NOVEL SYNTHESIS OF
DIARYL AMINE DERIVATIVES VIA TRANSITION-METAL-FREE
N-ARYLATION OF BETA-TETRALONE

By
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A dissertation submitted to the
Graduate School-Newark
Rutgers, The State University of New Jersey
in partial fulfillment of the requirements
for the degree of
Master of Science
Graduate Program in Chemistry
written under the direction of
Stacey Brenner-Moyer
and approved by

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Newark, New Jersey
October, 2017
ABSTRACT OF THE DISSERTATION

NOVEL SYNTHESIS METHOD OF
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Dissertation Director:
Stacey Brenner-Moyer

Since the word “organocatalysis” has been created by MacMillan in 2000, it has growing very fast and soon being recognized as an important category of catalysis, alongside biocatalysis and transition metal catalysis. Thanks to continuous study of these reactions, amine catalysis can now be considered as one of the methods of choice for many asymmetric functionalizations of carbonyl compounds such as aldehydes or ketones. In this dissertation, we choose diarylamines structures as our target, owing to its widely used in different field. We are going to talk about a comprehensive review of how people synthesis this kind of structure in history and provide some new ideas. With the goal of generating diversity through cascades and heteroatomic substrates, the research target was focused on efficiently conducting N-arylation via organocatalysis. By using 2-tetralone and nitrosobenzene, we truly developed an easy and effectively method to reach diarylamines in high yield. Furthermore, this reaction for sure has potential to start with more simple starting material, aniline which may be more acceptable in industrial applications.
ACKNOWLEDGEMENTS

Completing the research reported in this dissertation, and my whole Master’s program, would not have been possible without the help of a number of individuals. First I need to thank my advisor, my advisor Professor Stacey Brenner-Moyer, who provide a very comfortable and resourceful working environment for me. Whenever we need some complicate starting material or reagents, she can always support us to her best. Besides, she also provides good guidance in enthusiasm, and shed light on clear direction, throughout these two year. These tips she taught me can not only be good use in doing research but can be applied in my life in future.

I would also like to thank my thesis committee, Professor Jordan, Professor Szostak, and Professor Pietrangelo. I greatly appreciate they spent time reading my dissertation and pointed out some perspectives and constructive suggestions. I am really looking forward to our future discussions.

I would like to thank the past and present members of the Brenner-Moyer group, including Dr. Qunsheng Guo, Dr. Kinthada Ramakumar, Nicole Fuhr, Melanie Rodriguez-Alvarado and Guang Hu. We are working together and always support each other and discuss about problems in chemistry. I would specifically thank Dr. Qunsheng Guo and Dr. Kinthada Ramakumar. Dr. Qunsheng Guo teach me a lot of thing in doing research and some useful knowledge beside chemistry, which is a great help in my future life. Dr. Kinthada Ramakumar, for his training and guidance early in these two years. I really feel very lucky to work with him, he is a very kind and knowledgeable people, whenever I have problem or need help he said nothing but OK to me. Besides, Guang Hu enter this lab with me at same time, and he is also my roommate in the second year of my life in US. He always provide constructive suggestion in chemistry and helps me a lot in my academic works.
In addition, I would like to thank my friends in college and friends met in US, when I came to US at first, they are the best support over the lonely time. I defiantly can not come over this two year without their companion.

Last but not least, I would like to thank my family. They strongly encouraged me to go to study abroad several years ago and have provided so much love and support over these years. Without your help, I can never needless to worry about the living commendation, just go all out in doing research. Many thanks !!!!!!
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<table>
<thead>
<tr>
<th>Symbol</th>
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<tbody>
<tr>
<td>$2^\circ$</td>
<td>secondary</td>
</tr>
<tr>
<td>Å</td>
<td>ångstrom</td>
</tr>
<tr>
<td>Ac</td>
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</tr>
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<td>acetate</td>
</tr>
<tr>
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<td>acetic acid</td>
</tr>
<tr>
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<td>aryl</td>
</tr>
<tr>
<td>Bn</td>
<td>benzyl</td>
</tr>
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<td>br</td>
<td>broad</td>
</tr>
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<td>Bu</td>
<td>butyl</td>
</tr>
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<td>benzoyle</td>
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<td>carbon-13 nuclear magnetic resonance</td>
</tr>
<tr>
<td>cat</td>
<td>catalyst</td>
</tr>
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<td>deuterated chloroform</td>
</tr>
<tr>
<td>conc</td>
<td>concentrated</td>
</tr>
<tr>
<td>Cy</td>
<td>tricyclohexylphosphine</td>
</tr>
<tr>
<td>$\delta$</td>
<td>nuclear magnetic shift</td>
</tr>
<tr>
<td>d</td>
<td>doublet</td>
</tr>
<tr>
<td>DABCO</td>
<td>1,4-diazabicyclo[2.2.2]octane</td>
</tr>
<tr>
<td>DBU</td>
<td>1,8-diazabicyclo[5.4.0]undec-7-ene</td>
</tr>
<tr>
<td>DCE</td>
<td>1,2-dichloroethane</td>
</tr>
<tr>
<td>DCM</td>
<td>dichloromethane</td>
</tr>
<tr>
<td>DMF</td>
<td>dimethylformamide</td>
</tr>
<tr>
<td>DMSO</td>
<td>dimethylsulfoxide</td>
</tr>
<tr>
<td>$\text{E}^+$</td>
<td>electrophile</td>
</tr>
<tr>
<td>EDG</td>
<td>electron-donating group</td>
</tr>
<tr>
<td>$ee$</td>
<td>enantiomeric excess</td>
</tr>
<tr>
<td>equiv</td>
<td>equivalents</td>
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</table>
Et  ethyl
EtOAc  ethyl acetate
EtOH  ethanol
Et₂O  diethyl ether
Et₃N  triethylamine
EWG  electron-withdrawing group
FT-IR  Fourier transform infrared spectroscopy
g  gram
h  hour
¹H NMR  proton nuclear magnetic resonance
HPLC  high performance liquid chromatography
HRMS  high resonance mass spectrometry
IR  infrared
J  coupling constant
m  multiplet
M  molar
μM  micromolar
mM  millimolar
Me  methyl
MeO  methoxy
MeOH  methanol
mg  milligram
MHz  megahertz
min  minutes
mL  milliliter
mmol  millimole
mol  mole
mol%  mole percent
MS  molecular-sieves
Nap  naphthyl
nBuLi  n-butyl lithium
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CHAPTER 1

ROAD TO DIARYLAMINE

1.1 Natural Product Synthesis

Natural product synthesis is without question the great milestone of chemistry development. In my opinion, the meaning of natural product synthesis is always changing with time. Before the 1960’s, when chemists separated some unknown natural products, they could hardly characterize them, owing to the underdevelopment of infrared, mass spectroscopy, or NMR equipment. Thus, to clarify those uncertainties, the best way was to synthesize them step by step. In other words, natural product total synthesis was a way to determine unknown structure at that time.

In modern days, which is during the gold rush of small molecule drug design, the technique of natural product synthesis became more and more important. In order to obtain target molecules more efficiently and less costly, instead of directly extracting them from nature, manufacturers synthesize precious natural precursors artificially. One famous example is by Baran and his coworkers. They published a 14 step synthesis of (+)-ingenol in 2013,[1] which is relatively inexpensive compared with extracting directly from the plant Euphorbia peplus.

In this study, we are focusing on diarylamine structures, which are widely used in industrial additives,[2] amyloid aggregation inhibitors,[3] and some important bioactive scaffold precursors.[4]

Figure 1.1 Diarylamine structures.
1.2 Diarylamine Synthesis

There are many approaches to obtain this kind of diarylamine scaffold. I have grouped those ways into three different categories:

1. Transition Metal-Catalyzed N-Arylation

The metal catalyzed reaction between a nitrogen-nucleophile, such as an amine or amide, and an aryl halide to assemble a new C-N linkage is also known as a N-arylation reaction (Scheme 1.1).

Scheme 1.1 Metal-catalyzed C-N bond formation.

2. Transition Metal-Free Reactions

Because most of the N-arylation reactions involve transition-metal catalysts, I grouped other methods that don’t use them in this section. These include organocatalytic and uncatalyzed reactions.

In order to study our new approach to the desired compound, some of the examples reported in the synthesis of diarylamine scaffolds will be discussed in the later sections.

3. Other Reactions

Beside those two major categories, there are still some special ways to obtain diarylamine structures. For example, it is possible to start with cyclic aliphatic compounds or acyclic alkynes, such as cyclohexanone followed by nucleophilic addition, dehydration and oxidative dehydrogenation (Scheme 1.2).
1.2.1 Transition Metal-Catalyzed N-Arylation

To acquire our target diarylamine derivative structure, arylation is the most simple and direct way. Since 1995 and the development of the highly efficient Buchwald–Hartwig coupling reaction (Scheme 1.3), [5][6] many studies reported using metal for amination reactions. During the gold rush of transition-metal coupling reactions, there are two major research topics. One is looking for unique ligands to facilitate the reaction, and the other is changing from classic Pd-catalyst to different potential candidates, such as Cu, Ni or Ru. [7]

Scheme 1.3 Buchwald-Hartwig coupling reaction.

