Studies on copper-catalyzed aerobic reactions of N-H imines

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**NANYANG
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**STUDIES ON COPPER-CATALYZED
AEROBIC REACTIONS OF *N*-H IMINES**

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SCHOOL OF PHYSICAL AND MATHEMATICAL SCIENCES

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**STUDIES ON COPPER-CATALYZED
AEROBIC REACTIONS OF *N*-H IMINES**

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List of Abbreviations

δ	chemical shift (ppm)
$^{\circ}\text{C}$	degree Celsius
Ac	acetyl
Ar	aryl (substituted aromatic ring)
Bn	benzyl
Br	broad singlet
calcd	calculated
cat.	catalytic
cm^{-1}	wave number
Cp	cyclopentadienyl
d	doublet
dd	doublet of doublets
DME	dimethoxyethane
DMF	<i>N,N</i> -dimethylformamide
Et	ethyl
EtOAc	ethyl acetate
equiv.	equivalent
ESIHRMS	Electrospray Ionization High Resolution Mass Spectrometry

Et ₂ O	diethyl ether
h	hour
HCl	hydrochloric acid
Hz	hertz
IR	infrared spectroscopy
<i>J</i>	coupling constants
M	concentration (mol/L)
M ⁺	parent ion peak (mass spectrum)
m	multiplet
Me	methyl
mg	milligram
MHz	megahertz
mmol	millimole
mp.	melting point
<i>n</i> -BuLi	<i>n</i> -butyllithium
NMP	methylpyrrolidone
NMR	nuclear magnetic resonance
Ph	phenyl
<i>p</i> -Tol	<i>p</i> -tolyl

q	quartet
rt	room temperature
s	singlet
sep	septet
SO ₃	sulfur trioxide
t	triplet
THF	tetrahydrofuran
TLC	thin layer chromatography
Ts	<i>p</i> -toluenesulfonyl

Abstract

On investigating copper-catalyzed aerobic reactions of *N*-H imines, it was discovered that the iminyl copper species formed from reaction of Grignard reactions with carbonitriles, could undergo either C-H oxygenation or C-C bond cleavage depending on the starting material.

The methylene C-H oxidation provides 1,2-diacylbenzenes, which could be further transformed into phthalazines and isoindolines, while a C-C bond cleavage provides carbonitriles using pivalonitrile as a cyanide source.

Both transformations are aided by the oxidation of the iminyl copper species with diradical oxygen to form a peroxycopper intermediate, followed by oxidation or homolytic cleavage to effect oxidation and C-C bond cleavage respectively.

Both reactions could provide a range of desired products in respectable yields.

Chapter 1 Introduction

1.1 Background of the iminyl metal species

Pioneering work on the putative iminyl metal species was performed in 1998, when Pombeiro¹ and Tillact² independently reported the reaction of oximes with lower valent rhenium(I) and titanium(II) complexes to form the corresponding iminyl metal intermediates (Scheme 1-1).

Scheme 1-1. Generation of iminyl metal species from oxidative addition of N-O bonds to lower valent Re(I) and Ti(II) complexes

Since then, there has been a fair amount of studies documenting research on this intermediate and its involvement in various chemical reactions. In this section, we will highlight chemical transformations with a participating iminyl metal species.

As an overview of examples featured in this chapter, Scheme 1-2 illustrates the generation of iminyl metal species from vinyl azides, N-O oximes, *N*-H imines, *N*-alkylated imines, α -azido carbonyl compounds, as well as carbonitriles. Thereafter, the iminyl metal species could undergo reactions of β -carbon eliminations, insertion with unsaturated C-C bonds, nucleophilic attack onto carbonyl compounds and even coupling with boronic acids.

Scheme 1-2. Iminyl metal intermediates: substrates and reactions

1.1.1 The iminyl metal species in C-C bond cleavages

In classical organometallic chemistry, β -hydrogen eliminations are characteristic of late transition metal complexes. On the other hand, analogous reactions that leads to C-C bond cleavages are not as common.

At the turn of the millenium, following a series of investigations into β -carbon eliminations, Uemura and co-workers reported a palladium-catalyzed formation of nitriles from cyclobutanone oximes *via* a cyclobutaniminopalladium(II) complex (Scheme 1-3).³ The authors postulate that the reaction commenced with the oxidative addition of the N-O bond of *O*-benzoyloxime to the palladium(0)-BINAP complex to afford an iminyl palladium(II) intermediate **I**. This highly strained cyclobutane structure then

underwent β -carbon elimination to form an alkylpalladium species **II**. Successive β -hydrogen elimination and isomerization then proceeded to afford the products, isomeric phenylbutenenitriles 3-phenylbut-3-enenitrile and (*E*)-3-phenylbut-2-enenitrile in 4% and 84% GLC yield respectively; the latter is the major product because it is the more stable alkene.

Scheme 1-3. Synthesis of carbonitriles from iminyl Pd(II) intermediate *via* β -carbon elimination

While the report intended to demonstrate the mechanistic novelty of β -carbon eliminations, made possible with thoughtful design of the substrates, it also highlighted the existence of the iminyl metal species in this class of reactions.

Similarly, Hartwig and Zhao were successful in observing C-C bond cleavages in β -carbon eliminations from the iminyl ligand of an isolated rhodium(I) iminyl complex, as confirmed by x-ray crystallographic analysis, forming a more stable rhodium(I) aryl complex and an aromatic nitrile (Scheme 1-4).⁴

Scheme 1-4. Formation of carbonitriles from iminyl Rh(I) intermediate *via* β -carbon elimination

Recently, our group also reported carbonitrile synthesis with C-C bond cleavages in α -azido carbonyl compounds *via* iminyl copper species (Scheme 1-

5).⁵ The reaction was accelerated under an oxygen atmosphere and tolerated a wide range of substrates to afford products in moderate to good yields.

Scheme 1-5. Formation of carbonitriles from α -azido carbonyl compounds via β -carbon elimination

In the catalytic cycle, the iminyl copper intermediate could be oxidized under an oxygen atmosphere to give a peroxy copper species which then adds to the intramolecular carbonyl moiety to induce C-C bond cleavage and provide carbonitriles (Scheme 1-6, path a).

Scheme 1-6. Proposed pathways for the formation of carbonitriles via iminyl copper intermediate

However, the possibility that the iminyl copper intermediate underwent a β -carbon elimination (Scheme 1-6, path b) to form carbonitriles could not be ruled out since product 2-naphthonitrile **1** could also be formed in the absence of oxygen, albeit in lower yields and longer reaction times.

1.1.2 The iminyl metal species in reactions with unsaturated C-C bonds

In 2002, Kitamura and Narasaka reported the reaction of iminyl palladium(II) species with an intramolecular alkene moiety for the synthesis of aza-heterocycles.⁶ This elegant amino-Heck process commenced with the oxidative addition of readily available acyloximes to palladium(0) complexes to generate alkylidene-aminopalladium(II) species which are key intermediates in the subsequent cyclization and C-N bond formation. The methodology could be expanded to provide pyrroles, pyridines, isoquinolines, spiro imines, azaazulenes and nitriles upon suitable modification of the substrates (Scheme 1-7).

Scheme 1-7. Synthesis of azaheterocycles via iminyl palladium(II) intermediate

Similarly, Zhu and co-workers applied this concept and developed an intermolecular version of this amino-Heck process, trapping the iminyl palladium species with benzyne or alkynes to form phenanthridines and isoquinolines, respectively.⁷ The choice of solvent is important in this domino aminopalladation/C-H functionalization sequence (Scheme 1-8). A slow generation of benzyne in butyronitrile due to low solubility and higher reaction temperatures will provide the desired products in higher yields.

Scheme 1-8. Annulation of acyloximes with arynes *via* iminyl Pd(II) intermediate

Our group has been interested in the use of the iminyl metal species for chemical transformations. In 2011, we developed a methodology for the synthesis of isoquinolines from α -aryl vinyl azides and internal alkynes using a $\text{Cu}(\text{OAc})_2$ - $[\text{Cp}^*\text{RhCl}_2]_2$ bimetallic relay system.⁸

Scheme 1-9. Isoquinolines synthesis from vinyl azides and alkynes by Rh-Cu bimetallic cooperation

The mechanism for this novel synthetic route commenced with the reduction of $\text{Cu}(\text{OAc})_2$ by DMF to form a $\text{Cu}(\text{I})$ species (Scheme 1-10). Then, as shown in Scheme 1-11, thermal denitrogenative decomposition of vinyl azide gave *2H*-azirine which could be reduced by the $\text{Cu}(\text{I})$ species to afford a radical anion **I** (path a). Subsequently, C-N bond cleavage of **I** forms the iminyl copper(II) radical intermediate **II** which could be further reduced with $\text{Cu}(\text{I})$ and protonated to deliver *N*-H imine. Alternatively, direct reduction of the vinyl azide by a $\text{Cu}(\text{I})$ forms the radical intermediate **II** through a vinyl azide anion radical **V** (path b).

Scheme 1-10. Generation of $\text{Cu}(\text{I})$ species by reduction of $\text{Cu}(\text{OAc})_2$ with DMF

Scheme 1-11. Reductive formation of *N*-H imines from vinyl azides and $\text{Cu}(\text{I})$ species

Finally, in Scheme 1-12, iminyl rhodium species **VI** formed from either *N*-H imine or iminyl copper species **IV** led to rhodacycle **VII** which undergoes alkyne insertion and reductive C-N elimination to provide isoquinoline.

Scheme 1-12. *Ortho* C-H rhodation, alkyne insertion and C-N reductive elimination

Besides offering an alternative way to generate iminyl metal species from vinyl azides, the reaction offered insights into the use of compatible metal catalysts for domino chemical transformations.

It is noteworthy that other than vinyl azides, aryl ketoxime derivatives could also react with internal alkynes for the synthesis of azaheterocycles using the $\text{Cu}(\text{OAc})_2$ - $[\text{Cp}^*\text{RhCl}_2]_2$ bimetallic relay system (Scheme 1-13).⁹ The reaction proceeded with both the *anti*- and *syn*-isomers of ketoximes to afford isoquinolines in good yields.

Scheme 1-13. Isoquinoline synthesis from aryl ketone *O*-acetyl oximes by Cu-Rh bimetallic relay catalysts

As illustrated in Scheme 1-14, the reaction begins with the reduction of the oxime N-O bond using lower valent Cu(I) to generate an iminyl copper species **A**,

which should be free to isomerize between *anti*- and *syn*-isomer. Since the metal reductant works independently of Rh(III), the resulting iminyl copper metal species undergoes transmetalation with Rh(III) to afford iminyl rhodium(III) intermediates. *Ortho* C-H rhodation and subsequent annulation with internal alkynes then afford the cyclized isoquinoline.

Scheme 1-14. Hypothesis for isoquinoline synthesis from aryl ketone O-acetyl oximes

Previously, when using the catalytic redox-neutral $[\text{Cp}^*\text{RhCl}_2]_2\text{-NaOAc}$ system,¹⁰ there is a stereochemical restriction on the oximes; the N-O bond of the oximes should be *anti* to the aryl moiety. The Cu-Rh bimetallic system removes this requirement and both the *anti*- and *syn*-isomers of the ketoximes could be utilized as substrates for this transformation.

1.1.3 The iminyl metal species in reactions with C=O bonds

Another type of chemical transformation involves the iminyl metal species undergoing nucleophilic attack onto the carbonyl moiety.

In 2008, our group reported a synthetic method to prepare pyrroles by a Mn(III)-catalyzed reaction of vinyl azides and 1,3-dicarbonyl compounds *via* a radical pathway as shown in Scheme 1-15.¹¹ The proposed mechanism commenced with the addition of Mn(III) enolate **I** to vinyl azide to give iminyl radical **II** with the release of dinitrogen and a Mn(II) species. This iminyl radical **II** then reacts with the Mn(II) species to generate iminyl Mn(III) species **III** which undergoes nucleophilic addition onto a carbonyl group to yield a cyclized intermediate **IV**. Protonation of **IV** with acetic acid followed by dehydration affords product pyrrole and regenerates the catalyst.

Scheme 1-15. Mn(III)-catalyzed synthesis of pyrroles *via* iminyl Mn(III) species

Further study revealed that cyclopropanols could be used as precursors to β -carbonyl radicals to react with vinyl azides, a three-atom unit including one nitrogen, leading to the formation of various azaheterocycles (Scheme 1-16).¹² This [3+3]-annulation process commenced with the generation of a β -keto radical **I** by a one-electron oxidation of 1-phenyl-cyclopropanol, which adds to vinyl azide to afford iminyl radical **II** and releases dinitrogen. Reaction of **II** with Mn(II) affords iminyl Mn(III) species **III** which then undergoes nucleophilic attack to the carbonyl moiety to give intermediate **IV** which is protonated to give tetrahydropyridine **V** and regenerates Mn(III) catalyst. Dehydration of **V** followed by oxidation then affords the desired pyridine product.

Scheme 1-16. [3+3]-Annulation of vinyl azides and cyclopropanols for the synthesis of pyridines

In a separate study, our group reported a Pd(II)-catalyzed ring expansion of cyclic 2-azidoalcohols to provide pyridines.¹³ Under basic conditions, the azidoalcohol reacts with Pd(II) complex to generate a palladium(II) alcoholate **I** with the release of dinitrogen (Scheme 1-17). β -carbon elimination of **I** generates a α -azidocarbometal species **II** which then undergoes a metal migration from C to N with the release of dinitrogen to form iminyl Pd(II) species **III**. Intramolecular nucleophilic attack of **III** to the formyl group forms a cyclized intermediate **IV**. Protonation followed by dehydration then yields product pyridine along with catalyst regeneration.

Scheme 1-17. Synthesis of pyridines via Pd(II)-catalyzed ring-expansion of cyclic 2-azidoalcohols

1.1.4 The iminyl metal species in cross-coupling reactions with C-C bond formation

Interestingly, the iminyl metal species has also been reported to participate in cross-coupling reactions for the formation of new C-C bonds.

In 2004, Barluenga and co-workers modified the Buchwald-Hartwig reaction for the preparation of *N*-substituted aldimines *via* a iminyl palladium complex.¹⁴ This synthesis is the first of its kind since previous attempts using unstable *N*-H aldimines were not successful. As shown in Scheme 1-18, *N*-trialkylsilylimines were coupled with aryl bromides and the amination reaction was completed in three steps: 1) oxidative addition of the aryl halide to a palladium(0) complex to form an aryl-palladium complex **I**; 2) transformation of **I** into an imido complex **II** with the use of a nucleophilic additive to promote N-Si bond cleavage; 3) reductive elimination to form the product and regenerate the palladium catalyst.

Scheme 1-18. Coupling of imines with aryl bromides using *N*-trimethylsilylimines

In another example, boronic acids were used as coupling partners with *O*-acyl ketoximes for the formation of *N*-substituted imines.¹⁵ Reported by Liebeskind and co-workers in 2007, this copper-catalyzed coupling reaction commenced with the oxidative addition of Cu(I) to the N-O bond of the *O*-pentafluorobenzoyl oxime to form an iminyl Cu(III) intermediate **I**. Transmetalation of the boronic acid to **I** provides the putative iminyl Cu(III) intermediate **II**. Finally, reductive elimination affords the *N*-iminated product and regenerates the catalyst (Scheme 1-19).

Scheme 1-19. Copper-catalyzed *N*-imation of boronic acids with *O*-acyl ketoximes

The authors went on to adapt the non-basic and non-oxidizing reaction conditions for the synthesis of substituted pyridines.¹⁶ This reaction cascade comprises (a) C-N cross-coupling of alkenyl boronic acids at the N-O bond of an oxime *O*-carboxylate to generate 3-azatrienes, (b) 6π -electrocyclization, and (c) aerobic oxidation (Scheme 1-20). Using catalytic amounts of $\text{Cu}(\text{OAc})_2$, various α,β -unsaturated ketoxime *O*-pentafluorobenzoates were reacted with *trans*-1-hexen-1-ylboronic acid to afford a variety of substituted pyridines. The mild,

neutral pH reaction conditions tolerated many functional groups, particularly iodides, providing substrates which could be used for further functional group transformation.

Scheme 1-20. Copper-catalyzed coupling of boronic acids with O-acyl ketoximes for pyridine synthesis

1.2 Summary

The iminyl metal species as an intermediate in four types of reactions has been discussed in this chapter.

In reactions involving C-C bond cleavages, driving forces such as the release of ring strain and the formation of thermodynamically stable products enable lesser-known processes such as β -carbon eliminations to proceed and hence form nitriles from the iminyl metal intermediates. When looking at reactions with unsaturated bonds, beginning with its role in the amino-Heck process described by Narasaka and Kitamura, the iminyl metal species went on to be utilized in oxidative coupling reactions with alkynes or arynes so as to form various nitrogen

heterocycles. The iminyl metal species could also undergo nucleophilic addition to the carbonyl moiety to effect cyclization reactions. Finally, iminyl metal species could undergo coupling reactions to form *N*-iminated products.

Work documented in this thesis describes the participation of the iminyl copper species in oxidation of methylene C-H bonds as well as C-C bond cleavage reactions. In Chapter 2, the iminyl copper species causes methylene C-H oxygenation *via* *N*-H imines as an intramolecular directing group to form 1,2-diacylbenzenes which could be further functionalized into phthalazines and isoquinolines (Scheme 1-21). The *N*-H imines were generated from nucleophilic attack of Grignard reagents with 2-benzyl benzonitriles.

Scheme 1-21. Copper-catalyzed CH₂-oxygenation of benzyl benzonitriles to 1,2-diacylbenzenes

In Chapter 3, by substituting the carbonitrile substrates with pivalonitriles, it was found that pivalonitriles could become a source of electrophilic cyanides reagents to transfer the cyanide group onto aryl and alkyl Grignard reagents (Scheme 1-22). These two synthetic methodologies contributes towards the C-H functionalization and C-C bond cleavage reactions known to the iminyl metal species.

Scheme 1-22. Copper-catalyzed C-C bond cleavage of *N*-H imines to carbonitriles

Chapter 2 Copper-Catalyzed Benzylic C-H Oxygenation under an Oxygen Atmosphere *via* N-H Imines as an Intramolecular Directing Group

2.1 Introduction

2.1.1 Overview

Aliphatic C-H bonds are prevalent in organic molecules, perhaps only second in occurrence to aliphatic C-C bonds. The ubiquitous nature of aliphatic C-H bonds is in part due to their stability and lack of reactivity to most chemical reagents even under strongly acidic and basic conditions. The only exception being when activation by adjacent functional groups such as carbonyl groups or with the use of organometallic complexes in C-H functionalization.

Scheme 2-1. Reactions typical of the aliphatic C-H bond

As shown in Scheme 2-1, saturated hydrocarbons containing aliphatic C-H bonds do react in combustion reactions to generation huge amounts of energy. However, such reactions are typically uncontrolled and give unattractive products-- carbon dioxide and water. On the other hand, cracking and dehydrogenation can

convert alkanes to alkenes, which are more useful, but such reactions are energy intensive and require high temperatures. Finally, exposure to highly reactive radicals in photochemical reactions can convert alkanes containing aliphatic C-H bonds to afford alkylhalides. Then again, there is little control over product selectivity.¹⁷

Over the years, various approaches have been developed for the oxidative functionalization of unactivated C-H bonds using transition metal catalysts.¹⁸ Some of these are examples of C-H oxygenation, with varying synthetic strategies depending on the choice of catalysts for C-H bond cleavage and oxygen source for subsequent oxygen atom incorporation.

While the use of oxygen-atom donors such as ozone, oxone, hydrogen peroxide and alkyl hydroperoxides have been reported,¹⁹ the focus of this introduction will be on the use of peroxides and molecular oxygen as oxidants for aliphatic C-H oxidation.

2.1.2 Transition metal-catalyzed C-H oxidation using peroxides

In 2009, Yi and co-workers reported the use of a cationic Ru(III) complex for the C-H oxidation of arylalkanes (Scheme 2-2).²⁰ Unlike most C-H functionalization reactions, this transformation did not require any directing group and proceeded smoothly *via* a solvent-caed mechanism in water, with *t*-butyl hydroperoxide as oxygen source, to afford the ketones and alcohols in good yields. However, the substrate scope was highly limited to benzylic compounds and one cyclic ether.

Scheme 2-2. Selected examples of Ru-catalyzed aqueous phase oxidative C-H functionalization

In 2010, remarkable progress in C-H oxidation was made with the findings of White and Chen with their report on the site-selective oxidation of isolated and unactivated methylene C-H bonds to afford ketones (Scheme 2-3).²¹ Here, ketone formation is highly favored at electron-rich methylene sites, farthest from any electron-withdrawing groups. Furthermore, hyperconjugation activates adjacent C-H bonds towards oxidation, thus enabling the formation of lactones from cyclic ethers. It was also demonstrated that oxidation at sites complementary to those obtained using enzymes were possible, thus broadening the application of this methodology for biological studies.

Scheme 2-3. Selected examples of selective Fe-catalyzed methylene oxidation

2.1.3 Transition metal-catalyzed C-H oxidation using molecular oxygen

The development of metal-catalyzed methods for selective oxidative functionalization of aliphatic C-H bonds is a huge challenge in synthetic organic chemistry.²² Among them, studies on aerobic C-H oxidation using atmospheric oxygenation as an oxygen atom source remains limited. This section illustrates some recent examples of aerobic C-H oxidation..

In 2009, Yu and Zhang reported a highly selective Pd(II)-catalyzed hydroxylation of arenes under an oxygen atmosphere to provide *ortho*-hydroxyl benzoic acids (Scheme 2-4).²³ While the exact reaction mechanism was not unknown, mechanistic studies using $^{18}\text{O}_2$ and H_2^{18}O supports a direct oxygenation of the aryl palladium intermediates rather than an acetoxylation/hydrolysis sequence.

Scheme 2-4. Pd(II)-catalyzed hydroxylation of arenes under an oxygen atmosphere

In 2010, Ritter and co-workers developed the α -hydroxylation of carbonyl compounds under an oxygen atmosphere, catalyzed by a dinuclear Pd(II) complex (Scheme 2-5).²⁴ The reaction proceeded in a chemo- and regioselective manner to afford a wide range of products in good yields. The experimental design targeted high-valent Pd oxygen species, accessible by bimetallic synergistic redox participation for oxidation chemistry. While preliminary studies have provided support for this theory, more work has to be done before the mechanism could be confirmed.

