Studies on the Development of Novel Transition-Metal-Free Reactions of Aromatic Amines

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July 2017

Doctoral Thesis at Osaka Prefecture University

Acknowledgment

The author would like to express his sincerest gratitude to the academic supervisor Professor Akiya Ogawa at Department of Applied Chemistry, Graduate School of Engineering, Osaka Prefecture University, for his continuous guidance and helpful suggestions throughout this challenging study.

The author would like to express his gratitude to Professor Hiroshi Ikeda and Professor Shigeyuki Yagi at Department of Applied Chemistry, Graduate School of Engineering, Osaka Prefecture University, for their helpful remarks and suggestions by reading of the manuscript.

The author would also like to express his deepest gratitude to Dr. Takumi Mizuno at Morinomiya Center, Osaka Research Institute of Industrial Science and Technology, for his kind guidance and invaluable assistance throughout this work.

The author is deeply indebted to Associate Professor Akihiro Nomoto at Department of Applied Chemistry, Graduate School of Engineering, Osaka Prefecture University, for his helpful suggestions and comments.

The author would also like to express my thanks to Guest Professor Michio Ueshima and Technical Assistant Shintarou Kodama at Department of Applied Chemistry, Graduate School of Engineering, Osaka Prefecture University, for their helpful suggestions.

The author is sincerely express his gratitude to the President Yoshihisa Takeda at Seika Corporation for providing a chance to carry out this work and his encouragement.

The author would like to express his deepest gratitude to Dr. Motonori Takeda (Senior Managing Director) at Seika Corporation for providing a chance to carry out this work and his warm-hearted encouragement during the course of this work.

The author deeply indebted to Dr. Masatoshi Mihara, Dr. Takeo Nakai, Dr. Takatoshi Ito and Dr. Toshiyuki Iwai at Morinomiya Center, Osaka Research Institute of Industrial Science and

Technology, for their helpful discussions.

The author is also indebted to Dr. Fukashi Matsumoto at Morinomiya Center, Osaka Research Institute of Industrial Science and Technology, for DFT calculations.

The author would like to express thanks to Mr. Seiichi Mori and Dr. Mitsutaka Imoto at Seika Corporation for their hearty supports and helpful discussions.

The author would also like to express thanks to a former corporate adviser Dr. Akihiro Tamaki at Seika Corporation for his valuable and helpful discussions.

Grateful acknowledgments are due to following contributors: Mr. Akinori Murata at Department of Applied Chemistry, Graduate School of Engineering, Osaka Prefecture University and Mr. Takuya Naka at Seika Corporation for experiments and their helpful discussions in this research.

The author most sincerely thanks all members of Seika Corporation for everything and wish to dedicate this doctoral thesis to the former chairman of the Seika Corporation, the late Mr. Minoru Takeda.

Finally, the author would like to express his deepest appreciation to his parents Dr. Hisaji Taniguchi and Hisako Taniguchi for their warm-hearted encouragement.

The author would also like to express his sincerest thanks to his wife Kanako Taniguchi and his son Kai Taniguchi.

July 2017

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Preface

This thesis deals with the studies conducted during September 2014 to September 2017 under the guidance of Professor Akiya Ogawa at the Department of Applied Chemistry, Graduate School of Engineering, Osaka Prefecture University.

This thesis is concerned with the development of transition-metal-free reactions of aromatic amines. The author focused on the utilization of aromatic amines for the new reactions.

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July 2017

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Contents

Chapter 1

General Introduction

Aniline that is the simplest aromatic amine has a long history. Aniline was first discovered by Unverdorben in 1826 (Fig. 1). He obtained a substance by distilling a dry indigo dye and called the substance *Crystallin*[1] (Helot maight have also prepared crude aniline in 1765, but he did not isolate as pure chemicals[2]). On the other hand, aniline was isolated from coal tar by Runge in 1834. The color of aniline turned into a beautiful blue color when it was treated with chloride of lime. He named aniline *kyanol* or *cyanol*.[3] Moreover, Fritzsche treated indigo with potassium hydroxide to obtain an oil that he named "aniline" in 1841. He is credited with coining the term "aniline" from the Sanskrit word for the indigo plant which is called "anil".[4] A few years later, Hoffman investigated their experiments thoroughly and proved by the elemental analysis in 1843 that the substance obtained in their experiment was exactly the same. Moreover, he managed to reduce nitrobenzene by the use of hydrogen for the first time.[5] Perkin who was a disciple of Hofmann developed the synthetic dye mauve (Mauveine) from aniline. He oxidized aniline using a strong oxidizing agent of potassium dichromate in 1856.[6] For these reasons, the dyestuff chemistry based

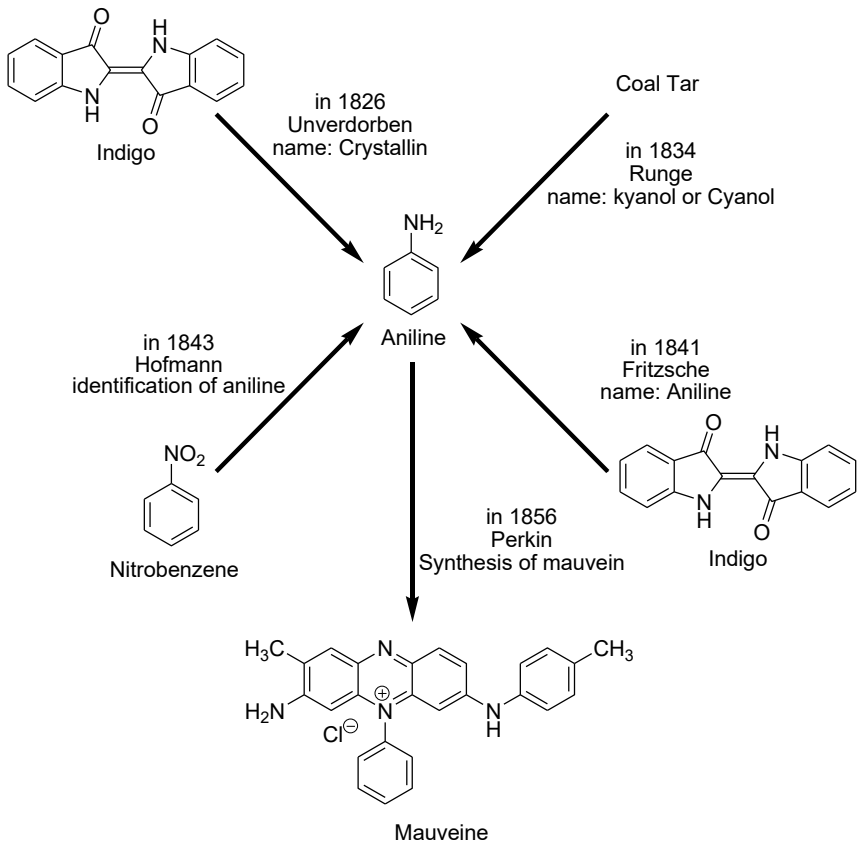


Figure 1. History of Aniline in Germany.

on aniline has developed mainly in Germany.

On the other hand, the textile industry of cotton fabrics had been flourishing mainly in Kishu (Wakayama) in the 19th century Japan. At that time, the synthetic dyes for the cotton dyeing were imported from Germany. Since the first World War broke out in 1914, however, the import of dyes was cut off. There was no technique to prepare aniline which was a main raw material of synthetic dyes. It is particularly worth noting that Yura succeeded in manufacturing aniline from benzene in 1914 in Wakayama.[7] This is the first example of the manufacture of aniline in Japan. Because of these facts, Wakayama became known as one of the birthplaces of organic chemistry in Japan.

The author has described the chemistry of anilines for the synthetic dyestuffs and pigments up to 19th century.[8] Thereafter, in the 20th century, aromatic amines played a key role in the fields of functional resins,[9] aromatic polymer materials,[10] medicines and agricultural chemical intermediates,[11] photosensitive materials,[12] organic semiconductor materials,[13] and high performance engineering plastics.[14] Therefore, aromatic amines have been still attracting much attention in the organic industry and academic fields.

Since the latter part of the 20th century, the use of transition-metal catalysts has helped to develop rapidly aromatic coupling reactions which are very important in organic chemistry. The great success of cross-coupling reactions using transition-metal catalysts led to the Nobel Prize in chemistry in 2010.[15] To use these reactions in industrial scale, however, researchers in companies often face to the following problems: 1) Most of the transition-metal catalysts, e.g., Pd catalysts, are very expensive, and some of them are toxic. 2) The removal of transition metal residues from the target products is very costly. The large consumption of transition metal is impossible from the perspective of the sustainable development in the chemical industry.[16] Therefore, the development of transformation and cross-coupling reactions in the absence of transition-metal catalysts is not only very attractive but also strongly desired from practical perspective.

In this thesis, the author has developed the transition-metal-free transformation and cross-coupling reactions using aromatic amines and their derivatives which are aryl diazonium salts and aryl

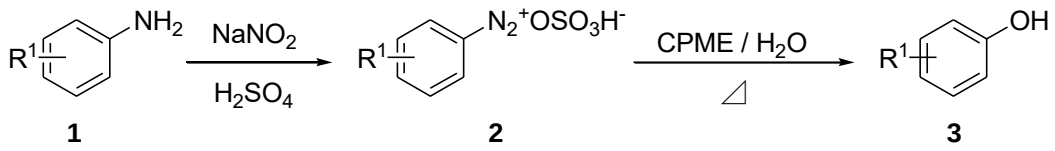
hydrazines. One important topic of this thesis is the development of a unique conversion reaction from aromatic amines to phenols (Chapter 2). The other topics are the novel transition metal free cross-coupling reactions of arylhydrazines with other compounds containing aminoheterocycles, aromatic diamines, disulfides, and diselenides (Chapters 3–6).

This thesis is consisted of seven chapters and the outlines of each chapter are summarized as follows.

Chapter 1 describes the background, general objectives, and the contents of this thesis.

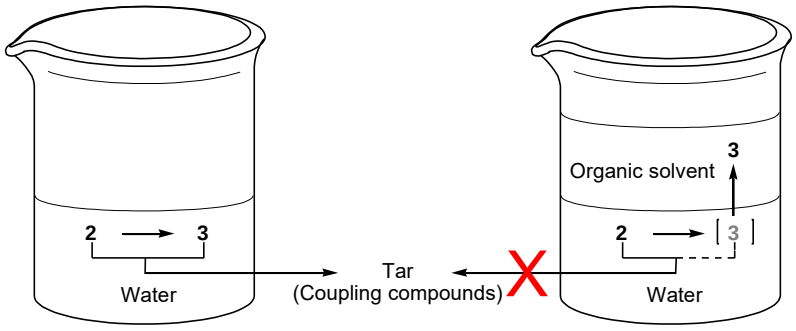
Chapter 2 describes the unique transformation to obtain efficiently corresponding phenols by the hydrolysis of diazonium salts using a two-phase system (CPME/Water) (Scheme 1).[17]

Scheme 1. Hydrolysis of Diazonium Salts Using a Two-Phase System of CPME and Water



The conversion reaction from aromatic amines to phenols is well known as the Sandmeyer reaction. However, as a practical matter, there were few practical methods because byproducts as tar are generated with target products. The tar formation suggests that a competitive reaction of phenols **3** with unreacted diazonium salts **2** occurs in the aqueous phase. In other words, the tar polymer or oligomer may be formed via the diazo coupling of diazonium salts **2** with the resulting phenols **3** before the nucleophilic substitution of **2** with water takes place. Therefore, the author investigated the reaction conditions of hydrolysis. As results of various studies, a two-phase system consisting of cyclopentyl methyl ether (CPME) and water is very effective for the hydrolysis of diazonium salts (Scheme 2).

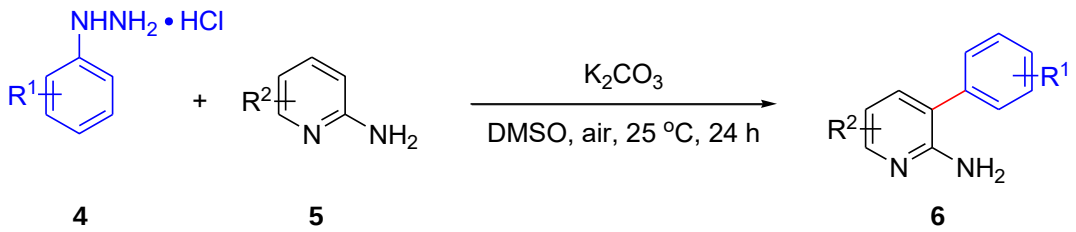
Scheme 2. Expected Effect of Two-Phase System of CPME and Water



As the author described above, the use of the present two-phase system of CPME and water brought about successfully the efficient conversions of several substituted anilines into the corresponding substituted phenols without the formation of tar.

Chapter 3 describes a novel metal-free cross-coupling reaction of arylhydrazines **4** with aminoheterocycles **5** (Scheme 3).[18] Recently, Heinrich and others reported an oxidative radical cross-coupling using arylhydraizes and aromatic amines under mild conditions (homolytic aromatic substitution (HAS) reaction). However, these reactions have drawbacks such as moderate yields of products and a lack of regioselectivity. In this chapter, the author investigated the metal-free C-H arylation of arylhydrazines with aminoheterocycles. The results in various studies show that the reaction proceeds via a HAS mechanism involving aryl radicals as the key intermediates.

Scheme 3. Metal-free C-H Arylation of Aminoheterocycles with Arylhydrazines

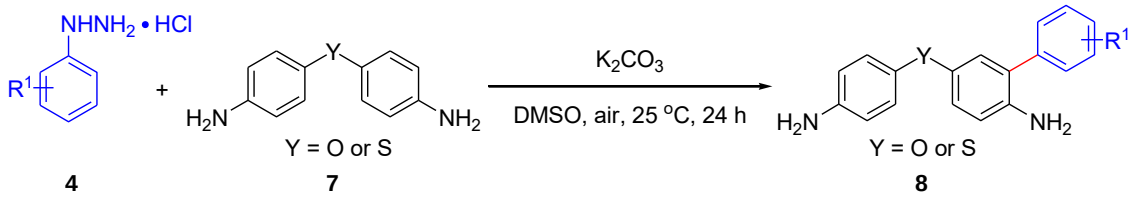


4 **5** **6**

This reaction took place readily at room temperature under the atmosphere in the presence of an inexpensive base to afford the corresponding products **6** in good yields. Moreover, the reactivity of this radical arylation correlated with the HOMO energy and the electron density of aminoheterocycles. This method provides not only a rapid access to diverse arylated heterocycles, but also an atom-efficient alternative to conventional transition-metal-catalyzed cross-coupling between halides and organometallics. Moreover, this metal-free arylation reaction is able to adapt a gram scale reaction. Therefore, this direct C-H arylation reaction in the absence of transition-metal catalysts could be a useful and practical method.

Chapter 4 describes the regioselective radical arylation of aromatic diamines **7** with arylhydrazines **4** (Scheme 4).[19] In recent years, the manufacture of unsymmetrical aromatic diamines for improved polyimides is strongly desired because of the requirement of the JAXA's space yacht (IKAROS). In general, the introduction of an aryl group to a symmetrical aromatic diamine as 4,4'-diaminodiphenyl ether (DPE) **7** required transition-metal-catalyzed reactions with very complicated steps. The author optimized the C-H arylation of arylhydrazines with aromatic diamines to develop a highly regioselective radical arylation. As the results, the arylation of aromatic diamines **7** with arylhydrazine hydrochlorides **4** under mild conditions afforded the corresponding unsymmetrical aromatic diamines **8** in reasonable yields.

Scheme 4. Regioselective Radical Arylation of Aromatic Diamines with Arylhydrazines

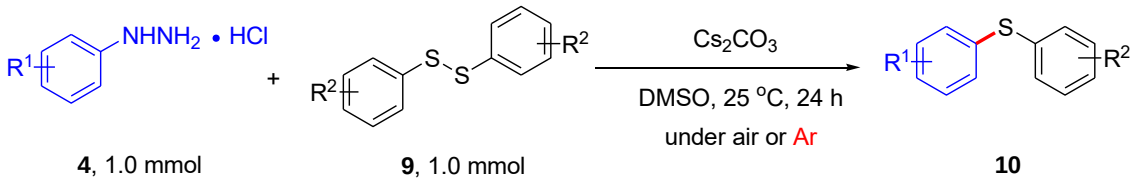


4 **7** **8**

This metal-free and simple reaction occurred at room temperature in the air using an inexpensive base. This transformation seems to proceed via a homolytic aromatic substitution (HAS) mechanism. The synthesized aromatic diamines are used as raw materials for polyimides including important aerospace materials, for example, Kapton®.

Chapter 5 describes a novel metal-free cross-coupling reaction using arylhydrazines **4** and one equivalent of disulfides **9** (Scheme 5).[20] In chapters 3 and 4, the author describes the cross-coupling of arylhydrazines **4** with aminoheterocycles **5** and aromatic diamines **7**; however, excess amounts of radical acceptors are generally required. In order to overcome this shortcoming, the author focused attention on disulfide compounds which might work as radical trappers. When the metal-free cross-coupling reaction of arylhydrazines **4** with one equivalent disulfides **9** was examined under mild conditions in the air, the corresponding unsymmetrical sulfides **10** were obtained in good yields.

Scheme 5. Transition-Metal-Free and Oxidant-Free Cross-Coupling of Arylhydrazines with Disulfides: Base-Promoted Synthesis of Unsymmetrical Aryl Sulfides

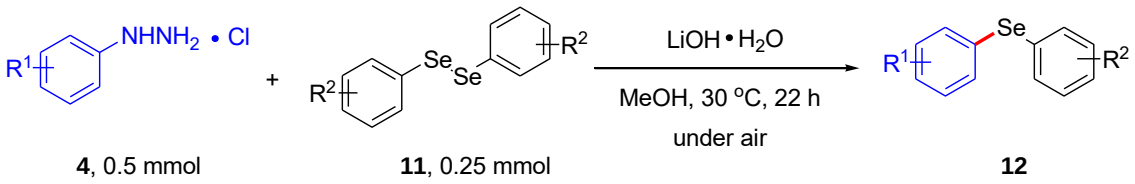


Interestingly, good yields of unsymmetrical sulfides **10** were also observed under the argon atmosphere. The author discovered a rare HAS-type reaction in which disulfides acted as oxidizing agents.

Chapter 6 describes the cross-coupling reaction of arylhydrazines with a stoichiometric amount of diselenides (Scheme 6).[21] One of the simplest organic diselenides is diphenyl diselenide which has a very high ability as the radical scavenger. The author aimed at developing the synthetic method of

an efficient unsymmetric diaryl selenide. As a result, the author found that the metal-free cross-coupling reaction of arylhydrazines with a stoichiometric amount of diselenides occurred under mild conditions.

Scheme 6 Transition-Metal-Free Synthesis of Unsymmetrical Diaryl Selenides Using Arylhydrazines and Diaryl Diselenides



4, 0.5 mmol **11**, 0.25 mmol **12**

This new and facile cross-coupling took place using an inexpensive base and methanol as the solvent in the air to provide unsymmetrical diaryl selenides in good yields. Because this reaction is an environment-friendly and low-cost cross-coupling reaction, the present method may be a useful for industrial synthesis of unsymmetrical diaryl selenides.

Chapter 7 describes the conclusion of this thesis.

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Chapter 2

Hydrolysis of Diazonium Salts Using a Two-Phase System of CPME and Water

2.1 INTRODUCTION

Phenoxyphenols play a key role in the field of aromatic polymer materials. In particular, 3-phenoxyphenols and 4-phenoxyphenols have received much attention as monomers of polyphenyleneoxide because they are more reactive than unsubstituted phenol, and less isomer formation occurs during the coupling reaction.[1,2]

In our project concerning the production of a raw material for functional plastics (polyimideresin), 3-(4-aminophenoxy)phenol and 3-(4-nitrophenoxy)phenol (**3a**) are very significant compounds.[3,4] Thus, many synthetic methods of **3a** have been reported. Among them, **3a** has typically been synthesized through the aromatic nucleophilic substitution of resorcinol with 4-halogenated nitrobenzenes.[5] However, this reaction required high temperature and prolonged reaction time, and the yields were moderate. Generally, the synthesis of 3-substituted phenols is difficult, because phenol has *ortho*-/*para*-directing property due to the electron-donating hydroxyl group. For *ortho*- and *para*-functionalization of phenols, many methodologies are well investigated. However, this strong directing effect prevents the selective direct functionalization of phenols at the meta position.[6]

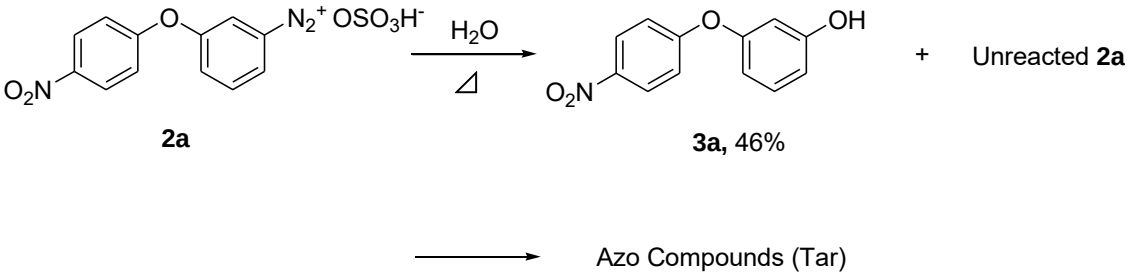
To develop a safe, simple, low-cost, and high yielding synthetic method, the synthesis of **3a** using the hydrolysis of diazonium salt **2a** prepared from 3-(4-nitrophenoxy)aniline (**1a**) was examined.[7] However, the classical reactions described in textbooks are not always practical and industrially feasible. In such reaction systems, large amounts of tar are formed during the reaction, making the reasonable access of suitable experimental manipulation difficult. To solve this problem, the use of a two phase system comprising a mixture of an organic solvent and water was envisioned.

After intensive examinations of the hydrolysis of **2a** prepared from **1a** using a variety of two-phase systems, we herein report the surprising effect of a two-phase system consisting of cyclopentyl methyl ether (CPME) and water. To the best of our knowledge, this is the first example of the hydrolysis of diazonium salts using the two-phase system.

2.2 RESULTS AND DISCUSSION

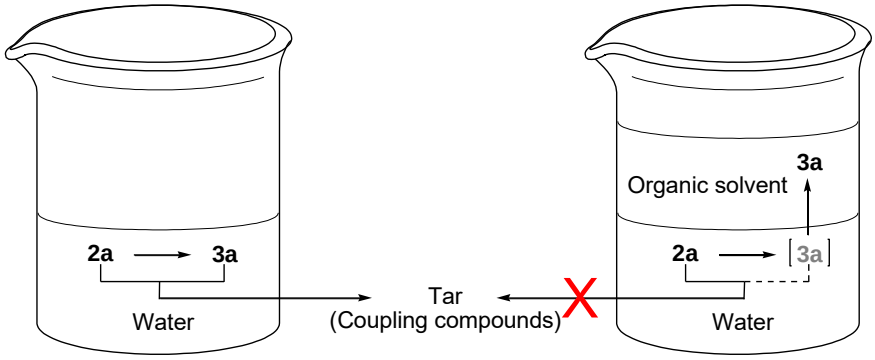
At the outset, we attempted to synthesize **3a** according to a literature method (Scheme 1).[7] The diazonium salts **2a**, which was prepared from **1a** using sodium nitrite and sulfuric acid, was poured into a dilute solution of sulfuric acid under heating at reflux temperature. In this hydrolysis procedure, tar was formed, and the yield of **3a** was 46% (Scheme 1). In thin layer chromatography analysis, many polar compounds were observed. The tar formation suggested that a competitive reaction of **3a** with unreacted **2a** occurred in the aqueous phase. In other words, the tar polymer or oligomer may be formed via diazo coupling of the diazonium salt **2a** with the resulting phenol **3a** before the nucleophilic substitution of **3a** with water takes place.

Scheme 1. Synthesis of 3a



To prevent the diazo coupling reaction, a two-phase system of organic solvent and water was devised (Scheme 2 and Table 1). Diazonium salt **2a**, formed in the aqueous phase, is converted into **3a**, which is immediately extracted by organic solvent. Using this two-phase system (organic solvent and water), it is possible to avoid the diazo coupling reaction between the diazonium salt **2a** and the obtained **3a**.

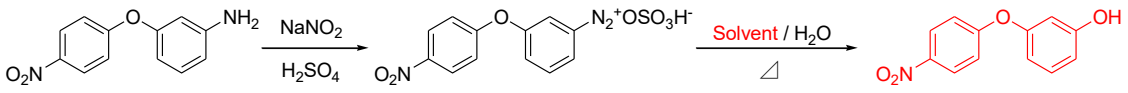
Scheme 2. Expected Effect of Two-Phase System



Diazonium salt **2a** was prepared from **1a** and sodium nitrite in concentrated sulfuric acid. The solution of **2a** was poured into a mixture of an organic solvent and water, and then the resulting solution was refluxed (Method A, see Experimental section).

The hydrolysis reaction using toluene as a co-solvent gave **3a** in low yield (26%) (Table 1, entry 1). As toluene has an electron-donating Me group, it can act as a good coupler for the diazo coupling reaction. Therefore, it was considered that the diazo coupling reaction of **2a** with toluene proceeded preferentially. Next, using ethyl acetate, the yield of **3a** was improved to 67% (entry 2). In the case of ethyl acetate, the two-phase system was maintained at the initial stage, but became monophasic at the end of the hydrolysis reaction. This is because of the hydrolysis of ethyl acetate with sulfuric acid, which affords acetic acid and ethanol. Keeping the good result of ethyl acetate (entry 2) in mind, tolerance of several esters under the strong acidic conditions was examined (entries 3–6). Butyl acetate and *s*-butyl acetate gave **3a** in high yields (entries 4 and 5). After the reaction, however, acetic acid was formed. Chlorinated solvents and nitrobenzene were also examined. In these cases, tar was formed and **3a** was produced in moderate yields (64–71%) (entries 7–11). In the hydrolysis of **2a** with water, product **3a** and tar tend to float at the surface of water. Hence, the extractive effect for **3a** with heavier solvents such as chlorinated solvents might be lower than that in lighter solvents. Also, chlorinated solvents are industrially less accessible. Ketones were also examined as cosolvents. The hydrolysis of **2a** proceeded with excellent yields in ketones (88–89%) (entries 12–14).

Table 1. Optimization of Organic Solvents for the Two-Phase System



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

entry	solvent	yield(%)[a]	entry	solvent	yield(%)[a]
1	Toluene	26[b]	13	Methyl isobutyl ketone	89
2	EtOAc	67[b]	14	Diisobutyl ketone	88
3	*i*-PrOAc	78	15	2-Methyl tetrahydrofuran	77[b]
4	*n*-BuOAc	84	16	Methyl *t*-butyl ether	64
5	*s*-BuOAc	85	17	Cyclopentyl methyl ether	96[b]
6	*t*-BuOAc	62	18	MeOH	63
7	$CHCl_3$	64[b]	19	MeCN	60
8	1,2-Dichloroethane	64	20	*i*-PrOH	66
9	Chlorobenzene	68	21	*t*-BuOH	70
10	1,2-Dichlorobenzene	70	22	Sulfolane	71
11	Nitrobenzene	71	23	Tetrahydrofuran	80[b]
12	2-Pentanone	88			

[a]HPLC yields. [b]Isolated yields.

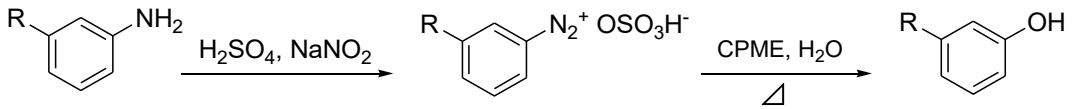
However, a highly unpleasant odor was occasionally generated as a result of oxidation of the ketones. Therefore, ketones are not suitable as cosolvents for the industrial production of phenols **3**. Then, the effect of ethers was examined (entries 15–17). To our surprise, the reaction using CPME proceeded smoothly to give **3a** in almost quantitative yield (entry 17). In diazotizations, few examples using a mixture of an organic solvent and water have been reported.[8,9] However, this is the first example of the hydrolysis of diazonium salts **2** in two-phase system (CPME and water).

Finally, solvents that are miscible with water were investigated (entries 18–23). The formation of **3a** in moderate yields (60–80%) was observed. However, tar was also formed in these reactions. The use of immiscible organic solvents with water is more effective for selective synthesis of **3a** than that of miscible solvents.

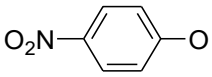
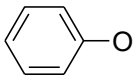
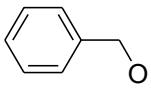
These results suggest that the ideal organic solvent for the two-phase system is immiscible with water, acid resistant, and lighter than water. CPME is the best cosolvent for this two-phase system. CPME has recently received much attention because of high boiling point (106 °C), resistance to peroxide formation, extremely easy dehydration, and high solubility with organic compounds. Also, CPME is applicable for a variety of synthetic methods using organolithium reagents, Grignard reactions, and various cross-coupling reactions in the presence of Pd catalysts.[10-17]

With the optimized reaction conditions in hand, the scope and limitations of the syntheses of various phenols (**3a**–**3j**) from anilines (**1a**–**1j**) through the hydrolyses of diazonium salt (**2a**–**2j**) using method A (see Scheme 2) or method B were examined. In method B, the syntheses of diazonium salts **2** were performed by reacting anilines **1** with sodium nitrite in sulfuric acid and CPME (see Experimental section). The results are shown in Table 2. The *meta*-substituted phenoxyanilines **1a** and **1b** gave **3a** and **3b**, respectively, in almost quantitative yields (Table 2, entries 1 and 2). However in the case of benzyloxyaniline (**1c**), **3c** was obtained in moderate yield (64%) (entry 3). The anilines featuring *meta*-substituted electron-donating group (**1d**–**1f**) and *meta*-substituted electron-withdrawing group (**1g**, **1i**, and **1j**) afforded the corresponding phenols (**3d**–**3g**, **3i**, and **3j**) in excellent yields (91–98%) (entries 4–7, 9, and 10). For the synthesis of *m*-nitrophenol (**3h**), higher reaction temperature was required and the yield of **3h** was lowered. Then, the use of pseudocumene (bp 169 °C) as a cosolvent afforded **3h** in reasonable yield (entry 8). These results show that a simple and useful synthetic method for *m*-substituted phenols was established successfully.

Table 2. Synthesis of *m*-Substituted Phenols (3a-j) in the Two-Phase System (CPME and Water)



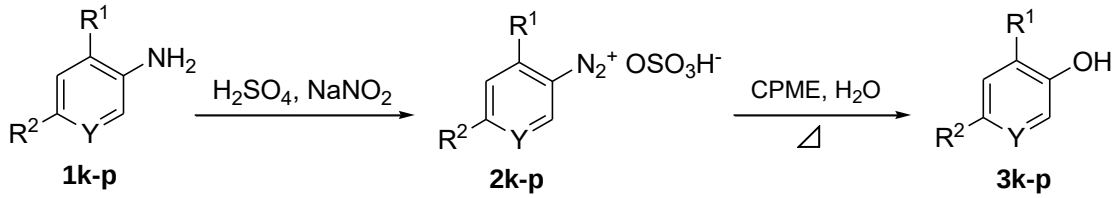
1a-j **2a-j** **3a-j**

entry	R	product	yield (%)[a]	method
1		**3a**	96	A
2		**3b**	95	B
3		**3c**	64	B
4	i-Pr	**3d**	96	B
5	Me	**3e**	93	B
6	MeO	**3f**	91	B
7	Ac	**3g**	92	B
8	NO_2	**3h**	56, 75[b]	B
9	CF_3	**3i**	94	A
10	COOH	**3j**	98	A

[a]Isolated yields. [b]Cosolvent is pseudocumene.

Furthermore, the syntheses of *ortho*- and *para*-substituted phenols **3k**–**3n** from the anilines **1k**–**1n** were investigated (Table 3). The corresponding products **3k**–**3n** were obtained in high yields (82–96%) (Table 3, entries 1–4). Also, aniline (**1o**) was smoothly converted into phenol (**3o**) in 93% yield (entry 5). Finally, 3-aminopyridine (**1p**) was converted into 3-hydroxypyridine (**3p**) quantitatively (entry 6).