The proper choice of catalyst and ligand is important for the success of these types of reactions. Therefore, it would be great if there were one or a small group of ligand[s] that is suitable for handling most substrates. In 2000, Buchwald’s group reported using different ligand (Figure 1.2) and palladium catalyst combinations in aryl amination processes, which successfully reduced the reaction temperature to room temperature and resulted in moderate to good yields (Table 1.1). [8]
Figure 1.2 Excellent ligands for C-N bond-forming reactions.

Table 1.1 Room-temperature Pd catalyzed N-arylation by Buchwald.

```
   R1                  R2      R3
  I + HNR2R3       Pd(OAc)2 (1-2 mol %)  ligand 1.3  NaOt-Bu
                  toluene, rt
  \( \rightarrow \)
  \( \text{selected products} \)

  1.5a: Ph 98%
  1.5b: NPh 94%
  1.5c: NBu 81%
  1.5d: n-Hex 71%
  1.5e: 78%
  1.5f: 92%
```

With regard to changing the central atom to copper, the classical Ullmann coupling is an important pioneer reaction in this field, but is restricted by harsh reaction conditions and a high level of catalyst loading. As a result, copper salts are not as popular as their palladium counterpart. However in 2001, Venkataraman and coworkers tried to do the reaction with Cu(PPh3)3Br, which had great success in their previous work making diaryl ethers (Table 1.2). To their surprise, this copper(I) complex, Cu(PPh3)3Br, was not only soluble in common organic solvents such as THF, DCM, acetonitrile, chloroform, DMF, DMSO, and toluene, but also
can be used to form aryl-nitrogen bonds under relatively mild conditions. Besides, this copper(I) species is selective for aryl iodides and this characteristic makes it possible to synthesize a tri-ortho-ester functionalized triphenylamine (1.6b) which is not possible to do using modern palladium-catalyzed methods.

**Table 1.2** Scope of Venkataraman’s work.

![Diagram of chemical reaction]

<table>
<thead>
<tr>
<th>Selected Products</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1.6a</strong></td>
<td>70%</td>
</tr>
<tr>
<td><strong>1.6b</strong></td>
<td>40%</td>
</tr>
<tr>
<td><strong>1.6c</strong></td>
<td>54%</td>
</tr>
<tr>
<td><strong>1.6d</strong></td>
<td>75%</td>
</tr>
<tr>
<td><strong>1.6e</strong></td>
<td>88%</td>
</tr>
<tr>
<td><strong>1.6f</strong></td>
<td>83%</td>
</tr>
</tbody>
</table>

* R = CO₂CH₃
* a-Dichlorobenzene was used as solvent

In 2008, Liu and coworkers found a new protocol coupling various amines with different aryl halides. By using Fe₂O₃ and L-proline, the yield of diaryl structure was improved (Table 1.3), which is a dramatic improvement compared with pioneer work done by Bolm et al. in 2007. Because of the easy availability of the catalyst, which is air and moisture stable, this method has strong potential to be applied in the industrial field.
Table 1.3 Scope of Liu’s work.

\[
\begin{align*}
\text{Fe}_2\text{O}_3 (0.1 \text{ eq.}) & \\ 
\text{L-proline (0.2 eq.)} & \\ 
\text{NaO\textsubscript{Bu} (0.3 eq.)} & \\ 
\text{DMSO, 135 °C, 24 h} & \\ 
\end{align*}
\]

selected products

\[
\begin{align*}
\text{1.7a} & \quad 72\% \\ 
& \quad 41\%^a \\
\text{1.7b} & \quad 85\% \\
\text{1.7c} & \quad 85\% \\
\text{1.7d} & \quad 33\% \\
\text{1.7e} & \quad 54\% \\ 
& \quad 18\%^a \\
\text{1.7f} & \quad \text{trace} \\
\end{align*}
\]

\[^a\text{Performed without Fe}_2\text{O}_3 \text{ and L-proline.}\]

In 2015, Bala and coworkers synthesized new N-heterocyclic carbene (NHC)-Co complexes, 3,3-(dimethylimidazolin-2-ylidene) lutidine chlorocobalt(II) hexafluorophosphate 1.8a, and 3,3-(dibenzylimidazolin-2-ylidine) lutidine chlorocobalt(II) hexafluorophosphate 1.8b.\cite{12} Studies on this kind of pincer chelating ligands have seldom been reported, and it is even more rare to combine them with cobalt. According to their report, when they applied these new (NHC)-Co complexes as the catalyst in aryl C-N coupling reactions, it gave good results at a very low catalyst loading of 1 mol % (Table 1.4).
Figure 1.3 Structure of N-heterocyclic carbene-cobalt complexes.

![Structure of N-heterocyclic carbene-cobalt complexes](image)

1.8a: R=CH₃
1.8b: R=CH₂C₆H₅

Table 1.4 Scope of Bala’s work.

<table>
<thead>
<tr>
<th>R</th>
<th>R₂</th>
<th>1.8a or 1.8b (1 mol %)</th>
<th>KO'Bu, THF, 12 h</th>
<th>1.9</th>
</tr>
</thead>
<tbody>
<tr>
<td>phenyl</td>
<td>phenyl</td>
<td>+</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
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<th>selected products</th>
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</thead>
<tbody>
<tr>
<td>1.9a</td>
</tr>
<tr>
<td>1.9b</td>
</tr>
<tr>
<td>1.9c</td>
</tr>
</tbody>
</table>

ᵃ Use 1.8a as catalyst.
ᵇ Use 1.8b as catalyst.

In another interesting study, Boche and co-workers successfully got N-arylation products in a biphasic organic/aqueous palladium-catalyzed system.³ By introducing the sulfonated BINAP derivative, BINAS-6 (Figure 1.4), and Pd(OAc)₂ will become water soluble, thus making the separation of products and catalyst an easy task and friendly to industrial applications (Scheme 1.4).
Figure 1.4 Structure of BINAS-6.

Scheme 1.4 Water–butanol system for N-arylation.

Besides those oxidative coupling procedures mentioned previously, the reaction of aromatic nitrogen compounds with aryl Grignards can also provide the desired diarylamine. The reaction of nitroarenes with various Grignard reagents have been frequently studied, but the product of this reaction is an unstable diarylhydroxylamine, which quickly turns into diarylnitroxyl radicals in air (Scheme 1.5).\textsuperscript{[14]}

Scheme 1.5 Diarylhydroxylamine decomposition.

To solve this problem, Knochel and coworkers reported a new method in 2002, adding a reductive work up in the protocol.\textsuperscript{[15]} These air-sensitive
diarylhydroxylamines are converted under mild conditions into diarylamines by addition of FeCl$_2$ and NaBH$_4$ (Scheme 1.6). Using a bromine or iodine-magnesium exchange reaction, they prepared various functionalized arylmagnesium reagents under mild conditions, which make this method compatible with different substituents, such as an ester, cyano, methoxy, or iodine (Table 1.5).

Scheme 1.6 Procedure of organometallic N-arylation.

Table 1.5 Scope of Knochel’s work.

According to the protocol they provided, we notice that this reaction requires two equivalents of the arylmagnesium reagent. The first is for the generation of the reactive nitrosoarene. Therefore, using the nitrosoarene species directly, we can
avoid wasted arylmagnesium reagent (Scheme 1.7). In 2003 following their previous work, Knochel and coworkers published another organometallic N-arylation by starting with nitrosoarene derivatives.\cite{16}

Scheme 1.7 Organometallic N-arylation cycle.

\[
\text{Ar}^2\text{NO}_2 \xrightarrow{\text{1. Ar}^1\text{MgX (2 equiv.)}} \text{Ar}^2\text{N}^\text{Ar}^1
\]

1.2.2 Transition-Metal-Free Reactions

Catalyst-free and organocatalytic reactions have been at the frontier of organic synthesis in recent years. Compared with its metal catalysis counterpart, several advantages including mild reaction conditions, environmental friendliness, and the facile recovery of catalysts, render organocatalysis important in the development of green chemistry and other sustainable applications.

In 1985, Shudo and coworkers reported a reaction which used arylhydroxylamine reacting with benzene in the presence of trifluoroacetic acid (TFA) or trifluoromethanesulfonic acid (TFSA).\cite{17} This method can yield diarylamines (1.13c) and biphenylamines (1.13a, 1.13b) (Scheme 1.8).
Scheme 1.8 Acid-catalyzed $N$-phenylhydroxylamine reaction with benzene.

In this reaction, the formation of 1.13a and 1.13b can be described as a nucleophilic attack on immonium ion 1.12 by benzene, and the formation of diarylamines 1.13c would be a $S_N2$ attack on the nitrogen atom of intermediate 1.14. When using TFA as catalyst, the major product was diarylamine. However, when increasing the acidity by adding small amounts of TFSA, the yield of diarylamine decreased while the yields of biphenylamines increased.

