, **4s**, **4u**, poor conversion of starting materials was observed.

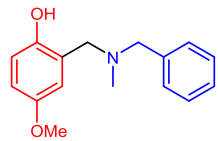
Table 4.2 Scope of *ortho*-aminomethylation reaction[a]



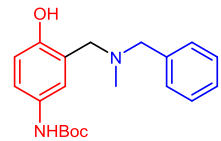
1 **2** **3** **4**



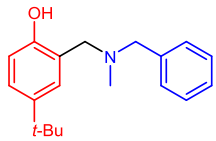
4a, 70%



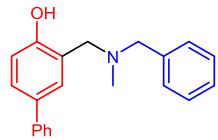
4b, 76%



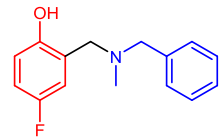
4c, 56%



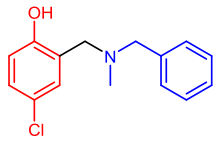
4d, 70%



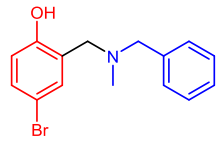
4e, 77%



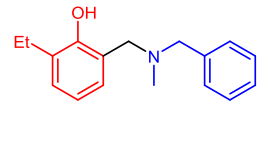
4f, 78%



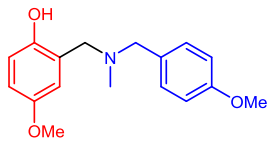
4g, 64%[c]



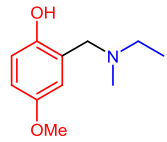
4h, 45%[b],[c],[d]



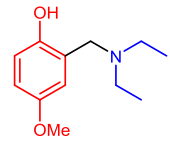
4i, 60%



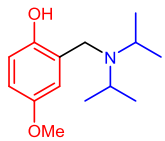
4j, 74%



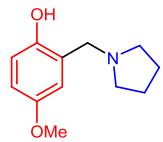
4k, 75%[b],[e]



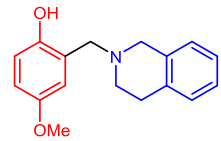
4l, 41%[b]



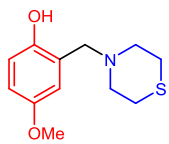
4m, N. D.[b]



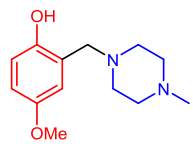
4n, 78%



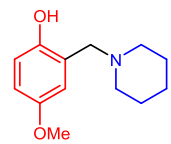
4o, 77%



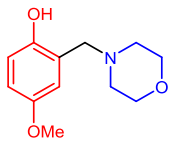
4p, 76%



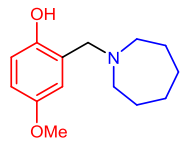
4q, 74%



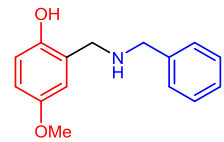
4r, 71%



4s, 42%



4t, 66%



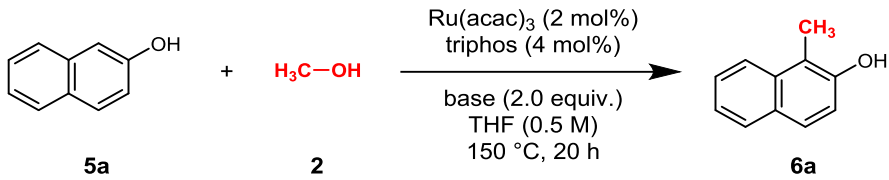
4u, 29%[b]

[a] *Reaction conditions:* **1** (0.50 mmol, 1.0 equiv.), **2** (2.50 mmol, 5.0 equiv.), **3** (1.0 mmol, 2.0 equiv.), Ru-MACHO-BH (0.01 mmol, 2 mol%), 150 °C, 20 h in toluene (1.0 mL, 0.5 M), in a sealed tube. N. D. = Not determined. Isolated yields reported. [b] 44 h. [c] 15 mol% of NaOMe were added. [d] 5 mol% of catalyst was used. [e] 4 equiv. of amine were used.

4.2.3 Optimization for the methylation of naphthol

Interestingly, when similar reaction conditions were applied to 2-naphthol, 1-methyl-2-naphthol (**6a**) was obtained almost quantitatively, with the production of **7** from **3a** (Table 4.3, entry 2). The reaction without methanol did not give **6a** (Table 4.3, entry 3). This result implies that methanol, rather than **3a**, is the methyl source for the product. The yield significantly dropped when a reduced temperature was applied (Table 4.3, entry 4). Surprisingly, **3a** showed superior efficiency compared to other inorganic bases (Table 4.3, entries 5–7). When the more economical pyrrolidine was introduced as a base, a quantitative yield was obtained, while the tertiary amine showed no reactivity (Table 4.3, entries 8 and 10). Substoichiometric amounts of pyrrolidine gave a reasonable, but slightly decreased, yield of the product (Table 4.3, entry 11).

Table 4.3 Effect of base on methylation of 2-naphthol[a]



5a **2** **6a**

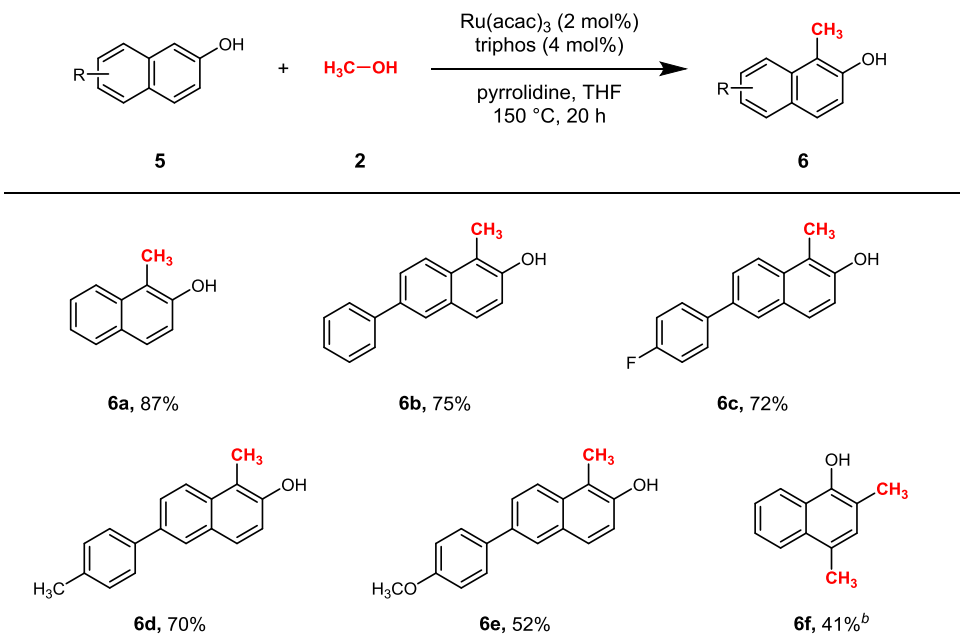
Entry	Base	Yield[b] (%)
1[c]	BnMeNH (**3a**)	24
2	BnMeNH (**3a**)	98
3[d]	BnMeNH (**3a**)	0
4[e]	BnMeNH (**3a**)	39
5	K_2CO_3	0
6	KOH	8
7	$NaHCO_3$	16
8	DIPEA	0
9	Hexamethyleneimin	49
10[f]	pyrrolidine	>99
11[g]	pyrrolidine	92

[a] *Reaction conditions:* **5a** (0.50 mmol, 1.0 equiv.), **2** (2.50 mmol, 5.0 equiv.), $Ru(acac)_3$ (0.01 mmol, 2 mol%), triphos (0.02 mmol, 4 mol%), base (1.00 mmol, 2.0 equiv.), 150 °C, 20 h in THF (1.0 mL, 0.5 M), in a sealed tube. [b] Yields were determined by ^1H NMR with CH_3NO_2 as an internal standard. [c] Ru-MACHO-BH (2 mol%) and toluene (1.0 mL, 0.5 M) were used instead of $Ru(acac)_3$, triphos, and THF. [d] **2** was not added. [e] 140 °C. [f] 1.0 equiv. of amine and 4.0 equiv. of **2** were used. [g] 0.5 equiv. of amine and 4.0 equiv. of **2** were used.

4.2.4 Substrate scope for the methylation of naphthol

We then investigated the substrate scope for the methylation of 2-naphthol (Table 4.4). Biaryl substrates with various kinds of substituents gave good yields of the desired products (**6b**–**6e**). When 1-naphthol was employed with increased amount of **2**, a moderate yield of the dimethylated product was obtained (**6f**). Compared to the previous catalytic methods utilizing methanol for the methylation of naphthols, our method operates under relatively milder reaction conditions and showed better substrate scope.[17] Furthermore, the overall reaction yields were better than methods utilizing stoichiometric amount of methyl iodide or diiodomethane.[22]

Table 4.4 Scope of methylation reaction[a]



[a] *Reaction conditions:* **5** (0.50 mmol, 1.0 equiv.), **2** (2.00 mmol, 4.0 equiv.), $Ru(acac)_3$ (0.01 mmol, 2 mol%), triphos (0.02 mmol, 4 mol%), pyrrolidine (0.50 mmol, 1.0 equiv.), 150 ℃, 20 h in THF (1.0 mL, 0.5 M), in a sealed tube. Isolated yields reported. [b] 10.0 equiv. of **2** were used.

4.2.5 Mechanistic studies

The possible reaction pathways for each reaction were investigated by observing the reactivities of phenol and naphthol. First, changes in the levels of each substrate and product in the *ortho*-aminomethylation of phenol over time were measured by ^{1}H NMR spectroscopy (Figure 4.1). The production of **4b** was observed as **1b** and **3a** were consumed. At the same time, gradual accumulation of formamide **7** was observed.

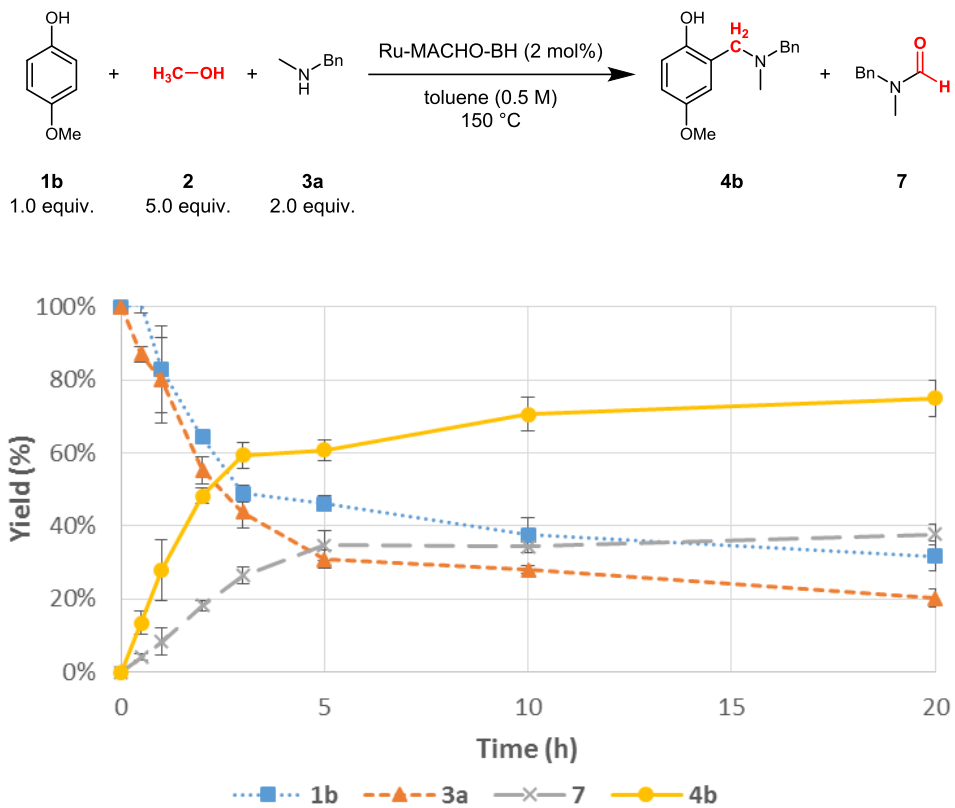
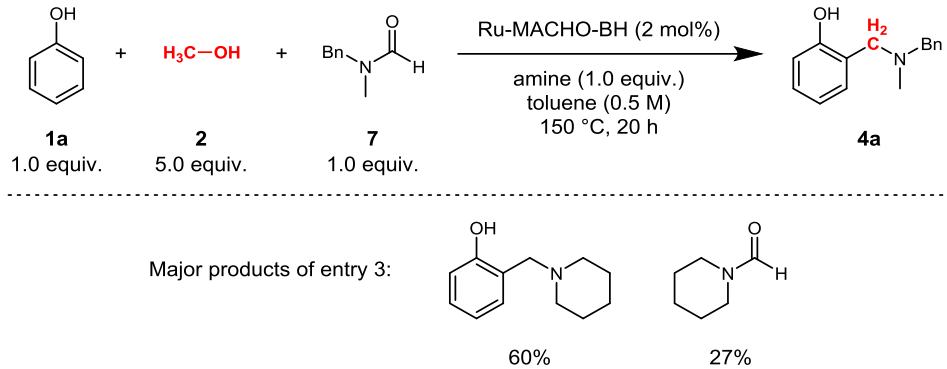


Figure 4.1 Kinetic profile of *ortho*-aminomethylation of **1b**. Error bars were calculated from three repetitions.

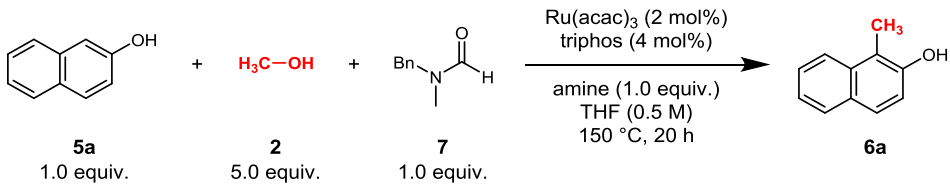
The reactions between the nucleophiles and **7** were performed to determine if formamide **7** acts as an electrophile in the reaction (Tables 4.5 and 4.6). For each reaction, the remained amount of **7**, and yields of **3a** and the desired products were measured via ^{1}H NMR spectroscopy. When **1a** was employed without base or with DIPEA, only marginal conversion of **7** was observed, with a poor yields of **4a** (Table 4.5, entries 1 and 2). When piperidine was added, the *ortho*-aminomethylated product and the formamide of piperidine were obtained in 60% and 27% yields, respectively. However, production of **4a** was still poor (Table 4.5, entry 3). The reactions between **5a** and **7** also gave poor yield of **6a** without significant conversion of **7** (Table 4.6, entry 1). When pyrrolidine was added, the yield of **6a** significantly increased (Table 4.6, entry 2). These experimental results strongly support our hypothesis that free secondary amine, and not formamide, is involved in both reactions.

Table 4.5 Reaction between phenol and formamide



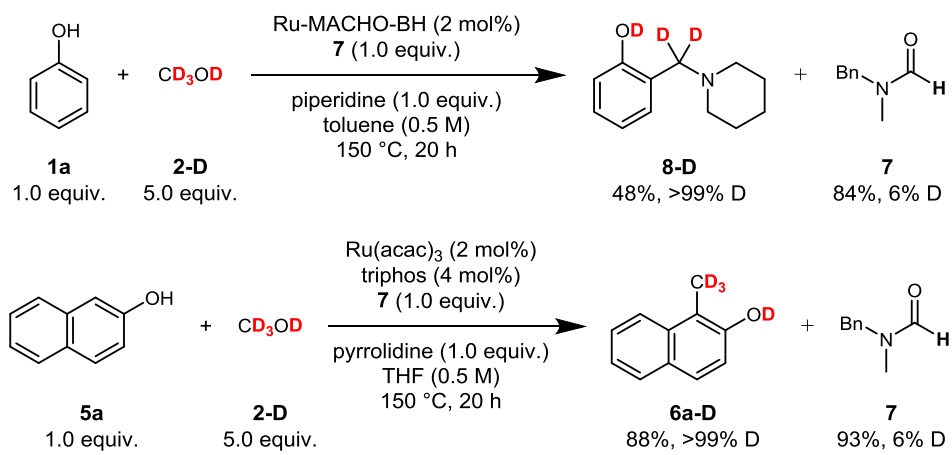
Entry	Amine	**7**	**3a**	**4a**
1	None	93%	1%	6%
2	DIPEA	94%	0%	6%
3	piperidine	84%	4%	3%

Table 4.6 Reaction between naphthol and formamide



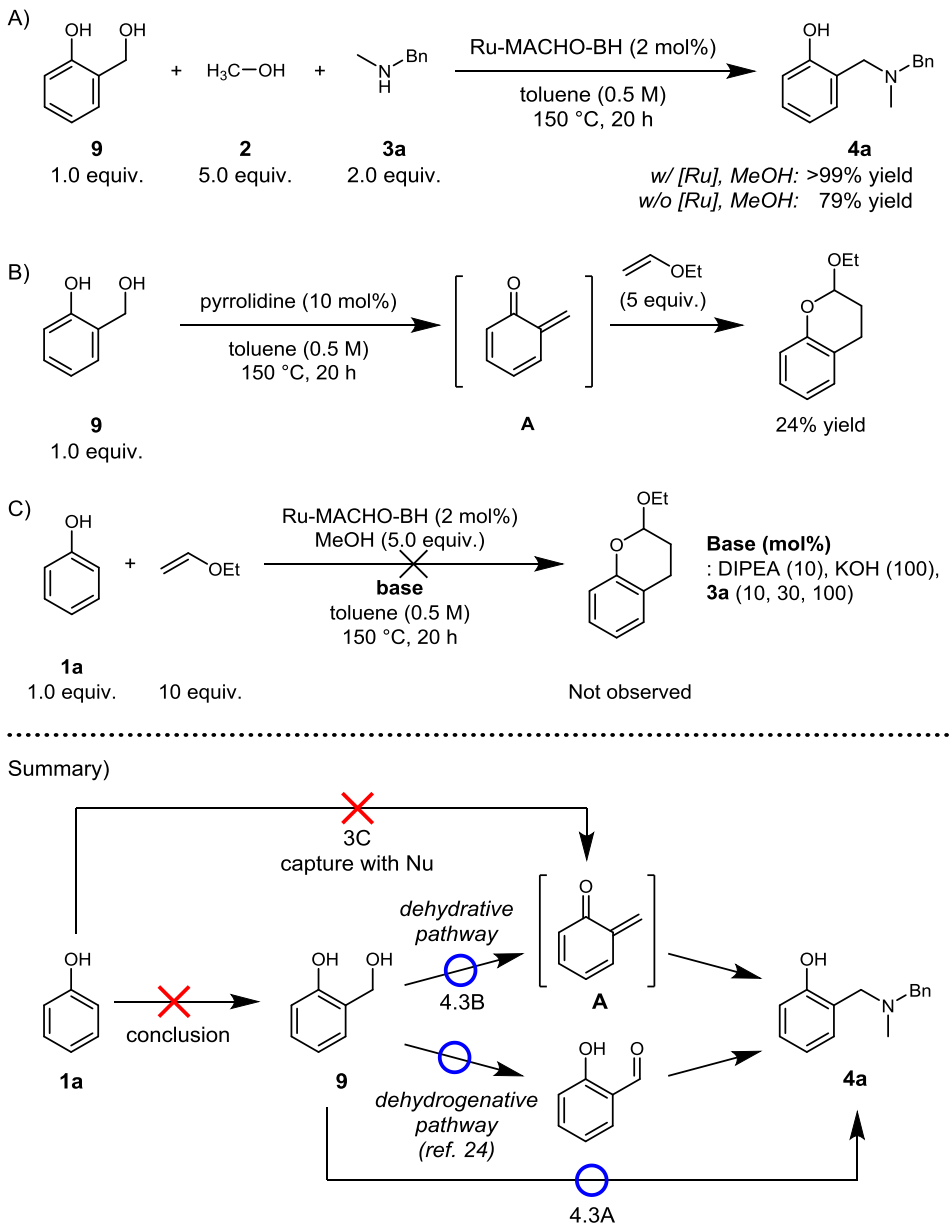
Entry	Amine	**7**	**3a**	**6a**
1	None	100%	0%	20%
2	pyrrolidine	90%	10%	89%

The involvement of formamide was further examined by deuterium labelling (Scheme 4.2). When reactions were conducted with deuterated methanol (**2-D**) in the presence of **7**, the deuterated products, **8-D** and **6a-D**, were obtained without formation of **8** and **6a**. Concurrently, deuterium scrambling on **7** occurred to a minimal extent. These results demonstrate that formamide formation is almost irreversible under the developed reaction conditions. Based on the control experiments and the deuterium labelling study, we concluded that formamide forms almost irreversibly and barely participates in both alkylation reactions.



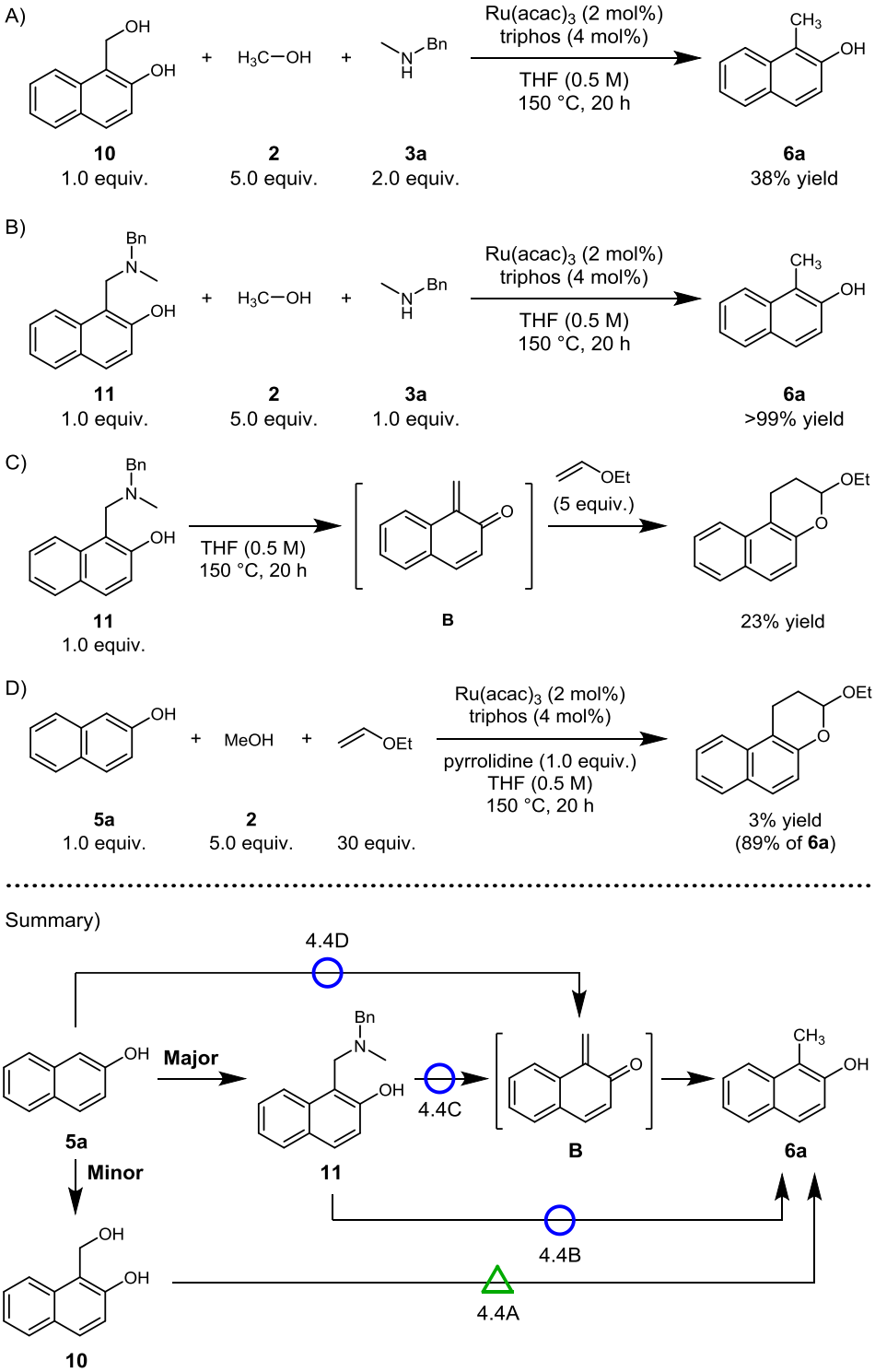
Scheme 4.2 Deuterium labelling study

We then hypothesized that formaldehyde or the iminium cation might react with nucleophiles in both reactions. If phenol reacts with the iminium cation, the aminomethylated product can be formed directly. Hence, in the case of phenol, involvement of formaldehyde was considered via control experiments (Scheme 4.3). Firstly, we examined the reactivity of 2-hydroxybenzyl alcohol (**9**) which can be formed from formaldehyde and phenol. **9** could be transformed to **4a** quantitatively under the standard reaction conditions (Scheme 4.3A). Noticeably, a significant amount of **4a** was still formed in the absence of Ru catalyst and methanol, possibly through dehydrative transformation to *ortho*-quinone methide.[23] Accordingly, we assumed that both the dehydrogenative pathway via reductive amination[24] and the dehydrative pathway via *ortho*-quinone methide[23] can significantly contribute to the reaction if **9** is generated during the reaction. The dehydrogenative pathway was previously reported,[24] and the feasibility of the dehydrative pathway was investigated by capturing *ortho*-quinone methide (**A**) from **9** via the Diels-Alder reaction (Scheme 4.3B).[25] However, when we started from **1a**, attempts to capture **A** with ethyl vinyl ether (Scheme 4.3C) or several nucleophiles, such as imidazole, 2-phenyl ethanethiol and 2,5-dimethylpyrrole, all failed, contrary to the reaction involving naphthol (Scheme 4.4D). In addition, we could not observe **9** and 2-methylphenol via the spectroscopic analyses done during the reaction. Reaction between phenol and formaldehyde also did not give any meaningful product such as **9**. Thus, we concluded that involvement of **9** is not likely in the case of phenol.



Scheme 4.3 Possible intermediates in *ortho*-aminomethylation of phenol

In the case of 2-naphthol, it is known that the reaction between formaldehyde and 2-naphthol forms 1-hydroxymethyl-2-naphthol (**10**) in the presence of base.[26] However, transformation of **10** into **6a** gave only 38% yield under the standard reaction conditions (Scheme 4.4A). In contrast, **11**, which can be formed from naphthol and iminium cation,[27] gave quantitative yield of **6a** (Scheme 4.4B). We postulated that deaminative pathway occurs via *ortho*-naphthoquinone methide (**B**) as an intermediate. Indeed, it could be captured by ethyl vinyl ether (Scheme 4.4C).[25] **B** can also be captured during the reaction (Scheme 4.4D), which further proves that **B** acts as a real intermediate.



Scheme 4.4 Possible intermediates in methylation of naphthol

Notably, deamination occurred only with **11** and not with **4a**, presumably due to the stronger basicity of naphtholate as a conjugate base, which in turn results from its lower aromaticity. Capturing of *ortho*-quinone methide (**A**) from **4a** by ethyl vinyl ether did not occur.

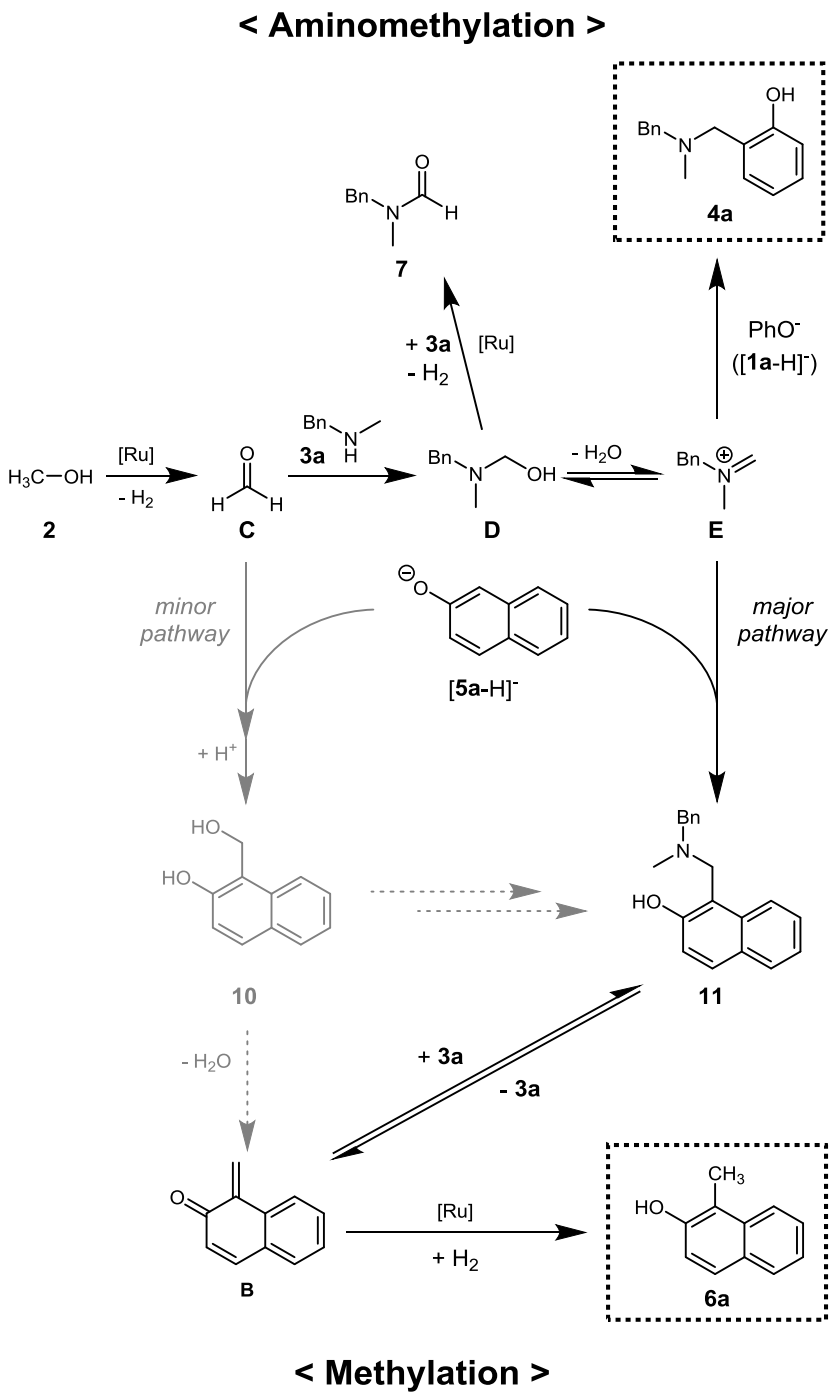
Since iminium cation is a plausible intermediate in both transformations, involvement of ruthenium-catalyst in the reaction between nucleophiles and iminium cation such as hydroaminomethylation and dehydrogenation sequence could be considered. However, ruthenium-catalyzed hydroaminomethyl-ation reaction occurs usually with terminal olefin,[16b-e] and only a few examples are with internal olefins.[16f,16g] Furthermore, reactivity with aromatic multiple bond have not been observed in the previous reports even though the applied reaction temperatures were as high (up to 140 ºC) as our reaction conditions.[16] Hence, we believe that an enolate-involved nucleophilic attack operates in our case rather than ruthenium-catalyzed sequential reactions.

On the basis of the experimental results, possible reaction pathways were proposed (Scheme 4.5). It is well known that methanol (**2**) can be dehydrogenated by ruthenium catalysts.[28] The generated formaldehyde (**C**) is attacked by **3a** to form the hemiaminal intermediate (**D**). Via subsequent dehydration, the iminium cation (**E**) is formed. Formamide **7** is also produced from dehydrogenation of **D**.[11a,11b] However, formamide does not directly participate in the reaction. In the case of the *ortho*-aminomethylation of phenol, the iminium cation is attacked by the phenolate anion ([**1a**-H]$^-$), generating **4a**. In the case of the methylation of 2-naphthol, both formaldehyde and the iminium cation react with the 2-naphtholate anion ([**5a**-H]$^-$). However, compound **10**, resulting from formaldehyde and [**5a**-H]$^-$, is not efficiently

converted to **6a**. On the other hand, compound **11** undergoes reversible deamination via an E1cB mechanism and reduction to successfully form **6a**.[29] In this pathway, **3a** is liberated and can participate in the generation of **11**. The amine acts as a catalyst as well as a base in the methylation of naphthol, and this suggestion is consistent with the previous experimental results (Table 4.3, entry 11).

4.3 Conclusion

We developed novel alkylation reactions of phenol derivatives by using methanol as the C1 source. Initiated by dehydrogenation of methanol and subsequent nucleophilic attack on formaldehyde, methanol could be directly incorporated into the organic molecules, phenol and naphthol. The developed reactions could be applied to a range of substrates with good yields. Based on our mechanistic studies, the iminium cation is proposed to be the key electrophile in both reactions. In the case of the methylation of naphthol, an *ortho*-naphthoquinone methide intermediate and the dual role of the amine as a catalyst and a base, were suggested.



Scheme 4.5 Plausible mechanism

4.4 Experimental section

4.4.1 General information

Unless otherwise noted, all reactions were carried out using standard Schlenk techniques or in an argon-filled glove box. All anhydrous solvents were purchased from commercial suppliers and degassed with dry argon before usage. **1c**,[30] **5b**-**5e**,[31] **10**,[26] and **11**[27] were prepared by the methods reported in the literature, and all other substrates and catalysts were purchased from commercial suppliers and used as received without purification. HRMS analyses were performed at the Organic Chemistry Research Center of Sogang University.