Table 3. Synthesis of 3k-p in the Two-Phase System (CPME and Water)



entry	R^1	R^2	Y	product	yield(%)[a]
1	Me	H	CH	**3k**	83
2	COOH	H	CH	**3l**	89
3	H	Me	CH	**3m**	82
4	H	COOH	CH	**3n**	96
5	H	H	CH	**3o**	93
6	H	H	N	**3p**	100

[a]Method B was used. Isolated yields.

2.3 CONCLUSION

In summary, a useful synthetic method for various phenols **3** without the formation of tar was developed. The hydrolysis of diazonium salts **2** prepared from anilines **1** gave **3** in good to excellent yields using the two-phase system of CPME and water. From the practical and industrial viewpoints, the present method for producing a variety of phenols **3** is very noteworthy because of the use of easily available and cheap reagents and solvents, and mild reaction conditions.

2.4 EXPERIMENTAL SECTION

General Information. Melting points were determined with a YAMATO MP-21 instrument (Yamato Scientific Co., Ltd., Tokyo, Japan) and were uncorrected. ^{1}H and ^{13}C NMR spectra were obtained on JEOL JNM-AL300 (300 MHz, 75 MHz) and JEOL JNM-ECX400 (400 MHz, 100 MHz) instruments (JEOL Ltd., Tokyo, Japan). Mass spectra were measured on GC-MS Varian 3400 with Varian SATURN 2000 (Agilent Technologies, Inc., Santa Clara, USA) and Shimadzu LCMS-2020 featuring a DART (Direct Analysis Real Time) source (SHIMADZU CORPORATION, Kyoto,Japan).

General Procedure for the Synthesis of Phenols 3.

Method A. Into the concentrated sulfuric acid (8.0 mL), aniline **1** (5.0 mmol) was added carefully. A mixture of **1** and sulfuric acid was cooled with an ice bath with stirring. To the yellow or colorless solution, sodium nitrite (0.38 g, 5.5 mmol) was added at 5 °C. The solution was warmed to room temperature and stirred for additional 1 h to produce diazonium salt **2**. Next, the diazonium salt solution was poured into another flask containing water (40 mL) and CPME (35 mL) with stirring. The mixture was refluxed for 15–20 min. After the reaction, the product was extracted with AcOEt and dried over $MgSO_4$. After evaporation of organic solvents, product **3** was obtained by purification using silica gel column chromatography.

Method B. To a mixture of ice (26 g) and concentrated sulfuric acid (8.0 mL), aniline (5.0 mmol) was added slowly and stirred for several minutes at room temperature. CPME (35 mL) was added to the solution. An aqueous solution (14 mL) of sodium nitrite (0.38 g, 5.5 mmol) was added dropwise over 10 min, and the mixture was refluxed for 15–20 min. After completion of the reaction, the resulting solution was allowed to cool to room temperature, and then extracted with AcOEt and dried over $MgSO_4$. After purification by silica gel column chromatography, phenol **3** was obtained.

3-(4-Nitrophenoxy)phenol (3a). Yield 1.110 g (96%), mp 95–96 °C (Lit.[18] 96–97 °C); ^{1}H NMR ($CDCl_3$) δ 5.26 (s, 1H, OH), 6.59 (t, J = 2.4 Hz, 1H), 6.65 (ddd, J = 8.2, 2.4, 0.8 Hz, 1H), 6.72 (ddd, J = 8.2, 2.4, 0.8 Hz, 1H), 7.04 (dt, J = 9.2, 2.1 Hz, 2H), 7.27 (t, J = 8.2 Hz, 1H), 8.20 (dt, J = 9.2, 2.1 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 108.0, 112.6, 112.7, 117.4, 126.1, 131.1, 142.7, 155.9, 157.4, 163.2; MS (EI) *m/z* (%) 231 (M^+, 100), 207 (24), 128 (52), 65 (82).

3-Phenoxyphenol (3b). Yield 0.882 g (95%), oil (Lit.[19]); ^{1}H NMR ($CDCl_3$) δ 4.84 (s, 1H, OH), 6.48 (t, J = 2.4 Hz, 1H), 6.56 (dd, J = 8.2, 2.4, 1H), 6.58 (dd, J = 8.2, 2.4 Hz, 1H), 7.03 (d, J = 7.3 Hz, 2H), 7.12 (t, J = 7.3 Hz, 1H), 7.17 (t, J = 8.2 Hz, 1H), 7.34 (t, J = 7.3 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 106.0, 110.2, 111.1, 119.4, 123.7, 129.9, 130.5, 156.8, 156.9, 158.8; MS (EI) *m/z* (%) 186 (M^+, 100), 157 (21), 129 (27), 77 (35), 51 (94).

3-Benzyloxyphenol (3c). Yield 0.643 g (64%), mp 49–50°C (Lit.[20] 50–51 °C); ^{1}H NMR ($CDCl_3$) δ 4.71 (s, 1H, OH), 5.04 (s, 2H, CH_2), 6.44 (ddd, J = 8.2, 2.4, 0.9 Hz, 1H), 6.48 (t, J = 2.4 Hz, 1H), 6.57 (ddd, J = 8.2, 2.4, 0.9 Hz, 1H), 7.14 (t, J = 8.2Hz, 1H), 7.33–7.44 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 70.1, 102.6, 107.5, 108.2, 127.6, 128.1, 128.7, 130.3, 136.9, 156.7, 160.2; MS (EI) *m/z* (%) 200 (M^+, 11), 91 (100), 65 (15), 51 (6).

3-Isopropylphenol (3d). Yield 0.652 g (96%), oil (Lit.[21]); ^{1}H NMR ($CDCl_3$) δ 1.23 (d, J = 6.9 Hz, 6H, CH_3), 2.86 (sep, J = 6.9 Hz, 1H, CH), 4.76 (s, 1H, OH), 6.65 (ddd, J = 7.7, 2.2, 0.9 Hz, 1H), 6.71 (t, J = 2.2 Hz, 1H), 6.81 (d, J = 7.7 Hz, 1H), 7.16 (t, J = 7.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 24.0, 34.1, 112.7, 113.4, 119.1, 129.5, 151.1, 155.6; MS (EI) *m/z* (%) 136 (M^+, 38), 121 (100), 103 (15), 91 (23), 77 (24), 65 (11), 51 (15), 41 (21).

m-Cresol (3e). Yield 0.504 g (93%), oil (Lit.[22]); ^{1}H NMR ($CDCl_3$) δ (ppm): 2.30 (s, 3H, CH_3), 4.78 (s, 1H, OH), 6.62–6.66 (m, 2H), 6.75 (d, J = 8.0 Hz, 1H), 7.12 (t, J = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 21.4, 112.4, 116.2, 121.8, 129.6, 140.0, 155.4; MS (EI) *m/z* (%) 108 (M^+, 100), 107 (97), 90 (17), 79 (41), 51 (35), 40 (21).

3-Methoxyphenol (3f). Yield 0.565g (91%), oil (Lit.[23]); ^{1}H NMR ($CDCl_3$) δ 3.77 (s, 3H, CH_3), 5.15 (s, 1H, OH), 6.41–6.44 (m, 2H), 6.50 (ddd, J = 8.1, 2.3, 0.9 Hz, 1H), 7.12 (t, J = 7.9 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 55.4, 101.7, 106.6, 108.0, 130.3, 156.8, 160.9. MS (EI) *m/z* (%) 124 (M^+, 100), 94 (61), 81 (33), 66 (33), 53 (62), 41 (18).

3-Acetylphenol (3g). Yield 0.629 g (92%), mp 95–96°C (Lit.[24] 96°C); ^{1}H NMR ($CDCl_3$) δ 2.61 (s, 3H, CH_3), 6.85 (s, 1H, OH), 7.12 (ddd, J = 8.0, 2.7, 0.9 Hz, 1H), 7.34 (t, J = 8.0 Hz, 1H), 7.51 (dt, J = 8.0, 0.9 Hz, 1H), 7.55–7.56 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 26.9, 114.8, 121.0, 121.2, 130.0, 138.4, 156.5, 199.5; MS (EI) *m/z* (%) 136 (M^+, 62), 121 (91), 93 (65), 65 (49), 43 (100).

3-Nitrophenol (3h). Yield 0.519 g (75%), mp 95–96°C (Lit.[7] 95–96°C); ^{1}H NMR ($CDCl_3$) δ 5.39 (s, 1H, OH), 7.18 (ddd, J = 8.2, 2.3, 0.9 Hz, 1H), 7.41 (t, J = 8.2 Hz, 1H), 7.70 (t, J = 2.3 Hz, 1H), 7.82 (ddd, J = 8.2, 2.3, 0.9 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 110.6, 116.0, 122.1, 130.4, 149.2, 156.3; MS (EI) *m/z* (%) 139 (M^+, 70), 93 (42), 81 (24), 65 (100), 53 (40).

3-Trifluoromethylphenol (3i). Yield 0.760 g (94%), oil (Lit.[25]); ^{1}H NMR ($CDCl_3$) δ 5.04 (s, 1H, OH), 7.01 (dd, J = 2.3, 8.2 Hz, 1H), 7.08 (s, 1H), 7.20 (dd, J = 8.2, 2.3 Hz, 1H), 7.36 (t, J = 8.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 112.5 (q, J = 3.7 Hz), 117.8, (q, J = 3.7 Hz), 119.0, 124.0 (q, J = 274 Hz), 130.4, 132.3 (q, J = 33 Hz), 155.8; MS (EI) *m/z* (%) 162 (M^+, 100), 143 (33), 112 (24), 63 (18).

3-Hydroxybenzoic acid (3j). Yield 0.678 g (98%), mp 197–198°C (Lit.[26] 199–200°C); ^{1}H NMR (DMSO-d_6) δ 7.01 (ddd, J = 7.9, 2.4, 1.2 Hz, 1H), 7.31 (t, J = 7.9 Hz, 1H), 7.35 (t, J = 2.4 Hz, 1H), 7.40 (d, J = 7.9 Hz, 1H), 9.77 (s, 1H, OH), 12.8 (brs, 1H, COOH); ^{13}C NMR (DMSO-d_6) δ 116.3, 120.4, 120.5, 130.1, 132.5, 157.9, 167.8; MS (Neg-DART) *m/z* 137 ($[M - H]^-$).

o-Cresol (3k). Yield 0.449 g (83%), oil (Lit.[22]); ^{1}H NMR ($CDCl_3$) δ 2.25 (s, 3H, CH_3), 4.72 (s, 1H, OH), 6.76 (d, J = 7.7 Hz, 1H), 6.85 (td, J = 7.7, 1.2 Hz, 1H), 7.06–7.13 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 15.9, 115.0, 120.9, 123.9, 127.3, 131.2, 153.8; MS (EI) *m/z* (%) 108 (M^+, 100), 107 (83), 90 (25), 79 (42), 51 (45), 40 (12).

Salicylic acid (3l). Yield 0.614 g (89%), mp 157.5–158.5 °C (Lit.[27] 157.5–158 °C); ^{1}H NMR (DMSO-d_6) δ 6.92 (t, J = 7.2 Hz, 1H), 6.95 (d, J = 7.2 Hz, 1H), 7.51 (td, J = 7.6, 0.6 Hz, 1H), 7.79 (dd, J = 7.6, 1.6 Hz, 1H), 11.50 (brs, 1H); ^{13}C NMR (DMSO-d_6) δ 113.5, 117.6, 119.7, 130.8, 136.2, 161.7, 172.5; MS (Neg-DART) *m/z* 137 ($[M - H]^-$).

p-Cresol (3m). Yield 0.444 g (82%), oil (Lit.[22]); ^{1}H NMR ($CDCl_3$) δ 2.27 (s, 3H, CH_3), 4.75 (s, 1H, OH), 6.73 (dd, J = 8.2, 2.0 Hz, 2H), 7.03 (d, J = 8.2 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 20.6, 115.2, 130.2, 153.2; MS (EI) *m/z* (%) 108 (M^+, 94), 107 (100), 90 (12), 77 (33), 51 (42), 40 (11).

4-Hydroxybenzoic acid (3n). Yield 0.660 g (96%), mp 209.5–210.5 °C (Lit.[28] 210–211 °C); ^{1}H NMR (DMSO-d_6) δ 6.82 (d, J = 8.6 Hz, 2H), 7.78 (d, J = 8.6 Hz, 2H), 10.2 (brs, 1H, OH), 12.4 (brs,

1H, COOH); ^{13}C NMR (DMSO-d_6) δ 115.6, 121.9, 132.1, 162.1, 167.7; MS (Neg-DART) *m/z* 137 ([M – H]$^-$).

Phenol (3o). Yield 0.435 g (93%), mp 40.5–41.5 °C (Lit.[29] 41–43 °C); ^{1}H NMR ($CDCl_3$) 4.82 (s, 1H, OH), 6.81–6.85 (m, 2H), 6.93 (t, J = 7.4 Hz, 1H), 7.22–7.27 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 115.4, 120.9, 129.8, 155.5; MS (EI) *m/z* (%) 94 (M^+, 100), 66 (39), 55 (18), 40 (39).

3-Hydroxypyridine (3p). Yield 0.479 g (100%), mp 126–127 °C (Lit.[30] 127 °C); ^{1}H NMR (Acetone-d_6) δ 7.20 (t, J = 2.1 Hz, 2H), 8.08 (t, J = 3.2 Hz, 1H), 8.21 (t, J = 1.6 Hz, 1H), 8.92 (brs, 1H, OH); ^{13}C NMR (Acetone-d_6) δ 121.9, 124.0, 138.1, 140.9, 153.7. MS (EI) *m/z* (%) 95 (M^+, 100), 67 (24), 40 (79).

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Chapter 3

Metal-Free C-H Arylation of Aminoheterocycles with Arylhydrazines

3.1 INTRODUCTION

The use of transition-metal catalysts helped to rapidly develop aromatic coupling reactions, which are very important in organic chemistry, e.g., Mizoroki–Heck reaction,[1] Suzuki–Miyaura coupling,[2] and Negishi coupling.[3] The great success of cross-coupling reactions using transition-metal catalysts led to the Nobel Prize in chemistry in 2010. To use these reactions in industrial scale, however, researchers in companies often face to the following problems: 1) Most of the transition-metal catalysts, e.g., Pd catalysts, are very expensive, and some of them are toxic. 2) The removal of transition metal residues from the target products is very costly. Therefore, the development of aromatic substitutions in the absence of transition-metal catalysts is strongly desired from practical perspective.

A conceptually different approach about aromatic substitution is the direct C–H radical arylation of arenes involving a homolytic aromatic substitution (HAS) mechanism.[4] A similar type of reaction was first reported by Gomberg and Bachmann in 1924.[5] Recently, much attention has been paid to the use of arylhydrazines as the radical sources in HAS mechanism.[6] New elegant arylations of anilines with arylhydrazines or aryldiazonium salts have been reported to be a valuable alternative to transition-metal-based arylations.[7] In the reported reaction systems, the free amino functionality of anilines led to high *ortho* regioselectivities, and 2-arylanilines have been synthesized in reasonable yields.

Substituted heterocycles are valuable building blocks in many fields such as medicinal chemistry and materials science. In particular, an important subgroup of substituted heterocycles is diaminoheterocycles. For example, lamotrigine was developed as an anticonvulsant for the treatment of bipolar depression.[8] Moreover, compounds **A** and **B** are selective Nav1.8 modulators[9] (Fig. 1).

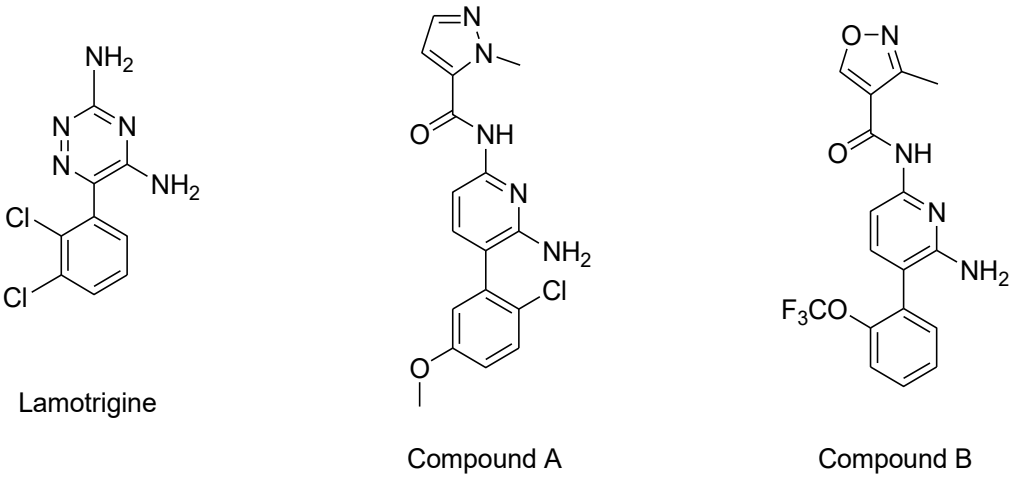


Figure 1. Lamotrigine and compounds A and B.

Our company manufactures aromatic diamines, which are not only useful as the raw materials of functional plastics, but also significant as the polymer intermediates for aerospace applications and information technology. Therefore, we studied the practical arylation of heterocyclic diamines without using transition-metal catalysts. Particularly, the challenge was to perform the radical arylation of aminoheterocycles with regioselectivity. Recently, the direct arylation of pyridines with arylhydrazine hydrochlorides under mild conditions was reported, although the regioselectivity of this arylation reaction was not satisfactory.[6f]

3.2 RESULTS AND DISCUSSION

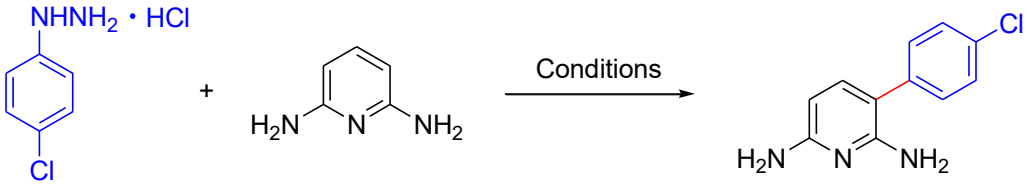
First, the arylation of 2,6-diaminopyridine **2a** (10 equiv) with *p*-chlorophenylhydrazine hydrochloride **1a** in the presence of potassium carbonate at 25 °C for 24 h in air was investigated. To our delight, a regioselective reaction occurred, affording 2,6-diamino-3-(4′-chlorophenyl)pyridine **3aa** in a high yield (78%, Table 1, entry 1). Herein, we report the arylation of aminoheterocycles with arylhydrazine hydrochlorides as the radical source in detail. To the best of our knowledge, this is the first example of the radical arylation of aminoheterocycles with arylhydrazines.

In the selection of solvents, a combination of DMSO and potassium carbonate[6c,6g] worked well the present radical arylation, producing **3aa** in a good yield (78%, entry 1). When DMF or DMA was

used instead of DMSO, the yield of **3aa** decreased (entries 2 and 3). Acetonitrile provided **3aa** in a moderate yield[6b,6d,7f] (entry 4). Because **2a** is soluble in water, the use of water as a solvent was also investigated for the arylation. However, the arylation in water almost did not proceed (entry 5). The use of HFIP (1,1,1,3,3,3-hexafluoro-2-propanol), an effective radical stabilizer for the chelated radical–anion oxidative coupling of phenols in the presence of an iron catalyst,[10a] provided an inferior result. The product **3aa** was not obtained at all (entry 6).

Next, several bases were screened; **3aa** was obtained in moderate-to-good yields when lithium carbonate, sodium carbonate, or cesium carbonate was used (entries 7–9). The addition of an aqueous solution of KOH or NaOH was not effective for the formation of **3aa** (entries 10 and 11). Triethylamine furnished **3aa** in a moderate yield (entry 12). Surprisingly, in the absence of a base, the product **3aa** was obtained in a fair yield (55%, entry 13). Excess **2a** may have worked as a base as shown in the previous report.[6f] High reaction temperatures did not improve the yield of **3aa** (entries 14 and 15). The best yield (85%) of **3aa** was obtained when 20 equiv of **2a** was used (entry 16). Under a nitrogen atmosphere, a low yield of **3aa** was obtained (entry 17). When the amount of **2a** was reduced, the yield of **3aa** decreased (entries 18 and 19). Slow addition of **1a** was tried into the mixture of **2a** (1equiv) and K_2CO_3 for 4 h using syringe pump (entry 20). However, improvement of the yield was not observed. Different reaction times (48 h or 8 h) did not improve the yield of **3aa** (entries 21 and 22).

Table 1. Optimization of synthesis of 3aa



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

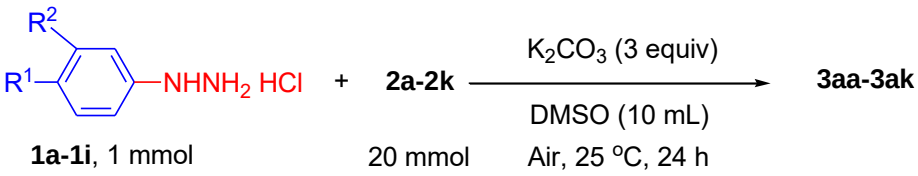
entry	solvent	base	temp. (°C)	equiv of **2a**	time (h)	yield(%)[a]
1	DMSO	K_2CO_3	25	10	24	78
2	DMF	K_2CO_3	25	10	24	44
3	DMA	K_2CO_3	25	10	24	61
4	MeCN	K_2CO_3	25	10	24	48
5	H_2O	K_2CO_3	25	10	24	trace
6	HFIP[b]	K_2CO_3	25	10	24	0
7	DMSO	Li_2CO_3	25	10	24	66
8	DMSO	Na_2CO_3	25	10	24	76
9	DMSO	Cs_2CO_3	25	10	24	43
10	DMSO	KOH	25	10	24	trace[c]
11	DMSO	NaOH	25	10	24	trace[c]
12	DMSO	Et_3N	25	10	24	49
13	DMSO	none	25	10	24	55
14	DMSO	K_2CO_3	50	10	24	66
15	DMSO	K_2CO_3	100	10	24	16
16	DMSO	K_2CO_3	25	20	24	85
17	DMSO	K_2CO_3	25	20	24	40[d]
18	DMSO	K_2CO_3	25	5	24	59
19	DMSO	K_2CO_3	25	2	24	40
20	DMSO	K_2CO_3	25	1	24	26[e]
21	DMSO	K_2CO_3	25	10	48	76
22	DMSO	K_2CO_3	25	10	8	74

Reaction conditions: **1a** (1.0 mmol), base (3.0 mmol), and solvent (10 mL) in air.
[a]Isolated yields based on **1a**. [b]1,1,1,3,3,3-Hexafluoro-2-propanol. [c]An aqueous solution (1 N, 3.0 mL) of KOH or NaOH was used. [d]Under a nitrogen atmosphere. [e]DMSO (5 mL) solution of **1a** was slowly into the mixture of **2a** (1equiv) and K_2CO_3 in DMSO (5 mL) for 4 h.

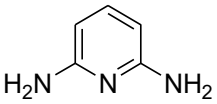
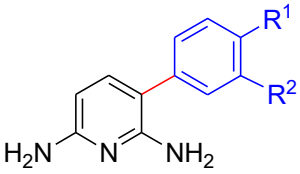
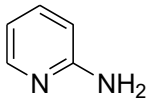
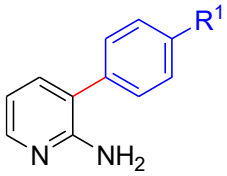
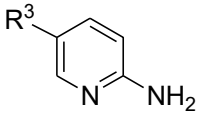
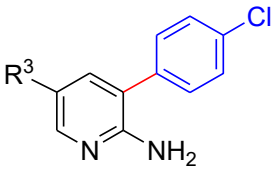
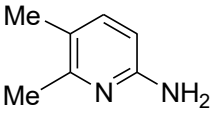
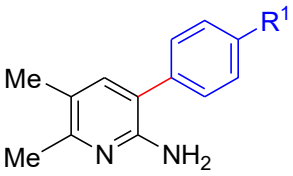
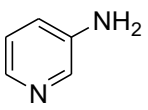
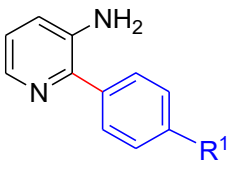
With the optimized conditions, the substrate scope and limitations of the arylation of aminoheterocycles **2a**–**2k** with various arylhydrazine hydrochlorides **1a**–**1i** were investigated (Table 2). The arylation of 2,6-diaminopyridine **2a** with arylhydrazine hydrochlorides **1a**–**1e** bearing electron-withdrawing groups such as Cl, F, Br, and CN smoothly afforded the corresponding target compounds **3aa**–**3ea** in good-to-excellent yields (entries 1–5). Moreover, phenylhydrazine hydrochloride and arylhydrazine hydrochlorides bearing electron-donating groups such as OMe and Me showed similar reactivities, producing **3fa**–**3ha** in good yields (entries 6–8). However, 4-nitrophenylhydrazine **1i** bearing a strong electron-withdrawing group provided a trace amount of **3ia** (entry 9). The results clearly indicate the high radical-scavenging ability of 2,6-diaminopyridine **2a** for phenyl radicals. The attack of phenyl radicals may be facilitated at the *ortho* and *para* positions of the amino group in **2a**.

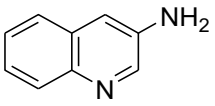
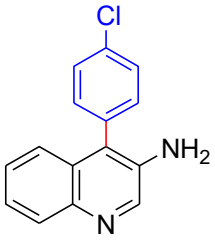
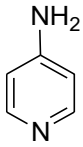
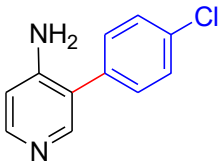
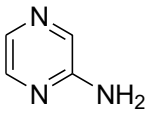
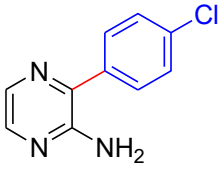
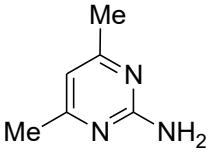
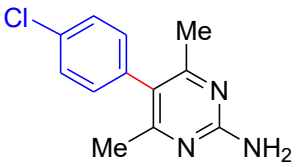
Next, 2-aminopyridine **2b** underwent cross-coupling reaction at the 3-position preferentially, affording **3ab** and **3cb** in moderate yields (entries 10 and 11). Moreover, 5-substituted and 5,6-disubstituted 2-aminopyridines produced the corresponding products **3ac**, **3ad**, **3ae**, **3af**, and **3bf** in moderate yields (entries 12–16). Further, 3-aminopyridine **2g** underwent cross-coupling reaction at the 2-position preferentially, furnishing **3ag**–**3cg** in moderate-to-good yields (entries 17–19). A reported oxidative chlorination of **2g** with hydrochloric acid and hydrogen peroxide showed similar regioselectivity, resulting in the chlorination of **2g** at the 2-position.[11] As shown in entries 17–19, 4-isomers **3ag′**–**3cg′** and 6-isomers **3ag″**–**3cg″** were obtained as the minor products. Interestingly, 3-aminoquinoline **2h** afforded 4-substituted product **3ah** in a good yield (entry 20). The radical intermediate obtained by the reaction of **2h** might be resonance-stabilized, and 4-isomer **3ah** was obtained selectively. Moreover, 2-isomer **3ah′** was obtained as a minor product. In contrast, 4-aminopyridine did not afford the corresponding product **3ai** (entry 21). These results clearly show the difference in the reactivities between 2,6-diaminopyridine **2a**, 2-aminopyridine **2b**, 3-aminopyridine **2g**, and 4-aminopyridine **2i**. Finally, the cross-coupling reactions with other aminoheterocycles **2j** and **2k** were carried out successfully (entries 22 and 23).

Table 2. The Reaction of Arylhydrazones with Aminoheterocycles



1a-1i, 1 mmol 20 mmol

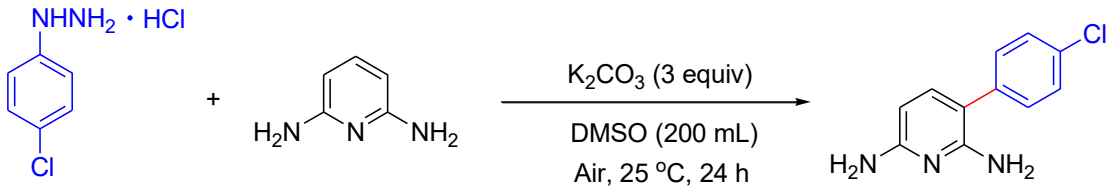
entry	2a-2k	3aa-3ak	yield (%)[a]
1			
2		**3aa;** R^1 = Cl, R^2 = H	85
3		**3ba;** R^1 = F, R^2 = H	76
4		**3ca;** R^1 = Br, R^2 = H	74
5		**3da;** R^1 = CN, R^2 = H	60
6		**3ea;** R^1 = Cl, R^2 = Cl	63
7		**3fa;** R^1 = H, R^2 = H	59
8		**3ga;** R^1 = OMe, R^2 = H	58
9		**3ha;** R^1 = Me, R^2 = H	60
		3ia; R^1 = NO_2, R^2 = H	trace
	2a		
10			
11		**3ab;** R^1 = Cl	36[b]
		3cb; R^1 = Br	37[b]
	2b		
12			
13		**3ac;** R^3 = Me	37
14		**3ad;** R^3 = Cl	47
		3ae; R^3 = Br	49
	2c-2e		
15			
16		**3af;** R^1 = Cl	34
		3bf; R^1 = F	30
	2f		
17			
18		**3ag;** R^1 = Cl	75[c]
19		**3bg;** R^1 = F	55[d]
		3cg; R^1 = Br	63[e]
	2g		

20	 **2h**		**3ah**	83[f]
21	 **2i**		**3ai**	trace
22	 **2j**		**3aj**	56
23	 **2k**		**3ak**	19

[a]Isolated yields after purification by column chromatography, based on arylhydrazines. [b]A small amount of isomer was also formed, but not isolated. [c]2-Isomer (**3ag**, 52%), 4-isomer (**3ag′**, 15%) and 6-isomer (**3ag′′**, 8%) were obtained. [d]2-Isomer (**3bg**, 38%), 4-isomer (**3bg′**, 11%) and 6-isomer (**3bg′′**, 6%) were formed. [e]2-Isomer (**3cg**, 47%) , 4-isomer (**3cg′**, 11%) and 6-isomer (**3cg′′**, 5%) were obtained. [f]4-Isomer (**3ah**, 74%) and 2-isomer (**3ah′**, 9%) were formed.

Next, the feasibility of a large-scale synthesis (20-fold) of **3aa** was investigated (Scheme 1). Starting from **1a** and **2a**, the desired 2,6-diamino-3-(4′-chlorophenyl)pyridine (**3aa**) was obtained in 81% yield and excess **2a** was recovered in almost 90% yield without the formation of any byproducts.

Scheme 1. Large-Scale Synthesis of 3aa



1a 3.58 g (20 mmol)

2a 43.65 g (400 mmol)

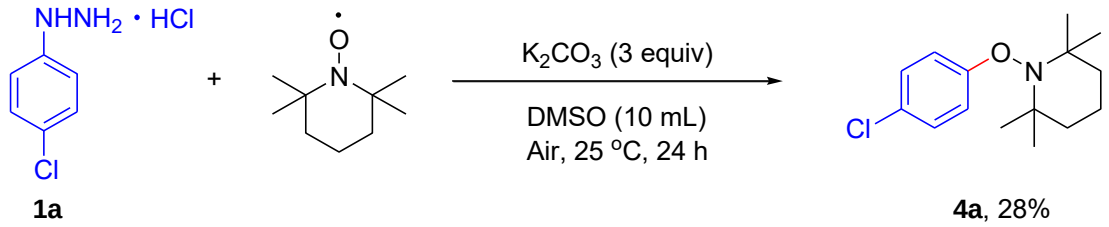
3aa, 81% 3.54 g (16.1 mmol)

To better understand the arylation with **2**, DFT calculations at the B3LYP/6-31G (d,p) level were carried out. Recently, a correlation between the energy of the HOMO of a molecule and its relative nucleophilicity was shown in the radical–anion oxidative coupling of phenols, and a global scale of calculated nucleophilicity, N, was determined.[10] The HOMO energy levels of the aminoheterocycles in this arylation system correlated with their nucleophilicity. 2,6-Diaminopyridine (**2a**) with a high HOMO energy (–5.14 eV) had a high global nucleophilicity. In fact, **2a** showed a high reactivity with *p*-chlorophenyl radical, producing **3aa** in an excellent yield (Table 2, entry 1). 2-Aminopyridine (**2b**) and 3-aminopyridine (**2g**) had moderate HOMO energies, –5.74 eV and –5.77 eV, respectively, and reacted with aryl radicals to afford the corresponding products in moderate to good yields. Conversely, 4-aminopyridine (**2i**) with a very low HOMO energy (–6.10 eV) was expected to have a low global nucleophilicity. When **2i** was used, the corresponding product **3ai** was not obtained.