Later, a similar mechanism was developed using phenylhydrazines. In 2001, Kikugawa and coworkers reported using AlCl$_3$-mediated heterolytic cleavage of the N-N bond, which can produce a phenylnitrenium ion and undergo nucleophilic attack by benzene.$^{[18]}$ Similar to the work done by Shudo, a positive charge will resonate between the ortho- and para-positions as well as the nitrogen atom. Therefore, they can also acquire different kinds of products such as diarylamines and biphenylamines (Scheme 1.9). This reaction proceeds with several benzene derivatives and with varying results (Table 1.6).

Scheme 1.9 Reaction of phenylhydrazines with arenes in the presence of AlCl$_3$. 
Table 1.6 Scope of Kikugawa’s work.

<table>
<thead>
<tr>
<th>R</th>
<th>NH₂</th>
<th>R'</th>
<th>NH₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph</td>
<td>H</td>
<td>Ph</td>
<td>H</td>
</tr>
<tr>
<td>1.15aa</td>
<td>44%</td>
<td>1.15ba</td>
<td>8%</td>
</tr>
<tr>
<td>1.15ab</td>
<td>28%</td>
<td>1.15bb</td>
<td>15%</td>
</tr>
<tr>
<td>1.15cb</td>
<td>9%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Beside using AlCl₃ mediated cleavage of phenylhydrazines, the groups of Prakash and Olah reported a highly efficient way for diarylamine formation using triflic acid and phenyl azide (Scheme 1.10)[19]. For similar reasons mentioned above, a mixture of ortho/para products are observed. Therefore, the mechanism is likely similar to the previously work described. However, using this method, an aminodiazonium ion is formed by protonation by triflic acid, then reacts with aromatic hydrocarbons to give good yields (Table 1.7).

Scheme 1.10 Triflic acid catalyzed azide N-arylation.
Table 1.7 Scope of Prakash’s and Olah’s work.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.16a</td>
<td>82%</td>
</tr>
<tr>
<td>1.16b</td>
<td>94%</td>
</tr>
<tr>
<td>1.16c</td>
<td>90%</td>
</tr>
<tr>
<td>1.16d</td>
<td>trace</td>
</tr>
<tr>
<td>1.16e</td>
<td></td>
</tr>
</tbody>
</table>

In 2001, Beller and coworkers published a new transition metal-free amination using aryl chlorides as the starting material.\(^{[20]}\) The use of potassium tert-butoxide as base formed aryne intermediates in situ, which react with several amines (Scheme 1.11). Using this method, they also acquired diaminated product by starting with dihalogenated arene. However, this method only applicable in the synthesis of meta-substituted anilines. (Table 1.8).

Scheme 1.11 Base catalyzed aryl chlorides N-arylation.
Table 1.8 Scope of Beller’s work.

\[
\begin{align*}
\text{Cl} & + R^2R^3N^+H^- & \xrightarrow{KO'Bu (3 \text{ equiv})} & R^2R^3N^-R^1 + R^1N^+R^3 \\
\text{selected products} & & & \\
\text{MeO}-\begin{array}{c} \text{H} \\ \text{N} \\ \text{N} \end{array} & -\begin{array}{c} \text{H} \\ \text{N} \end{array} & -\begin{array}{c} \text{H} \\ \text{N} \end{array} & -\begin{array}{c} \text{H} \\ \text{N} \end{array} \\
1.17a & 77\% & 1.17b & 81\% & 1.17c & 85\% \\
\text{O} & \begin{array}{c} \text{N} \\ \text{N} \end{array} & \begin{array}{c} \text{N} \\ \text{N} \end{array} & \begin{array}{c} \text{N} \\ \text{N} \end{array} & \begin{array}{c} \text{N} \\ \text{N} \end{array} & \begin{array}{c} \text{N} \\ \text{N} \end{array} \\
1.17d^a & 78\% & 1.17e^a & 86\% \\
\end{align*}
\]

\(a\) KO'Bu loading is 4 equiv.

In 2006, Ramachary and coworkers developed a one-pot organocatalyzed reaction. By using Hagemann’s esters, nitrosobenzenes, and different kinds of secondary amines, three types of amination products resulted (Scheme 1.11).\(^{[21]}\) Two of them are di-aminated and the other one is our desired structure, a diarylamine.

In this work, the reaction begins with enamine condensation. Owing to the possibility of forming two different kinds of dienamine intermediates, the reaction can go two ways, as shown in Scheme 1.12. Depending on a variety of conditions, the diimine ion can also go a different route. When using DMSO as solvent, the amination product, 1.18, is the major product. However, the same reaction in protic
solvents such as EtOH end up with a totally different result, giving dimation products, 1.19 and 1.20, with poor selectivity. Slow addition of nitrosobenzene to the reaction and using pyrrolidine as the catalyst provides good selectivity and yield (Table 1.9).

Scheme 1.12 Synthesis of highly substituted anilines.

Table 1.9 Scope of Ramachary’s work.

<table>
<thead>
<tr>
<th>R¹</th>
<th>R²</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OH</td>
<td>NPh</td>
<td>1.18⁵</td>
<td>85%</td>
</tr>
<tr>
<td>OH</td>
<td>NPh</td>
<td>1.18a⁴</td>
<td>86%</td>
</tr>
<tr>
<td>OH</td>
<td>NPh</td>
<td>1.18b⁴</td>
<td>90%</td>
</tr>
<tr>
<td>OH</td>
<td>NPh</td>
<td>1.18c⁴</td>
<td>96%</td>
</tr>
<tr>
<td>OH</td>
<td>NPh</td>
<td>1.18d⁴</td>
<td>80%</td>
</tr>
<tr>
<td>OH</td>
<td>NPh</td>
<td>1.19a⁴</td>
<td>90%</td>
</tr>
<tr>
<td>OH</td>
<td>NPh</td>
<td>1.19b⁴</td>
<td>30%</td>
</tr>
<tr>
<td>OH</td>
<td>NPh</td>
<td>1.19c⁴</td>
<td>75%</td>
</tr>
</tbody>
</table>

⁵ pyrrolidine (5 mol%), DMSO, rt
⁴ pyrrolidine (0.3 mol%), EtOH, rt
In 2008, Luo and coworkers published a novel way to obtain ortho-aminated naphthol derivatives, by heating N,N-disubstituted hydrazines with 2-naphthol (Scheme 1.13).\cite{22}

**Scheme 1.13** Scheme of 2-naphthol with N,N-disubstituted hydrazines.

Generally, the result of reactions between naphthol and hydrazines were usually the substitution of the hydroxyl group on naphthol. When followed by benzidine rearrangement, carbazoles can be acquired instead of arylamines (Scheme 1.13).\cite{23}

In this work, they heated a mixture of 2-naphthol and N-methyl-N-phenylhydrazine at 80 °C. α-Aminated product, 1-amino-2-naphthol, and N-methylaniline can easily be formed without using a catalyst. Following this discovery, they tested other types of N,N-disubstituted hydrazine derivatives which also reacted smoothly with 2-naphthol in good yields (Table 1.10).

![Scheme 1.13](image-url)
In 2013, Singh and coworkers developed an ionic liquids (ILs) catalyst system to do N-arylation through S_N_Ar type substitution. In ILs catalyzed reactions, inorganic bases are usually used to assist the deprotonation or coordination of the nucleophile. Recently, instead of using inorganic bases, organic ionic bases have been widely used in coupling reactions. It is because organic ionic bases have some key features that make them easier to use in reactions, such as high solubility, low melting point, and more stability in air. In this work, they used [DBU][HOAc] pair and a Brønsted acid additive, p-toluenesulfonic acid, to do the C-N bond forming reaction (Table 1.11).

Table 1.10 Reaction Results of 2-Naphthol with N,N-Disubstitued Hydrazines.

<table>
<thead>
<tr>
<th>Product</th>
<th>Reaction Conditions</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.21a</td>
<td>Br^+</td>
<td>94%</td>
</tr>
<tr>
<td>1.21b</td>
<td>HO^-</td>
<td>92%</td>
</tr>
<tr>
<td>1.21c</td>
<td>NH^-</td>
<td>58%</td>
</tr>
<tr>
<td>1.21d^a</td>
<td>NH^-</td>
<td>40%</td>
</tr>
<tr>
<td>1.21e^b</td>
<td>NH^-</td>
<td>10%</td>
</tr>
<tr>
<td>1.22a</td>
<td>NH^-</td>
<td>96%</td>
</tr>
<tr>
<td>1.22b</td>
<td>NH^-</td>
<td>92%</td>
</tr>
<tr>
<td>1.22c</td>
<td>NH^-</td>
<td>95%</td>
</tr>
<tr>
<td>1.22d</td>
<td>NH^-</td>
<td>95%</td>
</tr>
</tbody>
</table>

^a Starting with 1-naphthalenamine.
^b Starting with 2-naphthalenamine.
Table 1.11 Scope of Singh’s work.