4.4.2 General procedure for *ortho*-aminomethylation of phenol

To an oven-dried 50 mL-screw capped RBF equipped with a stirring bar, Ru-MACHO-BH (5.9 mg, 0.01 mmol), **1** (0.50 mmol), **2** (101 μL, 2.50 mmol), **3** (1.00 mmol) and anhydrous toluene (1.0 mL) were added inside a glovebox. The reaction tube was then taken out of the box and stirred for 20-44 h at 150 ℃. The resulting reaction mixture was cooled to room temperature and concentrated under reduced pressure. The crude products were purified via silica gel column chromatography.

4.4.3 General procedure for methylation of naphthol To an oven-dried 50 mL-screw capped RBF equipped with a stirring bar, $Ru(acac)_3$ (4.0 mg, 0.01 mmol), triphos (12.5 mg, 0.02 mmol), **5** (0.50 mmol), **2** (81 μL, 2.00 mmol), pyrrolidine (42 μL, 0.50 mmol) and anhydrous toluene (1.0 mL) were added inside a glovebox. The

reaction tube was then taken out of the box and stirred for 20 h at 150 ℃. The resulting reaction mixture was cooled to room temperature and concentrated under reduced pressure. The crude products were purified via silica gel column chromatography.

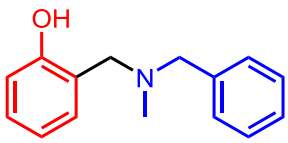
4.4.4 General procedure for the capture of *ortho*-quinone methide (Scheme 4.3B)

To an oven-dried 50 mL-screw capped RBF equipped with a stirring bar, **9** (62.1 mg, 0.50 mmol), ethyl vinyl ether (239 μL, 2.50 mmol), pyrrolidine (4.2 μL, 0.05 mmol) and anhydrous toluene (1.0 mL) were added inside a glovebox. The reaction tube was then taken out of the box and stirred for 20 h at 150 ℃. The resulting reaction mixture was cooled to room temperature and concentrated under reduced pressure. 25 μL of nitromethane was added as an internal standard. The crude mixture was analyzed by ^{1}H NMR spectroscopy. Schemes 4.3C, Scheme 4.4B, and Scheme 4.4C were conducted analogously to the method described here.

4.4.5 Characterization data

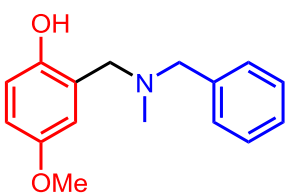
Reactions were performed in 0.50 mmol scale. All compounds were identified by ^{1}H, ^{13}C NMR. All new compounds were further identified by HR-MS. All reported compounds–**4l**[32], **4r**[33], **4s**[34], **6a**[35] and **6f**[36]– were also identified by spectral comparison with literature data.

2-((Benzyl(methyl)amino)methyl)phenol (4a): Colourless liquid (80 mg, 70%); ^{1}H



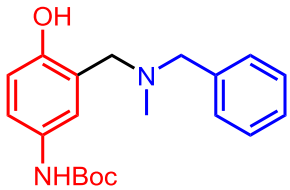
NMR (300 MHz, $CDCl_3$) δ = 11.12 (br. s., 1 H), 7.45-7.29 (m, 5 H), 7.23 (td, *J* = 7.3, 0.9 Hz, 1 H), 7.05 (d, *J* = 7.0 Hz, 1 H), 6.92 (dd, *J* = 8.1, 0.8 Hz, 1 H), 6.84 (td, *J* = 7.3, 1.1 Hz, 1 H), 3.79 (s, 2 H), 3.63 (s, 2 H), 2.28 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 157.9, 136.9, 129.4, 128.8, 128.6, 128.6, 127.7, 121.9, 119.2, 116.1, 61.5, 60.9, 41.3; HRMS-ESI (m/z) $[M+H]^+$ calcd for $C_{15}H_{18}NO$, 228.1383; found: 228.1385.

2-((Benzyl(methyl)amino)methyl)-4-methoxyphenol (4b): Light yellow liquid



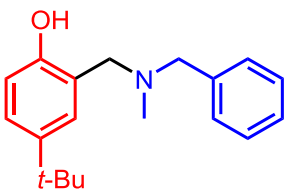
(98 mg, 76%); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 10.44 (br. s., 1 H), 7.40-7.27 (m, 5 H), 6.87-6.72 (m, 2 H), 6.62 (d, *J* = 2.6 Hz, 1 H), 3.76 (s, 3 H), 3.72 (s, 2 H), 3.60 (s, 2 H), 2.25 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 152.5, 151.6, 136.9, 129.4, 128.6, 127.7, 122.6, 116.4, 114.5, 113.6, 61.4, 61.0, 55.7, 41.3; HRMS-ESI (m/z) $[M+H]^+$ calcd for $C_{16}H_{20}NO_2$, 258.1489; found: 258.1488.

***tert*-Butyl (3-((benzyl(methyl)amino)methyl)-4-hydroxyphenyl)carbamate (4c):**



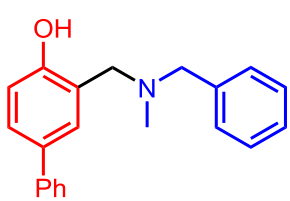
Beige solid (95 mg, 56%); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 10.30 (br. s., 1 H), 7.38-7.26 (m, 5 H), 7.23 (br. s., 1 H), 6.99 (dd, *J* = 8.6, 2.5, 1 H), 6.78 (d, *J* = 8.7 Hz, 1 H), 6.51 (s, 1 H), 3.71 (s, 2 H), 3.57 (s, 2 H), 2.21 (s, 3 H), 1.51 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 153.8, 153.4, 136.9, 130.1, 129.4, 128.6, 127.7, 122.2, 120.0, 120.0, 116.2, 80.1, 61.5, 61.0, 41.2, 28.5; HRMS-ESI (m/z) $[M+H]^+$ calcd for $C_{20}H_{27}N_2O_3$, 343.2016; found: 343.2014.

2-((Benzyl(methyl)amino)methyl)-4-(*tert*-butyl)phenol (4d): Light yellow liquid



(99 mg, 70%); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 10.65 (br. s., 1 H), 7.42-7.29 (m, 5 H), 7.25 (dd, *J* = 8.5, 2.1 Hz, 1 H), 7.05 (d, *J* = 1.9 Hz, 1 H), 6.85 (d, *J* = 8.5 Hz, 1 H), 3.79 (s, 2 H), 3.64 (s, 2 H), 2.29 (s, 3 H), 1.34 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 155.4, 141.8, 137.1, 129.4, 128.6, 127.7, 125.5, 125.4, 121.1, 115.5, 61.6, 61.4, 41.4, 34.0, 31.7; HRMS-ESI (m/z) $[M+H]^+$ calcd for $C_{19}H_{26}NO$, 284.2009; found: 284.2010.

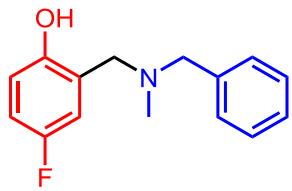
3-((Benzyl(methyl)amino)methyl)-[1,1'-biphenyl]-4-ol (4e): Yellow liquid (118



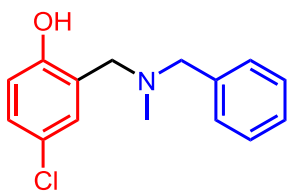
mg, 77%); ^{1}H NMR (499 MHz, $CDCl_3$) δ = 11.05 (br. s., 1 H), 7.60 (d, *J* = 7.3 Hz, 2 H), 7.51-7.32 (m, 9 H), 7.31 (d, *J* = 2.0 Hz, 1 H), 7.01 (d, *J* = 8.3 Hz, 1 H), 3.86 (s, 2 H), 3.67 (s, 2 H), 2.32 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 157.6, 141.0, 136.8,

132.3, 129.4, 128.8, 128.7, 127.7, 127.5, 127.3, 126.6, 126.5, 122.1, 116.5, 61.5, 61.0, 41.3; HRMS-ESI (m/z) $[M+H]^+$ calcd for $C_{21}H_{22}NO$, 304.1696; found: 304.1694.

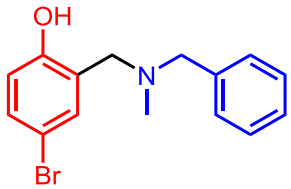
2-((Benzyl(methyl)amino)methyl)-4-fluorophenol (4f): Light yellow liquid (92 mg, 75%); ^{1}H NMR (499 MHz, $CDCl_3$) δ = 10.45 (br. s., 1 H), 7.39-7.35 (m, 2 H), 7.33-7.29 (m, 3 H), 6.89 (td, *J* = 8.6, 2.9 Hz, 1 H), 6.80 (dd, *J* = 9.0, 4.6 Hz, 1 H), 6.74 (dd, *J* = 8.8, 2.9 Hz, 1 H), 3.71 (s, 2 H), 3.60 (s, 2 H), 2.25 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 156.07 (d, *J* = 236.4 Hz), 153.84 (d, *J* = 1.8 Hz), 136.68, 129.40, 128.70, 127.83, 122.82 (d, *J* = 7.2 Hz), 116.76 (d, *J* = 7.8 Hz), 115.14 (d, *J* = 3.6 Hz), 114.83 (d, *J* = 3.0 Hz), 61.48, 60.53, 41.30; HRMS-ESI (m/z) $[M+H]^+$ calcd for $C_{15}H_{17}NO$, 246.1289; found: 246.1289.



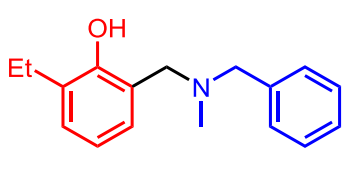
2-((Benzyl(methyl)amino)methyl)-4-chlorophenol (4g): Off-white solid (83 mg, 64%); ^{1}H NMR (499 MHz, $CDCl_3$) δ = 11.09 (br. s., 1 H), 7.40-7.34 (m, 2 H), 7.34-7.28 (m, 3 H), 7.14 (dd, *J* = 8.6, 2.7 Hz, 1 H), 6.99 (d, *J* = 2.4 Hz, 1 H), 6.80 (d, *J* = 8.8 Hz, 1 H), 3.71 (s, 2 H), 3.60 (s, 2 H), 2.25 (s, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 156.7, 136.6, 129.4, 128.7, 128.6, 128.3, 127.9, 123.7, 123.4, 117.5, 61.5, 60.5, 41.3; HRMS-ESI (m/z) $[M+H]^+$ calcd for $C_{15}H_{17}ClNO$, 262.0993; found: 262.0993.



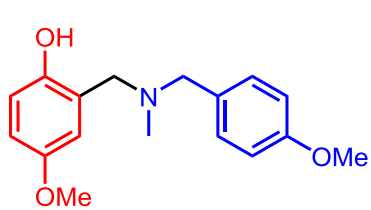
2-((Benzyl(methyl)amino)methyl)-4-bromophenol (4h): White solid (69 mg, 45%); ^{1}H NMR (499 MHz, $CDCl_3$) δ = 11.24 (br. s., 1 H), 7.38-7.33 (m, 2 H), 7.33-7.24 (m, 4 H), 7.11 (s, 1 H), 6.74 (d, J = 8.8 Hz, 1 H), 3.71 (s, 2 H), 3.60 (s, 2 H), 2.24 (s, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 157.2, 136.6, 131.6, 131.2, 129.5, 128.8, 127.9, 124.0, 118.1, 110.9, 61.6, 60.5, 41.4; HRMS-ESI (m/z) $[M+H]^+$ calcd for $C_{15}H_{17}BrNO$, 306.0488; found: 306.0489.



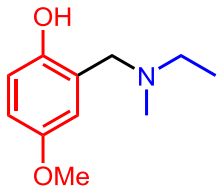
2-((Benzyl(methyl)amino)methyl)-6-ethylphenol (4i): Light yellow liquid (64 mg, 50%); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 11.16 (br. s, 1 H), 7.43-7.29 (m, 5 H), 7.13 (dd, J = 7.3, 1.5 Hz, 1 H), 6.91 (dd, J = 7.3, 1.5 Hz, 1 H), 6.79 (t, J = 7.3 Hz, 1 H), 3.79 (s, 2 H), 3.63 (s, 2 H), 2.74 (q, J = 7.4 Hz, 2 H), 2.27 (s, 3 H), 1.30 (t, J = 7.7 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 155.7, 137.1, 131.0, 129.5, 128.7, 128.3, 127.7, 126.3, 121.4, 118.9, 61.5, 61.2, 41.2, 23.0, 14.3; HRMS-ESI (m/z) $[M+H]^+$ calcd for $C_{17}H_{22}NO$, 256.1696; found: 256.1697.



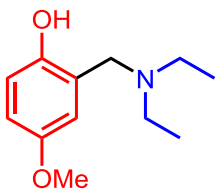
4-Methoxy-2-(((4-methoxybenzyl)(methyl)amino)methyl)phenol (4j): Light yellow liquid (106 mg, 74%); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 9.53 (br. s., 1 H), 7.25 (d, J = 8.5 Hz, 2 H), 6.91 (d, J = 8.7 Hz, 2 H), 6.86-6.74 (m, 2 H), 6.63 (d, J = 2.8 Hz, 1 H), 3.81 (s, 3 H), 3.77 (s, 3 H), 3.72 (s, 2 H), 3.56 (s, 2 H), 2.25 (s, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 159.2, 152.6, 151.7, 130.6, 129.0, 122.7,



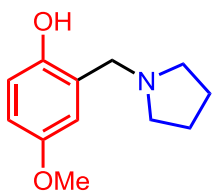
116.5, 114.6, 114.0, 113.6, 60.8, 55.8, 55.3, 41.2; HRMS-ESI (m/z) $[M+H]^+$ calcd for $C_{17}H_{22}NO_3$, 288.1594; found: 288.1595.

2-((Ethyl(methyl)amino)methyl)-4-methoxyphenol (4k): Yellow liquid (73 mg, 75%); 

^{1}H NMR (300 MHz, $CDCl_3$) δ = 9.63 (br. s., 1 H), 6.78-6.67 (m, 2 H), 6.54 (d, J = 1.7 Hz, 1 H), 3.73 (s, 3 H), 3.65 (s, 2 H), 2.53 (q, J = 7.2 Hz, 2 H), 2.27 (s, 3 H), 1.13 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 152.5, 152.0, 122.8, 116.4, 114.4, 113.4, 61.1, 55.9, 50.8, 40.9, 12.2; HRMS-ESI (m/z) $[M+H]^+$ calcd for $C_{11}H_{18}NO_2$, 196.1332; found: 196.1333.

2-((Diethylamino)methyl)-4-methoxyphenol (4l):[32] Brown liquid (43 mg, 41%); 

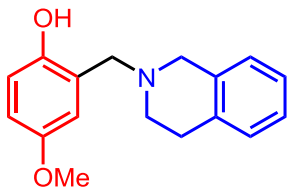
^{1}H NMR (300 MHz, $CDCl_3$) δ = 10.42 (br. s., 1 H), 6.75-6.70 (m, 2 H), 6.55 (s, 1 H), 3.77-3.65 (m, 5 H), 2.60 (q, J = 7.1 Hz, 4 H), 1.09 (t, J = 7.1 Hz, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 152.5, 152.2, 123.0, 116.4, 114.5, 113.3, 57.2, 55.9, 46.4, 11.3.

4-Methoxy-2-(pyrrolidin-1-ylmethyl)phenol (4n): Dark yellow liquid (81 mg, 78%); 

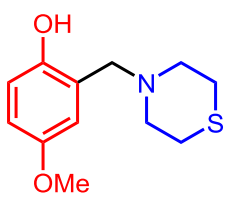
^{1}H NMR (300 MHz, $CDCl_3$) δ = 10.56 (br. s., 1 H), 6.81-6.66 (m, 2 H), 6.55 (s, 1 H), 3.76 (s, 2 H), 3.72 (s, 3 H), 2.68-2.53 (m, 4 H), 1.91-1.76 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$)

δ = 152.3, 151.8, 123.2, 116.2, 113.8, 113.3, 58.9, 55.7, 53.5, 23.7; HRMS-ESI (m/z) $[M+H]^+$ calcd for $C_{12}H_{18}NO_2$, 208.1332; found: 208.1333.

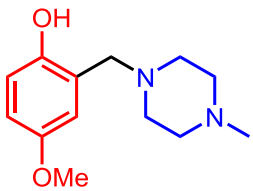
2-((3,4-Dihydroisoquinolin-2(1*H*)-yl)methyl)-4-methoxyphenol (4o): Light orange solid (103 mg, 77%); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 9.98 (br. s., 1 H), 7.25-7.12 (m, 3 H), 7.09-7.00 (m, 1 H), 6.87-6.77 (m, 2 H), 6.67 (d, J = 1.1 Hz, 1 H), 3.87 (s, 2 H), 3.83-3.74 (m, 5 H), 2.98 (t, J = 5.6 Hz, 2 H), 2.88 (t, J = 5.4 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 152.6, 151.7, 133.6, 133.4, 128.7, 126.6, 126.6, 126.0, 122.0, 116.6, 114.6, 113.7, 61.2, 55.8, 55.4, 50.0, 28.7; HRMS-ESI (m/z) $[M+H]^+$ calcd for $C_{17}H_{20}NO_2$, 270.1489; found: 270.1491.



4-Methoxy-2-(thiomorpholinomethyl)phenol (4p): White solid (84 mg, 76%); ^{1}H NMR (499 MHz, $CDCl_3$) δ = 10.01 (br. s., 1 H), 6.75-6.70 (m, 2 H), 6.53 (d, J = 2.0 Hz, 1 H), 3.72 (s, 3 H), 3.65 (s, 2 H), 2.85-2.76 (m, 4 H), 2.72-2.68 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 152.6, 151.3, 121.5, 116.5, 114.7, 113.7, 62.3, 55.7, 54.4, 27.9; HRMS-ESI (m/z) $[M+H]^+$ calcd for $C_{12}H_{18}NO_2S$, 240.1053; found: 240.1052.

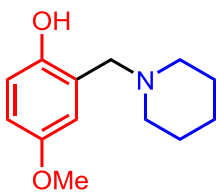


4-Methoxy-2-((4-methylpiperazin-1-yl)methyl)phenol (4q): Light yellow liquid

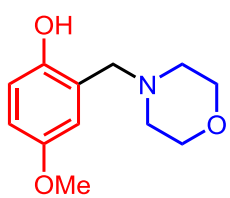


(88 mg, 74%); ^{1}H NMR (499 MHz, $CDCl_3$) δ = 10.23 (br. s., 1 H), 6.72-6.66 (m, 2 H), 6.52 (d, *J* = 2.4 Hz, 1 H), 3.69 (s, 3 H), 3.62 (s, 2 H), 2.53 (br. s., 8 H), 2.26 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 152.5, 151.4, 121.8, 116.4, 114.4, 113.6, 61.4, 55.7, 54.9, 52.4, 45.8; HRMS-ESI (m/z) $[M+H]^+$ calcd for $C_{13}H_{21}N_2O_2$, 237.1598; found: 237.1596.

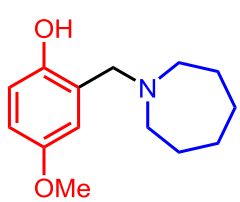
4-Methoxy-2-(piperidin-1-ylmethyl)phenol (4r):[33] Light brown liquid (79 mg, 71%); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 10.05 (br. s., 1 H), 6.77-6.70 (m, 2 H), 6.55 (s, 1 H), 3.72 (s, 3 H), 3.61 (s, 2 H), 2.67-2.30 (m, 4 H), 1.71-1.55 (m, 4 H), 1.55-1.30 (m, 2 H).



4-Methoxy-2-(morpholinomethyl)phenol (4s):[34] Colourless liquid (47 mg, 42%); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 10.12 (br. s., 1 H), 6.81-6.67 (m, 2 H), 6.55 (d, *J* = 1.3 Hz, 1 H), 3.76-3.71 (m, 7 H), 3.65 (s, 2 H), 2.64-2.46 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 152.7, 151.3, 121.4, 116.5, 114.7, 113.9, 66.9, 62.0, 55.8, 53.0.

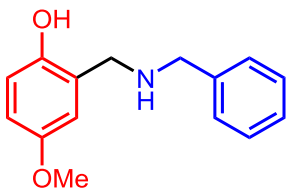


2-(Azepan-1-ylmethyl)-4-methoxyphenol (4t): Light yellow liquid (78 mg, 66%); ^{1}H NMR (499 MHz, $CDCl_3$) δ = 9.79 (br. s., 1 H), 6.76-6.70 (m, 2 H), 6.53 (d, J = 2.9 Hz, 1 H), 3.74-3.71 (m, 5 H), 2.69 (t, *J* = 4.9 Hz, 4 H), 1.71-1.66 (m, 4 H), 1.65-1.60 (m, 4 H); ^{13}C



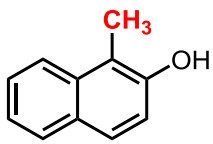
NMR (75 MHz, $CDCl_3$) δ = 152.4, 152.2, 123.1, 116.4, 114.4, 113.4, 62.2, 55.8, 55.4, 27.8, 26.7; HRMS-ESI (m/z) $[M+H]^+$ calcd for $C_{14}H_{22}NO_2$, 236.1645; found: 236.1645.

2-((Benzylamino)methyl)-4-methoxyphenol (4u): Colourless liquid (36 mg, 29%);

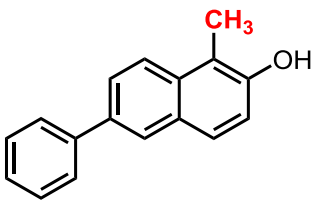


^1H NMR (300 MHz, $CDCl_3$) δ = 7.41-7.27 (m, 5 H), 6.83-6.70 (m, 2 H), 6.58 (d, J = 2.8 Hz, 1 H), 6.08 (br. s., 2 H), 3.97 (s, 2 H), 3.81 (s, 2 H), 3.75 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 152.6, 152.0, 138.5, 128.8, 128.5, 127.7, 123.0, 116.9, 114.6, 113.8, 55.9, 52.7, 52.1; HRMS-ESI (m/z) $[M+H]^+$ calcd for $C_{15}H_{18}NO_2$, 244.1332; found: 244.1332.

1-Methylnaphthalen-2-ol (6a):[35] Light yellow solid (69 mg, 87%); ^1H NMR (499 MHz, $CDCl_3$) δ = 7.98 (d, J = 8.8 Hz, 1 H), 7.83 (d, J = 8.3 Hz, 1 H), 7.66 (d, J = 8.8 Hz, 1 H), 7.56 (t, J = 8.3 Hz, 1 H), 7.42 (t, J = 7.3 Hz, 1 H), 7.09 (d, J = 8.8 Hz, 1 H), 5.28 (br. s., 1 H), 2.59 (s, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 150.5, 133.9, 129.3, 128.5, 127.4, 126.4, 123.2, 117.7, 115.5, 10.6.

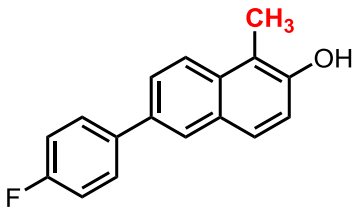


1-Methyl-6-phenylnaphthalen-2-ol (6b): White solid (89 mg, 75%); ^{1}H NMR (499



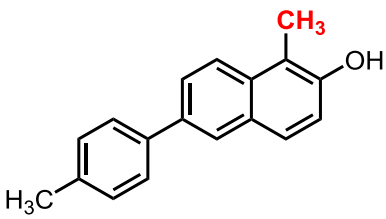
MHz, DMSO-d_6) δ = 9.57 (s, 1 H), 8.11-8.06 (m, 1 H), 7.93 (d, J = 8.8 Hz, 1 H), 7.80-7.74 (m, 3 H), 7.71 (d, J = 8.8 Hz, 1 H), 7.48 (t, J = 7.6 Hz, 2 H), 7.35 (t, J = 6.8 Hz, 1 H), 7.21 (d, J = 8.8 Hz, 1 H), 2.45 (s, 3 H); ^{13}C NMR (126 MHz, DMSO-d_6) δ = 152.5, 140.1, 133.7, 133.0, 128.9, 128.3, 127.2, 127.0, 126.6, 125.7, 124.9, 123.6, 118.5, 114.6, 10.5; HRMS-ESI (m/z) [M-H]$^-$ calcd for $C_{17}H_{13}O$, 233.0972; found: 233.0970.

6-(4-Fluorophenyl)-1-methylnaphthalen-2-ol (6c): White solid (91 mg, 72%); ^{1}H



NMR (499 MHz, DMSO-d_6) δ = 9.58 (s, 1 H), 8.04 (d, J = 2.0 Hz, 1 H), 7.91 (d, J = 8.8 Hz, 1 H), 7.81-7.75 (m, 2 H), 7.72 (dd, J = 8.8, 2.0 Hz, 1 H), 7.69 (d, J = 8.8 Hz, 1 H), 7.32-7.26 (m, 2 H), 7.21 (d, J = 8.8 Hz, 1 H), 2.44 (s, 3 H); ^{13}C NMR (126 MHz, DMSO-d_6) δ = 161.65 (d, J = 244.1 Hz), 152.48, 137.05 (d, J = 2.9 Hz), 132.95, 132.72, 128.44 (d, J = 7.6 Hz), 128.23, 127.19, 125.60, 124.83, 123.62, 118.54, 115.68 (d, J = 21.0 Hz), 114.56, 10.44; HRMS-ESI (m/z) [M-H]$^-$ calcd for $C_{17}H_{12}FO$, 251.0878; found: 251.0876.

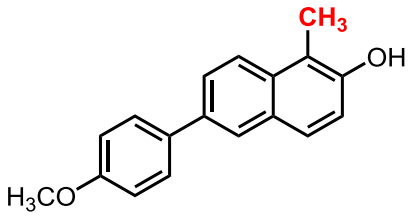
1-Methyl-6-(*p*-tolyl)naphthalen-2-ol (6d): White solid (86 mg, 70%); ^{1}H NMR



(499 MHz, DMSO-d_6) δ = 9.54 (s, 1 H), 8.04 (d, J = 1.5 Hz, 1 H), 7.90 (d, J = 8.8 Hz, 1 H), 7.74 (dd, J = 8.8, 2.0 Hz, 1 H), 7.69 (d, J = 8.8 Hz, 1

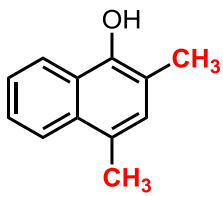
H), 7.65 (d, J = 7.8 Hz, 2 H), 7.27 (d, J = 8.3 Hz, 2 H), 7.20 (d, J = 8.8 Hz, 1 H), 2.44 (s, 3 H), 2.35 (s, 3 H); ^{13}C NMR (126 MHz, DMSO-d_6) δ = 152.3, 137.2, 136.2, 133.6, 132.9, 129.5, 128.3, 127.1, 126.4, 125.2, 124.8, 123.5, 118.4, 114.5, 20.7, 10.4; HRMS-ESI (m/z) $[M-H]^-$ calcd for $C_{18}H_{15}O$, 247.1128; found: 247.1131.

6-(4-Methoxyphenyl)-1-methylnaphthalen-2-ol (6e): White solid (69 mg, 52%);



^{1}H NMR (499 MHz, DMSO-d_6) δ = 9.51 (s, 1 H), 8.00 (d, J = 2.0 Hz, 1 H), 7.89 (d, J = 8.8 Hz, 1 H), 7.74-7.65 (m, 4 H), 7.19 (d, J = 8.8 Hz, 1 H), 7.03 (d, J = 8.8 Hz, 2 H), 3.80 (s, 3 H), 2.43 (s, 3 H); ^{13}C NMR (126 MHz, DMSO-d_6) δ = 158.6, 152.2, 133.4, 132.6, 132.5, 128.3, 127.6, 127.0, 124.8, 123.5, 118.4, 114.5, 114.4, 55.1, 10.4; HRMS-ESI (m/z) $[M-H]^-$ calcd for $C_{18}H_{15}O_2$, 263.1078; found: 263.1078.

2,4-Dimethylnaphthalen-1-ol (6f):[36] White solid (35 mg, 41%); ^{1}H NMR (499



MHz, $CDCl_3$) δ = 8.24-8.19 (m, 1 H), 7.99-7.94 (m, 1 H), 7.57-7.51 (m, 2 H), 7.12 (s, 1 H), 5.06 (br. s., 1 H), 2.64 (s, 3 H), 2.40 (s, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 147.0, 132.2, 129.6, 126.3, 125.3, 125.1, 124.7, 124.3, 121.5, 116.0, 18.8, 15.6.

4.5 References

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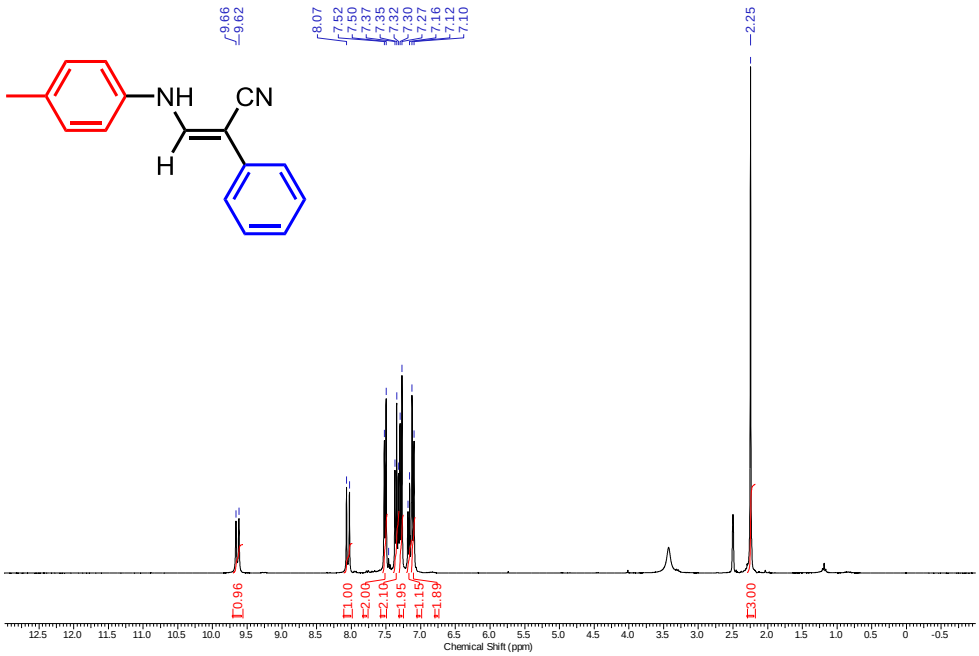
Appendix – NMR spectra

Chapter 2

^{1}H NMR (**3aa**) (DMSO-d_6)



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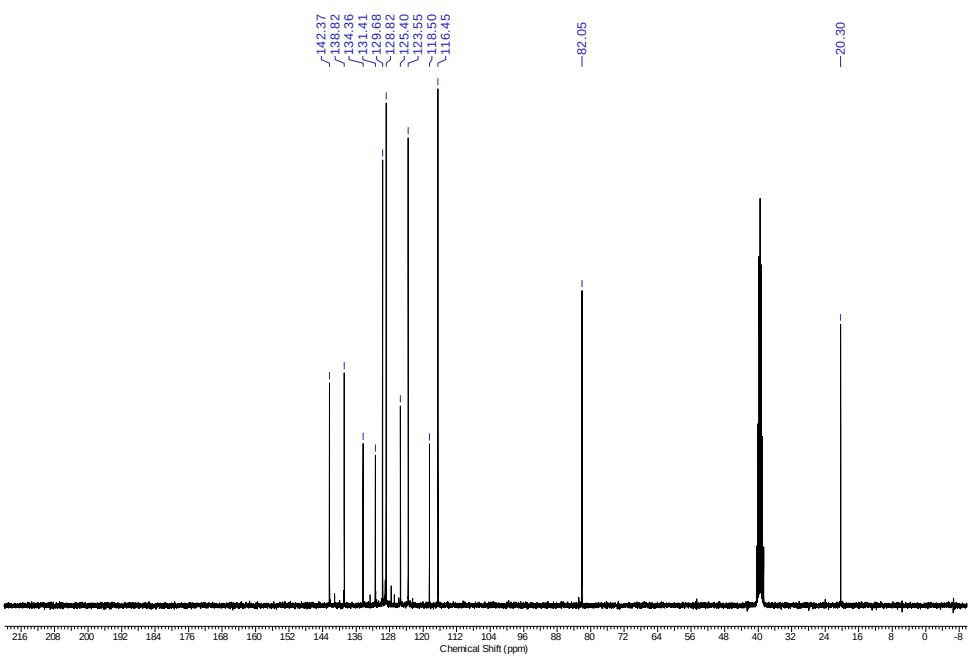