To support the radical mechanism, a radical-trapping experiment was carried out using TEMPO. The oxidation of **1a** with TEMPO (1.5 equiv) in air under the optimized conditions (Table 1, entry 16) afforded 4-chloro-1-(2,2,6,6-tetramethylpiperidinyloxy)

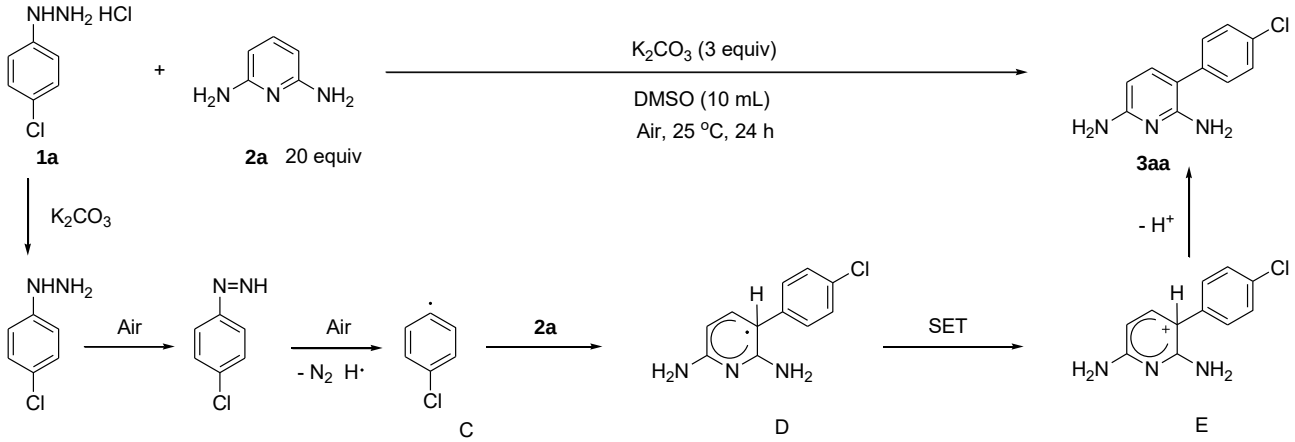
benzene **4a** in 28% yield (Scheme 2).

Scheme 2. Phenyl radical-Trapping Experiment



Based on the experimental results and previous studies on HAS reactions,[4,7] a plausible reaction mechanism for the arylation of **2a** with **1a** is proposed in Scheme 3. After the preparation of the free-base hydrazine from **1a** by treating with K_2CO_3, the free-base hydrazine is oxidized by air to form the corresponding diazene. Then, the diazene is converted into radical **C** by oxidation with air. The addition of radical **C** to **2a** provides the intermediate cyclohexadienyl radical **D**. The radical **D** converts into cation **E** via single electron transfer (SET). Finally, the elimination of a hydrogen cation from cation **E** affords **3aa**.

Scheme 3. Plausible Reaction Mechanism for the Formation of 3aa



3.3 CONCLUSION

In conclusion, a metal-free arylation of aminoheterocycles with arylhydrazine hydrochlorides was developed with air as the oxidant. In this reaction system, the HOMO energy levels of the aminoheterocycles correlated with their nucleophilicity. This direct C–H arylation reaction without

transition-metal catalysts could be not only a useful and practical method but also an alternative for Pd-catalyzed cross-coupling reactions.

3.4 EXPERIMENTAL SECTION

General Information

All starting materials were purchased from commercial sources and used without further purification. IR spectra were reported in wave numbers (cm^{-1}). ^{1}H NMR spectra were recorded on 400 MHz spectrometers using $CDCl_3$ or DMSO-d_6 as solvent referenced to TMS (0 ppm) and $CHCl_3$ (7.26 ppm) or DMSO (2.50 ppm). ^{13}C NMR spectra were recorded at 100 MHz in $CDCl_3$ and DMSO-d_6 using $CDCl_3$ (77.0 ppm) and DMSO-d_6 (39.5 ppm) as standard. Chemical shifts are reported in parts per million (ppm). Coupling constants are reported in hertz (*J*, Hz). The following abbreviations are used for the description of signals: s (singlet), bs (broad singlet), d (doublet), dd (double doublet), t (triplet), q (quadruplet), m (multiplet). Mass spectra and exact mass spectra were recorded using electron impact (EI), electrospray ionization (ESI), and direct analysis in real time (DART). Analytical TLC was carried out on silica gel plates using short wave (254 nm) UV light. Silica gel (230−400 mesh) was used for column chromatography. DFT calculations were carried out at the B3LYP/6-31G (d,p) level using the Q-Chem 4.0.1 program package.[12] Optimized geometries of calculated compounds were confirmed by the absence of imaginary frequencies.

General Procedure for the Arylation of Aminoheterocycles with Arylhydrazine Hydrochlorides

A mixture of the arylhydrazine hydrochlorides (1.0 mmol), aminopyridines (20.0 mmol), and potassium carbonate (415 mg, 3.0 mmol) in DMSO (10 mL) was stirred at 25 °C in air. The reactions were completed after 24 h, monitored by thin layer chromatography (TLC). Then, quenched by the addition of water, the reaction mixture was extracted with ethyl acetate. The organic layer was washed with water and brine solution and dried over anhydrous $MgSO_4$. The solvent was removed under

reduced pressure to give the crude products. Purified by column chromatography over silica gel (hexane/AcOEt), the pure products were afforded.

2,6-Diamino-3-(4'-chlorophenyl)pyridine (3aa).

Compound **3aa** was synthesized from 4-chlorophenylhydrazine hydrochloride **1a** (179 mg, 1.0 mmol) and 2,6-diaminopyridine **2a** (2.18 g, 20.0 mmol) according to the general procedure. The excess of **2a** was almost removed by extracted with water. By the purification with column chromatography (inner diameter: 2 cm and length: 30 cm), **3aa** (188 mg, 0.85 mmol, 85%) was obtained. Recrystallized from hexane/AcOEt=1:1, **3aa** was given as a pale brown crystal; R_f (hexane/AcOEt=1:3) 0.3; mp 116.5-117.5 °C (Lit.[13] 114-115 °C); FT-IR (neat) 3469, 3427, 3303, 3103, 1591, 1467, 1421, 1082 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.26 (bs, 2H, N-H), 4.35 (bs, 2H, N-H), 5.98 (d, J = 8.0 Hz, 1H, C-H), 7.16 (d, J = 8.0 Hz, 1H, C-H), 7.34 (d, J = 9.0 Hz, 2H, C-H), 7.38 (d, J = 9.0 Hz, 2H, C-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 98.5, 110.2, 129.0, 130.1, 132.5, 137.3, 140.0, 154.5, 157.1; *m/z* (EI) 219 (100, M^+), 183 (15), 140 (27), 92 (29), 43 (52%); HRMS (ESI): MH^+, found 220.0610. $C_{11}H_{11}ClN_3$ requires 220.0636.

2,6-Diamino-3-(4'-fluorophenyl)pyridine (3ba).

Compound **3ba** was synthesized from 4-fluorophenylhydrazine hydrochloride **1b** (163 mg, 1.0 mmol) and **2a** (2.18 g, 20.0 mmol) according to the general procedure. The excess of **2a** was almost removed by extracted with water. Purification with column chromatography (inner diameter: 2 cm and length: 30 cm) gave **3ba** (154 mg, 0.76 mmol, 76%). Recrystallized from hexane/AcOEt=3:7, **3ba** was given as a pale brown needle; R_f (AcOEt) 0.3; mp 124.0-125.0 °C; FT-IR (neat) 3460, 3397, 3308, 3144, 1593, 1475, 1430, 1353, 1214 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.26 (bs, 2H, N-H), 4.35 (bs, 2H, N-H), 5.98 (d, J = 7.7 Hz, 1H, CH), 7.09 (dd, J_{HF} = 9.0 Hz, J = 9.0 Hz, 2H, C-H), 7.15 (d, J = 7.7 Hz, 1H, C-H), 7.36 (dd, J_{HF} = 5.5 Hz, J 9.0 Hz, 2H, C-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 98.4, 110.5, 115.7 (d, J_{CF} = 21.1 Hz), 130.4 (d, J_{CF} = 8.6 Hz), 134.7, 140.1, 154.6, 157.1, 161.7 (d, J_{CF} = 247.2 Hz);

m/z (EI) 203 (100, M^+), 185 (13), 158 (18), 133 (17), 44 (54%); HRMS (ESI): MH^+, found 204.0922. $C_{11}H_{11}FN_3$ requires 204.0932.

2,6-Diamino-3-(4'-bromophenyl)pyridine (3ca). Compound **3ca** was prepared from 4-bromophenylhydrazine hydrochloride **1c** (224 mg, 1.0 mmol) and **2a** (2.18 g, 20.0 mmol) according to the general procedure. The excess of **2a** was almost removed by extracted with water. By the purification with column chromatography (inner diameter: 2 cm and length: 30 cm), **3ca** (195 mg, 0.74 mmol, 74%) was obtained. Recrystallized from hexane/AcOEt=1:1, **3ca** was given as a cream color solid; R_f (hexane/AcOEt=2:13) 0.3; mp 129.0-130.0 °C; FT-IR (neat) 3432, 3365, 3302, 3112, 1589, 1469, 1420, 1067 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.27 (bs, 2H, N-H), 4.36 (bs, 2H, N-H), 5.99 (d, J = 8.2 Hz, 1H, C-H), 7.16 (d, J = 8.2 Hz, 1H, C-H), 7.29 (d, J = 8.5 Hz, 2H, C-H), 7.53 (d, J = 8.5 Hz, 2H, C-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 98.5, 110.2, 120.6, 130.4, 132.0, 137.8, 140.0, 154.5, 157.2; *m/z* (EI) 263 (100, M^+), 183 (39), 140 (45), 92 (62), 43 (68%); HRMS (ESI): MH^+, found 264.0110. $C_{11}H_{11}{}^{79}BrN_3$ requires 264.0131.

2,6-Diamino-3-(4'-cyanophenyl)pyridine (3da). Compound **3da** was obtained from 4-cyanophenylhydrazine hydrochloride **1d** (170 mg, 1.0 mmol) and **2a** (2.18 g, 20.0 mmol) according to the general procedure. The excess of **2a** was almost removed by extracted with water. To the AcOEt solution including the product, hexane was added slowly. The generated precipitate was filtered with a funnel to give **3da** (26 mg, 0.60 mmol, 60%). Recrystallized from AcOEt, **3da** was given as a pale orange solid; R_f (hexane/AcOEt=1:3) 0.4; mp 221.5-222.5 °C; FT-IR (neat) 3429, 3377, 3174, 2225, 1570, 1471, 1442 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 5.37 (bs, 2H, N-H), 5.76 (bs, 2H, N-H), 5.85 (d, J = 8.0 Hz, 1H, C-H), 7.13 (d, J = 8.0 Hz, 1H, C-H), 7.57 (d, J = 8.5 Hz, 2H, C-H), 7.78 (d, J = 8.5 Hz, 2H, C-H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 97.7, 106.0, 107.4, 119.3, 128.6, 132.5, 139.5, 144.8, 155.2, 158.9; *m/z* (EI) 210 (100, M^+), 192 (21), 155 (13), 139 (13), 44 (96%); HRMS (ESI): MH^+, found 211.0958. $C_{12}H_{11}N_4$ requires 211.0978.

2,6-Diamino-3-(3',4'-dichlorophenyl)pyridine (3ea). Compound **3ea** was prepared from 3,4-dichlorophenylhydrazine hydrochloride **1e** (213 mg, 1.0 mmol) and **2a** (2.18 g, 20.0 mmol) according to the general procedure. The excess of **2a** was almost removed by extracted with water. Purification with column chromatography (inner diameter: 2 cm and length: 30 cm) gave **3ea** (161 mg, 0.63 mmol, 63%). Recrystallized from hexane/AcOEt=1:3, **3ea** was given as a white solid; R_f (hexane/AcOEt=1:3) 0.3; mp 126.0-127.0 °C; FT-IR (neat) 3417, 3338, 3132, 1574, 1460, 1435, 1022 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 5.32 (bs, 2H, N-H), 5.67 (bs, 2H, N-H), 5.82 (d, J = 8.4 Hz, 1H, C-H), 7.08 (d, J = 8.4 Hz, 1H, C-H), 7.34 (dd, J = 2.2 Hz, J = 8.5 Hz, 1H, C-H), 7.56 (d, J = 2.2 Hz, 1H, C-H), 7.58 (d, J = 8.5 Hz, 1H, CH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 97.4, 105.4, 128.4, 129.8, 130.6, 131.1, 139.4, 140.4, 155.1, 158.7; *m/z* (EI) 253 (100, M^+), 217 (16), 174 (24), 109 (20), 91 (16), 43 (84%); HRMS (ESI): MH^+, found 254.0223. $C_{11}H_{10}Cl_2N_3$ requires 254.0246.

2,6-Diamino-3-phenylpyridine (3fa). Compound **3fa** was given from phenylhydrazine hydrochloride **1f** (145 mg, 1.0 mmol) and **2a** (2.18 g, 20.0 mmol) according to the general procedure. The excess of **2a** was almost removed by extracted with water. Purification with column chromatography (inner diameter: 2 cm and length: 30 cm) gave **3fa** (109 mg, 0.59 mmol, 59%). Recrystallized from hexane/AcOEt=1:3, **3fa** was given as a white needle; R_f (hexane/AcOEt=1:3) 0.3; mp 113.5-114.5 °C (Lit.[13] 114-115 °C); FT-IR (neat) 3429, 3379, 3309, 3130, 1593, 1469, 1408 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.25 (bs, 2H, N-H), 4.41 (bs, 2H, N-H), 5.99 (d, J = 7.8 Hz, 1H, C-H), 7.20 (d, J = 7.8 Hz, 1H, C-H), 7.28-7.31 (m, 1H, C-H), 7.40-7.42 (m, 4H, C-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 98.4, 111.6, 126.7, 128.8, 128.9, 138.8, 140.1, 154.6, 157.0; *m/z* (EI) 185 (100, M^+), 140 (17), 92 (17), 43 (29%); HRMS (ESI): MH^+, found 186.1029. $C_{11}H_{12}N_3$ requires 186.1026.

2,6-Diamino-3-(4'-methoxyphenyl)pyridine (3ga). Compound **3ga** was prepared from 4-methoxyphenylhydrazine hydrochloride **1g** (175 mg, 1.0 mmol) and **2a** (2.18 g, 20.0 mmol) according to the general procedure. The excess of **2a** was almost removed by extracted with water. Purification

with column chromatography (inner diameter: 2 cm and length: 30 cm) gave **3ga** (125 mg, 0.58 mmol, 58%). Recrystallized from hexane/AcOEt=1:3, **3ga** was given as a pale yellow solid; R_f (hexane/AcOEt=1:3) 0.2; mp 129.5-130.5 °C; FT-IR (neat) 3440, 3327, 3186, 1585, 1477, 1427, 1174 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.83 (s, 3H, O-CH_3), 4.21 (bs, 2H, N-H), 4.36 (bs, 2H, N-H), 5.98 (d, J = 8.0 Hz, 1H, C-H), 6.95 (d, J = 8.7 Hz, 2H, C-H), 7.16 (d, J = 8.0 Hz, 1H, C-H), 7.32 (d, J = 8.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.3, 98.3, 111.3, 114.3, 129.9, 131.0, 140.0, 154.8, 156.7, 158.5; *m/z* (EI) 215 (100, M^+), 200 (69), 156 (12), 128 (13), 100 (13), 43 (25%); HRMS (ESI): MH^+, found 216.1109. $C_{12}H_{14}N_3O$ requires 216.1131.

2,6-Diamino-3-(4'-tolyl)pyridine (3ha). Compound **3ha** was obtained from 4-methylphenylhydrazine hydrochloride **1h** (159 mg, 1.0 mmol) and **2a** (2.18 g, 20.0 mmol) according to the general procedure. The excess of **2a** was almost removed by extracted with water. Purification with column chromatography (inner diameter: 2 cm and length: 30 cm) gave **3ha** (119 mg, 0.60 mmol, 60%). Recrystallized from hexane/AcOEt=1:3, **3ha** was given as a cream color needle; R_f (hexane/AcOEt=1:3) 0.4; mp 119.5-120.3 °C; FT-IR (neat) 3464, 3425, 3309, 3111, 1591, 1471, 1419 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 2.38 (s, 3H, -CH_3), 4.21 (bs, 2H, N-H), 4.38 (bs, 2H, N-H), 5.98 (d, J = 7.8 Hz, 1H, C-H), 7.18 (d, J = 7.8 Hz, 1H, C-H), 7.22 (d, J = 8.5 Hz, 2H, C-H), 7.30 (d, J = 8.5 Hz, 2H, C-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.1, 98.4, 111.6, 128.6, 129.6, 135.8, 136.4, 140.1, 154.7, 156.8; *m/z* (EI) 199 (100, M^+), 181 (17), 99 (21), 43 (25%); HRMS (ESI): MH^+, found 200.1155. $C_{12}H_{14}N_3$ requires 200.1182.

2-Amino-3-(4'-chlorophenyl)pyridine (3ab). Compound **3ab** was prepared from **1a** (179 mg, 1.0 mmol) and 2-aminopyridine **2b** (1.88 g, 20.0 mmol) according to the general procedure. The excess of **2b** was almost removed by extracted with water. Purification with column chromatography (inner diameter: 2 cm and length: 30 cm) gave **3ab** (74 mg, 0.36 mmol, 36%. Recrystallized from hexane/AcOEt=7:3, **3ab** was given as a white solid; R_f (hexane/AcOEt=1:1) 0.3; mp 121.0-122.0 °C;

FT-IR (neat) 3437, 3286, 3134, 1631, 1577, 1446, 1090 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.54 (bs, 2H, N-H), 6.75 (dd, J = 5.0 Hz, J = 7.3 Hz, 1H, C-H), 7.33 (dd, J = 2.0 Hz, J = 7.3 Hz, 1H, C-H), 7.39 (d, J = 8.8 Hz, 2H, C-H), 7.44 (d, J = 8.8 Hz, 2H, C-H), 8.08 (dd, J = 2.0 Hz, J = 5.0 Hz, 1H, C-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 114.6, 120.6, 129.3, 130.1, 133.8, 136.5, 137.8, 147.7, 155.7; *m/z* (EI) 204 (57, M^+), 203 (100), 168 (46), 115 (15), 84 (34%); HRMS (ESI): MH^+, found 205.0510. $C_{11}H_{10}ClN_2$ requires 205.0527.

2-Amino-3-(4'-bromophenyl)pyridine (3cb). Compound **3cb** was prepared from **1c** (224 mg, 1.0 mmol) and **2b** (1.88 g, 20.0 mmol) according to the general procedure. The excess of **2b** was almost removed by extracted with water. Purification with column chromatography (inner diameter: 3 cm and length: 30 cm) gave **3cb** (92 mg, 0.37 mmol, 37%). Recrystallized from hexane/AcOEt=9:1, **3cb** was given as a white needle; R_f (hexane/AcOEt=1:2) 0.34; mp 126.0-127.0 °C; FT-IR (neat) 3433, 3284, 3129, 1631, 1576, 1443, 1071 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.54 (bs, 2H, N-H), 6.75 (dd, J = 5.0 Hz, J = 8.0 Hz, 1H, C-H), 7.33 (d, J = 8.0 Hz, 1H, C-H), 7.33 (d, J = 8.0 Hz, 2H, C-H), 7.59 (d, J = 8.0 Hz, 2H, C-H), 8.08 (dd, J = 2.0 Hz, J = 5.0 Hz, 1H, C-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 114.6, 120.6, 121.9, 130.4, 132.3, 137.0, 137.7, 147.7, 155.6; HRMS (ESI): MH^+, found 248.9996. $C_{11}H_{10}{}^{79}BrN_2$ requires 249.0022.

2-Amino-3-(4'-chlorophenyl)-5-methylpyridine (3ac). Compound **3ac** was prepared from **1a** (179 mg, 1.0 mmol) and 2-amino-5-methylpyridine **2c** (2.16 g, 20.0 mmol) according to the general procedure. Purification with column chromatography (inner diameter: 2 cm and length: 30 cm) gave **3ac** (80 mg, 0.37 mmol, 37%). Recrystallized from hexane/AcOEt=1:1, **3ac** was given as a pale orange solid; R_f (hexane/AcOEt=1:1) 0.44; mp 164.0-165.0 °C; FT-IR (neat) 3448, 3278, 3130, 1628, 1468, 1089 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.23 (s, 3H, $-CH_3$), 4.37 (bs, 2H, NH), 7.18 (d, J = 2.0 Hz, 1H, C-H), 7.39 (d, J = 8.7 Hz, 2H, C-H), 7.43 (d, J = 8.7 Hz, 2H, C-H), 7.91 (d, J = 2.0 Hz, 1H, C-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.3, 120.3, 123.5, 129.2, 130.0, 133.6, 136.6, 138.8, 147.2, 153.6; *m/z*

(EI) 218 (73, M^+), 217 (100), 182 (34), 91 (19), 44 (80%); HRMS (ESI): MH^+, found 219.0655. $C_{12}H_{12}ClN_2$ requires 219.0684.

2-Amino-5-chloro-3-(4'-chlorophenyl)pyridine (3ad). Compound **3ad** was obtained from **1a** (179 mg, 1.0 mmol) and 2-amino-5-chloropyridine **2d** (2.57 g, 20.0 mmol) according to the general procedure. By the purification with column chromatography (inner diameter: 5 cm and length: 30 cm), **3ad** (112 mg, 0.47 mmol, 47%) was obtained. Recrystallized from hexane/AcOEt=1:1, **3ad** was given as a pale yellow needle; R_f (hexane/AcOEt=1:2) 0.76; mp 156.8-157.7 °C (Lit.[14] 140-141 °C); FT-IR (neat) 3450, 3280, 3143, 1624, 1456, 1090, 1011 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 4.54 (bs, 2H, N-H), 7.33 (d, J = 2.6 Hz, 1H, C-H), 7.38 (d, J = 8.6 Hz, 2H, C-H), 7.45 (d, J = 8.6 Hz, 2H, CH), 8.03 (d, J = 2.6 Hz, 1H, C-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 121.3, 121.6, 129.5, 129.9, 134.4, 135.2, 137.3, 145.8, 154.1; *m/z* (EI) 238 (68, M^+), 237(100), 202 (41), 168 (27), 140 (31%); HRMS (ESI): MH^+, found 239.0123. $C_{11}H_9Cl_2N_2$ requires 239.0137.

2-Amino-5-bromo-3-(4'-chlorophenyl)pyridine (3ae). Compound **3ae** was prepared from **1a** (179 mg, 1.0 mmol) and 2-amino-5-bromopyridine **2e** (3.46 g, 20.0 mmol) according to the general procedure. Purification with column chromatography (inner diameter: 5 cm and length: 30 cm) gave **3ae** (140 mg, 0.49 mmol, 49%). Recrystallized from hexane/AcOEt=1:2, **3ae** was given as a pale orange needle; R_f (hexane/AcOEt=1:2) 0.79; mp 150.0-151.0 °C; FT-IR (neat) 3454, 3284, 3151, 1620, 1454, 1088, 1011 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.59 (bs, 2H, N-H), 7.37 (d, J = 8.8 Hz, 2H, C-H), 7.44 (d, J = 2.4 Hz, 1H, C-H), 7.48 (d, J = 8.8 Hz, 2H, C-H), 8.11 (d, J = 2.4 Hz, 1H, C-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 108.5, 122.2, 129.5, 129.9, 134.4, 135.1, 139.7, 148.0, 154.4; *m/z* (EI) 283 (100), 282 (59, M^+), 281(76), 202 (52), 168 (45), 140 (38), 84 (48%); HRMS (ESI): MH^+, found 282.9605. $C_{11}H_9{}^{79}BrClN_2$ requires 282.9632.

2-Amino-3-(4'-chlorophenyl)-5,6-dimethylpyridine (3af). Compound **3af** was prepared from

1a (179 mg, 1.0 mmol) and 2-amino-5,6-dimethylpyridine **2f** (2.44 g, 20.0 mmol) according to the general procedure. Purification with column chromatography (inner diameter: 2 cm and length: 30 cm) gave **3af** (78 mg, 0.34 mmol, 34%). Recrystallized from hexane/AcOEt=1:1, **3af** was given as a pale orange needle; R_f (hexane/AcOEt=1:1) 0.2; mp 109.5-110.5 °C; FT-IR (neat) 3483, 3438, 3288, 3156, 1450, 1391, 1092 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.18 (s, 3H, -CH_3), 2.37 (s, 3H, -CH_3), 4.35 (bs, 2H, N-H), 7.09 (s, 1H, C-H), 7.37 (d, J = 8.8 Hz, 2H, C-H), 7.40 (d, J = 8.8 Hz, 2H, C-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.9, 21.9, 117.9, 121.5, 129.1, 130.1, 133.3, 136.8, 139.5, 153.0, 154.6; HRMS (ESI): MH^+, found 233.0813. $C_{13}H_{14}ClN_2$ requires 233.0840.

2-Amino-3-(4'-fluorophenyl)-5,6-dimethylpyridine (3bf). Compound **3bf** was prepared from **1b** (163 mg, 1.0 mmol) and **2f** (2.44 g, 20.0 mmol) according to the general procedure. Purification with column chromatography (inner diameter: 3 cm and length: 30 cm) gave **3bf** (64 mg, 0.30 mmol, 30%). Recrystallized from hexane/AcOEt=9:1, **3bf** was given as a pale orange plate crystal; R_f (hexane/AcOEt=1:2) 0.28; mp 109.0-110.0 °C; FT-IR (neat) 3480, 3292, 3169, 1454, 1216 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.18 (s, 3H, -CH_3), 2.38 (s, 3H, -CH_3), 4.33 (bs, 2H, N-H), 7.09 (s, 1H, C-H), 7.12 (dd, J_{HF} = 8.8 Hz, J = 8.8 Hz, 2H, C-H), 7.40 (dd, J_{HF} = 5.4 Hz, J = 8.8 Hz, 2H, C-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.9, 21.9, 115.9 (d, J_{CF} = 21.0 Hz), 118.2, 121.4, 130.4 (d, J_{CF} = 7.6 Hz), 134.3, 139.7, 153.1, 154.3, 162.1 (d, J_{CF} = 245.1 Hz); HRMS (ESI): MH^+, found 217.1127. $C_{13}H_{14}FN_2$ requires 217.1136.

3-Amino-2-(4'-chlorophenyl)pyridine (3ag), 3-Amino-4-(4'-chlorophenyl)pyridine (3ag'), and 3-Amino-6-(4'-chlorophenyl)pyridine (3ag''). Compounds **3ag**, **3ag′**, and **3ag′′** were synthesized from **1a** (179 mg, 1.0 mmol) and 3-aminopyridine **2g** (1.88 g, 20.0 mmol) according to the general procedure. Purification with column chromatography (inner diameter: 2 cm and length: 30 cm) gave **3ag** (107 mg, 0.52 mmol, 52%), and **3ag′** (31 mg, 0.15 mmol, 15%), and **3ag′′** (17 mg, 0.08 mmol, 8%). 3-Amino-2-(4′-chlorophenyl)pyridine (**3ag**): Recrystallized from hexane/AcOEt=1:1, **3ag**

was given as a pale yellow needle; R_f (hexane/AcOEt=1:3) 0.64; mp 86.6-87.5 °C; FT-IR (neat) 3458, 3309, 3184, 1631, 1579, 1444, 1088 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.80 (bs, 2H, N-H), 7.05 (dd, J = 1.8 Hz, J = 8.0 Hz, 1H, C-H), 7.08 (dd, J = 4.8 Hz, J = 8.0 Hz, 1H, C-H), 7.45 (d, J = 8.8 Hz, 2H, C-H), 7.64 (d, J = 8.8 Hz, 2H, C-H), 8.12 (dd, J = 1.8 Hz, J = 4.8 Hz, 1H, C-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 122.9, 123.3, 129.0, 129.9, 134.1, 137.0, 139.9, 140.1, 143.7; *m/z* (EI) 203 (100, M^+), 168 (45), 84 (22), 41 (47%); HRMS (ESI): MH^+, found 205.0504. $C_{11}H_{10}ClN_2$ requires 205.0527. 3-Amino-4-(4′-chlorophenyl)-pyridine (**3ag′**): Recrystallized from hexane/AcOEt=9:1, **3ag′** was given as a brown needle; R_f (hexane/AcOEt=1:3) 0.16; mp 146.5-147.5 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 3.77 (bs, 2H, N-H), 7.00 (d, J = 5.0 Hz, 1H, C-H), 7.41 (d, J = 8.6 Hz, 2H, C-H), 7.46 (d, J = 8.6 Hz, 2H, C-H), 8.07 (d, J = 5.0 Hz, 1H, C-H), 8.16 (s,1H, C-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 123.9, 129.3, 129.8, 132.3, 134.3, 135.3, 138.3, 139.6, 140.3; HRMS (ESI): MH^+, found 205.0509. $C_{11}H_{10}ClN_2$ requires 205.0527. 3-Amino-6-(4′-chlorophenyl)-pyridine (**3ag′′**): Recrystallized from hexane/AcOEt=9:1, **3ag′′** was given as a brown solid; mp 96.5-98.2 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 3.77 (bs, 2H, N-H), 7.05 (dd, J = 3.1 Hz, J = 8.3 Hz, 1H, CH), 7.39 (d, J = 8.6 Hz, 2H, C-H), 7.51 (d, J = 8.3 Hz, 1H, C-H), 7.83 (d, J = 8.6 Hz, 2H, C-H), 8.17 (d, J = 3.1 Hz, 1H, C-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 120.6, 122.2, 127.2, 128.7, 133.6, 137.2, 137.9, 141.5, 146.8; HRMS (ESI): MH^+, found 205.0501. $C_{11}H_{10}ClN_2$ requires 205.0527.