The biggest advantage of the ionic liquids catalyst system is the recyclability of the catalyst. After removal of water by heating and vacuum, the recovered ionic liquid was reused five times without significant loss of activity. Representative results are shown in Figure 1.5.

Figure 1.5 Reusability of the ionic liquid from Table 1.11.
In 2014, Unnikrishnan and coworkers discovered a new C-to-N aryl migration using Burgess reagent, methyl N-(triethylammoniumsulfonyl)carbamate (Figure 1.6).\textsuperscript{[25]} It is usually used to convert secondary and tertiary alcohol with an adjacent proton into alkenes.

**Figure 1.6** Structure of Burgess reagent.

However, in this work, it was used to trigger transformations of nitrones, which involve a [3 + 2] annulation across a S-N bond and C-to-N aryl migration (Scheme 1.14). Generally speaking, nitrones exhibit remarkable nucleophilicity and can react with Burgess reagent to give 1,2,3,5-oxathiadiazolidine intermediates (1.24) via a [3 + 2] annulation reaction across a nitrogen–sulfur bond. Followed by hydrolysis, the transformation yielded diphenylamine and compound 1.25.
Scheme 1.14 Mechanism of C-to-N aryl migration.

In 2015, the groups of Cao and Shi developed a simple and effective nucleophilic aromatic substitution via selective C–F bond cleavage.\textsuperscript{26} With the participation of different primary and secondary aromatic amines, diarylamine structure was acquired in good to excellent yields. The first step of this reaction was the generation of the C$_6$H$_5$NH\textsuperscript{−} anion, which is known as the “active species” in the reaction, followed by attack on fluorinated carbon (Table 1.12).
Table 1.12 Scope of Cao and Shi’s work.

\[
\begin{align*}
\text{NH}_2 \quad & \quad \text{F} \\
\text{R}^1 \quad & \quad \text{F} \\
\end{align*}
\]

\[
\begin{array}{ccc}
\text{NH} & \text{N} & \text{H} \\
\text{1.26a} & \text{87\%} & \text{1.26b} & \text{83\%} & \text{1.26c} & \text{81\%} \\
\text{1.26d} & \text{81\%} & \text{1.26e} & \text{87\%} \\
\end{array}
\]

1.2.3 Other Reactions

Besides directly attaching an aryl amine onto an aromatic group, using dehydrogenation to form aromatic compounds is also an effective way to reach the diarylamine structure. The first group to successfully employ this method was Stahl, who presented a palladium-catalyzed dehydrogenation under aerobic conditions in 2011.\[27\] In this report, they started from substituted cyclohexanones and end up with the corresponding phenols. As shown in Scheme 1.15, two successive $\beta$-H eliminations and aerobic oxidation of palladium removing hydrogen atoms from saturated carbon-carbon bonds, followed by tautomerization, yielded the aromatized product.

Returning to heteroatom junctions, especially C-N linkages, the groups of Deng and Li reported an efficient method for the preparation of aromatic amines in 2012.\[28\][29] Inspired by Stahl’s work, they also used the concept of aerobic dehydrogenation of cyclohexanone, but they introduced some primary or secondary
amines. This way, they developed an effective method for the preparation of aromatic amines. The mechanism is outlined in Scheme 1.16

**Scheme 1.15** Strategy for oxidative dehydrogenation of cyclohexanone derivatives.

**Scheme 1.16** Proposed mechanism for the palladium-catalyzed arylation of amines.
The reaction starts with the formation of enamine 1.29, which will undergo metallation of palladium to form the iminium intermediate 1.31. This intermediate may quickly undergo tautomerization and turn into a relatively stable form, 1.32. Then, after β-hydride-elimination, amino cyclic diene 1.34 and a metal-hydride 1.33 can be acquired, and the latter could reform the initial palladium catalyst 1.30 in the presence of oxygen. The arylamine product 1.35 will be formed in a second catalytic cycle by dehydrogenation of the diene species.

According to their report, this reaction can successfully generate C-N coupled tertiary amines with different kinds of alkylamines, such as piperidine, morpholine, dibenzylamine, indole, and even diallylamine (Table 1.13).

**Table 1.13** Scope of Deng and Li’s work.

![Reaction Scheme](attachment:image.png)

<table>
<thead>
<tr>
<th>Selected Products</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.36a</td>
<td>82%</td>
</tr>
<tr>
<td>1.36b</td>
<td>66%</td>
</tr>
<tr>
<td>1.36c</td>
<td>94%</td>
</tr>
<tr>
<td>1.36d</td>
<td>73%</td>
</tr>
<tr>
<td>1.36e</td>
<td>82%</td>
</tr>
<tr>
<td>1.36f R=CH₃</td>
<td>86%</td>
</tr>
<tr>
<td>1.36g R=OEt</td>
<td>77%</td>
</tr>
<tr>
<td>1.36h</td>
<td>82%</td>
</tr>
<tr>
<td>1.36i</td>
<td>77%</td>
</tr>
<tr>
<td>1.36j</td>
<td>83%</td>
</tr>
</tbody>
</table>

* [(PMesPh₂)PdCl₂] (2 mol %), PhCO₂H (20 mol %), 100 °C, 18 h
* Pd(OAc)₂, 1,10-phenanthroline (10 mol %), 135 °C, 36 h
* NMR yield
In the same year, 2012, Yoshikai and coworkers also described a dehydrogenation approach for the synthesis of arylamines via a Pd(OAc)$_2$/ Bu$_4$NBr / DMSO system.$^{[30]}$ Similar to the work done by Deng and Li, Yoshikai changed the starting material to different kinds of cyclohexanone imines, either preformed or formed in situ. Their reaction underwent a similar mechanism including palladation and β-H elimination to give arylamines in moderate to good yields (Table 1.14). To sum up aerobic dehydrogenation reactions, the tolerance of functional groups such as an aryl-Br bond is pretty good, which shows a great potential for the applicability of the present reaction instead of using Buchwald-Hartwig and the Ullmann-type coupling reactions.

Table 1.14 Scope of Yoshikai’s work.

<table>
<thead>
<tr>
<th>Route</th>
<th>Product</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>1.37a</td>
<td>79%$^a$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>52%$^b$</td>
</tr>
<tr>
<td>B</td>
<td>1.37b$^a$</td>
<td>91%</td>
</tr>
<tr>
<td></td>
<td>1.37c$^a$</td>
<td>79%</td>
</tr>
<tr>
<td></td>
<td>1.37d$^b$</td>
<td>66%</td>
</tr>
<tr>
<td></td>
<td>1.37e$^b$</td>
<td>52%</td>
</tr>
<tr>
<td></td>
<td>1.37f$^b$</td>
<td>62%</td>
</tr>
</tbody>
</table>

$^a$ Pd(OAc)$_2$ (10 mol %), Bu$_4$NBr (2 equiv), O$_2$ (1 atm), 3 Å MS, 90 ºC, 12 h, toluene/DMSO (9:1)

$^b$ Pd(OAc)$_2$ (10 mol %), Bu$_4$NBr (1.5 equiv), O$_2$ (1 atm), 3 Å MS, 90 ºC, 12 h, DMSO
In 2013, Lemaire and coworkers developed a new method of synthesizing arylamines from nonaromatic substrates such as cyclohexanone or tetralone (Table 1.15). By using renewable heterogeneous Pd/C catalyst under neat conditions, yields can go up to 90%. Unfortunately, when the dehydrogenation reaction used secondary amines, some simple primary amines may be generated (Scheme 1.17). Therefore, the less hindered primary amine reacts with the starting material, giving the same product as primary amines.

**Table 1.15** Scope of Lemaire’s work.

![Table 1.15 Scope of Lemaire’s work.](image)

**Scheme 1.17** Mechanism for N,N-dibutylamine dehydrogenation.

![Scheme 1.17 Mechanism for N,N-dibutylamine dehydrogenation.](image)
1.3 Conclusion

With respect to the preparation of diarylamine derivatives, we were strongly interested in using organocatalysts, not only because of their low toxicity and cost but also for the potential for asymmetric modifications. Based on previous work, enamine activation can provide smooth routes for modifications of α,β-unsaturated aldehydes or ketones. After dehydration, unsaturated cyclic ketone can be transformed into desired diarylamine structure (Scheme 1.18). However, in the methods mentioned previously, regioselectivity remain a problem that need to be solved.