Scheme 2-5. α -hydroxylation of carbonyl compounds catalyzed by Pd(II)-dinuclear complex

Recently, our group has been exploring the intriguing chemical reactivity of the iminyl copper species for aerobic oxidation. In one study, we reported a copper-catalyzed synthesis of azaspirocyclohexadienones from α -azido-*N*-arylamines under an oxygen atmosphere (Scheme 2-6).²⁵ The reaction commenced with the base-mediated dinitrogenative formation of the iminyl copper species **I**, which then undergoes oxidation by molecular oxygen to form peroxycopper(III) **II**. An intramolecular imino-cupration gives intermediate **III**, followed by isomerization to **IV** which then eliminates the copper species to afford the desired product.

Scheme 2-6. Cu(II)-catalyzed synthesis of azaspirocyclohexadienones

In another study, our group developed a method for oxidation tertiary C-H bonds using amidines as directing group to afford dihydrooxazoles, incorporating an oxygen atom from molecular oxygen.²⁶ The reaction commenced the generation of Cu(II) catalyst from CuBr•SMe₂ and oxygen. The catalyst then oxidises the amidine starting material to form a 1,3-diazaallyl radical **I** which then undergoes a 1,5-H radical shift to form radical species **II**. Further reaction with molecular oxygen provides superoxo radical **III** followed by a Fenton-type fragmentation to afford Cu(II)-alkoxide **IV**. A final intramolecular nucleophilic attack of **IV** onto the amidine moiety then delivers the dihydrooxazole, accompanied by the elimination of ammonia.

Scheme 2-7. Cu-catalyzed aerobic aliphatic C-H oxygenation directed by an amidine moiety

2.1.4 Immediate concerns

Despite the above-mentioned examples of C-H oxidation, the continued development of catalytic reactions to realize selective oxidative C-H functionalization remains a challenge in organic synthesis. This prompted us to develop a copper-catalyzed methylene C-H oxidation under an oxygen atmosphere *via* a copper iminyl species to provide 1,2-diacylbenzenes **3** (Scheme 2-8). The transformation is a two-step sequence starting with the addition of a Grignard reagent to 2-benzylbenzonitriles to form *N*-H imines, followed by oxygenation to form C=O bonds.

Scheme 2-8. Formation of 1,2-diacylbenzenes **3** from 2-benzylbenzonitriles **1** *via* iminyl copper species

Given the importance of 1,2-diketones and the lack of established methods for its formation, development of new and versatile pathways leading to such products remains relevant and will help advance research into their uses in other areas of chemistry.

2.2 Synthesis of starting materials

Four methods were applied for the preparation of starting material carbonitriles used in this chapter.

Method A: The two-step sequence of benzylic bromination followed by the Friedel-Crafts reaction was used to prepare a series of 2-benzylbenzonitriles **1**. The 2-methylbenzonitriles **9** were formed from the reaction between 1-bromo-2-methylarenes and copper(I) cyanide in NMP. NBS-mediated bromination of 2-methylbenzonitriles **9** afforded the substituted bromobenzonitriles which were then reacted with AlCl_3 in benzene under reflux conditions. This method was used to prepare 2-benzylbenzonitriles **1a** as well as substituted 2-benzylbenzonitriles **1j**, **1k**, **1m**, **1n** and **1q**.

Scheme 2-9. Preparation of benzylbenzonitriles (Method A)

Method B: The Pd(0)-catalyzed Suzuki-Miyaura cross coupling reaction of 2-(bromomethyl)benzonitrile and aryl boronic acids was utilized to prepare substituted 2-benzylbenzonitriles **1b-1i**, **1l**, **1o** and **1p**.

Scheme 2-10. Preparation of benzylbenzonitriles (Method B)

Method C: A procedure involving the coupling of 2-chlorobenzonitrile and alkyl Grignard reagents catalyzed by MnCl_2 was employed to synthesize 2-butylbenzonitrile **1r**. This method was also applied for the preparation of alkylbenzonitriles **1s** and **1t**.

Scheme 2-11. Preparation of alkylbenzonitriles (Method C)

Method D: To prepare 2,2-dimethyl-4-phenylbutanenitrile, isobutyronitrile deprotonated with LDA was reacted with (2-bromoethyl)benzene in an $\text{S}_{\text{N}}2$ manner.

Scheme 2-12. Synthesis of carbobenzonitrile **1u**

2.3 Synthesis of 1,2-diacylbenzenes

2.3.1 Optimization of reaction conditions

In the benzylic C-H oxygenation of 2-benzylbenzonitrile **1a**, when the reaction conditions for phenanthridine synthesis was applied, 1,2-dibenzoylbenzene **3aa** was formed in 38% yield, accompanied by the formation of 1*H*-isoindol-1-ol **4aa** in 43% yield (Table 2-1, entry 1).

Table 2-1. Optimization of reaction conditions

entry	reaction condition ^a	time (h)	yield (%) ^b	
			3aa	4aa
1	Standard reaction condition	20	38	43
2	Standard reaction condition	7	34	58
3	Add 4 Å molecular sieves	15	26	52
4	MeOH (0.5 equiv.)	11	28	55
5	MeOH (0.0 equiv.)	19	23	48
6	60 °C under O ₂	12	32	47
7	100 °C under O ₂	19	28	60
8	Cu(OAc) (20 mol%)	20	30	48
9	Addition of additive, 2,2'-bipyridine (20 mol%)	21	27	57
10	Addition of K ₂ CO ₃ (1.0 equiv.)	21	38	51
11	Quench with 3 M HCl and stirred in O ₂ at 80 °C	8.5	82	0
12	CuTC (10 mol%)	19	31	59

^aStandard reaction condition: the reaction was carried out using 0.5 mmol of 2-benzylbenzonitrile **1** with 1.3 equiv. of Grignard reagents **2** in Et₂O (1 M) at 60 °C (sealed tube) for 2 h followed by addition of MeOH (3.0 equiv.), DMF (0.1 M) and Cu(OAc)₂ (10 mol %). The mixture was stirred at 80 °C under an O₂ atmosphere. The reaction was quenched with pH 9 ammonium buffer. ^bIsolated yields.

To achieve optimized reaction conditions for the 1,2-diacylbenzene formation, various reactions conditions were screened with 2-benzylbenzonitrile (**1a**). The results are summarized in Table 2-1.

When the reaction time was decreased from 20 h to 7 h, the yield of the desired product 1,2-dibenzoylbenzene **3aa** did not increase (entries 1 and 2). Instead, the yield of by-product 1*H*-isoindol-1-ol **4aa** increased from 43% to 58%. Addition of 4 Å molecular sieves to remove water, as well as the reducing the amount of MeOH used to quench the Grignard reagent did not increase the yield of the desired product (entries 3-5). A lower or higher reaction time was also not beneficial to the reaction (entries 6 and 7). The addition of 2,2'-bipyridine, thought to restrict conformational changes in the intermediate and so puts the reactant in the proper position for oxygenation, did not yield positive results either (entry 9).

Gratifyingly, the yield of product **3aa** was significantly raised from 34% to 82% with a change in the quenching method: addition of 3 N HCl and stirring at 80 °C under O₂. The 1*H*-isoindole **4aa** was hydrolyzed by acid and converted to the desired product **3aa** (entry 11). Thus, it can be concluded that quenching the reaction with base preserved the 1*H*-isoindole structure while quenching with acid leads to the hydrolyzed 1,2-diacylbenzene.

2.3.2 Scope and limitations

Having obtained the optimized reaction conditions, the scope and limitations of the copper-catalyzed methylene oxygenation was investigated using a range of substituted 2-benzylbenzonitriles and Grignard reagents.

Scheme 2-13. Product with anotated rings

As illustrated in Scheme 2-13, the starting materials were functionalized at rings **A**, **B** and **C**. Installation of functional groups at ring **C** was achieved with a variety of Grignard reagents while those at rings **A** and **B** were accomplished *via* different methods of starting material synthesis as described in the previous section.

Firstly, the scope of Grignard reagents was examined using 2-benzylbenzonitrile **1a**. Both electron-rich and electron-deficient phenyl as well as thienyl rings can be installed with good yields as shown in Table 2-2.

Table 2-2. Reaction scope of Grignard reagents

entry ^a	R ¹	product	time (h)	yield (%) ^b
1	4-Me-C ₆ H ₄	3aa	8.5	82
2	4-MeO-C ₆ H ₄	3ab	4.5	89
3	2-MeO-C ₆ H ₄	3ac	6	49
4	4-Cl-C ₆ H ₄	3ad	2	91
5	4-F-C ₆ H ₄	3ae	6	60
6	1-naphthyl	3af	5	71
7	2-naphthyl	3ag	6	77
8	2-thienyl	3ah	16	63
9	3-Cl-C ₆ H ₄	3ai	22	88
10	4-CF ₃ -C ₆ H ₄	3aj	22	71

^aUnless otherwise noted, the reactions were carried out using 0.5 mmol of 2-benzylbenzonitrile **1** with 1.3 equiv. of Grignard reagents **2** in Et₂O (1 M) at 60 °C (sealed tube) for 2 h followed by addition of MeOH (3.0 equiv.), DMF (0.1 M) and Cu(OAc)₂ (10 mol %). The mixture was stirred at 80 °C under an O₂ atmosphere. ^bIsolated yields.

Next, the reactivity of the copper-catalyzed methylene oxygenation was probed for substrates containing substituents on rings **A** and **B** (Table 2-3). Various 2-benzylbenzonitriles **1** were reacted with *p*-tolymagnesium bromide **2a** to prepare substituted 1,2-diacetylbenzene derivatives. Both electron-donating and electron-withdrawing groups installed to give the desired product in good yields (entries 1 to 6). The reaction also proceeded smoothly for substrates with sterically hindered 2-methylphenyl and 1-naphthyl groups (entries 7 and 8). Substrates bearing substituents such as F, Cl, and alkoxy groups on ring **B** could also undergo

the oxygenation to provide the desired products in good yields (entries 9-12). Furthermore, 1,2-diaclynaphthalene, 2,3-diacylindole, 2,3-diacylthiophene could also be synthesized using this method (entries 13-15). This method could also be used to prepare 1,2,3-triacylbenzene **3qa** from 2,6-dibenzylbenzonitrile, accompanied by a mono-carbonylated product **3qa'**(entry 16).

It is interesting to note that the reaction of 2-cyclohexylbenzonitrile **1t** with a tertiary benzylic C-H bond delivered [benzo[*d*][1,2]dioxin-1-amine **5ta** in 70% yield, possibly *via* formation of the peroxy species followed by its cyclization to the C=N bond (entry 17). When 2,2-dimethyl-4-phenylbutanenitrile **1u** was used as starting material, the corresponding 1,4-diketone **6ua** was isolated in 68% yield *via* benzylic methylene oxygenation (entry 18).

Table 2-3. Reaction scope of different substituents on 2-benzylbenzonitriles^a

entry	starting material	product	time (h)	yield (%) ^b	
1	 1b	 3ba	7	82	
2	 1c	 3ca	2.5	85	
3	 1d	 3da	3	78	
4	 1e	 3ea	3.5	79	
5	 1f	 3fa	5	81	

Table 2-3. continued...

entry	starting material	product	time (h)	yield (%) ^b	
6			6	64	
7			5	58	
8			3	69	
9			6.5	76	
10			1.5	85	

Table 2-3. continued...

entry	starting material	product	time (h)	yield (%) ^b		
11	 1l	 3la	3	79		
12	 1m	 3ma	4	57		
13	 1n	 3na	6	69		
14	 1o	 3oa	2	65		
15	 1p	 3pa	3	77		

Table 2-3. continued...

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entry	starting material	product	time (h)	yield (%) ^b
16	<p>1q</p>	<p>3qa</p>	6	56 (19) ^c
17	<p>1t</p>	<p>5ta</p>	2	70
18	<p>1u</p>	<p>6ua</p>	3	58

^aUnless otherwise noted, the reactions were carried out using 0.5 mmol of 2-benzylbenzonitrile **1** with 1.3 equiv. of Grignard reagents **2** in Et₂O (1 M) at 60 °C (sealed tube) for 2 h followed by addition of MeOH (3.0 equiv.), DMF (0.1 M) and Cu(OAc)₂ (10 mol %). The mixture was stirred at 80 °C under an O₂ atmosphere. ^bIsolated yields. ^cValue in parenthesis denote yield of mono-carbonylated product **3qa**.

2.3.3 Discussion on the reaction mechanism

To probe the reaction mechanism of this reaction, the role of oxygen and importance of the imine intermediate were tested. The results demonstrated that atmospheric oxygen is essential in the reaction, without which only the imine intermediate was formed by reaction of the Grignard reagent with the cyano group (Scheme 2-14).

Scheme 2-14. Reaction under an argon atmosphere

In addition, if the imine were not formed, oxygenation cannot proceed and the starting material was recovered almost exclusively (Scheme 2-15).

Scheme 2-15. Reaction in the absence of *N*-H imine intermediate

Isotope labeling studies using $^{18}\text{O}_2$ confirmed that the both oxygen in the product came from atmospheric oxygen (Scheme 2-16).

Scheme 2-16. Isotope labelling experiment

Based on these results, a proposed catalytic cycle is shown in Scheme 2-17. Addition of Grignard reagents **2** to benzylnitriles **1**, followed by proper protonation with MeOH affords *N*-H imines **I**. The reaction of *N*-H imines **I** with copper(II) catalyst leads to the formation of the iminyl copper(II) species **II** which is then oxidized by atmospheric oxygen to a peroxycopper(III) intermediate **III**. Intramolecular 1,5-H-shift of **III** proceeds to afford benzylic radical **IV**, which is converted into peroxycopper species **V**. Elimination of [Cu(II)-OH] **VI** would then furnish the keto imine **VII** which is then converted into either diketones **3** or 1*H*-isoindole **4**.

Scheme 2-17. A proposed catalytic cycle

2.4 Synthesis of phthalazines and isoindolines

2.4.1 Existing methodologies for phthalazine synthesis

The present methodology could also be applied to the synthesis of phthalazines and isoindolines as described in this section.

In the last decade, diverse biological and medical applications of phthalazine derivatives have been reported. In particular, they were found to possess anti-tumor and anti-inflammatory activities (Scheme 2-18).²⁷ Phthalazine derivatives have also been used in material sciences as ligands in iridium(III) complexes, which has the potential to be used as organic light-emitting diodes (OLEDs).²⁸ Furthermore, phthalazine-based compounds were reported to be the most general ligands in the catalytic asymmetric dihydroxylation of alkenes.²⁹

Scheme 2-18. Phthalazine derivatives tested for anti-inflammatory activities

In 1893, Gabriel and co-workers reported the first synthesis of phthalazine.³⁰ This reaction involving the ring closing of ortho-carbonylbenzaldehyde with hydrazine remains the standard route for the preparation of phthalazine today. In one example, Tsoungas and Searcey developed a six-step procedure starting from 5-methoxy-2-nitrobenzaldehyde to prepare 6-methoxyphthalazine in an overall yield of 20%. The final step of this synthetic route involved the ring closing reaction of a dialdehyde with hydrazine to afford the product in 82% yield (Scheme 2-19). However, this methodology of phthalazine formation is generally preceded by many steps and the resultant low overall yield overshadows the high single-step yield for phthalazine synthesis.

Scheme 2-19. Tsoungas and Searcey's multi-step synthesis of phthalazine

Recently, Wegner and Kessler reported a novel one-pot synthesis of phthalazines from aromatic aldehydes.³¹ Their strategy involved the transformation of an aromatic aldehyde into a directed *ortho*-metalation group by reacting it with lithium amides. The resultant α -aminoalkoxides then underwent *ortho*-lithiation with *n*-BuLi followed by reaction with DMF and finally, hydrolysis with a solution of aqueous ammonium chloride and hydrazine, to provide the product phthalazines in good yields (Scheme 2-20). This procedure can also be used to synthesize other pyridazino-heteroaromatics when heteroaromatic aldehydes were employed as starting materials.

Scheme 2-20. A one-pot method to prepare phthalazines from aromatic aldehydes

2.4.2 Synthesis of phthalazines

Our procedure complements existing methodologies for the synthesis of phthalazine derivatives as it offers an alternative pathway to 1,4-disubstituted phthalazines starting from carbonitriles.

In the present methodology, phthalazine formation proceeded *via* a one-pot three-step sequence. After the Grignard reaction with carbonitriles and copper-catalyzed oxygenation, aqueous hydrazine was added to the reaction mixture and heated at 80 °C until TLC showed complete consumption of the intermediate formed in the oxygenation step. By varying the Grignard reagents, benzene rings with both electron-donating and electron-withdrawing groups, as well as a thienyl moiety, could be installed at the 4-position to obtain 1,4-disubstituted phthalazines in moderate to good yields (Table 2-4).

Bulky substrates such as 1-naphthyl group could also be installed (Table 2-4, entry 5 and 10). However, the reaction did not form phthalazines for the very bulky 1,3,5-trimethylbenzenes despite extended reactions times (Table 2-4, entry 9). Instead, the corresponding 1*H*-isoindo-1-ol **7al** was formed in 80% yield which could then be reduced to form insoindolines (*vide infra*).

Table 2-4. Reaction scope of different Grignard reagents for phthalazine formation^a

entry	Ar	product	time (h) ^b	yield (%) ^c
1	4-MeC ₆ H ₄	7aa	3/ 5/ 3	79
2	4-OMeC ₆ H ₄	7ab	4/ 4/ 4	73
3	3-ClC ₆ H ₄	7ad	3/ 4/ 4	63
4	4-FC ₆ H ₄	7ae	2/ 6/ 3	72
5	1-naphthyl	7af	5/ 5/ 12	41
6	2-thienyl	7ah	2/ 8/ 1	54
7	4-CF ₃ C ₆ H ₄	7aj	4/ 4/ 3	50
8	4-PhOC ₆ H ₄	7ak	2/ 5/ 4	55
9	1,3,5-Me ₃ C ₆ H ₂	7al	14/ 5/ 2	0 (80) ^d
10	2-MeC ₆ H ₄	7am	2/ 7/ 3	50

^aUnless otherwise noted, the reactions were carried out using 0.5 mmol of 2-benzylbenzonitrile **1** with 1.3 equiv. of Grignard reagents **2** in Et₂O (1 M) at 60 °C (sealed tube) for 2 h followed by addition of MeOH (3.0 equiv.), DMF (0.1 M) and Cu(OAc)₂ (10 mol %). The mixture was stirred at 80 °C under an O₂ atmosphere. When the reaction was completed, 5.0 equiv. of aq. N₂H₄ was added and the reaction was stirred at 80 °C. ^bTime-1/ Time-2/ Time-3. ^cIsolated yields. ^dValue in paranthesis denotes yield of corresponding 1*H*-isindol-1-ol.

By varying the starting materials, the scope of the product phthalazine is expanded (Table 2-5). When the ortho benzyl moiety were substituted with both electron-donating and electron-withdrawing groups, the reaction proceeded smoothly (entres 1-3). In addition, indole and thiophene substrates could be converted to the corresponding pyridazines (entries 5 and 6). Carbonitriles modified to include alkyl groups ortho to the cyano moiety, phthalazine products could also be formed in good yields (entries 7 ans 8).

Table 2-5. Reaction scope of different substrates for phthalazine formation^a

entry	starting material	product	time (h) ^b	yield (%) ^c
1			2/ 8/ 4	50
2			4/ 4/ 3	78
3			2/ 8/ 3	52
4			3/ 22/ 7	52
5			4/ 2/ 2	69
6			3/ 4/ 3	84
7			2/ 6/ 3	70
8			2/ 7/ 3	53

^aUnless otherwise noted, the reactions were carried out using 0.5 mmol of 2-benzylbenzonitrile **1** with 1.3 equiv. of Grignard reagents **2** in Et₂O (1 M) at 60 °C (sealed tube) for 2 h followed by addition of MeOH (3.0 equiv.), DMF (0.1 M) and Cu(OAc)₂ (10 mol %). The mixture was stirred at 80 °C under an O₂ atmosphere. When the reaction was completed, 5.0 equiv. of aq. N₂H₄ was added and the reaction was stirred at 80 °C. ^bTime-1/ Time-2/ Time-3. ^cIsolated yields.

2.4.3 Synthesis of isoindolines

In addition, isoindoline derivatives are also attractive targets in medicinal chemistry as studies have revealed their potential in the treatment of Alzheimer's disease since it inhibits the amyloid protein aggregation.³² As shown in Scheme 2-21, they could also be antipsychotic agents due to their ability to modulate the dopamine D₃ receptor,³³ and as selective antagonism of the ETA receptor, indicating that they may play a pathophysiological role in a large number of heart- and lung-related diseases.³⁴

Scheme 2-21. Biologically active compounds containing isoindoline core

The present methodology could be applied for the concise synthesis of isoindolines. Upon completion of the copper-catalyzed oxidation, the crude mixture containing 1,2-diacylbenzenes **3aa** and isoindole **4aa** were treated with NH₄OAc in the presence of a catalytic amount of NaOEt, followed by zinc-copper couple in acetic acid to afford isoindoline **8aa** in 57% over three steps (Scheme 2-22). The product is trans-selective as confirmed by X-ray crystallographic analysis of the tosylated product **8aa-Ts**.

Scheme 2-22. A two-pot synthesis of isoindoline **8aa-Ts**

While investigating the substrate scope for phthalazine formation, the use of bulky 1,3,5-trimethylphenylmagnesium bromide did not provide the corresponding phthalazine product. Instead, the corresponding 1*H*-isoindo-1-ol **4al** was formed in 80% yield which could then be reduced to form insoindoline **8lb** in 48% yield (Scheme 2-23).

Scheme 2-23. A two-pot synthesis of isoindoline **8al** from 1*H*-isoindo-1-ol **7al**

This method was successfully applied to prepare isoindoline **8gb**, a precursor of the endothelin receptor antagonists from 2-bromomethylbenzonitrile

via Suzuki-Miyaura coupling and a subsequent two-pot isoindoline formation (Scheme 2-24).

Scheme 2-24. A concise synthesis of the endotheline receptor antagonist precursor **8gb**

2.5 Conclusion

In summary, copper-catalyzed aerobic benzylic C-H oxygenation was developed using carbonitriles and Grignard reagents. This one-pot two-step sequence provided 1,2-diacylbenzenes in good yields and could be extended for the formation of phthalazines and isoindolines. One major limitation of this reaction would be the indispensable use of Grignard reagents for the generation of *N*-H imines which prohibits the use of electrophilic substituents and thus limits the substrate scope. To further improve the reaction, it is important to develop alternative *N*-H imine formation so that substituents such as the carbonyl functionality could be installed.