3-Amino-2-(4'-fluorophenyl)pyridine (3bg), 3-Amino-4-(4'-fluorophenyl)pyridine (3bg'), and 3-Amino-2-(4'-fluorophenyl)pyridine (3bg''). Compounds **3bg**, **3bg′**, and **3bg′′** were synthesized from **1b** (163 mg, 1.0 mmol) and **2g** (1.88 g, 20.0 mmol) according to the general procedure. Purification with column chromatography (inner diameter: 3 cm and length: 30 cm) gave **3bg** (71 mg, 0.38 mmol, 38%), and **3bg′** (21 mg, 0.11 mmol, 11%), and **3bg′′** (12 mg, 0.06 mmol, 6%). 3-Amino-2-(4′-fluorophenyl)pyridine (**3bg**): Recrystallized from hexane/AcOEt=9:1, **3bg** was given as a pale yellow needle; R_f (hexane/AcOEt=1:3) 0.52; mp 74.4-75.4 °C; FT-IR (neat) 3393, 3295, 3208, 3055, 1624, 1584, 1509, 1217 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.79 (bs, 2H, N-H), 7.05 (dd, J =

1.8 Hz, J = 7.8 Hz, 1H, CH), 7.08 (dd, J = 3.8 Hz, J = 7.8 Hz, 1H, C-H), 7.16 (dd, J_{HF} = 8.8 Hz, J = 8.8 Hz, 2H, C-H), 7.67 (dd, J_{HF} = 5.6 Hz, J = 8.8 Hz, 2H, C-H), 8.12 (dd, J = 1.8 Hz, J = 3.8 Hz, 1H, C-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 115.7 (d, J_{CF} = 21.0 Hz), 122.8, 123.1, 130.3 (d, J_{CF} = 7.7 Hz), 134.7, 139.9, 140.1, 144.1, 162.9 (d, J_{CF} = 246.0 Hz); HRMS (ESI): MH^+, found 189.0796. $C_{11}H_{10}FN_2$ requires 189.0823. 3-Amino-4-(4′-fluorophenyl)pyridine (**3bg′**): Recrystallized from hexane/AcOEt=9:1, **3bg′** was given as a pale yellow needle; R_f (hexane/AcOEt=1:3) 0.12; mp 108.5-109.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.81 (bs, 2H, N-H), 6.99 (d, J = 5.2 Hz, 1H, C-H), 7.17 (dd, J_{HF} = 8.8 Hz, J = 8.8 Hz, 2H, C-H), 7.44 (dd, J_{HF} = 5.2 Hz, J = 8.8 Hz, 2H, C-H), 8.05 (d, J = 5.2 Hz, 1H, C-H), 8.15 (s, 1H, C-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 116.1 (d, J_{CF} = 21.0 Hz), 124.1, 130.2 (d, J_{CF} = 8.6 Hz), 132.6, 132.8, 138.2, 139.7, 140.2, 162.5 (d, J_{CF} = 247.0 Hz); HRMS (ESI): MH^+, found 189.0808. $C_{11}H_{10}FN_2$ requires 189.0823. 3-Amino-6-(4′-fluorophenyl)pyridine (**3bg′′**): Recrystallized from hexane/AcOEt=9:1, **3bg′′** was given as a pale orange crystal; R_f (hexane/AcOEt=1:3) 0.40; mp 98.0-99.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.74 (bs, 2H, N-H), 7.04 (dd, J = 2.8 Hz, J = 8.4 Hz, 1H,C-H), 7.10 (dd, J_{HF} = 8.8 Hz, J = 8.8 Hz, 2H, CH), 7.48 (d, J = 8.4 Hz, 1H), 7.86 (dd, J_{HF} = 5.6 Hz, J = 8.8 Hz, 2H, CH), 8.16 (d, J = 2.8 Hz, 1H, C-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 115.4 (d, J_{CF} = 21.0 Hz), 120.4, 122.4, 127.6 (d, J_{CF} = 7.7 Hz), 135.7, 137.1, 141.3, 147.2, 162.7 (d, J_{CF} = 245.0 Hz); HRMS (ESI): MH^+, found 189.0801. $C_{11}H_{10}FN_2$ requires 189.0823.

3-Amino-2-(4'-bromophenyl)pyridine (3cg), 3-Amino-4-(4'-bromophenyl)pyridine (3cg'), and 3-Amino-6-(4'-bromophenyl)pyridine (3cg'). Compounds **3cg**, **3cg′**, and **3cg′′** were synthesized from **1c** (224 mg, 1.0 mmol) and **2g** (1.88 g, 20.0 mmol) according to the general procedure. Purification with column chromatography (inner diameter: 3 cm and length: 30 cm) gave **3cg** (117 mg, 0.47 mmol, 47%), and **3cg′** (27 mg, 0.11 mmol, 11%), and **3cg′′** (13 mg, 0.05 mmol, 5%). 3-Amino-2-(4′-bromophenyl)pyridine (**3cg**): Recrystallized from hexane/AcOEt=9:1, **3cg** was given as a pale yellow solid; R_f (hexane/AcOEt=1:3) 0.60; mp 98.0-99.0 °C (Lit.[15] 99-101 °C); FT-IR (neat) 3467, 3313, 3183, 1633, 1579, 1445, 1075 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.80 (bs, 2H, N-H), 7.05 (dd,

J = 2.0 Hz, *J* = 8.0 Hz, 1H, C-H), 7.08 (dd, *J* = 4.0 Hz, *J* = 8.0 Hz, 1H, C-H), 7.58 (d, *J* = 8.8 Hz, 2H, C-H), 7.61 (d, *J* = 8.8 Hz, 2H, C-H), 8.13 (dd, *J* = 2.0 Hz, *J* = 4.0 Hz, 1H, C-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 122.4, 122.9, 123.3, 130.2, 131.9, 137.5, 139.9, 140.2, 143.7; HRMS (ESI): MH^+, found 249.0016. $C_{11}H_{10}{}^{79}BrN_2$ requires 249.0022. 3-Amino-4-(4′-bromophenyl)pyridine (**3cg′**): Recrystallized from hexane/AcOEt=9:1, **3cg′** was given as a pale orange solid; R_f (hexane/AcOEt=1:3) 0.14; mp 159.0-160.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.80 (bs, 2H, N-H), 6.99 (d, *J* = 4.8 Hz, 1H, C-H), 7.35 (d, *J* = 8.6 Hz, 2H, C-H), 7.61 (d, *J* = 8.6 Hz, 2H, C-H), 8.06 (d, *J* = 4.8 Hz, 1H, C-H), 8.15 (s, 1H, C-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 122.4, 123.8, 130.1, 132.3, 135.7, 138.3, 139.5, 140.2; HRMS (ESI): MH^+, found 248.9995. $C_{11}H_{10}{}^{79}BrN_2$ requires 249.0022. 3-Amino-6-(4′-bromophenyl)pyridine (**3cg′′**): Recrystallized from hexane/AcOEt=9:1, **3cg′′** was given as a pale orange block crystal; R_f (hexane/AcOEt=1:3) 0.42; mp 133.0-134.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.78 (bs, 2H, N-H), 7.03 (dd, *J* = 2.8 Hz, *J* = 8.6 Hz, 1H, C-H), 7.50 (d, *J* = 8.6 Hz, 1H, C-H), 7.53 (d, *J* = 8.8 Hz, 2H, C-H), 7.77 (d, *J* = 8.8 Hz, 2H, C-H), 8.15 (d, *J* = 2.8 Hz, 1H, C-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 120.5, 121.8, 122.2, 127.5, 131.7, 137.2, 138.4, 141.6, 146.7; HRMS (ESI): MH^+, found 249.0001. $C_{11}H_{10}{}^{79}BrN_2$ requires 249.0022.

3-Amino-4-(4'-chlorophenyl)quinoline (3ah) and 3-Amino-2-(4'-chlorophenyl)quinoline (3ah'). Compounds **3ah** and **3ah′** were synthesized from **1a** (179 mg, 1.0 mmol) and 3-aminoquinoline **2h** (2.88 g, 20.0 mmol) according to the general procedure. Purification with column chromatography (inner diameter: 5 cm and length: 30 cm) gave **3ah** (189 mg, 0.74 mmol, 74%) and **3ah′** (22 mg, 0.09 mmol, 9%). 3-Amino-4-(4′-chlorophenyl)quinoline (**3ah**): Recrystallized from AcOEt, **3ah** was given as a pale yellow needle; R_f (hexane/AcOEt=1:1) 0.24; mp 217.5-218.5 °C; FT-IR (neat) 3448, 3289, 3178, 1625, 1581, 1479, 1380, 1347, 1085 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 5.23 (bs, 2H, N-H), 7.15 (dd, *J* = 1.6 Hz, *J* = 7.6 Hz, 1H, C-H), 7.31-7.36 (m, 2H, C-H), 7.35 (d, *J* = 8.2 Hz, 2H, C-H), 7.63 (d, *J* = 8.2 Hz, 2H, CH), 7.84 (dd, *J* = 1.6 Hz, *J* = 7.6 Hz, 1H, C-H), 8.59 (s, 1H, C-H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 120.9, 122.8, 123.9, 126.7, 127.8, 129.0, 129.3, 132.0,

132.6, 133.4, 138.8, 141.1, 143.7; HRMS (ESI): MH^+, found 255.0666. $C_{15}H_{12}ClN_2$ requires 255.0684. 3-Amino-2-(4′-chlorophenyl)quinoline (**3ah′**): Recrystallized from AcOEt, **3ah′** was given as a yellow solid; R_f (hexane/AcOEt=1:1) 0.74; ^{1}H NMR (400 MHz, DMSO-d_6) δ 5.32 (bs, 2H, N-H), 7.34-7.42 (m, 2H, C-H), 7.41 (s, 1H, C-H), 7.57 (d, J = 8.4 Hz, 2H, C-H), 7.65 (dd, J = 1.6 Hz, J = 7.6 Hz, 1H, C-H), 7.78 (d, J = 8.4 Hz, 2H, C-H), 7.79-7.81 (m, 1H, C-H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 114.8, 124.7, 125.2, 126.6, 128.5, 128.6, 129.1, 130.5, 133.1, 137.5, 140.1, 141.3, 148.4; HRMS (ESI): MH^+, found 255.0655. $C_{15}H_{12}ClN_2$ requires 255.0684.

2-Amino-3-(4'-chlorophenyl)pyrazine (3aj). Compound **3aj** was prepared from **1a** (179 mg, 1.0 mmol) and 2-aminopyrazine **2j** (1.90 g, 20.0 mmol) according to the general procedure. Purification with column chromatography (inner diameter: 2 cm and length: 30 cm) gave **3aj** (116 mg, 0.56 mmol, 56%). Recrystallized from hexane/AcOEt=9:1, **3aj** was given as a color less needle; R_f (hexane/AcOEt=1:2) 0.52; mp 125.5-126.5 °C; FT-IR (neat) 3303, 3153, 1643, 1525, 1433, 1088 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.76 (bs, 2H, N-H), 7.48 (d, J = 8.4 Hz, 2H, C-H), 7.68 (d, J = 8.4 Hz, 2H, C-H), 7.99 (d, J = 2.6 Hz, 1H, C-H), 8.03 (d, J = 2.6 Hz, 1H, C-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 129.3, 129.5, 134.7, 135.1, 135.6, 139.6, 141.3, 152.2; *m/z* (EI) 205 (97, M^+), 170 (38), 151 (23), 137 (30), 42 (100), 41 (97%); HRMS (ESI): MH^+, found 206.0455. $C_{10}H_9ClN_3$ requires 206.0480.

2-Amino-5-(4'-chlorophenyl)-4,6-dimethylpyrimidine (3ak). Compound **3ak** was given from **1a** (179 mg, 1.0 mmol) and 2-amino-4,6-dimethylpyrimidine **2k** (2.46 g, 20.0 mmol) according to the general procedure. By the purification with column chromatography (inner diameter: 2 cm and length: 30 cm), **3ak** (45 mg, 0.19 mmol, 19%) was given. Recrystallized from hexane/AcOEt=1:1, **3ak** was given as a white solid; R_f (hexane/AcOEt=1:4) 0.30; mp 204.7-205.5 °C; FT-IR (neat) 3307, 3186, 1626, 1545, 1466, 1090 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.09 (s, 6H, -CH_3), 4.99 (bs, 2H, N-H), 7.09 (d, J = 8.6 Hz, 2H, C-H), 7.41 (d, J = 8.6 Hz, 2H, C-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.8, 123.4, 129.0, 131.1, 133.5, 136.0, 161.3, 165.5; *m/z* (EI) 233 (100, M^+), 197 (17), 115 (46), 42 (69%);

HRMS (ESI): MH^+, found 234.0768. $C_{12}H_{13}ClN_3$ requires 234.0793.

A larger-scale synthesis of 3aa. Compound **3aa** was prepared from a mixture of 4-chlorophenylhydrazine hydrochloride **1a** (3.58 g, 20.0 mmol), 2,6-diaminopyridine **2a** (43.65 g, 400 mmol) and potassium carbonate (8.29 g, 60.0 mmol) in DMSO (200 mL), according to the general procedure. The reaction was completed after 24 h, monitored by thin layer chromatography (TLC). Then, quenched by the addition of water, the reaction mixture was extracted with ethyl acetate. The excess of **2a** was isolated in almost 90% yield by extracted with water. The organic layer was washed with water and brine solution, and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure to give a crude product. Purified by column chromatography (inner diameter: 5 cm and length: 30 cm) over silica gel (hexane/AcOEt=1:4), the pure product **3aa** (3.54g, 81%) was afforded.

Radical-trapping experiment with TEMPO (4a).

To a mixture of 4-chlorophenylhydrazine hydrochloride (**1a**, 895 mg, 5.0 mmol) and TEMPO (1.17 g, 7.5 mmol) in DMSO (50 mL), potassium carbonate (2.07 g, 15.0 mmol) was added. The solution was stirred at room temperature in air for 24 h. The resulting solution was quenched by the addition of water and extracted with ethyl acetate. The organic layer was washed with water and brine solution, and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure to give a crude product. Purification by column chromatography over silica gel using hexane, 4-chloro-1-(2,2,6,6-tetramethylpiperidinyloxy)-benzene (**4a**) (380 mg, 1.42 mmol, 28%) was afforded. Recrystallized from hexane, **4a** was given as a colorless plate crystal; R_f (hexane) 0.62; mp 89.5-90.5 °C; FT-IR (neat) 2977, 2925, 1585, 1480, 827 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.99 (s, 6H, $-CH_3$), 1.21 (s, 6H, $-CH_3$), 1.38-1.44 (m, 1H, CH_2), 1.53-1.68 (m, 5H, CH2), 7.11 (d, J = 9.4 Hz, 2H, C-H), 7.15 (d, J = 9.4 Hz, 2H, C-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.0, 20.4, 32.5, 39.7, 60.4, 115.2, 124.3, 128.5, 162.2; HRMS (DART): MH^+ found 268.1462. $C_{15}H_{23}ClNO$ requires 268.1463.

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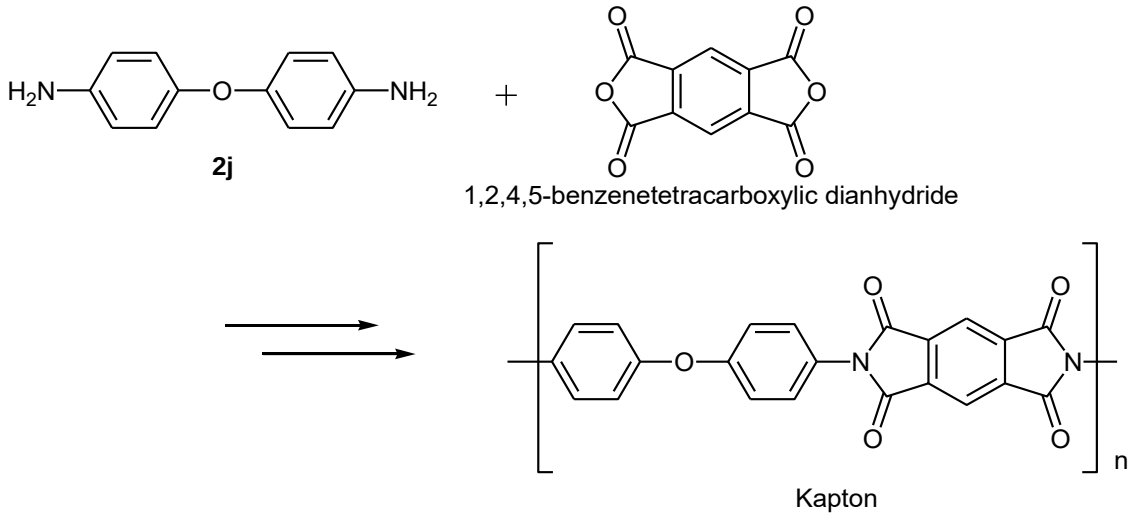
Chapter 4

Regioselective Radical Arylation of Aromatic Diamines with Arylhydrazines

4.1 INTRODUCTION

Polyimides are generally synthesized by the reaction of aromatic diamines with aromatic tetracarboxylic acid dianhydrides. They are interesting materials because of their remarkable strength and heat and chemical resistance.[1] Nowadays, polyimides play an important role as engineering plastic materials such as liquid crystal orientation membranes[2] and aerospace materials.[3] A typical example is Kapton®, synthesized from 4,4′-diaminodiphenyl ether (**2j**) and 1,2,4,5-benzenetetracarboxylic dianhydride (Scheme 1).[1e]

Scheme 1. Synthesis of Kapton®



Many aromatic diamines developed to date are symmetrical molecules, and because of their rigid main chain structure, the synthesized polyimides are difficult to dissolve in organic solvents. In order to overcome this shortcoming, unsymmetrical aromatic diamines have been used as the diamine

components of polyimides.[4] This modification increased the solubility of polyimides in organic solvents;[5] in particular, the introduction of an aryl group into the structure of **2j** leads to a promising monomer for the formation of aerospace materials (e.g., Kapton®).[6] However, the introduction of the aryl group required a transition-metal-catalyzed reaction and very complicated steps.[7] Thus, an easy and practical synthetic method for unsymmetrical aromatic diamines, for example, via direct C–H arylation of symmetric compounds, is highly desirable.

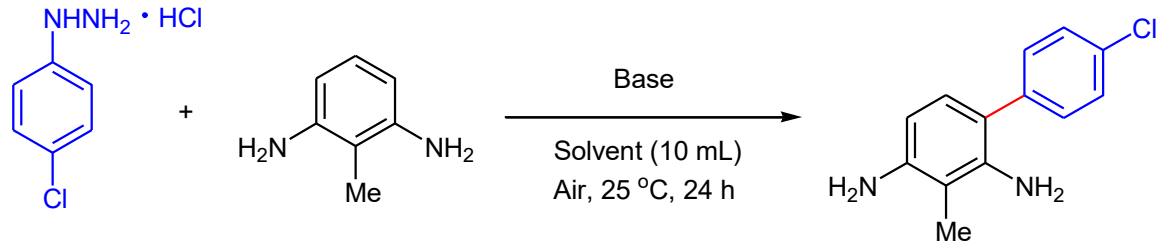
Aromatic coupling reactions using transition-metal catalysts, such as the Mizoroki–Heck reaction,[8] Suzuki–Miyaura coupling,[9] and Negishi coupling,[10] which are very important in organic chemistry, have been rapidly developed. To use these reactions in industrial scale, however, researchers often face the following problems: (1) Most of the transitionmetal catalysts, for example, Pd catalysts, are very expensive, and some of them are toxic; and (2) The removal of transition-metal residues from the target products is very costly. Hence, the development of aromatic substitutions in the absence of transition-metal catalysts is strongly desired for practical applications.

In a conceptually different approach, the aromatic substitution reaction is based on the direct C–H radical arylation of arenes via a homolytic aromatic substitution (HAS) mechanism.[11] A similar transformation was first reported by Gomberg and Bachmann in 1924.[12] Recently, much attention has been focused on the use of arylhydrazines as the radical sources in HAS reactions.[13] New elegant arylations of anilines with arylhydrazines or aryldiazonium salts have been reported as a valuable alternative to transition-metal-based arylations.[14] Very recently, we also reported the C–H arylation of aminoheterocycles with arylhydrazines.[15] In our study, the free amino functionality of the heterocycles led to high regioselectivities, and the reaction proceeded smoothly in good yields. Herein, we report a novel regioselective arylation of aromatic diamines, which provides numerous important monomers for functional plastics.

4.2 RESULTS AND DISCUSSION

Initially, we set out to optimize the reaction conditions using 2,6-diaminotoluene (**2a**) as a model substrate. The arylation of **2a** (20 equiv) with 4-chlorophenylhydrazine hydrochloride (**1a**) in the presence of potassium carbonate (3 equiv) at 25 °C for 24 hours under an air atmosphere was investigated (Table 1). The regioselective reaction proceeded to afford 2,6-diamino-3-(4′-chlorophenyl)toluene (**3aa**) in a good yield (Table 1, entry 1). Various solvents were screened, and DMSO provided the best result (entries 1–6). Moreover, the yield of **3aa** decreased when the amount of **2a** was reduced (entries 7–10). Interestingly, the best yield was obtained when using two equivalents of K_2CO_3 (entry 11). Under a nitrogen atmosphere, **3aa** was obtained in a low yield (entry 11, footnote c). When the amount of K_2CO_3 was reduced to one equivalent, the yield of **3aa** was not improved (entry 12) and, in the absence of a base, the reaction resulted in a low yield (entry 13). Next, several bases were examined. The product **3aa** was obtained in moderate to good yields when lithium carbonate, sodium carbonate, cesium carbonate, sodium phosphate, or triethylamine was used (entries 14–18). Varying the reaction time (48 h or 8 h) (entry 19) or increasing the reaction temperature (entry 20) did not improve the yield.

Table 1. Optimization of Reaction Conditions



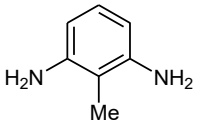
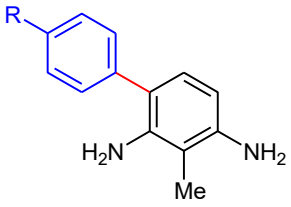
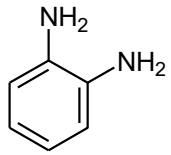
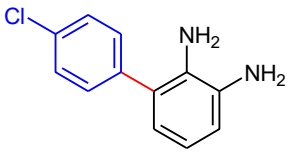
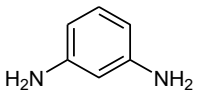
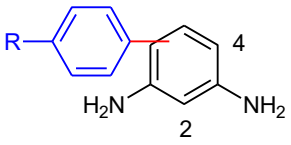
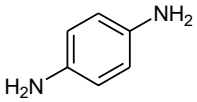
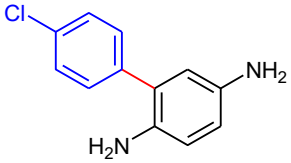
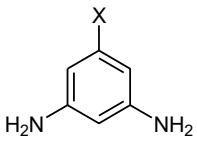
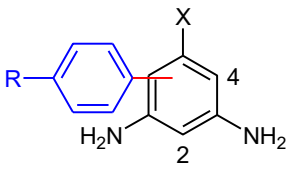
1a **2a** **3aa**

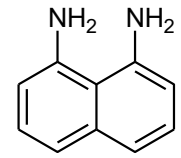
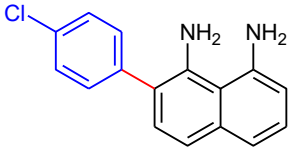
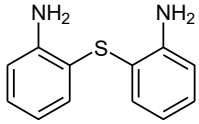
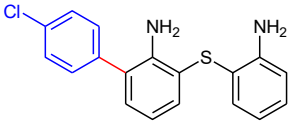
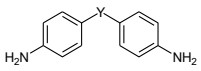
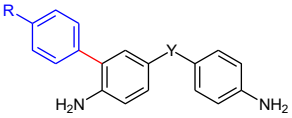
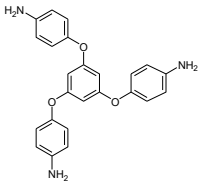
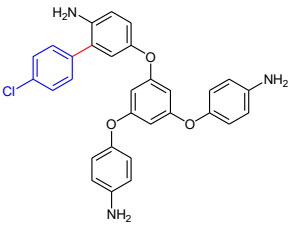
entry	solvent	base (equiv)	equiv of **2a**	yield (%)[a]
1	DMSO	K_2CO_3 (3)	20	62, 54[b]
2	DMF	K_2CO_3 (3)	20	48
3	DMA	K_2CO_3 (3)	20	35
4	NMP	K_2CO_3 (3)	20	29
5	MeCN	K_2CO_3 (3)	20	54
6	MeOH	K_2CO_3 (3)	20	38
7	DMSO	K_2CO_3 (3)	10	55
8	DMSO	K_2CO_3 (3)	5	46
9	DMSO	K_2CO_3 (3)	2	29
10	DMSO	K_2CO_3 (3)	1	19
11	DMSO	K_2CO_3 (2)	20	65, 60[b],12[c]
12	DMSO	K_2CO_3 (1)	20	56
13	DMSO	—	20	9
14	DMSO	Li_2CO_3 (2)	20	59
15	DMSO	Na_2CO_3 (2)	20	63
16	DMSO	Cs_2CO_3 (2)	20	58
17	DMSO	Na_3PO_4 (2)	20	59
18	DMSO	Et_3N (2)	20	32
19	DMSO	K_2CO_3 (2)	20	46[d], 61[e]
20	DMSO	K_2CO_3 (2)	20	51[f], 24[g]

[a]HPLC yield. [b]Isolated yield. [c]Under N_2 atmosphere. [d]Reaction time was 8 h.
[e]Reaction time was 48 h. [f]Reaction temperature was 50 °C. [g]Reaction temperature was 100 °C.

With the optimized conditions in hand, the substrate scope and limitations of the arylation reaction of aromatic diamines **2a**–**k** with various arylhydrazine hydrochlorides **1a**–**d** were investigated (Table 2). At first, we examined the arylation of 2,6-diaminotoluene (**2a**) with arylhydrazine hydrochlorides bearing an electron-withdrawing group, namely, Cl or Br, which afforded the corresponding products **3aa** and **3ba** in good yields (Table 2, entries 1 and 2). On the other hand, the reaction of **2a** with phenylhydrazine hydrochloride (**1c**) and 4-methoxyphenylhydrazine hydrochloride (**1d**) afforded **3ca** and **3da**, respectively, in low yields (entries 3 and 4). Moreover, the reaction of *o*-phenylenediamine (**2b**) with **1a** proceeded to provide **3ab** in a low yield (entry 5), whereas *m*-phenylenediamine (**2c**) afforded **3ac**–**cc** in good to excellent yields (entries 6–8). In particular, using arylhydrazine hydrochloride **1a**, **3ac** was obtained in 92% yield as a mixture of regioisomers (C_2:C_4 = 41:59) (entry 6). Products **3bc** and **3cc** were also obtained as mixtures of regioisomers (C_2:C_4 = 42:58) (entries 7 and 8). *p*-Phenylenediamine (**2d**) reacted with **1a** to give **3ad** in 33% yield (entry 9). When 5-trifluoromethyl-1,3-phenylenediamine (**2e**) was used as a radical acceptor, the arylation process proved to be efficient, and products **3ae** and **3be** were obtained in high yields as mixtures of regioisomers (C_2:C_4) (entries 10 and 11). Moreover, 1,3,5-triaminobenzene (**2f**) underwent the cross-coupling reaction with **1a** to give **3af** in a high yield (entry 12). Next, bicyclic diamines were subjected to the optimized reaction conditions (entries 13–17). 1,8-Diaminonaphthalene (**2g**) produced the corresponding product in a moderate yield (entry 13). The arylation of bis(aminophenyl) sulfides **2h**,**i** with **1a** proceeded to afford products **3ah** and **3ai** in moderate to good yields (entries 14 and 15). Fortunately, an important 4,4′-diaminodiphenyl ether (**2j**) reacted with **1a** and **1b** to provide the corresponding products **3aj** and **3bj** regioselectively in reasonable yields (entries 16 and 17). Finally, 1,3,5-tris(4′-aminophenoxy)benzene (**2k**) was allowed to react with **1a** to afford **3ak** in a good yield.

Table 2. Reaction of Arylhydrazines with Aromatic Diamines[a]

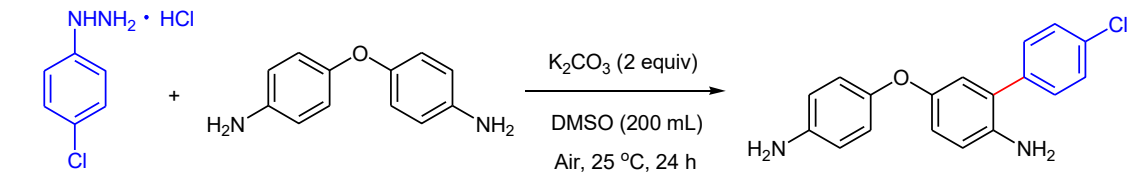
entry	2a-k	3aa-ak		yield (%)[b]
1			**3aa;** R^1 = Cl	60
2			**3ba;** R^1 = Br	57
3			**3ca;** R^1 = H	28
4			**3da;** R^1 = OMe	22
	2a			
5			**3ab**	15
	2b			
6			**3ac;** R = Cl	92[c] (C_2:C_4 = 41:59)[d]
7			**3bc;** R = Br	78[c] (C_2:C_4 = 42:58)[d]
8			**3cc;** R = H	50[c] (C_2:C_4 = 42:58)[d]
	2c			
9			**3ad**	33
	2d			
10			**3ae;** X = CF_3, R = Cl	85[c] (C_2:C_4 = 48:52)[d]
11			**3be;** X = CF_3, R = Br	88[c] (C_2:C_4 = 44:56)[d]
12			**3af;** X = NH_2, R = Cl	82
	2e, 2f			

13	 **2g**		**3ag**	45
14	 **2h**		**3ah**	43
15	 **2i, 2j**		**3ai;** Y = S, R = Cl	65
16			**3aj;** Y = O, R = Cl	63
17			**3bj;** Y = O, R = Br	66
18	 **2k**		**3ak**	70

[a]Reaction conditions: **1** (1.0 mmol), **2** (20 mmol), K_2CO_3 (2 equiv), DMSO (10 mL), 25 °C, 24 h, in air. [b]Isolated yields. [c]Total yield of all isomers. [d]Ratio of 2-isomer to 4-isomer.

Next, the feasibility of a large-scale synthesis (20-fold) of 4,4′-diamino-3-(4″-chlorophenyl)diphenyl ether (**3aj**) was investigated (Scheme 2). Starting from **1a** and **2j**, the desired **3aj** was obtained in 65% yield, and excess **2j** was recovered in 87% yield without formation of any by-products.

Scheme 2. Large-Scale Synthesis of 3aj



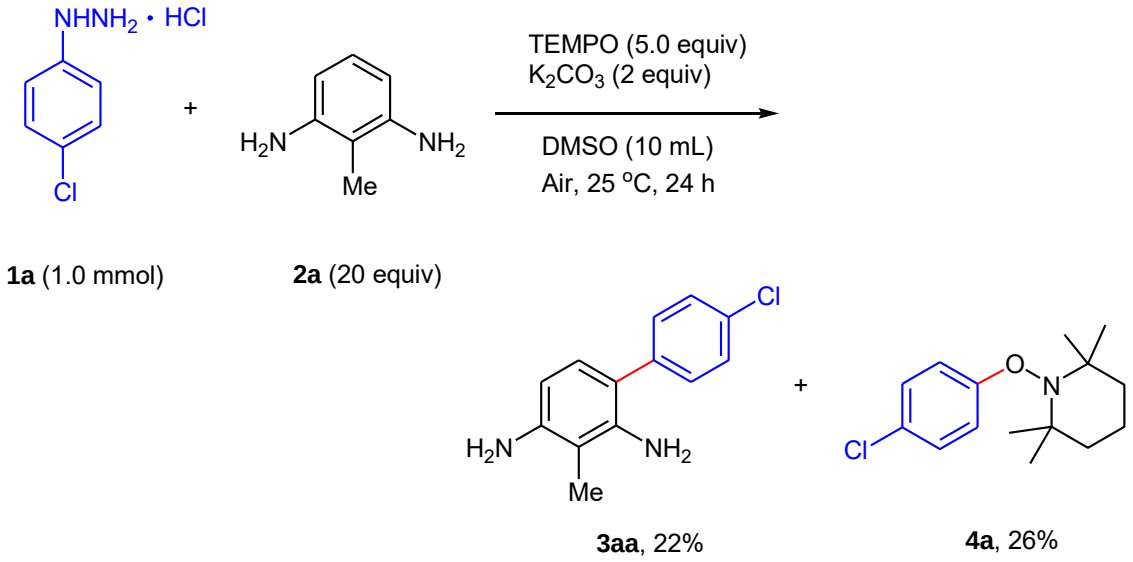
1a 3.58 g, 20 mmol

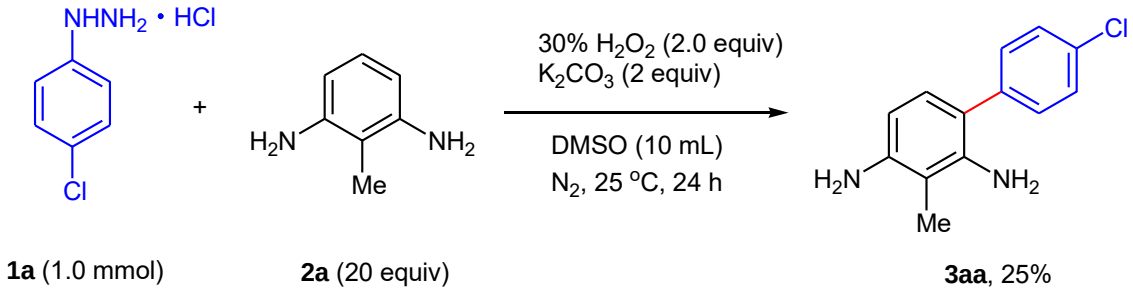
2j 80.10 g, 400 mmol

3aj, 65% 4.05 g, 13 mmol

In order to provide evidence for the radical mechanism, a control experiment of the cross-coupling reaction of **2a** with **1a** was conducted by employing 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO) as a radical scavenger. The coupling product **3aa** and 4-chloro-1-(2′,2′,6′,6′-tetramethylpiperidinyloxy)benzene (**4a**) from phenyl radical with TEMPO were observed in 22% and 26% yields, respectively (Scheme 3, top). A separate radical-trapping experiment of **1a** with TEMPO was already performed.[15] Furthermore, the arylation of **2a** with **1a** was carried out using H_2O_2 as an oxidant under nitrogen atmosphere. The product **3aa** was obtained in 25% yield (Scheme 3, bottom).