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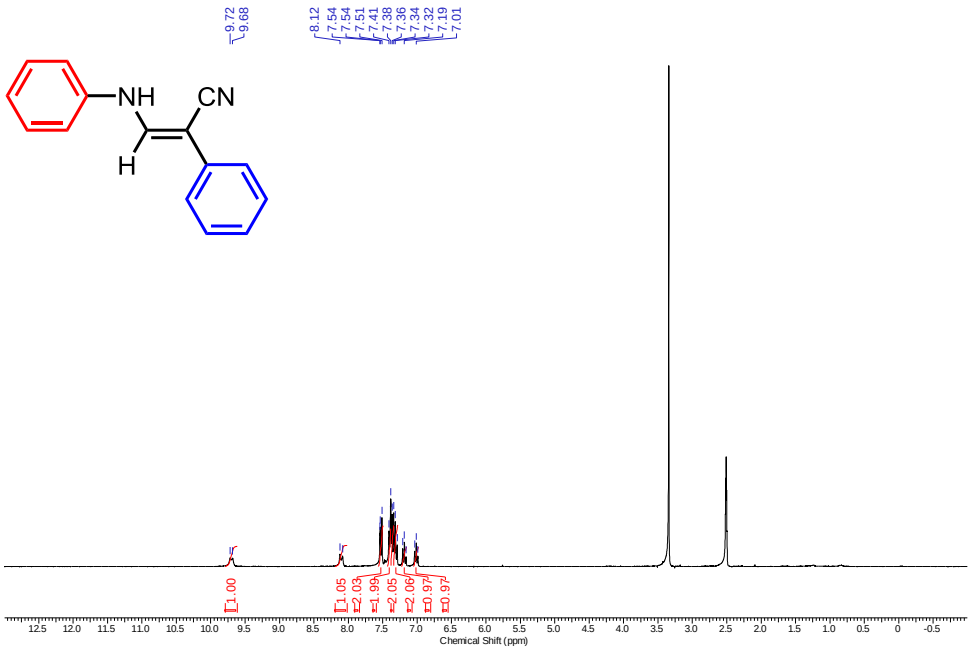
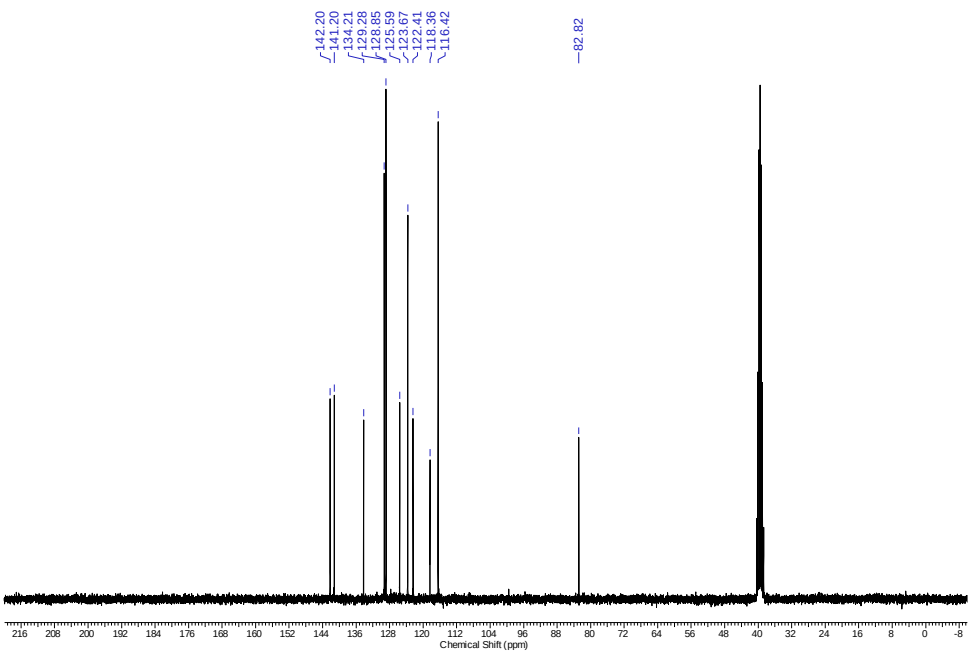
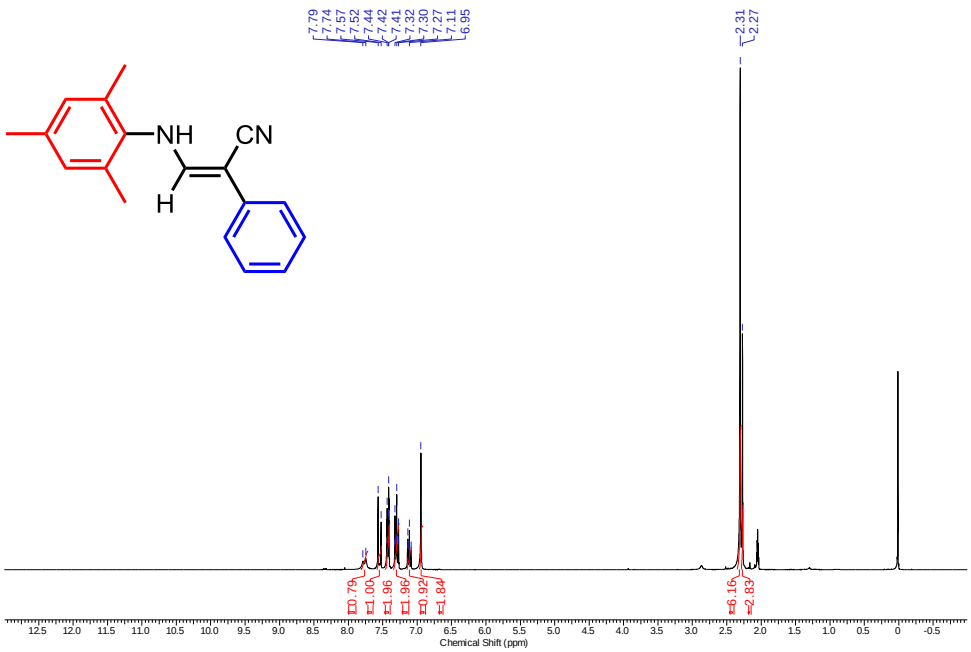


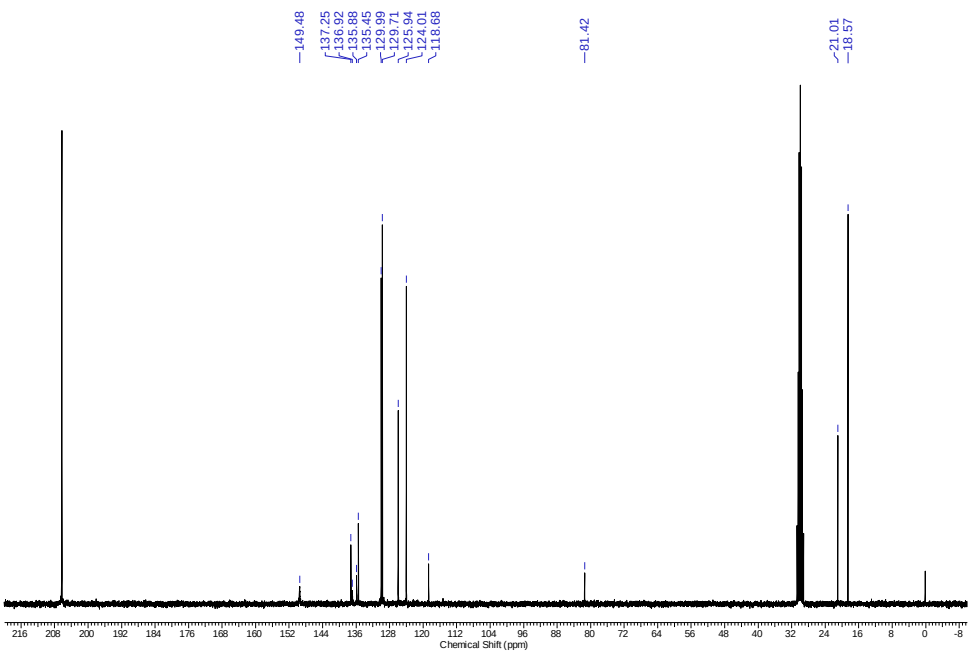
^{13}C NMR (**3ba**) (DMSO-d_6)



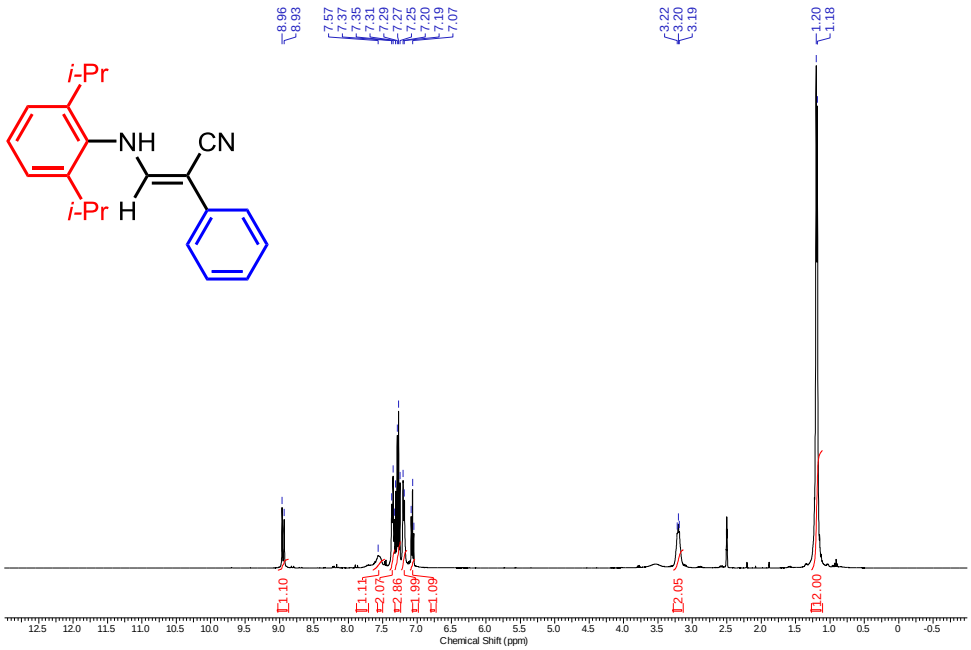
^{1}H NMR (**3ca**) (Acetone-d_6)



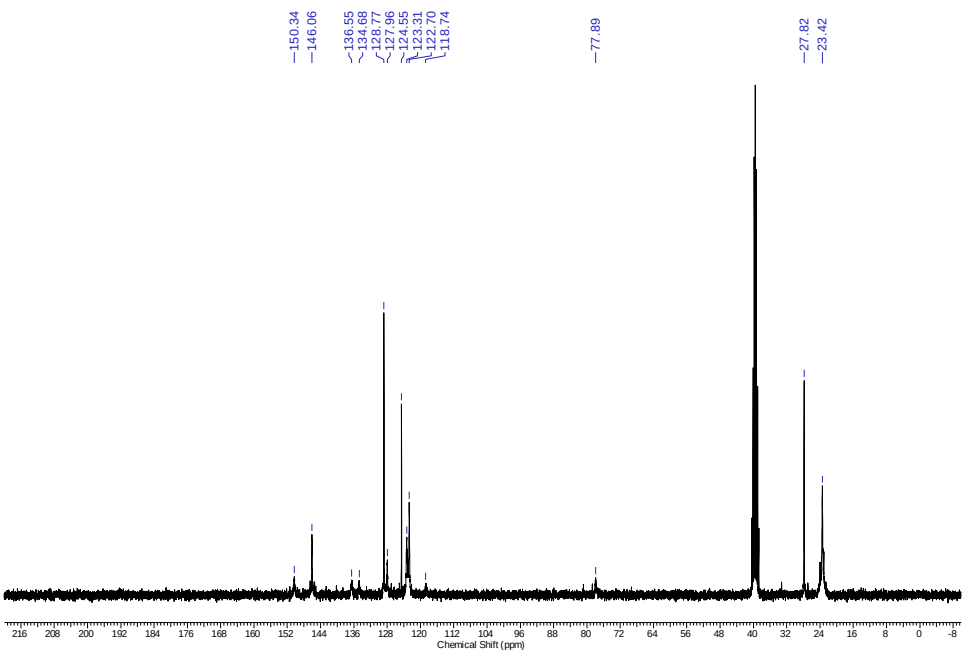
^{13}C NMR (**3ca**) (Acetone-d_6)



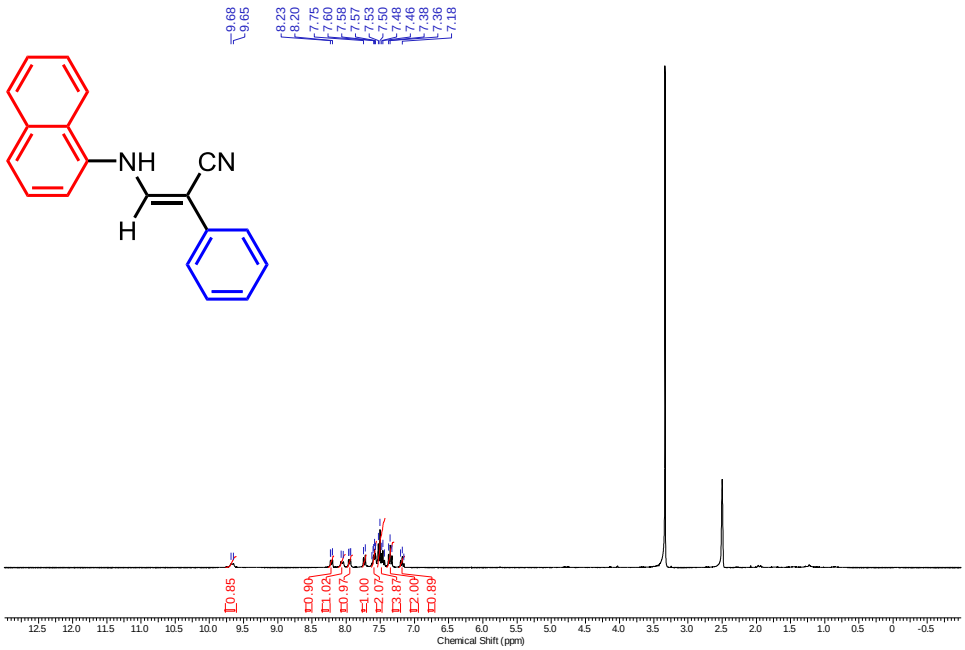
^{1}H NMR (**3da**) (DMSO-d_6)



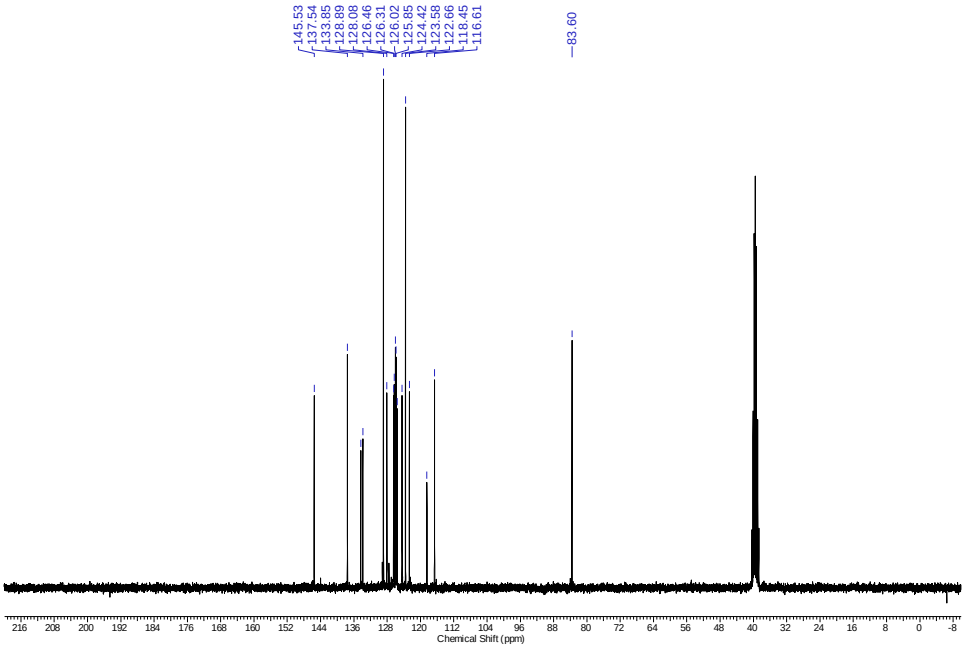
^{13}C NMR (**3da**) (DMSO-d_6)



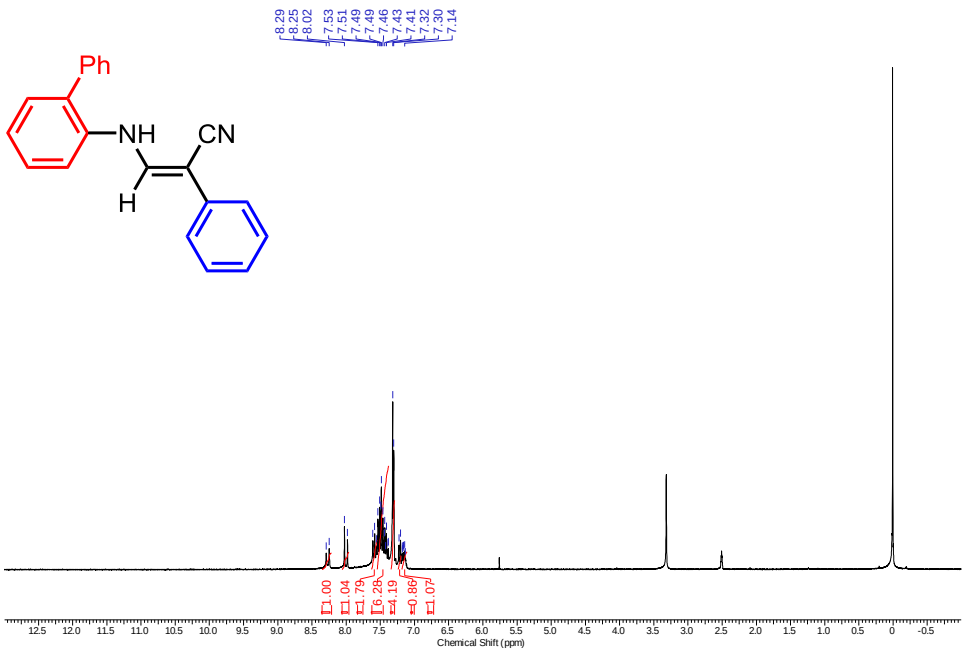
^{1}H NMR (**3ea**) (DMSO-d_6)



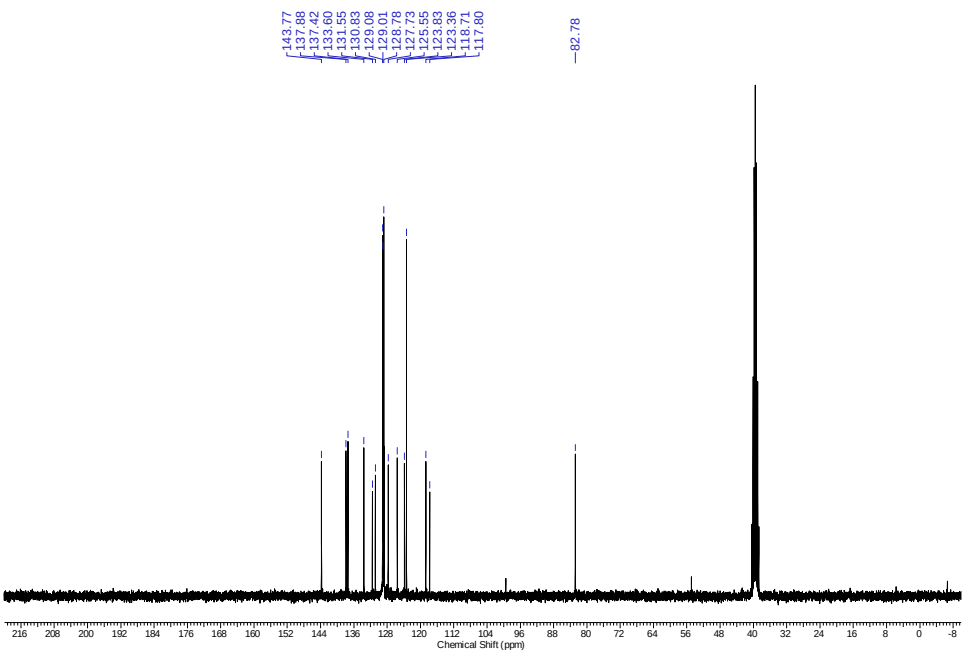
^{13}C NMR (**3ea**) (DMSO-d_6)



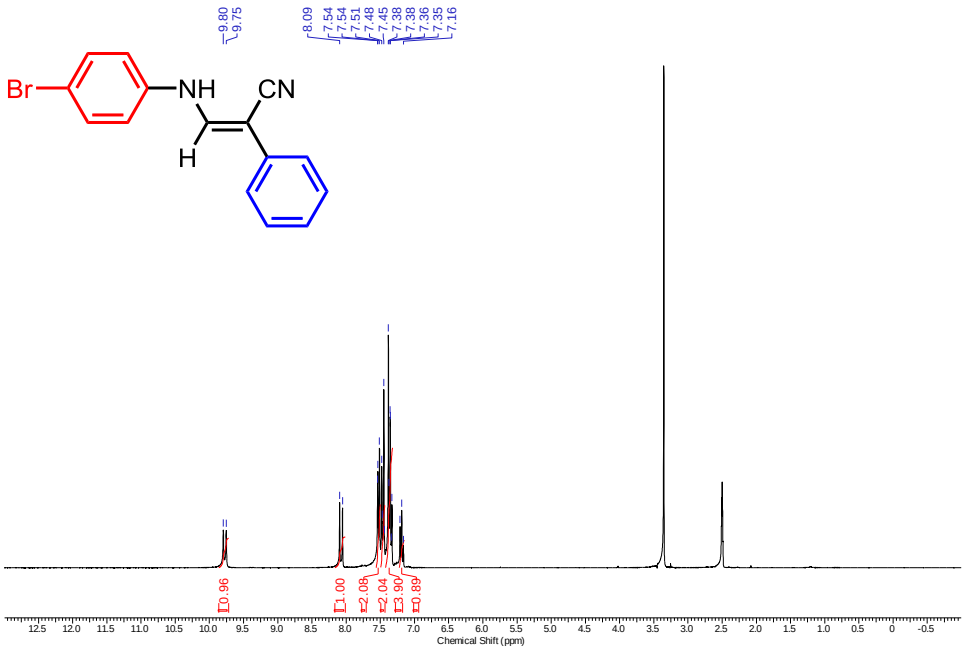
^{1}H NMR (**3fa**) (DMSO-d_6)



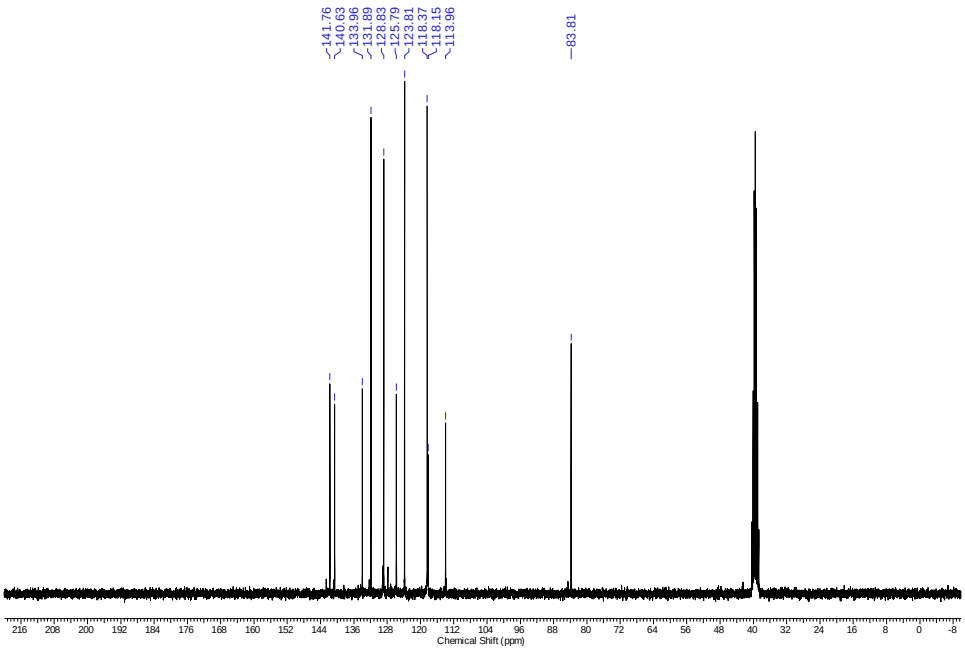
^{13}C NMR (**3fa**) (DMSO-d_6)



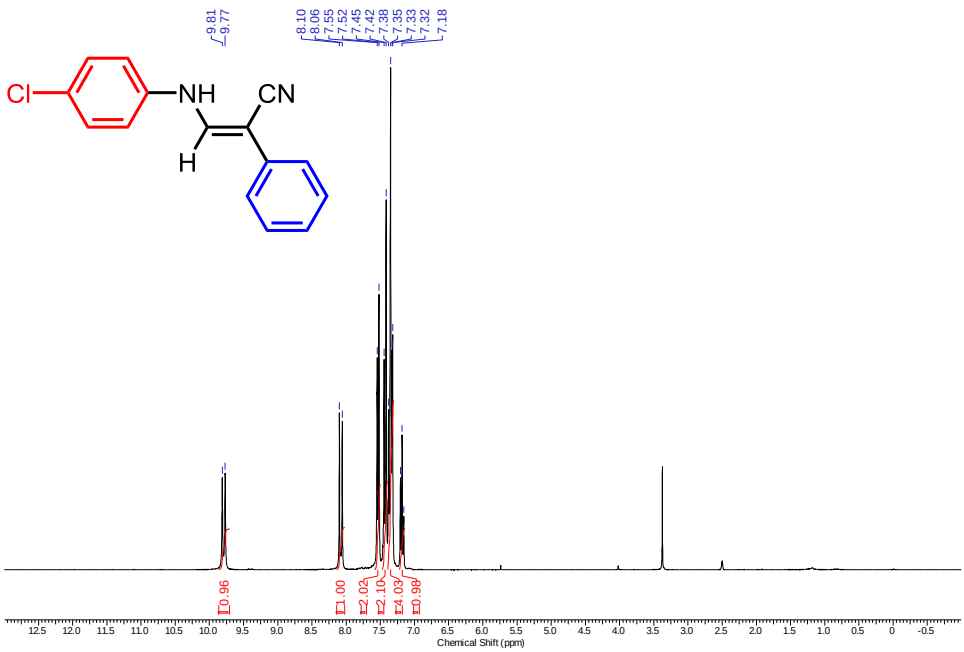
^{1}H NMR (**3ga**) (DMSO-d_6)



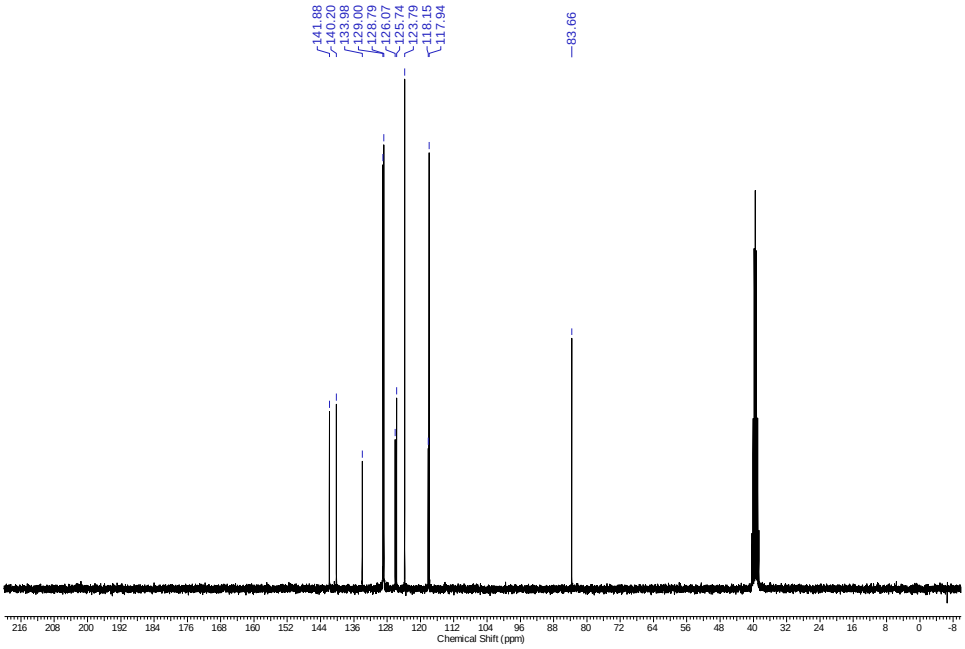
^{13}C NMR (**3ga**) (DMSO-d_6)



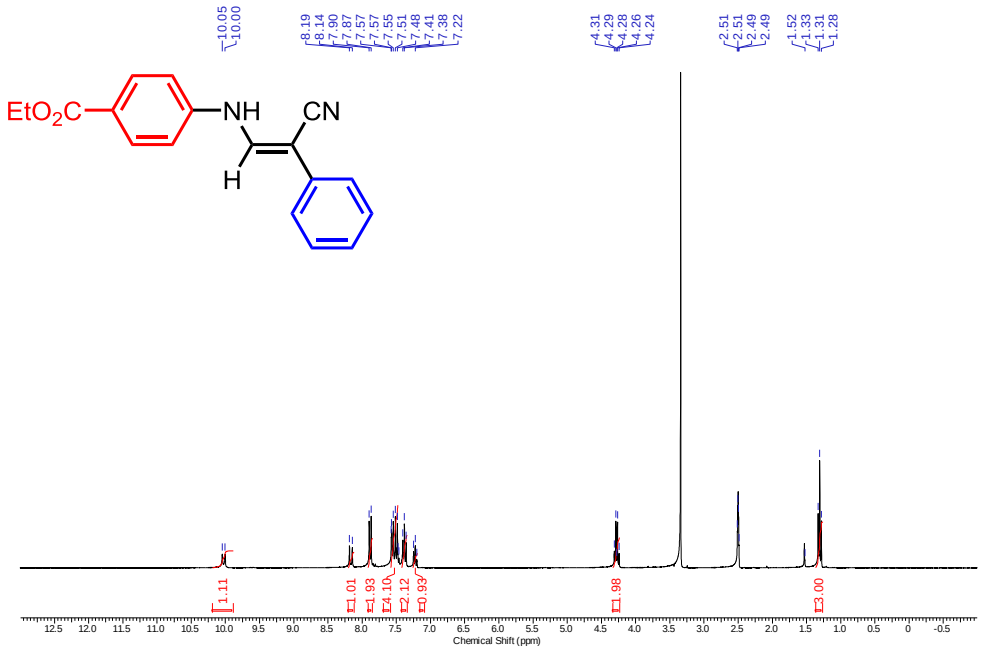
^{1}H NMR (**3ha**) (DMSO-d_6)



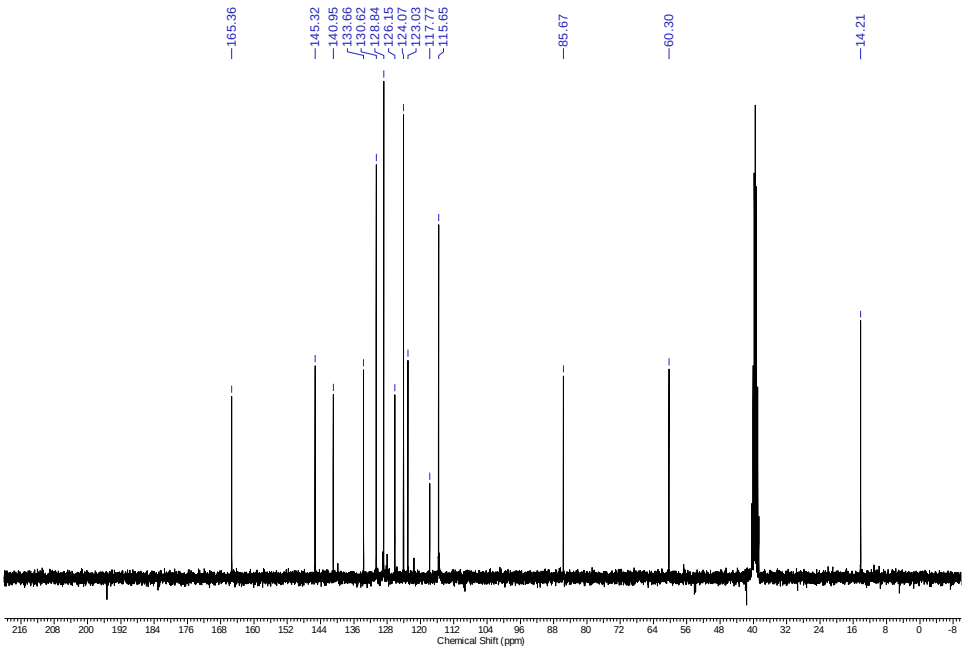
^{13}C NMR (**3ha**) (DMSO-d_6)



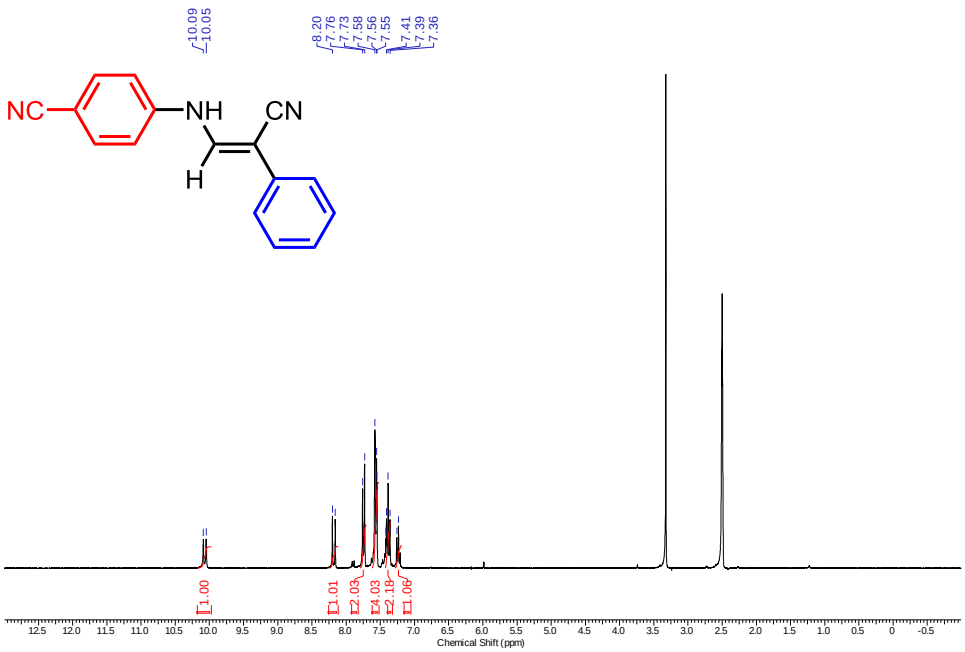
^{1}H NMR (**3ia**) (DMSO-d_6)