Scheme 1.18 Proposed synthesis strategy.
1.4 References

CHAPTER 2
ENAMINE-CATALYZED CASCADE REACTIONS

2.1 Enamine-Catalyzed Reactions

With the introduction of the previous work in Chapter 1, there was potential for the development of organocatalytic reactions to achieve this goal. One of the benefits is that organocatalysis is an efficient way to synthesize of natural products and drug precursors without using expensive and toxic metal catalysts. Also, cascade reactions are the best candidates to develop complex molecules. In enamine-iminium system (Scheme 2.1), the amine catalyst 2.2 can combine with carbonyl 2.1 forming iminium ion 2.3, followed by α-deprotonation to form enamine 2.4. This reactive intermediate can react with an electrophile in solution, generating α-functionalized iminium ion 2.5. The reaction finally undergoes hydrolysis to get α-functionalized carbonyl 2.6 and regeneration of catalyst 2.2.

Scheme 2.1 Enamine organocatalytic cycle.
This kind of enamine catalysis system has been widely used in asymmetric catalysis since 2000. List et al. first reported the proline-catalyzed asymmetric intermolecular aldol reaction,[1] followed by MacMillan et al. who reported an asymmetric Diels–Alder reaction catalyzed by their chiral imidazolidinone catalyst.[2] In this work, we don’t use asymmetric catalysis, rather we use only simple enamine catalysis to process the reaction.

2.1.1 Nitrosobenzene

As shown in Scheme 2.1 in enamine catalysis system, we need to find a proper electrophile to be attacked by enamine intermediate. On the basis of previous study,[3] nitrosobenzene has long been used as an electrophile in enamine catalyzed reactions especially acting as the heteroatom source.[4] Some unique properties makes it a good target for study. Unlike other common electrophiles, nitrosobenzene can act as either a nitrogen electrophile or an oxygen electrophile, depending on the reaction conditions (Scheme 2.2).[5]

Scheme 2.2 Possible nucleophilic addition on nitrosobenzene.

Generally speaking, under neutral conditions an oxyminated product, 2.11, is formed, while in the presence of Lewis acid catalysts, the whole reaction is apt to generate α-aminooxy product, 2.10, which is highly O-selective.[6]

However, there also some problems when using nitrosobenzene as a substrate for
example, the dimerization of nitrosobenzene in solution (Scheme 2.3) is quite rapid. Although some reports\textsuperscript{[7]} state that it won’t affect the reaction, the rapid consumption of starting material 2.7 and the formation of irreversible product 2.13 remains a problem needing to be solved.

**Scheme 2.3** Formation of nitrosobenzene dimers.

![Scheme 2.3 Formation of nitrosobenzene dimers.](image)

### 2.1.2 The Planned Organocascade

Using the concept of enamine catalysis, we propose a novel cascade reaction (Scheme 2.4). Starting with 2-tetralone (2.14) and combine with amine catalyst (2.15), the iminium ion 2.16 was formed. Then, the intermediate quickly turns into enamine 2.17 and the α-position of enamine attacks the nitrogen site of nitrosobenzene 2.7, forming another α-substituted iminium ion 2.18. After that, followed by several dehydrations and enol-keto tautomerism, the reaction should finish with highly functionalized arylamine products 2.23.

These kind of arylamines are of considerable importance in a variety of industries.\textsuperscript{[8]} For example, o-hydroxydiarylamines (Figure 2.1) are useful materials as additives for rubbers and plastics, antioxidants, antibacterial activity, and hair dyes.\textsuperscript{[9]}
Scheme 2.4 Proposed enamine cascade mechanism.

Figure 2.1 o-Hydroxydiarylamines.
2.2 Result and Discussion

2.2.1 Optimization

For optimization of this cascade, a number of solvents and well-known amine catalysts for amination were screened. Also 1 - 1.2 equiv. of tetralone were used, as shown in Table 2.1.

The reaction was initially run without catalyst (Table 2.1, entry 1), using Brønsted-acid catalyst, benzoic acid (entry 2), and with secondary amine catalyst, pyrrolidine (entry 3). It is important to note that Brønsted-acid may trigger simple aldol condensation. When there is no catalyst, none of the product is observed, which tells us that the reaction will not go spontaneously. Between benzoic acid and pyrrolidine catalyst, we can see a clear difference in yield from 23% to 55%, which means in this case, enamine catalysis is better than traditional acidic catalysis. Therefore, we chose several amine catalysts for screening, which are listed in Figure 2.2.

Figure 2.2 Amine catalyst used in screening.
Table 2.1 Optimization Table

![Reaction Scheme]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Solvent</th>
<th>Tetralone (equiv.)</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>DMSO</td>
<td>1.0</td>
<td>1</td>
<td>—</td>
</tr>
<tr>
<td>2&lt;sup&gt;c&lt;/sup&gt;</td>
<td>PhCO₂H</td>
<td>DMSO</td>
<td>1.0</td>
<td>1</td>
<td>23</td>
</tr>
<tr>
<td>3&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Pyrrolidine</td>
<td>DMSO</td>
<td>1.0</td>
<td>1</td>
<td>55</td>
</tr>
<tr>
<td>4</td>
<td>Pyrrolidine</td>
<td>DMSO</td>
<td>1.0</td>
<td>1</td>
<td>62</td>
</tr>
<tr>
<td>5</td>
<td>L-Proline</td>
<td>DMSO</td>
<td>1.0</td>
<td>18</td>
<td>20</td>
</tr>
<tr>
<td>6</td>
<td>Piperidine</td>
<td>DMSO</td>
<td>1.0</td>
<td>1</td>
<td>76</td>
</tr>
<tr>
<td>7</td>
<td>Morpholine</td>
<td>DMSO</td>
<td>1.0</td>
<td>1</td>
<td>56</td>
</tr>
<tr>
<td>8</td>
<td>PhCO₂H</td>
<td>DMSO</td>
<td>1.0</td>
<td>24</td>
<td>—</td>
</tr>
<tr>
<td>9</td>
<td>DABCO</td>
<td>DMSO</td>
<td>1.0</td>
<td>1</td>
<td>52</td>
</tr>
<tr>
<td>10</td>
<td>DBU</td>
<td>DMSO</td>
<td>1.0</td>
<td>1</td>
<td>46</td>
</tr>
<tr>
<td>11</td>
<td>Triethylamine</td>
<td>DMSO</td>
<td>1.0</td>
<td>1</td>
<td>23</td>
</tr>
<tr>
<td>12</td>
<td>Piperidine</td>
<td>DMF</td>
<td>1.0</td>
<td>1</td>
<td>65</td>
</tr>
<tr>
<td>13</td>
<td>Piperidine</td>
<td>CHCl₃</td>
<td>1.0</td>
<td>1</td>
<td>57</td>
</tr>
<tr>
<td>14</td>
<td>Piperidine</td>
<td>DCE</td>
<td>1.0</td>
<td>1</td>
<td>71</td>
</tr>
<tr>
<td>15</td>
<td>Piperidine</td>
<td>THF</td>
<td>1.0</td>
<td>1</td>
<td>60</td>
</tr>
<tr>
<td>16</td>
<td>Piperidine</td>
<td>C₆H₅CH₃</td>
<td>1.0</td>
<td>1</td>
<td>73</td>
</tr>
<tr>
<td>17</td>
<td>Piperidine</td>
<td>EtOH</td>
<td>1.0</td>
<td>1</td>
<td>67</td>
</tr>
<tr>
<td>18</td>
<td>Piperidine</td>
<td>DMSO</td>
<td>1.2</td>
<td>1</td>
<td>75</td>
</tr>
<tr>
<td>19&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Piperidine</td>
<td>DMSO</td>
<td>1.0</td>
<td>1</td>
<td>84</td>
</tr>
<tr>
<td>20&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Piperidine</td>
<td>DMSO</td>
<td>1.0</td>
<td>1</td>
<td>71</td>
</tr>
<tr>
<td>21&lt;sup&gt;f&lt;/sup&gt;</td>
<td>Piperidine</td>
<td>DMSO</td>
<td>1.0</td>
<td>1</td>
<td>96</td>
</tr>
</tbody>
</table>

<sup>a</sup> Reactions were carried out at tetralone/DMSO solution (0.5M, 1mL) in the presence of 0.5 mmol nitrosobenzene and 20 mol% catalyst at room temperature. <sup>b</sup> Isolated yield. <sup>c</sup> Reaction performed at 100 °C. <sup>d</sup> 0.6 mmol of nitrosobenzene used. <sup>e</sup> To the mixture of tetralone (0.5 mmol) and piperidine (0.1 mmol) in DMSO (0.2 mL) was added a DMSO (0.8 mL) solution of nitrosobenzene (0.5 mmol) over a period of 1h at rt. <sup>f</sup> To the mixture of tetralone (0.5 mmol) and piperidine (0.1 mmol) in DMSO (0.2 mL) was added a DMSO (0.8 mL) solution of nitrosobenzene (0.6 mmol) over a period of 1h at rt.
Among these secondary amine catalysts, piperidine had the best yield (entry 6) 76%, followed by pyrrolidine (entry 4) 62%, morpholine (entry 7) 56% and L-proline (entry 5) 20%. The reason for differences in yield may be due to many reasons. For L-proline, the extending carboxyl group may partially block the reactive site causing steric hindrance and reduce the yield. For morpholine, it has similar structure to piperidine, but owing to an oxygen atom, the basicity is weaker than piperidine, which may be the major reason.