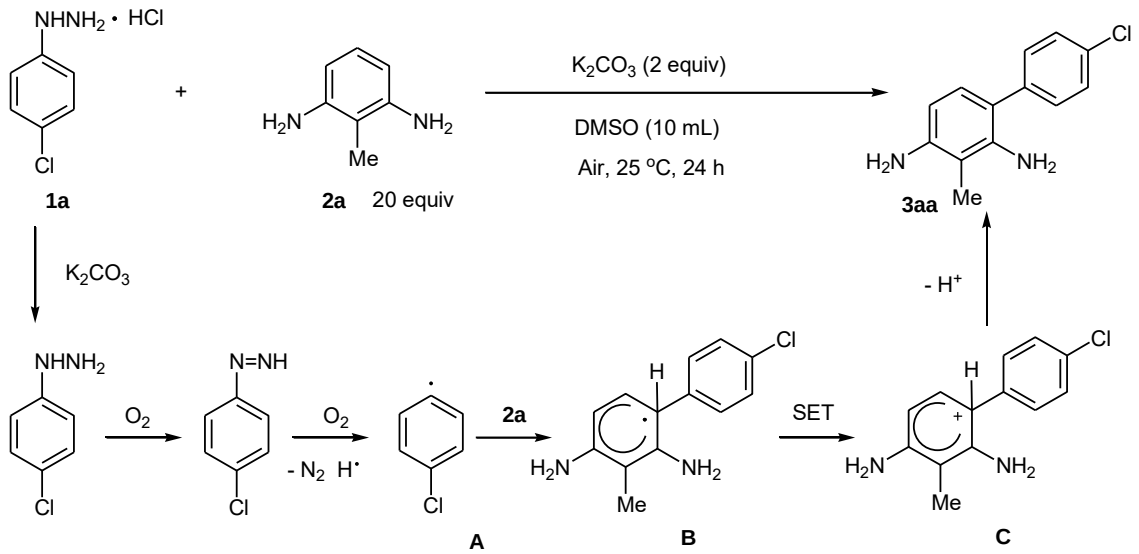
Scheme 3. Reaction with TEMPO or H_2O_2





Based on the experimental results and previous studies on HAS reactions,[11,13,14] a plausible mechanism for the arylation of **2a** with **1a** is proposed in Scheme 4. After liberation from **1a** by K_2CO_3, the free base hydrazine is oxidized by O_2 to form the corresponding diazene. Next, the diazene is converted into radical **A** by oxidation with O_2. The addition of radical **A** to **2a** provides the intermediate cyclohexadienyl radical **B**, which gets converted into cation **C** via single electron transfer (SET). Finally, elimination of a proton from cation **C** affords **3aa**. The formation of cation from cyclohexadienyl radical by SET is well described in the literature.[11g]

Scheme 4. A Plausible Reaction Mechanism for the Formation of 3aa



4.3 CONCLUSION

In conclusion, a metal-free arylation of aromatic diamines with arylhydrazine hydrochlorides using air as an oxidant was developed. This direct C–H arylation reaction without transition-metal catalysts provides not only a useful and practical method but also an alternative to Pd-catalyzed cross-coupling reactions. This new and simple method for the synthesis of unsymmetrical aromatic diamines as monomers of polyimides might find applications in the field of aerospace materials.

4.4 EXPERIMENTAL SECTION

General Information

Chemicals were purchased from commercial sources and used without further purification, except 1,3,5-triaminobenzene (**2f**) and 1,3,5-tris(4′-aminopheoxy)benzene (**2k**). 1,3,5-Triaminobenzene (**2f**) was prepared by the hydrogenation of 3,5-dinitroaniline. 1,3,5-Tris(4′-aminopheoxy)benzene (**2k**) was synthesized by the reaction of 1,3,5-trihydroxybenzene with 4-chloronitrobenzene, and the hydrogenation of nitro groups. Melting points were determined with Yamato MP-21 instrument and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Jeol JNM-ECX400 spectrometer. ^{1}H NMR spectra were recorded on 400 MHz spectrometers using DMSO-d_6 as solvent referenced to TMS (0 ppm) and DMSO (2.50 ppm). ^{13}C NMR spectra were recorded at 100 MHz in DMSO-d_6 using DMSO-d_6 (39.5 ppm) as standard. Chemical shifts were reported in parts per million (ppm). Coupling constants were reported in hertz (*J*, Hz). Exact mass spectra were recorded on a Shimadzu LCMS-IT-TOF instrument using electrospray ionization (ESI). FT-IR spectra were recorded on a Jasco FT/IR-4100 instrument and reported in wavenumbers (cm^{-1}). Analytical TLC was carried out on silica gel plates using short wave (254 nm) UV light. Silica gel (230–400 mesh) was used for column chromatography.

General Procedure for Arylation of Aromatic Diamines with Arylhydrazine Hydrochlorides

A mixture of arylhydrazine hydrochloride **1** (1.0 mmol), aromatic diamine **2** (20.0 mmol), and K_2CO_3 (276 mg, 2.0 mmol) in DMSO (10 mL) was stirred at 25 °C in air. The reaction was monitored by TLC and was completed in 24 h. Next, after quenching by the addition of H_2O, the mixture was extracted with EtOAc. The organic layer was washed with H_2O and brine, and dried (anhyd $MgSO_4$). The solvent was removed under reduced pressure to give the crude product. Purification by column chromatography on silica gel (hexane/EtOAc) afforded the pure product (Table 2).

2,6-Diamino-3-(4'-chlorophenyl)toluene (3aa).

Yield: 137 mg (60%); pale yellow prisms; recrystallized from hexane/EtOAc (1:1); mp 135.3–136.2 °C; R_f = 0.30 (hexane/EtOAc, 1:1); IR (KBr) 3464, 3463, 3377, 3357, 1614, 1475, 1442, 1389, 1088, 798 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ 7.42 (d, J = 8.5 Hz, 2 H, CH), 7.33 (d, J = 8.5 Hz, 2 H, CH), 6.58 (d, J = 8.4 Hz, 1 H, CH), 6.09 (d, J = 8.4 Hz, 1 H, CH), 4.73 (br s, 2 H, NH), 4.24 (br s, 2 H, NH), 1.89 (s, 3 H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ 146.6, 142.7, 139.9, 130.6, 130.2, 128.5, 127.4, 114.6, 105.1, 105.0, 10.8; HRMS (ESI): m/z [M + H^+] calcd for $C_{13}H_{14}ClN_2$: 233.0840; found: 233.0812.

2,6-Diamino-3-(4'-bromophenyl)toluene (3ba).

Yield: 129 mg (57%); pale orange prisms; recrystallized from hexane/EtOAc (3:1); mp 134.5–135.5 °C; R_f = 0.46 (hexane/EtOAc, 1:1); IR (neat) 3423, 3344, 3071, 3036, 1605, 1474, 1008, 796 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 7.55 (d, J = 8.7 Hz, 2 H, CH), 7.27 (d, J = 8.7 Hz, 2 H, CH), 6.58 (d, J = 8.4 Hz, 1 H, CH), 6.09 (d, J = 8.4 Hz, 1 H, CH), 4.74 (br s, 2 H, NH), 4.25 (br s, 2 H, NH), 1.88 (s, 3 H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ 146.6, 142.7, 140.3, 131.4, 131.0, 127.4, 118.7, 114.6, 105.1, 105.0, 10.8; HRMS (ESI): m/z [M + H^+] calcd for $C_{13}H_{14}BrN_2$: 277.0335; found: 277.0305.

2,6-Diamino-3-phenyltoluene (3ca).

Yield: 56 mg (28%); red brown oil; R_f = 0.44 (hexane/EtOAc, 1:1); IR (neat) 3451, 3363, 3224, 3026, 1613, 1481, 770, 705 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 7.39 (t, J = 7.3 Hz, 2 H, CH), 7.31 (d, J = 7.3 Hz, 2 H, CH), 7.25 (t, J = 7.3 Hz, 1 H, CH), 6.59 (d, J = 8.2 Hz, 1 H, CH), 6.10 (d, J = 8.2 Hz, 1 H, CH), 4.69 (br s, 2 H, NH), 4.19 (br s, 2 H, NH), 1.89 (s, 3 H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ 146.3, 142.6, 141.0, 128.8, 128.6, 127.4, 125.7, 116.1, 105.2, 105.0, 10.8; HRMS (ESI): m/z [M + H^+] calcd for $C_{13}H_{15}N_2$: 199.1230; found: 199.1221.

2,6-Diamino-3-(4'-methoxyphenyl)toluene (3da).

Yield: 50 mg (22%); pale brown solid; mp 94.0–95.0 °C; R_f = 0.38 (hexane/EtOAc, 1:1); IR (neat) 3427, 3358, 3237, 3012, 2933, 2835, 1485, 1230, 805 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 7.21 (d, J = 8.9 Hz, 2 H, CH), 6.96 (d, J = 8.9 Hz, 2 H, CH), 6.55 (d, J = 8.2 Hz, 1 H, CH), 6.07 (d, J = 8.2 Hz, 1 H, CH), 4.63 (br s, 2 H, NH), 4.13 (br s, 2 H, NH), 3.77 (s, 3 H, CH_3), 1.88 (s, 3 H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ 157.4, 146.0, 142.7, 133.1, 129.9, 127.3, 115.9, 114.0, 105.2, 104.8, 55.0, 10.9; HRMS (ESI): m/z [M + H^+] calcd for $C_{14}H_{17}N_2O$: 229.1335; found: 229.1316.

3-(4'-Chlorophenyl)-1,2-phenylenediamine (3ab).

Yield: 33 mg (15%); brown block crystals; recrystallized from hexane/EtOAc (9:1); mp 105.5–106.5 °C; R_f = 0.50 (hexane/EtOAc, 1:1); IR (neat) 3398, 3322, 3291, 1465, 1082, 737, 726 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 7.47 (d, J = 8.5 Hz, 2 H, CH), 7.39 (d, J = 8.5 Hz, 2 H, CH), 6.57 (dd, J = 1.6, 7.7 Hz, 1 H, CH), 6.49 (t, J = 7.7 Hz, 1 H, CH), 6.33 (dd, J = 1.6, 7.7 Hz, 1 H, CH), 4.61 (br s, 2 H, NH), 4.11 (br s, 2 H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 139.3, 135.5, 131.3, 131.2, 130.6, 128.5, 125.2, 118.7, 117.6, 114.1; HRMS (ESI): m/z [M + H^+] calcd for $C_{12}H_{12}ClN_2$: 219.0684; found: 219.0657.

2-(4'-Chlorophenyl)-1,3-phenylenediamine (3ac).

Yield: 82 mg (38%); brown solid; mp 77.5–78.6 °C; R_f = 0.70 (hexane/EtOAc, 1:1); IR (neat) 3460, 3372, 1601, 1585, 1092, 783 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 7.52 (d, J = 8.5 Hz, 2 H, CH), 7.23 (d, J = 8.5 Hz, 2 H, CH), 6.73 (t, J = 7.9 Hz, 1 H, CH), 6.02 (d, J = 7.9 Hz, 2 H, CH), 4.16 (br s, 4 H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 145.6, 135.1, 132.6, 131.7, 129.4, 128.4, 110.6, 103.9; HRMS (ESI): m/z [M + H^+] calcd for $C_{12}H_{12}ClN_2$: 219.0684; found: 219.0655.

4-(4'-Chlorophenyl)-1,3-phenylenediamine (3ac').

Yield: 117 mg (54%); pale orange needles; recrystallized by vapor diffusion using hexane/EtOAc; mp 107.2–108.2 °C; R_f = 0.24 (hexane/EtOAc, 1:1); IR (neat) 3423, 3326, 3189, 1612, 1481, 1450, 1089,

800 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 7.39 (d, J = 8.9 Hz, 2 H, CH), 7.35 (d, J = 8.9 Hz, 2 H, CH), 6.68 (d, J = 8.2 Hz, 1 H, CH), 5.97 (d, J = 1.8 Hz, 1 H, CH), 5.93 (dd, J = 1.8, 8.2 Hz, 1 H, CH), 4.89 (br s, 2 H, NH), 4.54 (br s, 2 H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 149.1, 145.5, 139.4, 130.6, 130.2, 129.9, 128.4, 113.6, 104.6, 100.4, HRMS (ESI): m/z [M + H^+] calcd for $C_{12}H_{12}ClN_2$: 219.0684; found: 219.0662.

2-(4'-Bromophenyl)-1,3-phenylenediamine (3bc).

Yield: 87 mg (33%); brown solid; mp 72.5–73.5 °C; R_f = 0.76 (hexane/EtOAc, 1:1); IR (neat) 3459, 3339, 3203, 3027, 1606, 1574, 1459, 1068, 999, 825, 781 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 7.65 (d, J = 8.4 Hz, 2 H, CH), 7.16 (d, J = 8.4 Hz, 2 H, CH), 6.73 (t, J = 7.8 Hz, 1 H, CH), 6.02 (d, J = 7.8 Hz, 2 H, CH), 4.17 (br s, 4 H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 145.6, 135.5, 132.9, 132.3, 128.4, 120.3, 110.6, 103.9; HRMS (ESI): m/z [M + H^+] calcd for $C_{12}H_{12}BrN_2$: 263.0178; found: 263.0174.

4-(4'-Bromophenyl)-1,3-phenylenediamine (3bc').

Yield: 119 mg (45%); pale pink needles; recrystallized by vapor diffusion using hexane/EtOAc; mp 122.0–123.0 °C; R_f = 0.33 (hexane/EtOAc, 1:1); IR (neat) 3393, 3280, 3186, 1622, 1579, 1478, 1448, 1001, 802 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 7.52 (d, J = 8.5 Hz, 2 H, CH), 7.30 (d, J = 8.5 Hz, 2 H, CH), 6.68 (d, J = 8.2 Hz, 1 H, CH), 5.97 (d, J = 2.0 Hz, 1 H, CH), 5.94 (dd, J = 2.0, 8.2 Hz, 1 H, CH), 4.89 (br s, 2 H, NH), 4.55 (br s, 2 H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 149.1, 145.4, 139.8, 131.3, 130.5, 118.3, 113.5, 104.6, 100.4; HRMS (ESI): m/z [M + H^+] calcd for $C_{12}H_{12}BrN_2$: 263.0178; found: 263.0150.

2-Phenyl-1,3-phenylenediamine (3cc).

Yield: 39 mg (21%); brown oil; R_f = 0.66 (hexane/EtOAc, 1:1); IR (neat) 3448, 3358, 3024, 1603, 1464, 1438, 703 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 7.49 (t, J = 7.8 Hz, 1 H, CH), 7.36 (tt, J =

1.4, 7.8 Hz, 1 H, CH), 7.22 (dd, J = 1.4, 7.8 Hz, 2 H, CH), 6.73 (t, J = 8.0 Hz, 1 H, CH), 6.03 (d, J = 8.0 Hz, 2 H, CH), 4.09 (br s, 4 H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 145.5, 136.1, 130.4, 129.4, 128.1, 127.1, 112.0, 103.9; HRMS (ESI): m/z [M + H$^+$] calcd for $C_{12}H_{13}N_2$: 185.1073; found: 185.1056.

4-Phenyl-1,3-phenylenediamine (3cc').

Yield: 54 mg (29%); brown oil; R_f = 0.32 (hexane/EtOAc, 1:1); IR (neat) 3421, 3397, 3317, 3200, 3033, 3009, 2925, 1604, 1479, 1433, 636 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.32–7.38 (m, 4 H, CH), 7.21 (t, J = 6.9 Hz, 1 H, CH), 6.69 (d, J = 8.0 Hz, 1 H, CH), 5.98 (d, J = 2.3 Hz, 1 H, CH), 5.94 (dd, J = 2.3, 8.0 Hz, 1 H, CH), 4.84 (br s, 2 H, NH), 4.48 (br s, 2 H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 148.7, 145.3, 140.5, 130.6, 128.5, 128.4, 125.5, 115.0, 104.5, 100.4; HRMS (ESI): m/z [M + H$^+$] calcd for $C_{12}H_{13}N_2$: 185.1073; found: 185.1050.

2-(4'-Chlorophenyl)-1,4-phenylenediamine (3ad).

Yield: 72 mg (33%); black solid; recrystallized from hexane/EtOAc (9:1); mp 72.0–73.0 °C; R_f = 0.26 (hexane/EtOAc, 1:2); IR (neat) 3397, 3291, 3195, 1615, 1500, 1483, 1087, 831, 746, 709 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.46 (d, J = 8.7 Hz, 2 H, CH), 7.41 (d, J = 8.7 Hz, 2 H, CH), 6.54 (d, J = 8.4 Hz, 1 H, CH), 6.41 (dd, J = 2.4, 8.4 Hz, 1 H, CH), 6.34 (d, J = 2.4 Hz, 1 H, CH), 4.34 (br s, 2 H, NH), 4.02 (br s, 2 H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 139.8, 139.2, 135.3, 131.0, 130.4, 128.4, 125.7, 117.1, 116.0, 115.5; HRMS (ESI): m/z [M + H$^+$] calcd for $C_{12}H_{12}ClN_2$: 219.0684; found: 219.0656.

2-(4'-Chlorophenyl)-5-trifluoromethyl-1,3-phenylenediamine (3ae).

Yield: 118 mg (41%); colorless prisms; recrystallized from hexane/EtOAc (2:1); mp 148.7–149.5 °C; R_f = 0.65 (hexane/EtOAc, 2:1); IR (neat) 3479, 3390, 1610, 1386, 1264, 1110, 832 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.55 (d, J = 8.2 Hz, 2 H, CH), 7.23 (d, J = 8.2 Hz, 2 H, CH), 6.30 (s, 2 H, CH), 4.63 (s, 4 H, NH); HRMS (ESI): m/z [M + H$^+$] calcd for $C_{13}H_{11}ClF_3N_2$: 287.0557; found:

287.0535.

4-(4'-Chlorophenyl)-5-trifluoromethyl-1,3-phenylenediamine (3ae').

Yield: 126 mg (44%); pale pink prisms; recrystallized from hexane/EtOAc (2:1); mp 119.8–120.8 °C; R_f = 0.30 (CH_2Cl_2); IR (neat) 3443, 3357, 3221, 1633, 1610, 1373, 1115, 827 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 7.45 (d, J = 8.5 Hz, 2 H, CH), 7.14 (d, J = 8.5 Hz, 2 H, CH), 6.26 (d, J = 2.0 Hz, 1 H, CH), 6.17 (d, J = 2.0 Hz, 1 H, CH), 5.27 (s, 2 H, NH), 4.41 (s, 2 H, NH); HRMS (ESI): m/z [M + H^+] calcd for $C_{13}H_{11}ClF_3N_2$: 287.0557; found: 287.0530.

2-(4'-Bromophenyl)-5-trifluoromethyl-1,3-phenylenediamine (3be).

Yield: 129 mg (39%); orange prisms; recrystallized from hexane/EtOAc (9:1); mp 161.3–162.3 °C; R_f = 0.90 (hexane/EtOAc, 1:1); IR (neat) 3479, 3390, 1611, 1579, 1384, 1266, 1111, 828 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 7.68 (d, J = 8.5 Hz, 2 H, CH), 7.17 (d,
J = 8.5 Hz, 2 H, CH), 6.30 (s, 2 H, CH), 4.63 (s, 4 H, NH); HRMS (ESI): m/z [M + H^+] calcd for $C_{13}H_{11}BrF_3N_2$: 331.0052; found: 331.0026.

4-(4'-Bromophenyl)-5-trifluoromethyl-1,3-phenylenediamine (3be').

Yield: 161 mg (49%); pale yellow needles; recrystallized from hexane/EtOAc (9:1); mp 83.0–84.0 °C; R_f = 0.44 (hexane/EtOAc, 1:1); IR (neat) 3442, 3344, 3221, 1627, 1611, 1372, 1119, 835, 823 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 7.58 (d, J = 8.5 Hz, 2 H, CH), 7.07 (d, J = 8.5 Hz, 2 H, CH), 6.26 (d, J = 2.0 Hz, 1 H, CH), 6.16 (d, J = 2.0 Hz, 1 H, CH), 5.27 (s, 2 H, NH), 4.42 (s, 2 H, NH); HRMS (ESI): m/z [M + H^+] calcd for $C_{13}H_{11}BrF_3N_2$: 331.0052; found: 331.0023.

1,3,5-Triamino-2-(4'-chlorophenyl)benzene (3af).

Yield: 188 mg (82%); white solid; recrystallized from EtOAc; mp 176.5–177.5 °C; R_f = 0.50 (EtOAc); IR (neat) 3459, 3423, 3336, 3192, 1605, 1577, 1490, 1458, 1088, 824 cm^{-1}; ^1H NMR (400 MHz,

DMSO-d_6) δ 7.45 (d, J = 8.5 Hz, 2 H, CH), 7.19 (d, J = 8.5 Hz, 2 H, CH), 5.37 (s, 2 H, CH), 4.51 (s, 2 H, NH), 3.92 (s, 4 H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 148.6, 145.8, 136.0, 133.1, 130.8, 129.0, 101.4, 91.2; HRMS (ESI): m/z [M + H$^+$] calcd for $C_{12}H_{13}ClN_3$: 234.0793; found: 234.0768.

1,8-Diamino-2-(4'-chlorophenyl)naphthalene (3ag).

Yield: 121 mg (45%); red brown solid; mp 92.0–93.0 °C; R_f = 0.38 (hexane/EtOAc, 3:1); IR (neat) 3459, 3410, 3366, 3317, 3049, 2923, 1589, 1569, 1556, 1086, 813 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.53 (d, J = 8.7 Hz, 2 H, CH), 7.48 (d, J = 8.7 Hz, 2 H, CH), 7.01–7.14 (m, 4 H , CH), 6.70 (dd, J = 1.4, 7.4 Hz, 1 H, CH), 5.42 (s, 2 H, NH), 5.40 (s, 2 H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 146.2, 142.3, 139.0, 136.2, 131.3, 128.9, 127.8, 126.4, 119.2, 117.9, 117.2, 115.9, 112.0; HRMS (ESI): m/z [M + H$^+$] calcd for $C_{16}H_{14}ClN_2$: 269.0840; found: 269.0812.

2,2'-Diamino-3-(4''-chlorophenyl)diphenyl Sulfide (3ah).

Yield: 139 mg (43%); brown oil; R_f = 0.36 (hexane/EtOAc, 3:1); IR (neat) 3410, 3391, 3281, 3174, 3060, 2923, 2852, 1614, 1476, 1439, 1088, 739 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.50 (d, J = 8.5 Hz, 2 H, CH), 7.42 (d, J = 8.5 Hz, 2 H, CH), 7.15 (dd, J = 1.4, 7.5 Hz 1 H, CH), 7.10 (dd, J = 1.4, 7.5 Hz, 1 H, CH), 7.05 (td, J = 1.4, 7.5 Hz, 1 H, CH), 6.96 (dd, J = 1.4, 7.3Hz, 1 H, CH), 6.75 (dd, J = 1.4, 8.2 Hz, 1 H, CH), 6.65 (t, J = 7.5 Hz, 1 H, CH), 6.55 (td, J = 1.4, 7.5 Hz, 1 H, CH), 5.33 (s, 2 H, NH), 4.87 (s, 2 H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 148.7, 144.2, 138.0, 133.6, 132.2, 131.9, 130.7, 129.9, 129.3, 128.8, 125.7, 117.9, 117.4, 116.9, 115.0, 114.9; HRMS (ESI): m/z [M + H$^+$] calcd for $C_{18}H_{16}ClN_2S$: 327.0717; found: 327.0692.

4,4'-Diamino-3-(4''-chlorophenyl)diphenyl Sulfide (3ai).

Yield: 213 mg (65%); brown oil; R_f = 0.50 (hexane/EtOAc, 1:1); IR (neat) 3459, 3362, 3209, 3026, 1614, 1595, 1492, 1474, 1088, 818 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.47 (dt, J = 2.3, 8.7 Hz, 2 H, CH), 7.38 (d, J = 8.7 Hz, 2 H, CH), 7.06 (d, J = 8.4 Hz, 2 H, CH), 7.01 (dd, J = 2.3, 8.2 Hz, 1 H,

CH), 6.90 (d, J = 2.3 Hz, 1 H, CH), 6.71 (d, J = 8.2 Hz, 1 H, CH), 6.51 (d, J = 8.4 Hz, 2 H, CH), 5.25 (s, 2 H, NH), 4.98 (s, 2 H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 148.5, 144.5, 137.7, 133.3, 132.4, 131.6, 131.4, 130.4, 128.7, 125.0, 123.1, 120.0, 116.1, 114.5; HRMS (ESI): m/z [M + H$^+$] calcd for $C_{18}H_{16}ClN_2S$: 327.0717; found: 327.0698.

4,4'-Diamino-3-(4''-chlorophenyl)diphenyl Ether (3aj).

Yield: 197 mg (63%); brown solid; mp 124.0–125.3 °C; R_f = 0.70 (EtOAc); IR (neat) 3441, 3425, 3347, 3205, 3051, 1496, 1480, 1219, 1089, 829 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.46 (d, J = 8.7 Hz, 2 H, CH), 7.42 (d, J = 8.7 Hz, 2 H, CH), 6.67–6.74 (m, 4 H, CH), 6.56 (d, J = 2.4 Hz, 1 H, CH), 6.52 (d, J = 8.7 Hz, 2 H, CH), 4.83 (s, 2 H, NH), 4.60 (s, 2 H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 149.4, 147.7, 144.4, 140.4, 138.1, 131.5, 130.4, 128.7, 125.1, 119.4, 119.1, 118.4, 116.6, 114.8; HRMS (ESI): m/z [M + H$^+$] calcd for $C_{18}H_{16}ClN_2O$: 311.0946; found: 311.0926.

4,4'-Diamino-3-(4''-bromophenyl)diphenyl Ether (3bj).

Yield: 234 mg (66%); brown solid; mp 131.0–132.0 °C; R_f = 0.80 (hexane/EtOAc, 1:4); IR (neat) 3439, 3422, 3344, 3203, 3079, 3050, 1496, 1478, 1218, 1006, 828 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.60 (d, J = 8.2 Hz, 2 H, CH), 7.36 (d, J = 8.2 Hz, 2 H, CH), 6.68–6.74 (m, 4 H, CH), 6.57 (d, J = 2.8 Hz, 1 H, CH), 6.53 (d, J = 8.8 Hz, 2 H, CH), 4.83 (s, 2 H, NH), 4.61 (s, 2 H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 149.4, 147.7, 144.4, 140.3, 138.4, 131.6, 130.7, 125.1, 120.1, 119.4, 119.0, 118.4, 116.6, 114.8. HRMS (ESI): m/z [M + H$^+$] calcd for $C_{18}H_{16}BrN_2O$: 355.0441; found: 355.0433.

5-[4'-Amino-3'-(4''-chlorophenyl)pheoxy]-1,3-bis(4'''-aminopheoxy)benzene (3ak).

Yield: 355 mg (70%); pale cream solid; mp 75.5–76.5 °C; R_f = 0.40 (hexane/EtOAc, 1:3); IR (neat) 3436, 3358, 3215, 3038, 1596, 1501, 1482, 1454, 1203, 1183, 1113, 1089, 1002, 823 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.51 (d, J = 8.7 Hz, 2 H, CH), 7.37 (d, J = 8.7 Hz, 2 H, CH), 6.80 (dd, J = 2.8, 8.7 Hz, 1 H, CH), 6.72–6.76 (m, 5 H, CH), 6.66 (d, J = 2.8 Hz, 1 H, CH), 6.55 (d, J = 8.7 Hz, 4 H,

CH), 5.97 (s, 3 H, CH), 5.00 (s, 4 H, NH), 4.77 (s, 2 H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.1, 160.5, 145.8, 145.4, 144.6, 142.1, 137.6, 131.7, 130.5, 128.8, 125.2, 121.6, 121.2, 120.7, 116.5, 114.7, 98.2, 97.9. HRMS (ESI): *m*/*z* [M + H$^+$] calcd for $C_{30}H_{25}ClN_3O_3$: 510.1579; found: 510.1553.

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Chapter 5

Transition-Metal-Free and Oxidant-Free Cross-Coupling of Arylhydrazines with Disulfides: Base-Promoted Synthesis of Unsymmetrical Aryl Sulfides

5.1 INTRODUCTION

Diaryl sulfides, which are used as pharmaceuticals, bioactive compounds, functional polymer materials,[1] and synthetic chemicals,[2] have received considerable attention. In particular, unsymmetrical aryl sulfides are of great importance as medicines for the treatment of various medical conditions such as cancer, Alzheimer's, Parkinson's, AIDS, neoplastic, HCV, diabetic, and parasitic diseases.[3] The importance of diaryl sulfides in biologically and pharmaceutically active compounds has sparked an increased interest toward improving methodologies to form these unsymmetrical compounds.

One of the most popular synthetic methods of unsymmetrical diaryl sulfides is the traditional Stadler−Ziegler reaction (Scheme 1),[4] where aryl amines are converted into the corresponding diazonium salts. These salts react with thiolates to yield unsymmetrical diaryl sulfides. The Stadler−Ziegler reaction has also been applied to the industrial manufacturing of diaryl sulfides.[5] Recently, a cross-coupling reaction of diazonium salts with thiols using a SET photoredox catalyst was reported.[6] In this reaction, diazonium salts and diazosulfides are formed as key intermediates, which are explosive and therefore their use is better avoided. [7]

Among the numerous synthetic methods for the aryl C−S bond formation, a powerful approach is the transition-metal-catalyzed C−S coupling reaction. Hitherto, many transition-metal-catalyzed systems including palladium,[8] nickel,[9] zinc,[10] copper,[11] iron,[12] rhodium,[13] silver,[14] and iridium[15] have been reported (Scheme 1). Although these reports were great breakthroughs for the synthesis of

unsymmetrical sulfides, these transition-metal-catalyzed reactions usually need harsh conditions such as high temperatures[8–14] and microwave irradiation.[11f] Furthermore, high loadings of catalysts bearing specially designed ligands and/or strong bases are often required, because the strong coordination of thiolates to transition metal catalysts causes deactivation of the catalysts.[1b,16,17] Also, the tolerance of functional groups is limited due to the high temperatures and strong bases required in these reactions.

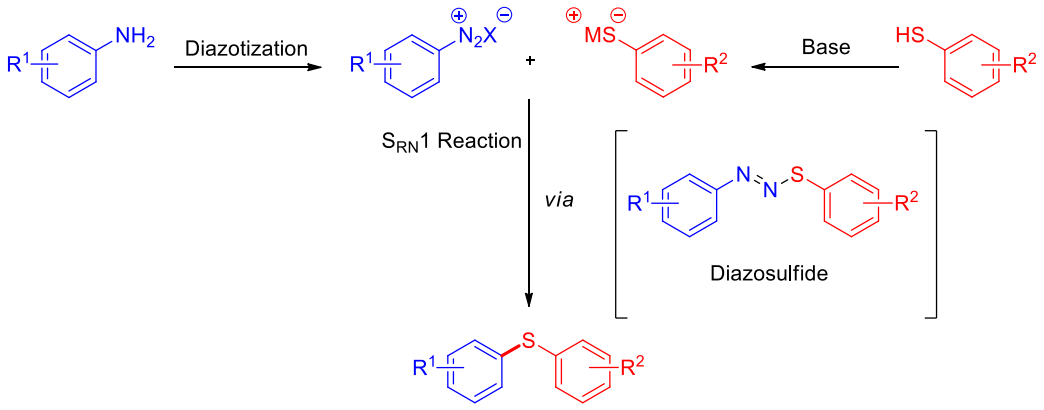
Moreover, to apply these reactions to industrial scale production, researchers often face the following problems: 1) Most of the transition metal catalysts, e.g., palladium catalysts, are very expensive, and some of them are toxic; and 2) The removal of transition metal residues from the target products is very costly. Therefore, the development of diaryl sulfide synthetic methods in the absence of transition metal catalysts is strongly desired from a practical perspective.