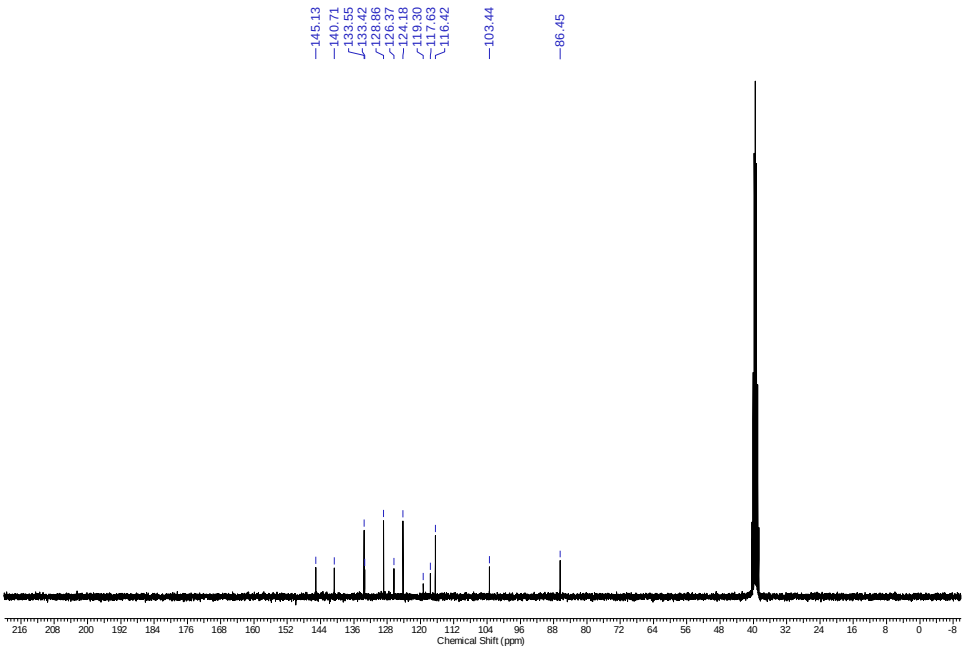
^{13}C NMR (**3ia**) (DMSO-d_6)



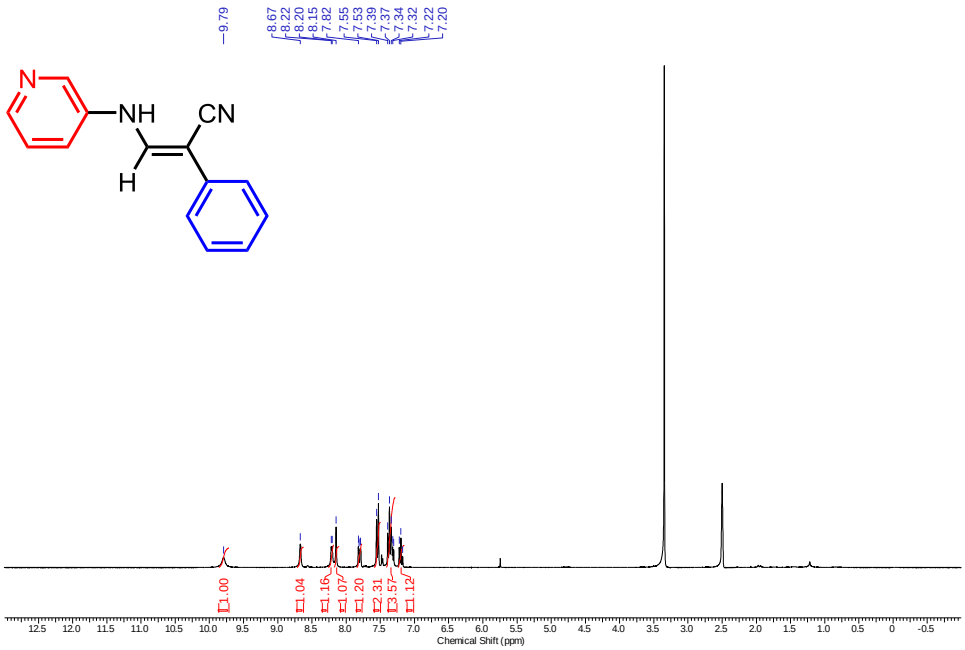
^{1}H NMR (**3ja**) (DMSO-d_6)



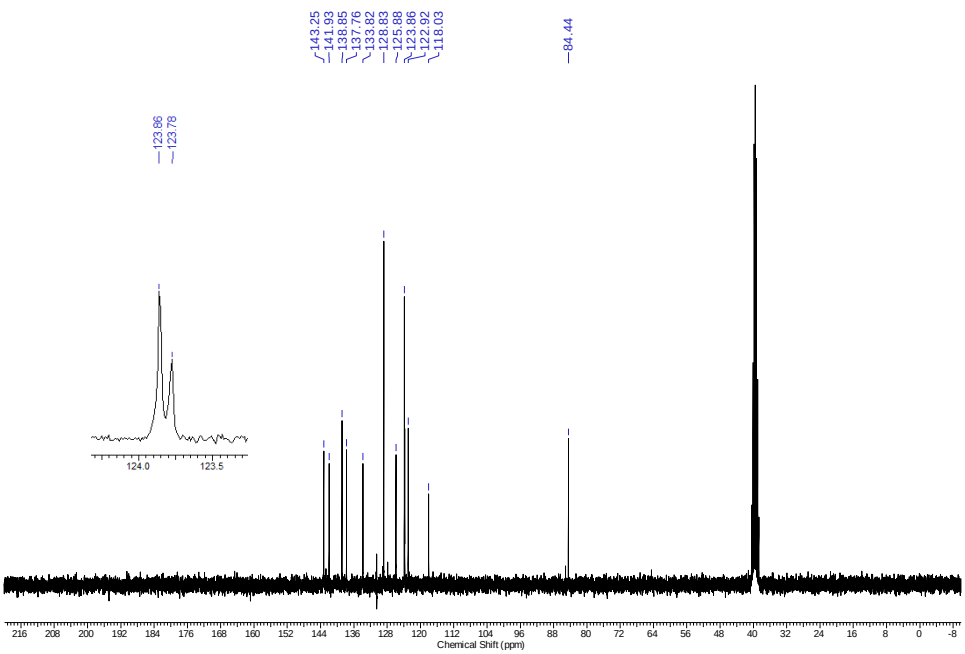
^{13}C NMR (**3ja**) (DMSO-d_6)



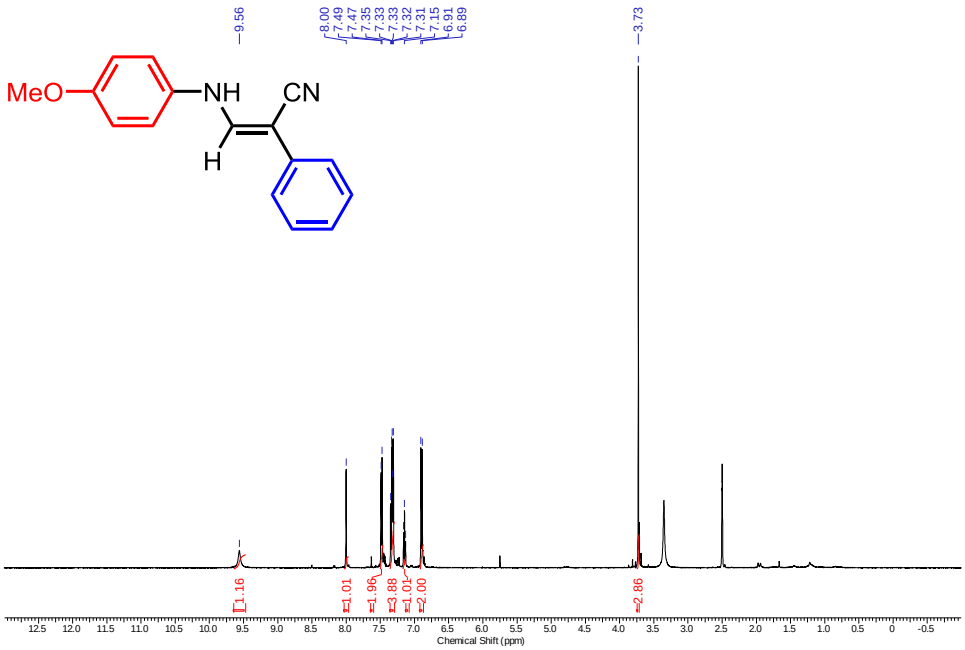
^{1}H NMR (**3ka**) (DMSO-d_6)



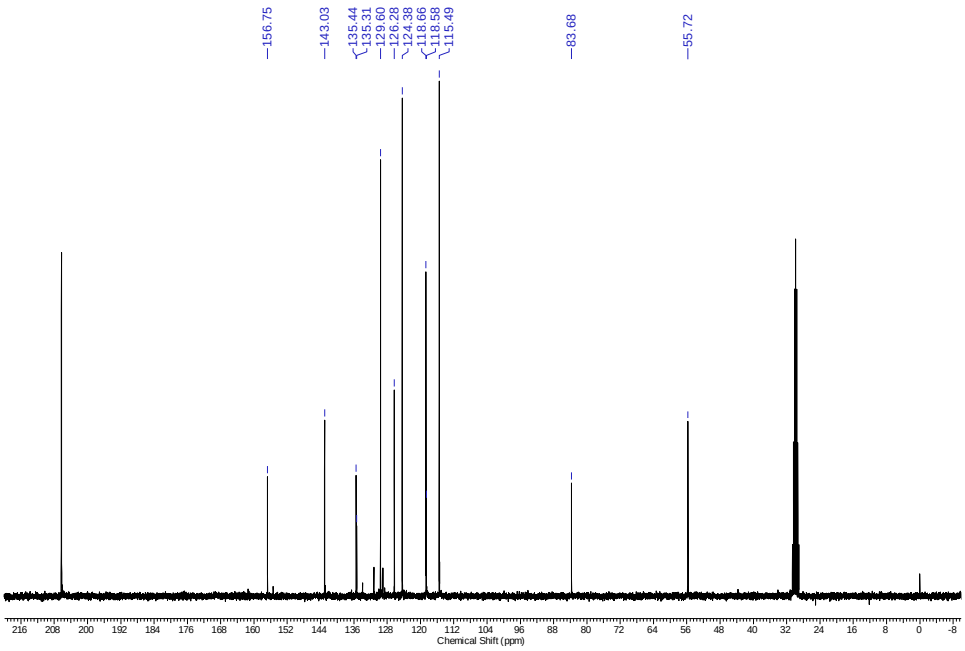
^{13}C NMR (**3ka**) (DMSO-d_6)



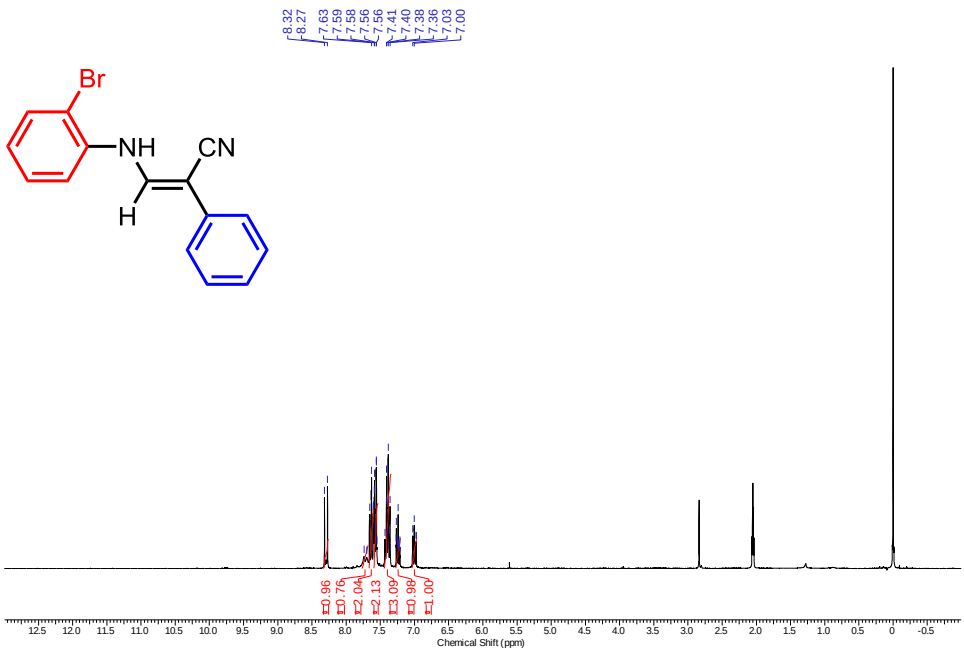
^{1}H NMR (**3la**) (DMSO-d_6)



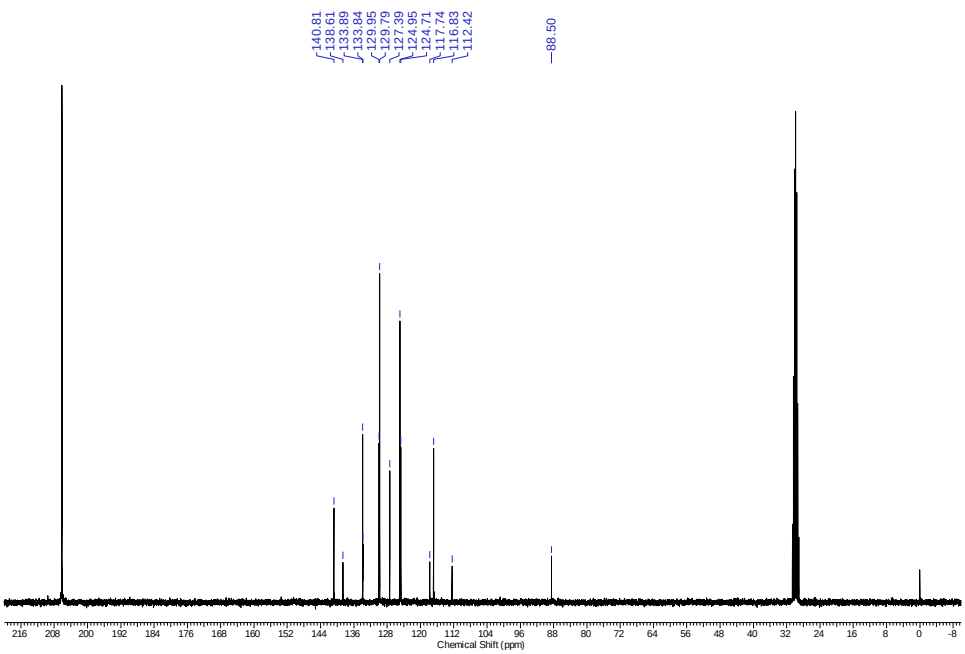
^{13}C NMR (**3la**) (Acetone-d_6)



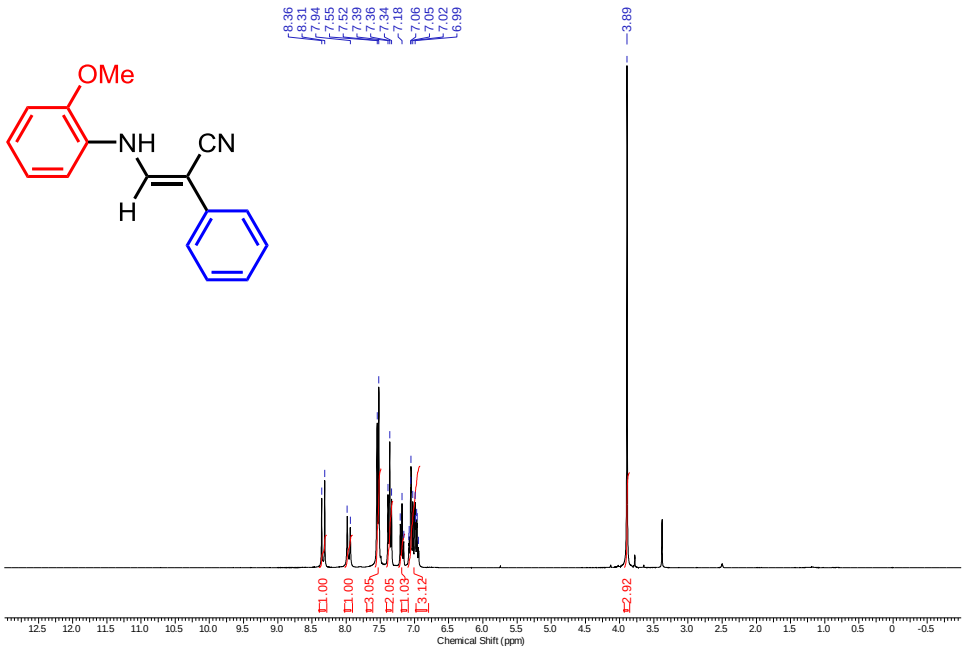
^{1}H NMR (**3ma**) (Acetone-d_6)



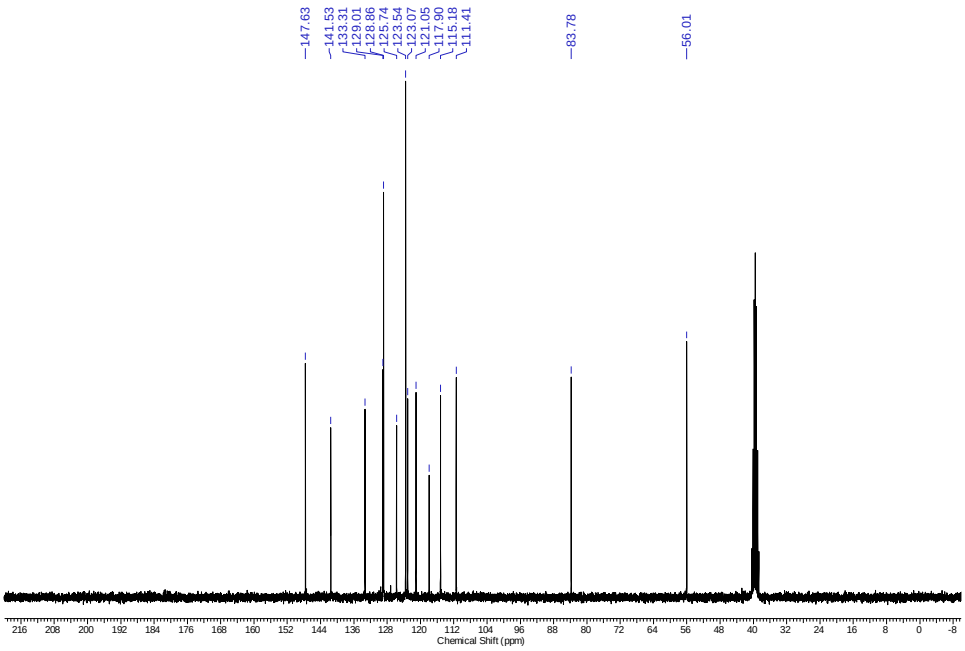
^{13}C NMR (**3ma**) (Acetone-d_6)



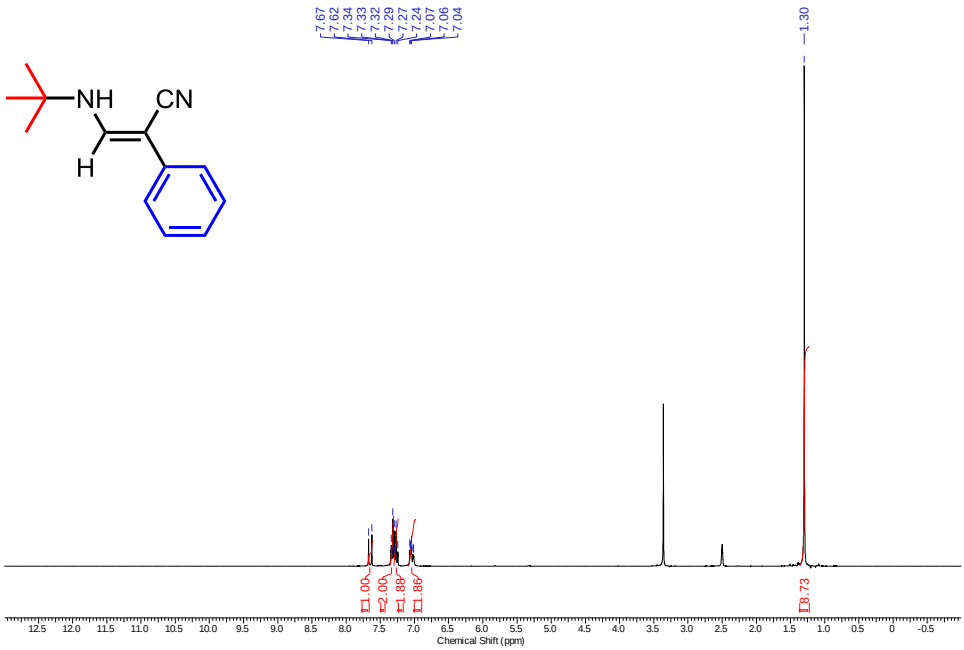
^{1}H NMR (**3na**) (DMSO-d_6)



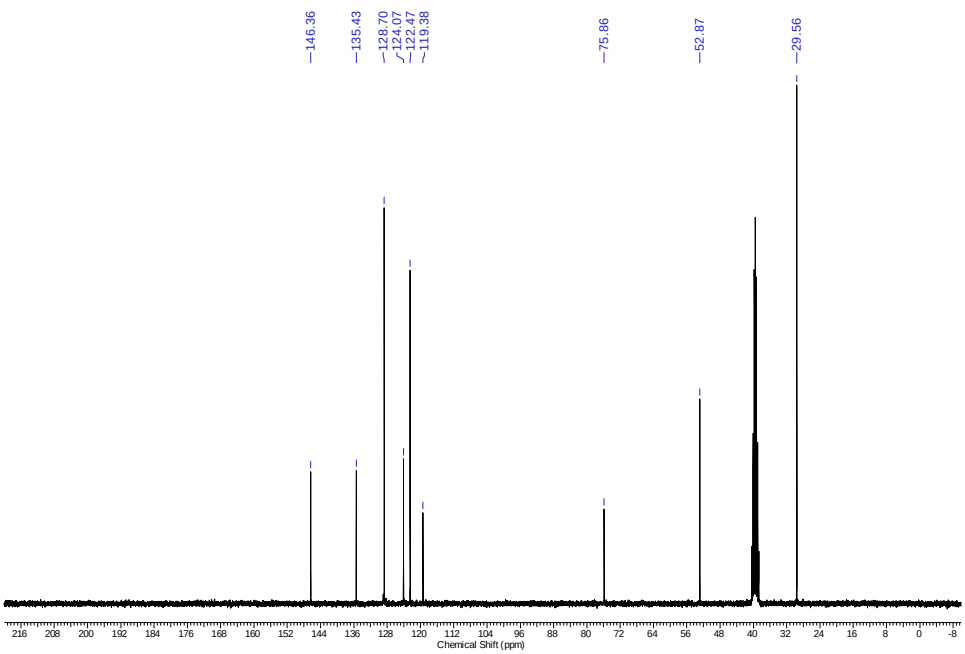
^{13}C NMR (**3na**) (DMSO-d_6)



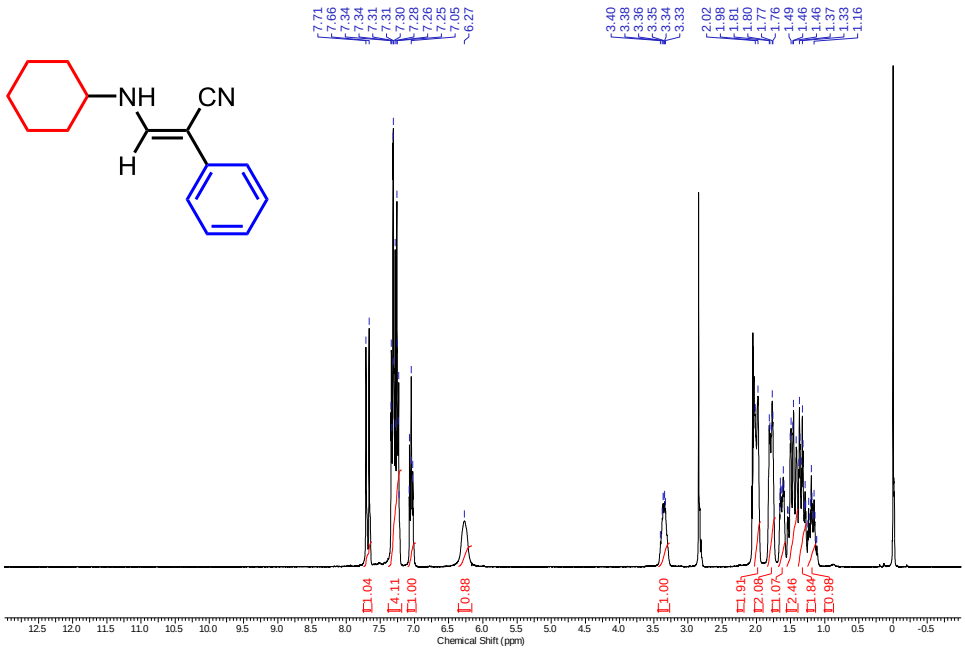
^{1}H NMR (**3oa**) (DMSO-d_6)



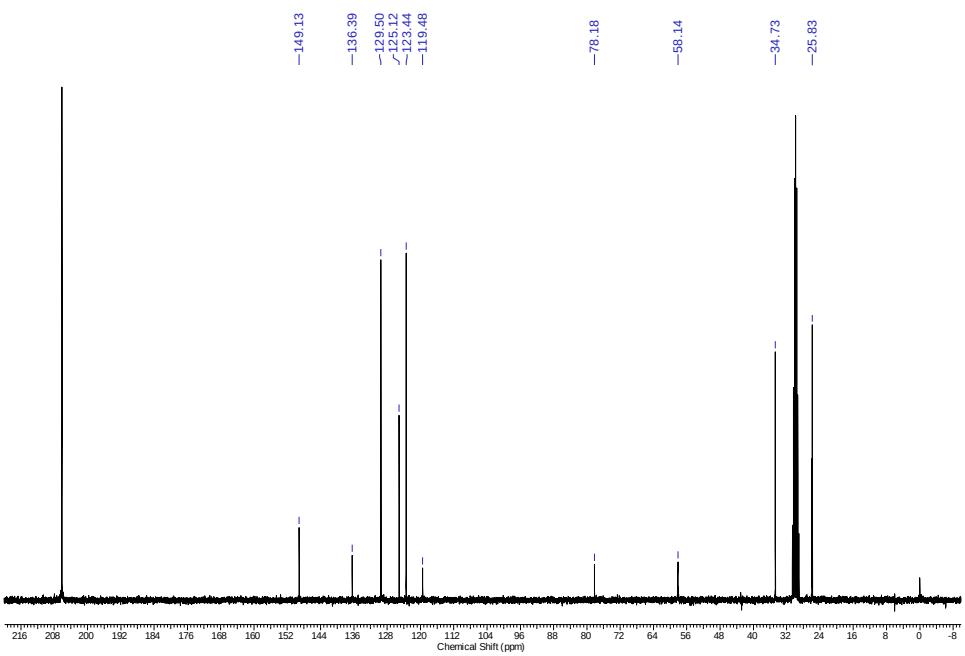
^{13}C NMR (**3oa**) (DMSO-d_6)



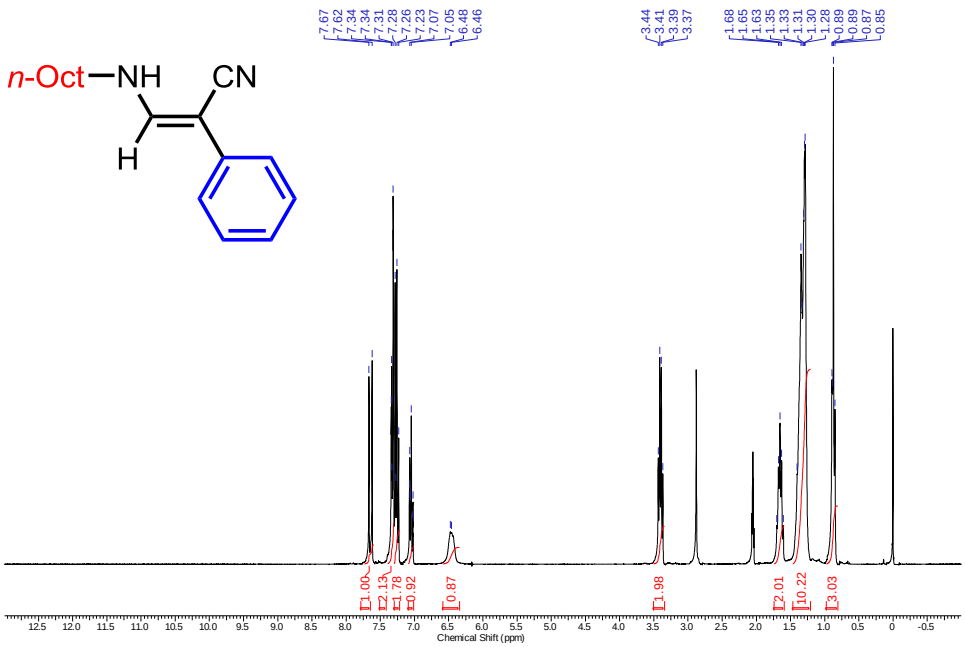
^{1}H NMR (**3pa**) (Acetone-d_6)



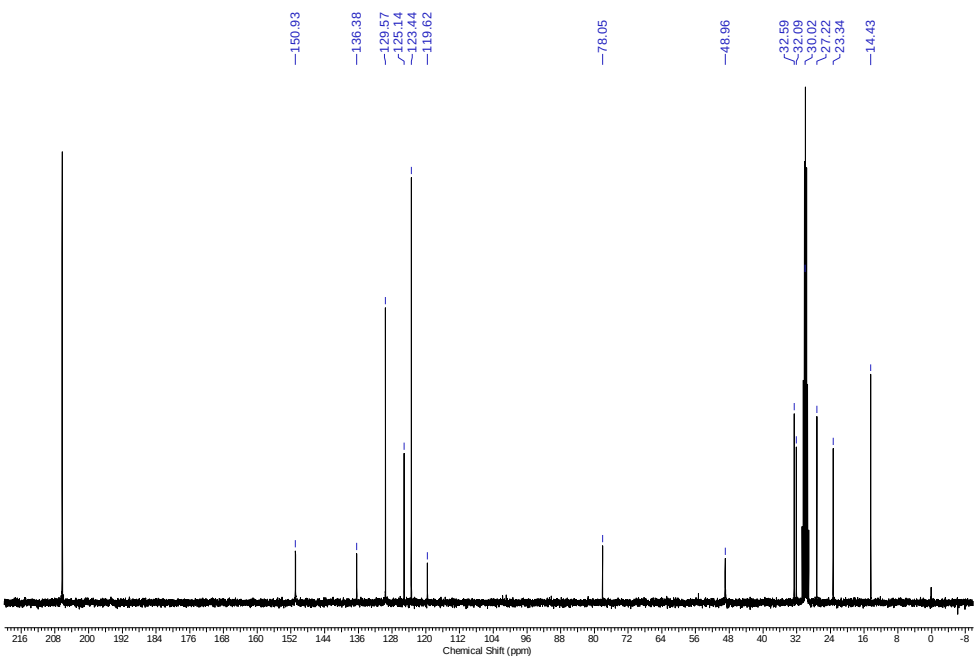
^{13}C NMR (**3pa**) (Acetone-d_6)



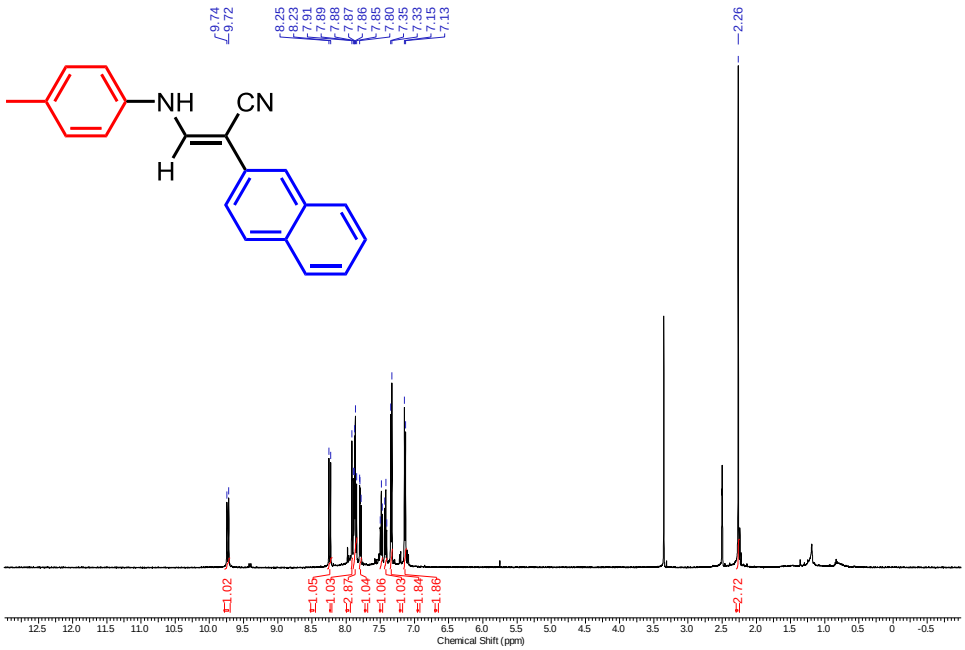
^{1}H NMR (**3qa**) (Acetone-d_6)



