Studies on the Development of Metal-Free Oxidation Reactions of Amine Derivatives

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Preface

This thesis deals with the studies conducted during April 2016 to March 2019 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 metal-free oxidative methods of benzylamines and arylhydrazines. One important topic of this thesis is the metal-free oxidative coupling of benzylamines and its application to the synthesis of nitrogen-containing heterocycles, bis-amides, and blue dyes. Another topic of this thesis is the development of a metal- and base-free method for the synthesis of aryl iodides from arylhydrazines.

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Contents

Chapter 1

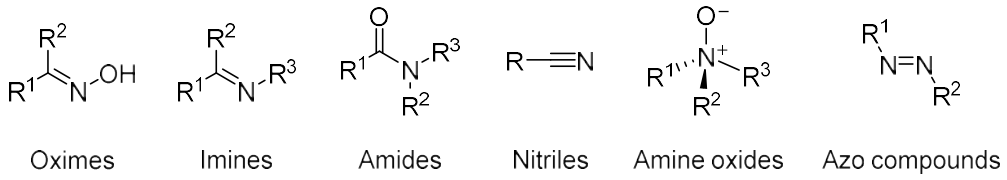
General Introduction

Oxidation reactions play an important role in organic chemistry for the production of key chemicals and intermediates. There is about 30% of total chemical productions from oxidation process, which is the second largest chemical process in the industry.[1] During recent decades, the development of useful oxidation methods has attracted considerable attention. Catalytic oxidations are considered as the selective, efficient, and mild process.[2] In the past century, it was generally accepted that metal catalysis and biocatalysis were the two main classes of efficient oxidation processes. About twenty years ago, this view was significantly altered, and organocatalysis was emerged as the third main approach for catalytic oxidations.[3] However, compared to metal catalysis and biocatalysis, the development of efficient and facile organocatalytic oxidation is still strongly desired.

Nitrogen comprises 78% of the earth's atmosphere by volume, which make it to be an important component of diverse organic compounds. One of the largest of organic nitrogen containing compounds is amines, which can be thought of as derivatives of ammonia. About 3% to 4% of the total worldwide output of ammonia was used in the production of amines.[4] The oxidation of amines provides an efficient approach for the production of important nitrogen-containing compounds, such as oximes, imines, amides, nitriles, amine oxides, and azo compounds (Scheme 1-1).[5] Some of these compounds are key nitrogen-containing building blocks, and display a wide range of biological, environmental, and industrial functions.[6]

In recent decade, Professor Ogawa's research group has developed many efficient

methods for the oxidation of amines. The green oxidation reactions of benzylamines to imines in the presence of transition metal catalysts were intensively investigated.[7] Additionally, the development of novel transition-metal-free oxidation of arylhydrazines was studied. This method was also applied to the arylation of aminoheterocycles and aromatic diamines; and the synthesis of unsymmetrical aryl sulfides and diaryl selenides.[8]



Scheme 1-1. Important Nitrogen-Containing Compounds

In this thesis, the author has developed metal-free oxidative methods of benzylamines and arylhydrazines. Using salicylic acid derivatives as organocatalysts, benzylamines could be oxidized to imines. This amine oxidation could also be applied to the synthesis of nitrogen-containing heterocycles, bis-amides, and blue dyes (Chapter 2–5). Arylhydrazines could be oxidized by iodine to form aryl radical and then combined with iodine radical to afford aryl iodides (Chapter 6).

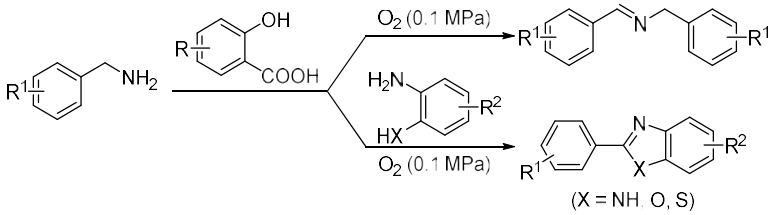
This thesis consists of seven chapters and the outlines of each chapter are summarized as follows.

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

Chapter 2 describes the oxidative coupling of benzylamines to imines using salicylic acid derivatives as organocatalysts under an oxygen atmosphere and its application to the synthesis of nitrogen-containing heterocycles (Scheme 1-2).[9] Traditional methods for the homo-coupling of benzylamines usually require transition metal catalysts;[7] however, contamination of the final products by these metal residues could become a serious problem.

Therefore, the development of metal-free catalysts for imine synthesis is desired.

Salicylic acid derivatives, which are usually used as ligands for metal complexes, were found to be efficient organocatalysts to catalyze the oxidation of benzylamines. In the presence of electron-rich salicylic acid derivatives such as 4,6-dimethoxysalicylic acid and 4,6-dihydroxysalicylic acid, benzylamines were oxidized to give the corresponding imines in high yields. For the perspective of the sustainable chemistry, silica gel supported with 4.7 wt% of 4,6-dihydroxysalicylic acid was prepared as a recyclable catalyst, and oxidized benzylamines to imines four times successfully. Besides, this amine oxidation can also be applied to the synthesis of nitrogen-containing heterocycles such as benzimidazoles, benzoxazoles, and benzothiazoles. Using 4,6-dimethoxysalicylic acid or 4,6-dihydroxysalicylic acid as the organocatalyst, the oxidative cyclization of benzylamines with *o*-substituted aniline derivatives, i.e., *o*-phenylenediamines, *o*-aminophenols, and *o*-aminothiophenols, proceeded well to afford the corresponding *N*-containing heterocycles in good yields. These applications might proceed via the oxidative dehydrogenation of benzylamines ($ArCH_2NH_2$), generating the corresponding imines (ArCH=NH) as key intermediates.

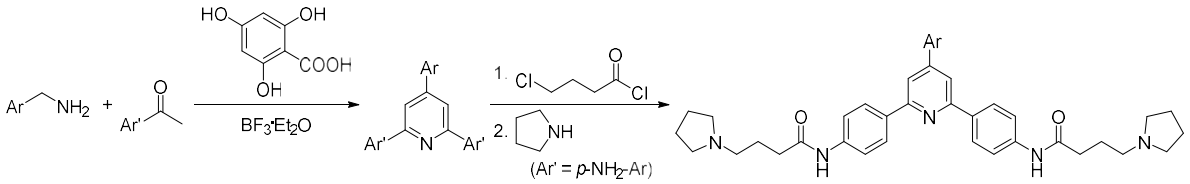


Scheme 1-2. Chapter 2

Chapter 3 describes a metal-free oxidative coupling reaction of benzylamines and acetophenones to synthesize 2,4,6-trisubstituted pyridines in the presence of 4,6-dihydroxysalicylic acid and $BF_3{\cdot}Et_2O$ (Scheme 1-3).[10] Triarylpyridines are important building blocks for many anticancer drugs and excellent ligands for various metals. The traditional three-component condensation reactions for the synthesis of triarylpyridines have been reported

widely, but all of these methods require an additional nitrogen source. Recently, some nitrogen-containing compounds were found to be the substrates for the synthesis of triarylpyridines. However, most of them are not commercially available and the related reactions usually need metal catalysts. Therefore, the author developed salicylic acid derivatives-catalyzed synthesis of 2,4,6-trisubstituted pyridines using benzylamines and acetophenones as substrates under air atmosphere. Benzylamines are considered as efficient substrates and play a dual role of providing an aryl functionality at the 4-position of pyridines as well as being nitrogen source. In the presence of 4,6-dihydroxysalicylic acid and $BF_3{\cdot}Et_2O$, triarylpyridines were synthesized from benzylamines and acetophenones successfully.

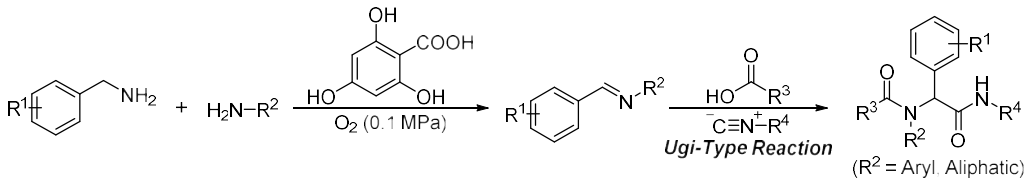
2,4,6-Trisubstituted pyridines are a class of G-quadruplex binding ligands to stabilize G-quadruplex DNA (G4-DNA) and provide an efficient approach to cancer treatment. The reported methods for the synthesis of G-quadruplex binding ligands usually started from the three-component reaction of aldehydes, 4-aminoacetophenones and nitrogen donors; then the isolated triarylpyridines reacted with 4-chlorobutyryl chloride and pyrrolidine stepwise, which needed three or four steps. The author applied the triarylpyridines synthesis method to obtain G-quadruplex binding ligands via two steps. This synthesis procedure started from the oxidative coupling reaction of benzylamines and 4-aminoacetophenones, and then the resulting mixture was allowed to directly react with 4-chlorobutyryl chloride without any purification. After simple work-up, the residue next reacted with pyrrolidine to afford G-quadruplex binding ligands.



Scheme 1-3. Chapter 3

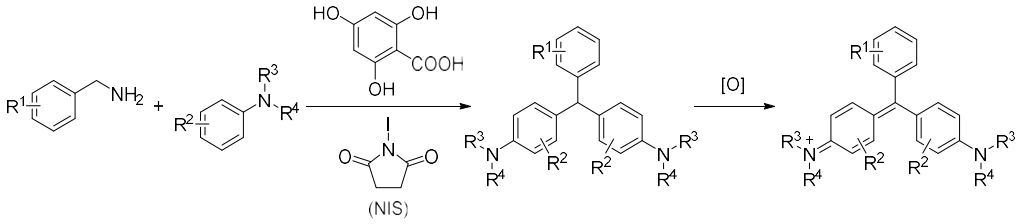
Chapter 4 describes an efficient and metal-free oxidative Ugi reactions for the synthesis of bis-amides promoted by 4,6-dihydroxysalicylic acid as an organocatalyst under oxygen atmosphere (Scheme 1-4).[11] Ugi four-component reactions (U-4CRs) are one of the most widely applied multicomponent reactions and can synthesize many important chemical scaffolds with high levels of atom efficiency. Imines, which are commonly accepted intermediates during the U-4CRs, are generally *in situ* formed from the aldehydes and the primary amines. As described in chapter 2, imines could be formed efficiently via the homo-coupling of benzylamines catalyzed by 4,6-dihydroxysalicylic acid under O_2 atmosphere.[9a] Thus, oxidative Ugi reactions, wherein the imine intermediates are *in situ* formed by the oxidation of amines, are described in this chapter.

Oxidative Ugi reactions are usually performed in the presence of organic oxidants or transition-metal catalysts with O_2, whereas organocatalytic oxidative Ugi reactions are seldom reported. In this study, 4,6-dihydroxysalicylic acid-catalyzed oxidative Ugi reactions under O_2 atmosphere were performed efficiently via homo-coupling of benzylamines and subsequently condensation with isocyanides and carboxylic acids. Besides, the cross-coupling of two different amines also proceeded smoothly under this oxidative reaction condition. Considering all of the reported methods based on homo-coupling of amines or oxidation of heterocyclic secondary amines, the author continued to examine the oxidative Ugi four-component reaction of an isocyanide and a carboxylic acid with the imine *in situ* formed by the cross-coupling of two different amines in the presence of 4,6-dihydroxysalicylic acid as an organocatalyst under O_2 atmosphere, which provided a very rare example of the oxidative Ugi reactions.



Scheme 1-4. Chapter 4

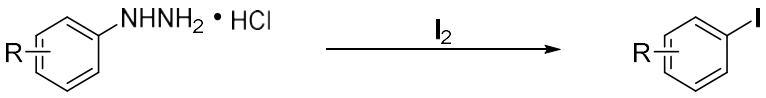
Chapter 5 describes a convenient, novel, and metal-free method for the synthesis of 4,4′-diaminotriarylmethanes (DTMs) (Scheme 1-5).[12] As dye precursors, DTMs can be oxidized to produce malachite green derivatives, which are one of the most important dyes. Although the methods for the synthesis of triarylmethane derivatives have been widely developed, the synthesis procedure from benzylamine substrates has not yet been reported. Therefore, the author developed a one-pot method based on the condensation of benzylamines with *N*,*N*-dimethylaniline derivatives using 4,6-dihydroxysalicylic acid as a catalyst and *N*-iodosuccinimide as a co-oxidant. The present method provides the first reported synthesis of DTMs from benzylamines via oxidative C–N bond cleavage and subsequent double C–C bond formations. The obtained DTMs were easily converted into a series of blue dyes upon treatment with tetrachloro-1,4-benzoquinone (chloranil). The chloroform solutions of these dyes showed green to blue colors. This blue dye synthetic method is advantageous in that it is a metal-free, straightforward process, and does not require the use of toxic heavy metals, corrosive acids, or hazardous reagents.



Scheme 1-5. Chapter 5

Chapter 6 describes a metal- and base-free method for the synthesis of aryl iodides from arylhydrazine hydrochlorides and iodine (Scheme 1-6).[13] Arylhydrazine hydrochlorides are usually used as an arylating agent due to their ability to generate aryl radicals.[8] Aryl iodides are important synthetic building blocks in organic chemistry. The Sandmeyer reaction is a classic method for the synthesis of aryl iodides via the diazotization of aromatic amines, followed by iodination with iodides. However, this method usually requires corrosive nitrous acid and a strong acidic medium for the diazotization step. Therefore, the author reported a facile method for the

synthesis of aryl iodides by an equimolar reaction of arylhydrazine hydrochlorides and I_2 in the absence of any metal catalysts and additives. In the iodination step, arylhydrazines are oxidized by iodine to form arenediazonium salts, which undergo single-electron transfer from iodide anion to give aryl and iodine radicals; subsequent combination of them affords the corresponding aryl iodides.



Scheme 1-6. Chapter 6

Chapter 7 describes the conclusion of this thesis.

This thesis describes that a series of benzylamines and arylhydrazines were oxidized by metal-free methods, and that the organocatalyst-assisted oxidative coupling method of benzylamines could be applied to the synthesis of nitrogen-containing heterocycles (i.e., benzimidazoles, benzoxazoles, benzothiazoles, and triarylpyridines), bis-amides, and blue dyes successfully. These works will open up a new field for eco-friendly oxidation of amines by organocatalysis.

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Chapter 2

Metal-Free Oxidation Coupling of Benzylamines to Imines under an Oxygen Atmosphere Promoted Using Salicylic Acid Derivatives as Organocatalysts and Its Application to Synthesis of *N*-Containing Heterocycles

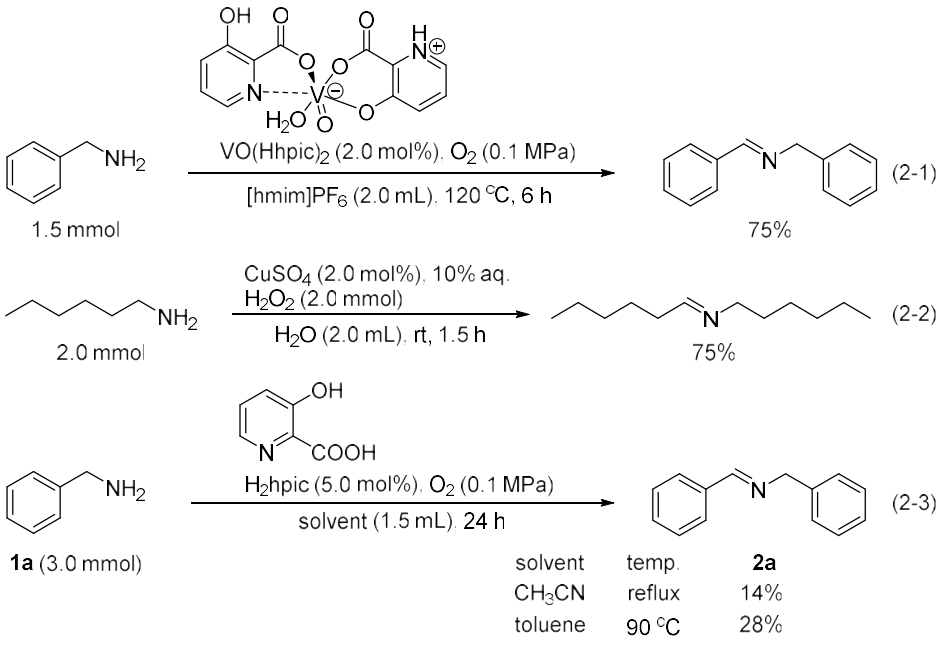
2-1 Introduction

Imines are of great importance for the synthesis of industrial materials and biologically active compounds such as amines, chiral amines, amides, pyrrolines, oxaziridines, hydroxyamines, and nitrones.[1] To synthesize imines, many useful oxidation methods have been developed,[2] which include oxidation of primary or secondary amines and oxidative condensation of amines with alcohols. Typical strategies require transition-metal catalysts including noble metals[3] and non-noble biocompatible metals;[4] however, contamination of the final products by these metal residues becomes a serious problem in the synthesis of medicines and functional materials. From the perspective of green chemistry, chemists have shifted their attention to other, more eco-friendly methods. Metal-free catalysts such as graphene oxide,[5] 4-*tert*-butyl-2-hydroxybenzoquinone (TBHBQ),[6] and azobisisobutyronitrile (AIBN)[7] can oxidize benzylic amines to secondary imines. In biology, copper-containing amine oxidases (CuAOs) have high activity and specificity toward the oxidation of primary amines. Thus, bioinspired catalysts, electrogenerated *ortho*-iminoquinone species,[8] *ortho*-quinone,[9] and other mimicry of monoamine oxidase compounds,[10] were used for this purpose. Visible-light-induced transformation of amines to imines is also an alternative approach, which allows different kinds

of photocatalyses to be investigated.[11] However, most of these metal-free catalysts are of complex structures and high prices. Therefore, the development of more easily available metal-free catalysts for imine synthesis is still desired strongly.