The formation of unsymmetrical aryl sulfides from diaryl disulfides, which are easy to handle, and aryl radicals generated from diazonium salts under reducing conditions is well-known.[14,18] Moreover, the generation of aryl radicals from arylhydrazines under oxidative conditions has been reported (homolytic aromatic substitution (HAS) reaction),[19] although, excess amounts of radical acceptors are generally required. Furthermore, diaryl disulfides are easily oxidized under air in the presence of a base and converted into benzenesulfonic acids.[20]

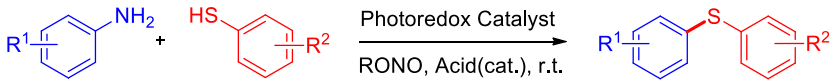
Herein, we report a transition-metal-free and oxidant-free cross-coupling reaction of arylhydrazines with diaryl disulfides overcoming the above difficulties. To the best of our knowledge, this is the first example of the synthesis of unsymmetrical diaryl sulfide using arylhydrazines and one equivalent of diaryl disulfides under oxidant-free conditions.

Scheme 1. Synthesis of Unsymmetrical Diaryl Sulfides

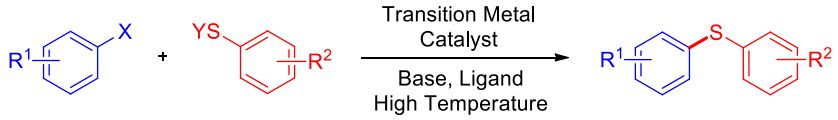
Traditional Stadler-Ziegler Reaction:



Efficient Method for C-S Bond Formation by Photoredox Catalyst:

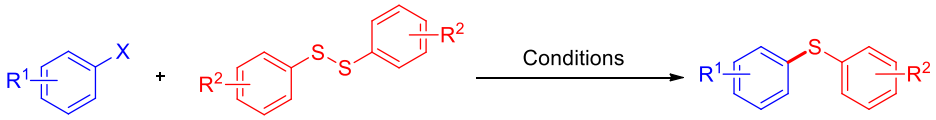


Transition-Metal-Catalyzed Cross-Coupling Reactions:



X = Cl, Br, I,$B(OH)_2$; Y = H, SAr

Efficient Method for C-S Bond Formation Using Diaryldisulfides:



X = I, COOH; Conditions: Transition Metal Catalyst

X = $\overset{\oplus}{N_2}\overset{\ominus}{X}$; Conditions: Photoredox Catalyst or Reductant

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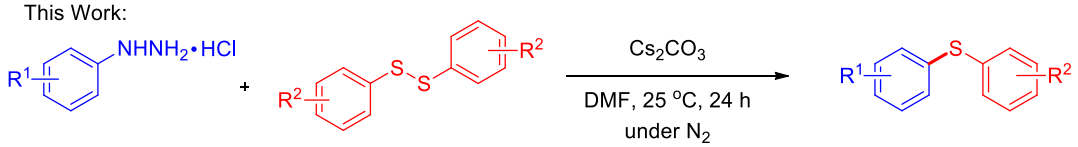
This Work:



TM Free
Oxidant Free

5.2 RESULTS AND DISCUSSION

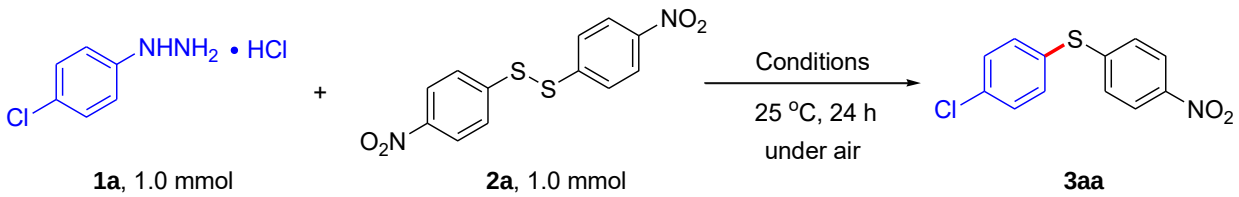
In the course of our previous studies on the cross-coupling of arylhydrazines with aminoheterocycles[21] and aromatic diamines,[22] we examined the cross-coupling reaction of 4-chlorophenylhydrazine hydrochloride (**1a**) with 4,4′-dinitrodiphenyl disulfide (**2a**) (Table 1). The coupling reaction of **1a** with one equivalent of **2a** in the presence of potassium carbonate (2.0 equiv) in dimethyl sulfoxide (DMSO) occurred to afford 4-chlorophenyl 4′-nitrophenyl sulfide (**3aa**) in 75% yield (Table 1, entry 1).

A shorter reaction time slightly lowered the yield of **3aa** (Table 1, entry 1, footnote b). When the amounts of **2a** were decreased to 0.5 mmol and 0.75 mmol, the yields of **3aa** were lowered (Table 1, entry 1, footnotes c and d). However, increasing the amounts of **2a** to 1.5 mmol and 2.0 mmol, the similar yields of **3aa** were obtained (Table 1, entry 1, footnotes e and f). Another solvents (DMF, DMA, MeCN, and MeOH) gave **3aa** in reduced yields (Table 1, entries 2-5).

Using rubidium carbonate or cesium carbonate as base, **3aa** was formed in similar yields (Table 1, entries 6 and 7). However, the use of lithium carbonate or sodium carbonate resulted in poor yields of **3aa** (Table 1, entries 8 and 9). Higher reaction temperatures (35 °C and 80 °C for 1 hour) in the presence of cesium carbonate as base gave slightly lowered the yields of **3aa** (Table 1, entry 7, footnotes g and h). When the reaction time was longer than 1 hour at 80 °C, a complex mixture such as tar was formed.

As to organic bases, DBU was effective in this cross-coupling reaction and gave **3aa** in 54% yield (Table 1, entry 10). The use of DABCO or triethylamine was ineffective (Table 1, entries 11 and 12). In the absence of a base, **3aa** was not obtained (Table 1, entry 13). The yields of **3aa** decreased when one equivalent of K_2CO_3 or Rb_2CO_3 in 5 mL of DMSO were used (Table 1, entries 14 and 15). Instead, in the presence of one equivalent of Cs_2CO_3, desired **3aa** was synthesized in good yield (Table 1, entry 17).

Table 1. Optimization of Synthesis of 3aa



1a, 1.0 mmol **2a**, 1.0 mmol **3aa**

entry	solvent (mL)	base (equiv)	yield (%)[a]
1	DMSO (10)	K_2CO_3 (2.0)	75, 42[b], 44[c], 63[d], 77[e], 74[f]
2	DMF (10)	K_2CO_3 (2.0)	38
3	DMA (10)	K_2CO_3 (2.0)	39
4	MeCN (10)	K_2CO_3 (2.0)	9
5	MeOH (10)	K_2CO_3 (2.0)	17
6	DMSO (10)	Rb_2CO_3 (2.0)	74
7	DMSO (10)	Cs_2CO_3 (2.0)	73, 67[g], 61[h]
8	DMSO (10)	Li_2CO_3 (2.0)	11
9	DMSO (10)	Na_2CO_3 (2.0)	19
10	DMSO (10)	DBU (2.0)	54
11	DMSO (10)	DABCO (2.0)	16
12	DMSO (10)	Et_3N (2.0)	7
13	DMSO (10)	none	trace
14	DMSO (5)	K_2CO_3 (1.0)	69
15	DMSO (5)	Rb_2CO_3 (1.0)	42
16	DMSO (10)	Cs_2CO_3 (1.0)	72
17	DMSO (5)	Cs_2CO_3 (1.0)	79
18	DMSO (3)	Cs_2CO_3 (1.0)	82, 82[i]
19	DMSO (3)	Cs_2CO_3 (0.5)	5
20	DMSO (2)	Cs_2CO_3 (1.0)	81

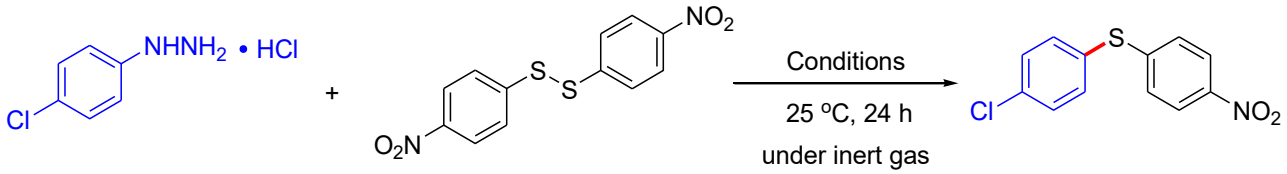
Reaction conditions: **1a** (1.0 mmol) and **2a** (1.0 mmol) at 25 °C for 24 h under air.
[a]HPLC yields, calibration curve was shown in Figure S23. [b]Reaction time was 18 h. [c]**2a** (0.5 mmol). [d]**2a** (0.75 mmol). [e]**2a** (1.5 mmol),[f]**2a** (2.0 mmol). [g]Reaction temperature was 35 °C. [h]Reaction temperature was 80 °C for 1 hour. [i]Isolated yield.

The best result was obtained under high concentrated conditions (DMSO, 3 mL), and product **3aa** was generated in 82% yield (Table 1, entry 18). Using 0.5 equivalent of base resulted in a remarkable decrease of yield of **3aa** (Table 1, entry 19). These results show that the base plays an important role in this cross-coupling reaction. Reducing the volume of solvent to 2 mL did not improve further the yield of **3aa** (Table1, entry 20).

Surprisingly, **3aa** was formed in 41% yield under an atmosphere of nitrogen (Table 2, entry 1). Under these conditions the yield was further increased when the amount of DMSO was increased to 5mL, 7.5 mL, and 10 mL (Table 2, entries 2, 3, and 4), and improved to 78% when the reaction time was increased (45 h) (Table 2, entry 4, footnote b). A similar yield of **3aa** was observed under an argon atmosphere (Table 2, entry 4, footnote c) and the reaction also proceeded smoothly in DMF or DMA (*N*,*N*-dimethylacetamide) under nitrogen or argon atmospheres (Table 2, entries 5 and 6). These results strongly suggest that oxidants are not necessary for this cross-coupling reaction. However, **3aa** was hardly obtained when other solvents such as MeCN or MeOH were employed under an argon atmosphere (Table 2, entries 7 and 8). These low yields might be attributable to the very low solubility of **2a** in MeCN or MeOH.

With the optimized conditions in hand, the scope and limitations of the cross-coupling reaction of 4-chlorophenylhydrazine hydrochloride (**1a**) with a series of disulfides (**2a**−**2k**) were investigated (Table 3). The reaction of **1a** with 3,3′-dinitrodiphenyl disulfide (**2b**) provided compound **3ab** in 75% yield. In the case of 2,2′-dinitrodiphenyl disulfide (**2c**), the yield of **3ac** was lower probably due to steric effects. The reaction of **1a** with a diaryl disulfide bearing an electron-donating group such as methyl group provided **3ad** in 30% yield under air. A similar yield of **3ad** was also observed under an argon atmosphere.

Table 2. Synthesis of 3aa under Inert Gas



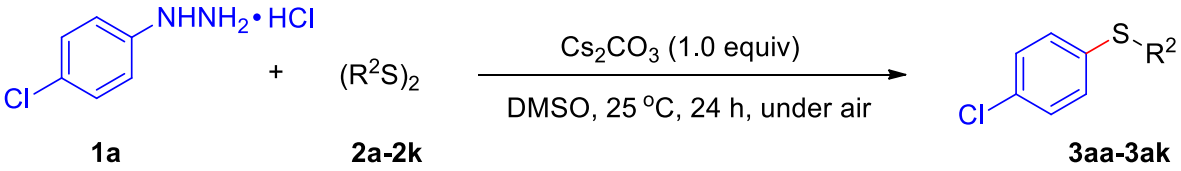
1a, 1.0 mmol **2a**, 1.0 mmol **3aa**

entry	solvent (mL)	base (equiv)	yield (%)[a]
1	DMSO (3)	Cs_2CO_3 (1.0)	41
2	DMSO (5)	Cs_2CO_3 (1.0)	54
3	DMSO (7.5)	Cs_2CO_3 (1.0)	59
4	DMSO (10)	Cs_2CO_3 (1.0)	64, 78[b], 70[c]
5	DMF (10)	Cs_2CO_3 (1.0)	70[b]
6	DMA (10)	Cs_2CO_3 (1.0)	65[c]
7	MeCN (10)	Cs_2CO_3 (1.0)	2[c]
8	MeOH (10)	Cs_2CO_3 (1.0)	Trace[c]

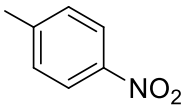
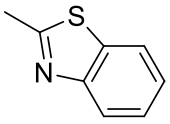
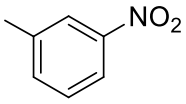
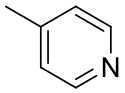
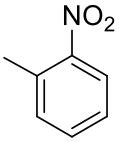
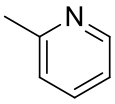
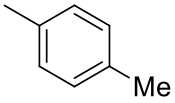
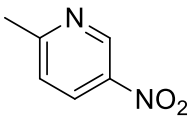
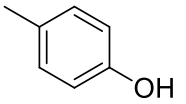
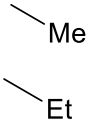
Reaction conditions: **1a** (1.0 mmol) and **2a** (1.0 mmol) at 25 °C for 24 h under N_2.
[a]HPLC yields. [b]Reaction time was 45 h. [c]Under argon atmosphere.

The coupling reaction of **1a** with 4,4′-dihydroxydiphenyl disulfide (**2e**) having acidic protons using 1.0 equiv or 3.0 equiv of cesium carbonate was performed to afford the corresponding **3ae** in moderate yields. However, the coupling reaction of **1a** with 4,4′-diaminodiphenyl disulfide gave a complicated mixture. Additionally, the cross-coupling with heteroaryl disulfides was successful. Thus, 2,2′-dibenzothiazolyl disulfide (**2f**) gave **3af** in high yield (76%) and with 4,4′-dipyridyl disulfide (**2g**) **3ag** was obtained in good yield. Instead, the use of 2,2′-dipyridyl disulfide (**2h**) resulted in a low yield (20%) of **3ah**. Interestingly, in the case of the 2,2′-dipyridyl disulfide derivative bearing a nitro group (**2i**), the coupling reaction provided **3ai** in excellent yield (93%). In addition, the coupling reactions with alkyl disulfides gave the corresponding unsymmetrical sulfides in good to high yields (**3aj** and **3ak**).

Table 3. Cross-Coupling Reaction of 1a with Disulfides 2



1a **2a-2k** (R^2 = aryl, heteroaryl, or alkyl) **3aa-3ak**

R^2	yield (%)[a]	R^2	yield (%)[a]
	**3aa**, 82%, 70%[b]		**3af**, 76%
	**3ab**, 75%		**3ag**, 65%
	**3ac**, 40%		**3ah**, 20%
	**3ad**, 30%, 37%[b]		**3ai**, 93%
	**3ae**, 58%, 53%[c]		**3aj**, 81% **3ak**, 62%

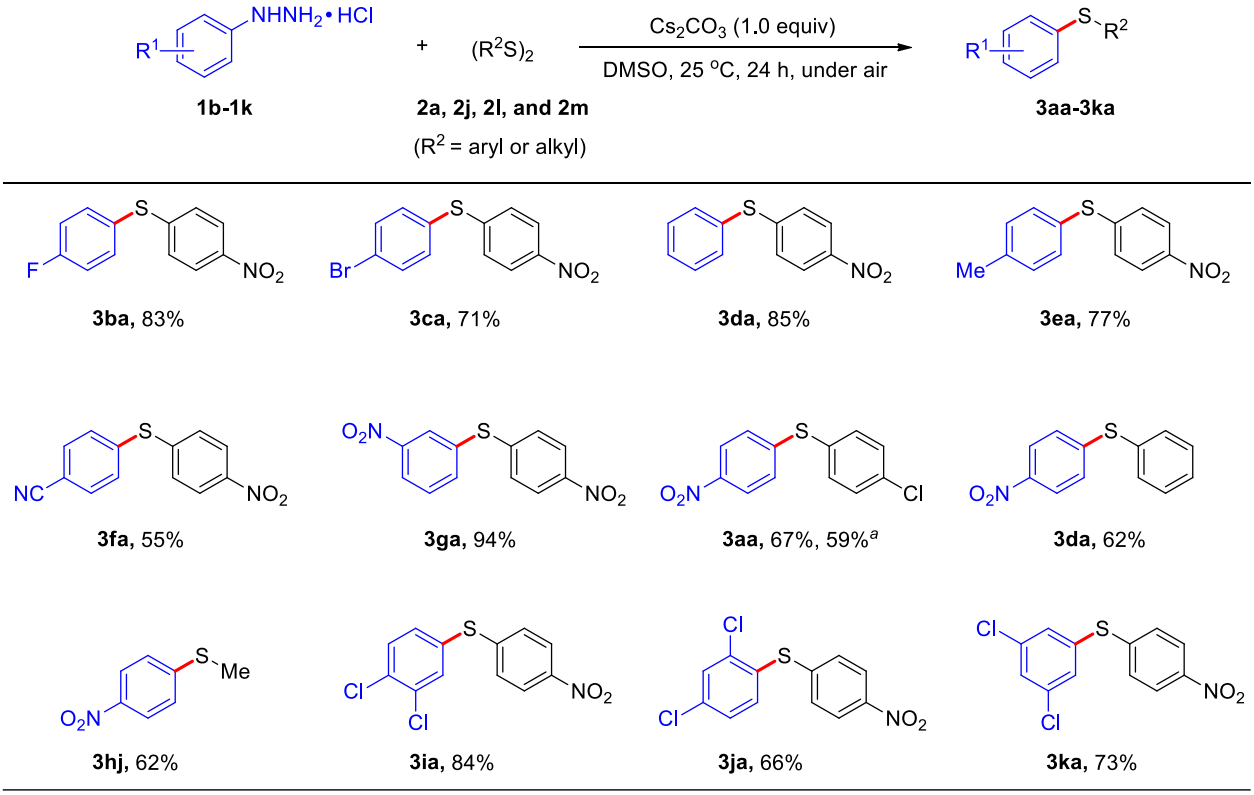
Reaction conditions: **1a** (1.0 mmol) and **2** (1.0 mmol) at 25 °C for 24 h under air.
[a]Isolated yields. [b]Under argon atmosphere. [c]Cesium carbonate (3.0 mmol) was used.

Next, the cross-coupling between a variety of arylhydrazine hydrochlorides (**1b**–**1k**) and several disulfides (**2a**, **2j**, **2l**, and **2m**) was examined, and the results are summarized in Table 4. The cross-coupling reaction of arylhydrazine hydrochlorides bearing either electron-withdrawing groups (i.e., fluoro, bromo, cyano, and nitro groups) or electron-donating groups (i.e., methyl group) with 4,4′-dinitrodiphenyl disulfide (**2a**) successfully afforded **3ba**–**3ga** in good to excellent yields (55–94%). However, the reaction of 4-methoxyphenylhydrazine hydrochloride having an electron-donating group

with **2a** gave a complex mixture. Sulfide **3aa** was synthesized from 4-nitrophenylhydrazine hydrochloride (**1h**) and 4,4′-dichlorodiphenyl disulfide (**2l**) (67% under air and 59% under argon). Compound **1h** was allowed to react with diphenyl disulfide (**2m**) to afford **3da** in good yield (62%).

Using 4-nitrophenylhydrazine hydrochloride (**1h**) and dimethyl disulfide (**2j**), **3hj** was obtained in good yield (62%). Finally, the cross-coupling reaction could be applied to more hindered dichlorophenylhydrazine hydrochlorides (**1i**−**1k**) with 4,4′-dinitrodiphenyl disulfide (**2a**), giving the corresponding products (**3ia**−**3ka**) in good yields.

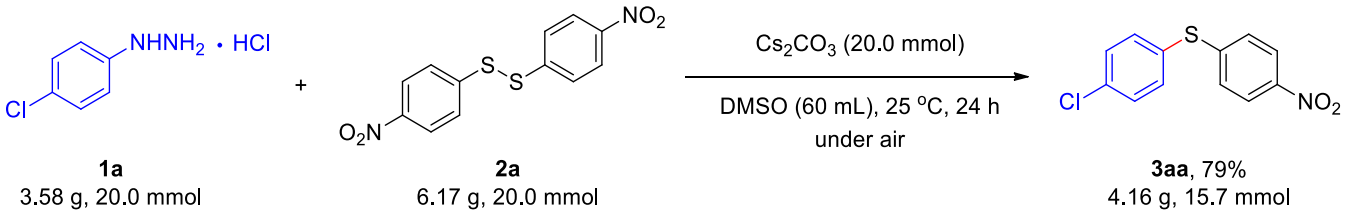
Table 4. Reaction of Arylhydrazines 1b−1k with Disulfides 2a, 2j, 2l, and 2m



Reaction conditions: **1a** (1.0 mmol) and **2** (1.0 mmol) at 25 °C for 24 h under air.
Isolated yields are shown. [a]Under argon atmosphere.

Even in a large-scale reaction (20 mmol), the cross-coupling of **1a** with **2a** proceeded smoothly to afford **3aa** in 79% yield (Scheme 2).

Scheme 2. Large-Scale Reaction



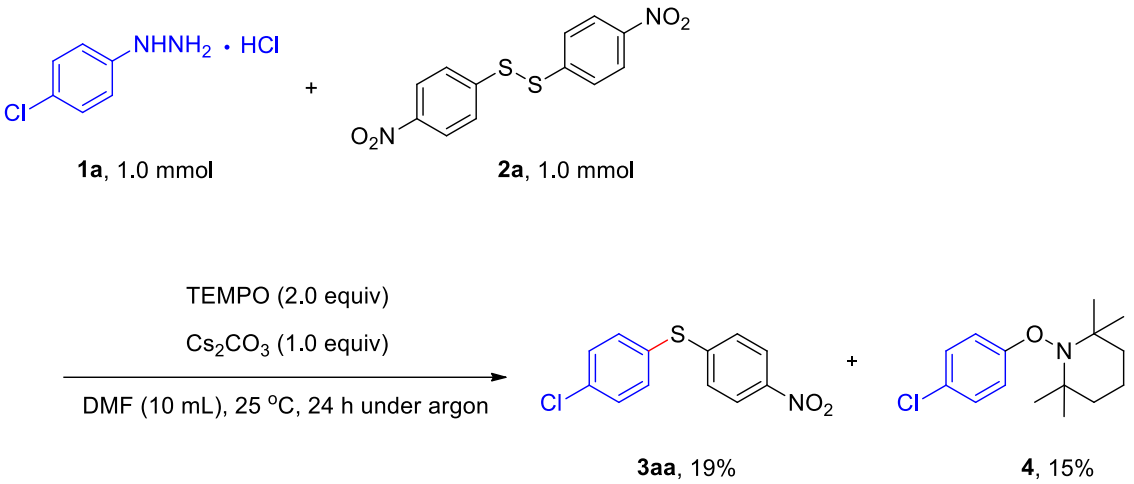
1a
3.58 g, 20.0 mmol

2a
6.17 g, 20.0 mmol

3aa, 79%
4.16 g, 15.7 mmol

To clarify the mechanistic pathway for the cross-coupling reaction of arylhydrazines with disulfides, a radical trapping experiment was performed. Thus, using 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO) under argon in DMF, the 4-chlorophenyl radical was trapped to afford **4** in 15% yield. Also, **3aa** was formed in a reduced yield (Scheme 3).

Scheme 3. Radical Trapping Experiment with TEMPO



1a, 1.0 mmol

2a, 1.0 mmol

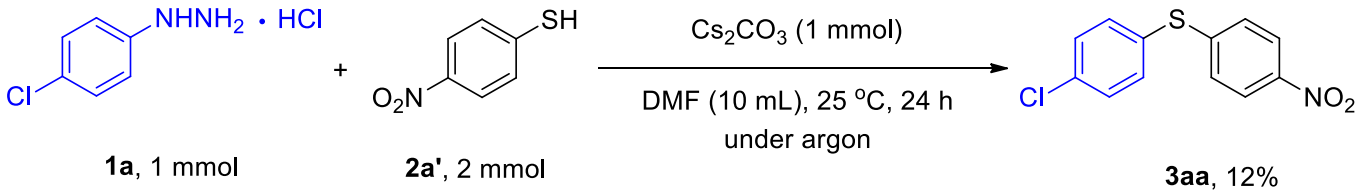
3aa, 19%

4, 15%

Next, the reaction of 4-chlorophenylhydrazine hydrochloride (**1a**) with two equivalents of 4-nitrobenzenethiol (**2a′**) instead of 4,4′-nitrodiphenyl disulfide (**2a**) was investigated (Scheme 4). The

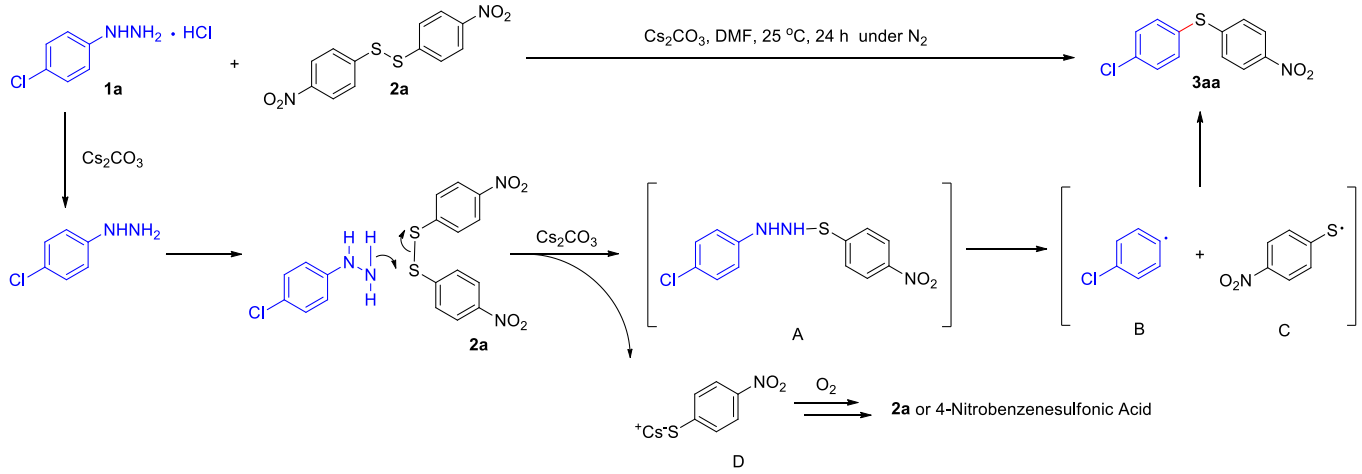
desired product **3aa** was formed in a low yield (12%) under argon atmosphere. This result suggests that disulfide **2a** may formally act as an oxidant.

Scheme 4. Reaction of 4-Nitrobenzenethiol with 1a



Keeping in mind the fact that the present unsymmetrical sulfide synthesis proceeds even under inert gas atmospheres (nitrogen or argon), a possible reaction path is proposed in Scheme 5. The hydrazine free base, obtained from **1a** by treating with Cs_2CO_3, reacts with 4,4′-dinitrodiphenyl disulfide (**2a**) to afford intermediate **A**. This intermediate converts into 4-chlorophenyl radical **B** and arylthio radical **C** via elimination of nitrogen or diazene (HN=NH) as previously suggested in the literature.[23,24] Finally, the radical cross-coupling of radical **B** with **C** affords the desired product **3aa**. The cesium salt of 4-nitrobenzene thiolate **D** is formed concomitantly, which was detected by LCMS. This salt **D** easily converts under air into **2a** or 4-nitrobenzenesulfonic acid, observed by LCMS.

Scheme 5. Plausible Mechanism of the Reaction of 1a with 2a



5.3 CONCLUSION

In summary, the generation of aryl radicals from arylhydrazines (HAS-type reaction) was successfully achieved in the absence of any oxidant. The base-promoted cross-coupling reaction of arylhydrazines with one equivalent of disulfides under inert gas provides unsymmetrical aryl sulfides in good yields. This rare HAS-type reaction provides a practical synthesis of unsymmetrical aryl sulfides.

5.4 EXPERIMENTAL SECTION

General Information. All the starting materials were purchased from commercial sources and used without further purification. IR spectra were reported in wave numbers (cm^{-1}). ^{1}H NMR spectra were recorded on a 400 MHz spectrometer using $CDCl_3$ or DMSO-d_6 as solvent referenced to TMS (0 ppm) and $CHCl_3$ (7.26 ppm) or DMSO (2.50 ppm). ^{13}C NMR spectra were recorded at 100 MHz in $CDCl_3$ and DMSO-d_6 using $CDCl_3$ (77.0 ppm) and DMSO-d_6 (39.5 ppm) as standards. Chemical shifts are reported in parts per million (ppm). Coupling constants are in reported in hertz (*J*, Hz). The following abbreviations are used for the description of signals: s (singlet), d (doublet), t (triplet), q (quadruplet), and m (multiplet). Exact mass spectra were recorded using direct analysis in real time (DART-

TOFMS). Analytical TLC was carried out on silica gel plates using short wave (254 nm) UV light. Silica gel (230−400 mesh) was used for column chromatography.

General Procedure for the Synthesis of Unsymmetrical Aryl Sulfide 3. A mixture of arylhydrazine hydrochlorides **1** (1.0 mmol), disulfides **2** (1.0 mmol), and cesium carbonate (326 mg, 1.0 mmol) in DMSO (3.0 mL) was stirred at 25 °C in air. The reactions were monitored by thin layer chromatography (TLC) and upon completion (24 h) quenched by the addition of water. Then, the reaction mixtures were extracted with ethyl acetate. The organic layer was washed with water and brine and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure to give crude products, which were purified by column chromatography (inner diameter: 3.0 cm and length: 30 cm) over silica gel (hexane/AcOEt) to afford pure products.

4-Chlorophenyl 4′-nitrophenyl sulfide (3aa). Compound **3aa** was synthesized from 4-chlorophenylhydrazine hydrochloride (**1a**) (179 mg, 1.0 mmol) and 4,4′-dinitrodiphenyl disulfide (**2a**) (308 mg, 1.0 mmol) according to the general procedure. Purification by column chromatography (hexane/AcOEt = 95:5) and recrystallization from hexane/AcOEt (9:1) gave **3aa** (218 mg, 0.82 mmol, 82%) as a pale yellow block crystal; R_f = 0.44 (hexane/AcOEt = 95:5) (UV); mp 84.5−85.5 °C (Lit.[25] 83−84 °C); FT-IR (neat) 3091, 3059, 1502, 1331, 1078, 845 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 7.32 (d, J = 8.9 Hz, 2H), 7.59 (s, 4H), 8.14 (d, J = 8.9 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 124.4, 127.3, 129.0, 130.3, 134.8, 136.0, 145.3, 146.7; HRMS (DART-TOFMS) calcd for $C_{12}H_8ClNO_2S$ [M^+]: 264.9964, found: 264.9944.

4-Chlorophenyl 3′-nitrophenyl sulfide (3ab). Compound **3ab** was prepared from 4-chlorophenylhydrazine hydrochloride (**1a**) (179 mg, 1.0 mmol) and 3,3′-dinitrodiphenyl disulfide (**2b**) (308 mg, 1.0 mmol) according to the general procedure. Purification by column chromatography (hexane/AcOEt = 95:5) and recrystallization from hexane/AcOEt (9:1) gave **3ab** (198 mg, 0.75 mmol,

75%) as a pale yellow needle; R_f = 0.34 (hexane/AcOEt = 95:5) (UV); mp 70.5−71.5 °C (Lit.[26] 70−71 °C); FT-IR (neat) 3083, 3066, 1521, 1343, 727 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 7.50-7.55 (m, 4H), 7.64 (t, J = 8.2 Hz, 1H), 7.69 (td, J = 1.6 Hz, J = 8.2 Hz, 1H), 7.97 (t, J = 1.6 Hz, 1H), 8.10 (ddd, J = 1.6 Hz, J = 2.3 Hz, J = 8.2 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 121.8, 123.0, 130.0, 130.9, 131.1, 133.8, 134.3, 135.3, 138.2, 148.4; HRMS (DART-TOFMS) calcd for $C_{12}H_8ClNO_2S$ [M^+]: 264.9964, found: 264.9943.