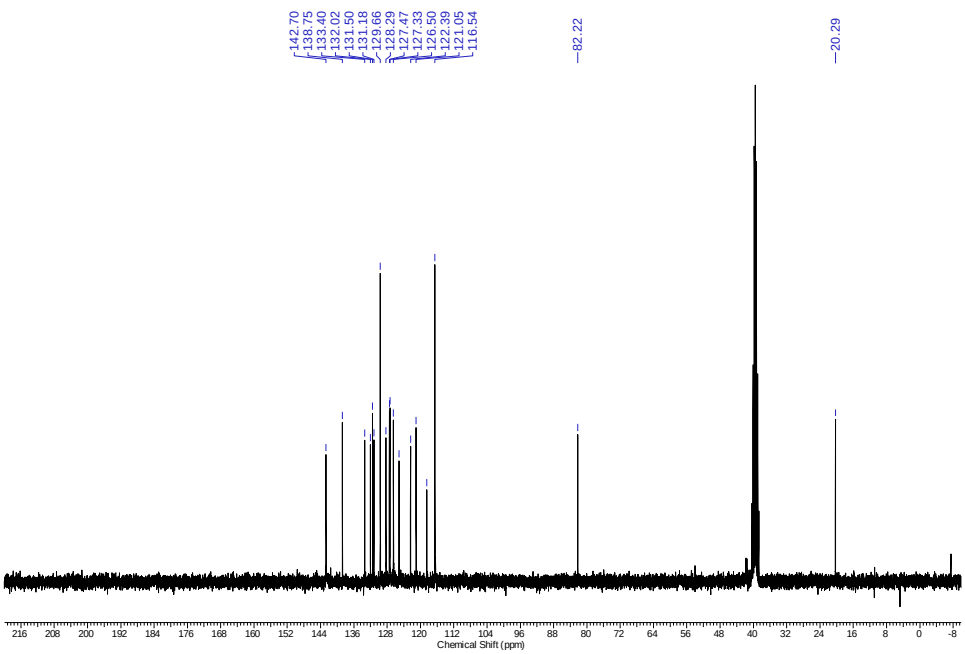
^{13}C NMR (**3qa**) (Acetone-d_6)



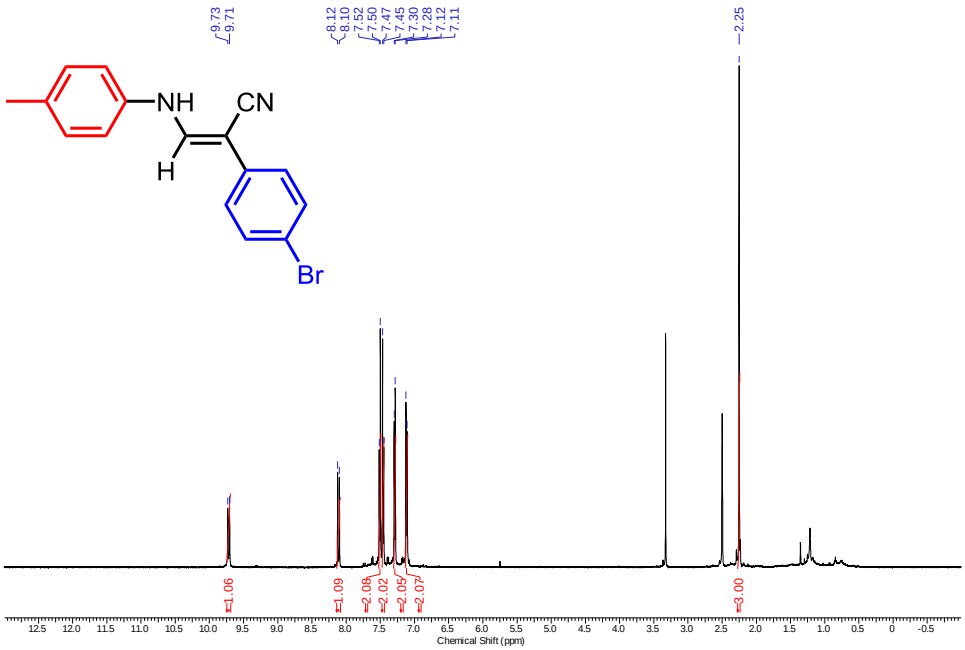
^{1}H NMR (**3ab**) (DMSO-d_6)



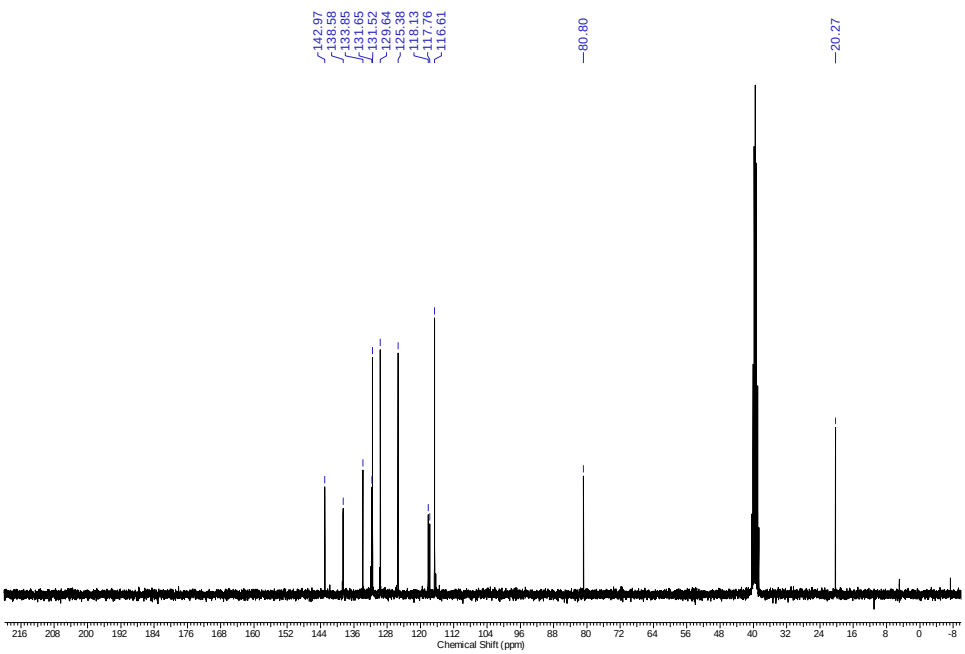
^{13}C NMR (**3ab**) (DMSO-d_6)



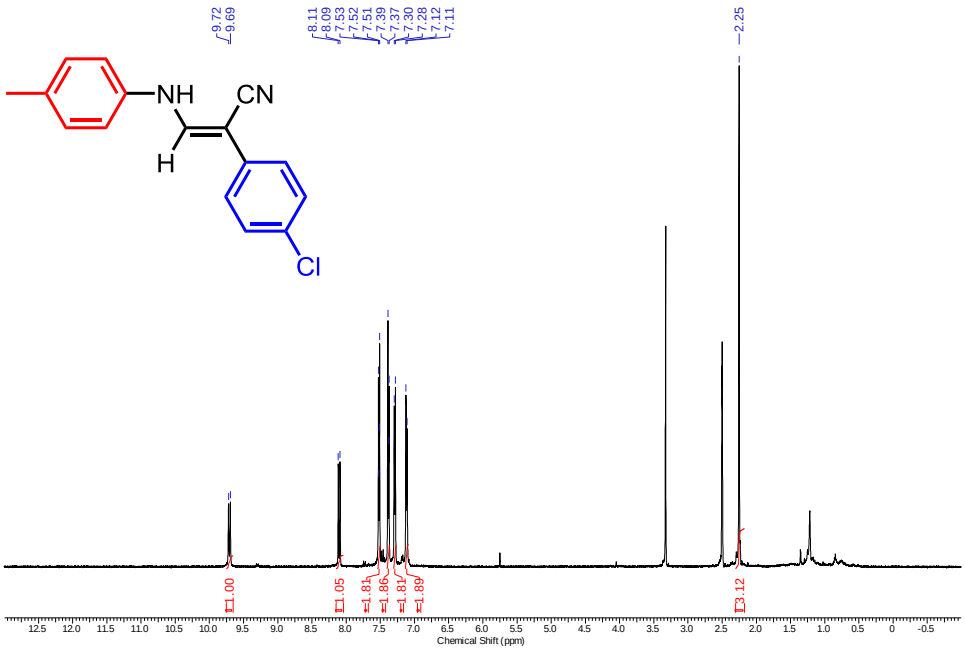
^{1}H NMR (**3ac**) (DMSO-d_6)



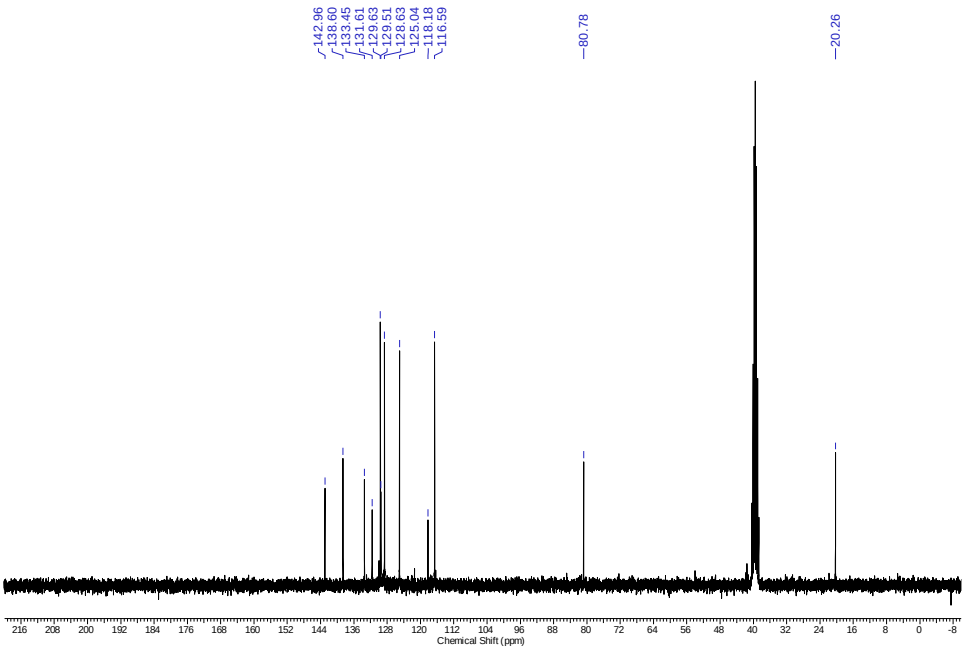
^{13}C NMR (**3ac**) (DMSO-d_6)



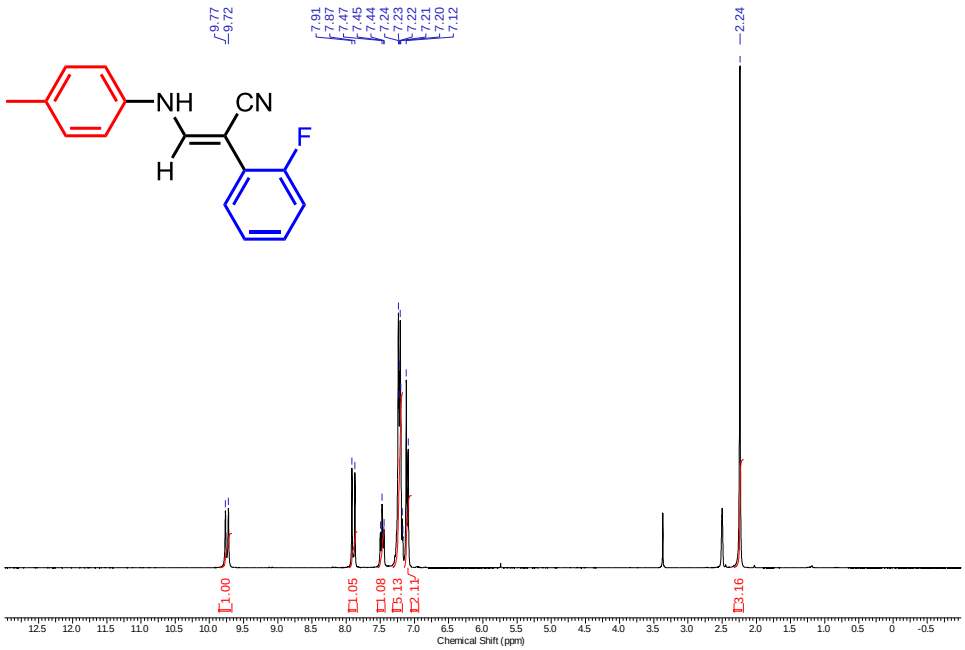
^{1}H NMR (**3ad**) (DMSO-d_6)



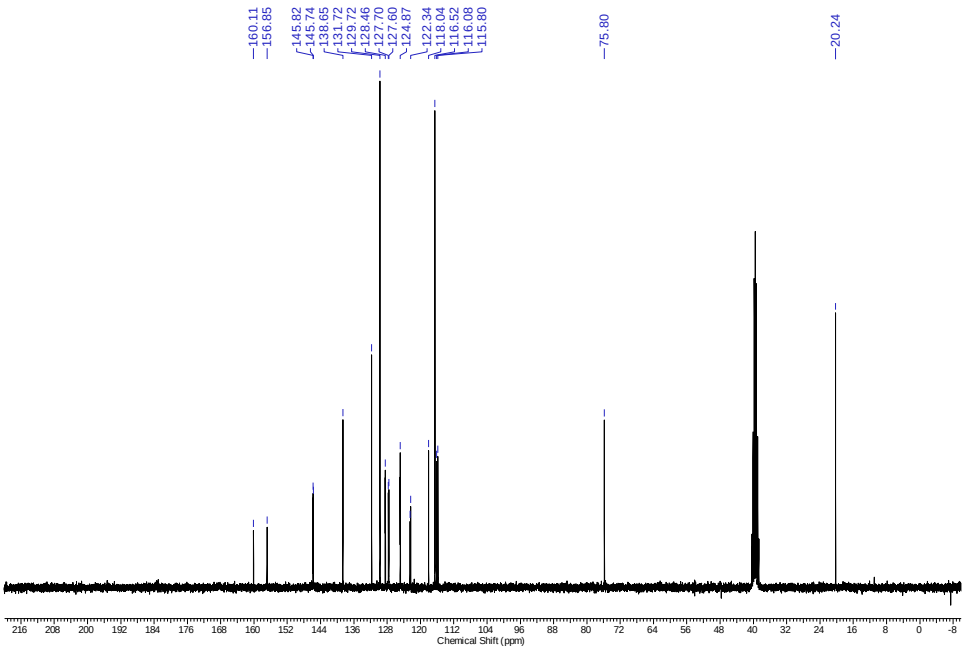
^{13}C NMR (**3ad**) (DMSO-d_6)



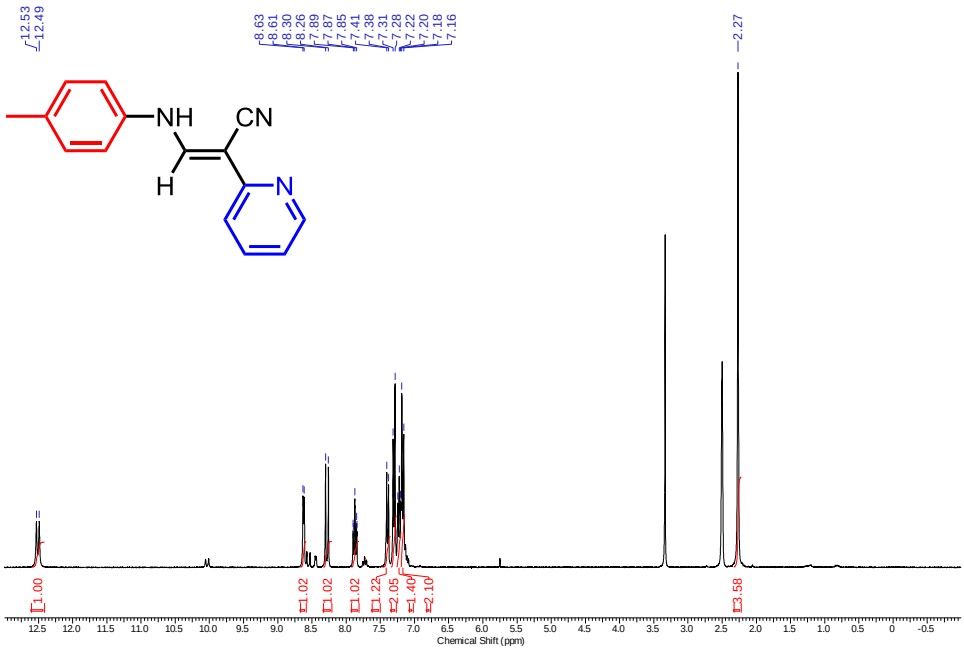
^{1}H NMR (**3ae**) (DMSO-d_6)



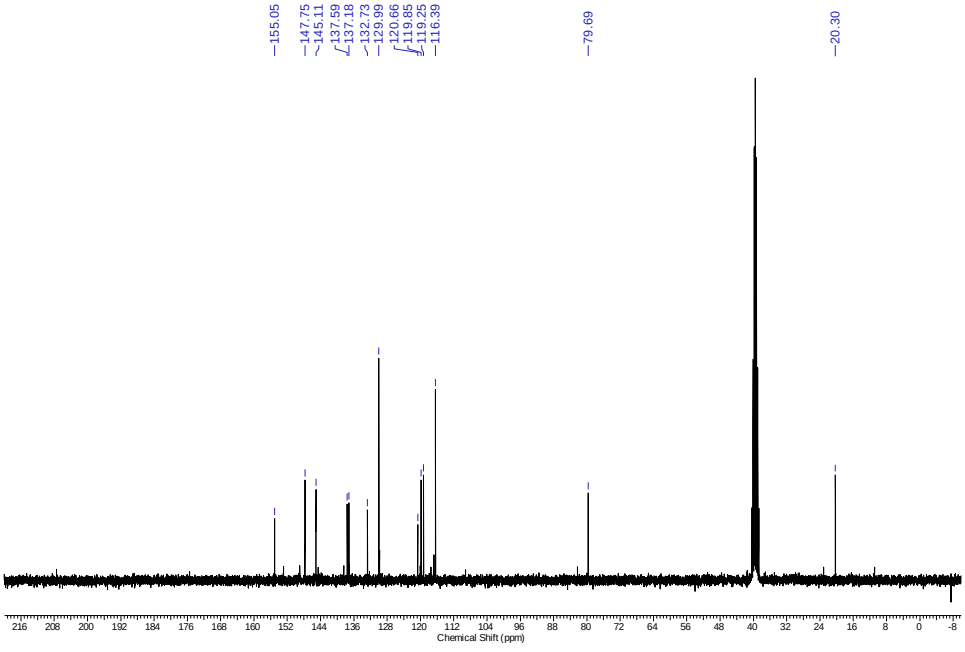
^{13}C NMR (**3ae**) (DMSO-d_6)



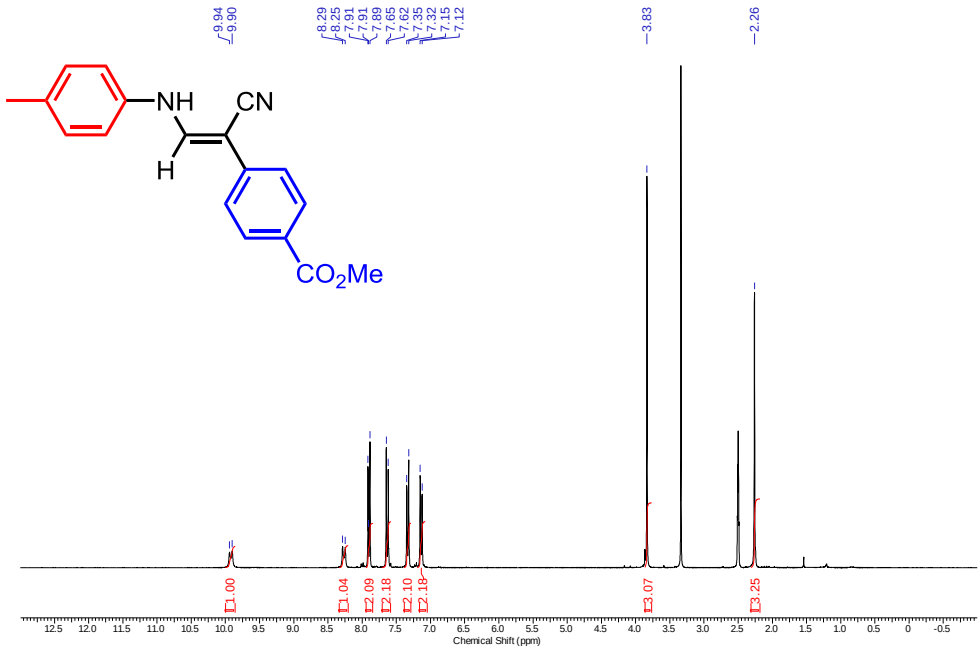
^{1}H NMR (**3af**) (DMSO-d_6)



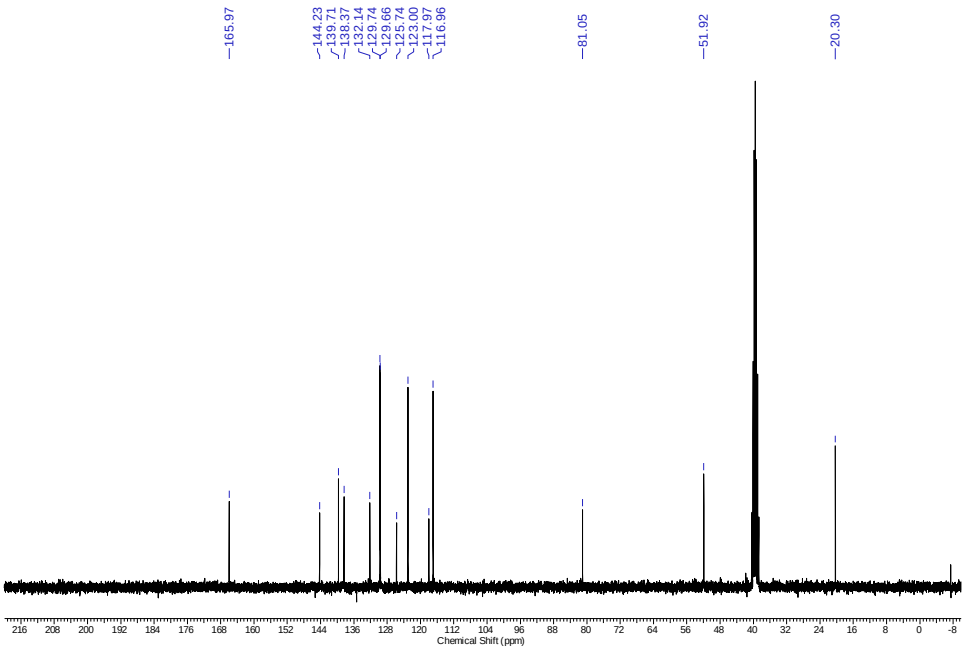
^{13}C NMR (**3af**) (DMSO-d_6)



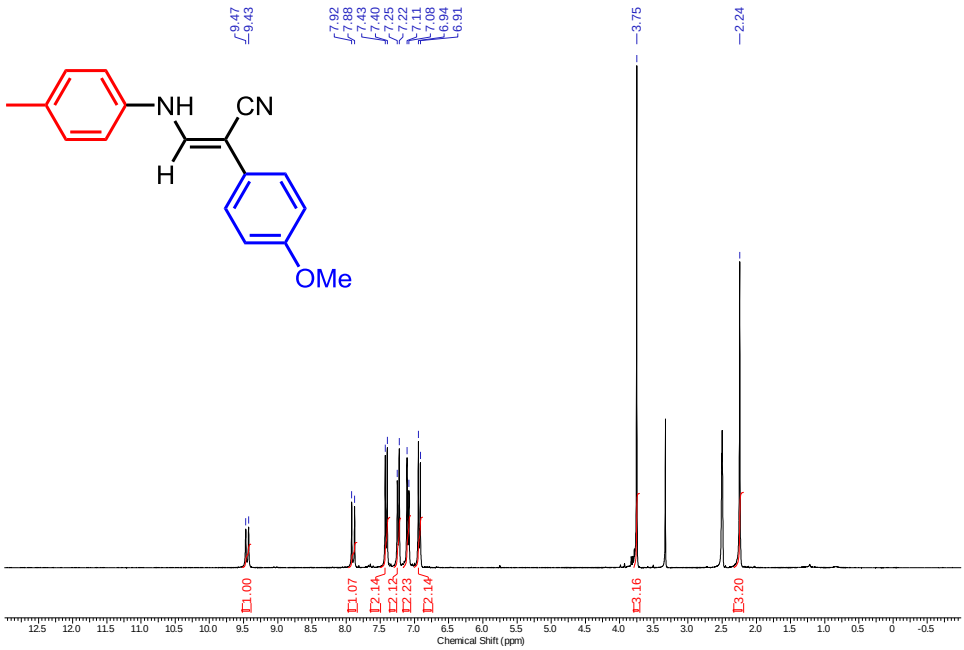
^{1}H NMR (**3ag**) (DMSO-d_6)



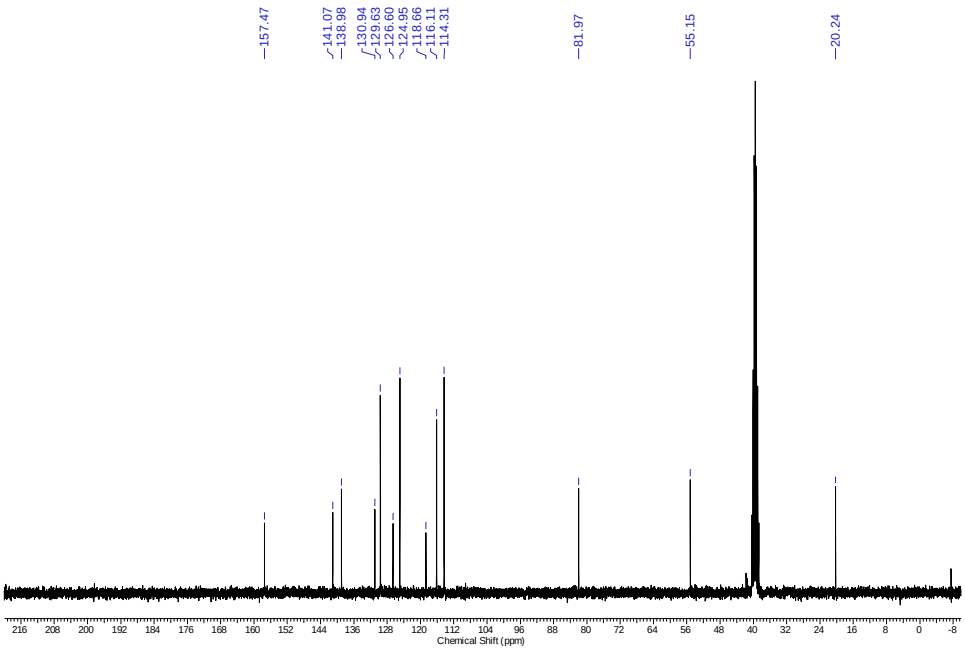
^{13}C NMR (**3ag**) (DMSO-d_6)



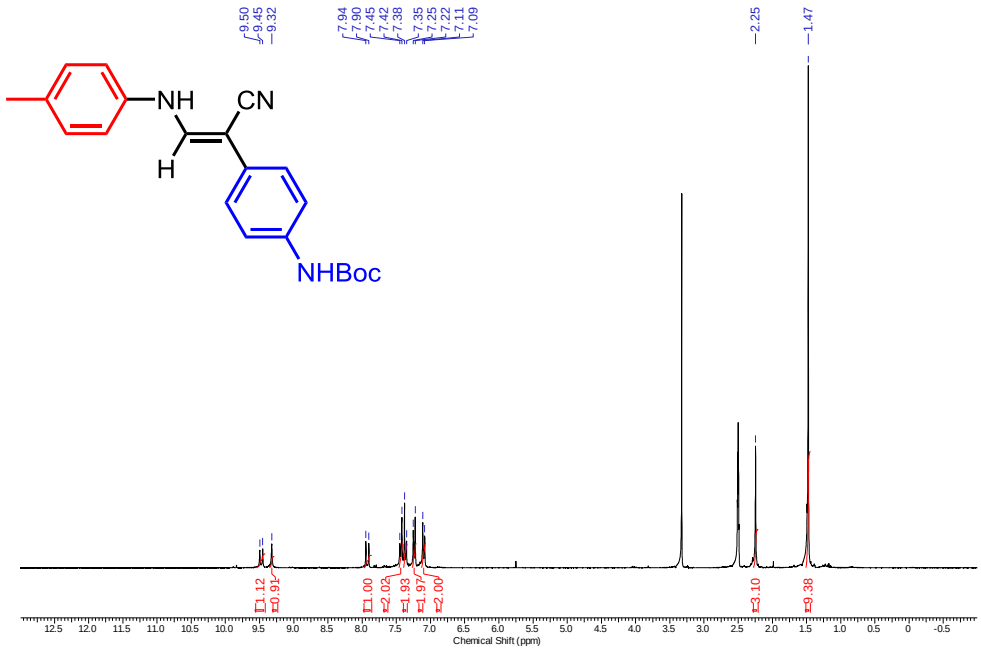
^{1}H NMR (**3ah**) (DMSO-d_6)



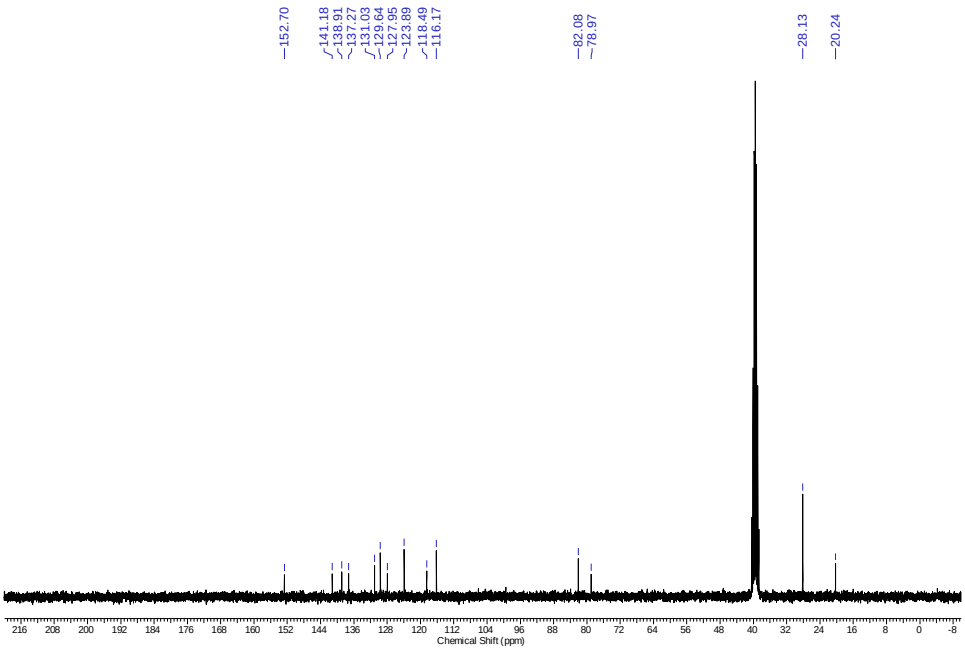
^{13}C NMR (**3ah**) (DMSO-d_6)



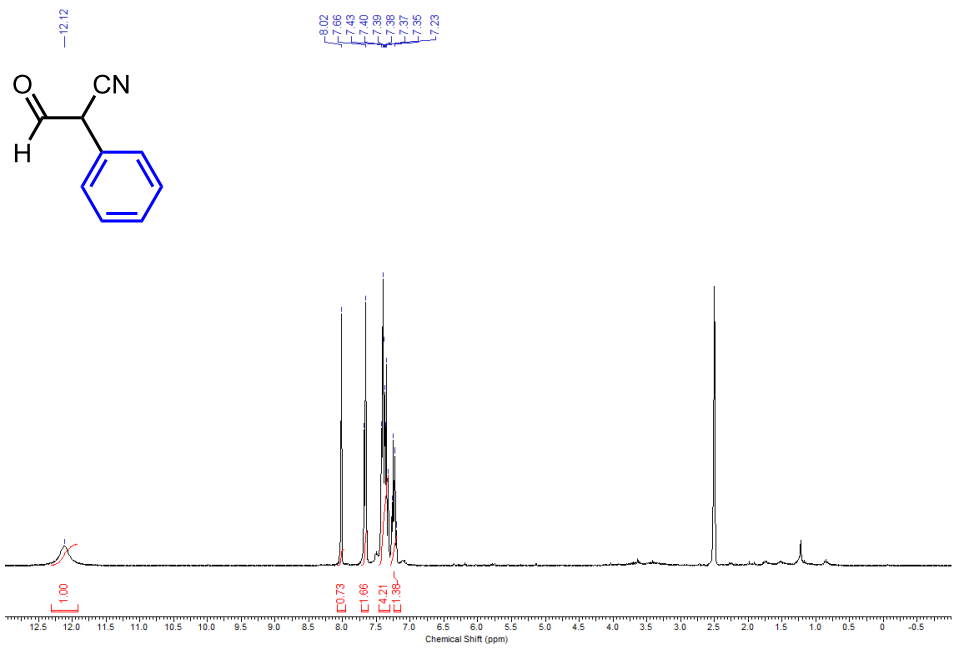
^{1}H NMR (**3ai**) (DMSO-d_6)