Chapter 3 Electrophilic cyanation of Grignard Reagents with Pivalonitrile *via* Copper-Catalyzed Aerobic β -Carbon Elimination of N-H Imine Intermediates

3.1 Introduction

3.1.1 Overview

Carbonitriles are important components in the synthesis of pharmaceuticals, natural products, agricultural chemicals, dyes and materials.³⁵ Examples of pharmaceutically important drugs containing the cyano moiety include Citalopram hydrobromide[®] used for the treatment of alcohol dependency, Periciazine[®] used as an antipsychotic drug, Fadozole[®] used as an oncolytic drug and Letrozole[®] used in breast cancer therapy (Scheme 3-1).³⁶

Scheme 3-1. Examples of pharmaceutically active benzonitriles

Moreover, the cyano moiety is an important intermediate for the introduction of other functional groups such as carboxylic acids, amides, imines, ketones, aldehydes, and amines (Scheme 3-2).³⁷ Development of new methodologies for their preparation remains relevant because of their industrial importance and synthetic utility in the fields of biology and chemistry.

Scheme 3-2. Transformations of the C≡N functional group

3.1.2 Classical methods for the synthesis of carbonitriles

There are various ways to achieve cyanation of aromatic nitriles. On the industrial scale, ammoxidation is the choice method.³⁸ The Sohio process is used for the production of acrylonitrile when propene is reacted with oxygen and ammonia at high temperatures in the presence of a fixed-bed catalyst (Scheme 3-3). Such harsh reaction conditions limit the use of this method for the production of functionalized carbonitriles.

Scheme 3-3. The Sohio process for the production of acrylonitrile

On a micro- as well as macro-scale, the Rosenmund-von Braun reaction for nitrile formation involved heating aryl halides with excess copper(I) cyanide at high temperatures in polar solvents (Scheme 3-4).³⁹

Scheme 3-4. Rosenmund-von Braun reaction: synthesis of aryl carbonitriles from aryl halides

Another established method is the diazotization of anilines and subsequent Sandmeyer reaction for the synthesis of aromatic nitriles (Scheme 3-5).⁴⁰

Scheme 3-5. Sandmeyer reaction: synthesis of aryl carbonitriles from aryl diazonium salts

Traditionally, both methods depended on the use of stoichiometric amounts of toxic CuCN and drastic reaction conditions but developments in synthetic organic chemistry have since been replace these methods with their transition metal-catalyzed versions (*vide infra*).⁴¹

3.1.3 Recent methods for the synthesis of carbonitriles

3.1.3.1 Metal-catalyzed methods for the synthesis of carbonitriles

More recently, increasingly benign and useful procedures for the preparation of substituted carbonitriles have been developed as milder alternatives to the traditional methods of preparation. The first palladium-catalyzed cyanation of aryl halides using KCN as cyanating reagents was reported by Takagi and co-workers in 1973 (Scheme 3-6).⁴² While most known cyanide sources are highly toxic, KCN, however, has the lowest lethal dose of 2.86 mg/ kg for oral consumption in humans.

Scheme 3-6. The first Pd(II)-catalyzed synthesis of aryl nitriles from aryl halides

Since then, palladium, nickel and copper complexes have emerged as catalysts for the installation of the cyano moiety onto aromatic compounds using readily available cyanation agents like NaCN and KCN.⁴³

In 2002, Buchwald and co-workers developed the first catalytic variant of the Rosenmund-von Braun reaction, a novel copper- catalyzed domino halogen

exchange-cyanation methodology using stoichiometric *N,N*-dimethylethane-1,2-diamine and NaCN (Scheme 3-7).⁴⁴

Scheme 3-7. Copper-catalyzed domino halide exchange-cyanation of aryl bromides

The success of this *in-situ* copper-catalyzed conversion of aryl bromides into more reactive iodides and subsequent cyanation relied upon matching the relative rates of the halogen exchange and cyanation steps in the domino reaction sequence (Scheme 3-8).

Scheme 3-8. Matching the relative rates of the halide exchange and cyanation steps

Another remarkable progress in the synthesis of nitriles was made in 2004, when Beller and co-workers discovered catalytic cyanation using potassium hexacyanoferrate (II) $\text{K}_4[\text{Fe}(\text{CN})_6]$ (Scheme 3-9),⁴⁵ which is non-toxic and has even been used in the food industry for metal precipitation.⁴⁶ In this reaction, the amount of catalyst had to be tweaked for optimal yields of different substrates to achieve high turnover numbers for a wide range of aromatic bromides. Following this study, several other reports were published detailing the use of this benign cyanide source in cyanation.⁴⁷

Scheme 3-9. Pd(II)-catalyzed cyanation of aryl halides using $\text{K}_4[\text{Fe(CN)}_6]$

3.1.3.2 Use of organic precursors for the synthesis of carbonitriles

As early as 1967, organic precursors have been found to be utilized for carbonitriles synthesis. In a report by Lohaus, aromatics could react with chlorosulfonyl isocyanate to form *N*-chlorosulfonyl amides, which when treated with DMF provided aromatic nitriles, giving SO_3 and HCl as by-products (Scheme 3-10).⁴⁸

Scheme 3-10. The first synthesis of nitriles using organic precursors

With the discovery of various organic cyanide sources, it was not until recently that DMF was again used for the synthesis of carbonitriles. In 2010, Togo and co-workers, reported a metal-free one-pot conversion of electron-rich aromatics into aromatic nitriles.⁴⁹ The transformation commenced with the Vilsmeier-Haack reaction using DMF and POCl_3 to generation intermediate I. Subsequent dehydrohalogenation using molecular iodine in aqueous ammonia then provides the carbonitrile products (Scheme 3-11).

Scheme 3-11. Metal-free one-pot formation of aromatic nitriles

In the same year, Chang and co-workers also reported using DMF and ammonia as a combined source for the cyano unit to achieve regioselective cyanation.⁵⁰ Interestingly, isotopic labelling experiments indicated that the carbon and nitrogen of the cyano group were derived from the *N,N*-dimethyl moiety of DMF and ammonia, respectively, allowing an unprecedented formation of doubly labelled benzonitriles (Scheme 3-12).

entry	condition	result
1	$^{15}\text{NH}_3$ (aq) with $\text{H}-\overset{\text{O}}{\parallel}{\text{C}}-\text{N}(\text{CH}_3)_2$	CN (98% ^{15}N incorporation)
2	$^{15}\text{NH}_3$ (aq) with $\text{H}-\overset{\text{O}}{\parallel}{\text{C}}-\text{N}(^{13}\text{CH}_3)_2$	CN (96% ^{13}C incorporation)
3	$^{15}\text{NH}_3$ (aq) with $\text{H}-\overset{\text{O}}{\parallel}{\text{C}}(^{13}\text{C})-\text{N}(\text{CH}_3)_2$	CN (<5% ^{13}C incorporation)

Scheme 3-12. Isotope labelling experiments for the cyanation of aryl C-H bonds

Besides DMF, other organic molecules have also been used as cyanide sources. In 2006, Yu and co-workers reported a copper-catalyzed cyanation of 2-phenylpyridine using nitromethane as the cyanide source (Scheme 3-13).⁵¹ This cyanation was among a list of C-H functionalizations carried out under aerobic conditions.

Scheme 3-13. Cu(II)-mediated cyanation using nitromethane

In other examples by Togo and co-workers, iodine reagents in aqueous ammonia have also been used for the oxidative conversion of alcohols, amines and alkyl halides to nitriles (Scheme 3-14).⁵²

Scheme 3-14. Conversion of halides, alcohols and amines to nitriles using iodine reagents in aqueous ammonia

Recently, Beller and co-workers published a versatile methodology for the copper-catalyzed cyanation of aryl and heteroaryl bromides with acetone cyanohydrin (Scheme 3-15).⁵³ Compared to other catalysts, copper catalysts in

cyanation reactions generally exhibited lower reactivity but are also cheaper and more environmentally friendly. To overcome the problem of catalyst deactivation by coordination to cyanide, acetone cyanohydrin was added using a syringe pump over the course of the reaction to ensure a slow release of cyanide anions for reaction.

Scheme 3-15. Cu(I)-catalyzed cyanation using acetone cyanohydrin

3.1.3.3 Electrophilic cyanation for carbonitrile synthesis

A complementary but less well-studied approach to the transition metal-catalyzed nucleophilic cyanation reactions would be electrophilic cyanation reactions.⁵⁴

As early as 1970, Leusen and Jagt employed *p*-toluene sulfonyl cyanide, an electrophilic cyanide source, for cyanide transfer reactions with nucleophilic reagents *via* an addition-elimination process.⁵⁵ The tosyl group inductively withdraws electron density from the cyano carbon, thereby enhancing its reactivity towards nucleophilic reagents (Scheme 3-16).

Scheme 3-16. Addition-elimination process using TsCN as cyanide source

In another example, Ohe and co-workers reported the use of a pseudohalide, cyanogen bromide, in a gallium-catalyzed bromocyanation of alkynes to provide a wide range of α,β -unsaturated nitriles in respectable yields that can undergo further functionalizations (Scheme 3-17).⁵⁶ A major drawback of this synthetic method is that cyanogen bromide is highly toxic.

Scheme 3-17. Ga(III)-catalyzed cyanation and further functionalizations of β -bromo- α,β -unsaturated nitriles

Other than using electrophilic cyanides on their own, they could also be used together with organometallic reagents to achieve cyanation. In one example, Beller and co-workers reported the synthesis of benzonitriles from *in-situ*

generation of functionalized Grignard reagents and their subsequent electrophilic cyanation (Scheme 3-18).⁵⁷ The reaction was conducted under mild reaction conditions and both electron-donating and -withdrawing groups can be installed without compromising the efficiency of the cyanation.

Scheme 3-18. Electrophilic cyanation with *N*-cyanobenzimidazole

Beller and co-workers went on to design another cyanating reagent, *N*-cyano-*N*-phenyl-*p*-methylbenzenesulfonamide, to be used under similar reaction conditions.⁵⁸ The advantage of this improved reagent lies in its preparation from phenyl urea and *p*-toluenesulfonyl chloride, which avoids the use of toxic cyanogen bromide (Scheme 3-19).

Scheme 3-19. Preparation of electrophilic cyanide source, *N*-cyano-*N*-phenyl-*p*-methylbenzenesulfonamide

The medley of reagents and synthetic methods is testimony to the advances in the formation of carbonitriles. Nevertheless, catalysts commonly employed for cyanation remains limited by their toxicity, high cost (especially so for palladium catalysts) and deactivation due to their high affinity for cyanide ions. Hence, there continues to be an academic interest in the development of new and more convenient methods for the formation of carbonitriles.

In Chapter 2, the author reported the copper-catalyzed benzylic C-H oxygenation starting from reaction of carbonitriles and Grignard reagents under an oxygen atmosphere *via* an iminyl copper species (Scheme 3-20).⁵⁹

Scheme 3-20. Copper(II)-catalyzed benzylic C-H oxygenation under an oxygen atmosphere *via* iminyl copper species

Various carbonitrile substrates were screened to demonstrate the versatility of the reaction conditions. In the course of this study, it was found that the benzonitrile reacts with butylmagnesium bromide under standard reaction conditions to provide the desired product 1,4-diphenylbutane-1,4-dione in moderate yield, with unexpected benzonitrile observed in the crude ¹H NMR (Scheme 3-21). Since the starting material was confirmed to have been completely consumed in the reaction with the Grignard reagent, it was apparent that the carbonitrile was reformed during the copper-catalyzed aerobic reaction of the *N*-H imine intermediate. Intrigued by this result, we decided to subject a simpler nitrile, pivalonitrile, to the reaction conditions hoping to uncover another organic cyanide source.

Scheme 3-21. Copper(II)-catalyzed benzylic C-H oxygenation with unexpected nitrile formation

We envisaged a copper-catalyzed cyanation of Grignard reagents using pivalonitrile as a cyanide source under an oxygen atmosphere to afford carbonitriles *via* a transient iminyl copper species. The transformation is aided by the oxidation of the iminyl copper species with diradical oxygen to form a peroxycopper intermediate, followed by homolytic cleavage to afford product carbonitriles (Scheme 3-22).

Scheme 3-22. Copper(II)-catalyzed cyanation using pivalonitrile as organic cyanide source

3.2 Electrophilic cyanation of Grignard reagents with pivalonitrile

3.2.1 Optimization of reaction conditions

We commenced our study with the reactions of pivalonitrile and 2-naphthyl magnesium bromide and subsequent protonation with MeOH to give an *N*-H imine intermediate. The reaction mixture was diluted with DMF (0.1 M) and metal salts (10 mol %) were added. The reaction was then stirred at $80\text{ }^\circ\text{C}$ under an oxygen atmosphere until TLC showed completion of the reaction. Due to the difficulty in monitoring the pivalonitrile spot on TLC, step one of the reaction was left for 2 h and 6 h, to confirm that the yields of the carbonitriles were not affected by any unreacted starting material (Table 3-1, entries 1 and 2). Based on the results of the optimization studies, several copper salts were found to catalyze the reaction for the formation of naphthonitrile (Table 3-1, entries 1-9), with CuBr_2 giving the best yield of 85%. Interestingly, both cobalt and iron salts were also able to catalyze the

reaction, albeit with longer reaction times and lower product yields, while palladium salts showed no reactivity at all (Table 3-1, entries 10-15).

Table 3-1. Optimization studies^a

entry	time (h) ^c	catalyst (mol %)	yield (%) ^b
1	2/ 8	Cu(OAc) ₂ (10)	73
2	6/ 5	CuOAc (10)	74
3	2/ 24	Cu ₂ O (10)	75
4	2/ 8	CuBr (10)	72
5	2/ 6	CuCl (10)	74
6	2/ 24	CuI (10)	66
7	2/ 7	CuBr•SMe ₂ (10)	74
8	2/ 6	CuBr ₂ (10)	85
9	2/ 7	CuCl ₂ (10)	79
10	2/ 24	CoBr ₂ (10)	76
11	2/ 24	Co(OAc) ₂ (10)	59
12	2/ 24	Pd(OAc) ₂ (10)	(68) ^d
13	2/ 24	FeBr ₂ (10)	64
14	2/ 24	FeBr ₃ (10)	65
15	2/ 24	FeCl ₃ (10)	74

^aUnless otherwise noted, the reactions were carried out using 1 mmol of pivalonitrile with 1.3 equiv. of naphthyl magnesium bromide in Et₂O (1 M) at 60 °C in a sealed tube for 2 h, followed by addition of anhydrous MeOH (3.0 equiv.), DMF (0.1 M) and metal salts (10 mol %). The reaction was then stirred at 80 °C under an O₂ atmosphere. ^bIsolated yields. ^cTime for Grignard reaction/ Time for C-C bond cleavage. ^dValue in parenthesis denote isolated yield of 2,2-dimethyl-1-(naphthalen-2-yl)propan-1-one **6**.

3.2.2 Scope and limitations

Having obtained the optimized reaction conditions, the substrate scope of the electrophilic cyanation was investigated as shown in Table 3-2. The reaction proceeded smoothly to enable cyanide transfer from organic carbonitriles to Grignard reagents. In essence, it transformed aryl halides to aryl carbonitriles in a one-pot two-step reaction.

For the synthesis of aryl nitriles, installation of both electron- donating and electron-withdrawing groups were possible. Substrates bearing electron donating groups (Table 3-2, entries 1-5) were obtained in higher yields compared to those with electron-withdrawing groups; (Table 3-2, entry 6) the latter also required longer reaction times. Moreover, sterically demanding substrates such as 1-naphthyl and 2,4,6-trimethyl Grignard reagents could be used to form the corresponding aromatic nitriles in good yields. Based on the differing stability of primary and tertiary carbon radicals, we were also able to apply the reaction conditions for the formation of primary alkyl carbonitriles (Table 3-2, entry 9).

Table 3-2. Reaction scope using different Grignard reagents^a

$ \begin{array}{c} \text{R-MgBr } \mathbf{2} \\ (1.3 \text{ equiv.}) \\ \xrightarrow[\text{Et}_2\text{O, 60 } ^\circ\text{C}]{\text{in sealed tube}} \\ \text{then MeOH} \end{array} \xrightarrow[\text{DMF, 80 } ^\circ\text{C}]{\text{CuBr}_2 (10 \text{ mol\%}) \text{ under O}_2} \begin{array}{c} \text{R-CN} \\ \mathbf{3} \end{array} $						
entry	R-MgBr	product	time (h) ^c	yield (%) ^b		
1			12/ 18	76		
2			22/10	74		
3			50/ 18	67 ^d		
4			48/ 55	70		
5			56/19	81 ^d		
6			48/ 24	63 ^e		
7			48/ 24	81		
8			48/ 24	42 ^e		

^aUnless otherwise noted, the reactions were carried out using 1 mmol of pivalonitrile with 1.3 equiv. of Grignard reagents **2** in Et₂O (1 M) at 60 °C in a sealed tube for 2 h, followed by addition of anhydrous MeOH (3.0 equiv.), DMF (0.1 M) and CuBr₂ (10 mol %). The reaction was then stirred at 80 °C under an O₂ atmosphere. ^bIsolated yields. ^cTime for Grignard reaction/ Time for C-C bond cleavage. ^dThe reaction was conducted using Cu(OAc)₂ as the catalyst. ^e¹H NMR yield.

3.2.3 Discussion on the reaction mechanism

To probe the reaction mechanism of this catalytic cycle under an oxygen atmosphere, carbonitriles with a bulky carbon chain was employed as the cyanide source. Under the optimal reaction conditions, the treatment of carbonitrile **4** with Grignard reagent **2c** led to the formation of 4-methoxybenzonitrile **3c**, along with alkene **5** in 83% and 16% yields, respectively (Scheme 3-23).

Scheme 3-23. Reaction using 2,2-diphenyloctanenitrile as cyanide source to probe side-products

The reaction performed in the absence of oxygen provided ketone **6** in 83% after acid hydrolysis (Scheme 3-24).

Scheme 3-24. Reaction in the absence of oxygen

In addition, in the absence of $\text{Cu}(\text{OAc})_2$, oxygenation cannot proceed and the corresponding ketone **1b** was recovered almost exclusively (Scheme 3-25).

Scheme 3-25. Reaction in the absence of copper catalyst

Based on these preliminary results, a possible mechanism for the reaction is proposed as shown in Scheme 3-26. Addition of Grignard reagents to carbonitriles followed by protonation with MeOH provides N-H imines. The reaction of N-H imines with the $\text{Cu}(\text{II})$ catalyst leads to an iminyl copper species that is oxidized with molecular oxygen to form peroxycopper(III). Homolytic cleavage of the C-C bond afforded product carbonitrile and a tertiary carbon radical which is then oxidized by the peroxycopper(I) to a carbocation. Elimination under the basic reaction conditions would provide the corresponding alkene while the addition of water followed by deprotonation would deliver an alcohol.

Scheme 3-26. A proposed catalytic cycle for the cyanation reaction

3.3 Conclusion

In summary, we have found a copper-catalyzed cyanation of Grignard reagents under an oxygen atmosphere to provide carbonitriles *via* homolytic cleavage of the transient iminyl copper species.

This reaction, using pivalonitrile as an electrophilic cyanation reagent, may be limited in reaction scope due to the use of Grignard reagents in the reaction process. Nevertheless, it provides an interesting scope to the utility of iminyl metal species and pushed the boundaries for carbonitrile formation using organic precursors.

Chapter 4 Summary

The results presented in this thesis contributes towards existing knowledge of the iminyl copper species and its application in synthetic organic chemistry. The reactions allowed the synthesis of useful products from easily prepared starting materials under relatively mild reaction conditions.

Chapter 2 described the oxidative C-H bond functionalization of 2-benzylbenzonitriles to afford a range of 1,2-diacylbenzenes *via* the iminyl copper species and using *N*-H imines as an intramolecular directing group to effect oxidation of the benzylic C-H bonds. This methodology could be extended to provide good yields of phthalazines and isoindolines, which constitutes the skeleton of important azaheterocycles with diverse biological applications.

Chapter 3 described the copper-catalyzed reaction of Grignard reagents under an oxygen atmosphere to provide carbonitriles *via* homolytic cleavage of the transient iminyl copper species. This electrophilic cyanation of Grignard reagents *via* a radical-mediated process may be limited in substrate scope, but is unique in using pivalonitrile as an organic electrophilic cyanation reagent.

Chapter 5 Experimental

5.1 General considerations

^1H NMR (400MHz) spectra were recorded on a Bruker Avance 400 spectrometers in CDCl_3 [using $(\text{CH}_3)_4\text{Si}$ (for ^1H , $\delta = 0.00$) as internal standard]. ^{13}C NMR (75 MHz) spectra on a Bruker Avance 400 spectrometers in CDCl_3 [using CDCl_3 (for ^{13}C , $\delta = 77.00$) as internal standard]. ^{13}C NMR (100 MHz) spectra on a Bruker Avance 400 spectrometers in CDCl_3 [using CDCl_3 (for ^{13}C , $\delta = 77.00$) as internal standard]. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, m = multiplet, br = broad. IR spectra (NaCl) and IR spectra (ATR) were recorded on a Shimadzu IR Prestige-21 FT-IR Spectrometer and a Shimadzu IRAffinity-1 FT-IR Spectrometer respectively and are reported in wavenumbers (cm^{-1}). High-resolution mass spectra were obtained with a Finnigan MAT 95 XP mass spectrometer (Thermo Electron Corporation). Melting points were uncorrected and were recorded on a Buchi B-54 melting point apparatus.

Flash column chromatography was performed using Merck silica gel 60 with distilled solvents. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were taken from a solvent purification system (PS-400-5, innovative technology Inc.). *N,N*-Dimethylformamide (DMF) anhydrous, Copper(II) acetate (98%), Copper(II) bromide (98%) was purchased from Sigma-Aldrich Co., Inc. Pivalonitrile was purchased from Sigma-Aldrich Co., Inc. and distilled before use.