Recently, Ogawa, Marui, and co-workers reported a series of eco-friendly oxidations of alcohols and amines using metal catalysts: for example, the vanadium complex-catalyzed oxidation of benzyl alcohols[12] or benzylamines with atmospheric O_2 in water or ionic liquid[13] and the copper sulfate-catalyzed oxidation of amines with H_2O_2 in water[14] (Scheme 2-1, eqs 2-1 and 2-2, respectively). In the former catalytic oxidation, 3-hydroxypicolinic acid (H_2hpic) or its analogues were used as ligands for oxovanadium complexes. During these studies, the author was surprised to find that some of the ligands such as salicylic acid and its derivatives themselves functioned as organocatalysts and catalyzed amine oxidation (Scheme 2-1, eq 2-3).

Scheme 2-1. Catalytic Oxidation of Amines to Imines



In this chapter, the author describes a convenient, salicylic acid derivative catalyzed oxidation of benzylamines to the corresponding imines under an atmosphere of O_2. Furthermore,

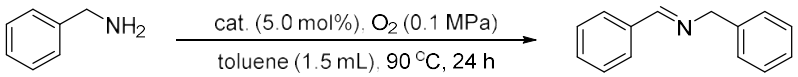
this new metal-free oxidation method can be applied to the synthesis of nitrogen-containing heterocycles such as benzimidazoles, benzoxazoles, and benzothiazoles. Moreover, the recyclability of the organocatalyst has been demonstrated successfully by supporting 4,6-dihydroxysalicylic acid on silica gel.

2-2 Oxidative Coupling of Benzylamines to Imines

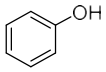
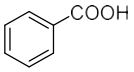
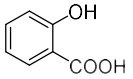
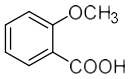
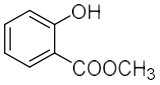
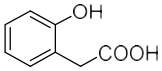
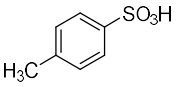
Initially, H_2hpic, which was used as a ligand for the vanadium catalyst in the previous work,[12-14] was used alone (in the absence of metal catalyst) for the oxidation of benzylamine **1a** under an O_2 atmosphere; interestingly, the formation of the desired product **2a** was observed (Scheme 2-1, eq 2-3). Hence, the author next explored the functional subunits of H_2hpic, such as the phenol and benzoic acid groups, and their combinations, by using them as catalysts for the amine oxidation (Table 2-1). Phenol and benzoic acid are ineffective for the transformation (Table 2-1, entries 2 and 3). Surprisingly, salicylic acid is found to have great catalytic activity for the oxidation of benzylamine under O_2, affording *N*-benzylidenebenzylamine **2a** in 80% yield (Table 2-1, entry 4). However, 2-methoxybenzoic acid or methyl 2-hydroxybenzoate is less effective than salicylic acid itself (Table 2-1, entries 5 and 6). Introduction of a methylene group between the carboxylic acid and phenyl groups also reduces the yield of **2a** (Table 2-1, entries 7 and 8). On the other hand, simple Brønsted acids such as *p*-toluenesulfonic acid and acetic acid, which have recently been reported to promote the oxidation of amines,[15] are ineffective (Table 2-1, entries 8 and 9).

To optimize the catalyst for this metal-free oxidation, the amine oxidation was examined using several salicylic acid derivatives (Table 2-2). 4-Substituted salicylic acids demonstrated almost the same reactivity as nonsubstituted salicylic acid after 24 h (Table 2-2, entries 1, 3, and 5). However, at a shorter reaction time (12 h), 4-methoxysalicylic acid **3c** showed higher

Table 2-1. Oxidation of Benzylamine Catalyzed by H_2hpic Analogues



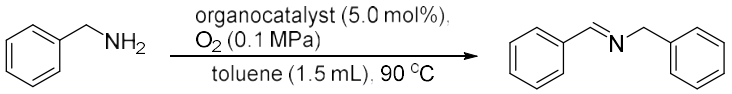
1a (3.0 mmol) **2a**

entry	cat.	yield[a] (%)
1	none	N.R.
2		7
3		32
4		80
5		6
6		11
7		32
8	CH_3COOH	3
9		N.R.

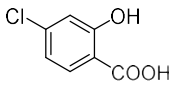
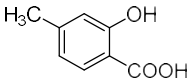
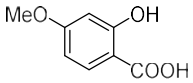
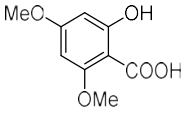
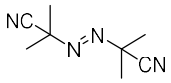
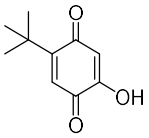
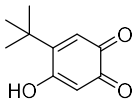
[a]Determined by ^{1}H NMR using an internal standard 1,3,5-trioxane; yield of **2a** is based on the substrate **1a**. N.R.: no reaction.

reactivity than the others (Table 2-2, entries 2, 4, and 6). Further optimization revealed that 4,6-dimethoxysalicylic acid **3d** as a catalyst was the most efficient in this metal-free oxidation, affording the desired product in 95% yield (Table 2-2, entry 9). To compare with other organocatalysts that have been reported by other research groups, the author examined the amine

Table 2-2. Oxidation of Benzylamine Catalyzed by Salicylic Acid Derivatives



1a (3.0 mmol) **2a**

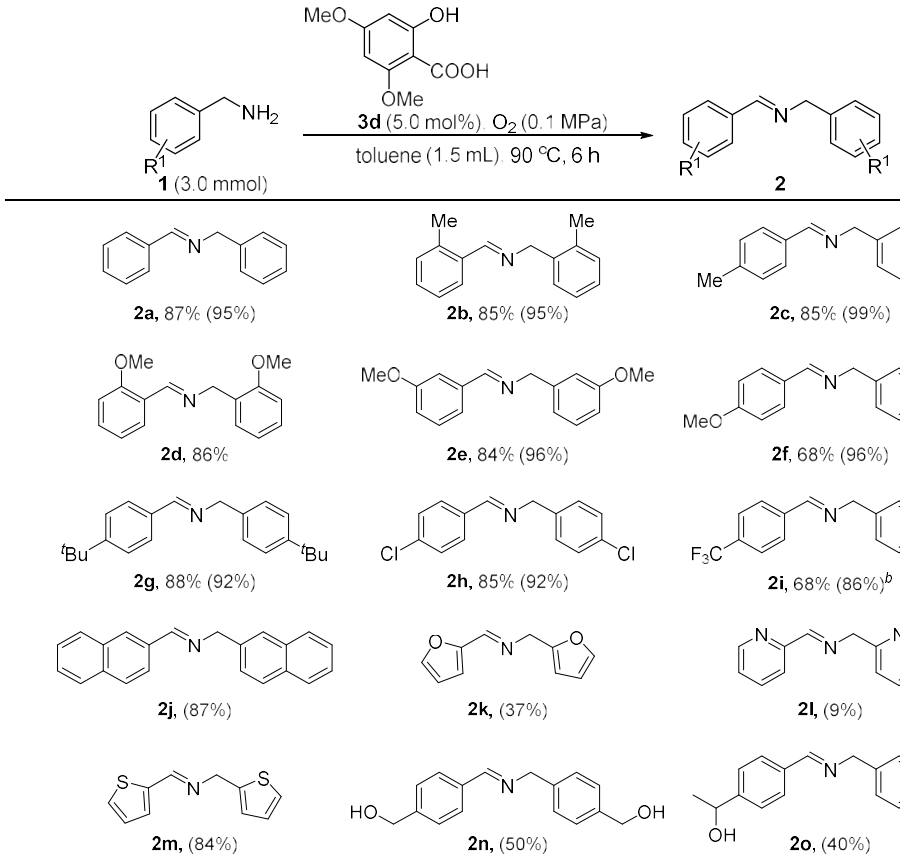
entry	organocatalyst		time (h)	yield[a] (%)
1		**3a**	24	81
2		**3a**	12	14
3		**3b**	24	74
4		**3b**	12	15
5		**3c**	24	90
6		**3c**	12	81
7		**3c**	8	43
8		**3d**	12	88
9		**3d**	6	95(87)
10		**3d**	2	65
11		**AIBN**	6	33
12		**TBHBQ**	6	93
13		***ortho*-Q**	6	84

[a]Determined by ^{1}H NMR using an internal standard 1,3,5-trioxane (isolated yield); yield of **2a** is based on the substrate **1a**.

oxidation using AIBN,[7] TBHBQ,[6] and *ortho*-quinone (*ortho*-Q)[9] under the optimized reaction conditions. TBHBQ and *ortho*-quinone indicated similar catalytic ability with the catalyst **3d**

(Table 2-2, entries 12 and 13), whereas a lower yield of the corresponding imine was obtained in the case of AIBN as the catalyst (Table 2-2, entry 11).

Table 2-3. Oxidation of Benzylamine Derivatives[a]



[a]Yield of isolated product is based on **1** (^{1}H NMR yield using an internal standard 1,3,5-trioxane), [b]Reaction time: 8 h.

Using the optimized reaction conditions (Table 2-2, entry 9), the oxidation of different benzylamine substrates was examined (Table 2-3). Benzylamine derivatives with electron-donating [**1c** (R = *p*-Me), **1f** (R = *p*-OMe), and **1g** (R = *p*-^{t}Bu)] or electron-withdrawing [**1e** (R = *m*-OMe), **1h** (R = *p*-Cl), and **1i** (R = *p*-CF_3)] groups at the *para*- or *meta*-position can be oxidized to the corresponding imines in high yields. It is noteworthy that sterically hindered *ortho*-substituted benzylic amines **1b** (R = *o*-Me) and **1d** (R = *o*-OMe) undergo oxidative coupling efficiently. Besides, similar oxidation of activated primary amines such as 1-naphthylmethylamine **1j**, furfurylamine **1k**, 2-pyridinemethylamine **1l**, and

2-thiophenemethyamine **1m** was examined. 1-Naphthylmethylamine and 2-thiophenemethyamine can be transformed into the corresponding imines in good yields. By contrast, the oxidation of secondary amines, aliphatic amines, and 4-hydroxybenzylamine was difficult under these conditions. On the other hand, benzylamine featuring primary or secondary alcohol underwent oxidative coupling to afford the corresponding imines **2n** and **2o** in moderate yields, respectively.

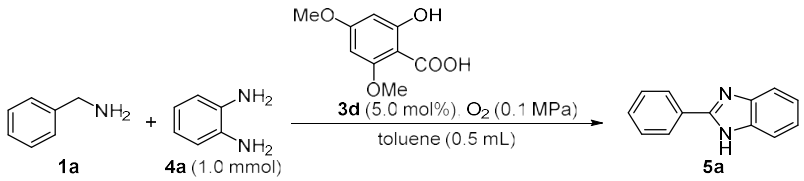
2-3 Synthesis of Benzimidazoles Using 4,6-Dimethoxysalicylic Acid

The successful synthesis of imine derivatives prompted the author to apply this method to the synthesis of benzimidazole derivatives. The benzimidazole skeleton is an important structural framework found in a large variety of naturally occurring compounds and pharmaceutical agents. Conventionally, numerous methods have been reported for the construction of benzimidazoles. For example, several efficient methods for the synthesis of benzimidazoles from alcohols,[16] benzaldehydes,[17] imines,[18] β-diketones,[19] and carboxylic acids[20] as well as intermolecular condensation of 1,2,4-oxadiazol-5(4*H*)-ones[21] have recently been developed. Besides, examples of benzimidazole synthesis through the cyclization of 1,2-diaminobenzene derivatives with benzylamines under metal[22] or metal-free[11d, 23] oxidation conditions have also been reported recently. Owing to the importance of developing a new metal-free oxidative system for the synthesis of benzimidazoles, the author applied this oxidation protocol to the synthesis of benzimidazole derivatives (Table 2-4).

When the reaction of **1a** with 1,2-diaminobenzene **4a** (1 equiv) was performed at 90 °C in the presence of salicylic acid derivative **3d** as the organocatalyst, the desired product **5a** was obtained successfully in 83% yield (Table 2-4, entry 1). Apparently, the use of 1.5 equiv of **1a** at a higher temperature can slightly improve the yield of **5a** (Table 2-4, entries 2 and 3). However, a shorter or longer reaction time resulted in a decrease in the yield of **5a** (Table 2-4, entries 4 and 5),

and this oxidation reaction could not proceed well at 60 °C (Table 2-4, entry 6).

Table 2-4. Optimization of Conditions for the Oxidative Cyclization of Benzylamine to Benzimidazole[a]



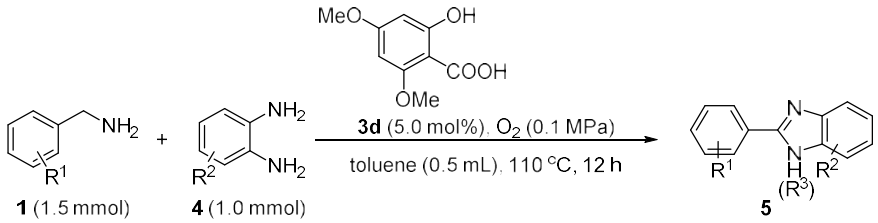
1a 4a (1.0 mmol) 5a

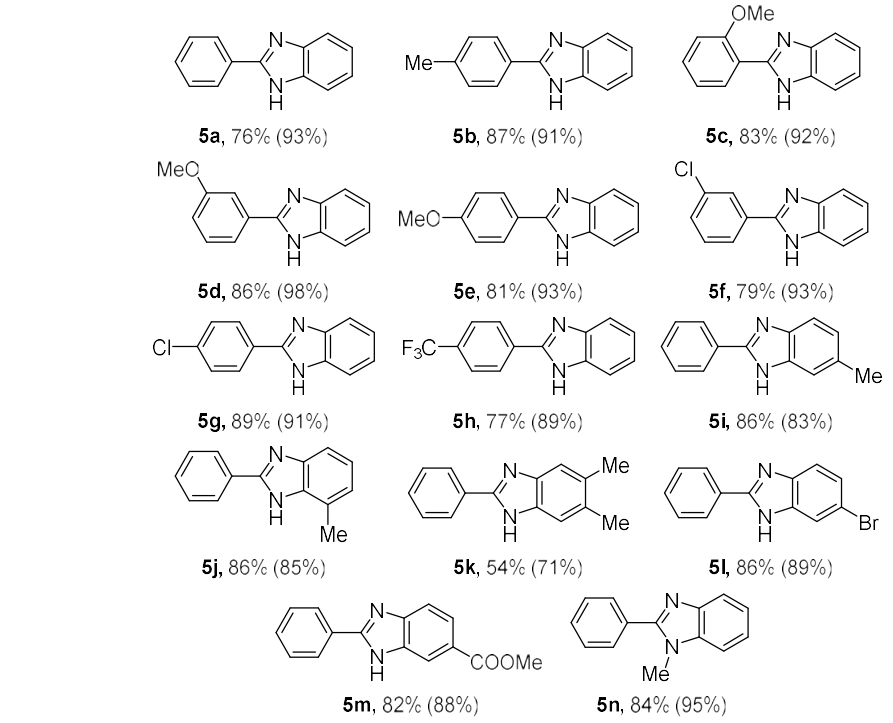
entry	equiv. of **1a**	temp. (°C)	time (h)	yield[a] (%)
1	1	90	12	83
2	1.5	90	12	87
3	1.5	110	12	(93)
4	1.5	110	6	75
5	1.5	110	24	86
6	1.5	60	12	5

[a]Determined by ^{1}H NMR using an internal standard 1,3,5-trioxane (isolated yield); Yield of **5a** is based on substrate **4a**.

Under the optimized conditions (Table 2-4, entry 3), the salicylic acid derivative-catalyzed cyclization of several benzylamine derivatives **1** with 1,2-diaminobenzene **4a** was demonstrated and the corresponding benzimidazoles **5** were obtained in high yields (Table 2-5, **5a**–**h**). Many substituents on the phenyl group of benzylamine, such as *p*-Me, *o*-MeO, *m*-MeO, *p*-MeO, *m*-Cl, *p*-Cl, and *p*-CF_3, were tolerant to the oxidative cyclization. Moreover, several 1,2-diaminobenzene derivatives **4** were also screened. Electron-donating or electron-withdrawing groups on the aromatic ring of 1,2-diaminobenzenes were well-tolerated under these cyclization reaction conditions, and the desired benzimidazoles **5** were obtained in good yields (Table 2-5, **5i**–**n**).