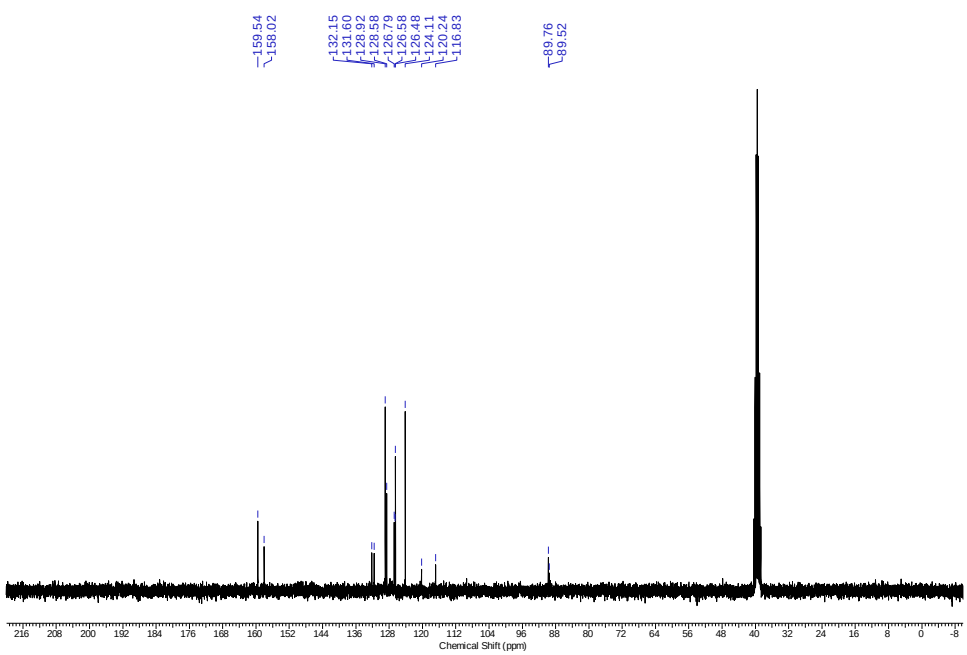
^{13}C NMR (**3ai**) (DMSO-d_6)



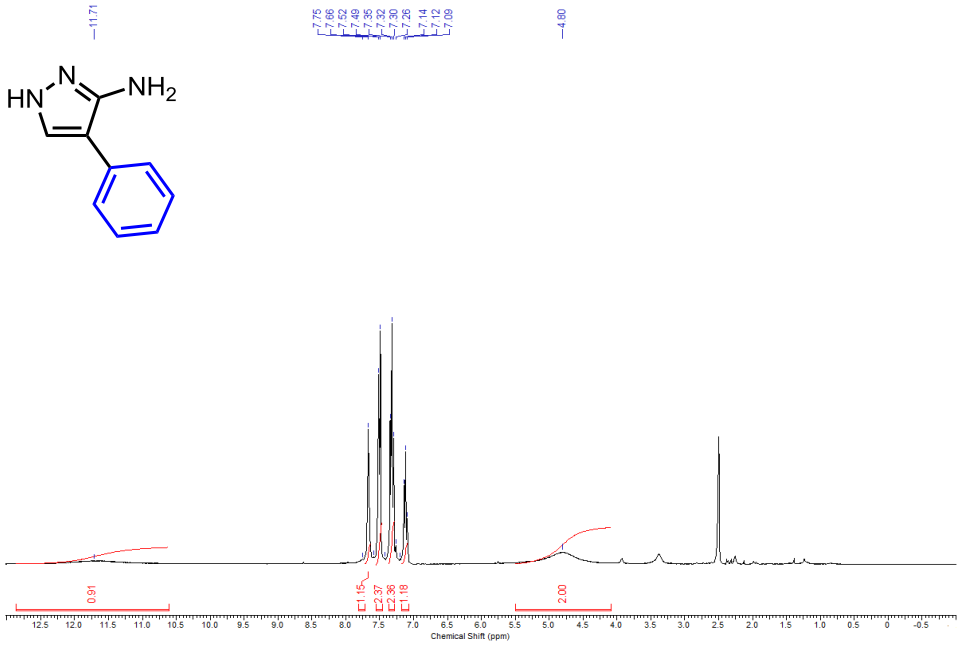
^{1}H NMR (**4**) (DMSO-d_6)



^{13}C NMR (**4**) (DMSO-d_6)

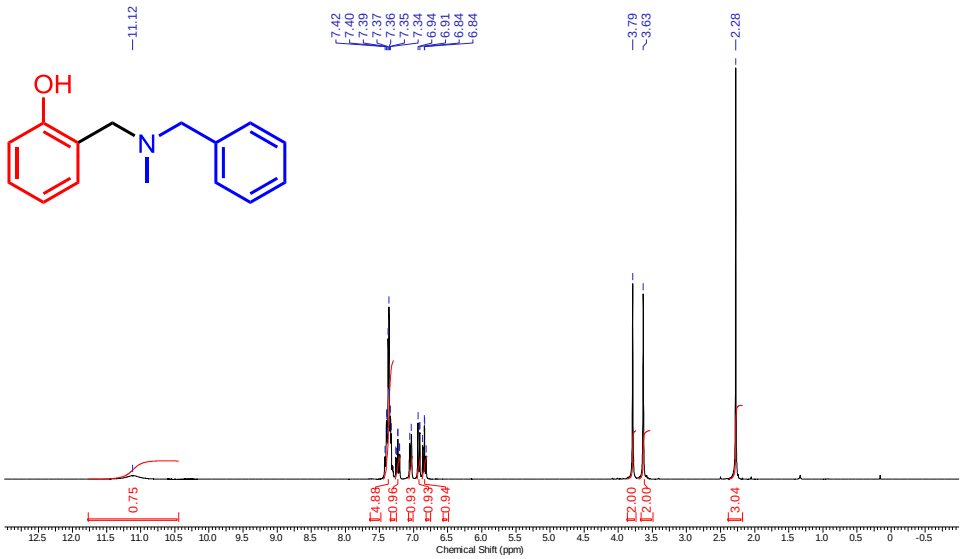


^{1}H NMR (**5**) (DMSO-d_6)

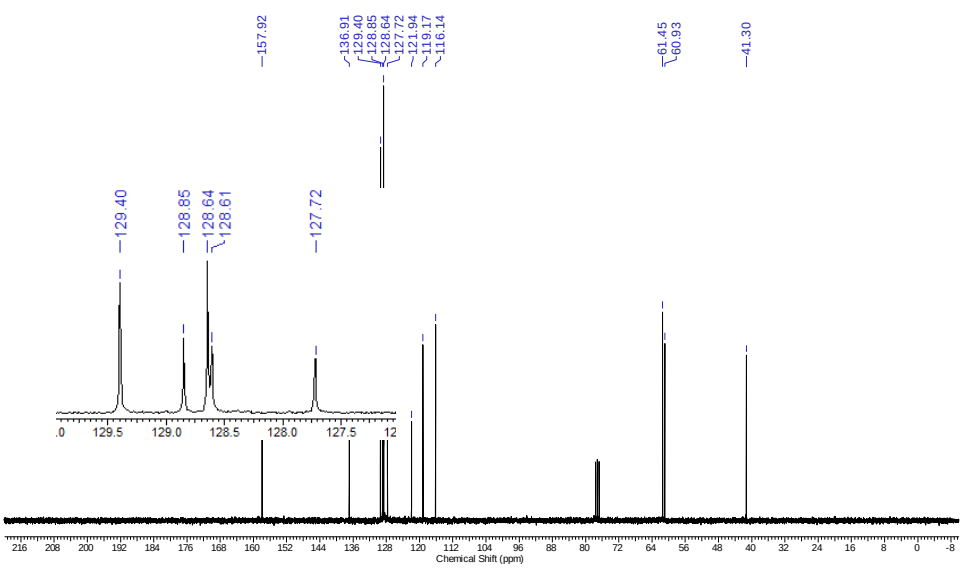


Chapter 4

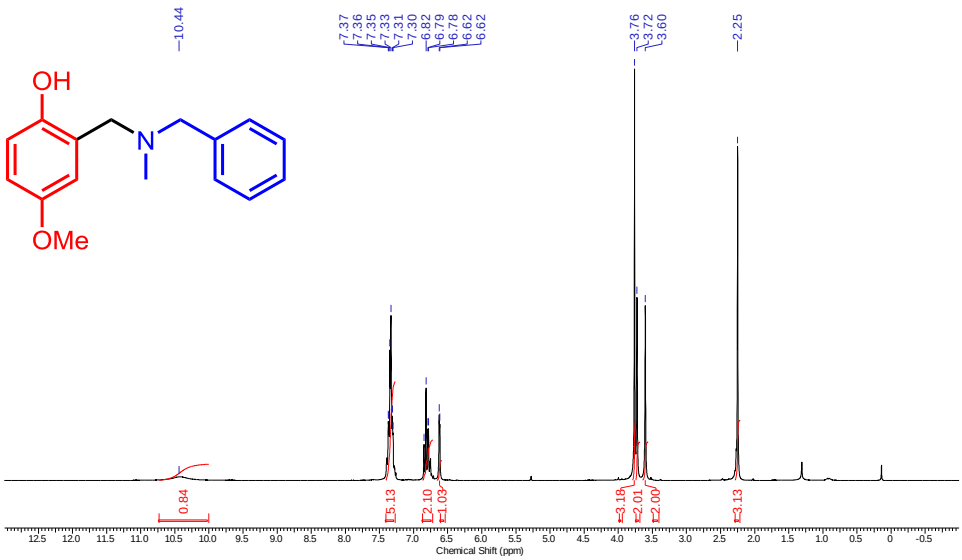
^{1}H NMR (**4a**) ($CDCl_3$)



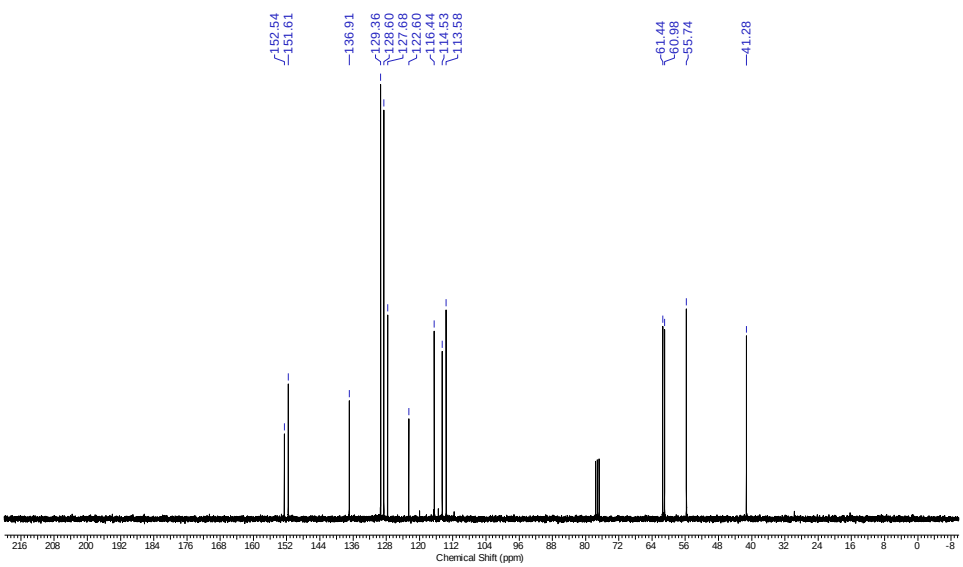
^{13}C NMR (**4a**) ($CDCl_3$)



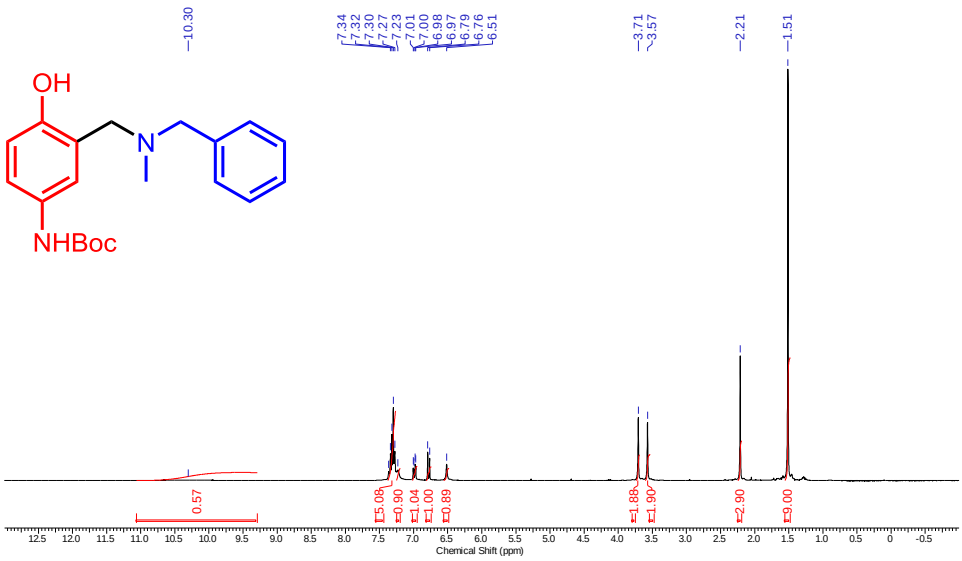
^{1}H NMR (**4b**) ($CDCl_3$)



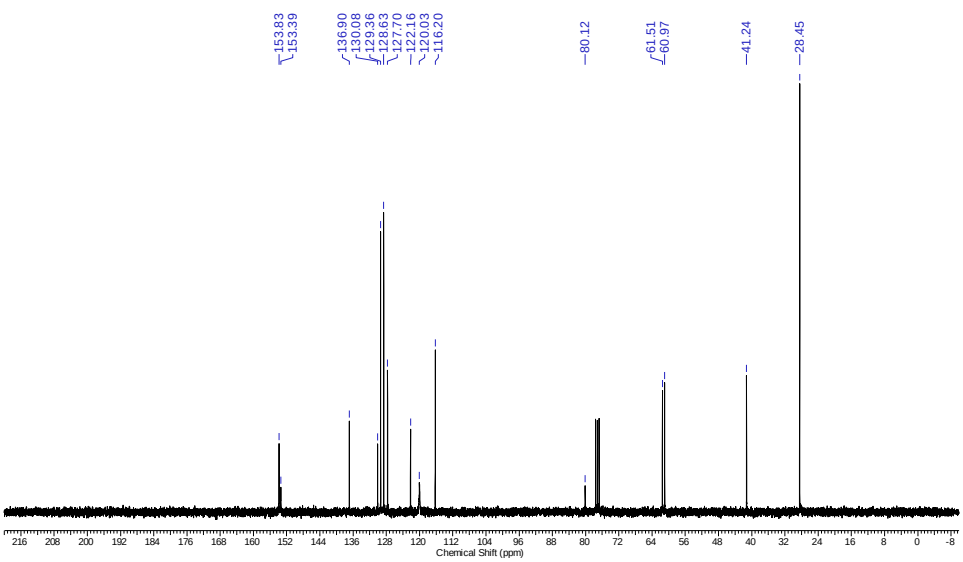
^{13}C NMR (**4b**) ($CDCl_3$)



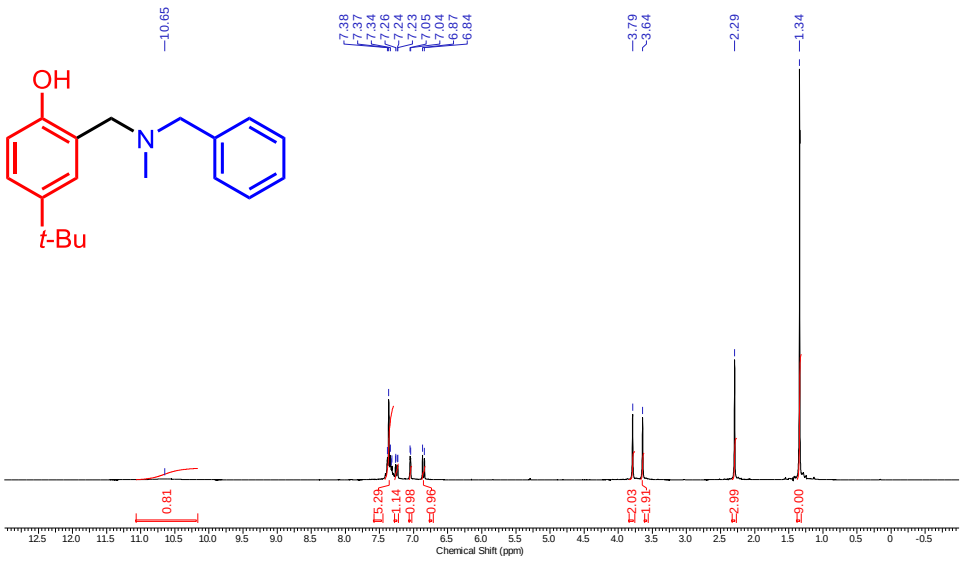
^{1}H NMR (**4c**) ($CDCl_3$)



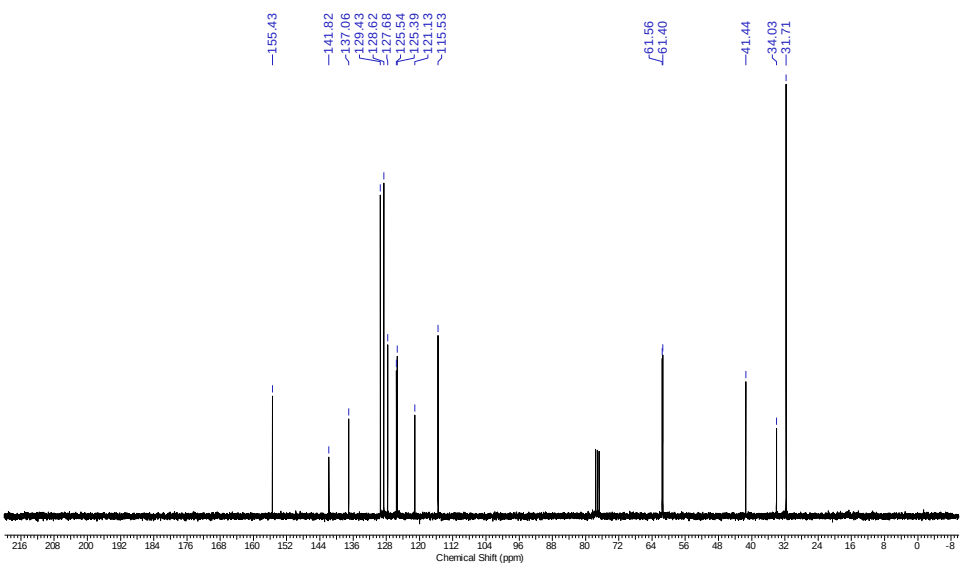
^{13}C NMR (**4c**) ($CDCl_3$)



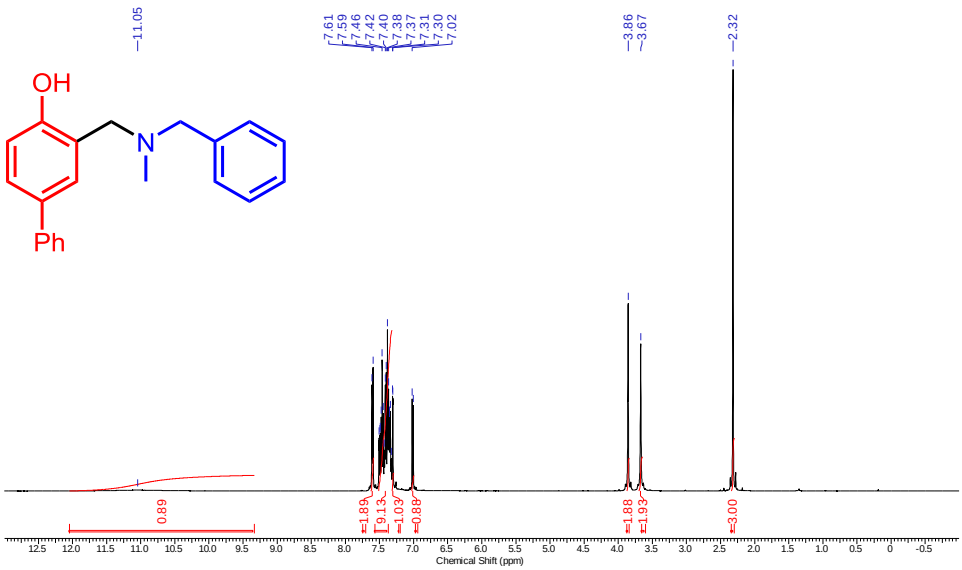
^{1}H NMR (**4d**) ($CDCl_3$)



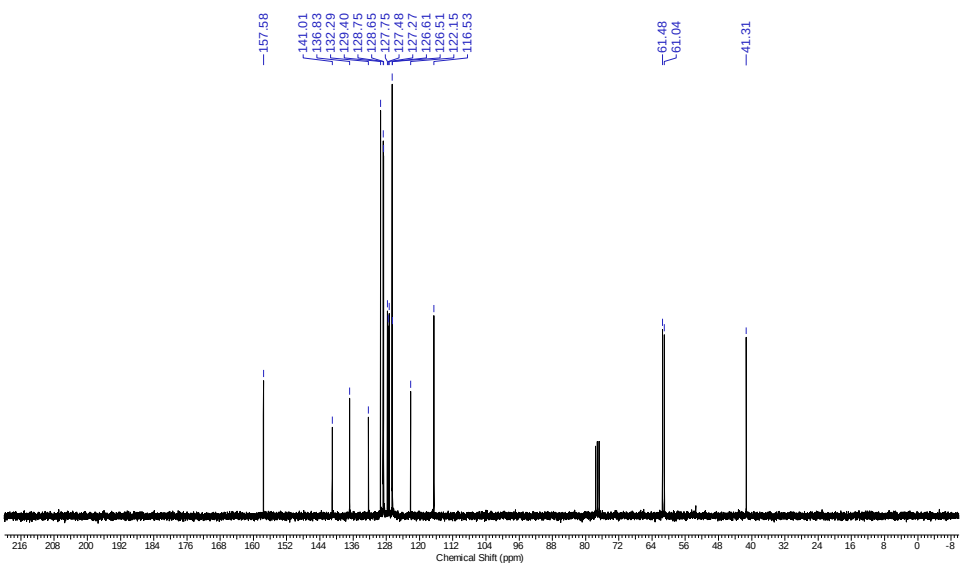
^{13}C NMR (**4d**) ($CDCl_3$)



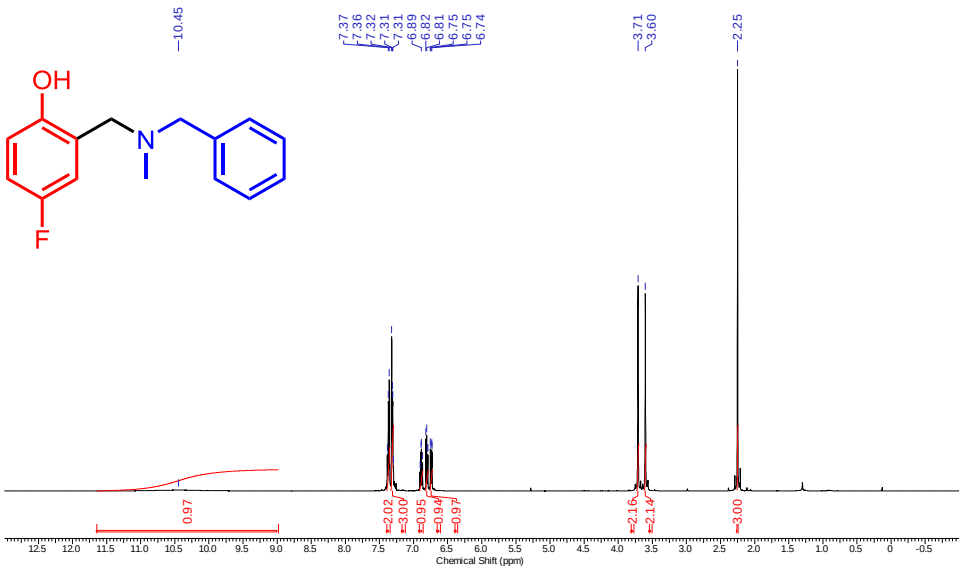
^{1}H NMR (**4e**) ($CDCl_3$)



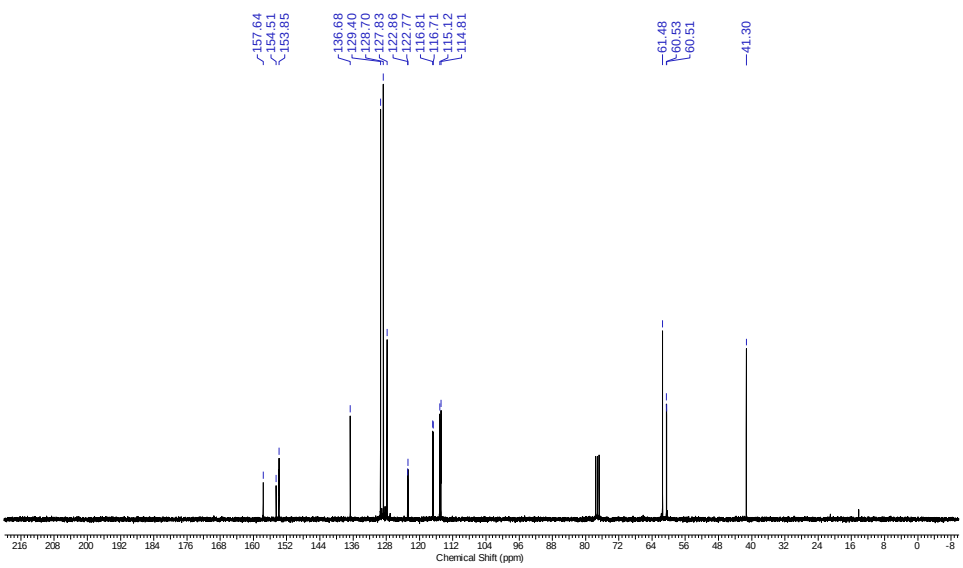
^{13}C NMR (**4e**) ($CDCl_3$)



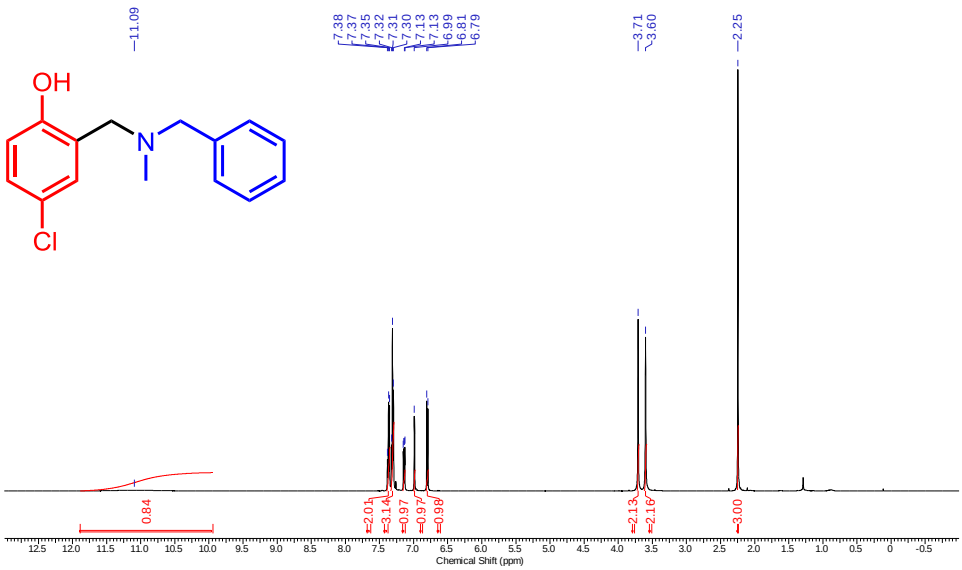
^{1}H NMR (**4f**) ($CDCl_3$)



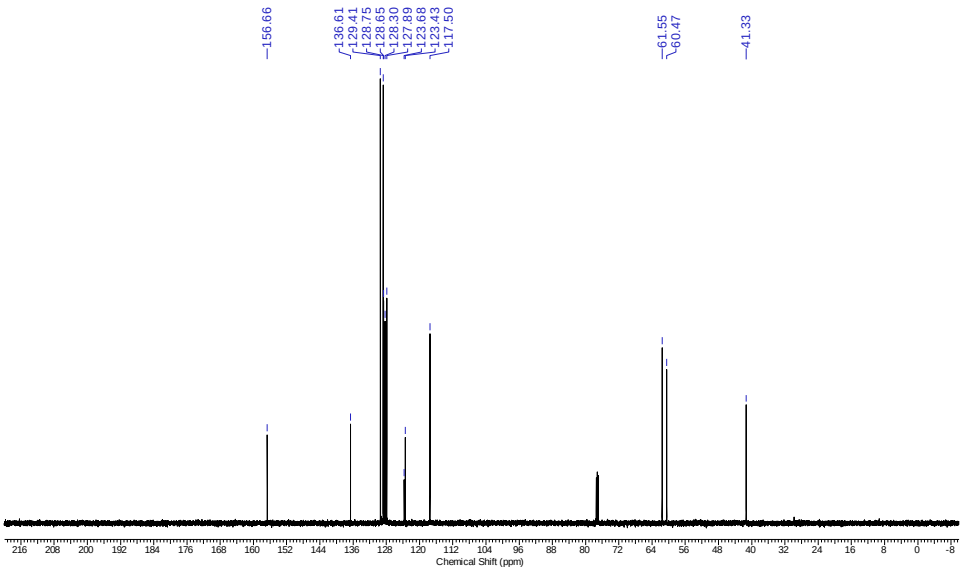
^{13}C NMR (**4f**) ($CDCl_3$)



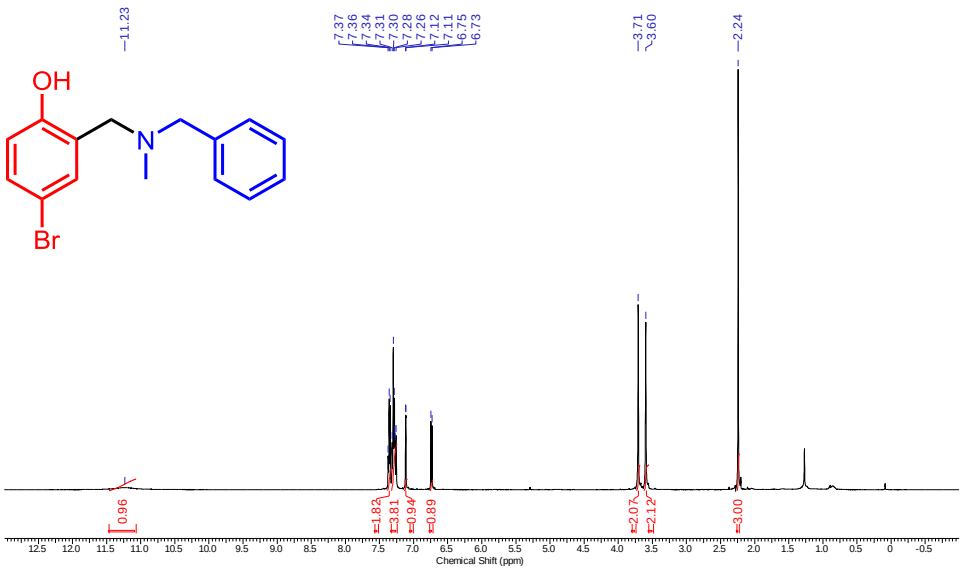
^{1}H NMR (**4g**) ($CDCl_3$)



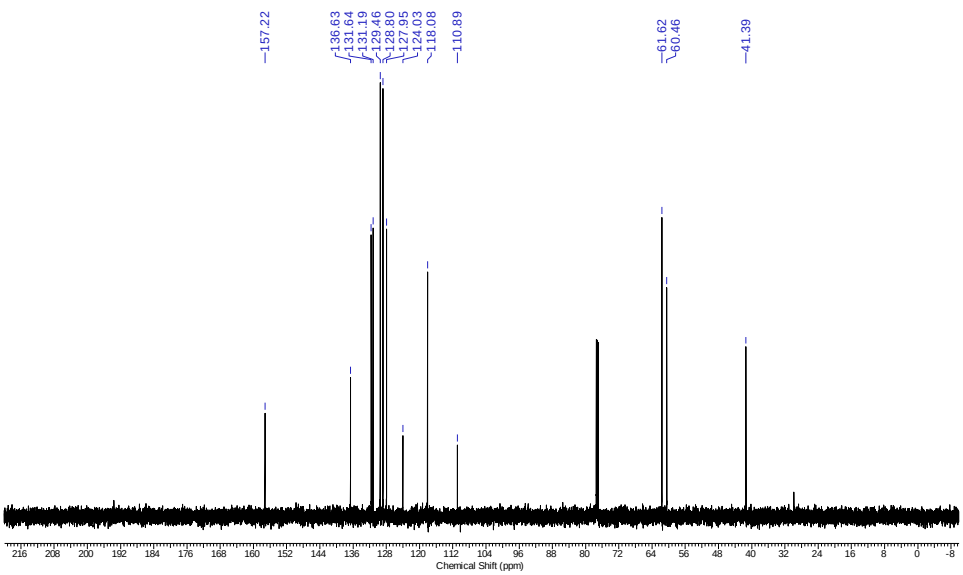
^{13}C NMR (**4g**) ($CDCl_3$)