All the Grignard reagents were prepared according to the general procedure⁶⁰ and were used after the titration by following the literature method.⁶¹

5.2 Copper-Catalyzed Benzylic C-H Oxygenation under an Oxygen Atmosphere *via* *N*-H Imines as an Intramolecular Directing Group

5.2.1 Preparation of starting material

5.2.1.1 Method 1: Benzylic bromination of 2-methylbenzonitriles **9** followed by the Friedel–Crafts reaction

Synthesis of 2-methylbenzonitriles **9**: A typical procedure for synthesis of 2-(bromomethyl)-1-naphthonitrile (**9n**)⁶²

To a flask charged with 1-bromo-2-methylnaphthalene (3.84 g, 17.4 mmol) and CuCN (1.86 g, 20.8 mmol) was added *N*-methyl-2-pyrrolidone (9 mL). The reaction mixture was heated at reflux for 3 h. When all the starting material was consumed, the reaction mixture was cooled and carefully poured into a solution of benzene with 20% NaCN (40 mL) and filtered through a Celite pad. After washing with benzene, the benzene layers were combined and washed with a solution of 10% NaCN then with water, and dried over anhydrous MgSO₄. The solvent was removed in vacuo, and the resulting crude material was subjected to flash column chromatography (hexane : ethyl acetate : CH₂Cl₂ = 90 : 10 : 5) to afford 2-methyl-1-naphthonitrile (1.28 g, 7.66 mmol) in 44% yield.

¹H NMR (400 MHz, CDCl₃) δ 2.75 (3H, s), 7.39 (1H, d, *J* = 8.4 Hz), 7.55 (1H, dd, *J* = 7.2, 8.0 Hz), 7.66 (1H, dd, *J* = 7.2, 8.4 Hz), 7.86 (1H, d, *J* = 8.0 Hz), 7.94 (1H, d, *J* = 8.4 Hz), 8.19 (1H, d, *J* = 8.4 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 21.3, 109.2, 117.0, 124.8, 126.6, 127.6, 128.3, 128.5, 131.2, 132.5, 132.7, 142.9.

2,6-dimethylbenzonitrile (**9q**)

Prepared from 2-bromo-1,3-dimethylbenzene (CAS. No 576-22-7) in 85% yield; Pink solid; mp. 90.0-91.9 °C; IR (NaCl) 3071, 2220, 1597, 1472 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 2.53 (6H, s), 7.12 (2H, d, $J = 7.6$ Hz), 7.34 (1H, t, $J = 7.6$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 20.7, 113.3, 117.2, 127.2, 132.0, 142.1; ESIHRMS: Found: m/z 132.0813. Calcd for $\text{C}_9\text{H}_{10}\text{N}$: ($\text{M}+\text{H}$) $^+$ 132.0813.

Synthesis of 2-bromomethylbenzonitriles **10**: A typical procedure for synthesis of 2-(bromomethyl)-1-naphthonitrile (**10n**)

To a CCl_4 solution (12 mL) of 2-methyl-1-naphthonitrile **9n** (0.980 g, 5.86 mmol) was added *N*-bromosuccinimide (1.25 g, 7.02 mmol) and benzoylperoxide (0.14 g, 0.58 mmol). The reaction mixture was heated at 100 °C for 20 h. When all the starting material was consumed, the reaction mixture was cooled to room temperature, filtered through a Celite pad, and the filtrate was washed with CCl_4 . The solvent was removed in vacuo, and the resulting crude material was subjected to flash column chromatography (hexane : EtOAc = 98 : 2) to afford 2-(bromomethyl)-1-naphthonitrile **10n** (1.02 g, 4.14 mmol) in 71% yield.

White Solid; mp. 93.8-94.8 °C; IR (NaCl) 3154, 3093, 2253, 1508, 1466 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 4.85 (2H, s), 7.61-7.65 (2H, m), 7.72 (1H, dd, $J = 8.4$, 7.2 Hz), 7.91 (1H, d, $J = 8.0$ Hz), 8.06 (1H, d, $J = 8.4$ Hz), 8.25 (1H, d, $J = 8.4$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 30.0, 109.6, 115.7, 125.6, 126.7, 128.0, 128.5, 129.1, 132.4, 132.5, 133.5, 141.4; ESIHRMS: Found: m/z 245.9892. Calcd for $\text{C}_{12}\text{H}_9\text{NBr}$: ($\text{M}+\text{H}$) $^+$ 245.9918.

2-(bromomethyl)-6-chlorobenzonitrile (10j)⁶³

Prepared from 2-chloro-6-methylbenzonitrile (CAS No 6575-09-3) in 34% yield; ¹H NMR (400 MHz, CDCl₃) δ 4.62 (2H, s), 7.45-7.54 (3H m); ¹³C NMR (100 MHz, CDCl₃) δ 29.0, 113.5, 113.9, 128.5, 129.7, 133.7, 137.8, 143.4.

2-(bromomethyl)-5-fluorobenzonitrile (10k)

Prepared from 5-fluoro-2-methylbenzonitrile (CAS No 77532-79-7) in 59% yield; White Solid; mp. 64.9-65.9 °C; IR (NaCl) 3021, 2980, 2253, 1612, 1587, 1495, 1283, 650 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 4.61 (2H, s), 7.13 (1H, ddd, *J*_{H-F} = 8.0 Hz, *J*_{H-H} = 8.0, 2.0 Hz), 7.29 (1H, dd, *J*_{H-F} = 8.8 Hz, *J*_{H-H} = 2.0 Hz), 7.68 (1H, dd, *J*_{H-F} = 5.6 Hz, *J*_{H-H} = 8.0 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 28.4, 108.5 (d, ⁴*J*_{C-F} = 3.5 Hz), 116.1, 116.6 (d, ²*J*_{C-F} = 22.5 Hz), 118.0 (d, ²*J*_{C-F} = 23.3 Hz), 135.5 (d, ³*J*_{C-F} = 9.5 Hz), 144.3 (d, ³*J*_{C-F} = 9.0 Hz), 164.9 (d, ¹*J*_{C-F} = 256.2 Hz); ESIHRMS: Found: *m/z* 213.9693. Calcd for C₈H₆NBrF: (M+H)⁺ 213.9668.

2-(bromomethyl)-5-methoxybenzonitrile (10l)

Prepared from 5-methoxy-2-methylbenzonitrile (CAS No 53078-70-9) in 85% yield; White solid; mp. 73.9-74.7 °C; IR (NaCl) 3015, 1972, 2222, 1499, 1464, 1251, 650 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 3.88 (3H, s), 4.59 (2H, s), 6.90 (1H, d, *J* = 8.8 Hz), 7.03 (1H, s), 7.58 (1H, d, *J* = 8.8 Hz); ¹³C NMR (100 MHz, CDCl₃) δ

29.4, 55.7, 104.0, 114.7, 116.0, 117.1, 134.8, 143.1, 163.0; ESIHRMS: Found: m/z 225.9849. Calcd for C_9H_9BrNO : $(M+H)^+$ 225.9868.

2,6-bis(bromomethyl)benzonitrile (**10q**)

Prepared from 2,6-dimethylbenzonitrile (**9q**) in 41% yield;

White solid; mp. 92.6-93.6 °C; IR (NaCl) 3019, 2226, 1470, 1443, 669 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$) δ 4.65 (4H, s), 7.50-7.60 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.2, 112.4, 114.7, 130.2, 133.3, 142.2; ESIHRMS: Found: m/z 287.9079. Calcd for $C_9H_8NBr_2$: $(M+H)^+$ 287.9023.

Synthesis of 2-benzylbenzonitriles **1** by the Friedel–Crafts reaction: A typical procedure for synthesis of 2-benzyl-1-naphthonitrile (**1n**)⁶⁴

To a flask charged with $AlCl_3$ (0.989 g, 7.42 mmol) in dry benzene (9.3 mL) was added 2-(bromomethyl)-1-naphthonitrile **10n** (0.911 g, 3.70 mmol) in an ice bath. The reaction mixture was warmed to room temperature and then heated to reflux for 45 min. When all the starting materials were consumed, as checked by TLC, the reaction mixture was cooled to room temperature, poured into ice and then acidified with 1 N HCl. The organic materials were extracted with CH_2Cl_2 . The combined organic extracts were washed with water and then with brine and dried over anhydrous $MgSO_4$. The solvents were removed in vacuo and the resulting crude material was subjected to flash column chromatography (hexane : EtOAc = 90 : 10) to afford 2-benzyl-1-naphthonitrile **1n** (0.711 g, 2.92 mmol) in 79% yield.

^1H NMR (400 MHz, CDCl_3) δ 4.42 (2H, s), 7.33-7.20 (5H, m), 7.37 (1H, d, $J = 8.4$ Hz), 7.57 (1H, dd, $J = 8.0, 8.4$ Hz), 7.68 (1H, dd, $J = 8.0, 8.4$ Hz), 7.86 (1H, d, $J = 8.4$ Hz), 7.95 (1H, d, $J = 8.4$ Hz), 8.25 (1H, d, $J = 8.4$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 40.9, 109.2, 117.1, 125.2, 126.7, 126.9, 127.0, 128.3, 128.6, 128.7, 128.9, 131.4, 132.7, 132.9, 138.9, 145.6.

2-benzylbenzonitrile (**1a**)⁶⁵

80% yield from 2-bromomethylbenzonitrile (CAS. No 22115-41-9); ^1H NMR (400 MHz, CDCl_3) δ 4.21 (2H, s), 7.23-7.33 (7H, m), 7.49 (1H, dd, $J = 7.2, 7.6$ Hz), 7.64 (1H, d, $J = 7.6$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 40.2, 112.6, 118.2, 126.7, 126.8, 128.7, 129.0, 130.0, 132.9, 133.0, 138.8, 145.0.

2-benzyl-6-chlorobenzonitrile (**1j**)

94% yield from **10j**; Yellow solid; mp. 36.0-37.0 °C; IR (NaCl) 3065, 2232, 1589, 1564, 1454, 1439, 669 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 4.21 (2H, s), 7.16 (1H, d, $J = 8.0$ Hz), 7.22-7.27 (3H, m), 7.31 (2H, d, $J = 7.2$ Hz), 7.35 (1H, d, $J = 8.4$ Hz), 7.41 (1H, dd, $J = 7.6, 8.0$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 40.5, 113.6, 115.2, 126.9, 127.6, 128.0, 128.8, 129.0, 133.3, 137.4, 138.0, 147.4; ESIHRMS: Found: m/z 228.0576. Calcd for $\text{C}_{14}\text{H}_{11}\text{NCl}$: $(\text{M}+\text{H})^+$ 228.0580.

2-benzyl-5-fluorobenzonitrile (**1k**)

75% yield from **10k**; Yellow oil; IR (NaCl) 3088, 3065, 3021, 2228, 1609, 1584, 1489, 1454, 1277 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 4.19 (2H, s), 6.93 (1H, dd,

$J_{\text{H-F}} = 9.6$ Hz, $J_{\text{H-H}} = 2.0$ Hz), 7.00 (1H, ddd, $J_{\text{H-F}} = 8.0$ Hz, $J_{\text{H-H}} = 8.4, 2.0$ Hz), 7.22-7.35 (5H, m), 7.65 (1H, dd, $J_{\text{H-F}} = 5.6$ Hz, $J_{\text{H-H}} = 8.4$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 40.1 (d, $^5J_{\text{C-F}} = 1.3$ Hz), 108.6 (d, $^4J_{\text{C-F}} = 3.1$ Hz), 114.5 (d, $^2J_{\text{C-F}} = 22.7$ Hz), 117.3 (d, $^2J_{\text{C-F}} = 22.7$ Hz), 117.4, 127.0, 128.9 (d, $^3J_{\text{C-F}} = 11.3$ Hz), 135.1 (d, $^3J_{\text{C-F}} = 9.6$ Hz), 137.8, 148.4, 148.5, 165.0 (d, $^1J_{\text{C-F}} = 254.9$ Hz); ESIHRMS: Found: m/z 212.0869. Calcd for $\text{C}_{14}\text{H}_{11}\text{NF}$: $(\text{M}+\text{H})^+$ 212.0876.

2-benzyl-5-(benzyloxy)benzonitrile (**1m**)

2-benzyl-5-hydroxybenzonitrile (**11-OH**)

92% yield from **10I** (demethylation was concurrently observed under the Friedel–Crafts reaction conditions) which was converted into **1m** by further benzylation; Gray solid; mp. 137.2-138.7 °C; IR (NaCl) 3065, 3032, 2932, 2874, 2222, 1603, 1568, 1495, 1454, 1244 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 4.14 (2H, s), 5.43 (1H, br), 6.66 (1H, s), 6.73 (1H, dd, $J = 8.4, 2.0$ Hz), 7.22-7.33 (5H, m), 7.52 (1H, d, $J = 8.4$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 40.1, 104.3, 114.3, 117.0, 118.5, 126.8, 128.7, 129.0, 134.9, 138.4, 147.6, 159.5; ESIHRMS: Found: m/z 210.0922. Calcd for $\text{C}_{14}\text{H}_{12}\text{NO}$: $(\text{M}+\text{H})^+$ 210.0919.

Benzylation of 11-OH to 1m: To a flask charged with 2-benzyl-5-hydroxybenzonitrile (0.331 g, 1.58 mmol) in MeCN (3.2 mL) was added K_2CO_3 (0.350 g, 2.53 mmol), benzyl chloride (0.20 mL, 1.74 mmol), and KI (2.6 mg, 0.016 mmol). The reaction mixture was stirred at reflux for 3 h. When all the starting materials were consumed, the reaction mixture was cooled to room temperature, and quenched with water. The organic materials were extracted with

EtOAc. The combined organic extracts were washed with water and then with brine and dried over anhydrous MgSO_4 . The solvents were removed in vacuo and the resulting crude material was subjected to flash column chromatography (hexane : EtOAc = 80 : 20) to afford 2-benzyl-5-(benzyloxy)benzonitrile (**1m**) (0.470 g, 1.57 mmol) in 99% yield.

2-benzyl-5-(benzyloxy)benzonitrile (**1m**)

Yellow solid; mp. 48.5-49.9 °C; IR (NaCl) 3065, 3032, 2932, 2874, 2222, 1603, 1568, 1495, 1454, 1244 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 4.15 (2H, s), 5.03 (2H, s), 6.80 (1H, d, $J = 2.4\text{ Hz}$), 6.86 (1H, dd, $J = 8.4, 2.4\text{ Hz}$), 7.21-7.38 (10H, m), 7.55 (1H, d, $J = 8.8\text{ Hz}$); ^{13}C NMR (100 MHz, CDCl_3) δ 40.3, 70.2, 104.5, 113.2, 116.5, 118.5, 126.7, 127.5, 128.3, 128.7 (overlapped), 129.0, 134.6, 135.6, 138.5, 147.1, 162.0; ESIHRMS: Found: m/z 300.1290. Calcd for $\text{C}_{21}\text{H}_{18}\text{NO}$: ($\text{M}+\text{H}$) $^+$ 300.1388.

2,6-dibenzylbenzonitrile (**1q**)

94% yield from **10q**; Pink Solid; mp. 74.3-75.3 °C; IR (NaCl) 3086, 3065, 2926, 2220, 1495, 1466, 1454 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 4.21 (4H, s), 7.09 (2H, d, $J = 8.0\text{ Hz}$), 7.20-7.25 (6H, m), 7.29-7.34 (4H, m), 7.37 (1H, t, $J = 8.0\text{ Hz}$); ^{13}C NMR (100 MHz, CDCl_3) δ 40.5, 112.8, 117.3, 126.7, 127.7, 128.7, 129.0, 132.5, 138.8, 125.5; ESIHRMS: Found: m/z 284.1443. Calcd for $\text{C}_{21}\text{H}_{18}\text{N}$: ($\text{M}+\text{H}$) $^+$ 284.1439.

5.2.1.2 Method 2: Pd-catalyzed Suzuki-coupling of 2-bromomethylbenzonitrile with arylboronic acids⁶⁶

A typical procedure for synthesis of 2-(biphenyl-4-ylmethyl)benzonitrile (1b)

A flask was charged with Pd(OAc)₂ (11.2 mg, 0.049 mmol), PPh₃ (26.2 mg, 0.099 mmol), biphenyl-4-ylboronic acid (1.49 g, 7.52 mmol), and K₃PO₄ (4.25 g, 20.0 mmol). The flask was evacuated and back filled with argon, and then the 2-(bromomethyl)benzonitrile (0.980 g, 5.00 mmol) in toluene (15 mL) were added. The reaction mixture was stirred at 80 °C for 9 h. When all the starting material has been consumed, the reaction mixture was quenched with water. The organic materials were extracted with Et₂O. The combined organic extracts were washed with water, and 1N NaOH solution and then with brine and dried over anhydrous MgSO₄. The solvents were removed in vacuo and the resulting crude material was subjected to flash column chromatography (hexane : EtOAc = 80 : 20) to afford 2-(biphenyl-4-ylmethyl)benzonitrile (1.27 g, 4.72 mmol) in 94% yield.

2-(biphenyl-4-ylmethyl)benzonitrile (1b)

White solid; mp. 112.9-113.8 °C; IR (NaCl) 3063, 3019, 2226, 1601, 1520, 1487, 1450 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 4.24 (2H, s), 7.30-7.35 (5H, m), 7.42 (2H, dd, *J* = 7.6, 7.6 Hz), 7.49-7.57 (5H, m), 7.65 (1H, d, *J* = 6.8 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 39.8, 112.6, 118.2, 126.8, 127.0, 127.2, 127.4, 128.7, 129.3, 130.0, 132.9 (overlapped), 137.8, 139.6, 140.7, 144.8; ESIHRMS: Found: *m/z* 270.1287. Calcd for C₂₀H₁₆N: (M+H)⁺ 270.1283.

2-(4-chlorobenzyl)benzonitrile (1c)

75% yield from 2-(bromomethyl)benzonitrile and 4-chlorophenylboronic acid; Colorless oil; IR (NaCl) 3065, 3048, 3028, 2222, 1493, 1483, 1447, 1408, 718 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 4.17 (2H, s), 7.16 (2H, d, $J = 8.4$ Hz), 7.25-7.29 (3H, m), 7.32 (1H, ddd, $J = 7.6, 7.6, 1.2$ Hz), 7.51 (1H, ddd, $J = 7.6, 7.6, 1.2$ Hz), 7.65 (1H, dd, $J = 7.6, 1.2$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 39.4, 112.4, 118.0, 127.0, 128.8, 129.9, 130.2, 132.5, 132.9, 133.0, 137.2, 144.2; ESIHRMS: Found: m/z 228.0588. Calcd for $\text{C}_{14}\text{H}_{11}\text{NCl}$: $(\text{M}+\text{H})^+$ 228.0580.

2-(4-(trifluoromethyl)benzyl)benzonitrile (1d)

86% yield from 2-(bromomethyl)benzonitrile and 4-trifluoromethylphenylboronic acid; Colorless oil; IR (NaCl) 3069, 2934, 2224, 1618, 1599, 1487, 1449, 1323 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 4.26 (2H, s), 7.28 (1H, d, $J = 8.0$ Hz), 7.33-7.36 (3H, m), 7.52-7.58 (3H, m), 7.66 (1H, dd, $J = 7.6, 1.2$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 39.9, 112.6, 117.9, 124.1 (q, $^1J_{\text{C-F}} = 270.2$ Hz), 125.6 (q, $^3J_{\text{C-F}} = 3.7$ Hz), 127.2, 129.2 (q, $^2J_{\text{C-F}} = 32.4$ Hz), 129.2, 130.0, 133.0, 133.1, 142.8, 143.7; ESIHRMS: Found: m/z 262.0844. Calcd for $\text{C}_{15}\text{H}_{11}\text{NF}_3$: $(\text{M}+\text{H})^+$ 262.0844.

2-(4-methoxybenzyl)benzonitrile (1e)⁶⁷

56% yield from 2-(bromomethyl)benzonitrile and 4-methoxyphenylboronic acid; ^1H NMR (400 MHz, CDCl_3) δ 3.78 (3H, s), 4.14 (2H, s), 6.84 (2H, d, $J = 8.8$ Hz), 7.15 (2H, d, $J = 8.8$ Hz), 7.25-7.31 (2H, m), 7.48 (1H, ddd, $J = 8.0, 7.6, 1.6$ Hz), 7.62 (1H, dd, $J = 7.6, 1.2$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 39.3, 55.2, 112.4, 114.1, 118.2, 126.7, 129.8, 129.9, 130.8, 132.8, 132.9, 145.4, 158.3.

2-(4-methylbenzyl)benzonitrile (1f)⁶⁸

81% yield from 2-(bromomethyl)benzonitrile and 4-methylphenylboronic acid; ^1H NMR (400 MHz, CDCl_3) δ 2.32 (3H, s), 4.16 (2H, s), 7.10-7.14 (4H, m), 7.25-7.30 (2H, m), 7.48 (1H, ddd, $J = 8.0, 7.6, 1.6$ Hz), 7.62 (1H, dd, $J = 7.6, 0.8$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 21.0, 39.8, 112.5, 118.2, 126.7, 128.9, 129.4 (overlapped), 130.0, 132.9, 135.7, 136.3, 145.3.

2-(benzo[d][1,3]dioxol-5-ylmethyl)benzonitrile (1g)

To a flask including 2-(bromomethyl)benzonitrile (0.199 g, 1.02 mmol) in dimethoxyethane (5 mL) was added benzo[d][1,3]dioxol-5-ylboronic acid (0.182 g, 1.09 mmol), CsF (0.383 g, 2.52 mmol), and $\text{Pd}(\text{Ph}_3)_4$ (46.2 mg, 0.0400 mmol). The mixture was stirred at 110 °C for 2.5 h. When all the starting material was consumed, the reaction was quenched with water at 0 °C. The organic materials were extracted thrice with EtOAc. The combined organic extracts were washed with 5% aqueous NaOH solution, water and brine. After that they were dried over anhydrous MgSO_4 . The solvents were removed in vacuo and the resulting crude material was subjected to flash column chromatography (hexane : EtOAc = 95 : 5) to afford 2-(benzo[d][1,3]dioxol-5-ylmethyl)benzonitrile (0.19 g, 0.80 mmol) in 78% yield.