Table 2-5. Synthesis of Benzimidazoles from Various Benzylamine and 1,2-Diaminobenzene Derivatives[a]



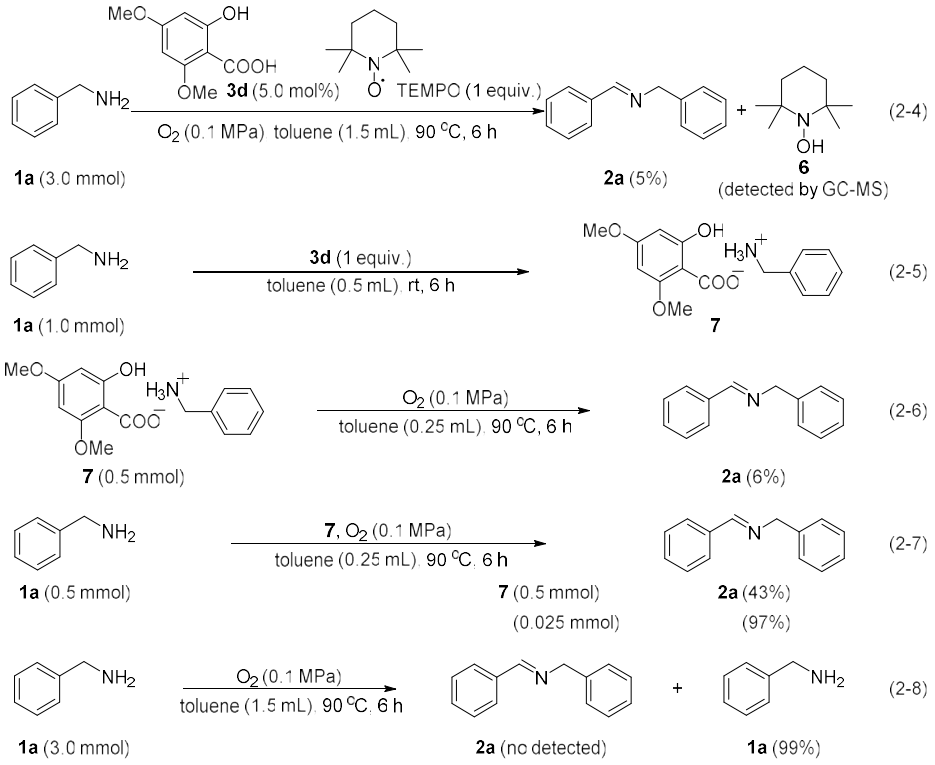


[a]Yield of isolated product is based on **4** (^{1}H NMR yield was determined using an internal standard 1,3,5-trioxane).

To clarify the mechanism of this oxidation reaction, the author performed several control experiments as shown in Scheme 2-2. At first, as the author suspected that the oxidation of benzylamine proceeds following a radical pathway, the radical scavenger TEMPO (2,2,6,6-tetramethylpiperidine 1-oxyl free radical) was added to the reaction mixture under the standard conditions (Scheme 2-2, eq 2-4). As a result, the yield of the desired imine **2a** dramatically decreased to 5%. Moreover, the formation of **6** was confirmed using gas chromatography-mass spectrometry (GC-MS) (*m*/*z* = 157 corresponding to **6**). These results

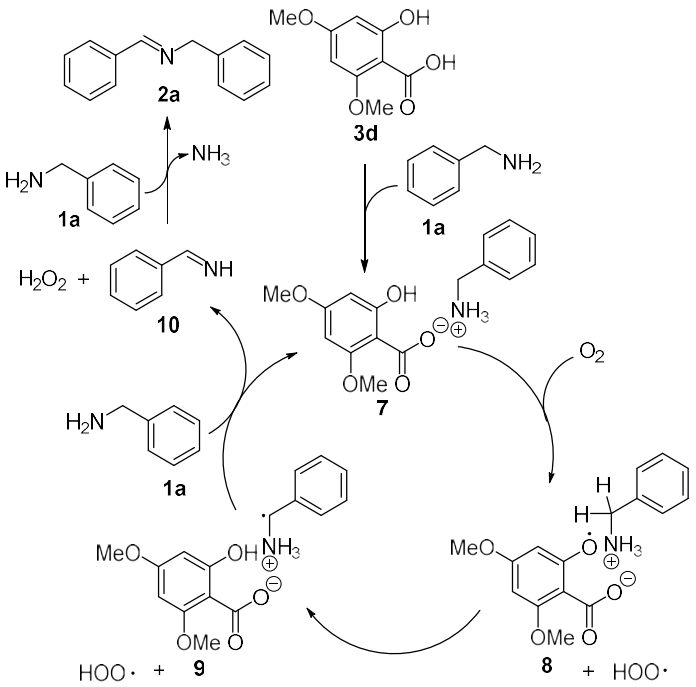
strongly suggest that the oxidation involves radical species. The findings in Table 2-1 and Table 2-2 clearly indicate that the salicylic acid structure is important for this oxidation. To further clarify the role of the salicylic acid derivatives, compound **7** was prepared from benzylamine **1a** and salicylic acid derivative **3d** (Scheme 2-2, eq 2-5) and then subjected to the optimized oxidation conditions. However, the imine product **2a** was generated in only 6% yield (Scheme 2-2, eq 2-6). Adding benzylamine **1a** (1 equiv) improved the yield to 43% (Scheme 2-2, eq 2-7), suggesting that the oxidation requires free amine **1a**. Furthermore, the catalytic oxidation of **1a** using **7** as a catalyst successfully afforded **2a** in 97% yield (Scheme 2-2, eq 2-7). In the absence of salicylic acid derivative **3d**, the oxidative coupling of benzylamine to imine could not proceed at all (Scheme 2-2, eq 2-8).

Scheme 2-2. Control Experiments



On the basis of these results, a possible catalytic pathway is proposed in Scheme 2-3. First, benzylamine **1a** and salicylic acid derivative **3d** form the corresponding salt **7**, which may be oxidized by O_2 to generate phenoxy radical **8** and HOO•. The hydrogen abstraction from benzylamine leads to the formation of **9**. Further hydrogen abstraction from the amino group by HOO• affords phenylmethanimine **10** with regeneration of the catalyst **7**; then intermediate **10** undergoes amino group exchange reaction with benzylamine **1a** to afford **2a**.

Scheme 2-3. A Possible Pathway for the Catalytic Oxidation of Benzylamine

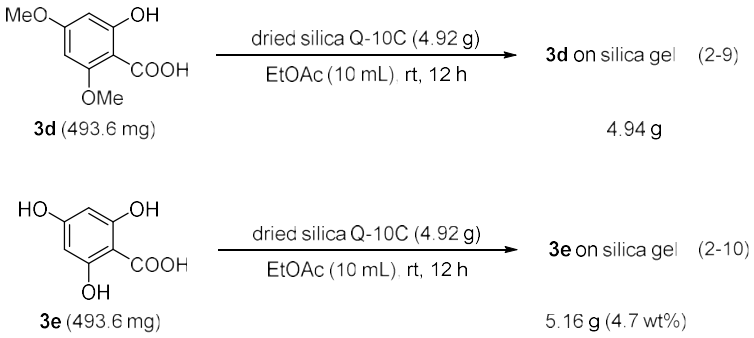


2-4 Recycling Study

In view of green chemistry, recyclability of the catalyst is of great importance. Hence, the author examined the preparation of silica gel-supported salicylic acid as a recyclable organocatalyst to develop the recyclable amine oxidation method (Scheme 2-4). To obtain the

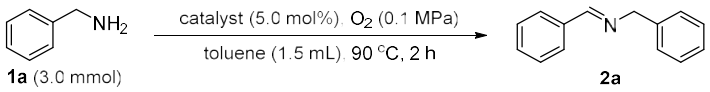
silica gel-supported 4,6-dimethoxysalicylic acid **3d** catalyst, silica gel was treated with **3d**. However, **3d** could not be supported efficiently on silica gel, and during the washing process of the silica gel with ethyl acetate, most of **3d** was removed from the silica gel (Scheme 2-4, eq 2-9). Considering the affinity with silica gel, 4,6-dihydroxysalicylic acid **3e**[24] was chosen as the organocatalyst. As we expected, silica gel supported with 4.7 wt % of **3e** (4.7 wt % **3e** on silica gel) was obtained successfully (Scheme 2-4, eq 2-10). Then, the silica gel-supported catalyst (4.7 wt % **3e** on silica gel) was used for the oxidation of benzylamine **1a** to imine **2a** (Table 2-6). Compared with 4,6-dihydroxysalicylic acid **3e** itself, the silica gel-supported catalyst (4.7 wt % **3e** on silica gel) showed a similar catalytic activity (Table 2-6, entries 1 and 2). On the other hand, the silica gel itself did not indicate any catalytic activity for the imine oxidation (Table 2-6, entry 3).

Scheme 2-4. Preparation of Silica Gel-Supported Salicylic Acid Catalyst

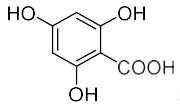


Then, recyclability of the silica gel-supported catalyst (4.7 wt % **3e** on the silica gel) was examined (Table 2-7). The oxidation of benzylamine **1a** was conducted using silica gel-supported **3e**, and the corresponding imine **2a** was obtained in 84% yield (first run). The resulting silica gel-supported **3e** was recovered by filtration, and reused for the second oxidation. The yield of **2a** was 95% (second run). Similarly, third and fourth oxidations were conducted, and the yields of **2a** were 64% (third run) and 53% (fourth run), respectively. To confirm the reproducibility of this

Table 2-6. Oxidation of Benzylamine by Silica Gel-Supported Catalyst

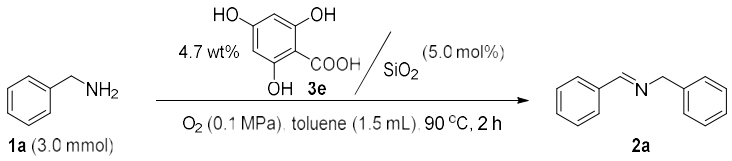


1a (3.0 mmol) **2a**

entry	catalyst	yield[a] (%)
1	 **3e**	86
2	4.7 wt% **3e** on silica gel	84
3	silica gel (500 mg)	N.R.

[a]Determined by ^{1}H NMR using an internal standard 1,3,5-trioxane; Yield of **2a** is based on the substrate **1a**; N.R.: no reaction.

Table 2-7. Recycling Study[a]



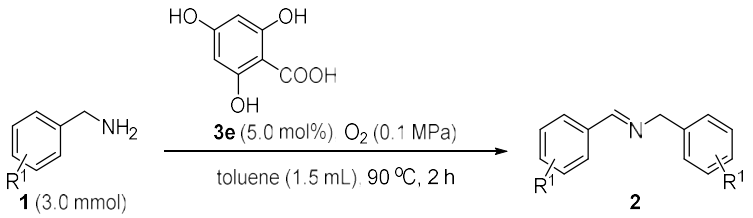
1a (3.0 mmol) **2a**

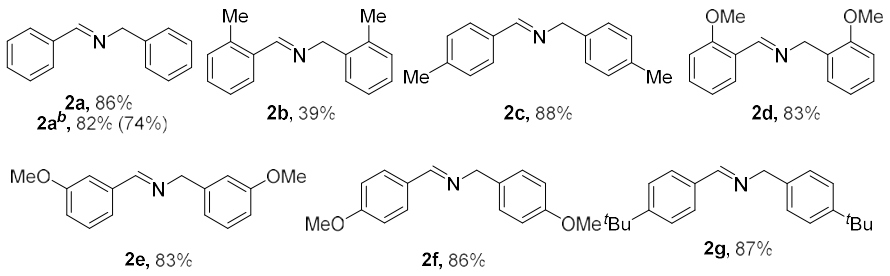
run	1st	2nd	3rd	4th
yield of **2a** (%, I)	84	95	64	53
yield of **2a** (%, II)	85	95	66	-

[a]Yield of **2a** is based on the substrate **1a**, and determined by ^{1}H NMR using an internal standard 1,3,5-trioxane.

recycling study, the same oxidation and recycling were attempted; similar results were obtained, as indicated in the second row of Table 2-7. In the second run, imine **2a** was obtained in a higher yield than in the first run. This is probably because some of **1a** and/or **2a** was absorbed by the silica gel in the first run and could not be washed away from the catalyst. After the reaction, the surface of the silica gel-supported catalyst was covered with an unidentified black compound that was hard to clean up. As a result, the catalyst was deactivated to some degree, and the yields of the third and fourth runs gradually decreased.

Table 2-8. Oxidation of Benzylamine Derivatives Using 4,6-Dihydroxysalicylic Acid as Organocatalyst[a]





[a]Determined by ^{1}H NMR using an internal standard 1,3,5-trioxane (isolated yield); Yield of **2** is based on the substrate **1**. [b]Gram scale: reaction was conducted on 10 mmol of **1a** in 3 mL of toluene using 50 mL two-neck flask.

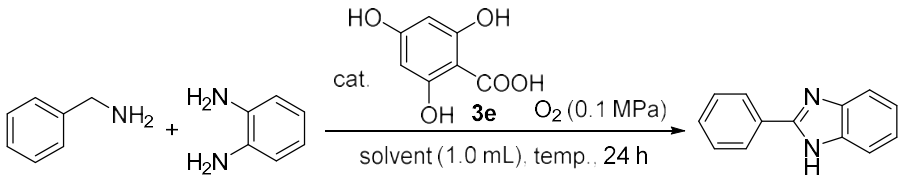
As can be seen from the recycling experiments (Table 2-7), 4,6-dihydroxysalicylic acid **3e** is also an effective catalyst for the oxidative coupling of benzylamines to imines. Thus, the author further investigates the oxidative coupling of benzylamines using 4,6-dihydroxysalicylic acid **3e** as the catalyst (Table 2-8). Compared with 4,6-dimethoxysalicylic acid **3d**, 4,6-dihydroxysalicylic acid **3e** indicated further excellent catalytic activity and induced the oxidative coupling in a shorter time (2 h). Although the reason why 4,6-dihydroxysalicylic acid **3e** exhibits a higher catalytic activity compared with 4,6-dimethoxysalicylic acid **3d** is not clear, a better electron-donating ability of the hydroxyl group [Hammett's σ value = –0.37 (*p*-OH)] compared with that of the methoxyl group [σ value = –0.27 (*p*-OMe)] might contribute to the efficiency in the present oxidation by increasing the electron density of the organocatalyst. By using the catalyst **3e**, the gram scale synthesis of imine **2a** was examined starting from 10 mmol of **1a** (1.07 g), and 0.72 g (3.7 mmol, 74% isolated yield) of **2a** was obtained successfully, as

shown in Table 2-8.

2-5 Synthesis of *N*-Heterocycles Using 4,6-Dihydroxysalicylic Acid

Compared with 4,6-dimethoxysalicylic acid **3d**, 4,6-dihydroxysalicylic acid **3e** has a higher oxidation ability and is less expensive. Therefore, the oxidative coupling between benzylamines **1** and *o*-phenylenediamines **4** was further examined under an oxygen atmosphere in the presence of 4,6-dihydroxysalicylic acid **3e** (10 mol%) as an organocatalyst.

Table 2-9. Optimization of Benzimidazole Synthesis



1a (4.5 mmol) **4a** (3.0 mmol) **5a**

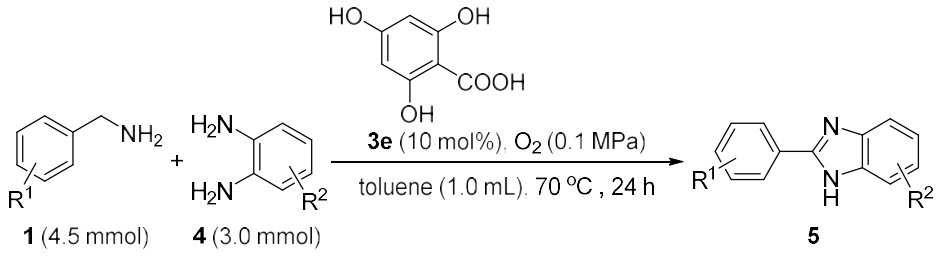
entry	solvent	cat. (mol%)	temp. (ºC)	yield[a] (%)
1	none	10	r.t.	N.D.
2	none	10	50	15
3	none	10	70	75
4	none	5	70	66
5	none	15	70	69
6	toluene	10	70	94 (83)
7	toluene	none	70	trace
8	toluene	10	50	61
9[b]	toluene	10	70	66

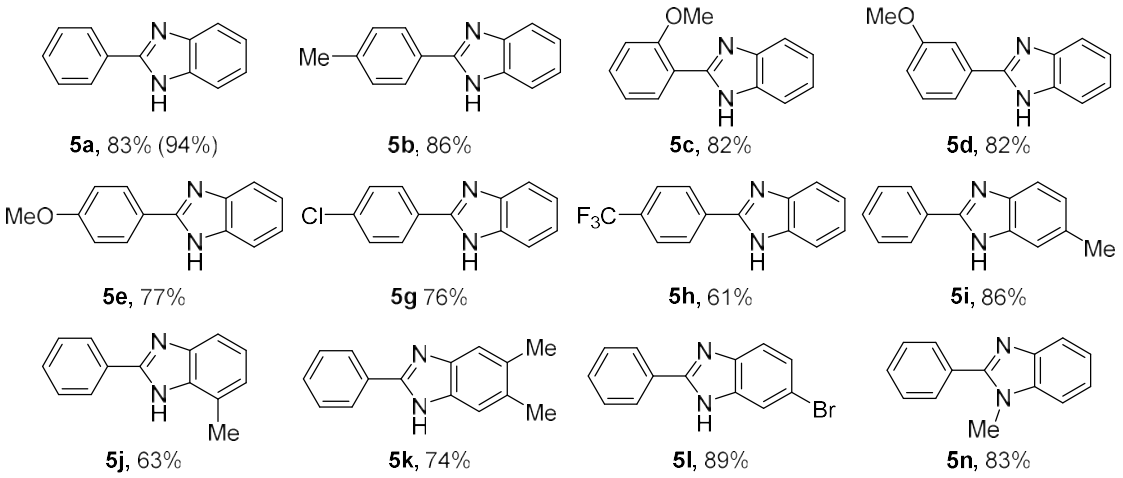
[a]Determined by ^{1}H NMR using 1,3,5-trioxane as the internal standard (isolated yield); yield of **5a** based on substrate **4a**. [b]Reaction time: 18 h.