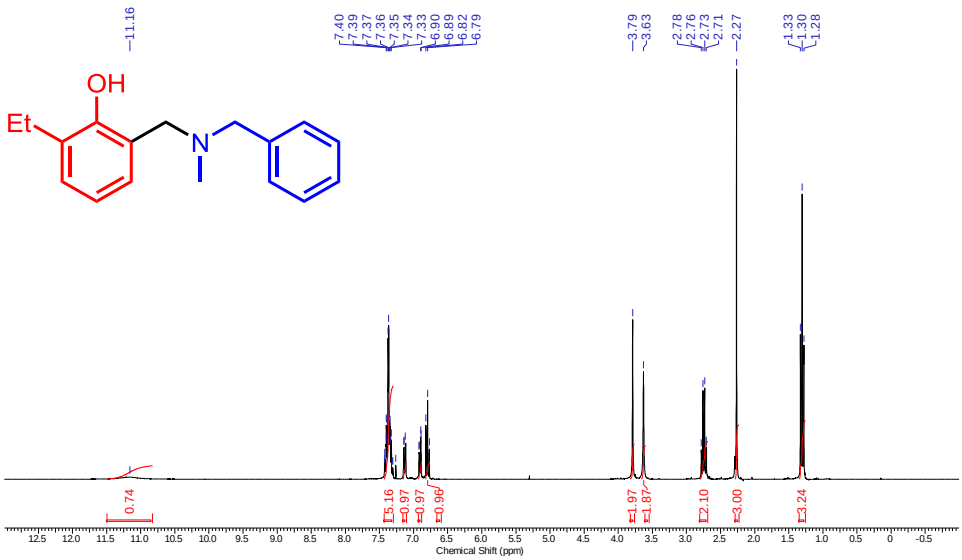
^{1}H NMR (**4h**) ($CDCl_3$)



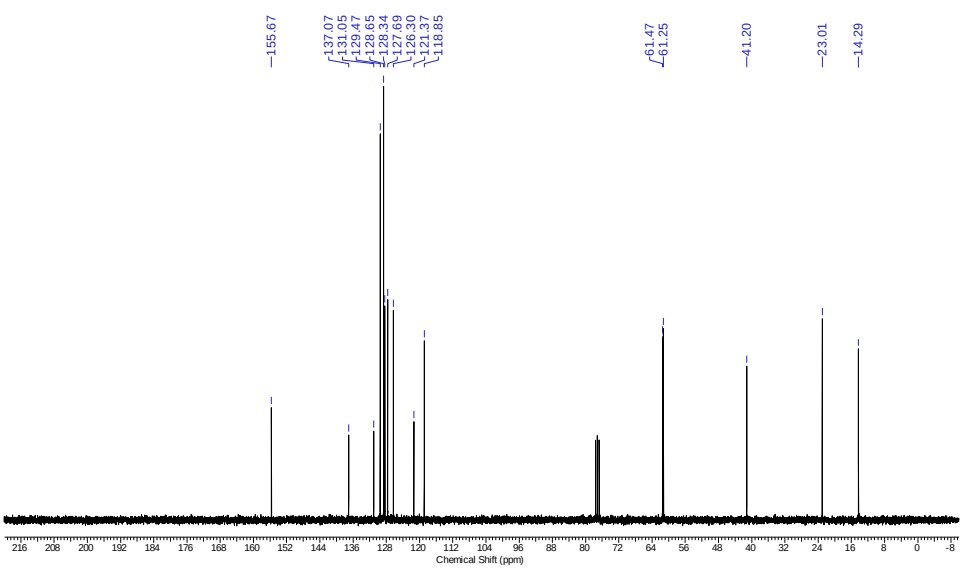
^{13}C NMR (**4h**) ($CDCl_3$)



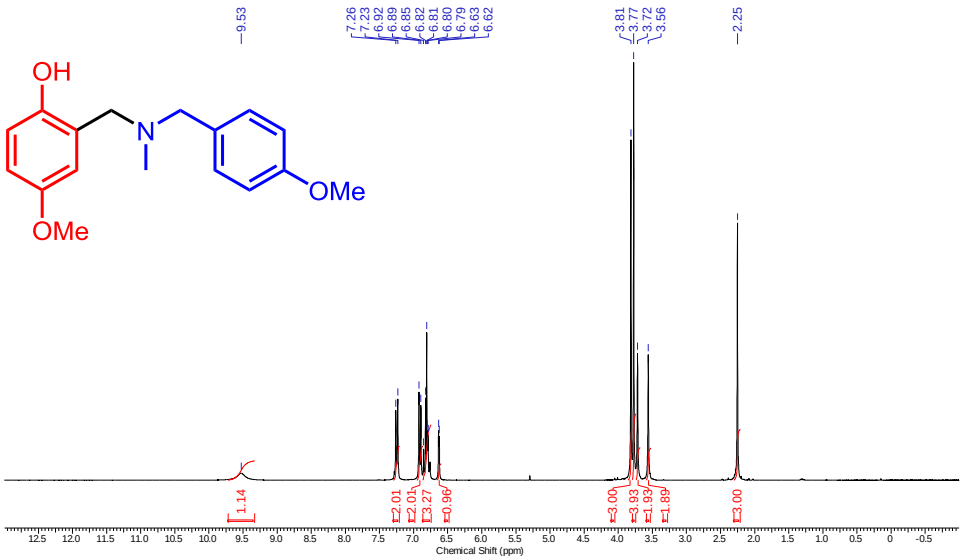
^{1}H NMR (**4i**) ($CDCl_3$)



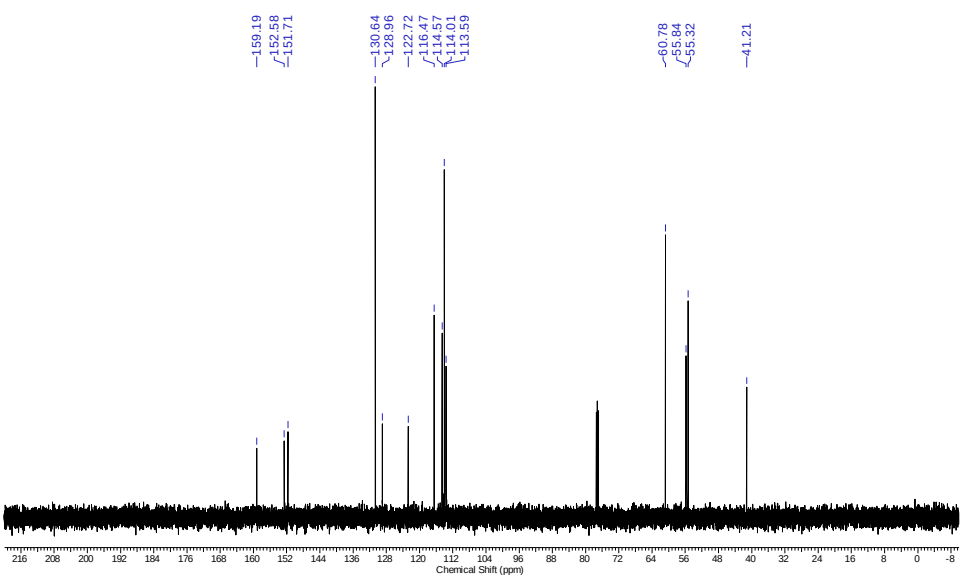
^{13}C NMR (**4i**) ($CDCl_3$)



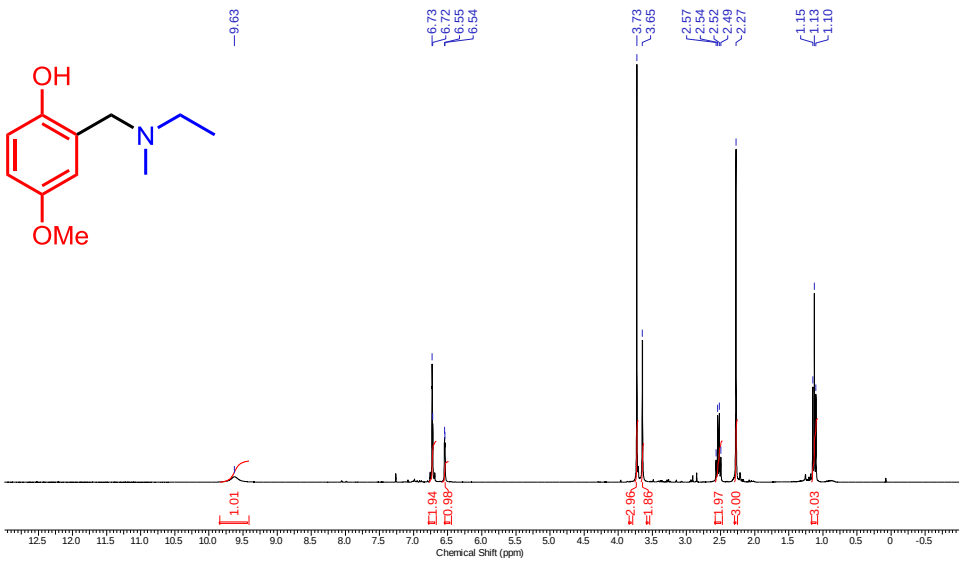
^{1}H NMR (**4j**) ($CDCl_3$)



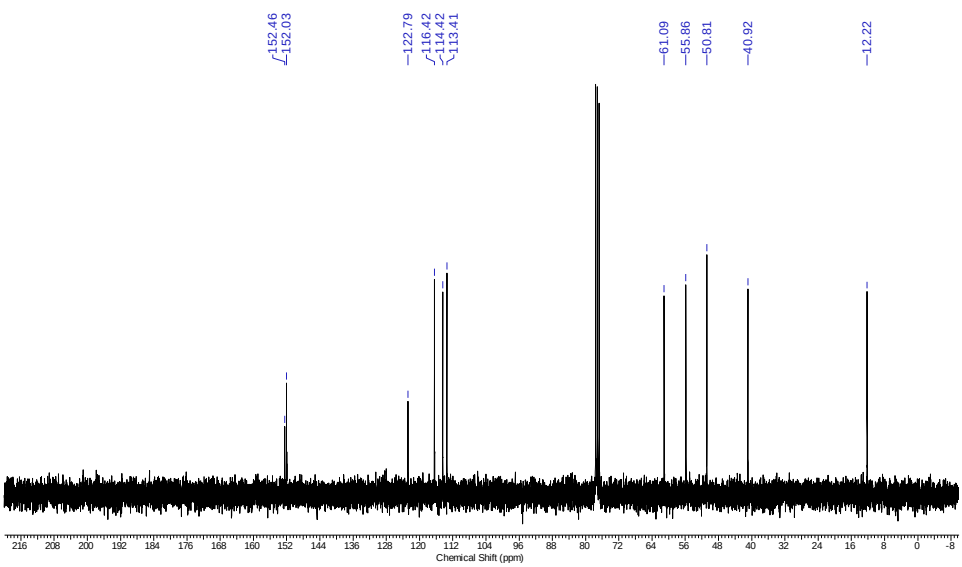
^{13}C NMR (**4j**) ($CDCl_3$)



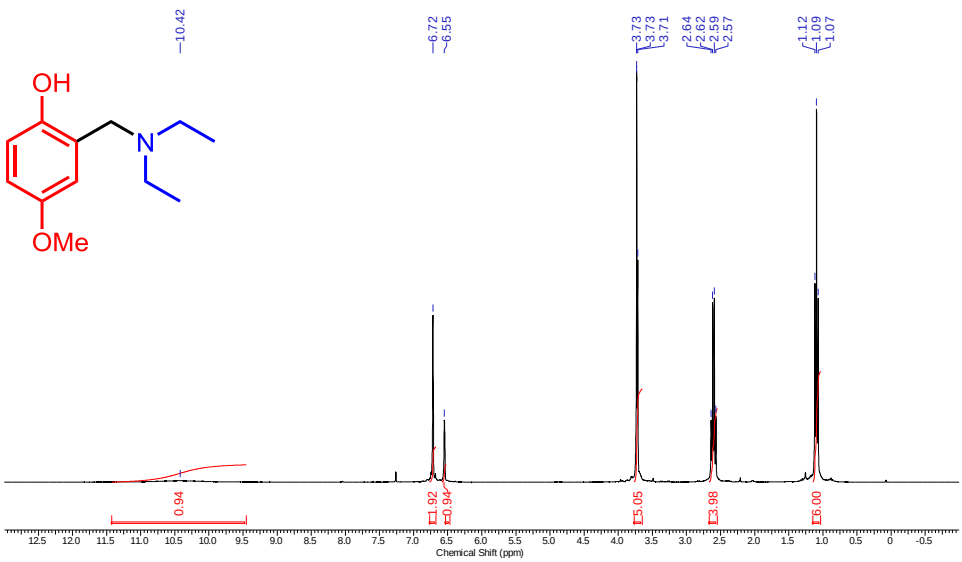
^{1}H NMR (**4k**) ($CDCl_3$)



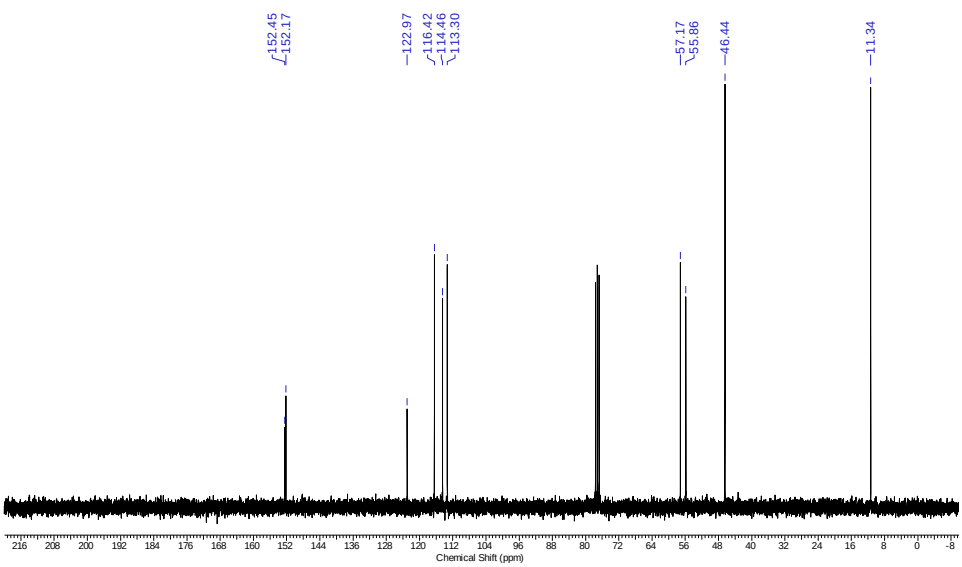
^{13}C NMR (**4k**) ($CDCl_3$)



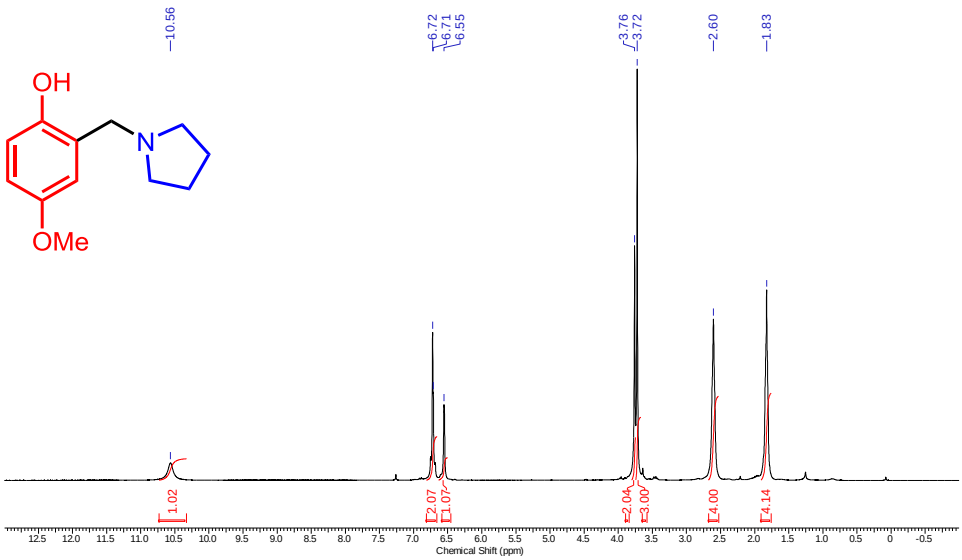
^{1}H NMR (**4l**) ($CDCl_3$)



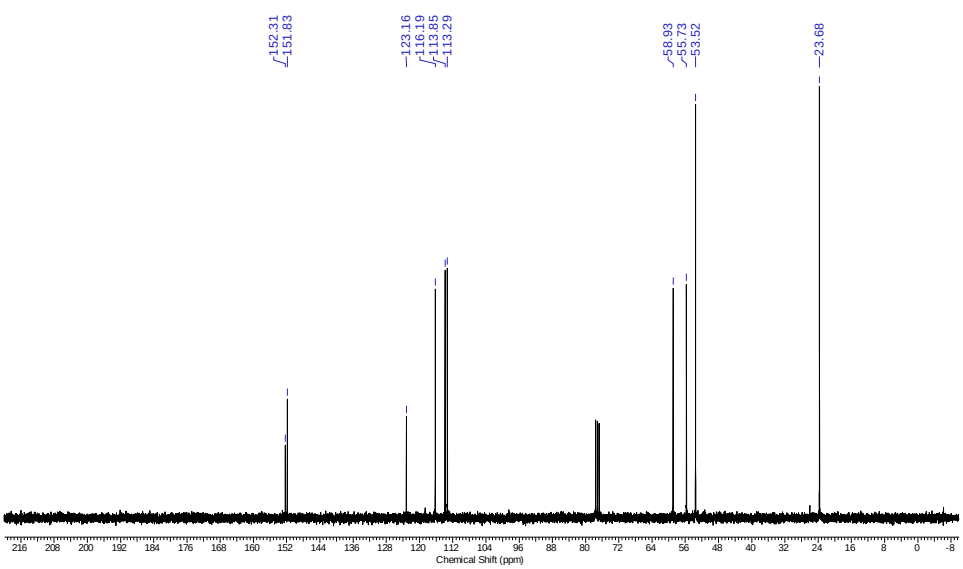
^{13}C NMR (**4l**) ($CDCl_3$)



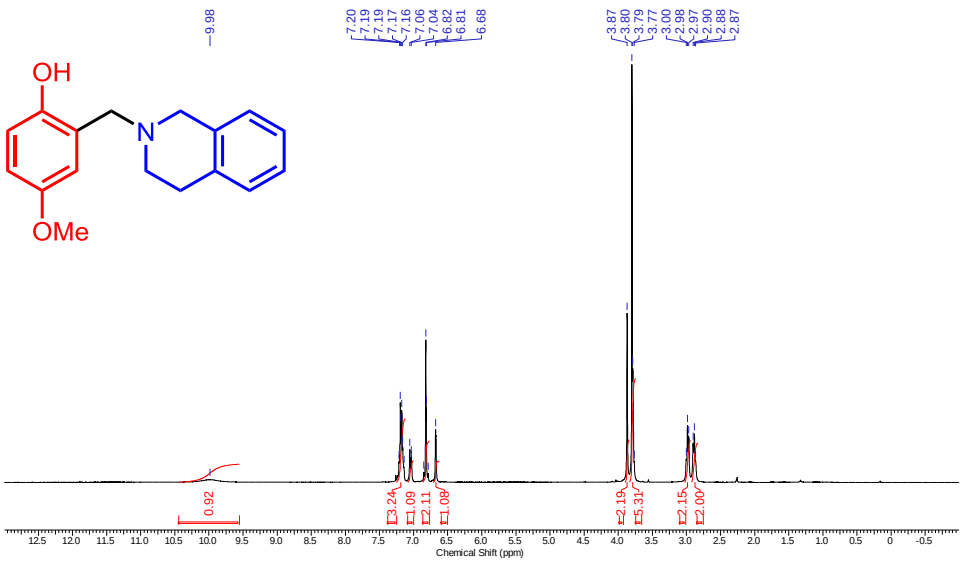
^{1}H NMR (**4n**) ($CDCl_3$)



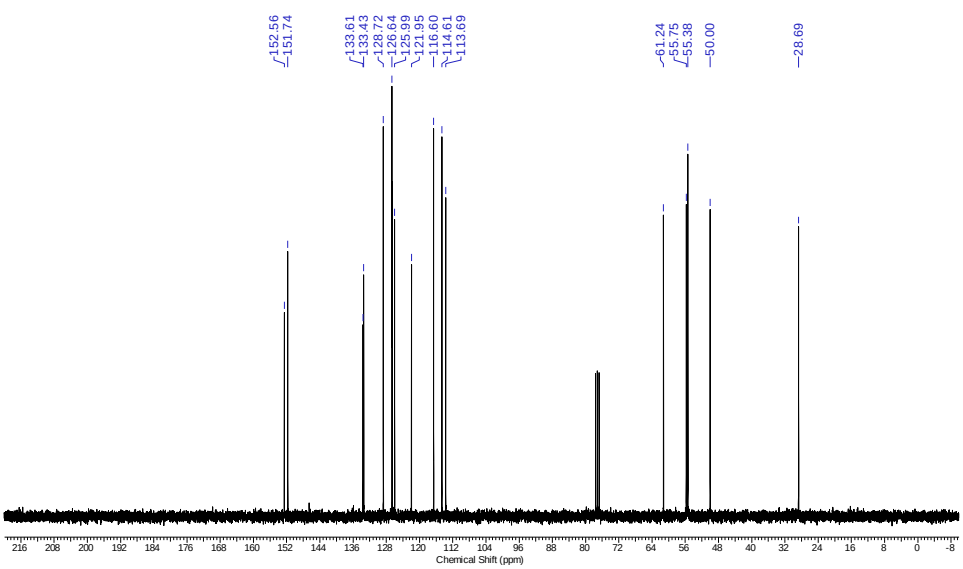
^{13}C NMR (**4n**) ($CDCl_3$)



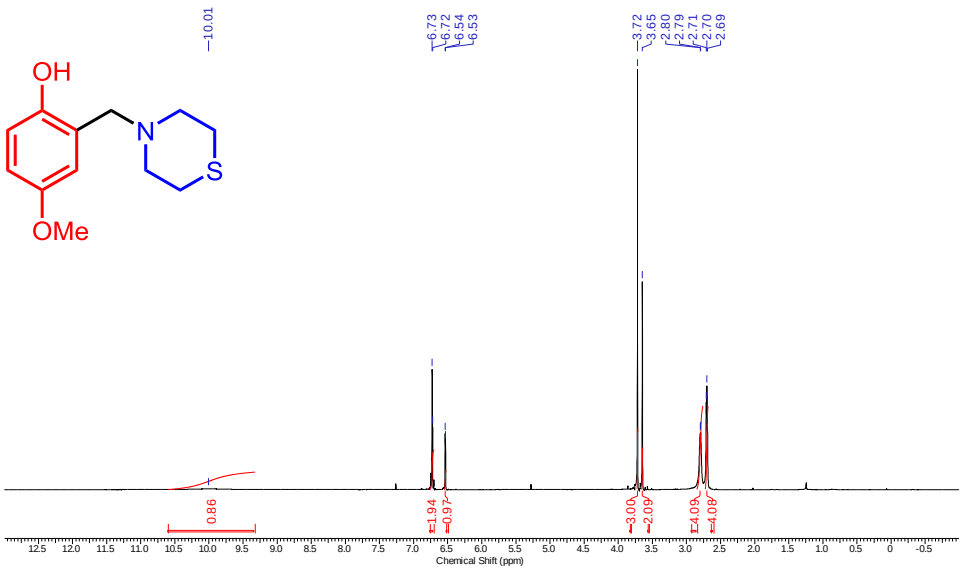
^{1}H NMR (**4o**) ($CDCl_3$)



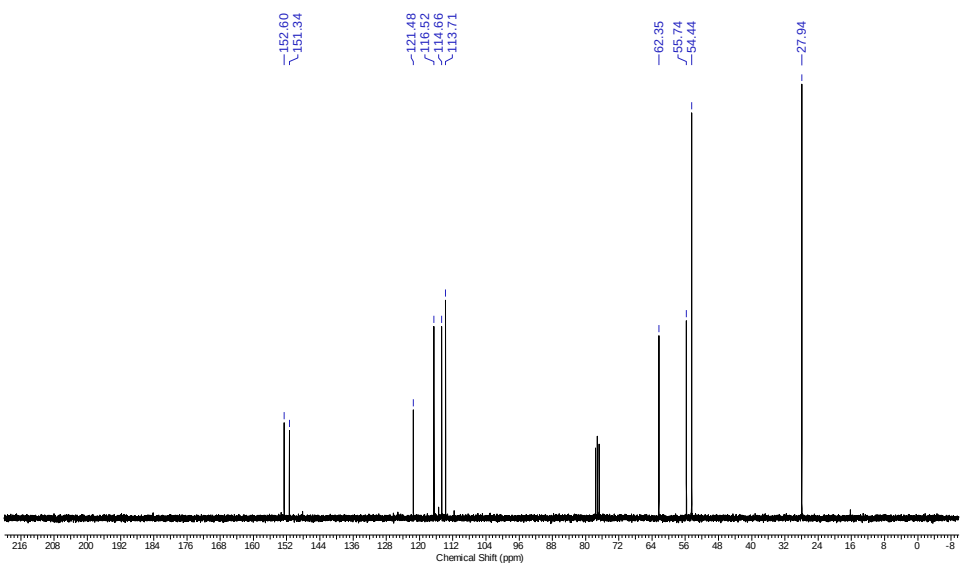
^{13}C NMR (**4o**) ($CDCl_3$)



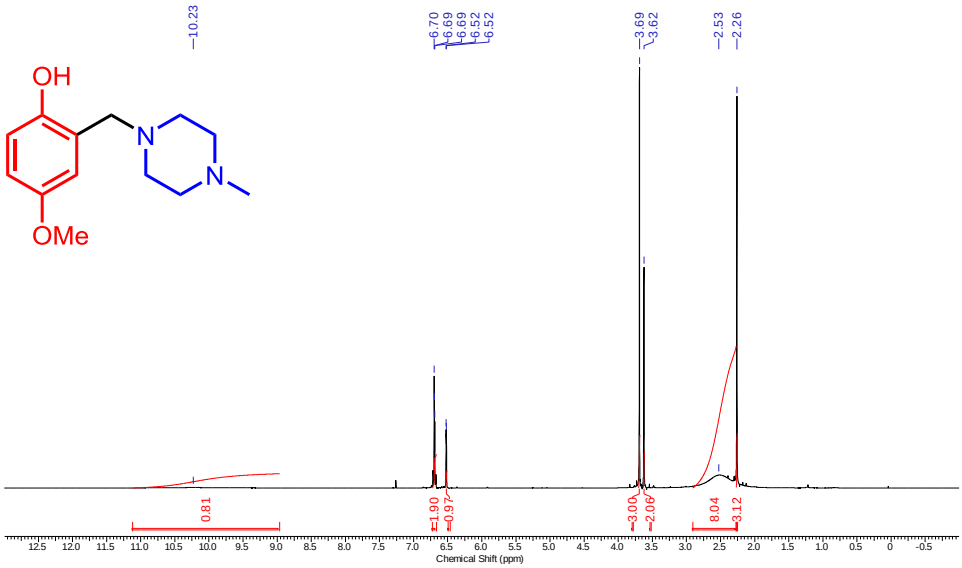
^{1}H NMR (**4p**) ($CDCl_3$)



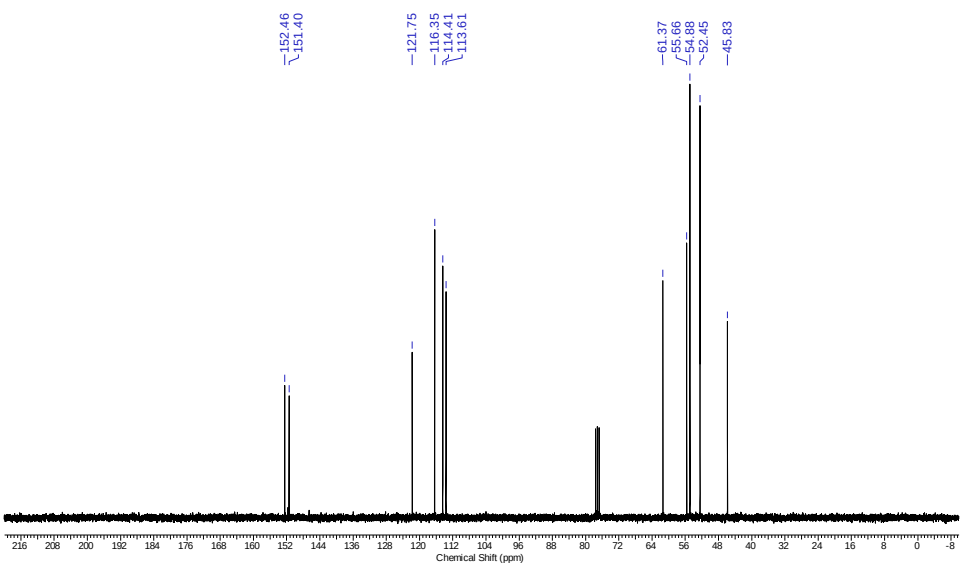
^{13}C NMR (**4p**) ($CDCl_3$)



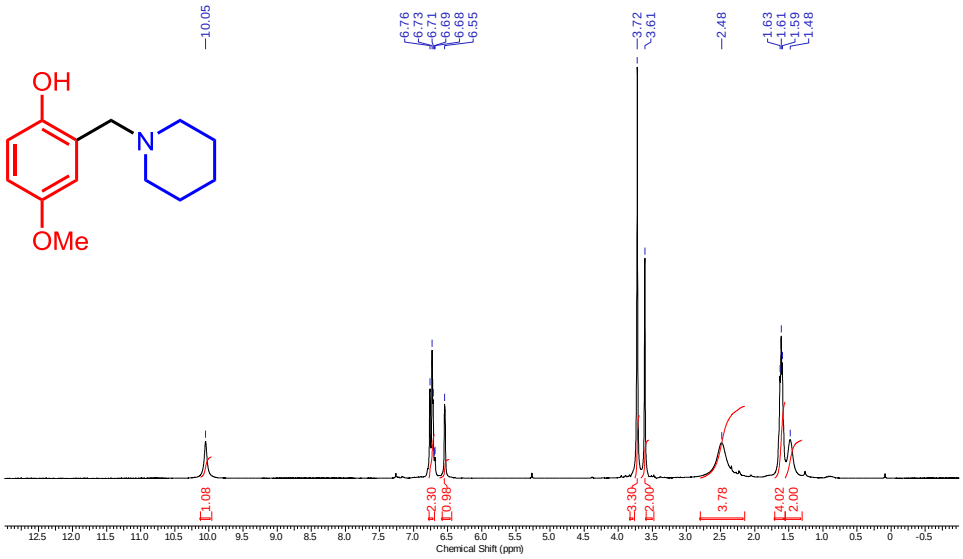
^{1}H NMR (**4q**) ($CDCl_3$)



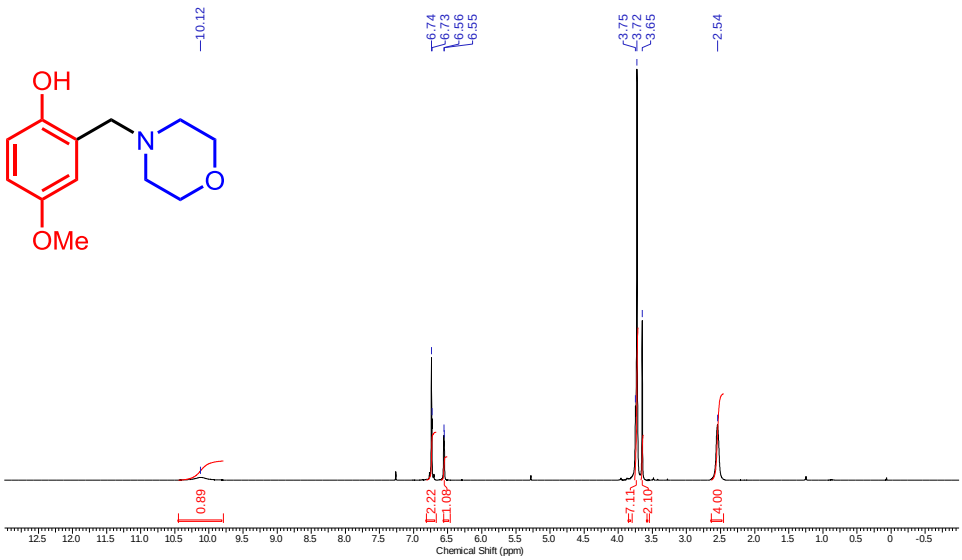
^{13}C NMR (**4q**) ($CDCl_3$)