Colorless oil; IR (NaCl) 3066, 2895, 2223, 1598, 1502 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 4.11 (2H, s), 5.92 (2H, s), 6.68-6.76 (3H, m), 7.26-7.32 (2H, m), 7.50 (1H, ddd, $J = 8.0, 7.6, 1.2$ Hz), 7.63 (1H, dd, $J = 8.0, 1.2$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 39.8, 101.0, 108.4, 109.3, 112.4, 118.1, 122.0, 126.8, 129.9, 132.5, 132.9 (overlapped), 145.0, 146.3, 147.9; ESIHRMS: Found: m/z 238.0861. Calcd for $\text{C}_{13}\text{H}_{12}\text{NO}_2$: $(\text{M}+\text{H})^+$ 238.0868.

2-(2-methylbenzyl)benzonitrile (1h)

69% yield from 2-(bromomethyl)benzonitrile and 2-methylphenylboronic acid; Colorless oil; IR (NaCl) 3065, 3019, 2947, 2922, 2224, 1599, 1485, 1450 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 2.24 (3H, s), 4.21 (2H, s), 7.02 (1H, d, $J = 8.0$ Hz), 7.04 (1H, d, $J = 6.4$ Hz), 7.16-7.21 (3H, m), 7.30 (1H, dd, $J = 7.6, 7.6$ Hz), 7.44 (1H, ddd, $J = 7.6, 7.6, 1.2$ Hz), 7.66 (1H, dd, $J = 7.6, 1.2$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 19.6, 37.5, 112.7, 118.0, 126.2, 126.6, 127.1, 129.4, 129.9, 130.5, 132.7, 132.8, 136.6, 136.7, 144.3; ESIHRMS: Found: m/z 208.1128. Calcd for $\text{C}_{15}\text{H}_{14}\text{N}$: $(\text{M}+\text{H})^+$ 208.1126.

2-(naphthalen-1-ylmethyl)benzonitrile (1i)

56% yield from 2-(bromomethyl)benzonitrile and 1-naphthylboronic acid; Colorless oil; IR (NaCl) 3063, 3048, 3009, 2972, 2222, 1597, 1508, 1485, 1450 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 4.66 (2H, s), 6.98 (1H, d, $J = 7.6$ Hz), 7.26-7.28 (2H, m), 7.35 (1H, ddd, $J = 8.0, 7.6, 1.6$ Hz), 7.41-7.48 (3H, m), 7.69 (1H, dd, $J = 7.6, 1.2$ Hz), 7.80 (1H, d, $J = 8.4$ Hz), 7.86-7.89 (2H, m); ^{13}C NMR (100 MHz, CDCl_3) δ 37.1, 112.4, 118.1, 123.8, 125.5, 125.8, 126.3, 126.7, 127.7, 127.8,

128.8, 129.6, 131.8, 132.8, 132.9, 133.9, 134.2, 144.4; ESIHRMS: Found: m/z 244.1121. Calcd for $C_{18}H_{14}N$: $(M+H)^+$ 244.1126.

2-benzyl-5-methoxybenzonitrile (**1l**)

72% yield from 2-(bromomethyl)-5-methoxybenzonitrile (**10l**) and phenylboronic acid; Brown oil; IR (NaCl) 3061, 3028, 2941, 2218, 1608, 1599, 1568, 1248 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$) δ 3.79 (3H, s), 4.16 (2H, s), 6.74 (1H, d, $J = 3.2$ Hz), 6.79 (1H, dd, $J = 11.6, 3.2$ Hz), 7.21-7.34 (5H, m), 7.57 (1H, d, $J = 11.6$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 40.3, 55.4, 104.3, 112.3, 115.8, 118.6, 126.7, 128.7, 128.9, 134.6, 138.6, 147.1, 162.9; ESIHRMS: Found: m/z 224.1083. Calcd for $C_{15}H_{14}NO$: $(M+H)^+$ 224.1075.

2-benzyl-1-methyl-1H-indole-3-carbonitrile (**1o**)

Prepared from 2-(bromomethyl)-1-methyl-1H-indole-3-carbonitrile (**10o**) by the same method with compound **1g**.

66% yield; Yellow solid; mp. 58.3-60.6 $^{\circ}C$; IR (NaCl) 3010, 2212, 1643, 1473 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$) δ 3.57 (3H, s), 4.33 (2H, s), 7.17 (2H, d, $J = 7.2$ Hz), 7.22-7.32 (6H, m), 7.71-7.74 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.6, 32.3, 86.1, 109.9, 116.5, 119.4, 122.1, 123.4, 127.0, 127.1, 128.2, 129.0, 136.0, 136.6, 147.2; ESIHRMS: Found: m/z 247.1235. Calcd for $C_{17}H_{15}N_2$: $(M+H)^+$ 247.1235.

1,2-dimethyl-1H-indole-3-carbonitrile (**9o**)

Prepared by the following procedure in 91% yield.

To a solution of THF (18 mL) of 2-methyl-1*H*-indole-3-carbonitrile⁶⁹ (0.845 g, 5.41 mmol) was added NaH (60% dispersion in mineral oil, 0.324 g, 8.10 mmol). The reaction mixture was stirred at 0 °C for 15 min, and at room temperature for another 1 h. After that MeI (0.45 mL, 7.2 mmol) was added. The reaction mixture was stirred at room temperature for 30 min. When all the starting material was consumed, as checked by TLC, the reaction mixture was quenched with NH₄Cl solution. The organic materials were extracted with ether. The combined organic extracts were washed with water and brine, and dried over anhydrous MgSO₄. The solvents were removed in vacuo and the resulting crude material was subjected to flash column chromatography (hexane : EtOAc : CH₂Cl₂ = 90 : 10 : 5) to afford 1,2-dimethyl-1*H*-indole-3-carbonitrile (0.835 g, 4.91 mmol) in 91% yield.

Yellow solid; mp. 104.6-105.7 °C ; IR (NaCl) 3016, 2212, 1639, 1544, 1477, 1215 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 2.57 (3H, s), 3.70 (3H, s), 7.21-7.33 (3H, m), 7.62-7.68 (1H, m); ¹³C NMR (100 MHz, CDCl₃) δ 12.0, 30.2, 84.8, 109.7, 116.5, 119.0, 121.9, 123.0, 127.0, 136.3, 145.6; ESIHRMS: Found: m/z 171.0925. Calcd for C₁₁H₁₁N₂: (M+H)⁺ 171.0922.

2-(bromomethyl)-1-methyl-1*H*-indole-3-carbonitrile (10o)

Prepared from 1,2-dimethyl-1*H*-indole-3-carbonitrile (**9o**) by the reaction with NBS in the presence of a catalytic amount of (PhCO₂)₂ in 64% yield.

Yellow solid; mp. 159.0-160.3 °C ; IR (NaCl) 3018, 2218, 1635, 1477, 1215 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 3.85 (3H, s), 4.74 (2H, s), 7.28-7.33 (1H, m), 7.36-7.41 (2H, m), 7.72 (1H, d, *J* = 8.0 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 19.8, 30.6, 87.0, 110.3, 114.9, 120.0, 122.7, 124.8, 126.6, 137.1, 141.8; ESIHRMS: Found: m/z 249.0045. Calcd for C₁₁H₁₀N₂Br: (M+H)⁺ 249.0027.

2-benzylthiophene-3-carbonitrile (**1p**)

Prepared from 2-(bromomethyl)thiophene-3-carbonitrile (**10p**) with same method with compound **1g**.

69% yield; Colorless oil; IR (NaCl) 2252, 1643 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 4.31 (2H, s), 7.13 (1H, d, $J = 5.6$ Hz), 7.17 (1H, d, $J = 5.6$ Hz), 7.27-7.29 (3H, m), 7.32-7.34 (2H, m); ^{13}C NMR (100 MHz, CDCl_3) δ 35.4, 108.5, 115.0, 125.0, 127.2, 128.3, 128.6, 128.9, 138.2, 156.0; ESIHRMS: Found: m/z 200.0507. Calcd for $\text{C}_{12}\text{H}_{10}\text{NS}$: $(\text{M}+\text{H})^+$ 200.0534.

2-methylthiophene-3-carbonitrile (**9p**)

Prepared by the following procedure⁷⁰ in 64% yield.

To a flask including with LDA prepared by diisopropylamine (2.3 mL, 16.4 mmol) and BuLi (1.6 M, 9.6 mL, 15.4 mmol) in THF (19 mL), was added thiophene-3-carbonitrile (1.60 g, 14.7 mmol) at -78 $^{\circ}\text{C}$. The mixture was stirred at the same temperature for 1 h. MeI (1.0 mL, 16.1 mmol) was added at -78 $^{\circ}\text{C}$. The reaction mixture was stirred at room temperature for 1 h, and then quenched with saturated aqueous NH_4Cl solution. The organic materials were extracted three times with Et_2O . The combined organic extracts were washed with brine and dried over anhydrous MgSO_4 . The solvents were removed in vacuo and the resulting crude material was subjected to flash column chromatography (hexane : $\text{EtOAc} = 95 : 5$) to afford 2-methylthiophene-3-carbonitrile (1.16 g, 9.42 mmol) in 64% yield.

Colourless oil; IR (NaCl) 2945, 2227, 1637, 1448 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 2.66 (3H, s), 7.09 (1H, d, $J = 5.2$ Hz), 7.13 (1H, d, $J = 5.2$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 14.6, 109.1, 115.0, 124.0, 128.2, 151.4; ESIHRMS: Found: m/z 124.0204. Calcd for $\text{C}_6\text{H}_6\text{NS}$: $(\text{M}+\text{H})^+$ 124.0221.

2-(bromomethyl)thiophene-3-carbonitrile (**10p**)

Prepared from 2-methylthiophene-3-carbonitrile (**9p**) by the reaction with NBS in the presence of a catalytic amount of (PhCO₂)₂ in 64% yield.

White solid; mp. 71.7-72.7 °C; IR (NaCl) 2223, 1635 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 4.79 (2H, s), 7.17 (1H, d, *J* = 5.6 Hz), 7.38 (1H, d, *J* = 5.6 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 22.3, 110.6, 113.7, 127.4, 128.8, 150.7; ESIHRMS: Found: *m/z* 201.9330. Calcd for C₆H₅NSBr: (M+H)⁺ 201.9326.

5.2.1.3 Method 3: Mn(II)-catalyzed coupling of 2-chlorobenzonitrile with alkyl Grignard reagents⁷¹

A typical procedure for synthesis of 2-butylbenzonitrile (**1r**)⁷¹

To a THF solution (38 mL) of 2-chlorobenzonitrile (2.06 g, 15.0 mmol) was added butylmagnesium bromide solution (1.0 M, 30.0 mL, 30.0 mmol) and MnCl₂ (188.7 mg, 1.50 mmol). After stirring at 0 °C for 1 h, the starting materials were consumed, as checked by TLC, and the reaction mixture was quenched with NH₄Cl solution. The organic materials were extracted with ether. The combined organic extracts were washed with water and brine and dried over anhydrous MgSO₄. The solvents were removed in vacuo and the resulting crude material was subjected to flash column chromatography (hexane : EtOAc = 95 : 5) to afford 2-butylbenzonitrile (**1p**) (1.63 g, 10.2 mmol) in 68% yield.

68% yield; ¹H NMR (400 MHz, CDCl₃) δ 0.95 (3H, t, *J* = 7.2 Hz), 1.40 (2H, m), 1.63-1.70 (2H, m), 2.84 (2H, t, *J* = 7.6 Hz), 7.25-7.32 (2H, m), 7.50 (1H, ddd, *J* = 7.6, 7.6, 1.6 Hz), 7.60 (1H, dd, *J* = 7.6, 1.6 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 13.8, 22.3, 33.0, 34.3, 112.3, 118.2, 126.2, 129.4, 132.6, 132.7, 146.8.

2-isobutylbenzonitrile (1s)

40% yield from 2-chlorobenzonitrile and isobutylmagnesium bromide; Colorless Oil; IR (NaCl) 2959, 2930, 2901, 2224, 1485, 1466, 1448 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 0.95 (6H, d, $J = 6.4$ Hz), 1.94-2.04 (1H, m), 2.71 (2H, d, $J = 7.2$ Hz), 7.27-7.30 (2H, m), 7.50 (1H, ddd, $J = 7.6, 7.6, 1.2$ Hz), 7.61 (1H, dd, $J = 8.0, 1.2$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 22.2, 30.2, 43.6, 112.7, 118.4, 126.3, 130.2, 132.4, 132.7, 145.6; ESIHRMS: Found: m/z 160.1133. Calcd for $\text{C}_{13}\text{H}_{14}\text{N}$: $(\text{M}+\text{H})^+$ 160.1126.

2-cyclohexylbenzonitrile (1t)⁷¹

88% yield from 2-chlorobenzonitrile and cyclohexylmagnesium bromide; ^1H NMR (400 MHz, CDCl_3) δ 1.25-1.51 (5H, m), 1.77-1.92 (5H, m), 2.95-3.01 (1H, m), 7.24-7.28 (1H, m), 7.36 (1H, d, $J = 8.0$ Hz), 7.53 (1H, ddd, $J = 7.6, 8.0, 1.2$ Hz), 7.60 (1H, dd, $J = 7.6, 1.2$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 25.9, 26.6, 33.7, 42.7, 111.8, 118.2, 126.2, 126.5, 132.8, 132.9, 151.5.

5.2.1.4 Method 4: Synthesis of 2,2-dimethyl-4-phenylbutanenitrile (1u)⁷²

To a flask charged with LDA, which was freshly prepared by diisopropylamine (4.6 mL, 32.8 mmol) and *n*-BuLi (1.6 M, 19.6 mL, 31.3 mmol) in THF (40 mL), was added isobutyronitrile (2.7 mL, 30.0 mmol) at -78 $^{\circ}\text{C}$. The mixture was stirred at the same temperature for 1 h. After that (2-bromoethyl)benzene (4.5 mL, 33.3 mmol) was added at -78 $^{\circ}\text{C}$. The reaction

mixture was stirred at room temperature for overnight, and then quenched with saturated aqueous NH_4Cl . The organic materials were extracted with Et_2O . The combined organic extracts were washed with brine and dried over anhydrous MgSO_4 . The solvents were removed in vacuo and the resulting crude material was subjected to flash column chromatography (hexane : EtOAc = 95 : 5) to afford 2,2-dimethyl-4-phenylbutanenitrile (**1s**) (2.85 g, 16.4 mmol) in 55% yield.

55% yield; ^1H NMR (400 MHz, CDCl_3) δ 1.40 (6H, s), 1.80-1.84 (2H, m), 2.78-2.82 (2H, m), 7.19-7.32 (5H, m); ^{13}C NMR (100 MHz, CDCl_3) δ 26.7, 31.8, 32.4, 43.0, 124.8, 126.2, 128.3, 128.5, 140.8.

5.2.2 $\text{Cu}(\text{OAc})_2$ -catalyzed methylene oxygenation

5.2.2.1 A typical procedure for synthesis of 1,2-diacylbenzenes **3**

To an ice-cooled solution of 2-benzylbenzonitrile (**1a**) (98.4 mg, 0.509 mmol) in Et_2O (0.5 mL) was added an Et_2O solution of *p*-tolylmagnesium bromide (**2a**) (1.0 M, 0.7 mL, 0.7 mmol). The reaction mixture was stirred at $60\text{ }^\circ\text{C}$ in a sealed tube for 2 h, and then anhydrous MeOH (62 μL) was added. $\text{Cu}(\text{OAc})_2$ (9.4 mg, 0.051 mmol) and anhydrous DMF (5.1 mL) was then added. The reaction mixture was stirred at $80\text{ }^\circ\text{C}$ under an oxygen atmosphere for 8.5 h. The reaction was quenched with 3N aqueous HCl solution, and the reaction mixture was stirred at $80\text{ }^\circ\text{C}$ for 2 h. The organic materials were extracted with Et_2O . The combined organic extracts were washed with water, and then with brine and dried over anhydrous MgSO_4 . The solvents were removed in vacuo and the resulting crude material was purified by flash column chromatography (hexane : EtOAc = 80 : 20) to afford (2-benzoylphenyl)(*p*-tolyl)methanone (**3aa**) (124.6 mg, 0.415 mmol) in 82% yield.

(2-benzoylphenyl)(*p*-tolyl)methanone (3aa)

White granular crystal; mp. 147.0-147.8 °C; IR (ATR) 1670, 1655, 1595, 1568 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 2.38 (3H, s), 7.17 (2H, d, *J* = 8.0 Hz), 7.37 (2H, dd, *J* = 7.6, 7.6 Hz), 7.51 (1H, dd, *J* = 7.2, 7.6 Hz), 7.59-7.61 (6H, m), 7.70 (2H, d, *J* = 8.0 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 21.7, 128.3, 129.0, 129.5, 129.6, 129.8, 130.0, 130.1, 130.3, 132.9, 134.6, 137.2, 139.9, 140.3, 143.9, 196.2, 196.6; ESIHRMS: Found: *m/z* 301.1254. Calcd for C₂₁H₁₇O₂: (M+H)⁺ 301.1229.

By quenching with pH 9 ammonium buffer, 1,2-dibenzoylbenzene **3aa** and 1*H*-isoindol-1-ol **4aa** were isolated in 34% and 58% yield, respectively.

1-phenyl-3-*p*-tolyl-1*H*-isoindol-1-ol (4aa)

58% yield; White granular crystal; mp. 196.8-197.6 °C; IR (NaCl) 3584, 3067, 3019, 1543, 1512, 1190 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 2.48 (3H, s), 5.20 (1H, br), 7.20-7.22 (3H, m), 7.37-7.51 (7H, m), 7.68-7.70 (1H, m), 7.90 (2H, d, *J* = 8.0 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 21.6, 100.9, 123.3, 123.6, 125.3, 127.8, 128.3, 128.5, 128.7, 129.5, 129.9, 130.6, 136.4, 140.8, 141.3, 155.0, 171.4; ESIHRMS: Found: *m/z* 300.1393. Calcd for C₂₁H₁₈NO: (M+H)⁺ 300.1388.

(2-benzoylphenyl)(4-methoxyphenyl)methanone (3ab)

89% yield; Yellow Solid; mp. 118.6-119.1 °C; IR (NaCl) 3019, 1655, 1599, 1578, 1508, 1260 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 3.84 (3H, s), 6.85 (2H, d, *J* = 8.8 Hz), 7.36 (2H, dd, *J* = 8.0, 7.6 Hz), 7.51 (1H, dd, *J* = 7.6, 7.2 Hz), 7.58-7.62 (4H,

m), 7.67-7.70 (4H, m); ^{13}C NMR (100 MHz, CDCl_3) δ 55.5, 113.6, 128.2, 129.3, 129.6, 129.8, 130.0, 130.2, 130.3, 132.2, 132.9, 137.2, 139.7, 140.4, 163.5, 195.2, 196.7; ESIHRMS: Found: m/z 317.1186. Calcd for $\text{C}_{21}\text{H}_{17}\text{O}_3$: $(\text{M}+\text{H})^+$ 317.1178.

(2-benzoylphenyl)(2-methoxyphenyl)methanone (3ac)

49% yield; Yellow solid; mp. 128.4-129.4 °C; IR (NaCl) 3061, 1666, 1597, 1485, 1257 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 3.66 (3H, s), 6.86 (1H, d, $J = 8.4$ Hz), 6.91 (1H, ddd, $J = 7.2, 7.6, 0.8$ Hz), 7.230 (1H, dd, $J = 7.6, 2.0$ Hz), 7.35 (2H, dd, $J = 7.6, 7.6$ Hz), 7.42 (1H, ddd, $J = 8.4, 7.6, 2.0$), 7.47-7.55 (3H, m), 7.60-7.63 (2H, m), 7.69-7.72 (2H, m); ^{13}C NMR (100 MHz, CDCl_3) δ 55.5, 111.5, 120.5, 127.8, 128.2, 128.6, 129.4, 129.7, 130.2, 131.0, 131.4, 132.7, 133.2, 137.3, 139.7, 140.4, 158.0, 196.4, 197.2; ESIHRMS: Found: m/z 317.1179. Calcd for $\text{C}_{21}\text{H}_{17}\text{O}_3$: $(\text{M}+\text{H})^+$ 317.1178.

(2-benzoylphenyl)(4-chlorophenyl)methanone (3ad)

91% yield; White Solid; mp. 196.6-140.2 °C; IR (NaCl) 3065, 3019, 1661, 1589, 669 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.35 (2H, d, $J = 8.8$ Hz), 7.40 (2H, dd, $J = 8.0, 7.6$ Hz), 7.54 (1H, dd, $J = 7.6, 7.2$ Hz), 7.58-7.67 (6H, m), 7.70 (2H, dd, $J = 8.4, 6.8$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 128.3, 128.7, 129.3, 129.8 (overlapped), 130.4, 130.5, 131.1, 133.1, 135.6, 137.1, 139.5, 139.7, 139.8, 195.3, 196.3; ESIHRMS: Found: m/z 321.0684. Calcd for $\text{C}_{20}\text{H}_{14}\text{O}_2\text{Cl}$: $(\text{M}+\text{H})^+$ 321.0682.

(2-benzoylphenyl)(4-fluorophenyl)methanone (3ae)

60% yield; Yellow viscous oil; IR (NaCl) 1660, 1598, 1504, 1278, 1149 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.04 (2H, dd, $J = 8.8, 8.4$ Hz), 7.39 (2H, dd, $J = 8.0, 7.6$ Hz), 7.53 (1H, t, $J = 7.6$ Hz), 7.58-7.66 (4H, m), 7.69-7.75 (4H, m); ^{13}C NMR (100 MHz, CDCl_3) δ 115.5 (d, $^2J_{\text{C-F}} = 21.9$ Hz), 128.4, 129.3, 129.8, 129.9, 130.3, 130.5, 132.3 (d, $^3J_{\text{C-F}} = 9.3$ Hz), 133.1, 133.6 (d, $^4J_{\text{C-F}} = 2.9$ Hz), 137.1, 139.8, 140.0, 165.7 (d, $^1J_{\text{C-F}} = 253.6$ Hz), 195.1, 196.4; ESIHRMS: Found: m/z 305.0976. Calcd for $\text{C}_{20}\text{H}_{14}\text{O}_2\text{F}$: $(\text{M}+\text{H})^+$ 305.0978.