When this coupling reaction was conducted under neat conditions at room temperature, benzimidazole **5a** was not formed (Table 2-9, entry 1). Fortunately, however, upon increasing the reaction temperature to 50 and 70 °C, the desired product **5a** was obtained in 15 and 75% yields,

respectively (Table 2-9, entries 2 and 3). Next, the amount of catalyst was examined, and 10 mol% of 4,6-dihydroxysalicylic acid **3e** was found to be suitable (Table 2-9, entries 3–5). When the reaction was conducted in toluene, **5a** was obtained in an improved yield of 94% (Table 2-9, entry 6). In the absence of 4,6-dihydroxysalicylic acid **3e** as the catalyst, the coupling reaction did not proceed (Table 2-9, entry 7). Lower reaction temperatures or shorter reaction times hindered the formation of **5a** (Table 2-9, entries 8 and 9).

Table 2-10. Substrate Scope of Benzimidazole Synthesis[a]





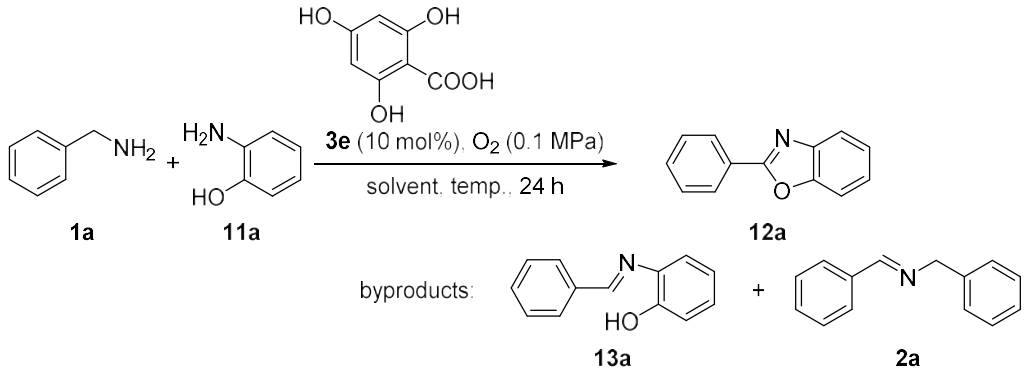
[a]Yield of the isolated product based on **4** (^{1}H NMR yield using 1,3,5-trioxane as the internal standard).

Under the optimized conditions (Table 2-9, entry 6), the scope of the 4,6-dihydroxysalicylic acid-catalyzed oxidative coupling was examined with a range of benzylamines and *o*-phenylenediamines (Table 2-10). *p*-, *m*-, and *o*-Methoxy-substituted benzylamines oxidatively coupled with **2a** to afford benzimidazoles in 77–82% yields (Table

2-10, **5c**–**e**). Functional groups at the *para*-position of benzylamines, including methyl, chloro, and trifluoromethyl groups, were tolerated in the oxidative coupling reaction, producing benzimidazoles in 61–86% yields (Table 2-10, **5b**, **5g**, and **5h**). Moreover, several *o*-phenylenediamine derivatives were employed as substrates with benzylamine **1a**. Under the developed conditions, *o*-phenylenediamines bearing electron-donating or electron-withdrawing groups on the aromatic ring could be oxidized to the desired benzimidazoles **5** in 63–89% yields (Table 2-10, **5i**–**5l, 5n**).

Next, the author examined the benzoxazole synthesis using 4,6-dihydroxysalicylic acid-catalyzed oxidative coupling of benzylamine **1a** and *o*-aminophenol **11a** under an oxygen atmosphere. Table 2-11 shows the results of the optimization of the reaction conditions for the benzoxazole synthesis. Among the tested solvents, nonpolar and aprotic solvents such as toluene seemed to be suitable for the oxidative coupling (Table 2-11, entries 1–3), and elevated temperatures (90 °C) led to the formation of the desired benzoxazole **12a** in 17% yield along with uncyclized product **13a** and the homo-coupling product **2a** of benzylamine **1a** (Table 2-11, entry 4). Dilution resulted in an increase in the yield of **13a**, probably because oxygen easily dissolved in the solution (Table 2-11, entry 5). Increasing the temperature to 110 °C afforded 34% of **12a** along with 35% of **13a** (Table 2-11, entry 6). Decreasing the amount of **1a** (4 mmol) led to an increase in the yield of **12a** (45%) (Table 2-11, entry 8). When the reaction was conducted at 140 °C using *p*-xylene, **12a** was formed in 50% yield; however, the material balance was lower unfortunately (Table 2-11, entry 10). Overall, in the synthesis of benzoxazoles, the oxidative coupling between benzylamine **1a** and the amino group of *o*-aminophenol **11a** proceeded efficiently; however, the decreased nucleophilicity of the phenolic -OH group might contribute to the increased difficulty of the cyclization process.

Table 2-11. Optimization of Benzoxazole Synthesis



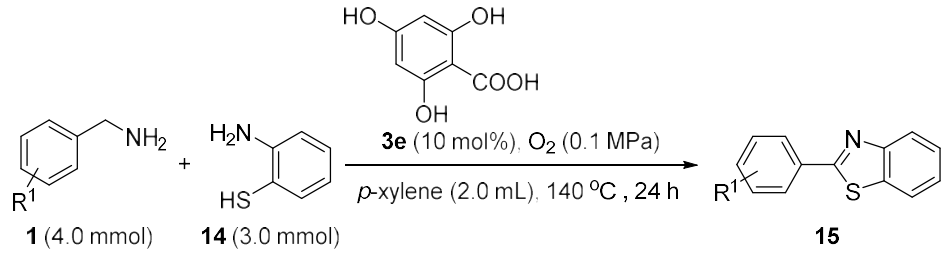
entry	solvent (mL)	**1a**/**11a** (mmol/mmol)	temp. (ºC)	yield[a] of **12a**/**13a**/**2a** (%)
1	toluene (1)	4.5/3.0	70	3/39/15
2	EtOAc (1)	4.5/3.0	70	1/21/2
3	CH_3CN (1)	4.5/3.0	70	4/14/1
4	toluene (1)	4.5/3.0	90	17/36/3
5	toluene (2)	4.5/3.0	90	13/61/7
6	toluene (2)	4.5/3.0	110	34/35/2
7	toluene (3)	4.5/3.0	110	24/56/2
8	toluene (2)	4.0/3.0	110	45/36/1
9	*p*-xylene (2)	4.5/3.0	140	44/1/1
10	*p*-xylene (2)	4.0/3.0	140	50/0/6

[a]Determined by ^{1}H NMR using 1,3,5-trioxane as the internal standard; yield of **12a**/**13a**/**2a** based on substrate **11a**.

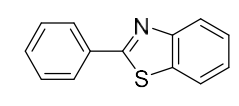
Since the nucleophilicity of -SH is much higher than that of -OH, the oxidative coupling between benzylamine **1a** and *o*-aminothiophenol **14a** was expected to proceed via nucleophilic cyclization to afford benzothiazole **15a**. Indeed, the reaction of **1a** (4 mmol) with **14a** (3 mmol) in the presence of 4,6-dihydroxysalicylic acid (10 mol%) in *p*-xylene (2 mL) under an O_2 atmosphere (0.1 MPa) at 140 °C for 24 h successfully afforded benzothiazole **15a** in 79% yield (Table 2-12, **15a**). In this reaction, the uncyclized product (PhCH=N-C_6H_4-SH-*o*, **16a**) was not obtained. The benzothiazole synthesis could be applied to a range of benzylamines (Table 2-12). For example, *p*- and *o*-methyl-substituted benzylamines underwent oxidative coupling to give the corresponding benzothiazoles in 83 and 80% yields, respectively (Table 2-12, **15b** and **15c**). *p*-,

m-, and *o*-Methoxy-substituted benzylamines could oxidatively couple with **14a** to afford the desired benzothiazoles in 78–88% yields (Table 2-12, **15d**–**15f**). Functional groups such as *p*-Cl, *m*-Cl, and *p*-CF_3 were tolerated in this oxidative coupling reaction, and lead to the formation of the desired benzothiazoles in 66–85% yields (Table 2-12, **15g**–**15i**). Moreover, *p*-*t*-butylbenzylamine and 1-naphthylmethylamine could be oxidized to the desired benzothiazoles in 87% and 72% yields, respectively (Table 2-12, **15j** and **15k**).

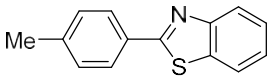
Table 2-12. Benzothiazole Synthesis[a]



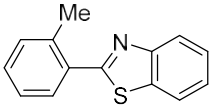
1 (4.0 mmol) **14** (3.0 mmol) **15**



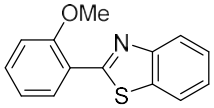
15a, 79% (91%)



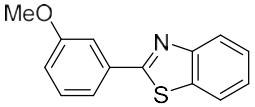
15b, 83% (97%)



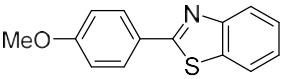
15c, 80% (99%)



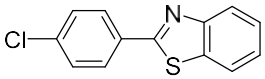
15d, 85% (71%)



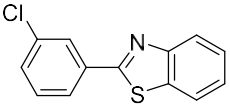
15e, 78% (77%)



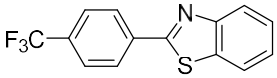
15f 88% (79%)



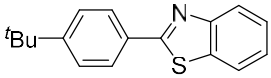
15g, 66% (87%)



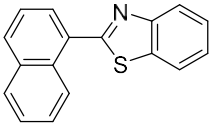
15h, 85% (68%)



15i, 77% (81%)



15j, 87% (71%)



15k, 72% (82%)

[a]Yield of isolated product based on **14**; ^{1}H NMR yield determined using 1,3,5-trioxane as internal standard provided in parenthesis.

2-6 Conclusion

In summary, the author has explored a novel metal-free oxidation method to synthesize imines and nitrogen-containing heterocycles from benzylamine derivatives. In this oxidative

transformation, the products can be obtained under an atmosphere of oxygen in good to high yields by using salicylic acid derivatives as organocatalysts. Furthermore, the silica gel-supported catalyst realized the oxidative coupling and could attain the recyclability of the catalyst. This oxidation system is cheap, efficient, and eco-friendly and can be easily operated. This work is expected to inspire other researchers to develop the metal-free oxidation methods.

2-7 Experimental Section

General Comment

Unless otherwise stated, all benzylamine derivatives, analogues of H_2hpic, salicylic acid derivatives, and silica Q-10C (pore volume = 0.8 cm^3/g; size = 0.85-1.76 mm) were obtained from commercial supplies. All solvents were distilled and degassed with nitrogen before use. ^{1}H NMR spectra were recorded on a JEOL JNM-ECS400 (400 MHz) FT NMR system or a JEOL JNM-ECX400 (400 MHz) FT NMR system in $CDCl_3$ and dimethyl sulfoxide (DMSO)-d_6 with Me_4Si as the internal standard. $^{13}C\{^1H\}$ NMR spectra were recorded on a JEOL JNM-ECX400 (100 MHz) FT NMR system or a JEOL JNM-ECS400 (100 MHz) FT NMR system in $CDCl_3$ and DMSO-d_6.

General Procedure for the Synthesis of Imine Derivatives (2).

Benzylamine derivatives **1** (3.0 mmol), 4,6-dimethoxysalicylic acid **3d** (5.0 mol %), and distilled toluene (1.5 mL) were added into a two-neck flask, the reaction vessel was connected to an O_2 balloon at room temperature, and the mixture was stirred at 90 °C under an O_2 atmosphere for 6 h. After the reaction was complete, the resulting mixture was transferred into a round-bottom flask using ethyl acetate and concentrated under reduced pressure. The residue was purified using gel permeation chromatography (eluent: chloroform) to give the product **2**.

N-(Benzylidene)benzylamine(2a).[25] yellow oil, 254.5 mg, 87% (isolated yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.34 (s, 1H), 7.79-7.71 (m, 2H), 7.42-7.19 (m, 8H), 4.79 (s, 2H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 161.8, 139.2, 136.0, 130.6, 128.5, 128.4, 128.2, 127.9, 126.9, 64.9.

N-(o-Methylbenzylidene)-o-methylbenzylamine (2b).[25] yellow oil, 284 mg, 85% (isolated yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.64 (s, 1H), 7.91 (d, J = 7.79 Hz, 1H), 7.32-7.10 (m, 7H), 4.80 (s, 2H), 2.48 (s, 3H), 2.37 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 160.4, 137.6, 137.5, 136.0, 134.1, 130.7, 130.1, 130.0, 128.2, 127.6, 126.9, 126.1, 125.9, 63.2, 19.3, 19.2.

N-(p-Methylbenzylidene)-p-methylbenzylamine (2c).[23b] white solid, 284 mg, 85% (isolated yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.31 (s, 1H), 7.65 (d, J = 7.92 Hz, 2H), 7.20 (t, J = 7.52 Hz, 4H), 7.13 (d, J = 8.31 Hz, 2H), 4.75 (s, 2H), 2.36 (s, 3H), 2.32 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 161.6, 140.9, 136.4, 136.3, 133.5, 129.2, 129.1, 128.1, 127.9, 64.7, 21.4, 21.0.

N-(o-Methoxybenzylidene)-o-methoxybenzylamine (2d).[23b] yellow oil, 329 mg, 86% (isolated yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.84 (s, 1H), 8.03 (dd, J = 6.80, 1.81 Hz, 1H), 7.38-7.26 (m, 3H), 7.00-6.81 (m, 4H), 4.82 (s, 2H), 3.81 (s, 3H), 3.80 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 158.6, 158.2, 156.9, 131.6, 128.9, 128.0, 127.8, 127.3, 124.7, 120.6, 120.3, 110.8, 110.0, 59.5, 55.3, 55.2.

N-(m-Methoxybenzylidene)-m-methoxybenzylamine (2e).[26] yellow oil, 321 mg, 84% (isolated yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.33 (s, 1H), 7.39-7.38 (m, 1H), 7.33-7.22 (m, 3H), 6.99-6.86 (m, 3H), 6.79 (dd, J = 8.0, 2.5 Hz, 1H), 4.78 (s, 2H), 3.81 (s, 3H), 3.78 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 161.9, 159.8, 159.7, 140.7, 137.5, 129.5, 129.4, 121.5, 120.2, 117.5, 113.5, 112.3, 111.5, 64.8, 55.3, 55.1.

N-(p-Methoxybenzylidene)-p-methoxybenzylamine (2f).[23b] yellow oil, 260 mg, 68% (isolated yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.24 (s, 1H), 7.68 (d, J = 9.06 Hz, 2H), 7.22 (d, J = 8.61

Hz, 2H), 6.86 (dd, *J* = 12.23, 8.61 Hz, 4H), 4.68 (s, 2H), 3.75 (s, 3H), 3.73 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 161.5, 160.7, 158.4, 131.5, 129.6, 128.9, 113.8, 113.7, 64.2, 55.1, 55.0.

N-(p-tert-Butylbenzylidene)-p-tert-butylbenzylamine (2g).[26] white solid, 405 mg, 88% (isolated yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.35 (s, 1H), 7.71 (d, *J* = 8.70 Hz, 2H), 7.42 (d, *J* = 8.70 Hz, 2H), 7.35 (d, *J* = 8.24 Hz, 2H), 7.25 (d, *J* = 8.24 Hz, 2H), 4.77 (s, 2H), 1.32 (s, 9H), 1.30 (s, 9H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 161.6, 154.10, 149.6, 136.4, 133.5, 128.0, 127.6, 125.4, 125.3, 64.7, 34.8, 34.4, 31.3, 31.2.

N-(p-Chlorobenzylidene)-p-chlorobenzylamine (2h).[23b] white solid, 335 mg, 85% (isolated yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.29 (s, 1H), 7.68 (d, *J* = 8.61 Hz, 2H), 7.36 (d, *J* = 8.61 Hz, 2H), 7.29 (d, *J* = 9.06 Hz, 2H), 7.23 (d, *J* = 9.06 Hz, 2H), 4.73 (s, 2H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 160.7, 137.5, 136.7, 134.3, 132.7, 129.4, 129.2, 128.8, 128.5, 64.0.

N-(p-(Trifluoromethyl)benzylidene)-p-(trifluoromethyl)benzylamine (2i).[25] yellow oil, 338 mg, 68% (isolated yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.35 (s, 1H), 7.83 (d, *J* = 8.31 Hz, 2H), 7.61 (d, *J* = 7.92 Hz, 2H), 7.56 (d, *J* = 8.31 Hz, 2H), 7.41 (d, *J* = 7.92 Hz, 2H), 4.80 (s, 2H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 161.1, 143.4, 139.3, 132.6 (q, *J* = 32.1 Hz), 129.4 (q, *J* = 32.4 Hz), 128.6, 128.2, 125.6 (q, *J* = 3.9 Hz), 125.5 (q, *J* = 3.8 Hz), 122.9 (d, *J* = 35.3 Hz), 120.2 (d, *J* = 36.2 Hz), 64.3.

General Procedure for the Synthesis of Benzimidazole Derivatives (5) (Method A).