4-Chlorophenyl 2′-nitrophenyl sulfide (3ac). Compound **3ac** was prepared according to the general procedure using 4-chlorophenylhydrazine hydrochloride (**1a**) (179 mg, 1.0 mmol) and 2,2′-dinitrodiphenyl disulfide (**2c**) (308 mg, 1.0 mmol). Purification by column chromatography (hexane/AcOEt = 95:5) and recrystallization from hexane/AcOEt (9:1) gave **3ac** (105 mg, 0.40 mmol, 40%) as a pale orange needle. R_f = 0.22 (hexane/AcOEt = 95:5) (UV); mp 96.0−97.0 °C (Lit.[27] 94−96 °C); FT-IR (neat) 3100, 1504, 1303, 1091 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 6.91 (dd, J = 1.4 Hz, J = 8.2 Hz, 1H), 7.42 (dt, J = 1.4 Hz, J = 8.2 Hz, 1H), 7.58−7.65 (m, 5H), 8.25 (dd, J = 1.4 Hz, J = 8.2 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 125.8, 126.4, 128.5, 129.4, 130.4, 134.5, 135.3, 136.6, 137.0, 145.0; HRMS (DART-TOFMS) calcd for $C_{12}H_8ClNO_2S$ [M^+]: 264.9964, found: 264.9947.

4-Chlorophenyl 4′-tolyl sulfide (3ad). The mixture of 4-chlorophenylhydrazine hydrochloride (**1a**) (179 mg, 1.0 mmol), 4,4′-ditolyl disulfide (**2d**) (246 mg, 1.0 mmol), and cesium carbonate (1.0 equiv) in DMSO (3 mL) provided the desired **3ad** (71 mg, 0.30 mmol, 30% in air, and 86 mg, 0.37 mmol, 37% under argon). Recrystallization from hexane, gave **3ad** as a white solid; R_f = 0.40 (hexane) (UV); mp 71.5−72.5 °C (Lit.[26] 70−71 °C); FT-IR (neat) 2917, 1472, 1085, 804 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 2.31 (s, 3H), 7.20 (d, J = 8.7 Hz, 2H), 7.23 (d, J = 8.0 Hz, 2H), 7.31 (d, J = 8.0 Hz, 1H), 7.38 (d, J = 8.7 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 20.7, 129.3, 129.4, 130.5, 130.5,

131.2, 132.5, 135.7, 138.2; HRMS (DART-TOFMS) calcd for $C_{13}H_{11}ClS$ [M^+]: 234.0270, found: 234.0255.

4-Chlorophenyl 4′-hydroxyphenyl sulfide (3ae). Following the general procedure, compound **3ae** was synthesized from 4-chlorophenylhydrazine hydrochloride (**1a**) (179 mg, 1.0 mmol) and 4,4′-dihydroxydiphenyl disulfide (**2e**) (250 mg, 1.0 mmol). Purification by column chromatography (hexane/AcOEt = 2:1) afforded **3ae** (138 mg, 0.58 mmol, 58%) as an orange solid; Rf = 0.50 (hexane/AcOEt = 2:1) (UV); mp 66.0−67.5 °C (Lit.[28] 54−55 °C); FT-IR (neat) 3283, 1582, 1489, 1092, 810 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 6.85 (d, J = 8.7 Hz, 2H), 7.06 (d, J = 8.7 Hz, 2H), 7.33 (d, J = 8.7 Hz, 2H), 7.33 (d, J = 8.7 Hz, 2H), 9.95 (bs, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 116.9, 119.6, 128.4, 129.0, 130.1, 136.3, 138.0, 158.6; HRMS (DART-TOFMS) calcd for $C_{12}H_9ClOS$ [M^+]: 236.0063, found: 236.0039.

2-[(4′-Chlorophenyl)thio]benzothiazole (3af). The desired product **3af** was synthesized from 4-chlorophenylhydrazine hydrochloride (**1a**) (179 mg, 1.0 mmol) and 2,2'-dibenzothiazolyl disulfide (**2f**) (332 mg, 1.0 mmol) according to the general procedure. Purification by column chromatography (hexane/AcOEt = 4:1) and recrystallization form hexane/AcOEt (9:1), gave **3af** (211 mg, 0.76 mmol, 76%) as a colorless plate crystal; R_f = 0.60 (hexane/AcOEt=4:1) (UV); mp 59.0−60.0 °C (Lit.[29] 60−61 °C); FT-IR (neat) 3079, 3058, 1454, 1390, 747, 723 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 7.36 (dt, J = 1.2 Hz, J = 7.6 Hz, 1H), 7.47 (dt, J = 1.2 Hz, J = 7.6 Hz, 1H), 7.65 (d, J = 8.6 Hz, 2H), 7.83 (d, J = 8.6 Hz, 2H), 7.84−7.87 (m, 1H), 7.96 (dd, J = 1.2 Hz, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 121.5, 121.8, 124.7, 126.5, 127.9, 130.3, 134.9, 137.0, 153.3; HRMS (DART-TOFMS) calcd for $C_{13}H_9ClNS_2$ [M + H^+]: 277.9859, found: 277.9839.

4-[(4'-Chlorophenyl)thio]pyridine (3ag). Compound **3ag** was obtained from 4-chlorophenylhydrazine hydrochloride (**1a**) (179 mg, 1.0 mmol) and 4,4′-dipyridyl disulfide (**2g**) (220

mg, 1.0 mmol) according to the general procedure. Purification by column chromatography (hexane/AcOEt = 2:3) gave **3ag** (144 mg, 0.65 mmol, 65%) as a brown solid; R_f = 0.40 (hexane/AcOEt = 2:3) (UV); mp 56.5−57.5 °C; FT-IR (neat) 3035, 1567, 1474, 1403, 1087, 822, 802 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 7.04 (dd, J = 1.6 Hz, J = 4.6 Hz, 2H), 7.59 (s, 4H), 8.38 (dd, J = 1.6 Hz, J = 4.6 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 120.8, 127.8, 130.2, 134.9, 136.5, 148.3, 149.7; HRMS (DART-TOFMS) calcd for $C_{11}H_9ClNS$ [M + H^+]: 222.0139, found: 222.0126.

2-[(4′-Chlorophenyl)thio]pyridine (3ah). Following the general procedure, compound **3ah** was synthesized from 4-chlorophenylhydrazine hydrochloride (**1a**) (179 mg, 1.0 mmol) and 2,2′-dipyridyl disulfide (**2h**) (220 mg, 1.0 mmol). Purification by column chromatography (hexane/AcOEt = 4:1) afforded **3ah** (44 mg, 0.20 mmol, 20%) as a brown oil; R_f = 0.50 (hexane/AcOEt = 4:1) (UV); FT-IR (neat) 3044, 2987, 1572, 1415, 1085, 755, 746 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 7.04 (td, J = 0.8 Hz, J = 8.0 Hz, 1H), 7.17 (ddd, J = 0.8 Hz, J = 4.4 Hz, J = 8.0 Hz, 1H), 7.53 (d, J = 8.4 Hz, 2H), 7.58 (d, J = 8.4 Hz, 2H), 7.67 (dt, J = 2.0 Hz, J = 8.0 Hz, 1H), 8.40 (ddd, J = 0.8 Hz, J = 2.0 Hz, J = 4.4 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 120.8, 121.5, 129.3, 129.8, 134.1, 136.2, 137.5, 149.7, 158.9; HRMS (DART-TOFMS) calcd for $C_{11}H_9ClNS$ [M + H^+]: 222.0139, found: 222.0120.

2-[(4'-Chlorophenyl)thio]-5-nitropyridine (3ai). The reaction of 4-chlorophenylhydrazine hydrochloride (**1a**) (179 mg, 1.0 mmol) with 2,2′-dithiobis(5-nitropyridine) (**2i**) (310 mg, 1.0 mmol) was performed according to the general procedure to afford compound **3ai**. Purification by column chromatography (hexane/AcOEt = 4:1) and recrystallization from hexane/AcOEt (9:1) gave **3ai** (249 mg, 0.93 mmol, 93%) as white needles; R_f = 0.50 (hexane/AcOEt = 4:1) (UV); mp 136.0−137.5 °C (Lit.[30] 136−138 °C); FT-IR (neat) 3053, 1568, 1508, 1343, 1089, 822, 747 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 7.21 (d, J = 9.0 Hz, 1H), 7.63 (d, J = 8.7 Hz, 2H), 7.69 (d, J = 8.7 Hz, 2H), 8.40 (dd, J = 2.8 Hz, J = 9.0 Hz, 1H), 9.18 (d, J = 2.8 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 120.5, 127.0,

130.2, 132.3, 135.4, 137.1, 141.6, 145.0, 167.5; HRMS (DART-TOFMS) calcd for $C_{11}H_8ClN_2O_2S$ [M + H^+]: 266.9990, found: 266.9968.

1-Chloro-4-(methylthio)benzene (3aj). Compound **3aj** was obtained from 4-chlorophenylhydrazine hydrochloride (**1a**) (179 mg, 1.0 mmol) and dimethyl disulfide (**2j**) (94 mg, 1.0 mmol) according to the general procedure. The crude product was purified by column chromatography using hexane and **3aj** (128 mg, 0.81 mmol, 81%) was obtained as a colorless oil; R_f = 0.30 (hexane) (UV); FT-IR (neat) 2984, 2919, 1474, 1093, 1010, 806 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.47 (s, 3H), 7.18 (d, J = 8.5 Hz, 2H), 7.25 (d, J = 8.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.1, 127.9, 128.9, 130.9, 137.0; HRMS (DART-TOFMS) calcd for C_7H_7ClS [M^+]: 157.9957, found: 157.9960.

1-Chloro-4-(ethylthio)benzene (3ak). Compound **3ak** was prepared from 4-chlorophenylhydrazine hydrochloride (**1a**) (179 mg, 1.0 mmol) and diethyl disulfide (**2k**) (122 mg, 1.0 mmol) according to the general procedure. The resulting crude reaction mixture was purified by column chromatography using hexane to give the corresponding product **3ak**(107 mg, 0.62 mmol, 62%) as a colorless oil; R_f = 0.36 (hexane) (UV); FT-IR (neat) 2973, 2927, 2870, 1474, 1093, 1010, 809 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.30 (t, J = 7.4 Hz, 3H), 2.92 (q, J = 7.4 Hz, 2H), 7.25 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 27.9, 128.9, 130.3, 131.7, 135.1; HRMS (DART-TOFMS) calcd for C_8H_9ClS [M^+]: 172.0113, found: 172.0113.

4-Fluorophenyl 4′-nitrophenyl sulfide (3ba). According to the general procedure, compound **3ba** was synthesized from 4-fluorophenylhydrazine hydrochloride (**1b**) (163 mg, 1.0 mmol) and 4,4′-dinitrodiphenyl disulfide (**2a**) (308 mg, 1.0 mmol). The crude mixture was purified by column chromatography (hexane/AcOEt = 95:5) and recrystallized from hexane to give **3ba** (206 mg, 0.83 mmol, 83%) as a pale yellow sticky crystal; R_f = 0.32 (hexane/AcOEt = 95:5) (UV); mp 97.4−98.4 °C (Lit.[31] 97−99 °C); FT-IR (neat) 3091, 1502, 1332, 1077, 831 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6)

δ 7.26 (d, J = 9.0 Hz, 2H), 7.40 (dd, J_{HF} = 9.0 Hz, J = 9.0 Hz, 2H), 7.68 (dd, J_{HF} = 5.4 Hz, J = 9.0 Hz, 2H), 8.13 (d, J = 9.0 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 117.5 (d, J_{CF} = 22.9 Hz), 124.3, 125.1, 126.5, 137.4 (d, J_{CF} = 8.6 Hz), 145.0, 147.7, 163.1 (d, J_{CF} = 246.9 Hz); HRMS (DART-TOFMS) calcd for $C_{12}H_8FNO_2S$ [M^+]: 249.0260, found: 249.0237.

4-Bromophenyl 4′-nitrophenyl sulfide (3ca). The reaction of 4-bromophenylhydrazine hydrochloride (**1c**) (224 mg, 1.0 mmol) with 4,4′-dinitrodiphenyl disulfide (**2a**) (308 mg, 1.0 mmol) was carried out according to the general procedure to provide the desired compound **3ca** (220 mg, 0.71 mmol, 71%) as a pale yellow block crystal after column chromatography (hexane) and recrystallization from hexane; R_f = 0.22 (hexane) (UV); mp 94.0−95.0 °C (Lit.[32] 94−96 °C); FT-IR (neat) 3092, 1504, 1334, 1008, 845, 742 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.33 (d, J = 9.2 Hz, 2H), 7.51 (d, J = 8.5 Hz, 2H), 7.72 (d, J = 8.5 Hz, 2H), 8.14 (d, J = 9.2 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) d 123.4, 124.4, 127.4, 129.6, 133.2, 136.1, 145.3, 146.5; HRMS (DART-TOFMS) calcd for $C_{12}H_8BrNO_2S$ [M^+]: 308.9459, found: 308.9447.

4-Nitrophenyl phenyl sulfide (3da). Compound **3da** was prepared from phenylhydrazine hydrochloride (**1d**) (145 mg, 1.0 mmol) and 4,4′-dinitrodiphenyl disulfide (**2a**) (308 mg, 1.0 mmol) according to the general procedure. Purification by column chromatography (hexane) and recrystallization from hexane/AcOEt (9:1) gave **3da** (196 mg, 0.85 mmol, 85%) as a pale orange plate crystal; R_f = 0.18 (hexane) (UV); mp 55.0−56.0 °C (Lit.[25] 54−55 °C); FT-IR (neat) 3096, 3052, 1501, 1333, 741 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.27 (d, J = 8.9 Hz, 2H), 7.52-7.59 (m, 5H), 8.12 (d, J = 8.9 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 124.3, 126.8, 129.7, 129.9, 130.3, 134.4, 145.0, 147.5; HRMS (DART-TOFMS) calcd for $C_{12}H_{10}NO_2S$ [M+H^+]: 232.0427, found: 232.0408.

4-Nitrophenyl 4′-tolyl sulfide (3ea). Compound **3ea** was synthesized from 4-tolylhydrazine hydrochloride (**1e**) (159 mg, 1.0 mmol) and 4,4′-dinitrodiphenyl disulfide (**2a**) (308 mg, 1.0 mmol)

according to the general procedure. Purification by column chromatography (hexane) and recrystallization from hexane/AcOEt (9:1) gave **3ea** (188 mg, 0.77 mmol, 77%) as pale yellow needles; R_f = 0.30 (hexane) (UV); mp 80.0−81.0 °C (Lit.[26] 78−79 °C); FT-IR (neat) 1508, 1338, 811, 738 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 7.23 (d, J = 9.2 Hz, 2H), 7.36 (d, J = 7.8 Hz, 2H), 7.49 (d, J = 7.8 Hz, 2H), 8.12 (d, J = 9.2 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 20.8, 124.3, 125.8, 126.2, 131.0, 134.9, 140.1, 144.8, 148.4; HRMS (DART-TOFMS) calcd for $C_{13}H_{11}NO_2S$ [M^+]: 245.0510, found: 245.0507.

4-Cyanophenyl 4′-nitrophenyl sulfide (3fa). Following the general procedure, compound **3fa** was obtained from 4-cyanophenylhydrazine hydrochloride (**1f**) (170 mg, 1.0 mmol) and 4,4′-dinitrodiphenyl disulfide (**2a**) (308 mg, 1.0 mmol). The crude mixture was purified by column chromatography with hexane/AcOEt = 4:1 to afford the desired compound **3fa** (140 mg, 0.55 mmol, 55%). Recrystallization from hexane/AcOEt (9:1) afforded **3fa** as pale yellow needles; R_f = 0.46 (hexane/AcOEt = 4:1) (UV); mp 153.5−154.5 °C (Lit.[33] 153−154 °C); FT-IR (neat) 3086, 2227, 1572, 1499, 1336, 825 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 7.55 (d, J = 9.2 Hz, 2H), 7.60 (d, J = 8.6 Hz, 2H), 7.90 (d, J = 8.6 Hz, 2H), 8.21 (d, J = 9.2 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 110.8, 118.3, 124.6, 130.5, 131.9, 133.5, 139.2, 142.9, 146.4; HRMS (DART-TOFMS) calcd for $C_{13}H_8N_2O_2S$ [M^+]: 256.0306, found: 256.0288.

3-Nitrophenyl 4′-nitrophenyl sulfide (3ga).[18a] Compound **3ga** was obtained from 3-nitrophenylhydrazine hydrochloride (**1g**) (190 mg, 1.0 mmol) and 4,4′-dinitrodiphenyl disulfide (**2a**) (308 mg, 1.0 mmol) according to the general procedure. Purification by column chromatography (hexane/AcOEt = 7:1) afforded the desired product **3ga** (258 mg, 0.94 mmol, 94%) as a yellow powder; R_f = 0.23 (hexane/AcOEt = 7:1) (UV); mp 122.0−123.0 °C (decomp.); FT-IR (neat) 3088, 1540, 1512, 1337, 1315, 850, 841, 738 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 7.84 (t, J = 7.9 Hz, 1H), 8.06 (d, J = 9.2 Hz, 2H), 8.11 (ddd, J = 0.8 Hz, J = 2.0 Hz, J = 7.9 Hz, 1H), 8.31 (t, J = 2.0 Hz, 1H), 8.34−8.38

(m, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 115.8, 124.4, 125.2, 128.1, 128.5, 131.2, 142.1, 147.2, 148.6, 151.3; HRMS (DART-TOFMS, neg) calcd for $C_{12}H_7N_2O_4S$ [M − H$^+$]: 275.0132, found: 275.0149.

4-(Methylthio)nitrobenzene (3hj). Following the general procedure, compound **3hj** was synthesized from 4-nitrophenylhydrazine hydrochloride (**1h**) (190 mg, 1.0 mmol) and dimethyl disulfide (**2j**) (94 mg, 1.0 mmol). Purification by column chromatography (hexane/AcOEt =9:1) and recrystallization from hexane gave **3hj** (105 mg, 0.62 mmol, 62%) as a pale brown plate crystal; R_f = 0.30 (hexane/AcOEt = 9:1) (UV); mp 69.4−70.4 °C (Lit.[34] 65−67 °C); FT-IR (neat) 3092, 3001, 2915, 1583, 1505, 1330, 1092, 829, 737 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.59 (s, 3H), 7.47 (d, J = 8.7 Hz, 2H), 8.14 (d, J = 8.7 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 14.0, 123.8, 125.3, 144.1, 149.0; HRMS (DART-TOFMS) calcd for $C_7H_7NO_2S$ [M$^+$]: 169.0197, found: 169.0195.

3,4-Dichlorophenyl 4′-nitrophenyl sulfide (3ia). Compound **3ia** was obtained from 3,4-dichlorophenylhydrazine hydrochloride (**1i**) (214 mg, 1.0 mmol) and 4,4′-dinitrodiphenyl disulfide (**2a**) (308 mg, 1.0 mmol) according to the general procedure. The crude product was purified by column chromatography (hexane/AcOEt = 95:5) and recrystallized from hexane/AcOEt (9:1) to give **3ia** (251 mg, 0.84 mmol, 84%) as white needles; R_f = 0.22 (hexane/AcOEt = 95:5) (UV); mp 110.0−111.0 °C; FT-IR (neat) 3088, 3058, 1579, 1500, 1336, 1079, 1032, 839, 812, 739 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.41 (d, J = 8.9 Hz, 2H), 7.53 (dd, J = 2.3 Hz, J = 8.2 Hz, 1H), 7.77 (d, J = 8.2 Hz, 1H), 7.87 (d, J = 2.3 Hz, 1H), 8.16 (d, J = 8.9 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) d 124.5, 128.2, 131.5, 132.1, 132.5, 132.6, 133.8, 135.0, 145.4, 145.6; HRMS (DART-TOFMS) calcd for $C_{12}H_7Cl_2NO_2S$ [M$^+$]: 298.9575, found: 298.9550.

2,4-Dichlorophenyl 4′-nitrophenyl sulfide (3ja). Compound **3ja** was synthesized from 2,4-dichlorophenylhydrazine hydrochloride (**1j**) (214 mg, 1.0 mmol) and 4,4′-dinitrodiphenyl disulfide

(**2a**) (308 mg, 1.0 mmol) according to the general procedure. Purification by column chromatography (hexane/AcOEt = 95:5) and recrystallization from hexane/AcOEt (9:1) gave **3ja** (198 mg, 0.66 mmol, 66%) as a pale brown block crystal; R_f= 0.20 (hexane/AcOEt = 95:5) (UV); mp 76.0−77.0 °C; FT-IR (neat) 3095, 1575, 1506, 1336, 1084, 1033, 846, 810, 742 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 7.35 (d, J = 8.9 Hz, 2H), 7.56 (dd, J = 2.3 Hz, J = 8.5 Hz, 1H), 7.66 (d, J = 8.5 Hz, 1H), 7.90 (d, J = 2.3 Hz, 1H), 8.16 (d, J = 8.9 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 124.5, 127.9, 128.5, 128.9, 130.3, 135.6, 137.2, 138.0, 144.3, 145.7; HRMS (DART-TOFMS) calcd for $C_{12}H_7Cl_2NO_2S$ [M^+]: 298.9575, found: 298.9549.

3,5-Dichlorophenyl 4′-nitrophenyl sulfide (3ka). Following the general procedure, the product **3ka** was synthesized from 3,5-dichlorophenylhydrazine hydrochloride (**1k**) (214 mg, 1.0 mmol) and 4,4′-dinitrodiphenyl disulfide (**2a**) (308 mg, 1.0 mmol). Purification by column chromatography (hexane/AcOEt = 95:5) and recrystallization from hexane/AcOEt (9:1) gave **3ka** (218 mg, 0.73 mmol, 73%) as a white block crystal; R_f= 0.19 (hexane/AcOEt = 95:5) (UV); mp 93.5−94.5 °C; FT-IR (neat) 3071, 1556, 1506, 1330, 1082, 840, 797, 666 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 7.48 (d, J = 9.2 Hz, 2H), 7.60 (d, J = 1.8 Hz, 2H), 7.74 (t, J = 1.8 Hz, 1H), 8.19 (d, J = 9.2 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 124.5, 128.9, 129.1, 131.1, 135.2, 144.3, 146.0; HRMS (DART-TOFMS) calcd for $C_{12}H_7Cl_2NO_2S$ [M^+]: 298.9575, found: 298.9548.

Large-Scale Synthesis of 3aa. Compound **3aa** was prepared from a mixture of 4-chlorophenylhydrazine hydrochloride (**1a**) (3.58 g, 20.0 mmol), 4,4′-dinitrodiphenyl disulfide (**2a**) (6.17 g, 20.0 mmol), and cesium carbonate (6.52 g, 20.0 mmol) in DMSO (60 mL) under air, according to the general procedure. The reaction was monitored by thin layer chromatography (TLC) and completed after 24 h. Purification by column chromatography (inner diameter: 5 cm and length: 30 cm) over silica gel (hexane/AcOEt = 95:5) gave product **3aa** (4.16 g, 79%) in a pure form.

Radical-Trapping Experiment with TEMPO. To a mixture of 4-chlorophenyl- hydrazine hydrochloride (**1a**) (179 mg, 1.0 mmol), 4,4′-dinitrodiphenyl disulfide (**2a**) (308 mg, 1.0 mmol), and cesium carbonate (326 mg, 1.0 mmol) in DMF (10 mL), TEMPO (313 mg, 2.0 mmol) was added. The solution was stirred at room temperature under an argon atmosphere for 24 h. The resulting solution was quenched by the addition of water and extracted with ethyl acetate. The organic layer was washed with water and brine, and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure to give a crude product. Purification by column chromatography over silica gel afforded **3aa** (19%) and 4-chloro-1-(2′,2′,6′,6′- tetramethylpiperidinyloxy)benzene (**4**) (40 mg, 15%).Compound **4** was recrystallized from hexane to give a colorless plate crystal; R_f= 0.62 (hexane); mp 89.5−90.5 °C (Lit.[21] 89.5−90.5 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.99 (s, 6H), 1.21 (s, 6H), 1.38−1.44 (m, 1H), 1.53−1.68 (m, 5H), 7.11 (d, J = 9.4 Hz, 2H), 7.15 (d, J = 9.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.0, 20.4, 32.5, 39.7, 60.4, 115.2, 124.3, 128.5, 162.2.

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Chapter 6

Transition-Metal-Free Synthesis of Unsymmetrical Diaryl Selenides Using Arylhydrazines and Diaryl Diselenides

6.1 INTRODUCTION

Organoselenium chemistry has gained interest for pharmaceutical and agrochemical applications over the past few decades.[1,2] This is because these compounds can act both as important reagents in organic synthesis and as potential drug candidates (*e.g.,* human cancer cell growth inhibitor,[3c] RAR agonist,[3d] and antioxidant[3e]).[3] Furthermore, it has also been recently reported that diaryl selenides are effective organic catalysts.[4] The development of practical and useful methods for synthesizing selenium compounds is therefore much desired.

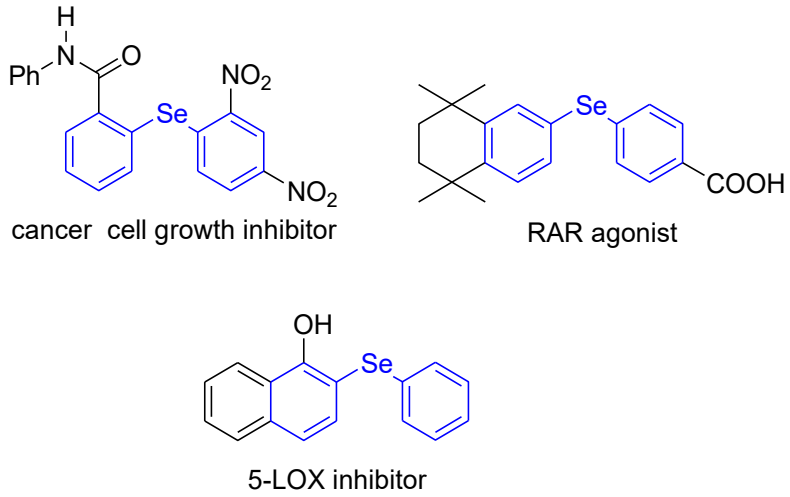
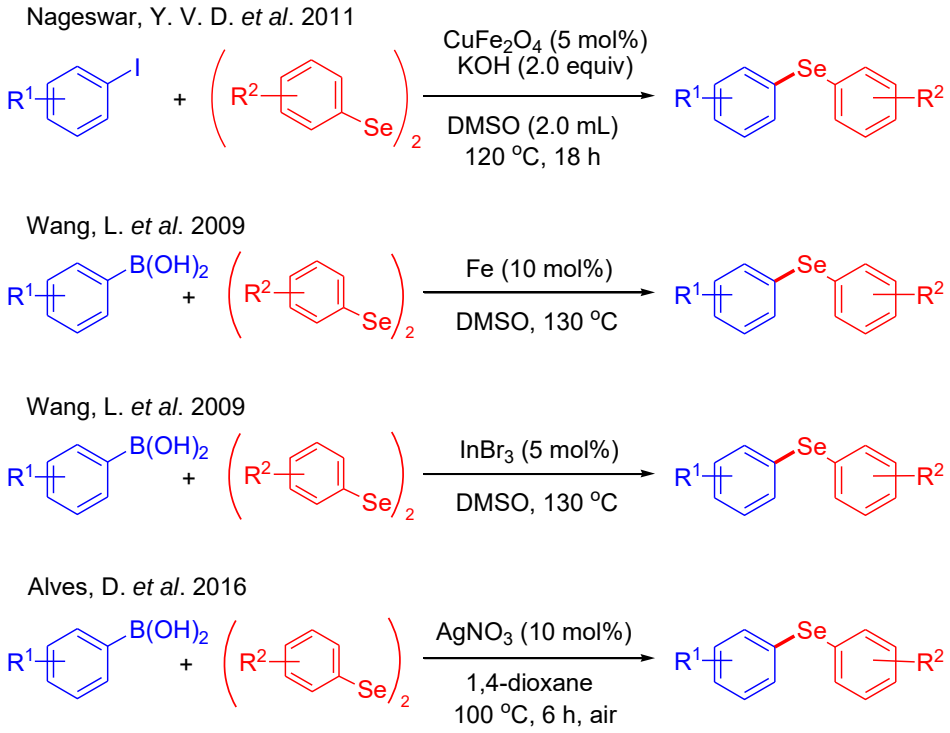


Fig. 1. Examples of bioactive selenides

Several methods for the synthesis of diaryl selenium compounds through C-Se bond generation have been widely reported. These methods, however, require harsh conditions such as high reaction temperature and long reaction times.[5] Alternatively, transition-metal-catalyzed (*e.g.,* such as

palladium,[6] nickel,[7] copper,[8] iron,[9] indium,[10] and silver[11]) C-Se coupling reaction was developed as a powerful approach for the synthesis of unsymmetrical diaryl selenides (Scheme 1). However, industrial-scale usage of transition-metal-catalyzed C-Se coupling reactions exhibits several drawbacks:[12] (1) most of the transition metal catalysts, such as palladium, are very expensive and toxic, and (2) the removal of transition metal residues from the target products is very costly. Therefore, the development of unsymmetrical diaryl selenides synthesis without using transition metal catalysts is crucial for the practical applications of diaryl selenium compounds.

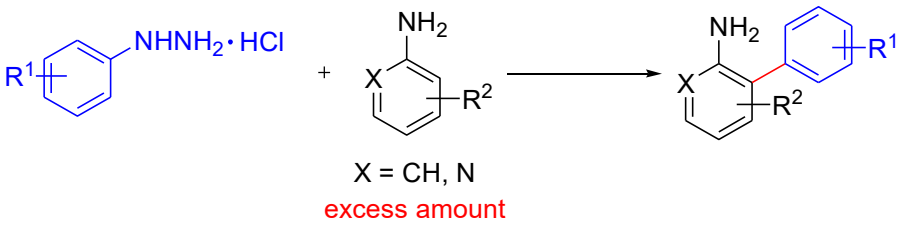
Scheme 1. Transition-metal-catalyzed cross-coupling reaction



A conceptually different approach for aromatic substitution is the direct C-H radical arylation of arenes by the homolytic aromatic substitution (HAS) mechanism. A similar reaction was first reported by Gomberg and Bachmann in 1924.[13] Recently, much attention has been paid to the use of aromatic amine derivatives as the radical sources in the HAS mechanism.[14] Generation of aryl radicals from arylhydrazines under oxidative conditions have been reported.[15] However, the excess amount of radical

acceptors required for the HAS reaction is a significant disadvantage for industrial-scale production (Scheme 2). [15c,15g,15h]

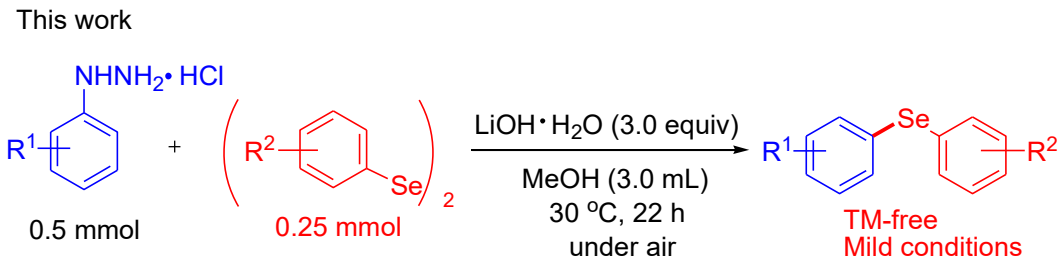
Scheme 2. The HAS reaction using arylhydrazines



Recently, we successfully synthesized unsymmetrical diaryl sulfides with arylhydrazines using the same amount (based on molar ratios) of disulfides as a cross-coupling partner with arylhydrazines. Thereby, improving upon the most significant disadvantage associated with HAS reaction. This approach, however, resulted in half of the disulfides being converted into benzene sulfonic acids.[16]

Herein, we report the transition-metal-free cross-coupling reaction of arylhydrazines with diaryl diselenides to overcome the difficulties mentioned above. To the best of our knowledge, this is the first example of the synthesis of unsymmetrical diaryl selenides using arylhydrazines and a half amount (based on molar ratios) of diaryl diselenides under mild conditions (Scheme 3).