When the optimization goes to tertiary amine examples, the original mechanism we proposed seemed to have some mistakes. In our assumption, the reaction should not work when run with DABCO (entry 9), DBU (entry 10), or triethylamine (entry 11), but unfortunately resulted in 52%, 46%, and 23% yields respectively. Therefore, instead of enamine catalysis, we confirmed that this mechanism was base catalyzed (Scheme 2.5).

**Scheme 2.5 Proposed base catalysis mechanism.**

Base on these results, we chose piperidine as our catalyst and tested it with some common organic solvents. Not surprisingly, there were variations in yields: 65% in DMF, 57% in chloroform, 71% in DCE, 60% in THF, 73% in toluene, 67% in
ethanol, and 76% in DMSO. In summary, the piperidine-DMSO combination (entry 6) produced the best yield amongst several candidates in the optimizations.

As we have mentioned previously, the dimerization of nitrosobenzene in reaction mixtures will consume starting material and effect the yield, so we decided to increase the amount of nitrosobenzene from 1 equiv to 1.2 equiv (entry 19), which raised the yield from 76% to 84%. To minimize the impact of dimerization, we finally figured out that dissolving nitrosobenzene into a small fraction of solvent and doing a dropwise addition over a period of one hour (entry 21) dramatically improved the yield to 96%. So, the final reaction conditions for the substrate scope were chosen as entry 21 of Table 2.1.

2.2.2 Substrate Scope

Using these optimal reaction conditions, the rest of the substrate scope was undertaken in two different categories. First, various substituted nitrosobenzenes were used as starting material (Figure 2.3 and Table 2.2). All reactions finished in one hour at room temperature, and all starting materials were consumed completely as confirmed by TLC. The yields were varied between substrates. The simple, single methyl substituted nitrosobenzene afforded yields of 91% for 2.23b and 95% for 2.23d. For electron-donating substituted substrates, we have yields of 85% for 2.23i, 88% for 2.23j, and 97% for 2.23n. For halogenated substrates a 90% yield was obtained for 2.23g, 94% for 2.23h, and 95% for 2.23m. Electron-withdrawing substitution provide yields at 86% for 2.23c, 92% for 2.23e, 85% for 2.23f, 88% for 2.23k, 85% for 2.23o, and 90% for 2.23p. We also tested a multi-substituted entry 2.23l, which gave a 90% yield.
Figure 2.3 List of nitrosobenzene used in reaction.

Although there was some variation in yields, all of them remained high at over 85%. It seems that substitution on nitrosobenzene does not play an important role in the reaction. No matter how we changed the substituting position or type of group, the difference in yields was no more than 12%.

It should be noted that all of these products were isolated by flash column chromatography and structures were determined by NMR spectroscopy. Details of the procedure will be discussed in Chapter 3.
Table 2.2 Substrate scope of N-Ar Coupling $^{a,b}$

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Product</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.14 + 2.7</td>
<td>2.23</td>
<td>96%</td>
</tr>
<tr>
<td>2.23b</td>
<td>91%</td>
<td></td>
</tr>
<tr>
<td>2.23c</td>
<td>86%</td>
<td></td>
</tr>
<tr>
<td>2.23d</td>
<td>95%</td>
<td></td>
</tr>
<tr>
<td>2.23e</td>
<td>92%</td>
<td></td>
</tr>
<tr>
<td>2.23f</td>
<td>85%</td>
<td></td>
</tr>
<tr>
<td>2.23g</td>
<td>90%</td>
<td></td>
</tr>
<tr>
<td>2.23h</td>
<td>94%</td>
<td></td>
</tr>
<tr>
<td>2.23i</td>
<td>85%</td>
<td></td>
</tr>
<tr>
<td>2.23j</td>
<td>88%</td>
<td></td>
</tr>
<tr>
<td>2.23k</td>
<td>88%</td>
<td></td>
</tr>
<tr>
<td>2.23l</td>
<td>90%</td>
<td></td>
</tr>
<tr>
<td>2.23m</td>
<td>95%</td>
<td></td>
</tr>
<tr>
<td>2.23n</td>
<td>97%</td>
<td></td>
</tr>
<tr>
<td>2.23o</td>
<td>85%</td>
<td></td>
</tr>
<tr>
<td>2.23p</td>
<td>90%</td>
<td></td>
</tr>
</tbody>
</table>

$^a$ Reactions were carried out in a mixture of tetralone (0.5 mmol) and piperidine (0.1 mmol) in DMSO (0.2 mL) with dropwise addition of nitrosobenzene (0.6 mmol) in DMSO (0.8 mL). $^b$ Isolated yield.
The second part of the substrate scope was also run with optimized conditions, which is shown in Table 2.3. Unlike the first part of substrate scope, when the reaction was run with a variety of tetralones, the difference in yield is pretty apparent. For electron-donating substituted substrates, we tried a methoxy group in different positions which yielded 67% for 2.23A, 83% for 2.23B, 43% for 2.23C, and 52% for 2.23D. For electron-withdrawing substituents, we tried one entry with fluorine in the 6-position (2.23E), which gave only 12% yield. For comparison in 2.23F we also used an electron-donating group and put it on the same position as in 2.23B. Not surprisingly, it provided a similar yield of 88%.

**Table 2.3 Substrate scope.**

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.23A</td>
<td>67%</td>
</tr>
<tr>
<td>2.23B</td>
<td>83%</td>
</tr>
<tr>
<td>2.23C</td>
<td>43%</td>
</tr>
<tr>
<td>2.23D</td>
<td>52%</td>
</tr>
<tr>
<td>2.23E</td>
<td>12%</td>
</tr>
<tr>
<td>2.23F</td>
<td>88%</td>
</tr>
</tbody>
</table>

*a* Reactions were carried out in a mixture of tetralone (0.5 mmol) and piperidine (0.1 mmol) in DMSO (0.2 mL) with dropwise addition of nitrosobenzene (0.6 mmol) in DMSO (0.8 mL). *b* Isolated yields. *c* Reaction was carried out in a mixture of tetralone (0.25 mmol) and piperidine (0.05 mmol) in DMSO (0.1 mL) with dropwise addition of nitrosobenzene (0.3 mmol) in DMSO (0.4 mL).
To explain this phenomenon, we needed to look back into the mechanism. When the ketone forms the carbanion intermediate, the α-position is negatively charged as shown in **Scheme 2.6**. But, when there are electron donating groups, they will push the electrons to the benzene ring and increase π-electron density, especially on the *ortho* and *para* positions. Therefore, the partial negative charges generated by directing groups will repel the driving force to form the carbanion and lead to a decrease in yield (**Scheme 2.7**).

**Scheme 2.6** 2-Tetralone deprotonation.

**Scheme 2.7** 2-Tetralone deprotonation with substitution.
2.3 Conclusion

In this project, we have successfully developed a practical and novel one-pot organocatalytic process to obtain highly substituted diarylamines via coupling between 2-tetralone and nitrosobenzene derivatives. This cascade provided excellent yields of up to 96%. This reaction has the potential for use in the construction of key intermediates in the synthesis of complex carbazole based natural products. But there is an issue to make this reaction more practical: high catalyst loading of up to 10 mol% is required. Though better than metal catalysts, these kind of secondary amines are still toxic\cite{10}. Nevertheless, we still believe that the design of novel sequences involving new substrates and developing new types of catalysts with alternate mechanisms will lead to new efficient synthetic routes to procure carbazoles and other classes of potentially bioactive molecules.
2.4 References


CHAPTER 3
EXPERIMENTAL AND CHARACTERIZATION

3.1 General Information
All chemicals and solvents were purchased from Sigma-Aldrich, Fisher Scientific, or TCI America. ¹H and ¹³C NMR data were acquired on Bruker 500 MHz NMR spectrometers. Flash chromatography was carried out with F60, 40-63 mm, 60 Å silica gel, and EMD silica 60 F254 glass TLC plates. Solvents were dried and kept air-free in a solvent purification unit, and were evaporated using a standard rotavapor and high vacuum. All reactions were carried out in oven-dried glassware under argon.

3.2 Experimental and Characterization
Preparation of Nitrosobenzene derivatives
Most of the nitrosobenzene derivatives used in the substrate scope were prepared using a known procedure[¹]. For 2.7c, e, f, g, h, i, j, k, l, m, n, and p, the counterpart aniline (1.5 mmol) was dissolved in CHCl₃ (2 mL) and the reaction completely converted with 2.2 equiv. of 35% aq. H₂O₂ as terminal oxidant and 5 mol% of Ph₂Se₂ catalyst after 1 hour at room temperature. Owing to the reactivity, compound 2.7d, e, and o were synthesized using toluene as solvent. After that, the reaction mixture was extracted with CHCl₃ and H₂O (3 times) and the combined organic layers were dried over MgSO₄ and filtered. After removal of solvent under reduced pressure, the residue was purified by flash column chromatography.