Benzylamine derivatives **1** (1.5 mmol), 1,2-diaminobenzene derivatives **4** (1.0 mmol), 4,6-dimethoxysalicylic acid **3d** (5.0 mol %), and distilled toluene (0.5 mL) were added into a two-neck flask, and the reaction vessel was connected with an O_2 balloon at room temperature. The mixture was stirred at 110 °C under an O_2 atmosphere for 12 h. After the reaction was

complete, the resulting mixture was transferred into a round-bottom flask using methanol (MeOH) and concentrated under reduced pressure. The residue was purified using silica gel chromatography [basified by Et_3N (25 wt %)] {eluent: hexane/ethyl acetate [added Et_3N (1.0 v/v %)]} to give the product **5**.

General Procedure for the Synthesis of Benzimidazole Derivatives (5) (Method B).

To a two-necked flask, benzylamine derivatives **1** (4.5 mmol), 1,2-diaminobenzene derivatives **4** (3.0 mmol), 4,6-dihydroxysalicylic acid **3e** (10.0 mol%), and distilled toluene (1.0 mL) were added, and then the reaction vessel was connected to a O_2 balloon at room temperature. The mixture was stirred in 70 °C under an O_2 atmosphere for 24 h. The resulting mixture was transferred into a round-bottom flask using methanol (MeOH) and concentrated under reduced pressure. The residue was purified by silica gel chromatography (basified with Et_3N (25 wt%) (eluent: hexane/ethyl acetate with 1.0 v/v% Et_3N) to give the product **5**.

2-Phenyl-1H-benzimidazole (5a).[27] yellowish solid, 147 mg, 76% (isolated yield, method A); ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.93 (br, 1H), 8.22-8.17 (m, 2H), 7.62-7.53 (m, 4H), 7.51-7.46 (m, 1H), 7.23-7.19 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ 151.8, 144.0, 130.7, 130.4, 130.1, 129.6, 129.5, 126.9, 122.6, 119.6, 111.9.

2-(4-Methylphenyl)-1H-benzimidazole (5b).[27] yellow solid, 181 mg, 87% (isolated yield, method A); ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.84 (br, 1H), 8.09 (d, J = 7.99 Hz, 2H), 7.64-7.53 (m, 2H), 7.35 (d, J = 8.39 Hz, 2H), 7.20-7.19 (m, 2H), 2.37 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ 151.9, 144.3, 140.1, 135.5, 130.0, 128.0, 126.9, 122.8, 122.1, 119.2, 111.7, 21.5.

2-(2-Methoxyphenyl)-1H-benzimidazole (5c).[27] yellow solid, 156 mg, 83% (isolated yield, method A); ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.16 (br, 1H), 8.37-8.35 (m, 1H), 7.66-7.63 (m, 2H), 7.49-7.45 (m, 1H), 7.24-7.02 (m, 4H), 4.01 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ

157.3, 149.5, 143.3, 135.3, 131.8, 130.3, 122.6, 122.0, 121.4, 118.9, 118.7, 112.6, 112.5, 56.3.

2-(3-Methoxyphenyl)-1H-benzimidazole (5d).[27] brown solid, 193 mg, 86% (isolated yield, method A); ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.89 (br, 1H), 7.78-7.55 (m, 4H), 7.46 (t, J = 7.59 Hz, 1H), 7.21 (s, 2H), 7.06 (d, J = 8.79 Hz, 1H), 3.86 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ 160.2, 151.6, 132.0, 130.6, 123.1, 119.3, 116.4, 111.9, 55.8.

2-(4-Methoxyphenyl)-1H-benzimidazole (5e).[27] yellow solid, 181 mg, 81% (isolated yield, method A); ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.78 (br, 1H), 8.16-8.14 (m, 2H), 7.58 (s, 2H), 7.18-7.10 (m, 4H), 3.83 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ 161.1, 151.9, 128.6, 123.3, 122.4, 118.9, 114.9, 111.5, 55.8.

2-(3-Chlorophenyl)-1H-benzimidazole (5f).[27] yellow solid, 180 mg, 79% (isolated yield, method A); ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.04 (br, 1H), 8.24 (s, 1H), 8.17-8.15 (m, 1H), 7.62-7.53 (m, 4H), 7.24-7.22 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ 150.3, 134.3, 132.7, 131.4, 130.0, 126.6, 125.5, 123.4, 122.8, 119.7, 112.1.

2-(4-Chlorophenyl)-1H-benzimidazole (5g).[27] yellow solid, 203 mg, 89% (isolated yield, method A); ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.00 (br, 1H), 8.21 (d, J = 6.80 Hz, 2H), 7.67-7.57 (m, 4H), 7.22 (s, 2H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ 150.7, 144.3, 144.2, 135.0, 129.6, 128.7, 123.2, 122.5, 119.5, 111.9.

2-(4-(Trifluoromethyl)phenyl)-1H-benzimidazole (5h).[28] yellow solid, 202 mg, 77% (isolated yield, method A); ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.17 (br, 1H), 8.40 (d, J = 7.19 Hz, 2H), 7.92 (d, J = 7.59 Hz, 2H), 7.65 (s, 2H), 7.25 (d, J = 2.80 Hz, 2H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ 150.2, 134.5, 130.3, 130.0, 129.7, 128.7, 127.6, 126.5, 126.4, 126.0, 123.3, 119.8, 112.3.

6-Methyl-2-phenyl-1H-benzimidazole (5i).[27] yellow solid, 179 mg, 86% (isolated yield, method

A); ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.79 (br, 1H), 8.22-8.17 (m, 2H), 7.56-7.36 (m, 5H), 7.02 (d, J = 7.99 Hz, 1H), 2.42 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ 151.4, 130.9, 130.2, 129.4, 126.8, 124.0, 119.0, 111.6, 21.9.

7-Methyl-2-phenyl-1H-benzimidazole (5j).[29] yellow solid, 178 mg, 86% (isolated yield, method A); ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.86 (br, 0.5H), 12.60 (br, 0.5H), 8.23 (s, 2H), 7.55 (t, J = 7.59 Hz, 2H), 7.49-7.30 (m, 2H), 7.09 (t, J = 7.39 Hz, 1H), 6.99 (d, J = 7.19 Hz, 1H), 2.59 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ 150.9, 143.7, 135.1, 130.9, 130.2, 129.4, 128.9, 127.0, 123.6, 122.9, 122.4, 116.8, 109.3, 17.3.

5,6-Dimethyl-2-phenyl-1H-benzimidazole(5k).[23c] yellow solid, 120 mg, 54% (isolated yield, method A); ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.67 (br, 1H), 8.16 (d, J = 6.79 Hz, 2H), 7.54-7.31 (m, 5H), 2.32 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ 150.9, 143.1, 134.1, 131.7, 131.0, 130.4, 129.9, 129.4, 126.7, 119.5, 111.9, 20.6.

6-Bromo-2-phenyl-1H-benzimidazole (5l).[30] yellow solid, 235 mg, 86% (isolated yield, method A); ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.15 (br, 1H), 8.27-8.17 (m, 2H), 7.81 (s, 1H), 7.57-7.49 (m, 4H), 7.35-7.33 (m, 1H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ 153.0, 130.7, 130.2, 129.5, 127.1, 125.5, 114.8.

Methyl-2-phenyl-1H-benzimidazole-6-carboxylate (5m).[31] yellow solid, 206 mg, 82% (isolated yield, method A); ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.15 (br, 1H), 8.27-8.21 (m, 3H), 7.86-7.84 (m, 1H), 7.68-7.66 (m, 1H), 7.59-7.52 (m, 3H), 3.86 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ167.3, 154.3, 130.9, 130.1, 129.5, 127.3, 123.9, 123.8, 52.5.

1-Methyl-2-phenyl-1H-benzimidazole (5n).[32] yellow solid, 175 mg, 84% (isolated yield, method A); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.87-7.85 (m, 2H), 7.71 (d, J = 7.20 Hz, 1H), 7.61-7.56 (m, 4H), 7.33-7.24 (m, 2H), 3.86 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ 153.5, 143.0,

137.1, 130.7, 130.1, 129.8, 129.2, 122.9, 122.4, 119.5, 111.1, 32.2.

General Procedure for the Synthesis of Benzothiazole Derivatives (15).

To a two-necked flask, benzylamine derivatives **1** (4.0 mmol), *o*-aminothiophenol **14** (3.0 mmol), 4,6-dihydroxysalicylic acid **3e** (10.0 mol%), and distilled *p*-xylene (2.0 mL) were added, and then the reaction vessel was connected to an O_2 balloon at room temperature. The mixture was stirred in 140 °C under O_2 atmosphere for 24 h. The resulting mixture was transferred into a round-bottom flask using ethyl acetate (EtOAc) and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluent: hexane/ethyl acetate) to give product **15**.

2-Phenylbenzothiazole (15a).[33] White solid, 500 mg, 79% (isolated yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06–8.01 (m, 3H), 7.75 (d, *J* = 8.4 Hz, 1H), 7.43–7.36 (m, 4H), 7.28–7.25 (m, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 167.7, 153.9, 134.8, 133.3, 130.6, 128.7, 127.2, 126.0, 124.9, 122.9, 121.3.

2-(4-Methylphenyl)benzothiazole (15b).[33] White solid, 559 mg, 83% (isolated yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03 (d, *J* = 8.0 Hz, 1H), 7.91 (d, *J* = 8.0 Hz, 2H), 7.76 (d, *J* = 8.0 Hz, 1H), 7.42–7.38 (m, 1H), 7.28–7.24 (m, 1H), 7.17 (d, *J* = 8.4 Hz, 2H), 2.30 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 167.9, 153.9, 141.1, 134.7, 130.7 129.4, 127.2, 125.9, 124.7, 122.8, 121.3 21.2.

2-(2-Methylphenyl)benzothiazole (15c).[34] Purple solid, 547 mg, 80% (isolated yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08 (d, *J* = 8.0 Hz, 1H), 7.82 (d, *J* = 8.0 Hz, 1H), 7.72 (dd, *J* = 1.0, 7.4 Hz, 1H), 7.45–7.41 (m, 1H), 7.33–7.21 (m, 4H), 2.63 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 167.9, 153.7, 137.2, 135.5, 133.0, 131.4, 130.4, 129.9, 126.07, 126.05, 125.0, 123.3, 121.3, 21.3.

2-(2-Methoxyphenyl)benzothiazole (15d).[33] White solid, 616 mg, 85% (isolated yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.53 (d, *J* = 7.6 Hz, 1H), 8.08 (d, *J* = 7.6 Hz, 1H), 7.87 (d, *J* = 8.4 Hz, 1H),

7.46–7.29 (m, 3H), 7.08 (t, *J* = 7.6 Hz, 1H), 6.95 (d, *J* = 8.0 Hz, 1H), 3.93 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 162.9, 157.0, 152.0, 135.9, 131.6, 129.3, 125.7, 124.4, 122.6, 122.0, 121.0, 120.9, 111.4, 55.4.

2-(3-Methoxyphenyl)benzothiazole (15e).[33] Purple solid, 563 mg, 78% (isolated yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05 (d, *J* = 8.4 Hz, 1H), 7.83 (d, *J* = 8.0 Hz, 1H), 7.65–7.59 (m, 2H), 7.47–7.43 (m, 1H), 7.35–7.32 (m, 2H), 6.99 (dd, *J* = 1.8, 8.2 Hz, 1H), 3.85 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 167.7, 159.9, 153.9, 134.9, 134.7, 129.8, 126.1, 125.0, 123.1, 121.4, 120.0, 117.1, 111.8, 55.3.

2-(4-Methoxyphenyl)benzothiazole (15f).[33] White solid, 627 mg, 88% (isolated yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02–7.98 (m, 3H), 7.82 (d, *J* = 8.0 Hz, 1H), 7.46–7.42 (m, 1H), 7.33–7.29 (m, 1H), 6.95 (d, *J* = 8.8 Hz, 2H), 3.81 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 167.7, 161.7, 154.1, 134.7, 128.9, 126.3, 126.0, 124.6, 122.7, 121.4, 114.2, 55.3.

2-(4-Chlorophenyl)benzothiazole (15g).[33] White solid, 627 mg, 88% (isolated yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02 (d, *J* = 8.0 Hz, 1H), 7.94 (d, *J* = 8.8 Hz, 2H), 7.81 (d, *J* = 7.6 Hz, 1H), 7.46–7.31 (m, 4H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 166.4, 153.9, 136.8, 134.9, 131.9, 129.0, 128.5, 126.3, 125.2, 123.1, 121.5.

2-(3-Chlorophenyl)benzothiazole (15h).[33] White solid, 617 mg, 85% (isolated yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06–8.02 (m, 2H), 7.86–7.81 (m, 2H), 7.47–7.30 (m, 4H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 166.0, 153.8, 135.0, 134.98, 134.94, 130.6, 130.0, 127.2, 126.3, 125.5, 125.4, 123.3, 121.5.

2-(4-(Trifluoromethyl)phenyl)benzothiazole (15i).[35] White solid, 643 mg, 77% (isolated yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.20 (d, *J* = 8.0 Hz, 2H), 8.10 (d, *J* = 8.4 Hz, 1H), 7.92 (d, *J* = 7.6 Hz, 1H), 7.75 (d, *J* = 8.4 Hz, 2H), 7.52 (t, *J* = 7.8 Hz, 1H), 7.43 (t, *J* = 7.6 Hz, 1H); $^{13}C\{^{1}H\}$

NMR (100 MHz, $CDCl_3$): δ 165.9, 153.9, 136.6, 135.1, 132.3 (q, J = 32.4 Hz), 127.6, 126.5, 125.9 (q, J = 3.8 Hz), 125.7, 123.7 (q, J = 271.7 Hz), 123.5, 121.6.

2-(4-tert-Butylphenyl)benzothiazole (15j).[34] White solid, 694 mg, 87% (isolated yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05 (d, J = 8.0 Hz, 1H), 7.99 (d, J = 8.4 Hz, 2H), 7.81 (d, J = 7.6 Hz, 1H), 7.47–7.41 (m, 3H), 7.32–7.28 (m, 1H), 1.32 (s, 9H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 168.2, 154.5, 154.3, 135.1, 131.0, 127.4, 126.3, 126.0, 125.1, 123.2, 121.7, 35.0, 31.3.

2-(Naphthalen-1-yl)benzothiazole (15k).[33] Purple oil, 557 mg, 72% (isolated yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.93 (d, J = 8.4 Hz, 1H), 8.19 (d, J = 8.4 Hz, 1H), 7.98–7.90 (m, 4H), 7.61–7.52 (m, 4H), 7.45–7.41 (m, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 167.5, 154.1, 135.4, 133.9, 131.0, 130.8, 130.6, 129.3, 128.3, 127.6, 126.4, 126.2, 125.8, 125.2, 124.9, 123.5, 121.3.

Experimental Procedure for the Synthesis of 4.7 wt % 3e on Silica Gel.

Silica Q-10C (5.0 g, pore volume = 0.8 cm^3/g, size = 0.85–1.76 mm) was added into a Kugelrohr distillation apparatus and dried at 150 °C (0.5 Torr) for 5 h to give dried silica Q-10C (4.92 g). Then, the dried silica Q-10C was mixed with 4,6-dihydroxy salicylic acid (**3e**, 493.6 mg, 10 wt % of dried silica Q-10C) and 10 mL of ethyl acetate in a round-bottom flask, and the resulting mixture was kept static for 12 h. After concentration by vacuum, the catalyst was dried using the Kugelrohr apparatus at 150 °C (1.1 Torr) for 5 h. The resultant small brown ball was washed using ethyl acetate (10 mL × 3). The filter cake was concentrated by vacuum and further dried using the Kugelrohr apparatus at 150 °C (0.8 Torr) for 6 h to afford 4.7 wt % 3e on silica gel (5.16 g).

Experimental Procedure for Recycling Study.

Benzylamine **1a** (321.4 mg, 3.0 mmol), catalyst 4.7 wt % **3e** on silica gel (542.9 mg, 0.15 mol), and distilled toluene (1.5 mL) were added into a two-neck flask, and the reaction

vessel was connected with an O_2 balloon at room temperature. After stirring at 90 °C under an O_2 atmosphere for 2 h, the reaction mixture was filtered. The filter cake was washed using ethyl acetate (5 mL × 3) and dried by vacuum to recover the catalyst 4.7 wt % **3e** on silica gel, which was used for the next run directly. The filtrate was concentrated under reduced pressure and detected using ^{1}H NMR to calculate the yield of product **2a** (84% for the first run).

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24. Recovery of 4,6-dihydroxysalicylic acid **3e** was also conducted using acid-base extraction. After the reaction was complete, the reaction mixture was concentrated in vacuo, the residue was added to 15% NaOH aqueous solution, and the product was extracted with ethyl acetate (EtOAc). Evaporation of the organic layer successfully afforded **2a** in 71% yield. In this treatment, the Na salt of **3e** might be moved to the aqueous layer. Thus, the aqueous layer was acidified with 3N HCl, and extraction with ethyl acetate (EtOAc) was performed. Unfortunately, however, the organic layer did not contain 4,6-dihydroxysalicylic acid **3e**, most

probably due to the decomposition of the catalyst **3e**. Therefore, further detailed optimization of reaction and extraction conditions is required for recovery of the catalyst **3e**.