(2-(1-naphthoyl)phenyl)(phenyl)methanone (3af)

77% yield; Yellow viscous oil; IR (NaCl) 1654, 1595, 1508, 1448, 1280 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.30 (2H, dd, $J = 8.0, 7.6$ Hz), 7.37-7.50 (4H, m), 7.55-7.70 (3H, m), 7.62-7.70 (4H, m), 7.83 (1H, d, $J = 7.2$ Hz), 7.94 (1H, d, $J = 8.0$ Hz), 8.29 (1H, d, $J = 8.0$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 123.9, 125.7, 126.4, 127.7, 128.1, 128.2, 128.9, 129.4, 130.0, 130.4, 130.8, 130.9, 131.3, 132.8, 133.0, 133.5, 135.1, 137.2, 140.5, 141.0, 196.9, 197.4; ESIHRMS: Found: m/z 337.1230. Calcd for $\text{C}_{24}\text{H}_{17}\text{O}_2$: $(\text{M}+\text{H})^+$ 337.1229.

(2-(2-naphthoyl)phenyl)(phenyl)methanone (3ag)

71% yield; Yellow solid; mp. 172.3-173.3 $^{\circ}\text{C}$; IR (NaCl) 3063, 3019, 1659, 1628, 1597, 1522 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.35 (2H, dd, $J = 7.6, 7.6$ Hz), 7.48

(1H, d, $J = 7.6$ Hz), 7.51 (1H, d, $J = 7.2$ Hz), 7.58 (1H, dd, $J = 8.4, 7.6$ Hz), 7.64-7.72 (6H, m), 7.80-7.86 (4H, m), 8.16 (1H, s); ^{13}C NMR (100 MHz, CDCl_3) δ 124.9, 126.7, 127.7, 128.3, 128.4, 128.5, 129.5, 129.7 (overlapped), 129.8, 130.3, 130.4, 132.1, 130.0, 134.6, 135.4, 137.1 (overlapped), 140.0, 140.2, 196.5, 196.6; ESIHRMS: Found: m/z 337.1227. Calcd for $\text{C}_{24}\text{H}_{17}\text{O}_2$: $(\text{M}+\text{H})^+$ 337.1229.

(2-benzoylphenyl)(thiophen-2-yl)methanone (3ah)

63% yield; Pink solid; mp. 132.5-133.3 °C; IR (NaCl) 3065, 3019, 1661, 1643, 1514, 1449, 1412 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.06 (1H, dd, $J = 4.0, 5.2$ Hz), 7.37 (2H, dd, $J = 8.0, 7.6$ Hz), 7.48 (1H, dd, $J = 4.0, 1.2$ Hz), 7.51 (1H, dd, $J = 7.6, 7.2$ Hz), 7.62-7.765 (4H, m), 7.69-7.75 (3H, m); ^{13}C NMR (100 MHz, CDCl_3) δ 127.9, 128.3, 129.0, 129.7, 129.8, 130.4, 130.5, 133.0, 134.8, 134.9, 137.1, 139.5, 139.7, 144.0, 188.2, 196.5; ESIHRMS: Found: m/z 293.0645. Calcd for $\text{C}_{18}\text{H}_{13}\text{O}_2\text{S}$: $(\text{M}+\text{H})^+$ 293.0636.

(2-benzoylphenyl)(3-chlorophenyl)methanone (3ai)

88% yield; Pale yellow oil; IR (NaCl) 1663, 1570, 1449 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.32 (1H, dd, $J = 7.8, 7.8$ Hz), 7.40 (2H, m), 7.47 (1H, ddd, $J = 8.0, 2.1, 1.1$ Hz), 7.54 (1H, dd, $J = 7.4, 7.4$ Hz), 7.58-7.66 (6H, m), 7.70 (2H, dd, $J = 8.0, 1.1$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 127.8, 128.9, 129.4, 129.5, 129.7, 129.8, 129.9, 130.5, 130.7, 132.9, 133.1, 134.6, 137.0, 138.8, 139.6, 139.8, 195.3, 196.3; ESIHRMS: Found: m/z 321.0686. Calcd for $\text{C}_{20}\text{H}_{14}\text{O}_2\text{Cl}$: $(\text{M}+\text{H})^+$ 321.0682.

(2-benzoylphenyl)(4-(trifluoromethyl)phenyl)methanone (3aj)

71% yield; Pale yellow oil; IR (NaCl) 3065, 1661, 1595, 1449, 1410, 1173, 1134 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.40 (2H, dd, $J = 7.9, 7.6$ Hz), 7.54 (1H, dd, $J = 7.4, 7.4$ Hz), 7.58-7.62 (1H, m), 7.63-7.66 (5H, m), 7.71 (2H, dd, $J = 7.0, 1.4$ Hz), 7.82 (2H, d, $J = 8.1$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 123.5 (q, $^1J_{\text{C-F}} = 271$ Hz), 125.6 (q, $^3J_{\text{C-F}} = 3.7$ Hz), 128.4, 129.5, 129.8, 129.9 (overlapped), 130.0, 130.7, 133.2, 134.1 (d, $^2J_{\text{C-F}} = 32.4$ Hz), 136.9, 139.4, 139.8, 139.9; ESIHRMS: Found: m/z 355.0946. Calcd for $\text{C}_{21}\text{H}_{14}\text{O}_2\text{F}_3$: $(\text{M}+\text{H})^+$ 355.0946.

biphenyl-4-yl(2-(4-methylbenzoyl)phenyl)methanone (3ba)

82% yield; Yellow solid; mp. 162.9-164.0 $^{\circ}\text{C}$; IR (NaCl) 2924, 1651, 1605, 1487, 1449 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 2.38 (3H, s), 7.17 (2H, d, $J = 8.0$ Hz), 7.38 (1H, dd, $J = 7.2, 7.2$ Hz), 7.45 (2H, dd, $J = 7.2, 7.6$ Hz), 7.58-7.66 (10H, m), 7.78 (2H, d, $J = 8.0$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 21.7, 127.0, 127.3, 128.2, 128.9, 129.0, 129.5, 129.6, 130.0, 130.1, 130.2, 130.4, 134.6, 135.9, 139.9, 140.0, 140.1, 143.9, 145.6, 169.2 (overlapped); ESIHRMS: Found: m/z 377.1531. Calcd for $\text{C}_{27}\text{H}_{21}\text{O}_2$: $(\text{M}+\text{H})^+$ 377.1542.

(2-(4-chlorobenzoyl)phenyl)(p-tolyl)methanone (3ca)

82% yield; Yellow solid; mp. 164.8-165.8 °C; IR (NaCl) 3063, 3026, 1655, 1605, 1587, 1570 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 2.39 (3H, s), 7.18 (2H, d, $J = 8.0$ Hz), 7.34 (2H, d, $J = 8.4$ Hz), 7.57-7.62 (6H, m), 7.64 (2H, d, $J = 8.4$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 21.6, 128.6, 129.1, 129.3, 129.7, 130.0, 130.3, 130.4, 131.1, 134.4, 135.6, 139.4, 139.6, 139.9, 144.0, 195.5, 196.0; ESIHRMS: Found: m/z 335.0842. Calcd for $\text{C}_{21}\text{H}_{16}\text{O}_2\text{Cl}$: $(\text{M}+\text{H})^+$ 335.0839.

(2-(4-methylbenzoyl)phenyl)(4-(trifluoromethyl)phenyl)methanone (3da)

78% yield; Yellow oil; IR (NaCl) 3065, 3030, 1663, 1605, 1593, 1570, 1325, 1312, 1281 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 2.39 (3H, s), 7.19 (2H, d, $J = 8.0$ Hz), 7.59-7.64 (8H, m), 7.81 (2H, d, $J = 8.0$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 21.6, 123.5 (q, $^1J_{\text{C-F}} = 271.1$ Hz), 125.3 (q, $^3J_{\text{C-F}} = 3.6$ Hz), 120.1, 129.4, 129.8, 129.9, 130.0, 130.5, 130.6, 134.1 (q, $^2J_{\text{C-F}} = 32.5$ Hz), 134.4, 139.3, 140.0, 144.2, 195.6, 195.9; ESIHRMS: Found: m/z 369.1104. Calcd for $\text{C}_{22}\text{H}_{16}\text{O}_2\text{F}_3$: $(\text{M}+\text{H})^+$ 369.1102.

(2-(4-methoxybenzoyl)phenyl)(p-tolyl)methanone (3ea)

79% yield; Pale yellow solid; mp. 166.9-167.8 °C; IR (NaCl) 2965, 2936, 1655, 1601, 1576, 1508, 1258 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 2.38 (3H, s), 3.85 (3H, s), 6.85 (2H, d, $J = 8.8$ Hz), 7.17 (2H, d, $J = 8.0$ Hz), 7.59-7.61 (6H, m), 7.68 (2H, d, $J = 8.8$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 21.6, 55.4, 113.5, 129.0, 129.3, 129.4, 129.9, 130.1, 130.1, 130.3, 132.2, 134.7, 140.0, 140.3, 143.8, 163.5, 195.3, 196.3; ESIHRMS: Found: m/z 331.1336. Calcd for $\text{C}_{22}\text{H}_{19}\text{O}_3$: $(\text{M}+\text{H})^+$ 331.1334.

1,2-phenylenebis(p-tolylmethanone) (3fa)

81% yield; Yellow solid; mp. 189.7-191.6 °C; IR (NaCl) 2924, 2872, 1659, 1605, 1570, 1512 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 2.38 (6H, s), 7.17 (4H, d, J = 8.0 Hz), 7.59-7.62 (8H, m); ^{13}C NMR (100 MHz, CDCl_3) δ 21.7, 129.0, 129.5, 130.0, 130.1, 134.7, 140.1, 143.8, 196.3; ESIHRMS: Found: m/z 315.1389. Calcd for $\text{C}_{22}\text{H}_{18}\text{O}_2$: $(\text{M}+\text{H})^+$ 315.1385.

benzo[d][1,3]dioxol-5-yl(2-(4-methylbenzoyl)phenyl)methanone (3ga)

64% yield; Yellow solid; mp. 172.2-173.4 °C; IR (NaCl) 3018, 1647, 1608, 1444, 1215 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 2.38 (3H, s), 5.99 (2H, s), 6.73 (1H, d, J = 8.0 Hz), 7.17 (2H, d, J = 8.0 Hz), 7.23-7.26 (2H, m), 7.56-7.59 (4H, m), 7.61 (2H, d, J = 8.0 Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 21.6, 101.8, 107.5, 109.0, 126.9, 128.9, 129.1, 129.5, 129.8, 130.0, 130.1, 132.0, 134.6, 139.8, 140.3, 143.8, 147.9, 151.8, 194.9, 196.1; ESIHRMS: Found: m/z 345.1126. Calcd for $\text{C}_{22}\text{H}_{17}\text{O}_4$: $(\text{M}+\text{H})^+$ 345.1127.

(2-(2-methylbenzoyl)phenyl)(p-tolyl)methanone (3ha)

58% yield; Yellow oil; IR (NaCl) 3063, 1661, 1607, 1572, 1518 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 2.28 (3H, s), 2.36 (3H, s), 7.11 (1H, dd, J = 7.6, 7.6 Hz), 7.14-7.18 (3H, m), 7.27-7.31 (2H, m), 7.49-7.61 (6H, m); ^{13}C NMR (100 MHz, CDCl_3) δ 20.3, 21.6, 125.0, 128.8, 129.0, 129.7, 129.8, 130.4 (overlapped), 131.1,

131.2, 131.3, 134.7, 137.3, 138.8, 139.9, 140.9, 143.8, 196.6, 197.9; ESIHRMS: Found: m/z 315.1397. Calcd for C₂₂H₁₉O₂: (M+H)⁺ 315.1385.

(2-(1-naphthoyl)phenyl)(p-tolyl)methanone (3ia)

57% yield; Yellow solid; mp. 139.7-140.4 °C; IR (NaCl) 2924, 2868, 1659, 1607, 1593, 1574 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 2.30 (3H, s), 7.04 (2H, d, *J* = 8.0 Hz), 7.37 (1H, dd, *J* = 7.6, 7.6 Hz), 7.41-7.48 (4H, m), 7.52-7.55 (1H, m), 7.57 (2H, d, *J* = 8.0 Hz), 7.62-7.70 (2H, m), 7.80 (1H, d, *J* = 7.6 Hz), 7.92 (1H, d, *J* = 8.0 Hz), 8.27 (1H, d, *J* = 8.4 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 21.6, 123.9, 125.7, 126.4, 127.4, 128.1, 129.0 (overlapped), 129.5, 130.0, 130.5, 130.7, 130.9, 131.4, 132.8, 133.5, 134.9, 135.2, 140.4, 141.2, 143.8, 196.6, 197.4; ESIHRMS: Found: m/z 351.1382. Calcd for C₂₅H₁₉O₂: (M+H)⁺ 351.1385.

(2-benzoyl-6-chlorophenyl)(p-tolyl)methanone (3ja)

76% yield; Yellow oil; IR (NaCl) 3063, 3030, 1662, 1605, 1562, 1449, 1431, 733 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 2.40 (3H, s), 7.23 (2H, d, *J* = 8.0 Hz), 7.42 (2H, dd, *J* = 7.6, 7.6 Hz), 7.47 (1H, d, *J* = 8.0 Hz), 7.52-7.58 (2H, m), 7.62 (1H, dd, *J* = 7.6, 0.8 Hz), 7.69-7.74 (4H, m); ¹³C NMR (100 MHz, CDCl₃) δ 21.8, 128.3, 128.7, 129.3, 129.4, 129.5, 130.3, 132.3, 132.6, 133.2, 134.6, 136.6, 139.3, 140.4, 144.4, 194.5, 194.9; ESIHRMS: Found: m/z 335.0841. Calcd for C₂₁H₁₆O₂Cl: (M+H)⁺ 335.0839.

(2-benzoyl-5-fluorophenyl)(p-tolyl)methanone (3ka)

85% yield; Green viscous oil; IR (NaCl) 3065, 3032, 2992, 1663, 1605, 1582, 1449, 1408, 1281 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 2.38 (3H, s), 7.17 (2H, d, $J = 8.0$ Hz), 7.26-7.30 (2H, m), 7.37 (2H, dd, $J = 7.6, 7.6$ Hz), 7.51 (1H, t, $J = 7.6$ Hz), 7.56 (2H, d, $J = 8.0$ Hz), 7.64 (1H, dd, $J_{\text{H-F}} = 5.2$ Hz, $J_{\text{H-H}} = 8.4$ Hz), 7.68 (2H, d, $J = 7.6$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 21.6, 116.6 (d, $^2J_{\text{C-F}} = 23.1$ Hz), 116.8 (d, $^2J_{\text{C-F}} = 21.4$ Hz), 128.4, 129.0, 129.6, 129.9, 132.1 (d, $^3J_{\text{C-F}} = 8.4$ Hz), 133.2, 134.4, 135.7 (d, $^4J_{\text{C-F}} = 3.3$ Hz), 136.6, 142.9 (d, $^3J_{\text{C-F}} = 6.8$ Hz), 144.0, 163.3 (d, $^1J_{\text{C-F}} = 252.8$ Hz), 194.7, 195.2; ESIHRMS: Found: m/z 319.1140. Calcd for $\text{C}_{21}\text{H}_{16}\text{O}_2\text{F}$: (M+H) $^+$ 319.1134.

(2-benzoyl-5-methoxyphenyl)(p-tolyl)methanone (3la)

79% yield; Colorless viscous oil; IR (NaCl) 2968, 2941, 1663, 1653, 1597, 1566, 1287 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 2.38 (3H, s), 3.89 (3H, s), 7.03 (1H, dd, $J = 8.4, 2.4$ Hz), 7.07 (1H, d, $J = 2.4$ Hz), 7.16 (2H, d, $J = 8.0$ Hz), 7.34 (2H, dd, $J = 8.0, 7.6$ Hz), 7.48 (1H, t, $J = 7.6$ Hz), 7.55 (2H, d, $J = 8.4$ Hz), 7.62 (1H, d, $J = 8.4$ Hz), 7.70 (2H, dd, $J = 8.4, 1.2$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 21.6, 55.7, 144.6, 144.7, 128.3, 128.9, 129.4, 129.9, 131.3, 132.5, 132.9, 135.0, 137.1, 143.2, 143.3, 161.6, 194.8, 196.7; ESIHRMS: Found: m/z 331.1337. Calcd for $\text{C}_{22}\text{H}_{19}\text{O}_3$: (M+H) $^+$ 331.1334.

(2-benzoyl-5-(benzyloxy)phenyl)(p-tolyl)methanone (3ma)

57% yield; Yellow oil; IR (NaCl) 3065, 1651, 1597, 1564, 1449, 1285 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 2.38 (3H, s), 5.16 (2H, s), 7.12 (1H, dd, $J = 8.4, 2.4$ Hz), 7.16-7.18 (3H, m), 7.32-7.42 (7H, m), 7.49 (1H, dd, $J = 7.2, 7.2$ Hz), 7.56 (2H, d, $J = 8.4$ Hz), 7.62 (1H, d, $J = 8.8$ Hz), 7.69 (2H, dd, $J = 1.2, 8.4$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 21.6, 70.4, 115.5, 115.6, 127.5, 128.3, 128.4, 128.7, 128.9, 129.5, 129.9, 131.8, 132.4, 132.9, 135.1, 135.9, 137.1, 143.1, 143.4, 160.6, 194.9, 196.6; ESIHRMS: Found: m/z 407.1642. Calcd for $\text{C}_{28}\text{H}_{23}\text{O}_3$: $(\text{M}+\text{H})^+$ 407.1647.

(2-benzoylnaphthalen-1-yl)(p-tolyl)methanone (3na)

63% yield; Colorless viscous oil; IR (NaCl) 3154, 3063, 3030, 1661, 1605, 1466, 1449 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 2.36 (3H, s), 7.16 (2H, d, $J = 8.0$ Hz), 7.41 (2H, dd, $J = 7.6, 7.6$ Hz), 7.47 (1H, t, $J = 7.6$ Hz), 7.55 (1H, dd, $J = 7.6, 7.2$ Hz), 7.60 (1H, dd, $J = 8.0, 7.2$ Hz), 7.64-7.77 (6H, m), 7.96 (1H, d, $J = 8.0$ Hz), 7.99 (1H, d, $J = 8.8$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 21.7, 125.9, 126.9, 127.6, 128.1, 128.2, 128.3, 128.7, 129.3, 129.6, 130.3, 130.6, 132.9, 134.3, 134.5, 135.8, 137.3, 140.3, 144.3, 196.5, 197.8; ESIHRMS: Found: m/z 351.1384. Calcd for $\text{C}_{25}\text{H}_{19}\text{O}_2$: $(\text{M}+\text{H})^+$ 351.1385.

(2-benzoyl-1-methyl-1H-indol-3-yl)(p-tolyl)methanone (3oa)

65% yield; Yellow solid; mp. 153.1-154.1 °C IR (NaCl) 3018, 1645, 1633, 1606, 1496, 1215 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 2.34 (3H, s), 3.92 (3H, s), 6.98 (2H, d, $J = 8.0$ Hz), 7.21 (2H, dd, $J = 8.4, 7.2$ Hz), 7.28-7.33 (3H, m), 7.39-7.51 (5H, m), 7.95 (1H, $J = 8.0$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 21.5, 31.6, 110.3, 119.6, 122.5, 122.8, 125.2, 126.0, 128.2, 128.7, 129.0, 129.2, 133.2, 137.9, 138.4, 138.9, 139.0, 142.4, 190.1, 191.7; ESIHRMS: Found: m/z 354.1497. Calcd for $\text{C}_{24}\text{H}_{20}\text{NO}_2$: $(\text{M}+\text{H})^+$ 354.1494.

(2-benzoylthiophen-3-yl)(p-tolyl)methanone (3pa)

77% yield; Brown oil; IR (NaCl) 1647, 1604, 1276 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 2.34 (3H, s), 7.08 (2H, d, $J = 8.0$ Hz), 7.26 (2H, dd, $J = 8.0, 7.6$ Hz), 7.34 (1H, d, $J = 5.2$ Hz), 7.42-7.46 (3H, m), 7.56 (2H, d, $J = 8.0$ Hz), 7.65 (1H, d, $J = 5.2$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 21.6, 128.1, 128.9, 129.0, 129.2, 129.4, 130.8, 132.7, 135.3, 138.1, 142.4, 143.9, 144.8, 188.3, 191.7; ESIHRMS: Found: m/z 307.0795. Calcd for $\text{C}_{19}\text{H}_{15}\text{O}_2\text{S}$: $(\text{M}+\text{H})^+$ 307.0793.

(2-(4-methylbenzoyl)-1,3-phenylene)bis(phenylmethanone) (3qa)

56% yield; Yellow oil; IR (NaCl) 3061, 2957, 1663, 1599, 1580, 1570, 1449 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 2.28 (3H, s), 7.03 (2H, d, $J = 8.0$ Hz), 7.39 (4H, dd, $J = 7.6, 7.6$ Hz), 7.47 (2H, d, $J = 8.4$ Hz), 7.54 (2H, t, $J = 7.6$ Hz), 7.61 (1H, t, $J = 8.0$ Hz), 7.70-7.74 (6H, m); ^{13}C NMR (100 MHz, CDCl_3) δ 21.6, 128.3, 128.4, 128.9, 129.2, 130.1, 131.6, 133.3, 135.3, 136.6, 139.9, 141.8, 143.8, 195.8, 195.9; ESIHRMS: Found: m/z 405.1496. Calcd for $\text{C}_{28}\text{H}_{21}\text{O}_3$: $(\text{M}+\text{H})^+$ 405.1491.

(2-benzoyl-6-benzylphenyl)(p-tolyl)methanone (3qa')

19% yield; Yellow viscous oil; IR (NaCl) 3018, 1662, 1606, 1209 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 2.35 (3H, s), 3.91 (2H, s), 7.07 (2H, d, $J = 7.2$ Hz), 7.12-7.16 (3H, m), 7.20 (2H, dd, $J = 7.6, 7.2$ Hz), 7.35-7.48 (5H, m), 7.53 (1H, dd, $J = 7.6, 7.2$ Hz), 7.61 (2H, d, $J = 8.0$ Hz), 7.69 (2H, d, $J = 7.2$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 21.7, 38.6, 126.3, 128.1, 128.2, 128.4, 128.6, 129.2, 129.3, 129.4, 130.2, 132.8, 133.4, 135.6, 137.2, 137.4, 139.5, 139.8, 140.9, 144.0, 196.2, 197.9; ESIHRMS: Found: m/z 391.1697. Calcd for $\text{C}_{28}\text{H}_{23}\text{O}_2$: $(\text{M}+\text{H})^+$ 391.1698.