General Procedure for the synthesis of compound 2.23
To the mixture of tetralone (0.5 mmol) and piperidine (0.1 mmol) in DMSO (0.2 mL) was added a solution of nitrosobenzene (0.6 mmol) in DMSO (0.8 mL) over a period of 1h at rt. After that, the reaction mixture was extracted with EtOAc and H₂O (3 times) to remove DMSO and the combined organic layers were dried over MgSO₄ and filtered. After removal of solvent under reduced pressure, the residue was purified by flash column chromatography.
2.23:

\[\text{1-(phenylamino)naphthalen-2-ol}\]

Yellow Solid (113mg, 96%); \(^1^\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.80 (dd, \(J = 18.8, 8.5\) Hz, 2H), 7.67 (d, \(J = 8.3\) Hz, 1H), 7.42 – 7.36 (m, 1H), 7.34 – 7.29 (m, 2H), 7.19 (t, \(J = 7.8\) Hz, 2H), 6.84 (t, \(J = 7.3\) Hz, 1H), 6.66 (d, \(J = 8.0\) Hz, 2H), 6.56 (s, 1H), 5.27 (s, 1H) ppm; \(^1^3^\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 152.03, 146.63, 132.01, 129.57, 129.03, 128.59, 126.96, 123.41, 121.43, 119.73, 118.59, 116.85, 114.20 ppm.
2.23b:

1-(o-tolylamino)naphthalen-2-ol

Green liquid (119 mg, 95%); $^1$H NMR (500 MHz, CDCl$_3$) δ 7.85 (dd, $J = 20.4$, 8.4 Hz, 2H), 7.58 (d, $J = 8.3$ Hz, 1H), 7.45 – 7.34 (m, 3H), 7.25 (d, $J = 7.4$ Hz, 1H), 6.98 (t, $J = 7.6$ Hz, 1H), 6.83 (t, $J = 7.3$ Hz, 1H), 6.53 (s, 1H), 6.25 (d, $J = 8.0$ Hz, 1H), 5.12 (s, 1H), 2.53 (s, 3H) ppm; $^{13}$C NMR (126 MHz, CDCl$_3$) δ 151.88, 144.37, 131.79, 130.57, 129.55, 128.88, 128.58, 127.44, 127.00, 123.43, 122.51, 121.18, 119.49, 118.76, 116.87, 112.54, 17.67 ppm.
2.23c:

![Structure of 1-((4-nitrophenyl)amino)naphthalen-2-ol](image)

**1-((4-nitrophenyl)amino)naphthalen-2-ol**

Yellow solid (86 mg, 61%); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.11 (d, $J$ = 9.2 Hz, 2H), 7.90 – 7.85 (m, 2H), 7.62 (d, $J$ = 8.4 Hz, 1H), 7.49 – 7.44 (m, 1H), 7.43 – 7.38 (m, 1H), 7.34 (d, $J$ = 8.9 Hz, 1H), 6.67 (d, $J$ = 8.5 Hz, 2H), 6.06 (s, 1H), 5.89 (s, 1H) ppm; $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 152.44, 151.57, 140.40, 131.52, 130.21, 129.67, 128.84, 127.61, 126.40, 124.06, 121.04, 117.31, 116.44, 113.24 ppm.
2.23d:

1-(p-tolylamino)naphthalen-2-ol

Brown solid (118 mg, 95%); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.83 (dd, $J = 23.0$, 8.0 Hz, 2H), 7.69 (d, $J = 8.1$ Hz, 1H), 7.42 (t, $J = 7.0$ Hz, 1H), 7.36 (d, $J = 6.0$ Hz, 2H), 7.03 (d, $J = 7.1$ Hz, 2H), 6.65 (s, 1H), 6.59 (d, $J = 7.6$ Hz, 2H), 5.14 (s, 1H), 2.29 (s, 3H ppm); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 152.09, 144.33, 132.10, 130.11, 129.61, 129.06, 128.94, 128.64, 126.97, 123.41, 121.49, 119.05, 116.86, 114.30, 20.51 ppm.
2.23e

3-((2-hydroxynaphthalen-1-yl)amino)benzonitrile

Yellow solid (120 mg, 92%); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.86 (t, 2H), 7.60 (d, $J = 6.6$ Hz, 1H), 7.44 (brrs, 1H), 7.39 (brrs, 1H), 7.34 (d, $J = 8.1$ Hz, 1H), 7.27 (s, 1H), 7.11 (d, $J = 5.5$ Hz, 1H), 6.86 (brrs, 2H), 6.34 (s, 1H), 5.49 (s, 1H) ppm; $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 151.91, 147.43, 131.65, 130.39, 129.78, 129.69, 128.85, 127.38, 123.82, 123.16, 121.20, 119.07, 118.62, 117.24, 116.96, 113.20 ppm.
2.23f

1-((4-(trifluoromethyl)phenyl)amino)naphthalen-2-ol
White solid (130 mg, 85%); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.84 (dd, $J = 14.4$, 8.5 Hz, 2H), 7.61 (d, $J = 8.2$ Hz, 1H), 7.42 (d, $J = 5.2$ Hz, 3H), 7.40 – 7.30 (m, 2H), 6.67 (d, $J = 7.6$ Hz, 2H), 6.28 (s, 1H), 5.44 (s, 1H) ppm; $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 151.90, 149.55, 131.78, 129.71, 128.77, 127.34, 127.03, 127.00, 123.79, 121.25, 117.40, 117.10, 113.71 ppm.
2.23g

1-((3-fluorophenyl)amino)naphthalen-2-ol
Brown solid (114 mg, 90%); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.92 (brs, 2H), 7.67 (s, 1H), 7.39 (brm, $J$ = 43.9 Hz, 3H), 7.15 (s, 1H), 6.52 (d, $J$ = 23.5 Hz, 2H), 6.42 (s, 1H), 6.32 (d, $J$ = 7.3 Hz, 1H), 5.36 (s, 1H) ppm; $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 165.14, 163.19, 152.01, 148.67, 148.59, 131.89, 130.85, 130.77, 129.63, 129.51, 128.71, 127.21, 123.64, 121.28, 117.92, 116.99, 109.99, 106.56, 106.39, 101.52, 101.32 ppm.
2.23h

1-((4-chlorophenyl)amino)naphthalen-2-ol
Brown solid (116 mg, 94%); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.83 (dd, $J = 18.2$, 8.4 Hz, 2H), 7.63 (d, $J = 8.2$ Hz, 1H), 7.50 – 7.29 (m, 3H), 7.15 (d, $J = 7.5$ Hz, 2H), 6.59 (d, $J = 7.5$ Hz, 2H), 6.48 (s, 1H) ppm; $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 152.03, 145.35, 131.84, 129.64, 129.50, 129.40, 128.74, 127.17, 124.53, 123.61, 121.29, 118.21, 116.96, 115.46 ppm.
2.23i

1-((4-methoxyphenyl)amino)naphthalen-2-ol
Brown solid (111 mg, 85%); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.07 – 7.47 (m, 3H), 7.38 (d, $J = 30.3$ Hz, 3H), 6.75 (d, $J = 29.8$ Hz, 3H), 6.62 (s, 2H), 5.08 (s, 1H), 3.75 (s, 3H) ppm; $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 153.53, 152.08, 140.51, 132.05, 129.61, 128.86, 128.69, 126.95, 123.39, 121.45, 119.49, 116.83, 115.41, 115.07, 55.73 ppm.
1-((3-methoxyphenyl)amino)naphthalen-2-ol
Brown oil (115 mg, 88%); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.95 (s, 2H), 7.86 – 6.81 (m, 4H), 6.68 (s, 1H), 6.56 (s, 1H), 6.39 (d, $J = 42.1$ Hz, 2H), 5.34 (s, 1H), 3.86 (s, 3H) ppm; $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 161.04, 152.03, 148.18, 132.10, 130.45, 129.60, 129.15, 128.62, 127.04, 123.50, 121.51, 118.53, 116.94, 107.12, 104.77, 100.56, 55.19 ppm.
1-((3-nitrophenyl)amino)naphthalen-2-ol
Brown solid (124 mg, 88%); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.86 (dd, $J = 12.7$, 8.6 Hz, 2H), 7.63 (dd, $J = 19.3$, 7.9 Hz, 2H), 7.50 (s, 1H), 7.44 (t, $J = 7.2$ Hz, 1H), 7.42 – 7.18 (m, 3H), 6.87 (d, $J = 6.9$ Hz, 1H), 6.37 (s, 1H), 5.58 (s, 1H) ppm; $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 151.93, 149.47, 147.95, 131.62, 130.35, 129.94, 129.73, 128.88, 127.44, 123.86, 121.12, 119.81, 117.24, 117.17, 114.44, 108.76 ppm.
2.23l