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Chapter 3

4,6-Dihydroxysalicylic Acid-Catalyzed Oxidative Coupling of Benzylic Amines and Aromatic Ketones for the Preparation of 2,4,6-Trisubstituted Pyridines and Its Application to Metal-Free Synthesis of G-Quadruplex Binding Ligands

3-1 Introduction

Pyridines are one of the most important *N*-containing heterocycles with applications in many fields[1] such as organic synthesis,[2] materials science,[3] and pharmaceutical science.[4] Currently, pyridine-based natural compounds continue to be discovered and studied for their properties and biosynthesis.[5] Within the pyridine family, 2,4,6-trisubstituted pyridines have garnered great attention because their excellent thermal stability[6] makes them excellent ligands for various metals.[7] For example, cyclometalated Au(III) complexes featuring a tridentate C^N^C scaffold have proven to be effective anticancer drugs (Figure 3-1, [Au(Ph-C^N^C)Cl]).[8] Moreover, 2,4,6-triarylpyridines are a class of G-quadruplex binding ligands that stabilize G-quadruplex DNA (G4-DNA) and provide an efficient approach to cancer treatment (Figure 3-1, G-quadruplex binding ligands).[9]

The traditional synthetic strategies toward the construction of 2,4,6-trisubstituted pyridines require three components, one of which is an additional nitrogen source.[10] Recently, simple two-component condensation reactions for the synthesis of 2,4,6-trisubstituted pyridines have been developed.[11] However, most of their starting materials, such as oximes[12] and

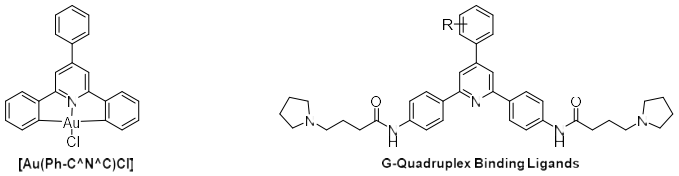


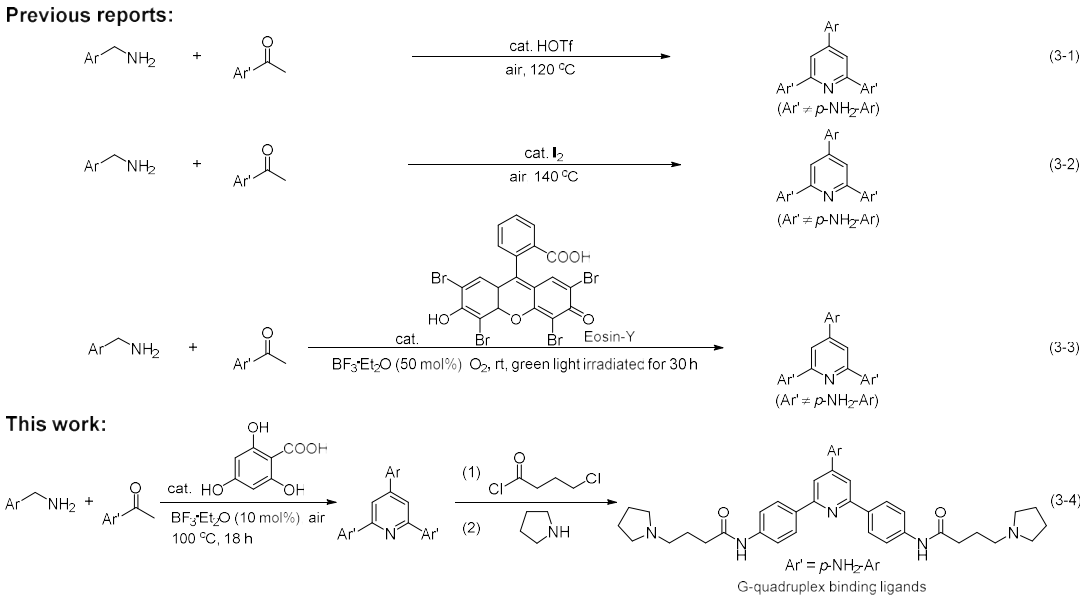
Figure 3-1. Structure of [Au(Ph-C^N^C)Cl] and G-Quadruplex Binding Ligands.

chalcones,[13] are not commercially available. Moreover, the synthetic methods require metal catalysts, and the metal residues in the products may cause significant problems in the drug discovery process. To avoid metal contamination[14] of the final products, development of metal-free synthetic methods is strongly desired. Benzylamines are considered efficient substrates for the synthesis of 2,4,6-trisubstituted pyridines and play a dual role of providing an aryl functionality at the 4-position of the pyridines as well as being a nitrogen source. Recently, three metal-free methods were reported for the synthesis of 2,4,6-triarylpyridines via the oxidative coupling reaction of benzylamines with acetophenones, as shown in Scheme 3-1. Although these limited methods provide complementary pathways toward the synthesis of 2,4,6-triarylpyridines, corrosive trifluoromethanesulfonic acid (HOTf) (eq 3-1),[15] iodine at relatively high temperature (140 °C) (eq 3-2),[16] or complex photoredox catalyst Eosin Y with a non-catalytic amount of $BF_3{\cdot}Et_2O$ (50 mol%) upon additional photoirradiation (eq 3-3)[17] were needed. Because of these disadvantages, development of a one-pot synthesis of drug candidates via the preparation of 2,4,6-triarylpyridines becomes difficult. In addition, their limited substrate scopes, especially difficulties with amino groups, make it impossible to apply these reactions to the synthesis of G-quadruplex binding ligands. Therefore, the development of metal-free, catalytic methods for 2,4,6-triarylpyridines synthesis is strongly desired.

The author recently developed a metal-free method to oxidize benzylamines to imines using salicylic acid derivatives as organocatalysts, and successfully applied this efficient method to synthesize *N*-containing heterocycles and blue dyes.[18] Herein, the author describes an efficient

protocol to synthesize 2,4,6-trisubstituted pyridines by the 4,6-dihydroxysalicylic acid-catalyzed oxidative coupling of benzylamines and acetophenones in the air, and the application of this method to the synthesis of G-quadruplex binding ligands in two steps (Scheme 3-1, eq 3-4). Note that most of the previously reported procedures to synthesize G-quadruplex binding ligands require three or four steps; all of these procedures start from the three-component reaction of aldehydes, 4-aminoacetophenones, and nitrogen donors to obtain 2,4,6-triarylpyridines, followed by stepwise reaction of the isolated 2,4,6-triarylpyridines with 4-chlorobutyryl chloride and pyrrolidine.[9] To the author's delight, this present work provides the first example for the synthesis of G-quadruplex binding ligands starting from benzylamines and 4-aminoacetophenones. The resulting mixtures containing 2,4,6-triarylpyridines bearing amino groups were then allowed to react directly with 4-chlorobutyryl chlorides without an intermediate purification step. After a simple work-up, the residues were next reacted with pyrrolidines to successfully afford G-quadruplex binding ligands. Therefore, this metal-free method for the synthesis of 2,4,6-trisubstituted pyridines and G-quadruplex binding ligands is facile, efficient, and time-saving.

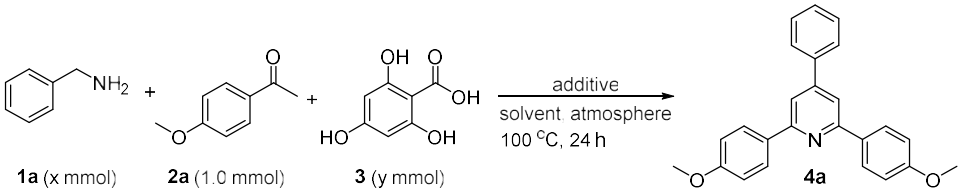
Scheme 3-1. Synthesis of 2,4,6-Trisubstituted Pyridines



3-2 4,6-Dihydroxysalicylic Acid-Catalyzed Synthesis of 2,4,6-Trisubstituted Pyridines

To begin the study, 4,6-dihydroxysalicylic acid (2.5 mol%)[18] was employed as an organocatalyst, and 4-methoxyacetophenone (**2a**, 1.0 mmol) was chosen as the model substrate for coupling with benzylamine (**1a**, 0.5 mmol) under 0.1 MPa of O_2 atmosphere (via an O_2 balloon) at 100 ℃ for 24 h. A survey of different solvents (0.5 mL) suggested that DMSO was the optimal solvent to afford 2,4,6-trisubstituted pyridine **4a** in 45% yield (Table 3-1, entries 1–7). Increasing the amount of **1a** up to 1.0 mmol resulted in the formation of **4a** in 56% yield under an O_2 atmosphere (Table 3-1, entry 8). Removing the O_2 balloon and conducting the reaction in air slightly improved the yield of **4a** (Table 3-1, entry 9). Therefore, the author continued to optimize the coupling reaction in air. A decrease in the amount of DMSO (0.1 mL) was favorable for the formation of **4a** (Table 3-1, entry 10). $BF_3{\cdot}Et_2O$ was found to be an efficient additive for the coupling reaction, and the loading of $BF_3{\cdot}Et_2O$ could be decreased to 10 mol% (Table 3-1, entries 11–17). In the presence of $BF_3{\cdot}Et_2O$ (5 mol%), 1.0 mmol of **2a** could be coupled with 1.5 mmol of benzylamine to form **4a** in 77% yield (Table 3-1, entry 13). Further increasing the amount of $BF_3{\cdot}Et_2O$ to 10 mol% promoted the formation of **4a** (79%, Table 3-1, entry 14). A higher loading of 4,6-dihydroxysalicylic acid (5 mol%) gave **4a** in 81% yield, while an even higher loading (10 mol%) was not needed (Table 3-1, entries 15–16). Using 5 mol% of 4,6-dihydroxysalicylic acid and increasing the amount of $BF_3{\cdot}Et_2O$ (20 mol%) hindered the coupling reaction (Table 3-1, entry 17). A large excess of benzylamine (3.0 mmol) gave a similar yield of **4a** (Table 3-1, entry 18) to the reaction with less benzylamine (1.5 mmol, Table 3-1, entry 15). The neat reaction was inefficient for the formation of **4a** (Table 3-1, entry 19). The optimal conditions for the coupling reaction were 4-methoxyacetophenone (**2a**, 1.0 mmol) and benzylamine (**1a**, 1.5 mmol) in the

Table 3-1. Optimization of Reaction Conditions for Synthesis of 2,4,6-Trisubstituted Pyridines[a]



1a (x mmol) **2a** (1.0 mmol) **3** (y mmol) **4a**

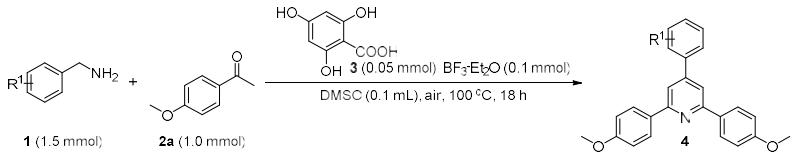
entry	x	y	solvent (mL)	additive (mmol)	atmosphere	yield[b] (%)
1	0.5	0.025	CH_3OH (0.5)	none	O_2 (0.1 MPa)	5[c]
2	0.5	0.025	$CHCl_3$ (0.5)	none	O_2 (0.1 MPa)	8[c]
3	0.5	0.025	CH_3CN (0.5)	none	O_2 (0.1 MPa)	14[d]
4	0.5	0.025	EtOAc (0.5)	none	O_2 (0.1 MPa)	16[d]
5	0.5	0.025	toluene (0.5)	none	O_2 (0.1 MPa)	27
6	0.5	0.025	DMF (0.5)	none	O_2 (0.1 MPa)	14
7	0.5	0.025	DMSO (0.5)	none	O_2 (0.1 MPa)	45
8	1.0	0.025	DMSO (0.5)	none	O_2 (0.1 MPa)	56
9	1.0	0.025	DMSO (0.5)	none	air	60
10	1.0	0.025	DMSO (0.1)	none	air	64
11	1.0	0.025	DMSO (0.1)	$BF_3{\cdot}Et_2O$ (0.025)	air	69
12	1.0	0.025	DMSO (0.1)	$BF_3{\cdot}Et_2O$ (0.05)	air	74
13	1.5	0.025	DMSO (0.1)	$BF_3{\cdot}Et_2O$ (0.05)	air	77
14	1.5	0.025	DMSO (0.1)	$BF_3{\cdot}Et_2O$ (0.1)	air	79
15	1.5	0.05	DMSO (0.1)	$BF_3{\cdot}Et_2O$ (0.1)	air	81
16	1.5	0.1	DMSO (0.1)	$BF_3{\cdot}Et_2O$ (0.1)	air	81
17	1.5	0.05	DMSO (0.1)	$BF_3{\cdot}Et_2O$ (0.2)	air	71
18	3.0	0.05	DMSO (0.1)	$BF_3{\cdot}Et_2O$ (0.1)	air	82
19	1.5	0.05	neat	$BF_3{\cdot}Et_2O$ (0.1)	air	70
20	1.5	0.05	DMSO (0.1)	$BF_3{\cdot}Et_2O$ (0.1)	air	83 (81)[e]
21	1.5	0.05	DMSO (0.1)	$BF_3{\cdot}Et_2O$ (0.1)	air	70[f]
22	1.5	0.05	DMSO (0.1)	$BF_3{\cdot}Et_2O$ (0.1)	air	43[de]
23	1.5	0.05	DMSO (0.1)	$BF_3{\cdot}Et_2O$ (0.1)	air	67[eg]

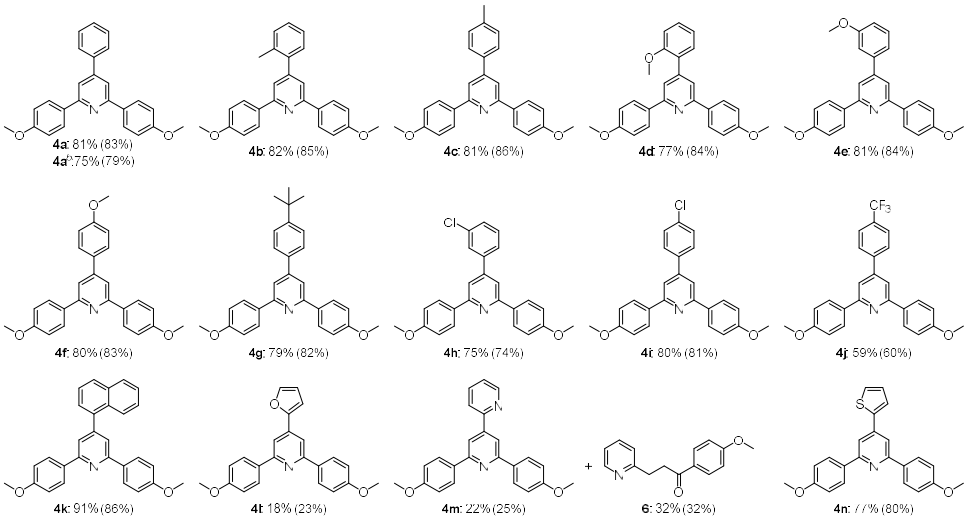
[a]Conditions: **1a**, **2a**, **3**, additive, and solvent were stirred at 100 °C for 24 h. [b]Determined by ^1H NMR using an internal standard of 1,3,5-trioxane (isolated yield). [c]Reaction temperature was 60 °C. [d]Reaction temperature was 80 °C. [e]Reaction time was 18 h. [f]Reaction time was 12 h. [g]Reaction temperature was 120 °C.

presence of 4,6-dihydroxysalicylic acid (5 mol%) as the organocatalyst and $BF_3{\cdot}Et_2O$ (10 mol%) as the additive at 100 °C for a short reaction time (18 h) in the air to form **4a** in 83% yield (Table 3-1, entry 20). A shorter reaction time (12 h), lower temperature (80 °C), or higher temperature (120 °C) gave disappointing results (Table 3-1, entries 21–23).

With the optimized reaction conditions in hand (Table 3-1, entry 20), the scope of the substrates was next investigated. A series of benzylamines were examined to couple with 4-methoxyacetophenone (Table 3-2). More specifically, when benzylamines with a methyl substituent at the *ortho* and *para* positions were employed as substrates, the corresponding 2,4,6-triarylpyridines **4b**–**4c** were obtained in high yields. A methoxy substituent at the *ortho*, *meta*, and *para* positions of benzylamines underwent the coupling reaction with **2a** to give the desired products **4d**–**4f**. Benzylamines bearing other substituents, such as 4-*tert*-butyl, 3-chloro, and 4-chloro, were also examined under the standard reaction conditions, and 2,4,6-triarylpyridines **4g**–**4i** were formed in good to high yields. A strong electron-withdrawing group, 4-trifluoromethyl, resulted in a sluggish reaction for the formation of the product **4j**. In addition, several activated primary amines such as 1-naphthylmethylamine (**1k**), furfurylamine (**1l**), 2-pyridinemethylamine (**1m**), and 2-thiophenemethylamine (**1n**) were examined. 1-Naphthylmethylamine and 2-thiophenemethylamine could be successfully transformed into the corresponding 2,4,6-triarylpyridines **4k** and **4n**. Product **4k** in particular was obtained in excellent yield (91%). The reactions of furfurylamine and 2-pyridinemethylamine did not proceed well, probably due to the low conversion of amines to imines (**4l**–**4m**). When 2-pyridinemethylamine was employed, the competitive α-alkylation reaction of ketones resulted in a 32% yield of **6**. The gram-scale synthesis of 2,4,6-trisubstituted pyridines was also successful under the standard reaction conditions; 1.38 g (3.75 mmol, 75% isolated yield) of **4a** was obtained from 10 mmol of **2a** (1.5 g) after increasing the reaction time to 3 days.