4-p-tolyl-4H-spiro[benzo[d][1,2]dioxine-1,1'-cyclohexan]-4-amine (5ta)

70% yield by acid quench; White granular crystal (CCDC 806338); mp. 140.8-141.0 °C; IR (NaCl) 3682, 2938, 2860, 1732, 1510, 1447, 1425 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.27-1.40 (1H, m), 1.64-1.83 (7H, m), 1.94-1.98 (2H, m), 2.32 (3H, s), 2.72 (2H, br), 7.09-7.14 (4H, m), 7.17 (1H, d, $J = 7.6$ Hz), 7.21-7.23 (1H, m), 7.40 (2H, d, $J = 8.0$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 21.1, 21.5, 21.8, 25.4, 35.0, 35.4, 81.1, 82.2, 123.5, 126.3, 126.9, 127.3, 128.2, 128.8, 137.3, 138.2 (overlapped), 140.9; ESIHRMS: Found: m/z 310.1800. Calcd for $\text{C}_{20}\text{H}_{24}\text{NO}_2$: $(\text{M}+\text{H})^+$ 310.1807.

2,2-dimethyl-4-phenyl-1-p-tolylbutane-1,4-dione (6ua)

58% yield; Yellow oil; IR (NaCl) 3059, 2972, 2924, 1682, 1609, 1472, 1449 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.47 (6H, s), 2.38 (3H, s), 3.53 (2H, s), 7.20 (2H, d, $J = 7.6$ Hz), 7.44 (2H, dd, $J = 8.0, 7.2$ Hz), 7.55 (1H, t, $J = 7.2$ Hz), 7.62 (2H, d, $J = 8.0$ Hz), 7.93 (2H, d, $J = 7.6$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 21.4, 26.9, 45.4, 50.4, 127.6, 127.9, 128.4, 128.5, 133.0, 136.7, 136.9, 140.6, 197.7, 209.1; ESIHRMS: Found: m/z 281.1549. Calcd for $\text{C}_{19}\text{H}_{21}\text{O}_2$: $(\text{M}+\text{H})^+$ 281.1542.

5.2.2.2 Synthesis of phthalazines

To an ice-cooled solution of 2-benzylbenzonitrile (97.6 mg, 0.505 mmol) in Et₂O (0.5 mL) was added an Et₂O solution of *p*-tolylmagnesium bromide (1.3 M, 0.6 mL, 0.8 mmol). The reaction mixture was stirred at 60 °C in a sealed tube for 2 h, and then anhydrous methanol (61 μL) was added. Copper acetate (9.4 mg, 0.051 mmol) and anhydrous DMF (5.1 mL) was then added. The reaction mixture was stirred at 80 °C under an oxygen atmosphere for 7 h. After that the reaction mixture was cooled to room temperature, and then NH₂·NH₂ solution (50 wt. % in H₂O, 157 μL, 2.52 mmol) was added. The mixture was stirred at 80 °C for another 1 h. Then pH 9 ammonium buffer was added to quench the reaction. The organic materials were extracted with Et₂O. The combined organic extracts were washed with water, and then with brine and dried over anhydrous MgSO₄. The solvents were removed in vacuo and the resulting crude material was purified by flash column chromatography (hexane : EtOAc = 80 : 20) to give 1-phenyl-4-*p*-tolylphthalazine (119.6 mg, 0.404 mmol) in 80% yield.

1-phenyl-4-*p*-tolylphthalazine (**7aa**)

White solid; mp. 172.1-173.4 °C; IR (NaCl) 3018, 1633, 1384, 1215 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 2.49 (3H, s), 7.40 (2H, d, *J* = 8.0 Hz), 7.51-7.63 (3H, m), 7.72 (2H, d, *J* = 8.0 Hz), 7.80-7.85 (4H, m), 8.11-8.19 (2H, m); ¹³C NMR (100

MHz, CDCl_3) δ 21.4, 125.8, 125.9, 126.5, 126.6, 128.5, 129.2 (overlapped), 130.1, 130.2 (overlapped), 131.8, 133.5, 136.5, 139.3, 158.9, 159.0; ESIHRMS: Found: m/z 297.1396. Calcd for $\text{C}_{21}\text{H}_{17}\text{N}_2$: $(\text{M}+\text{H})^+$ 297.1392.

1-(4-methoxyphenyl)-4-phenylphthalazine (7ab)

73% yield; White solid; mp. 156.4, 157.6 °C; IR (NaCl) 3109, 2974, 1611, 1516, 1387 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 3.92 (3H, s), 7.12 (2H, d, J = 11.6 Hz), 7.53-7.62 (3H, m), 7.76-7.87 (6H, m), 8.10-8.14 (1H, m), 8.15-8.20 (1H, m); ^{13}C NMR (100 MHz, CDCl_3) δ 55.4, 114.1, 125.9, 126.0, 126.5, 126.6, 126.7, 128.5, 128.8, 129.2, 130.2, 131.6, 131.8 (overlapped), 136.5, 158.6, 158.7, 160.6; ESIHRMS: Found: m/z 313.1331. Calcd for $\text{C}_{21}\text{H}_{17}\text{N}_2\text{O}$: $(\text{M}+\text{H})^+$ 313.1341.

1-(3-chlorophenyl)-4-phenylphthalazine (7ad)

63% yield; White solid; mp. 167.3-168.0 °C; IR (NaCl) 3017, 2984, 1568, 1418 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.51-7.63 (5H, m), 7.71 (1H, ddd, J = 3.6, 3.9, 6.7 Hz), 7.80-7.82 (3H, m), 7.86-7.91 (2H, m), 8.09-8.12 (1H, m), 8.15-8.18 (1H, m); ^{13}C NMR (100 MHz, CDCl_3) δ 125.7, 125.9, 126.1, 126.8, 128.4, 128.6, 129.4, 129.5, 129.8, 130.1, 130.2, 132.2, 134.6, 136.2, 138.2, 157.8, 159.4; ESIHRMS: Found: m/z 317.0841. Calcd for $\text{C}_{20}\text{H}_{14}\text{N}_2\text{Cl}$: $(\text{M}+\text{H})^+$ 317.0846.

1-(4-fluorophenyl)-4-phenylphthalazine (7ae)

72% yield; White solid; mp. 185.9-186.5 °C; IR (NaCl) 2988, 1732, 1514, 1385 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.28 (2H, dd, $J_{\text{H-F}} = 8.6$ Hz, 8.6 Hz), 7.56-7.61 (3H, m), 7.79-7.83 (4H, m), 7.84-7.88 (2H, m), 8.09-8.12 (1H, m), 8.13-8.16 (1H, m); ^{13}C NMR (100 MHz, CDCl_3) δ 115.7 (d, $^3J_{\text{C-F}} = 21.5$ Hz), 125.8, 125.9, 126.3, 126.7, 128.6, 129.4, 130.2, 132.01, 132.03, 132.06, 132.09, 132.5 (d, $^4J_{\text{C-F}} = 3.2$ Hz), 136.3, 158.6 (d, $^2J_{\text{C-F}} = 105.3$ Hz), 163.6 (d, $^3J_{\text{C-F}} = 105.3$ Hz); ESIHRMS: Found: m/z 301.1137. Calcd for $\text{C}_{20}\text{H}_{14}\text{N}_2\text{F}$: $(\text{M}+\text{H})^+$ 301.1141.

1-(naphthalen-1-yl)-4-phenylphthalazine (7af)

41% yield; White solid; mp. 152.2-153.2 °C; IR (NaCl) 2984, 1732, 1385, 1369 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.37 (1H, ddd, $J = 7.0, 7.0, 1.2$ Hz), 7.50-7.54 (2H, m), 7.59-7.72 (7H, m), 7.84 (1H, ddd, $J = 7.6, 7.6, 1.3$ Hz), 7.90 (2H, dd, $J = 7.9, 1.6$ Hz), 7.98 (1H, dd, $J = 8.7, 1.1$ Hz), 8.06 (1H, d, $J = 7.7$ Hz), 8.19 (1H, d, $J = 8.2$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 125.2, 125.4, 125.9, 126.1, 126.4, 126.5, 126.8, 127.3, 128.3, 128.5, 129.3, 129.5, 130.2, 131.9, 132.1, 132.3, 133.6, 133.8, 136.3, 159.1, 159.5; ESIHRMS: Found: m/z 333.1400. Calcd for $\text{C}_{24}\text{H}_{17}\text{N}_2$: $(\text{M}+\text{H})^+$ 333.1392.

1-phenyl-4-(thiophen-2-yl)phthalazine (7ah)

41% yield; White solid; mp. 160.2-161.0 °C; IR (NaCl) 2995, 1528, 1437, 1381 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.25-7.28 (1H, m), 7.54-7.61 (4H, m), 7.73 (1H, dd, J = 3.6, 1.0 Hz), 7.79 (1H, d, J =); ^{13}C NMR (100 MHz, CDCl_3) δ 125.2, 125.7, 125.8, 126.7, 127.6, 128.5, 128.9, 129.2, 129.7, 130.1, 132.0, 132.3, 136.2, 139.0, 152.8, 158.5; ESIHRMS: Found: m/z 289.0792. Calcd for $\text{C}_{18}\text{H}_{13}\text{N}_2\text{S}$: $(\text{M}+\text{H})^+$ 289.0799.

1-phenyl-4-(4-(trifluoromethyl)phenyl)phthalazine (7aj)

50% yield; White solid; mp. 188.4-189.3 °C; IR (NaCl) 2999, 1387, 1325 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.57-7.61 (3H, m), 7.82-7.97 (8H, m), 8.07-8.09 (1H, m), 8.18-8.21 (1H, m); ^{13}C NMR (100 MHz, CDCl_3) δ 124.0 (q, $^1J_{\text{C-F}}$ = 270.6 Hz), 125.6 (q, $^3J_{\text{C-F}}$ = 3.6 Hz), 125.7, 125.8, 125.9, 126.9, 128.6, 129.5, 130.2, 130.6, 130.9, 131.4 (q, $^2J_{\text{C-F}}$ = 32.4 Hz), 132.2, 132.3, 136.1, 140.0, 157.9, 159.6; ESIHRMS: Found: m/z 351.1102. Calcd for $\text{C}_{21}\text{H}_{14}\text{N}_2\text{F}_3$: $(\text{M}+\text{H})^+$ 351.1109.

1-(4-phenoxyphenyl)-4-phenylphthalazine (7ak)

55% yield; White solid; mp. 155.8-156.8 °C; IR (NaCl) 3003, 1587, 1508, 1489 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.13-7.18 (3H, m), 7.19-7.26 (2H, m), 7.40 (2H, dd, $J = 8.5, 1.0$ Hz), 7.56-7.61 (3H, m), 7.79-7.89 (6H, m), 7.79-7.81 (4H, m), 7.83-7.87 (2H, m), 8.13-8.15 (2H, m), 8.18-8.20 (2H, m); ^{13}C NMR (100 MHz, CDCl_3) δ 118.4, 119.5, 123.8, 125.8, 125.9, 126.4, 126.6, 128.5, 129.2, 129.9, 130.1, 131.0, 131.7, 131.9 (overlapped), 136.3, 156.5, 158.4, 158.7, 158.9; ESIHRMS: Found: m/z 375.1493. Calcd for $\text{C}_{26}\text{H}_{19}\text{N}_2\text{O}$: $(\text{M}+\text{H})^+$ 375.1497.

1-phenyl-4-(*o*-tolyl)phthalazine (7am)

50% yield; White solid; mp. 120.1-121.1 °C; IR (NaCl) 2984, 1732, 1383 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 2.19 (3H, s), 7.38-7.46 (4H, m), 7.57-7.63 (3H, m), 7.70 (2H, d, $J = 7.8$ Hz), 7.78- 7.87 (4H, m), 8.16 (1H, d, $J = 7.8$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 125.5, 125.8, 126.4, 126.5, 126.6, 128.5, 129.1, 129.3, 130.1, 130.2, 130.5, 131.9, 132.0, 135.8, 136.4, 137.0, 159.2, 159.8; ESIHRMS: Found: m/z 297.1389. Calcd for $\text{C}_{21}\text{H}_{17}\text{N}_2$: $(\text{M}+\text{H})^+$ 297.1392.

1-(4-chlorophenyl)-4-(*p*-tolyl)phthalazine (7ca)

50% yield; White solid; mp. 203.3- 204.0 °C; IR (NaCl) 3019, 1387, 1215 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 2.50 (3H, s), 7.40 (2H, d, J = 7.8 Hz), 7.57 (2H, d, J = 6.6 Hz), 7.71 (2H, d, J = 8.0 Hz), 7.77 (2H, 8.52 Hz), 7.85-7.87 (2H, m), 8.08-8.10 (1H, m), 8.17-8.20 (1H, m); ^{13}C NMR (100 MHz, CDCl_3) δ 21.4, 125.7, 125.9, 126.1, 126.8, 128.8, 129.3, 130.1, 131.5, 131.9, 132.0, 133.3, 134.9, 135.5, 139.4, 157.8, 159.2; ESIHRMS: Found: m/z 331.1001. Calcd for $\text{C}_{21}\text{H}_{16}\text{ClN}_2$: $(\text{M}+\text{H})^+$ 331.1002.

1-(4-methoxyphenyl)-4-(*p*-tolyl)phthalazine (7ea)

78% yield; White solid; mp. 186.8-187.2 °C; IR (NaCl) 3007, 2963, 1609, 1516, 1387 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 2.49 (3H, s), 3.92 (3H, s), 7.11 (2H, d, J = 8.8 Hz), 7.39 (2H, d, J = 7.8 Hz), 7.71 (2H, d, J = 8.0 Hz), 7.78 (2H, d, J = 8.8 Hz), 7.82-7.84 (2H, m), 8.14-8.19 (2H, m); ^{13}C NMR (100 MHz, CDCl_3) δ 21.4, 55.4, 114.0, 125.9, 126.0, 126.5, 126.6, 128.9, 129.2, 130.1, 131.6, 131.6, 131.7, 133.6, 139.2, 158.4, 158.7, 160.5; ESIHRMS: Found: m/z 327.1498. Calcd for $\text{C}_{22}\text{H}_{19}\text{N}_2\text{O}$: $(\text{M}+\text{H})^+$ 327.1497.

1,4-di-*p*-tolylphthalazine (7fa)

52% yield; White solid; mp. 224.6-225.5 °C; IR (NaCl) 3017, 1389 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 2.49 (6H, s), 7.39 (4H, d, J = 8.0 Hz), 7.72 (4H, d, J = 8.0 Hz), 7.83 (2H, dd, J = 6.3, 3.3 Hz), 8.16 (2H, dd, J = 6.3, 3.3 Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 21.4, 125.9, 126.6, 129.2, 130.1, 131.7, 133.6, 139.2, 158.8; ESIHRMS: Found: m/z 311.1538. Calcd for $\text{C}_{22}\text{H}_{19}\text{N}_2$: $(\text{M}+\text{H})^+$ 311.1538.

1-(naphthalen-1-yl)-4-(*p*-tolyl)phthalazine (7ia)

52% yield; White solid; mp. 192.5-193.0 °C; IR (NaCl) 3061, 3001, 2967, 1611, 1508, 1383, 1369 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 2.51 (3H, s), 7.37 (1H, ddd, J = 7.6, 7.6, 1.1 Hz), 7.44 (2H, d, 7.8 Hz), 7.50-7.53 (2H, m), 7.63 (2H, dd, J = 8.1, 8.1 Hz), 7.65-7.72 (2H, m), 7.79-7.85 (3H, m), 7.98 (1H, d, J = 7.7), 8.1 (1H, d, J = 7.4 Hz), 8.21 (1H, d, J = 8.3 Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 21.4, 125.2, 125.5, 125.9, 126.1, 126.5, 126.8, 127.3, 128.3, 128.4, 129.3, 129.5, 130.2 (overlapped), 131.8, 132.0, 132.3, 133.5, 133.6, 133.9, 139.4, 158.9, 159.5; ESIHRMS: Found: m/z 347.1545. Calcd for $\text{C}_{25}\text{H}_{19}\text{N}_2$: $(\text{M}+\text{H})^+$ 347.1548.

5-methyl-4-phenyl-1-(*p*-tolyl)-5*H*-pyridazino[4,5-*b*]indole (7oa)

69% yield; White solid; mp. 247.5-248.5 °C; ^1H NMR (400 MHz, CDCl_3) δ 2.54 (3H, s), 3.62 (3H, s), 7.30 (1H, dd, J = 7.6, 7.5 Hz), 7.47 (2H, d, J = 7.8 Hz), 7.55-7.60 (4H, m), 7.66-7.74 (3H, m), 7.88 (2H, d, J = 8.0 Hz), 7.92 (1H, d, J = 8.0 Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 21.5, 32.8, 110.1, 118.0, 119.7, 121.3, 123.4, 128.4, 128.7, 129.1, 129.3 (overlapped), 129.9, 134.4, 135.6, 136.8, 139.4, 141.9, 147.2, 155.1; ESIHRMS: Found: m/z 350.1656. Calcd for $\text{C}_{24}\text{H}_{20}\text{N}_3$: $(\text{M}+\text{H})^+$ 350.1657.

7-phenyl-4-(*p*-tolyl)thieno[2,3-*d*]pyridazine (7pa)

84% yield; White solid; mp. 225.3-226.2 °C; ^1H NMR (400 MHz, CDCl_3) δ 2.49 (3H, s), 7.42 (2H, d, J = 7.9 Hz), 7.55-7.61 (3H, m), 7.75 (1H, d, J = 5.5 Hz), 7.88 (1H, d, J = 5.5 Hz), 7.98 (2H, dd, J = 8.0, 1.5 Hz), 8.12 (2H, d, J = 8.2); ^{13}C NMR (100 MHz, CDCl_3) δ 21.5, 123.7, 128.3, 128.8, 129.3, 129.5, 129.7, 132.8, 134.0, 135.6, 137.1, 138.5, 140.4, 154.2, 154.8; ESIHRMS: Found: m/z 303.0956. Calcd for $\text{C}_{19}\text{H}_{15}\text{N}_2\text{S}$: $(\text{M}+\text{H})^+$ 303.0956.

1-propyl-4-p-tolylphthalazine (7ra)

70% yield; Yellow solid; mp. 118.9-119.9 °C; IR (NaCl) 2962, 1647, 1614, 1382 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.13 (3H, t, $J = 7.2$ Hz), 1.96-2.05 (2H, m), 3.38 (2H, t, $J = 6.8$ Hz), 7.35 (2H, d, $J = 7.6$ Hz), 7.64 (2H, d, $J = 7.6$ Hz), 7.80 (1H, dd, $J = 8.0, 8.0$ Hz), 7.88 (1H, dd, $J = 8.0, 8.0$ Hz), 8.09 (1H, d, $J = 8.0$ Hz), 8.16 (1H, d, $J = 8.0$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 14.3, 21.4, 22.6, 35.2, 124.3, 125.4, 126.0, 126.9, 129.1, 130.0, 131.4, 131.6, 133.7, 139.0, 158.8, 159.2; ESIHRMS: Found: m/z 263.1544. Calcd for $\text{C}_{18}\text{H}_{19}\text{N}_2$: $(\text{M}+\text{H})^+$ 263.1548.

1-isopropyl-4-(p-tolyl)phthalazine (7sa)

53% yield; White solid; mp. 92.5-93.3 °C; IR (NaCl) 3069, 2968, 2930, 2872, 1612, 1528, 1458 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.58 (6H, d, $J = 6.8$ Hz), 3.94 (sep, 6.8 Hz), 7.36 (2H, d, $J = 7.8$ Hz), 7.66 (2H, d, 7.8 Hz), 7.80 (1H, dd, $J = 7.7, 1.1$ Hz), 7.89 (1H, d, $J = 7.7, 1.1$ Hz), 8.12 (1H, d, $J = 8.6$ Hz), 8.23 (1H, d, $J = 8.6$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 21.4, 22.0, 30.4, 123.7, 125.4, 125.5, 127.1, 129.1, 130.1, 131.3, 131.6, 133.8, 139.0, 158.6, 162.8; ESIHRMS: Found: m/z 263.1542. Calcd for $\text{C}_{25}\text{H}_{19}\text{N}_2$: $(\text{M}+\text{H})^+$ 263.1548.

5.2.2.3 Synthesis of isoindolines

To an ice-cooled solution of 2-benzylbenzonitrile (**1a**) (98.0 mg, 0.507 mmol) in Et₂O (0.5 mL) was added an Et₂O solution of *p*-tolylmagnesium bromide (**2a**) (1.3 M, 0.6 mL, 0.8 mmol). The reaction mixture was stirred at 60 °C in a sealed tube for 2 h, and then anhydrous methanol (62 µL) was added. Copper acetate (9.4 mg, 0.051 mmol) and anhydrous DMF (5.1 mL) was then added. The reaction mixture was stirred at 80 °C under an oxygen atmosphere for 7 h. Then pH 9 ammonium buffer was added to quench the reaction. The organic materials were extracted with Et₂O. The combined organic extracts were washed with water, and then with brine and dried over anhydrous MgSO₄. The solvents were removed in vacuo and crude mixture was used for next step without further purification.

To an EtOH solution of crude of last step was added NH₄OAc (117.3 mg, 1.52 mmol) and EtONa (10 mg, 0.15 mmol). The reaction mixture was stirred at reflux for 2 h. After being cooled to room temperature, the solvents were removed in vacuo and crude mixture could be used for next step without further purification.

To an AcOH solution of crude of last step was added coppered zinc dust (0.550 g, 8.41 mmol)¹⁸ at 0 °C. The reaction mixture was stirred at room temperature for 1 h. After that the mixture was diluted with water, filtered through a Celite pad. The filtrate was neutralized with solid sodium hydroxide to pH = 10. The organic materials were extracted thrice with CH₂Cl₂. The combined organic extracts were washed with water, and then with brine and dried over anhydrous MgSO₄. The

solvents were removed in vacuo to give 1-phenyl-3-p-tolylisoindoline (82.3 mg, 0.288 mmol) in 57% yield.