5-((2-hydroxynaphthalen-1-yl)amino)-2-methylbenzonitrile
Brown solid (123 mg, 90%); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.00 – 7.70 (m, 2H), 7.60 (d, $J = 6.6$ Hz, 1H), 7.43 (s, 1H), 7.40 – 7.31 (m, 2H), 7.12 (s, 1H), 6.82 (d, $J = 8.4$ Hz, 2H), 6.39 (s, 1H), 5.35 (s, 1H), 2.44 (s, 3H) ppm; $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 152.00, 145.02, 132.84, 131.66, 131.42, 129.70, 128.85, 127.32, 123.73, 121.09, 118.92, 117.53, 117.24, 117.06, 113.48, 19.43 ppm.
2.23m

1-((2-iodophenyl)amino)naphthalen-2-ol
Brown solid (171 mg, 95%); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.84 (dd, \(J = 15.5, 7.4\) Hz, 3H), 7.57 (d, \(J = 8.1\) Hz, 1H), 7.44 (t, \(J = 7.3\) Hz, 1H), 7.39 – 7.33 (m, 2H), 7.05 (t, \(J = 7.3\) Hz, 1H), 6.60 (t, \(J = 7.2\) Hz, 1H), 6.40 (s, 1H), 6.24 (d, \(J = 8.0\) Hz, 1H), 5.75 (s, 1H) ppm; \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 152.06, 146.05, 139.19, 131.72, 129.78, 129.65, 129.55, 128.63, 127.36, 123.69, 121.46, 121.37, 118.57, 116.98, 113.68, 85.59 ppm.
1-((4-(trifluoromethoxy)phenyl)amino)naphthalen-2-ol
Brown solid (153 mg, 97%); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.84 (dd, $J = 17.7$, 8.4 Hz, 2H), 7.65 (d, $J = 8.3$ Hz, 1H), 7.45 (t, $J = 7.5$ Hz, 1H), 7.36 (dd, $J = 18.7$, 8.4 Hz, 2H), 7.06 (d, $J = 7.9$ Hz, 2H), 6.64 (d, $J = 8.1$ Hz, 2H), 6.46 (s, 1H), 5.31 (s, 1H) ppm; $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 152.02, 145.43, 142.21, 131.85, 129.66, 129.45, 128.75, 127.22, 123.65, 122.72, 121.64, 121.25, 119.61, 118.18, 117.58, 116.98, 114.79 ppm.
ethyl 4-((2-hydroxynaphthalen-1-yl)amino)benzoate

Purple solid (130 mg, 85%); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.90 (d, \(J = 7.7\) Hz, 2H), 7.85 (t, \(J = 9.4\) Hz, 2H), 7.64 (d, \(J = 8.2\) Hz, 1H), 7.42 (t, \(J = 7.3\) Hz, 1H), 7.36 (dd, \(J = 15.9, 8.3\) Hz, 2H), 6.66 (d, \(J = 7.5\) Hz, 2H), 6.31 (s, 1H), 5.60 (s, 1H), 4.34 (q, \(J = 6.7\) Hz, 2H), 1.37 (t, \(J = 6.7\) Hz, 3H) ppm; \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 166.52, 151.84, 150.75, 131.82, 131.73, 129.65, 129.62, 128.69, 127.27, 123.74, 121.68, 121.31, 117.40, 117.12, 113.36, 60.48, 14.41 ppm.
2.23p

![Chemical Structure](image)

**4-((2-hydroxynaphthalen-1-yl)amino)benzonitrile**

Brown solid (118 mg, 90%); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.86 (t, $J$ = 9.0 Hz, 2H), 7.61 (d, $J$ = 8.1 Hz, 1H), 7.48 – 7.44 (m, 3H), 7.39 (t, $J$ = 7.2 Hz, 1H), 7.33 (d, $J$ = 8.8 Hz, 1H), 6.68 (d, $J$ = 6.7 Hz, 2H), 6.16 (s, 1H), 5.69 (s, 1H) ppm; $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 151.73, 150.51, 134.10, 131.62, 129.99, 129.66, 128.80, 127.48, 123.93, 121.12, 117.24, 116.62, 114.16 ppm.
**5-methoxy-1-(phenylamino)naphthalen-2-ol**
Purple solid (89 mg, 67%); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.25 (d, $J = 9.1$ Hz, 1H), 7.35 – 7.24 (m, 3H), 7.20 (t, $J = 7.6$ Hz, 2H), 6.86 (t, $J = 7.2$ Hz, 1H), 6.70 (d, $J = 7.4$ Hz, 1H), 6.66 (d, $J = 7.8$ Hz, 2H), 6.59 (s, 1H), 5.24 (s, 1H), 4.02 (s, 3H) ppm; $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 156.23, 152.63, 146.79, 133.43, 129.59, 127.45, 123.30, 121.31, 119.73, 118.53, 115.66, 114.26, 113.91, 101.99, 55.57 ppm.
Yellow solid (110 mg, 83%); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.74 (t, $J$ = 8.3 Hz, 2H), 7.21 (t, $J$ = 7.4 Hz, 3H), 7.02 (d, $J$ = 8.7 Hz, 1H), 6.93 (s, 1H), 6.86 (t, $J$ = 7.1 Hz, 1H), 6.67 (d, $J$ = 7.4 Hz, 2H), 6.61 (s, 1H), 6.55 – 6.36 (m, 1H), 5.09 (s, 1H), 3.73 (s, 3H) ppm; $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 158.72, 152.74, 146.60, 133.51, 130.28, 129.62, 128.79, 124.89, 119.71, 118.09, 115.54, 114.27, 114.22, 100.83, 55.18 ppm.
8-methoxy-1-(phenylamino)naphthalen-2-ol
White solid (55 mg, 43%); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.71 (d, $J = 8.6$ Hz, 1H), 7.42 (d, $J = 8.0$ Hz, 1H), 7.35 (d, $J = 8.7$ Hz, 1H), 7.22 (t, $J = 7.4$ Hz, 3H), 6.91 – 6.63 (m, 6H), 3.81 (s, 3H) ppm; $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 155.42, 151.15, 147.09, 131.48, 129.27, 127.96, 123.39, 122.36, 121.60, 120.90, 120.07, 117.00, 115.39, 106.27, 55.98 ppm
6-methoxy-1-(phenylamino)naphthalen-2-ol
Brown solid (67 mg, 52%); $^1$H NMR (500 MHz, CDCl$_3$) δ 7.70 (d, $J = 8.4$ Hz, 1H), 7.60 (d, $J = 8.8$ Hz, 1H), 7.32 (d, $J = 8.4$ Hz, 1H), 7.24 – 7.16 (m, 3H), 7.09 (d, $J = 8.7$ Hz, 1H), 6.86 (t, $J = 7.0$ Hz, 1H), 6.66 (d, $J = 7.2$ Hz, 2H), 6.37 (s, 1H), 5.23 (s, 1H), 3.92 (s, 3H) ppm; $^{13}$C NMR (126 MHz, CDCl$_3$) δ 156.00, 150.35, 146.73, 130.56, 129.62, 127.64, 127.31, 123.15, 119.69, 119.47, 119.00, 117.40, 114.20, 107.07, 55.38 ppm.
6-fluoro-1-(phenylamino)naphthalen-2-ol

Brown solid (15 mg, 12%); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.73 (d, $J = 8.7$ Hz, 1H), 7.70 - 7.66 (m, 1H), 7.47 (d, $J = 9.3$ Hz, 1H), 7.37 (d, $J = 8.6$ Hz, 1H), 7.25 - 7.02 (m, 3H), 6.88 (t, $J = 6.9$ Hz, 1H), 6.66 (d, $J = 7.3$ Hz, 2H), 6.47 (s, 1H), 5.25 (s, 1H) ppm; $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 160.26, 158.32, 151.49, 146.42, 130.17, 130.10, 129.69, 129.06, 128.21, 128.17, 123.95, 123.88, 119.96, 118.96, 118.27, 117.19, 116.99, 114.21, 111.92, 111.75 ppm.
2.23F

This compound is not well dissolved in CDCl$_3$, so we choose to use DMSO-D6 as solvent to obtain NMR spectrum.

1-(phenylamino)naphthalene-2,7-diol

White solid (55 mg, 88%); $^1$H NMR (500 MHz, DMSO) $\delta$ 9.51 (s, 1H), 9.25 (s, 1H), 7.65 (d, $J$ = 8.5 Hz, 1H), 7.55 (d, $J$ = 8.6 Hz, 1H), 7.20 (s, 1H), 7.07 – 6.97 (m, 4H), 6.83 (d, $J$ = 8.6 Hz, 1H), 6.57 (t, $J$ = 6.9 Hz, 1H), 6.47 (d, $J$ = 7.5 Hz, 2H) ppm; $^{13}$C NMR (126 MHz, DMSO) $\delta$ 156.16, 151.84, 148.57, 134.73, 130.14, 129.09, 127.04, 123.74, 119.08, 116.91, 115.65, 115.60, 113.74, 104.72 ppm.
3.3 References