Table 3-2. Synthesis of 2,4,6-Trisubstituted Pyridines Using Various Benzylamines[a]



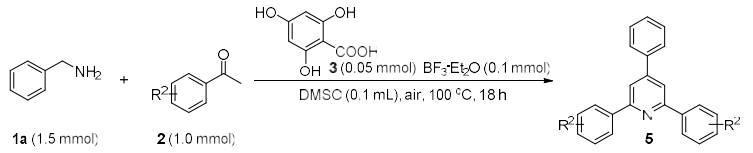


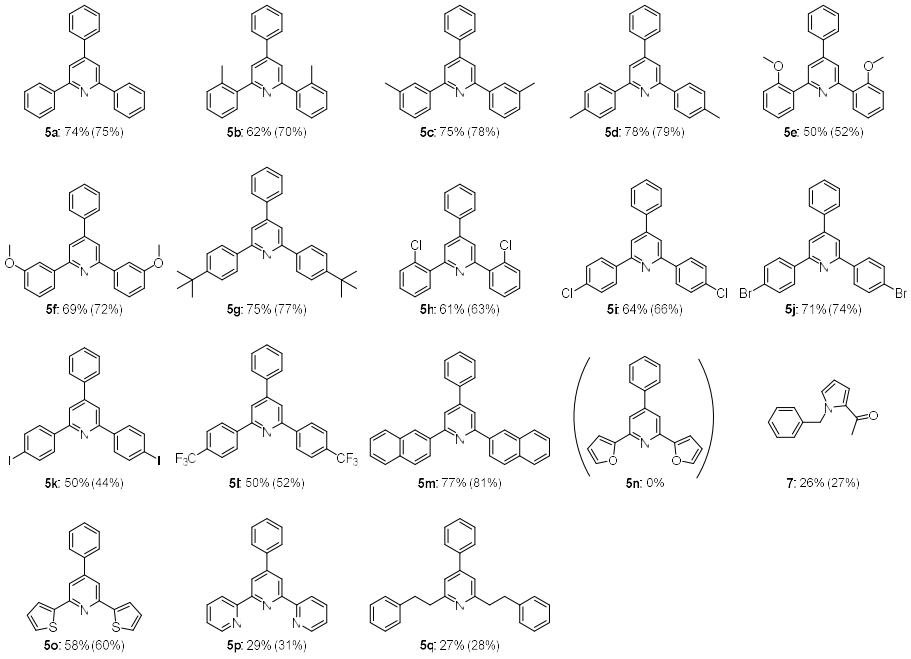
[a]Yield of isolated product is based on **2** (^{1}H NMR yield using an internal standard of 1,3,5-trioxane). [b]Gram scale: **1a** (15 mmol), **2a** (10 mmol), **3** (0.5 mmol), $BF_3{\cdot}Et_2O$ (1.5 mmol), and DMSO (1.0 mL) were stirred together for 3 days.

The substrate scope was further investigated using a variety of acetophenone derivatives to couple with benzylamine under the optimized reaction conditions (Table 3-3). First, acetophenone derivatives bearing methyl substituents at the *ortho*, *meta*, and *para* positions were examined and produced the corresponding 2,4,6-triarylpyridines in moderate to good yields. It is believed that steric hindrance of the *ortho*-methyl group might be responsible for the reduced yield of **5b** (compare **5b** vs **5c** and **5d**). This situation also occurred in the reaction with *ortho*-methoxyacetophenone; **5e** was formed in reduced yield while the outcomes of the *meta*- and *para*-methoxy substituents were better (compare **5e** vs **5f** and Table 3-2, **4a**). The acetophenone derivative with a *para*-*tert*-butyl substituent gave the corresponding product **5g** in good yield. In contrast, acetophenone derivatives bearing electron-withdrawing groups such as *ortho*-chloro, *para*-chloro, *para*-bromo, *para*-iodo, and *para*-trifluoromethyl gave moderate

yields of the products **5h**–**5l**. Activated ketones were also examined under the standard reaction conditions. The reaction of 2′-acetonaphthone afforded the corresponding 2,4,6-triarylpyridine **5m** in good yield. When 2-acetylfuran was employed, instead of **5n**, pyrrole derivative **7** was formed via the Clauson-Kaas reaction of 2-acetylfuran and benzylamine. 2-Acetylthiophene tolerated the coupling reaction to afford **5o** in moderate yield, while the reaction of 2-acetylpyridine gave the product **5p** in decreased yield. An aliphatic ketone was also examined under the optimized reaction conditions and gave an acceptable outcome (**5q**).

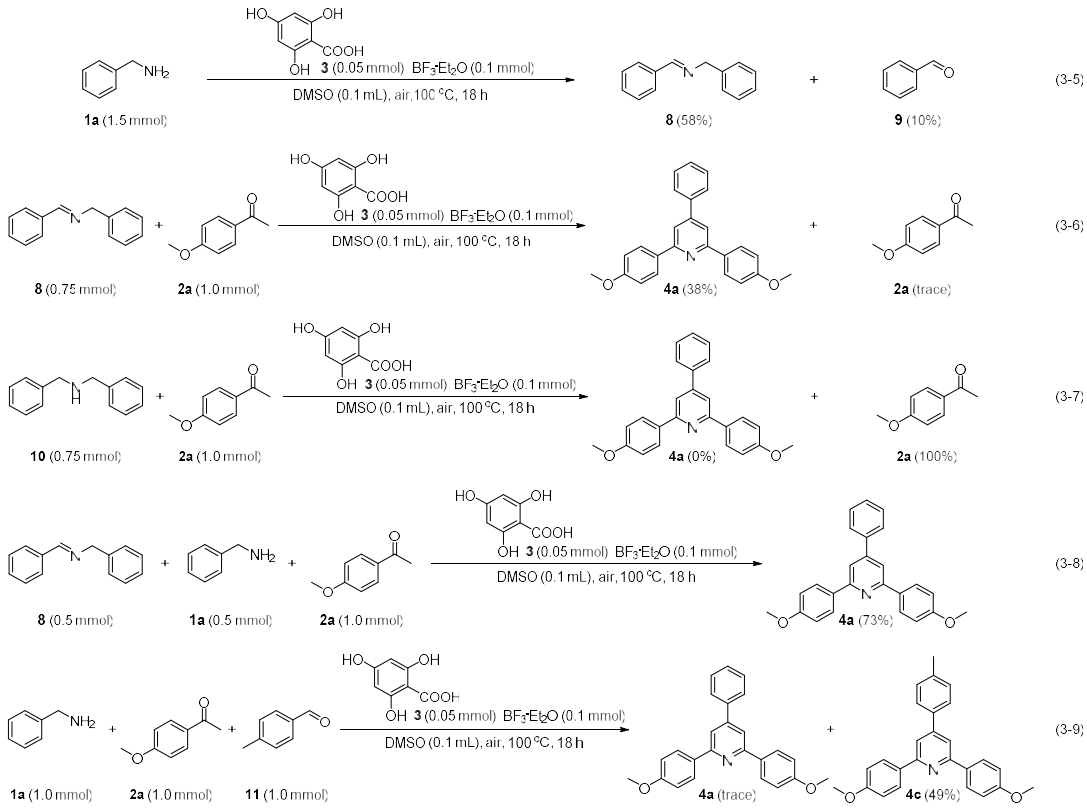
Table 3-3. Synthesis of 2,4,6-Trisubstituted Pyridines Using Various Acetophenones[a]





[a]Yield of isolated product is based on **2** (^{1}H NMR yield using an internal standard of 1,3,5-trioxane).

Scheme 3-2. Control Experiments

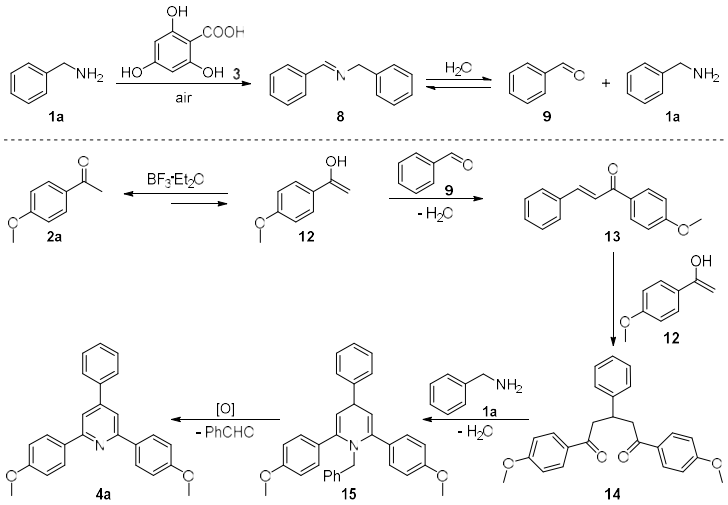


To gain insight into the reaction mechanism of this pyridine synthesis, several control experiments were conducted as shown in Scheme 3-2. As expected from the previous work,[18] benzylamine (**1a**) could be oxidized to imine **8** (58%) under the standard reaction conditions, along with 10% of aldehyde **9**, the formation of which might be explained by the hydrolysis of **8** with water from the air (Scheme 3-2, eq 3-5). Imine **8** was employed as substrate to couple with **2a** and afforded **4a** in 38% yield, whereas amine **10**, which could also be generated from benzylamine, failed to give the pyridine product (Scheme 3-2, eqs 3-6 and 3-7). The use of imine **8** in combination with benzylamine (**1a**, 0.5 mmol) as substrates for reaction with **2a** provided **4a** in 73% yield (Scheme 3-2, eq 3-8). These results suggested that an imine might be the intermediate for this pyridine synthesis, and that benzylamines play the dual role of providing the aryl moiety at the 4-position of the 2,4,6-trisubstituted pyridines as well as acting as the nitrogen donor. When the reaction of benzylamine (**1a**, 1.0 mmol), ketone **2a** (1.0 mmol), and

4-tolulaldehyde (**11**, 1.0 mmol) was conducted under the standard reaction conditions, **4c** bearing a *para*-methyl-substituted pyridine was obtained in 49% yield, whereas only a trace of **4a** was formed (Scheme 3-2, eq 3-9). This result might indicate that an aldehyde is the key intermediate for this pyridine synthesis.

Based on these control experiments, a mechanism for the synthesis of 2,4,6-trisubstituted pyridines is proposed, as shown in Scheme 3-3. Specifically, in the presence of 4,6-dihydroxysalicylic acid, benzylamine (**1a**) is oxidized to imine **8**. The hydrolysis of the imine may generate aldehyde **9** and **1a**, which is a reversible reaction. Promoted by $BF_3{\cdot}Et_2O$, the keto-enol tautomerism of ketone **2a** gives enol **12**, which subsequently undergoes a condensation reaction with aldehyde **9** to afford the intermediate **13**. A further addition reaction occurs between **13** and enol **12**, leading to the formation of **14**, which reacts with the nitrogen donor **1a** to form **15**. Finally, the pyridine product **4a** is readily obtained by the oxidation of **15**.

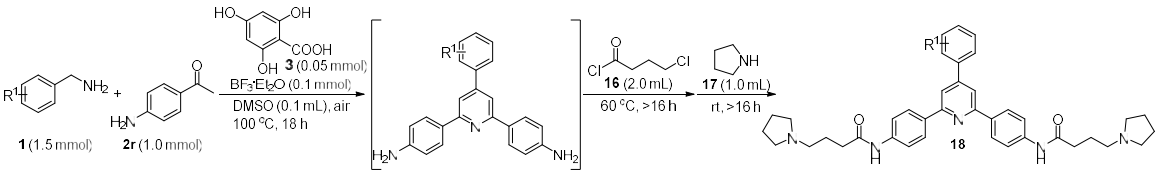
Scheme 3-3. A Possible Pathway for the Synthesis of 2,4,6-Trisubstituted Pyridines

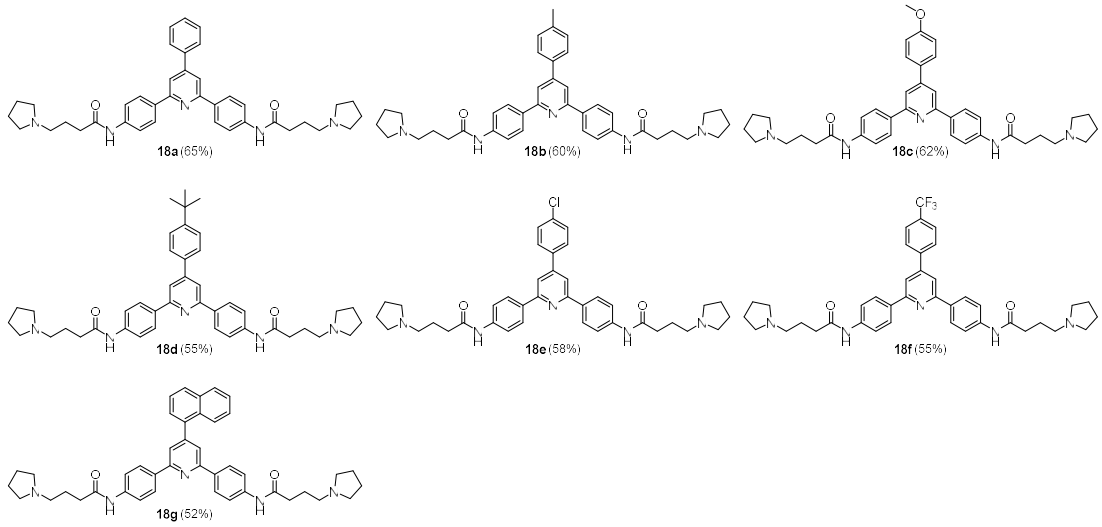


3-3 Metal-Free Synthesis of G-Quadruplex Binding Ligands

2,4,6-Triarylpyridines are a class of G-quadruplex binding ligands that stabilize G4-DNA, which is very important for the treatment of cancer.[9] Herein, the author applied this metal-free synthetic method of pyridines to synthesize a series of G-quadruplex binding ligands by adding 4-chlorobutyryl chloride (**16)** and pyrrolidine (**17**) (Table 3-4). First, benzylamine (**1a**) was employed as the substrate, and the oxidative coupling reaction of **1a** with 4-aminoacetophenone (**2r**) was conducted. Then, 4-chlorobutyryl chloride (**16**) was added directly into the reaction mixture and the mixture was stirred overnight (>16 h) at 60 °C. The resulting dark mixture was then basified with a saturated aqueous $NaHCO_3$ solution to obtain a dark oil, which was easily separated from the mixture by pouring out the water. The dark oil was then reacted with pyrrolidine **17** overnight (>16 h) at room temperature to successfully afford G-quadruplex binding ligand **18a** in 65% yield. Thereafter, a series of benzylamine derivatives were examined to synthesize G-quadruplex binding ligands. Benzylamines with electron-donating groups such as methyl, methoxy, and *tert*-butyl at the *para* positions afforded the corresponding ligands **18b**–**18d** in moderate yields. Benzylamines bearing electron-withdrawing groups such as *para*-chloro and *para*-trifluoromethyl also gave the G-quadruplex binding ligands **18e**–**18f** in satisfactory yields. 1-Naphthylmethylamine was also examined, and the product **18g** was successfully obtained. This method provides the first example for the synthesis of G-quadruplex binding ligands starting from benzylamines and 4-aminoactophenones. Compared with reported methods,[9] which all require three or four steps, this procedure is efficient and time-saving with only requiring two steps.

Table 3-4. Synthesis of G-Quadruplex Binding Ligands Using Various Benzylamines[a]





[a]Yield of isolated product is based on **2r**.

3-4 Conclusion

The author has developed a metal-free and efficient method to synthesize 2,4,6-trisubstituted pyridines from benzylamines and acetophenones in the presence of 4,6-dihydroxysalicylic acid and boron trifluoride-diethyl etherate in air. During this pyridine synthesis, benzylamines play a dual role of providing the aryl moiety at the 4-position of the pyridines and acting as the nitrogen donor. 4,6-Dihydroxysalicylic acid acts as an organocatalyst for the oxidation of benzylamines to imines, which then undergo a hydrolysis reaction to generate aldehydes. Facilitated by boron trifluoride-diethyl etherate, the condensation reaction of aldehydes with acetophenones and benzylamines occurs, and the adducts are readily oxidized to afford 2,4,6-trisubstituted pyridines. This facile method can be applied to the synthesis of

G-quadruplex binding ligands by using 4-aminoacetophenone as the substrate and subsequently adding 4-chlorobutyryl chloride and pyrrolidine to obtain the corresponding G-quadruplex binding ligands in moderate yields. This approach is simple, efficient, and easy to perform. Further investigations of metal-free oxidations are currently underway.

3-5 Experimental Section

General Comment

Unless otherwise stated, all starting materials and additives were purchased from commercial sources and used without further purification. All solvents were distilled and degassed with nitrogen before use. ^{1}H NMR spectra were recorded on a JEOL JNM-ECS400 (400 MHz) FT NMR system or JEOL JNM-ECX400 (400 MHz) FT NMR system in $CDCl_3$ with $(CH_3)_4Si$ as an internal standard. ^{13}C NMR spectra were recorded on a JEOL JNM-ECX400 (100 MHz) FT NMR or JEOL JNM-ECS400 (100 MHz) FT NMR in $CDCl_3$. IR spectra are reported in wave numbers (cm^{-1}). EI mass spectra were obtained by employing double focusing mass spectrometers.

General Procedure for the Synthesis of 2,4,6-Trisubstituted Pyridines (4).