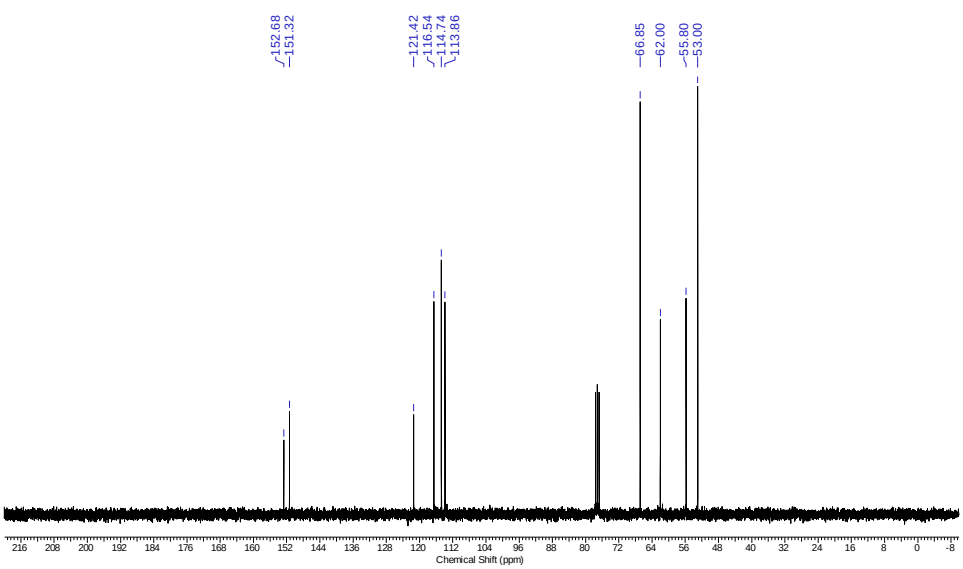
^{1}H NMR (**4r**) ($CDCl_3$)



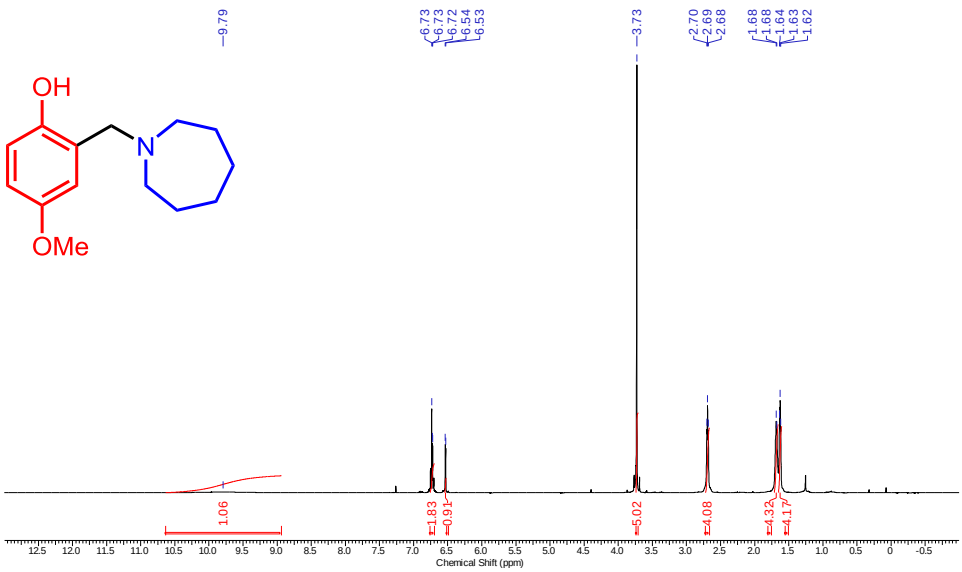
^{1}H NMR (**4s**) ($CDCl_3$)



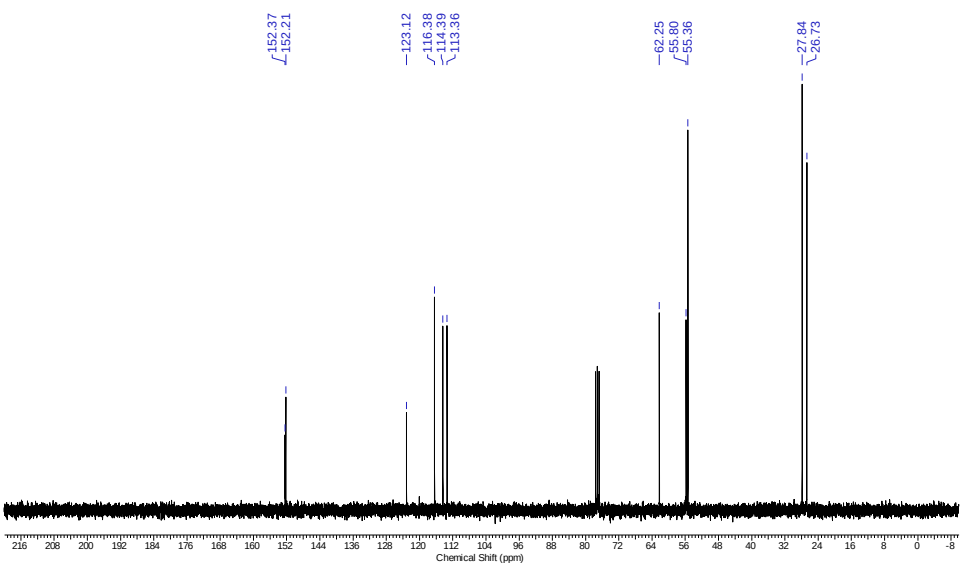
^{13}C NMR (**4s**) ($CDCl_3$)



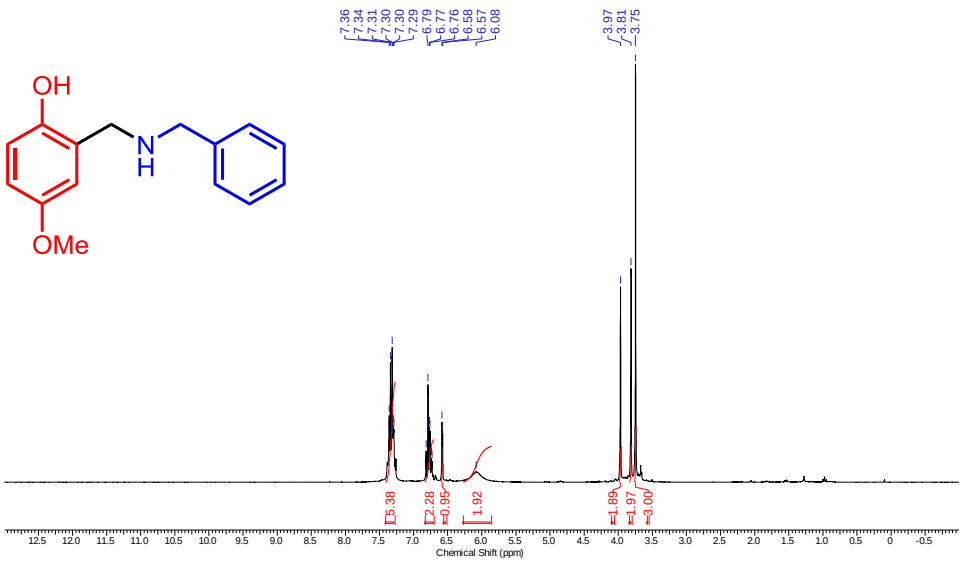
^{1}H NMR (**4t**) ($CDCl_3$)



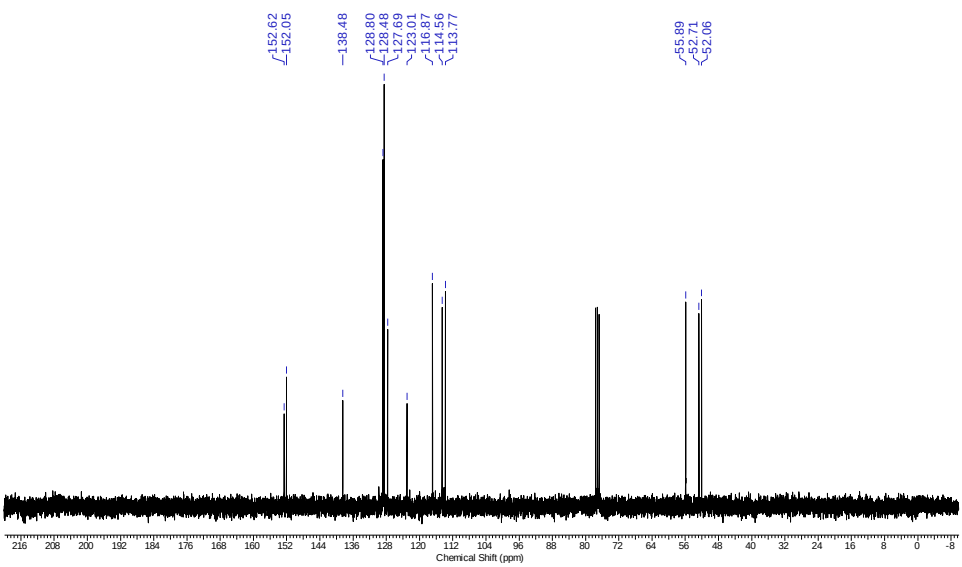
^{13}C NMR (**4t**) ($CDCl_3$)



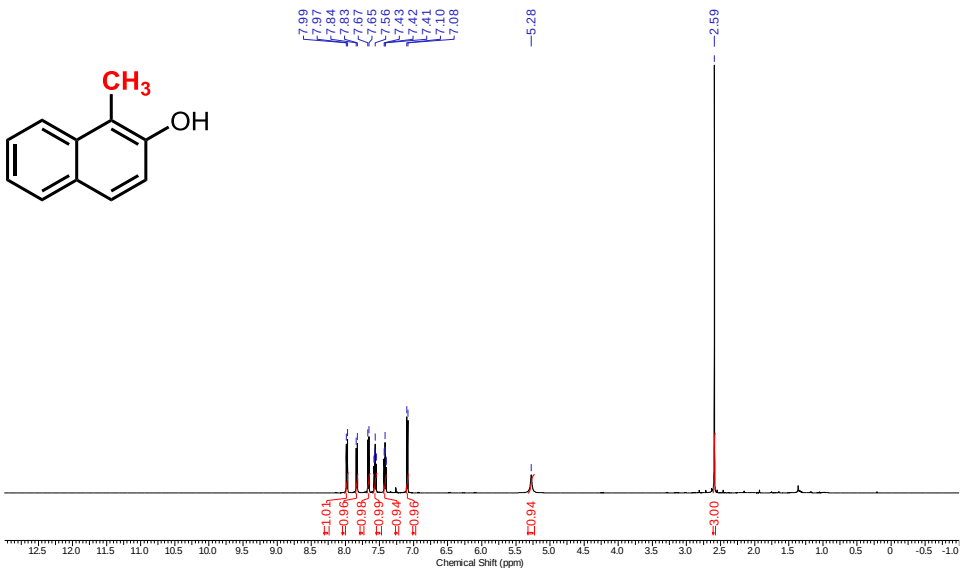
^{1}H NMR (**4u**) ($CDCl_3$)



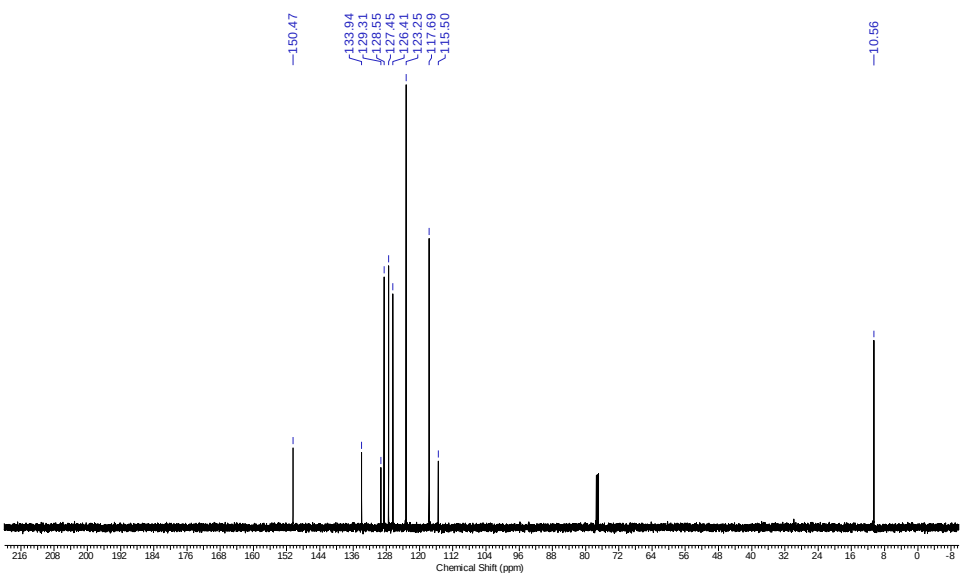
^{13}C NMR (**4u**) ($CDCl_3$)



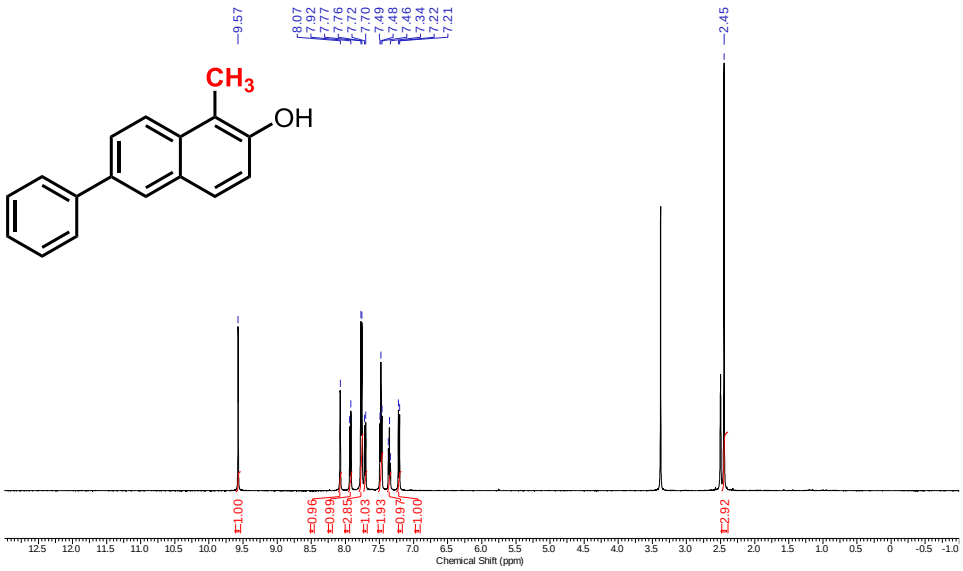
^{1}H NMR (**6a**) ($CDCl_3$)



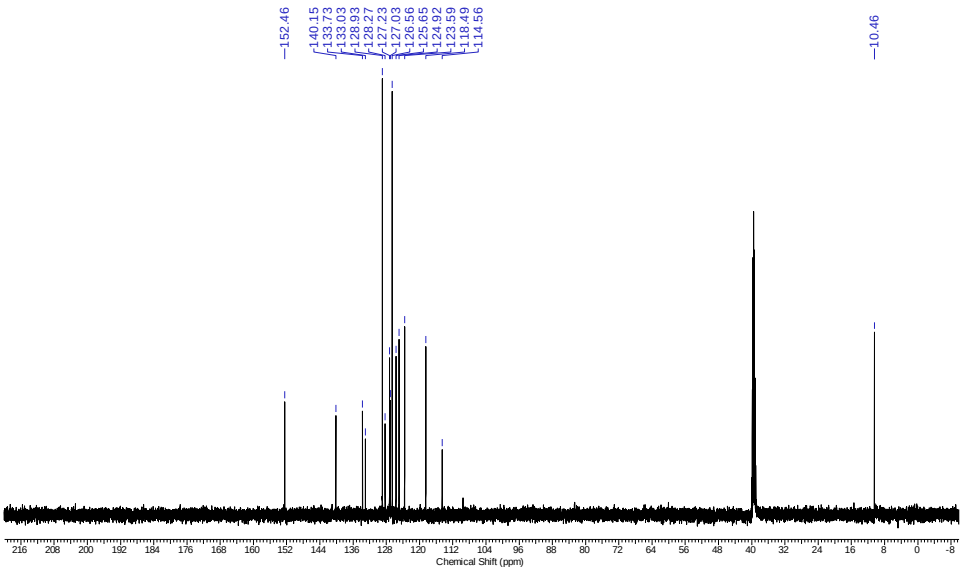
^{13}C NMR (**6a**) ($CDCl_3$)



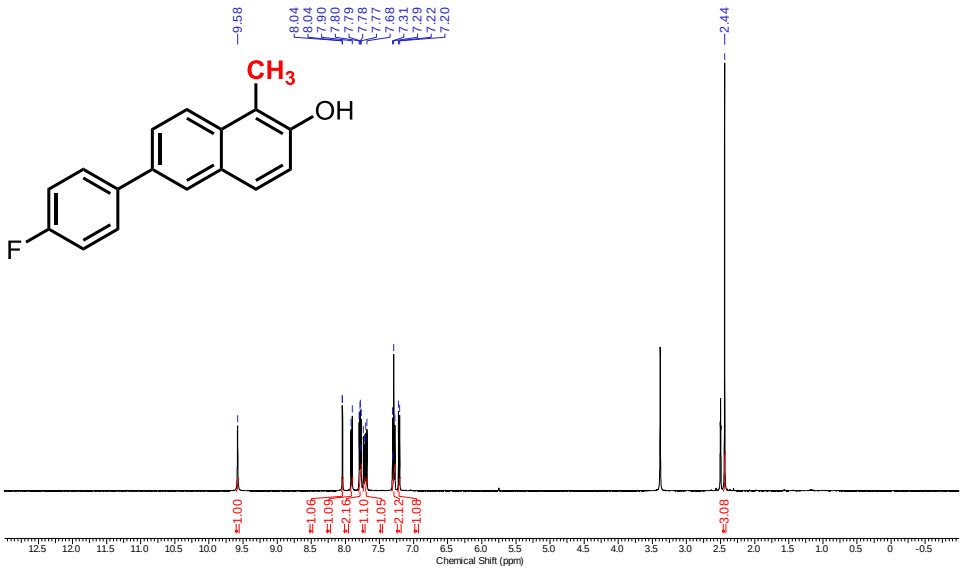
^{1}H NMR (**6b**) (DMSO-d_6)



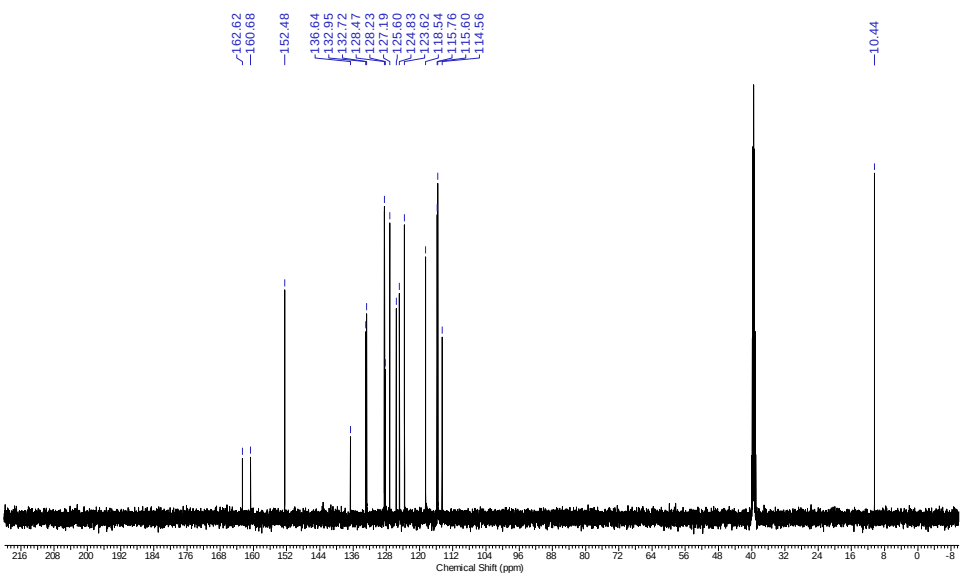
^{13}C NMR (**6b**) (DMSO-d_6)



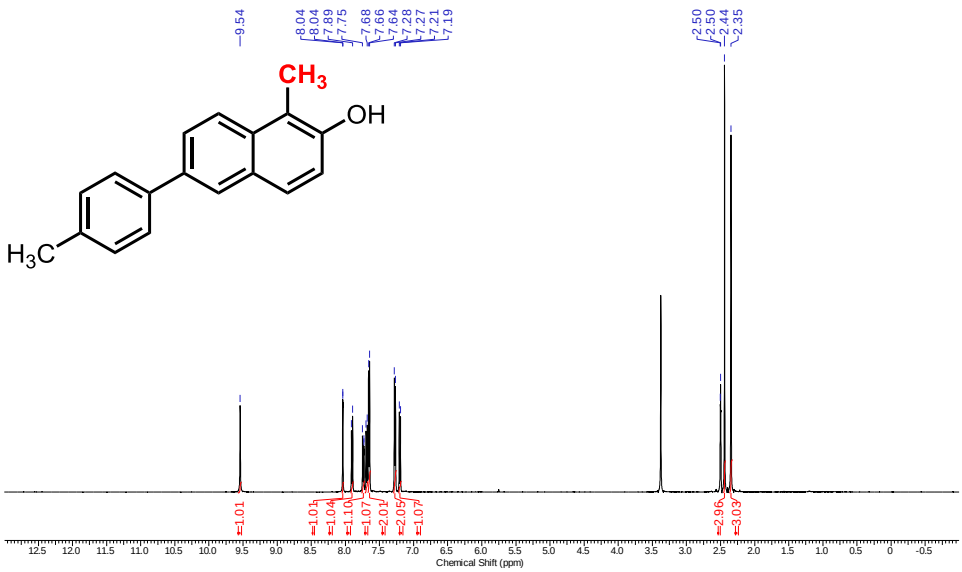
^{1}H NMR (**6c**) (DMSO-d_6)



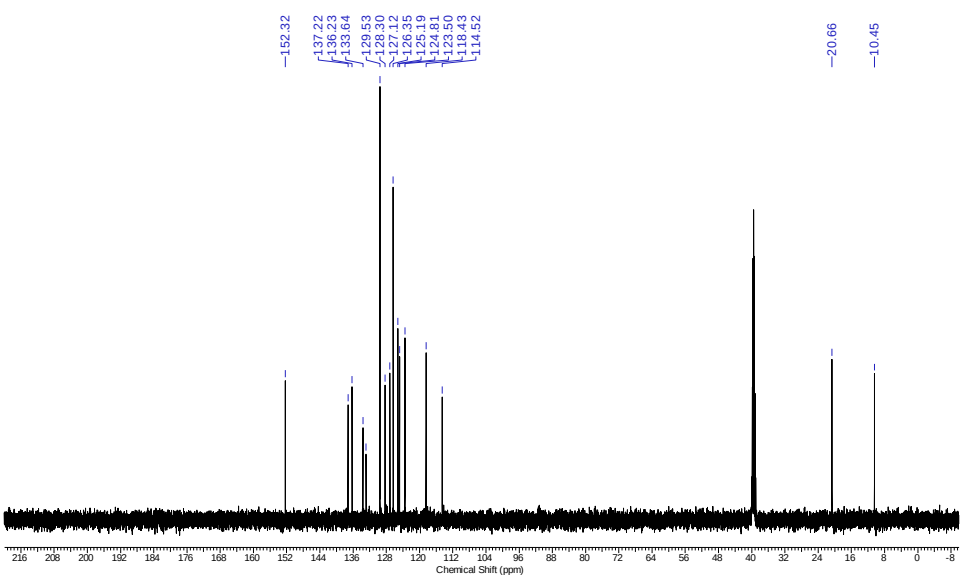
^{13}C NMR (**6c**) (DMSO-d_6)



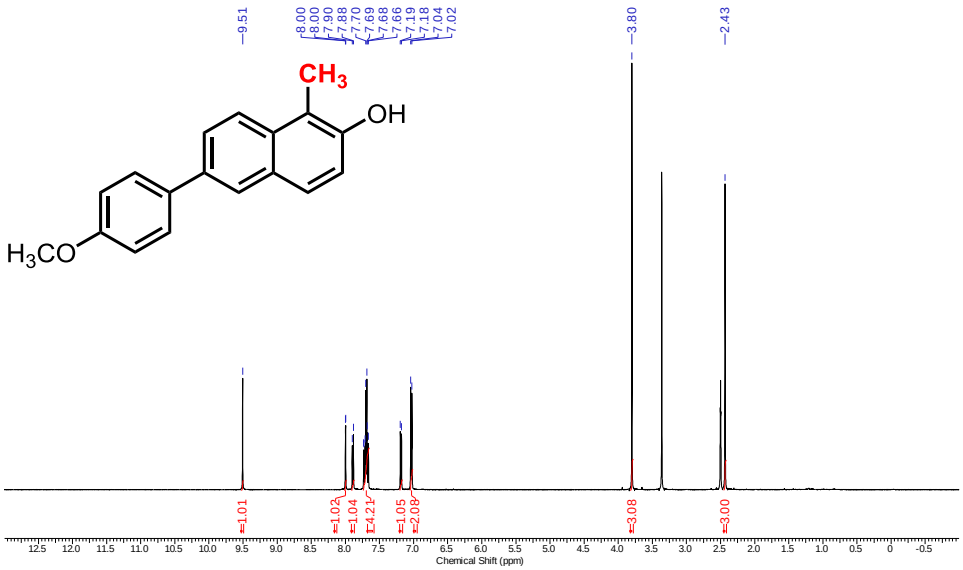
^{1}H NMR (**6d**) (DMSO-d_6)



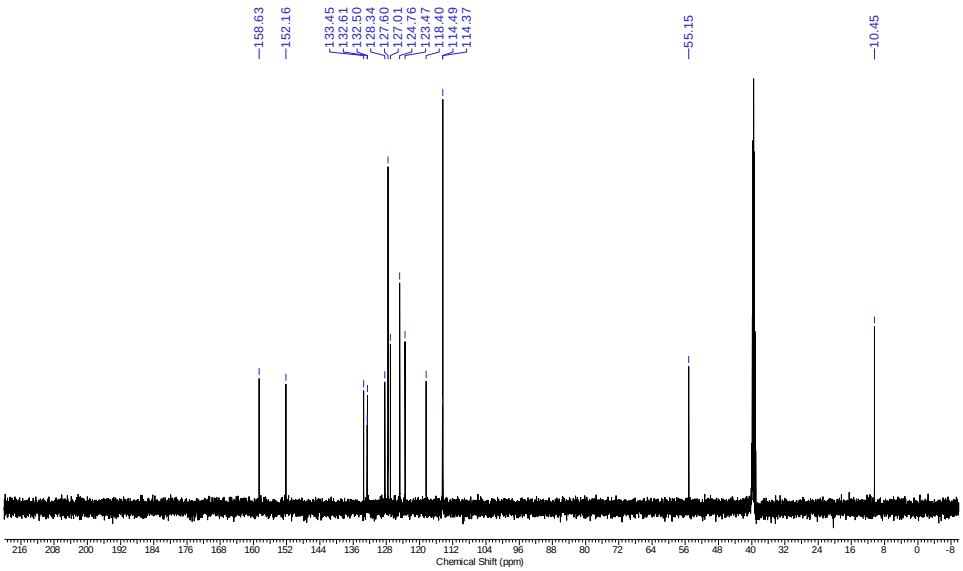
^{13}C NMR (**6d**) (DMSO-d_6)



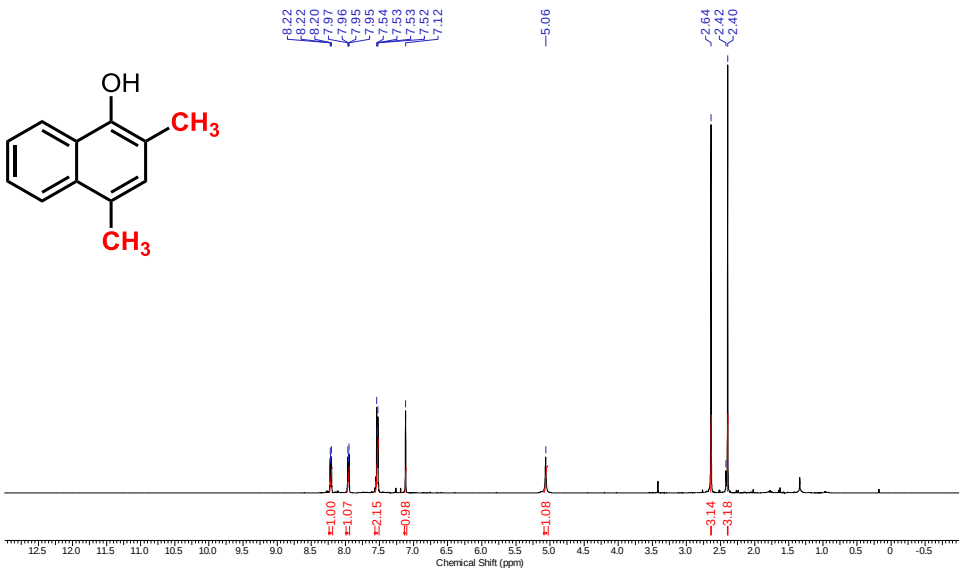
^{1}H NMR (**6e**) (DMSO-d_6)



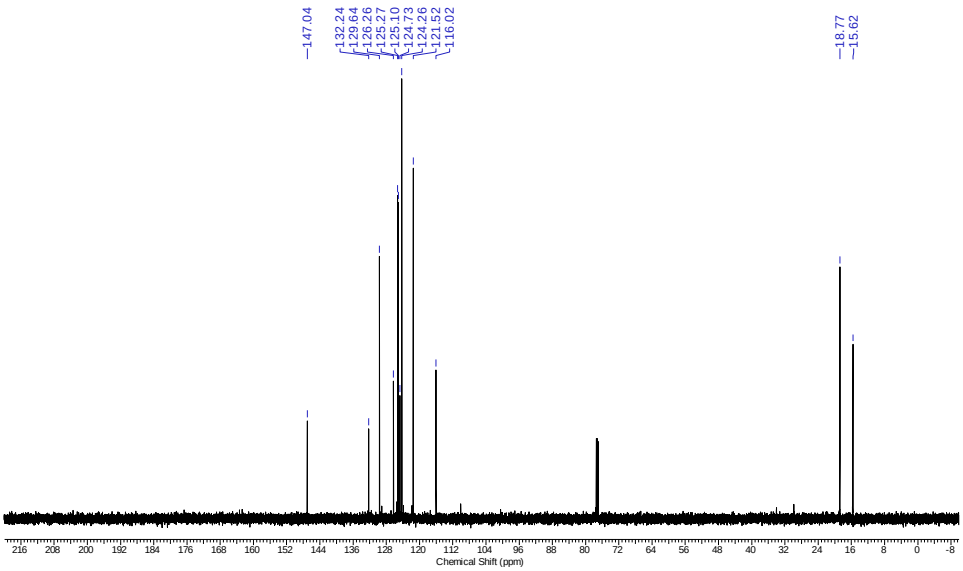
^{13}C NMR (**6e**) (DMSO-d_6)



^{1}H NMR (**6f**) ($CDCl_3$)



^{13}C NMR (**6f**) ($CDCl_3$)



국문초록

아이소사이아나이드 활성화 및 메탄올 탈수소화를 통한 이민의 촉매 반응 개발

이민은 탄소 원자와 질소 원자 사이에 이중 결합을 가지고 있는 구조로써 유기화학의 기초적인 작용기이다. 이민이 내재하고 있는 친전자적 특성을 활용한 반응성이 폭넓게 연구되었으며, 특히 다양한 탄소-탄소 결합 생성 반응이 개발되었다. 전이금속 촉매의 발전은 이민의 활용도를 더욱 높였다. 이 논문에서는 두 가지 서로 다른 전략을 활용한 이민의 촉매 반응에 대해 기술한다.

파트 1은 아이소사이아나이드 화학과 이를 활용한 *N*-아릴/알킬-β-엔아미노나이트릴 합성법에 대해 소개한다. 1장에서는 아이소사이아나이드의 역사 및 특성, 물리적 성질에 대해 설명하며, 아이소사이아나이드의 활성화 전략을 대표적인 예시와 함께 개괄한다. 2장에서는 전이금속 촉매의 아이소사이아나이드의 이동 삽입을 적용하여 *N*-아릴/알킬-β-엔아미노나이트릴의 합성법을 개발한 사례를 소개한다. 아이소사이아나이드를 질소 재료로 사용하여 폭넓은 기질에서 다양한 작용기로부터

방해를 받지 않고 반응이 수행될 수 있었다. 이민과 유사한 구조를 가지는 이미도일 구리 중간체가 반응에 참여한다.

파트 2는 메탄올을 C1 재료로 활용한 합성 사례와 메탄올을 이용한 페놀 유도체의 (아미노)메틸화반응을 서술한다. 일산화탄소는 독성과 가연성을 가졌음에도 불구하고 산업 원자재 합성에서 핵심적인 역할을 한다. 최근 메탄올은 안전성과 잠재적 재생가능성으로 인해 대안적인 C1 재료로 큰 주목을 받고 있다. 3장에서는 전이금속 촉매를 활용한 알코올의 탈수소화 방법과 함께 메탄올이 분자량이 큰 알코올들과 가지는 차이점에 대해 논의한다. 그 후, 탈수소화 방법을 통한 메탄올의 활용 예시들을 소개한다. 4장은 메탄올과 아민을 이용하여 페놀 유도체에 아미노메틸화 및 메틸화를 수행한 연구를 소개한다. 메탄올은 루테늄 핀서 촉매에 의해 탈수소화되며, 그로부터 생성된 포름알데하이드는 아민과의 축합반응을 통해 이민을 생성한다. 기질에 따른 반응성의 차이에 대해 면밀한 연구를 수행하였다.

주요어: 이민, 아이소사이아나이드, 구리, 엔아미노나이트릴, 메탄올, 탈수소화, 루테늄, 아미노메틸화, 메틸화, 페놀

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