1-phenyl-3-p-tolylisoindoline (8aa)

57% yield; Yellow solid; mp. 159.0-160.3 °C; IR (NaCl) 2974, 1637, 1454, 1217, 1047 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 2.34 (3H, s), 5.71 (1H, d, $J = 2.0$ Hz), 5.73 (1H, d, $J = 2.0$ Hz), 7.07-7.09 (2H, m), 7.14 (2H, d, $J = 8.0$ Hz), 7.19-7.23 (4H, m), 7.27-7.34 (5H, m); ^{13}C NMR (100 MHz, CDCl_3) δ 21.1, 67.0, 67.2, 123.4 (overlapped), 127.2, 127.3, 127.4, 127.4, 127.5, 128.6, 129.3, 137.0, 142.0, 143.8, 143.9, 145.0; ESIHRMS: Found: m/z 286.1595. Calcd for $\text{C}_{21}\text{H}_{20}\text{N}$: $(\text{M}+\text{H})^+$ 286.1596.

1-phenyl-3-p-tolyl-2-tosylisoindoline (8aa-Ts)

To a flask charged with 1-phenyl-3-p-tolylisoindoline (43.7 mg, 0.153 mmol) and pyridine (1.5 mL) was added 4-methylbenzene-1-sulfonyl chloride (32.1 mg, 0.168 mmol). The reaction mixture was stirred at 70 °C for overnight, and then quenched with water. The organic materials were extracted with Et_2O . The combined organic extracts were washed with brine and dried over anhydrous MgSO_4 . The solvents were removed in vacuo and the resulting crude material was purified by recrystallization with hexane and EtOAc to afford 1-phenyl-3-p-tolyl-2-tosylisoindoline (32.1 g, 0.0730 mmol) in 48% yield.

White rod crystal (CCDC 806339); Decomposed at 220 °C; IR (NaCl) 3018, 1637, 1215 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 2.30 (3H, s), 2.32 (3H, s), 6.13 (1H, d, $J = 2.8$ Hz), 6.17 (1H, d, $J = 2.8$ Hz), 6.89-6.91 (4H, m), 6.97-7.06 (6H, m), 7.12-7.18 (4H, m), 7.19-7.23 (3H, m); ^{13}C NMR (100 MHz, CDCl_3) δ 21.2, 21.4, 70.1, 70.3, 122.4, 123.4, 126.9, 127.7, 128.14, 128.18 (overlapped), 128.2, 128.3, 128.6, 129.0, 137.5, 137.8, 138.6, 140.5, 140.7, 141.7, 142.0; ESIHRMS: Found: m/z 440.1680. Calcd for $\text{C}_{28}\text{H}_{26}\text{NO}_2\text{S}$: $(\text{M}+\text{H})^+$ 440.1684.

1-(benzo[d][1,3]dioxol-5-yl)-3-(4-methoxyphenyl)isoindoline (8gb)

54% yield; Brown oil; IR (NaCl) 3404, 3016, 1610, 1506, 1217 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 3.80 (3H, s), 5.65 (1H, s), 5.67 (1H, s), 5.92 (2H, d, $J = 1.2$ Hz), 6.75-6.81 (3H, m), 6.86 (2H, d, $J = 8.4$ Hz), 7.05-7.09 (2H, m), 7.19-7.24 (4H, m); ^{13}C NMR (100 MHz, CDCl_3) δ 55.2, 66.5, 66.8, 100.9, 107.6, 108.0, 114.0, 120.5, 123.3, 123.4, 127.4, 127.5, 128.4, 137.0, 139.1, 143.7, 143.9, 146.8, 147.9, 158.9; ESIHRMS: Found: m/z 364.1444. Calcd for $\text{C}_{22}\text{H}_{20}\text{NO}_3$: $(\text{M}+\text{H})^+$ 364.1443.

Synthesis of (1*S*,3*R*)-1-mesityl-3-phenylisoindoline (**8al**)

Scheme 2-23. A two-pot synthesis of isoindoline **8al** from 1*H*-isoindo-1-ol **7al**

To an ice-cooled solution of 2-benzylbenzonitrile (**1a**) (104.3 mg, 0.540 mmol) in Et_2O (0.5 mL) was added an Et_2O solution of mesitylmagnesium bromide (**2l**) (1.2 M, 0.6 mL, 0.8 mmol). The reaction mixture was stirred at 60°C in a sealed tube for 14 h, and then anhydrous methanol (66 μL) was added. Copper acetate (10.4 mg, 0.058 mmol) and anhydrous DMF (5.0 mL) was then added. The reaction mixture was stirred at 80°C under an oxygen atmosphere for 4 h. Then pH 9 ammonium buffer was added to quench the reaction. The organic materials were extracted with Et_2O . The combined organic extracts were washed with water, and then with brine and dried over anhydrous MgSO_4 . The solvents were removed in vacuo and crude mixture was used for next step without further purification.

To an AcOH solution of crude of last step was added coppered zinc dust (1.148 g, 8.91 mmol)¹⁸ at 0°C . The reaction mixture was stirred at room temperature for 4 h. After that the mixture was diluted with water, filtered through a Celite pad. The filtrate was neutralized with solid sodium hydroxide to $\text{pH} = 10$. The organic materials were extracted thrice with CH_2Cl_2 . The combined organic extracts were washed with water, and then with brine and dried over anhydrous MgSO_4 . The solvents were removed in vacuo to give (1*S*,3*R*)-1-mesityl-3-phenylisoindoline (**8al**) (134 mg, 0.288 mmol) in 79% yield.

^1H NMR (400 MHz, CDCl_3) δ 1.91 (1H, br), 2.25 (1H, br), 2.50 (1H, br), 5.70 (1H, d, $J = 2.3$ Hz), 6.34 (1H, d, $J = 2.3$ Hz), 6.78-6.91 (2H, m), 6.92-6.93 (1H, m), 7.10-7.18 (3H, m), 7.21-7.27 (1H, m), 7.29-7.32 (4H, m).

3-mesityl-1-phenyl-1*H*-isoindol-1-ol (7al)

^1H NMR (400 MHz, CDCl_3) δ 1.83 (3H, s), 2.31 (3H, s), 2.40 (3H, s), 6.94 (1H, s), 7.00-7.02 (2H, m), 7.11-7.28 (5H, m), 7.35-7.38 (3H, m), 7.55 (1H, br); ^{13}C NMR (100 MHz, CDCl_3) δ 19.7, 20.4, 21.2, 102.0, 122.5, 123.3, 125.2, 127.6, 128.2, 128.4, 128.5, 128.6, 129.6, 130.1, 135.6, 136.4, 137.6, 138.4, 141.2, 154.1, 174.5.

5.2.2.4.1 Labeling experiments

Utilization of $^{18}\text{O}_2$ for the reaction of **1a** with **2a**.

3aa-labelling $^{18}\text{O}_2$

37% yield; White solid; mp. 147.0-147.8 °C; IR (ATR) 1641, 1628, 1595, 1568 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 2.38 (3H, s), 7.17 (2H, d, $J = 8.0$ Hz), 7.37 (2H, dd, $J = 7.6, 7.6$ Hz), 7.51 (1H, dd, $J = 7.2, 7.6$ Hz), 7.59-7.61 (6H, m), 7.70 (2H, d, $J = 8.0$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 21.7, 128.3, 129.0, 129.5, 129.6, 129.8, 130.0, 130.1, 130.3, 132.9, 134.6, 137.2, 139.9, 140.3, 143.9, 196.2, 196.6; ESIHRMS: Found: m/z 305.1313. Calcd for $\text{C}_{21}\text{H}_{17}^{18}\text{O}_2$: $(\text{M}+\text{H})^+$ 305.1313.

4aa-labelling $^{18}\text{O}_2$

49% yield; White solid; mp. 196.8-197.6 °C; IR (NaCl) 3553, 2924, 1663, 1603, 1557, 1512 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 2.50 (3H, s), 6.80 (1H, br), 7.11-7.17 (3H, m), 7.34-7.47 (7H, m), 7.64-7.67 (1H, m), 7.88 (2H, d, $J = 8.0$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 21.6, 100.9, 123.3, 123.6, 125.3, 127.8, 128.3, 128.5, 128.7, 129.5, 129.9, 130.6, 136.4, 140.8, 141.3, 155.0, 171.4; ESIHRMS: Found: m/z 302.1432. Calcd for $\text{C}_{21}\text{H}_{18}\text{N}^{18}\text{O}$: $(\text{M}+\text{H})^+$ 302.1431.

Figure S-1. Spectrum of ESI (LRMS) of **3aa-¹⁸O₂**

Figure S-2. Spectrum of ESIHRMS of **3aa-¹⁸O₂**

Elemental Composition Report

Page 1

Single Mass Analysis

Tolerance = 5.0 PPM / DBE: min = -1.5, max = 100.0

Element prediction: Off

Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions

8 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)

Elements Used:

C: 0-25 H: 0-20 ¹⁸O: 0-3

C₂₁H₁₆¹⁸O₂ MW304

ZLE-6113-1P 9 (0.220)

HAB333

13:39:51
 22-Oct-2010
 1: TOF MS ES+
 3.92e+003

Minimum:

Maximum:

5.0 5.0 -1.5

100.0

Mass Calc. Mass mDa PPM DBE i-FIT i-FIT (Norm) Formula

305.1313 305.1313 0.0 0.0 13.5 52.1 0.0 C₂₁ H₁₇ ¹⁸O₂

Figure S-3. Spectrum of ESI (LRMS) of **4aa**-¹⁸O₂

Figure S-4. Spectrum of ESIHRMS of **4aa**-¹⁸O₂

Elemental Composition Report

Page 1

Single Mass Analysis

Tolerance = 5.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
30 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)
Elements Used:
C: 0-25 H: 0-20 N: 0-3 O: 0-3
C21H17 18O MW301

ZLE-6113-2P 26 (0.588)

HAB333

13.50.53
22-Oct-2010
1: TOF MS ES+
2.16e+003

Minimum:				-1.5			
Maximum:				100.0			
		5.0	5.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
302.1432	302.1431	0.1	0.3	13.5	43.6	0.0	C21 H18 N 18O

IR of **3aa**

IR 1670 (C=O), 1654 (C=O) cm^{-1}

IR of 3aa-labelling $^{18}\text{O}_2$

IR 1641 (C=O), 1627 (C=O) cm^{-1}

By the harmonic oscillator calculation as shown below equation, $\Delta\nu$ of the carbonyl group of **3aa** and **3aa-labelling $^{18}\text{O}_2$** is about 70 cm^{-1} . However, IR spectrum indicated the value ($\Delta\nu$) is about 30 cm^{-1} .

$$\nu = (1/2\pi C) (k/\mu)^{-1/2} = 5.3 \times 10^{-12} (k/\mu)^{-1/2}$$

- k is force constant, about 1×10^6 dynes/cm
- μ is reduced mass

Although IR spectra actually indicated that the value ($\Delta\nu$) is about 30 cm^{-1} , it is known that the harmonic oscillator is just approximation and could be affected by molecular complexity.

Judging from IR values shifts of $\text{C}=\text{O}^{73}$ in the correct direction as well as mass spectra of **3aa** and **4aa**, ^{18}O atoms were obviously incorporated into the carbonyl groups in the present process.

5.3 Electrophilic cyanation of Grignard Reagents with Pivalonitrile via Copper-Catalyzed Aerobic β -Carbon Elimination of *N*-H Imine Intermediates

5.3.1 Unexpected finding of carbonitrile

To an ice-cooled solution of benzonitrile (**7**) (98.4 mg, 0.509 mmol) in Et_2O (0.5 mL) was added an Et_2O solution of *n*-butylmagnesium bromide (1.0 M, 0.7 mL, 0.7 mmol). The reaction mixture was stirred at 60°C in a sealed tube for 2 h, and then anhydrous MeOH (62 μL) was added. $\text{Cu}(\text{OAc})_2$ (9.4 mg, 0.051 mmol) and anhydrous DMF (5.1 mL) was then added. The reaction mixture was stirred at 80°C under an oxygen atmosphere for 8.5 h. The reaction was quenched with 3N aqueous HCl solution, and the reaction mixture was stirred at 80°C for 2 h. The organic materials were extracted with Et_2O . The combined organic extracts were washed with water, and then with brine and dried over anhydrous MgSO_4 . The solvents were removed in vacuo and the resulting crude material was purified by flash column chromatography (hexane : EtOAc = 80 : 20) to afford 1,4-diphenylbutane-1,4-dione (**8**) (60.6 mg, 0.255 mmol) in 50% yield.

1,4-diphenylbutane-1,4-dione (**8**)⁷⁴

50% yield; ^1H NMR (400 MHz, CDCl_3) δ 3.47 (4H, s), 7.49 (4H, dd, J = 7.6, 7.6 Hz), 7.58 (2H, t, J = 7.6 Hz), 8.04 (4H, d, J = 7.6 Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 32.6, 128.1, 128.6, 133.1, 136.7, 198.7.

5.3.2 Electrophilic cyanation of Grignard reagents with pivalonitrile

A typical procedure for synthesis of carbonitriles

To an ice-cooled solution of pivalonitrile (**1**) (120 μL , 1.085 mmol) in Et_2O (1.0 mL) was added an Et_2O solution of *p*-tolylmagnesium bromide (**2a**) (0.75 M, 1.88 mL, 1.410 mmol). The reaction mixture was stirred at $60\text{ }^\circ\text{C}$ in a sealed tube for 2 h, and then anhydrous MeOH (132 μL) was added. CuBr_2 (24.3 mg, 0.109 mmol) and anhydrous DMF (10.0 mL) was then added. The reaction mixture was stirred at $80\text{ }^\circ\text{C}$ under an oxygen atmosphere for 6 h. The reaction was quenched with pH 9 ammonium buffer and the organic materials were extracted with Et_2O . The combined organic extracts were washed with water, and then with brine and dried over anhydrous MgSO_4 . The solvents were removed in vacuo and the resulting crude material was purified by flash column chromatography (hexane : EtOAc = 90 : 10) to afford 2-Naphthonitrile (**3a**) (124.6 mg, 0.928 mmol) in 85% yield.

2-naphthonitrile (**3a**)⁷⁵

85% yield; ^1H NMR (400 MHz, CDCl_3) δ 7.58-7.67 (3H, m), 7.87-7.92 (3H, m), 8.21 (1H, s); ^{13}C NMR (100 MHz, CDCl_3) δ 109.3, 119.2, 126.3, 127.6, 128.0, 128.3, 129.0, 129.1, 132.2, 134.1, 134.6.

1-naphthonitrile (**3b**)⁷⁵

76% yield; ^1H NMR (400 MHz, CDCl_3) δ 7.54 (1H, dd, J = 7.2, 8.2 Hz), 7.63 (1H, dt, J = 1.2, 7.0 Hz), 7.71 (1H, dt, J = 1.2, 7.0 Hz), 7.92-7.95 (2H, m), 8.09 (1H, d,

$J = 8.3$ Hz), 8.25 (1H, d, $J = 8.3$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 110.1, 117.7, 124.8, 125.0, 127.5, 128.5, 128.6, 132.2, 132.5, 132.8, 133.2.

2,4,6-trimethylbenzonitrile (3c)⁷⁶

73% yield; ^1H NMR (400 MHz, CDCl_3) δ 2.32 (3H, s), 2.48 (6H, s), 6.93 (3H, s); ^{13}C NMR (100 MHz, CDCl_3) δ 20.6, 21.5, 110.3, 117.6, 128.2, 141.9, 142.8.

4-methoxybenzonitrile (3d)⁷⁶

74% yield; ^1H NMR (400 MHz, CDCl_3) δ 3.78 (3H, s), 6.95 (2H, d, $J = 8.9$ Hz), 7.59 (2H, d, $J = 8.9$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 55.5, 104.0, 114.7, 119.2, 134.0, 162.8.

2-methoxybenzonitrile (3e)⁷⁵

61% yield; ^1H NMR (400 MHz, CDCl_3) δ 3.93 (3H, s), 6.96- 7.03 (2H, m), 7.52- 7.57 (2H, m); ^{13}C NMR (100 MHz, CDCl_3) δ 56.0, 101.8, 111.2, 116.5, 120.7, 133.7, 134.3, 161.2.

4-phenoxybenzonitrile (3f)⁷⁷

81% yield; ^1H NMR (400 MHz, CDCl_3) δ 7.00 (2H, d, $J = 8.9$ Hz), 7.06-7.08 (2H, m), 7.21-7.27 (1H, m), 7.40-7.44 (2H, m), 7.60 (2H, d, $J = 8.9$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 105.8, 117.9, 118.2, 120.4, 125.1, 130.2, 134.1, 154.8, 161.3.

4-chlorobenzonitrile (3g)⁷⁸

70% yield; ¹H NMR (400 MHz, CDCl₃) δ 7.47 (2H, d, *J* = 8.4 Hz), 7.61 (2H, d, *J* = 8.4 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 110.7, 117.9, 129.7, 133.3, 139.5.

thiophene-2-carbonitrile (3h)⁷⁹

63% yield; ¹H NMR (400 MHz, CDCl₃) δ 7.13 (1H, dd, *J* = 5.0, 3.7 Hz); 7.61 (1H, dd, *J* = 5.0, 1.1 Hz), 7.64 (1H, dd, *J* = 3.7, 1.1 Hz)

3-phenylpropanenitrile (3i)⁸⁰

47% yield; ¹H NMR (400 MHz, CDCl₃) δ 2.62 (2H, t, *J* = 7.4 Hz); 2.96 (2H, t, *J* = 7.4 Hz), 7.22-7.39 (3H, m), 7.33-7.37 (2H, m); ¹³C NMR (100 MHz, CDCl₃) δ 19.3, 31.6, 119.1, 127.2, 128.2, 128.9, 138.0.

5.3.3.1 Mechanistic studies

Starting material synthesis: Synthesis of 2,2-diphenylheptanenitrile (4)⁸¹

To a flask charged with LDA, which was freshly prepared by diisopropylamine (3.1 mL, 22.0 mmol) and *n*-BuLi (1.6 M, 13.1 mL, 21.0 mmol) in THF (26 mL), was added diphenylacetone nitrile (3.87 g, 20.0 mmol) at -78 °C.

The mixture was stirred at the same temperature for 1 h. After that 1-bromohexane (3.1 mL, 22.0 mmol) was added at -78 °C. The reaction mixture was stirred at room temperature for overnight, and then quenched with saturated aqueous NH₄Cl. The organic materials were extracted thrice with Et₂O. The combined organic extracts were washed with brine and dried over anhydrous MgSO₄. The solvents were removed in vacuo and the resulting crude material

was subjected to flash column chromatography (hexane : EtOAc = 95 : 5) to afford 2,2-diphenylheptanenitrile (**4**) (3.60 g, 13.0 mmol) in 65% yield.

65% yield; ^1H NMR (400 MHz, CDCl_3) δ 0.85 (3H, t, J = 6.8), 1.25-1.27 (4H, m), 1.31- 1.41 (4H, m), 1.54 (1H, s), 2.33- 2.37 (2H, m), 7.26- 7.30 (2H, m), 7.32-7.39 (8H, m); ^{13}C NMR (100 MHz, CDCl_3) δ 14.0, 22.5, 25.6, 29.1, 31.4, 39.7, 51.8, 122.5, 126.8, 127.7, 128.8, 140.4.

Identification of side-products

To an ice-cooled solution of 2,2-diphenylheptanenitrile (**4**) (276.7 mg, 0.997 mmol) in Et_2O (1.0 mL) was added an Et_2O solution of *p*-tolylmagnesium bromide (**2d**) (0.85 M, 1.5 mL, 1.30 mmol). The reaction mixture was stirred at 60 °C in a sealed tube for 54 h, and then anhydrous MeOH (121 μL) was added. CuBr_2 (22.8 mg, 0.100 mmol) and anhydrous DMF (10.0 mL) was then added. The reaction mixture was stirred at 80 °C under an oxygen atmosphere for 24 h. The reaction was quenched with pH 9 ammonium buffer and the organic materials were extracted thrice with Et_2O . The combined organic extracts were washed with water, and then with brine and dried over anhydrous MgSO_4 . The solvents were removed in vacuo and the resulting crude material was purified by flash column chromatography (hexane : EtOAc = 98 : 2) to afford 4-Methoxybenzonitrile (**3d**) (110.1 mg, 0.830 mmol) and hept-1-ene-1,1-diylidibenzene (**5**) (40.1 mg, 0.160 mmol) in 83% and 16% yield respectively.

hept-1-ene-1,1-diylidibenzene (**5**)⁸²

16% yield; ^1H NMR (400 MHz, CDCl_3) δ 0.84-0.88 (3H, m), 1.25-1.29 (4H, m), 1.42-1.45 (2H, m), 2.10 (2H, q, J =7.44), 6.08 (2H, t, J =7.48), 7.16-7.24 (7H, m), 7.25-7.29 (1H, m), 7.30-7.36 (3H, m); ^{13}C NMR (100 MHz, CDCl_3) δ 14.0, 22.5,

29.6, 29.7, 31.5, 126.7, 126.8, 127.2, 128.0, 128.1, 129.9, 130.4, 140.3, 141.4, 142.9.

Importance of atmospheric oxygen

To an ice-cooled solution of pivalonitrile (**1**) (120 μ L, 1.085 mmol) in degassed Et₂O (1.0 mL) was added an Et₂O solution of *p*-tolylmagnesium bromide (**2a**) (0.74 M, 1.9 mL, 1.30 mmol). The reaction mixture was stirred at 60 °C in a sealed tube for 2 h, and then anhydrous degassed MeOH (132 μ L) was added. Cu(OAc)₂ (20.4 mg, 0.100 mmol) and anhydrous degassed DMF (10.0 mL) was then added. The reaction mixture was stirred at 80 °C under an N₂ atmosphere for 6 h. The reaction was quenched with 1 N HCl and the organic materials were extracted thrice with Et₂O. The combined organic extracts were washed with water, and then with brine and dried over anhydrous MgSO₄. The solvents were removed in vacuo and the resulting crude material was purified by flash column chromatography (hexane : Et₂O = 95 : 5) to afford 2,2-dimethyl-1-(naphthalen-2-yl)propan-1-one (**7**) (190.4 mg, 0.896 mmol) in 83% yield.

2,2-dimethyl-1-(naphthalen-2-yl)propan-1-one (**6**)⁸³

83% yield; ¹H NMR (300 MHz, CDCl₃) δ 7.48- 7.57 (2H, m), 7.76- 7.91 (4H, m), 8.22 (1H, s); ¹³C NMR (75 MHz, CDCl₃) δ 28.1, 44.3, 124.8, 126.5, 127.6, 127.7, 128.4, 129.0, 132.3, 134.2, 135.7, 208.9

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