Scheme 3. Synthesis of unsymmetrical diaryl selenides using arylhydrazines

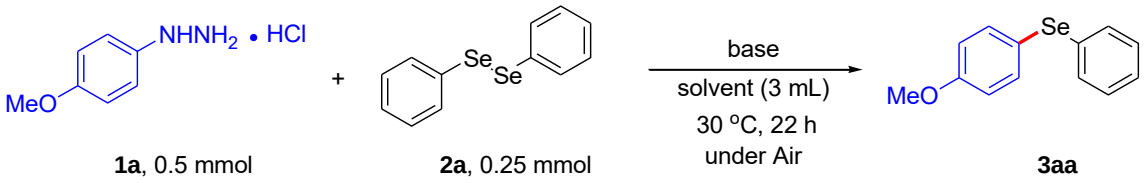


6.2 RESULTS AND DISCUSSION

In the course of our previous studies on the cross-coupling of arylhydrazines with aminoheterocycles,[15g] aromatic diamines[15h] and disulfides,[16] we examined the cross-coupling reaction of 4-methoxyphenylhydrazine hydrochloride (**1a**) with diphenyl diselenide (**2a**) (Table 1). The coupling reaction of **1a** with a half amount of **2a** in the presence of potassium carbonate (3.0 equiv) in dimethyl sulfoxide (DMSO) was performed to form 4-methoxyphenyl phenyl selenide (**3aa**) in 71% yield (Table 1, entry 1). Using DMF and MeCN as the aprotic polar solvents, **3aa** was obtained in good to high yields (52% and 77%, Table 1, entries 2 and 3). Surprisingly, when MeOH was used, the desired product **3aa** was obtained in a high yield (77%, Table 1, entry 4). In our previous study, the cross-coupling reaction did not proceed smoothly in protic polar solvents.[15h,16] However, using EtOH as the solvent, the yield of **3aa** decreased markedly (Table 1, entry 5).

Next, several bases were screened; **3aa** was obtained in moderate to good yields when lithium carbonate or sodium carbonate was used (Table 1, entries 6 and 7). The best yield (78%) of **3aa** was obtained using $LiOH{\cdot}H_2O$ as the base (Table 1, entry 8). When **2a** (0.5 mmol) was used, **3aa** was obtained in the same yield (Table 1, entry 8, footnote c). The use of NaOH allowed us to obtain **3aa** in a good yield (Table 1, entry 9). In regard to organic bases, triethylamine was effective in this cross-coupling reaction and afforded **3aa** in 75% yield (Table 1, entry 10). In the absence of a base, product **3aa** was hardly obtained (2%, Table 1, entry 11) and unreacted **2a** was recovered (96%). When the amount of $LiOH{\cdot}H_2O$ was reduced, product **3aa** was obtained in good yields (Table 1, entries 12 and 13). However, under a nitrogen atmosphere, the desired product **3aa** was afforded in a low yield (Table 1, entry 14). These results show that the air plays an important role as an oxidant in this cross-coupling reaction.

Table 1. Optimization of Synthesis of **3aa**



1a, 0.5 mmol **2a**, 0.25 mmol **3aa**

entry	solvent	base (equiv)	yield (%)[a]
1	DMSO	K_2CO_3 (3)	71
2	DMF	K_2CO_3 (3)	52
3	MeCN	K_2CO_3 (3)	77
4	MeOH	K_2CO_3 (3)	77
5	EtOH	K_2CO_3 (3)	18
6	MeOH	Li_2CO_3 (3)	64
7	MeOH	Na_2CO_3 (3)	70
8	MeOH	LiOH H_2O (3)	78, 76[b], 78[c]
9	MeOH	NaOH (3)	72
10	MeOH	Et_3N (3)	75
11	MeOH	None	2
12	MeOH	LiOH H_2O (2)	69
13	MeOH	LiOH H_2O (1)	71
14	MeOH	LiOH H_2O (3)	17[d]

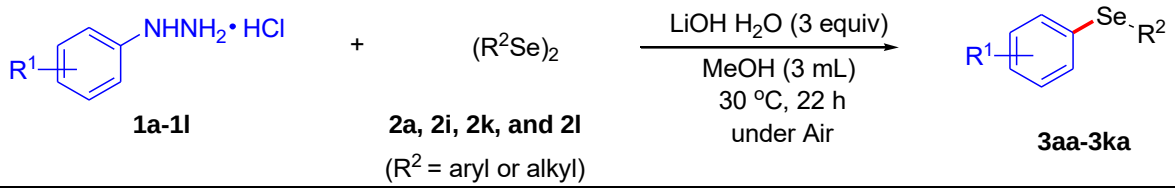
The reaction conditions: **1a** (0.5 mmol), **2a** (0.25 mmol), and solvent (3 mL) at 30 °C under air. [a]NMR yields based on **1a**. [b]Isolated yields. [c]**2a** (0.5 mmol) was used. [d]Under a nitrogen atmosphere.

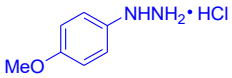
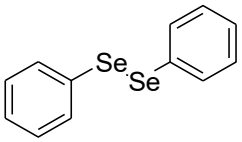
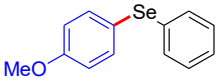
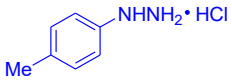
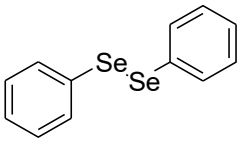
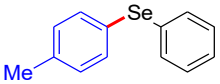
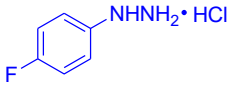
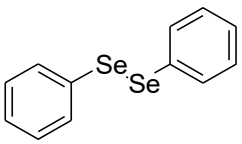
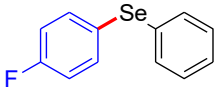
With the optimized conditions in hand, the reactivity of a variety of arylhydrazine hydrochlorides (**1a**-**1g**) with several diselenides (**2a**-**2e**) was examined (Table 2). The reaction of 4-tolylhydrazine hydrochloride (**1b**) with diphenyl diselenide (**2a**) provided compound **3ba** in a good yield (52%, Table 2, entry 2). The cross-coupling reaction of arylhydrazine hydrochlorides bearing an electron-withdrawing groups such as 4-fluoro, 4-chloro, 4-bromo, and 3-chloro groups with diphenyl diselenide (**2a**) proceeded smoothly to form **3ca**-**3fa** in good to high yields (68–72%, Table 2, entries

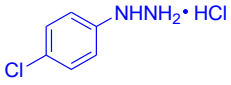
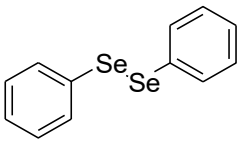
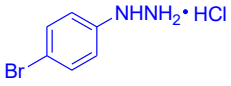
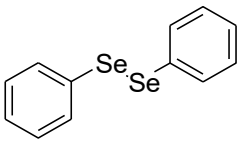
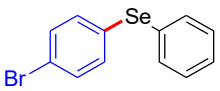
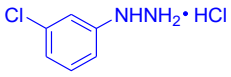
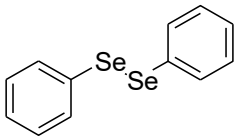
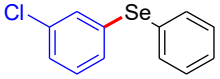
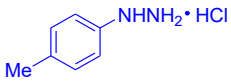
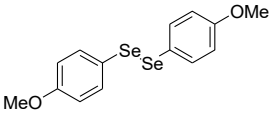
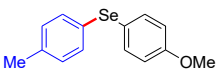
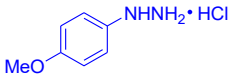
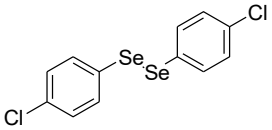
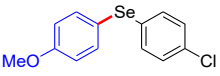
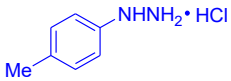
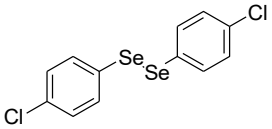
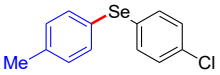
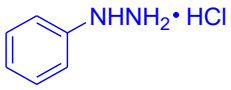
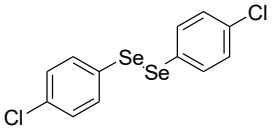
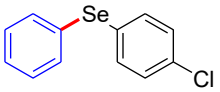
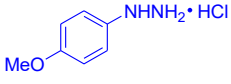
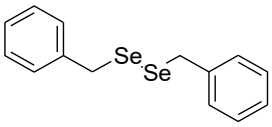
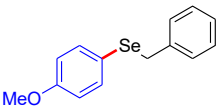
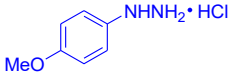
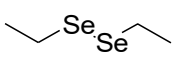
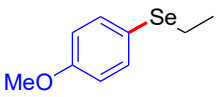
3-6). Compound **1b** was allowed to react with 4,4′-dimethoxydiphenyl diselenide (**2b**) to form product **3bb** in a moderate yield (30%, Table 2, entry 7). The reaction of **1a**, **1b**, and **1g** with diaryl diselenide bearing an electron-withdrawing group, such as a chloro group (**2c**), provided the corresponding products **3ac**, **3bc**, and **3da** in moderate yields (40-43%, Table 2, entries 8-10).

Fortunately, the cross-coupling reaction of arylhydrazines with alkyl diselenides was performed successfully. Using **1a** and dibenzyl diselenide (**2d**), the desired product **3ad** was obtained in 22% yield (Table 2, entry 11). Diethyl diselenide (**2e**) reacted with **1a** to afford **3ae** in 38% yield (Table 2, entry 12).

Table 2. Scope and limitation



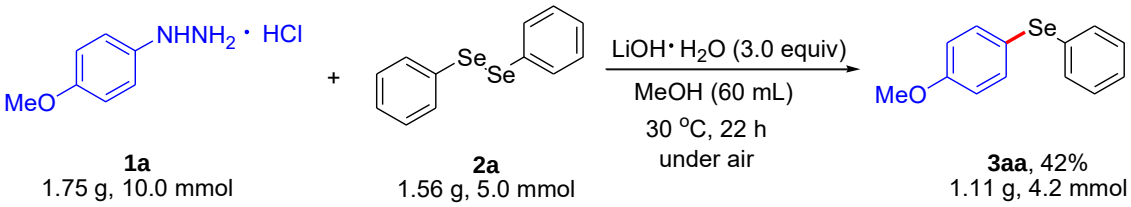
entry	arylhydrazines	diselenides	products	yield (%)[a]
1	 **1a**	 **2a**	 **3aa**	76
2	 **1b**	 **2a**	 **3ba**	52
3	 **1c**	 **2a**	 **3ca**	71

4				72
	1d	**2a**	**3da**	
5				68
	1e	**2a**	**3ea**	
6				70
	1f	**2a**	**3fa**	
7				30
	1b	**2b**	**3bb**	
8				40
	1a	**2c**	**3ac**	
9				40
	1b	**2c**	**3bc**	
10				43
	1g	**2c**	**3da**	
11				22
	1a	**2d**	**3ad**	
12				38
	1a	**2e**	**3ae**	

The reaction conditions: **1** (0.5 mmol), **2** (0.25 mmol), LiOH• H_2O (3 equiv), and MeOH (3 mL) at 30 °C in air. [a]Isolated yields, based on arylhydrazine hydrochlorides

Next, the feasibility of large-scale synthesis (20-fold) of 4-methoxyphenyl phenyl selenide (**3aa**) was investigated. Even at the gram-scale (10 mmol), the cross-coupling reaction of 4-methoxyphenylhydrazine hydrochloride (**1a**) with diphenyl diselenide (**2a**) proceeded smoothly to obtain **3aa** in a moderate yield (Scheme 4).

Scheme 4. Large-scale synthesis of **3aa**



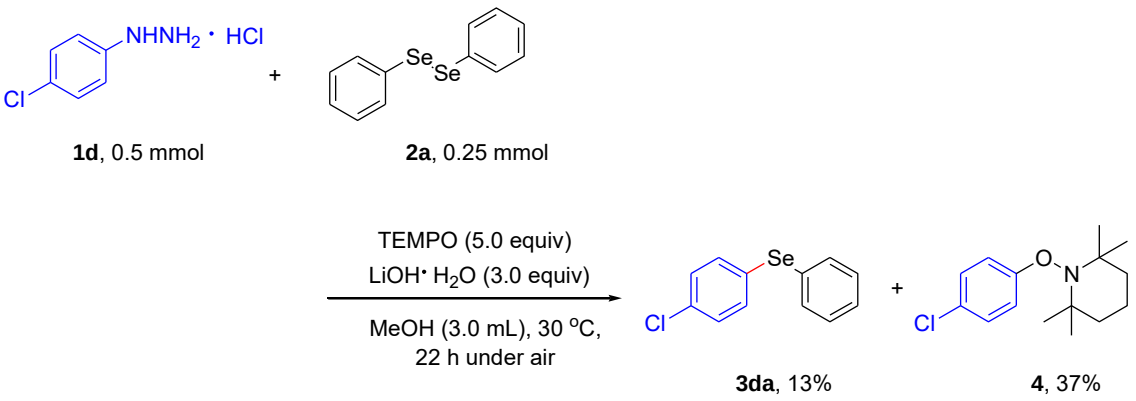
1a
1.75 g, 10.0 mmol

2a
1.56 g, 5.0 mmol

3aa, 42%
1.11 g, 4.2 mmol

In order to clarify the mechanism on the cross-coupling reaction of arylhydrazines with diselenides, a radical trapping experiment was performed. By using 2,2,6,6-tetramethyl-piperidine-1-oxyl (TEMPO) in air, the 4-chlorophenyl radical was trapped to afford **4** in 37% yield. Also, **3da** was obtained in a reduced yield (Scheme 5).

Scheme 5. Radical-trapping experiment



1d, 0.5 mmol

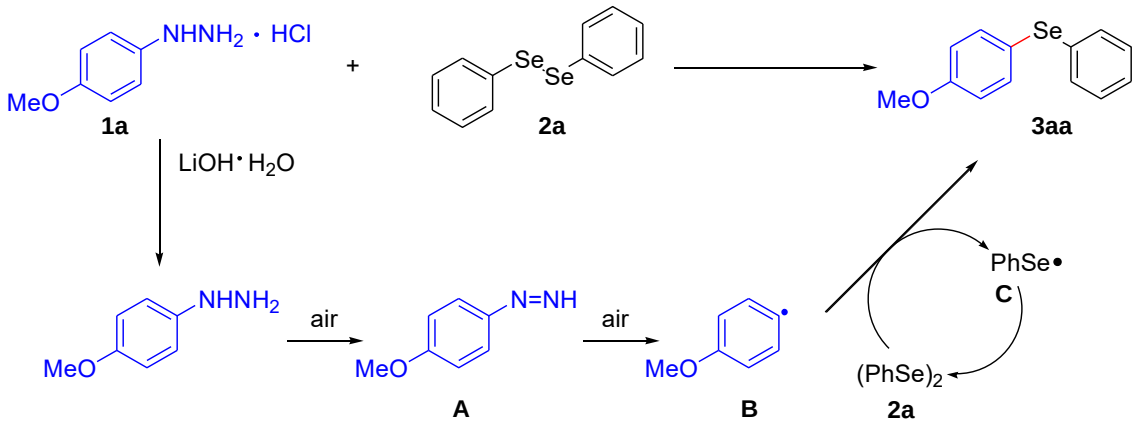
2a, 0.25 mmol

3da, 13%

4, 37%

Based on the experimental results and our previous studies on HAS reactions,[14,15] a plausible reaction mechanism for the cross-coupling reaction of **1a** with **2a** is proposed in Scheme 6. After the preparation of the free-base hydrazine from **1a** by treating with $LiOH·H_2O$, the free-base hydrazine is oxidized by air to form the corresponding diazene **A**. Then, diazene **A** is converted into 4-methoxyphenylradical **B** by oxidation with air. Radical **B** is trapped by diphenyl diselenide **2a** to afford the desired product **3aa**. The notion that radical **B** is trapped by diaryldiselenides was also proposed in our previous work.[17] In contrast, the phenylseleno radical **C** is easily converted into **2a** by radical homo-coupling under air.

Scheme 6. Plausible reaction mechanism for the formation of **3aa**



6.3 CONCLUSION

In conclusion, the transition-metal-free cross-coupling reaction of arylhydrazine hydrochlorides with a half amount (based on molar ratios) of diselenides was developed using air as an oxidant. By avoiding the use of transition metal catalysts in our reaction, we present an alternative method for Pd-catalyzed cross-coupling reactions, which is both useful and practical.

6.4 EXPERIMENTAL SECTION

General Information: All starting materials were purchased from commercial sources and used without further purification. ^{1}H NMR spectra were recorded on 400 MHz spectrometers using $CDCl_3$ as solvent referenced to TMS (0 ppm). ^{13}C NMR spectra were recorded at 100 MHz in $CDCl_3$ using $CDCl_3$ (77.16 ppm) as standard. ^{77}Se NMR spectra were recorded at 76 MHz in $CDCl_3$. Chemical shifts are reported in parts per million (ppm). Coupling constants are reported in hertz (*J*, Hz). The following abbreviations are used for the description of signals: s (singlet), d (doublet), t (triplet), q (quadruplet), m (multiplet). Mass spectra and exact mass spectra were recorded using electron impact (EI). Analytical TLC was carried out on silica gel plates using short wave (254 nm) UV light. Silica gel (230−400 mesh) was used for column chromatography.

General procedure: A mixture of the arylhydrazine hydrochlorides (0.5 mmol), diselenides (0.25 mmol), and lithium hydroxide monohydrate (1.5 mmol) in MeOH (3 mL) was stirred at 30 °C in air. The reactions were completed after 22 h, monitored by thin layer chromatography (TLC). Then, quenched by the addition of water, the reaction mixture was extracted with ethyl acetate. The organic layer was washed with water and brine solution and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to form the crude products. Purified by column chromatography over silica gel, preparative TLC, or GPC, the pure products were afforded.

4-Methoxyphenyl phenyl selenide (3aa)[18]: Following the general procedure, compound **3aa** was obtained from 4-methoxyphenylhydrazine hydrochloride (**1a**) (87 mg, 0.5 mmol) and diphenyl diselenide (**2a**) (78 mg, 0.25 mmol). Purification by column chromatography (hexane/AcOEt) afforded **3aa** (100 mg, 0.38 mmol) as a colorless oil; 76% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.77 (s, 3H),

6.83 (d, J = 8.9 Hz, 1H), 7.13-7.21 (m, 3H), 7.30-7.33 (m, 2H), 7.49 (d, J = 8.9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.4, 115.2, 120.0, 126.5, 129.2, 131.0, 133.3, 136.6, 159.9; ^{77}Se NMR (76 MHz, $CDCl_3$) δ 402; GC-MS (EI) m/z = 264 (M^+).

Phenyl 4-tolyl selenide (3ba)[18]: According with the general procedure, compound **3ba** was synthesized from 4-tolylhydrazine hydrochloride (**1b**) (79 mg, 0.5 mmol) and diphenyl diselenide (**2a**) (78 mg, 0.25 mmol). Purification by column chromatography (hexane) and GPC afforded **3ba** (65 mg, 0.26 mmol) as a pale yellow oil; 52% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.31 (s, 3H), 7.08 (d, J = 7.8 Hz, 2H), 7.19-7.24 (m, 3H), 7.38-7.41 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.3, 126.9, 127.0, 129.3, 130.3, 132.1, 132.2, 134.0, 137.8; ^{77}Se NMR (76 MHz, $CDCl_3$) δ 409; GC-MS (EI) m/z = 248 (M^+).

4-Fluorophenyl phenyl selenide (3ca)[18] Following the general procedure, compound **3ca** was afforded from 4-fluorophenylhydrazine hydrochloride (**1c**) (82 mg, 0.5 mmol) and diphenyl diselenide (**2a**) (78 mg, 0.25 mmol). Purification by column chromatography (hexane) afforded **3ca** (89 mg, 0.35 mmol) as a pale yellow oil; 71% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.95-7.00 (m, 2H), 7.22-7.27 (m, 3H), 7.34-7.41 (m, 2H), 7.45-7.50 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 116.7 (d, J_{C-F} = 21.0 Hz), 125.3 (d, J_{C-F} = 3.8 Hz), 127.3, 129.5, 131.8, 132.3, 135.84 (d, J_{C-F} = 7.6 Hz), 162.7 (d, J_{C-F} = 246.0 Hz); ^{77}Se NMR (76 MHz, $CDCl_3$) δ 411; GC-MS (EI) m/z = 252 (M^+).

4-Chlorophenyl phenyl selenide (3da)[18] Following the general procedure, compound **3da** was prepared from 4-chlorophenylhydrazine hydrochloride (**1d**) (90 mg, 0.5 mmol) and diphenyl diselenide (**2a**) (78 mg, 0.25 mmol). Purification by column chromatography (hexane) afforded **3da** (95 mg, 0.36 mmol) as a colorless oil; 72% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (d, J = 8.3 Hz,

2H), 7.25-7.28 (m, 3H), 7.35 (d, J = 8.3 Hz, 2H), 7.44-7.47 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 127.8, 129.6, 129.7, 130.8, 133.3, 133.6, 134.2; ^{77}Se NMR (76 MHz, $CDCl_3$) δ 416; GC-MS (EI) m/z = 268 (M^+).

4-Bromophenyl phenyl selenide (3ea)[19] Following the general procedure, compound **3ea** was synthesized from 4-bromophenylhydrazine hydrochloride (**1e**) (112 mg, 0.5 mmol) and diphenyl diselenide (**2a**) (78 mg, 0.25 mmol). Purification by column chromatography (hexane) afforded **3ea** (105 mg, 0.34 mmol) as a pale yellow oil; 68% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27-7.31 (m, 5H), 7.37 (d, J = 8.3 Hz, 2H), 7.45-7.48 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 121.6, 127.9, 129.6, 130.5, 130.6, 132.5, 133.4, 134.3; ^{77}Se NMR (76 MHz, $CDCl_3$) δ 416; GC-MS (EI) m/z = 312 (M^+).

3-Chlorophenyl phenyl selenide (3fa)[18] According with the general procedure, compound **3fa** was synthesized from 4-chlorophenyl-hydrazine hydrochloride (**1f**) (90 mg, 0.5 mmol) and diphenyl diselenide (**2a**) (78 mg, 0.25 mmol). Purification by column chromatography (hexane) afforded **3fa** (94 mg, 0.35 mmol) as a colorless oil; 70% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13-7.21 (m, 2H), 7.26-7.33 (m, 4H), 7.38 (t, J = 1.6 Hz, 1H), 7.49-7.53 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 127.3, 128.2, 129.7, 129.9, 130.2, 130.3, 131.8, 133.6, 134.0, 135.0; ^{77}Se NMR (76 MHz, $CDCl_3$) δ 428; GC-MS (EI) m/z = 268 (M^+).

4-Methoxyphenyl 4-tolyl selenide (3bb)[18] Following the general procedure, compound **3bb** was synthesized from 4-tolylhydrazine hydrochloride (**1b**) (79 mg, 0.5 mmol) and 4,4′-dimethoxydiphenyl diselenide (**2b**) (93 mg, 0.25 mmol). Purification by preparative TLC (hexane/AcOEt) afforded **3bb** (41 mg, 0.15 mmol) as a yellow solid; 30% yield; mp = 57-59 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.29 (s, 3H), 3.79 (s, 3H), 6.83 (d, J = 9.2 Hz, 2H), 7.04 (d, J = 7.8 Hz, 2H), 7.28 (d, J = 7.8 Hz, 2H), 7.46

(d, J = 9.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.2, 55.4, 115.2, 121.0, 129.1, 130.1, 132.0, 135.9, 136.8, 159.7; ^{77}Se NMR (76 MHz, $CDCl_3$) δ 395; GC-MS (EI) m/z = 278 (M^+).

4-Chlorophenyl 4-methoxyphenyl selenide (3ac)[18] Following the general procedure, compound **3ac** was given from 4-methoxyphenylhydrazine hydrochloride (**1a**) (87 mg, 0.5 mmol) and 4,4′-dichlorodiphenyl diselenide (**2c**) (95 mg, 0.25 mmol). Purification by preparative TLC (hexane/AcOEt) afforded **3ac** (59 mg, 0.20 mmol) as a yellow solid; 40% yield; mp = 54-57 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.81 (s, 3H), 6.86 (d, J = 8.9 Hz, 2H), 7.17 (d, J = 8.7 Hz, 2H), 7.23 (d, J = 8.7 Hz, 2H), 7.49 (d, J = 8.9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.4, 115.4, 119.6, 129.4, 131.7, 132.2, 132.6, 136.8, 160.1; ^{77}Se NMR (76 MHz, $CDCl_3$) δ 401; GC-MS (EI) m/z = 298 (M^+).

4-Chlorophenyl 4-tolyl selenide (3bc)[19] According with the general procedure, compound **3bc** was synthesized from 4-tolylhydrazine hydrochloride (**1b**) (79 mg, 0.5 mmol) and 4,4′-dichlorodiphenyl diselenide (**2c**) (95 mg, 0.25 mmol). Purification by preparative TLC (hexane/AcOEt) afforded **3bc** (55 mg, 0.20 mmol) as a pale yellow solid; 40% yield; mp = 69-71 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.34 (s, 3H), 7.11 (d, J = 7.8 Hz, 2H), 7.19 (d, J = 8.5 Hz, 2H), 7.31 (d, J = 8.5 Hz, 2H), 7.40 (d, J = 7.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.3, 126.5, 129.5, 130.5, 130.7, 133.1, 133.3, 134.2, 138.2; ^{77}Se NMR (76 MHz, $CDCl_3$) δ 407; GC-MS (EI) m/z = 282 (M^+).

Benzyl 4-methoxyphenyl selenide (3ad)[20] Following the general procedure, compound **3ad** was synthesized from 4-methoxyphenylhydrazine hydrochloride (**1a**) (87 mg, 0.5 mmol) and dibenzyl diselenide (**2d**) (85 mg, 0.25 mmol). Purification by column chromatography (hexane/AcOEt) afforded **3ad** (31 mg, 0.11 mmol) as a yellow solid; 22% yield; mp = 42-43 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.78 (s, 3H), 3.99 (s, 2H), 6.77 (d, J = 8.5 Hz, 2H), 7.11-7.24 (m, 5H), 7.36 (d, J = 8.5 Hz, 2H); ^{13}C

NMR (100 MHz, $CDCl_3$) δ 33.3, 55.4, 114.7, 120.2, 126.8, 128.5, 128.9, 136.7, 139.2, 159.7; ^{77}Se NMR (76 MHz, $CDCl_3$) δ 373; GC-MS (EI) *m/z* = 278 (M^+).

Ethyl 4-methoxyphenyl selenide (3ae)[21] Following the general procedure, compound **3ae** was obtained from 4-methoxyphenylhydrazine hydrochloride (**1a**) (87 mg, 0.5 mmol) and diethyl diselenide (**2e**) (54 mg, 0.25 mmol). Purification by column chromatography (hexane/AcOEt) afforded **3ae** (40 mg, 0.19 mmol) as a colorless oil; 38% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38 (t, *J* = 7.5 Hz, 3H), 2.82 (q, *J* = 7.5 Hz, 2H), 3.79 (s, 3H), 6.82 (d, *J* = 9.2 Hz, 2H), 7.47 (d, *J* = 9.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.7, 22.6, 55.4, 114.8, 120.0, 135.8, 159.4; ^{77}Se NMR (76 MHz, $CDCl_3$) δ 317; GC-MS (EI) *m/z* = 216 (M^+).

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Chapter 7

Conclusion

In this research work, the development of novel transition-metal-free reactions of aromatic amines has been investigated. The author focused on the utilization of aromatic amines for the new reactions.

In chapter 2, a new method for the hydrolysis of diazonium salts, without the formation of tar, was developed. A two-phase system consisting of cyclopentyl methyl ether (CPME) and water is very effective for the hydrolysis of diazonium salts. Using this solvent system, the diazonium salt prepared from 3-(4-nitrophenoxy)aniline gave 3-(4-nitrophenoxy)phenol in a high yield (96%) within 20 min. The synthesized phenol is an industrially important raw material in polymer syntheses. Furthermore, the use of the present two-phase system of CPME and water successfully brought about the efficient conversions of several *m*-substituted anilines into the corresponding *m*-substituted phenols. This is the first example of hydrolysis of diazonium salts using the two-phase system of CPME and water.

In chapter 3, a direct C-H arylation of aminoheterocycles with arylhydrazine hydrochlorides was developed. The reaction proceeds via a homolytic aromatic substitution mechanism involving aryl radicals as the intermediates. The new reaction takes place readily at room temperature in air and in the presence of an inexpensive base. Moreover, the reactivity of this radical arylation correlated with the HOMO energy of aminoheterocycles. This method provides not only a rapid access to diverse arylated heterocycles, but also an atom-efficient alternative to conventional transition-metal-catalyzed cross-coupling between halides and organometallics.

In chapter 4, the arylation of aromatic diamines with arylhydrazine hydrochlorides was achieved in reasonable yields. This new and simple reaction occurred at room temperature in air using an inexpensive base. This transformation seems to proceed via a homolytic aromatic substitution (HAS) mechanism. The synthesized aromatic diamines are used as raw materials for polyimides, including important aerospace materials, for example, Kapton®.

In chapter 5, a novel synthesis of unsymmetrical aryl sulfides, which requires no transition metal catalyst and no oxidant, was developed. This base-promoted cross-coupling reaction proceeded using arylhydrazines and one equivalent amount of disulfides under inert gas conditions to afford the unsymmetrical aryl sulfides in good yields.

In chapter 6, transition-metal-free cross-coupling reaction of arylhydrazines with a half amount (based on molar ratios) of diselenides was developed under mild conditions. The new and facile cross-coupling involved the use of an inexpensive base in air to form unsymmetrical diaryl selenides in good yields. This C-Se radical arylation of diaryl diselenides was performed by forming aryl radicals from arylhydrazines under oxidative conditions. The phenyl radical was trapped by using 2,2,6,6-tetramethyl-piperidine-1-oxyl (TEMPO) in air. The cross-coupling reaction involves homolytic aromatic substitution (HAS) mechanism. Considering that the method we describe is both low-cost and environmentally friendly, our cross-coupling reaction method may be useful for industrial-scale synthesis of unsymmetrical diaryl selenides.

In summary, this thesis described the development of transition-metal-free reactions of aromatic amines. The author believes that this study is the important development of aromatic amines in practical viewpoints and make a great contribution for the future field of organic synthesis.

List of Publications

(1) Hydrolysis of Diazonium Salts Using a Two-Phase System (CPME and Water)
Taniguchi, T.; Imoto, M.; Takeda, M.; Nakai, T.; Mihara, M.; Iwai, T.; Ito, T.; Mizuno, T.; Nomoto, A.; Ogawa, A.
Heteroatom Chem., **2015**, *26*, 411-416.

(Chapter 2)

(2) Metal-Free C-H Arylation of Aminoheterocycles with Arylhydrazines
Taniguchi, T.; Imoto, M.; Takeda, M.; Matsumoto, F.; Nakai, T.; Mihara, M.; Mizuno, T.; Nomoto, A.; Ogawa, A.
Tetrahedron **2016**, *72*, 4132-4140.

(Chapter 3)

(3) Regioselective Radical Arylation of Aromatic Diamines with Arylhydrazines
Taniguchi, T.; Imoto, M.; Takeda, M.; Nakai, T.; Mihara, M.; Mizuno, T.; Nomoto, A.; Ogawa, A.
Synthesis **2017**, *49*, 1623-1631.

(Chapter 4)

(4) Transition-Metal-Free and Oxidant-Free Cross-Coupling of Arylhydrazines with Disulfides: Base-Promoted Synthesis of Unsymmetrical Aryl Sulfides
Taniguchi, T.; Naka, T.; Imoto, M.; Takeda, M.; Nakai, T.; Mihara, M.; Mizuno, T.; Nomoto, A.; Ogawa, A.
J. Org. Chem. **2017**, *82*, 6647-6655.

(Chapter5)

(5) Transition-Metal-Free Synthesis of Unsymmetrical Diaryl Selenides Using Arylhydrazines and Diaryl Diselenides
Taniguchi, T.; Murata, A.; Takeda, M.; Mizuno, T.; Nomoto, A.; Ogawa, A.
Eur. J. Org. Chem. in press.

(Chapter 6)

Other Publication

(1) Synthesis of a Novel Cysteine-Incorporated Anthraquinone Derivative and Its Structural Properties
Nomoto, A.; Taniguchi, T.; Minatobe, Y.; Katao, S.; Kakiuchi, K.; Yano, S.; Ogawa, A.
Molecules **2015**, *20*, 10192-10204.