The desired benzylamine derivative **1** (1.5 mmol), 4-methoxyacetophenone (**2a**, 150.18 mg, 1.0 mmol), 4,6-dihydroxysalicylic acid (**3**, 8.5 mg, 0.05 mmol), and DMSO (0.1 mL) were added to a round-bottom flask, and then $BF_3{\cdot}Et_2O$ (12.5 μL, 0.1 mmol) was added to the mixture. The reaction mixture was stirred at 100 °C for 18 h under air, and then cooled to room temperature. The residue was purified by silica gel chromatography (eluent: hexane/ethyl acetate) to give **4**.

2,6-Bis(4-methoxyphenyl)-4-phenylpyridine (4a) [CAS: 50553-98-5].[17] yellow solid, 149.2 mg, 81% (isolated yield), mp 131–132 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.16 (d, J = 8.7 Hz, 4H), 7.78 (s, 2H), 7.74 (d, J = 6.9 Hz, 2H), 7.44-7.55 (m, 3H), 7.04 (d, J = 8.7 Hz, 4H), 3.89 (s, 6H); ^{13}C{^{1}H}

NMR (100 MHz, CDCl3): δ 160.6, 157.1, 150.1, 139.5, 132.5, 129.2, 129.0, 128.5, 127.3, 115.9, 114.2, 55.5.

2,6-Bis(4-methoxyphenyl)-4-(o-tolyl)pyridine (4b). yellow solid, 156.6 mg, 82% (isolated yield), mp 121–122 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13 (d, *J* = 8.7 Hz, 4H), 7.54 (s, 2H), 7.31-7.35 (m, 4H), 7.02 (d, *J* = 9.2 Hz, 4H), 3.88 (s, 6H), 2.35 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 160.6, 156.4, 151.3, 140.2, 135.3, 132.4, 130.8, 129.4, 128.5, 128.4, 126.2, 118.1, 114.2, 55.5, 20.5; IR (KBr, *v*/cm^{-1}): 2933, 2841, 1596, 1539, 1514, 1422, 1394, 1233, 1173, 1030, 834, 825, 773, 764; HRMS (EI) *m*/*z* calcd for $C_{26}H_{23}NO_2$ [M]$^{+}$: 381.1729, found: 381.1725.

2,6-Bis(4-methoxyphenyl)-4-(p-tolyl)pyridine (4c) [CAS: 681443-63-0].[19] yellow solid, 154.8 mg, 81% (isolated yield), mp 133–134 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.16 (d, *J* = 8.7 Hz, 4H), 7.76 (s, 2H), 7.64 (d, *J* = 8.2 Hz, 2H), 7.33 (d, *J* = 8.2 Hz, 2H), 7.03 (d, *J* = 8.7 Hz, 4H), 3.89 (s, 6H), 2.44 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 160.6, 157.1, 150.0, 139.0, 136.5, 132.6, 129.9, 128.5, 127.1, 115.7, 114.2, 55.5, 21.4.

4-(2-Methoxyphenyl)-2,6-bis(4-methoxyphenyl)pyridine (4d). white solid, 153.9 mg, 77% (isolated yield), mp 122–123 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13 (d, *J* = 8.7 Hz, 4H), 7.74 (s, 2H), 7.39-7.45 (m, 2H), 7.00-7.11 (m, 6H), 3.88 (s, 6H), 3.87 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 160.4, 156.7, 156.4, 147.8, 132.8, 130.6, 130.0, 128.9, 128.5, 121.2, 118.5, 114.1, 111.6, 55.8, 55.5; IR (KBr, *v*/cm^{-1}): 2948, 2845, 2835, 1607, 1576, 1544, 1545, 1494, 1456, 1422, 1394, 1280, 1242, 1173, 1028, 831, 759, 592; HRMS (EI) *m*/*z* calcd for $C_{26}H_{23}NO_3$ [M]$^{+}$: 397.1678, found: 397.1673.

4-(3-Methoxyphenyl)-2,6-bis(4-methoxyphenyl)pyridine (4e). white solid, 161.5 mg, 81% (isolated yield), mp 133–135 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.16 (d, *J* = 8.6 Hz, 4H), 7.76 (s, 2H), 7.44 (t, *J* = 7.9 Hz, 1H), 7.32 (d, *J* = 7.7 Hz, 1H), 7.25-7.26 (m, 1H), 6.99-7.04 (m, 5H), 3.91 (s, 3H), 3.89 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 160.6, 160.3, 157.1, 150.0, 141.0, 132.5,

130.2, 128.5, 119.7, 115.9, 114.2, 113.1, 55.6, 55.5; IR (KBr, ν/cm^{-1}): 2940, 2845, 1598, 1576, 1545, 1515, 1486, 1422, 1393, 1287, 1252, 1233, 1205, 1169, 1053, 1021, 871, 834, 785, 699; HRMS (EI) *m*/*z* calcd for $C_{26}H_{23}NO_3$ $[M]^+$: 397.1678, found: 397.1678.

2,4,6-Tris(4-methoxyphenyl)pyridine (4f) [CAS: 33567-23-6].[17] white solid, 159.6 mg, 80% (isolated yield), mp 131–133 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.15 (d, *J* = 8.7 Hz, 4H), 7.73 (s, 2H), 7.69 (d, *J* = 8.7 Hz, 2H), 7.01-7.06 (m, 6H), 3.88 (s, 9H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 160.6, 160.5, 157.1, 149.6, 132.6, 131.7, 128.5, 128.4, 115.4, 114.6, 114.2, 55.6, 55.5.

4-(4-(Tert-butyl)phenyl)-2,6-bis(4-methoxyphenyl)pyridine (4g). yellow solid, 167.8 mg, 79% (isolated yield), mp 123–124 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.15 (d, *J* = 8.7 Hz, 4H), 7.77 (s, 2H), 7.68 (d, *J* = 8.2 Hz, 2H), 7.54 (d, *J* = 8.2 Hz, 2H), 7.03 (d, *J* = 8.7 Hz, 4H), 3.89 (s, 6H), 1.39 (s, 9H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 160.6, 157.0, 152.3, 150.0, 136.6, 132.6, 128.5, 127.0, 126.2, 115.7, 114.2, 55.5, 34.9, 31.5; IR (KBr, ν/cm^{-1}): 2970, 2348, 1607, 1539, 1514, 1461, 1427, 1307, 1240, 1174, 1034, 826, 592; HRMS (EI) *m*/*z* calcd for $C_{29}H_{29}NO_2$ $[M]^+$: 423.2198, found: 423.2200.

4-(3-Chlorophenyl)-2,6-bis(4-methoxyphenyl)pyridine (4h) [CAS: 2097002-94-1].[10d] yellow solid, 151.2 mg, 75% (isolated yield), mp 120–121 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.15 (d, *J* = 8.6 Hz, 4H), 7.69-7.71 (m, 3H), 7.56-7.60 (m, 1H), 7.42-7.44 (m, 2H), 7.03 (d, *J* = 9.1 Hz, 4H), 3.88 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 160.7, 157.3, 148.7, 141.3, 135.2, 132.2, 130.4, 128.9, 128.5, 127.4, 125.5, 115.6, 114.2, 55.5.

4-(4-Chlorophenyl)-2,6-bis(4-methoxyphenyl)pyridine (4i) [CAS: 857500-67-5].[19] yellow solid, 160.6 mg, 80% (isolated yield), mp 123–124 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.14 (d, *J* = 8.7 Hz, 4H), 7.71 (s, 2H), 7.65 (d, *J* = 8.7 Hz, 2H), 7.48 (d, *J* = 8.2 Hz, 2H), 7.03 (d, *J* = 8.7 Hz, 4H), 3.88 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 160.7, 157.3, 148.9, 137.9, 135.1, 132.3, 129.4, 128.6, 128.5, 115.5, 114.2, 55.5.

2,6-Bis(4-methoxyphenyl)-4-(4-(trifluoromethyl)phenyl)pyridine (4j). white solid, 129.7 mg, 59% (isolated yield), mp 123–124 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.15 (d, *J* = 8.7 Hz, 4H), 7.81 (d, *J* = 8.2 Hz, 2H), 7.77 (d, *J* = 8.2 Hz, 2H), 7.73 (s, 2H), 7.03 (d, *J* = 8.7 Hz, 4H), 3.88 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 160.8, 157.3, 148.7, 143.1, 132.1, 130.9 (q, *J* = 32.5 Hz), 128.5, 127.7, 126.1 (q, *J* = 3.8 Hz), 124.2 (q, *J* = 272.8 Hz), 115.7, 114.2, 55.5; IR (KBr, *ν*/cm^{-1}): 2934, 2829, 2363, 1607, 1545, 1514, 1429, 1391, 1328, 1246, 1175, 1113, 1071, 1020, 826, 579, 517; HRMS (EI) *m*/*z* calcd for $C_{26}H_{20}F_3NO_2$ [M]$^{+}$: 435.1446, found: 43.1445.

2,6-Bis(4-methoxyphenyl)-4-(naphthalen-1-yl)pyridine (4k). yellow solid, 189.5 mg, 91% (isolated yield), mp 119–120 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.16 (d, *J* = 8.7 Hz, 4H), 7.92-7.96 (m, 3H), 7.71 (s, 2H), 7.44-7.59 (m, 4H), 7.02 (d, *J* = 9.2 Hz, 4H), 3.87 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 160.7, 156.6, 150.2, 138.5, 133.9, 132.3, 131.2, 128.8, 128.6, 128.5, 126.8, 126.7, 126.3, 125.7, 125.5, 118.8, 114.2, 55.5; IR (KBr, *ν*/cm^{-1}): 2940, 2837, 2370, 1607, 1542, 1513, 1394, 1241, 1173, 1029, 834, 802, 780, 578; HRMS (EI) *m*/*z* calcd for $C_{29}H_{23}NO_2$ [M]$^{+}$: 417.1729, found: 417.1730.

4-(Furan-2-yl)-2,6-bis(4-methoxyphenyl)pyridine (4l). light gray solid, 32.3 mg, 18% (isolated yield), mp 149–150 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.14 (d, *J* = 8.6 Hz, 4H), 7.81 (s, 2H), 7.57 (d, *J* = 1.8 Hz, 1H), 7.02 (d, *J* = 8.6 Hz, 4H), 6.94 (d, *J* = 3.2 Hz, 1H), 6.56 (q, *J* = 1.7 Hz, 1H), 3.88 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 160.7, 157.1, 152.3, 143.6, 139.0, 132.4, 128.4, 114.1, 112.2, 111.7, 108.3, 55.5; IR (KBr, *ν*/cm^{-1}): 2845, 1609, 1539, 1516, 1489, 1456, 1240, 1173, 1018, 832, 759, 579; HRMS (EI) *m*/*z* calcd for $C_{23}H_{19}NO_3$ [M]$^{+}$: 357.1365, found: 357.1364.

2',6'-Bis(4-methoxyphenyl)-2,4'-bipyridine (4m). yellow solid, 40.8 mg, 22% (isolated yield), mp 132–133 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.79 (d, *J* = 4.5 Hz, 1H), 8.21 (d, *J* = 9.1 Hz, 4H), 8.18 (s, 2H), 7.82-7.91 (m, 2H), 7.34-7.37 (m, 1H), 7.04 (d, *J* = 8.6 Hz, 4H), 3.89 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 160.7, 157.3, 155.8, 150.2, 148.1, 137.2, 132.4, 128.6, 123.8,

121.2, 115.1, 114.1, 55.5; IR (KBr, ν/cm^{-1}): 2363, 1609, 1514, 1471, 1394, 1291, 1249, 1175, 1030, 829, 785; HRMS (EI) *m*/*z* calcd for $C_{24}H_{20}N_2O_2$ $[M]^+$: 368.1525, found: 368.1525.

2,6-Bis(4-methoxyphenyl)-4-(thiophen-2-yl)pyridine (4n) [CAS: 170634-00-1]. yellow solid, 143.1 mg, 77% (isolated yield), mp 172–173 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13 (d, *J* = 9.1 Hz, 4H), 7.75 (s, 2H), 7.59 (dd, *J* = 3.6, 0.9 Hz, 1H), 7.42 (dd, *J* = 5.2, 1.1 Hz, 1H), 7.16 (dd, *J* = 5.0, 3.6 Hz, 1H), 7.03 (d, *J* = 8.6 Hz, 4H), 3.88 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 160.7, 157.3, 142.9, 142.4, 132.3, 128.5, 128.5, 126.8, 125.2, 114.2, 114.1, 55.5; IR (KBr, ν/cm^{-1}): 2837, 1600, 1545, 1511, 1423, 1405, 1239, 1172, 1035, 835, 822, 710, 580; HRMS (EI) *m*/*z* calcd for $C_{23}H_{19}NO_2S$ $[M]^+$: 373.1136, found: 373.1130.

1-(4-Methoxyphenyl)-3-(pyridin-2-yl)propan-1-one (6) [CAS: 343596-75-8].[14a] yellow solid, 78.6 mg, 32% (isolated yield), mp 50–51 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.52 (d, *J* = 4.5 Hz, 1H), 7.98 (d, *J* = 9.1 Hz, 2H), 7.59 (td, *J* = 7.7, 1.8 Hz, 1H), 7.25 (d, *J* = 7.7 Hz, 1H), 7.10 (dd, *J* = 7.2, 5.0 Hz, 1H), 6.92 (d, *J* = 8.6 Hz, 2H), 3.86 (s, 3H), 3.45 (t, *J* = 7.2 Hz, 2H), 3.22 (t, *J* = 7.5 Hz, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 198.0, 163.6, 161.1, 149.4, 136.5, 130.5, 130.1, 123.5, 121.3, 113.8, 55.6, 37.7, 32.4.

General Procedure for the Synthesis of 2,4,6-Trisubstituted Pyridines (5).

Benzylamine (**1a**, 160.74 mg, 1.5 mmol), the desired acetophenone derivative **2** (1.0 mmol), 4,6-dihydroxysalicylic acid (**3**, 8.5 mg, 0.05 mmol), and DMSO (0.1 mL) were added to a round-bottom flask, and then $BF_3{\cdot}Et_2O$ (12.5 μL, 0.1 mmol) was added to the mixture. The reaction mixture was stirred at 100 °C for 18 h under air, and then cooled to room temperature. The residue was purified by silica gel chromatography (eluent: hexane/ethyl acetate) to give **5**.

2,4,6-Triphenylpyridine (5a) [CAS: 580-35-8].[17] white solid, 114.3 mg, 74% (isolated yield), mp 137–138 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.21 (d, *J* = 8.2 Hz, 4H), 7.90 (s, 2H), 7.76 (d, *J* = 7.7

Hz, 2H), 7.43-7.56 (m, 9H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 157.7, 150.3, 139.7, 139.2, 129.3, 129.2, 129.1, 128.9, 127.3, 127.3, 117.3.

4-Phenyl-2,6-di-o-tolylpyridine (5b) [CAS: 816446-55-6].[10f] white solid, 103.5 mg, 62% (isolated yield), mp 134–135 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72 (d, *J* = 6.8 Hz, 2H), 7.59 (s, 2H), 7.42-7.51 (m, 5H), 7.26-7.30 (m, 6H), 2.48 (s, 6H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 160.3, 148.9, 140.9, 138.6, 136.1, 130.8, 130.0, 129.3, 129.2, 128.4, 127.3, 126.0, 120.3, 20.8.

4-Phenyl-2,6-di-m-tolylpyridine (5c) [CAS: 2040475-81-6].[10f] white solid, 125.9 mg, 75% (isolated yield), mp 157–158 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 (s, 2H), 7.97 (d, *J* = 8.2 Hz, 2H), 7.86 (s, 2H), 7.75 (d, *J* = 6.8 Hz, 2H), 7.45-7.55 (m, 3H), 7.40 (t, *J* = 7.5 Hz, 2H), 7.24-7.27 (m, 2H), 2.48 (s, 6H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 157.9, 150.2, 139.8, 139.3, 138.5, 129.93, 129.2, 129.1, 128.8, 128.0, 127.3, 124.5, 117.3, 21.8.

4-Phenyl-2,6-di-p-tolylpyridine (5d) [CAS: 16112-41-7].[10f] white solid, 130.4 mg, 78% (isolated yield), mp 160–161 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10 (d, *J* = 8.2 Hz, 4H), 7.83 (s, 2H), 7.73 (d, *J* = 7.2 Hz, 2H), 7.44-7.53 (m, 3H), 7.31 (d, *J* = 8.2 Hz, 4H), 2.42 (s, 6H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 157.5, 150.2, 139.4, 139.1, 137.0, 129.5, 129.2, 129.00, 127.3, 127.1, 116.7, 21.5.

2,6-Bis(2-methoxyphenyl)-4-phenylpyridine (5e) [CAS: 1428423-32-8].[10f] yellow solid, 91.6 mg, 50% (isolated yield), mp 154–155 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99 (s, 2H), 7.95 (dd, *J* = 7.7, 1.8 Hz, 2H), 7.72 (d, *J* = 7.2 Hz, 2H), 7.49 (t, *J* = 7.5 Hz, 2H), 7.41-7.44 (m, 1H), 7.37 (td, *J* = 7.8, 1.4 Hz, 2H), 7.10 (t, *J* = 7.5 Hz, 2H), 7.02 (d, *J* = 8.6 Hz, 2H), 3.88 (s, 6H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 157.2, 156.1, 147.8, 139.6, 131.7, 129.9, 129.8, 129.1, 128.7, 127.5, 121.6, 121.2, 111.6, 55.9.

2,6-Bis(3-methoxyphenyl)-4-phenylpyridine (5f) [CAS: 1333120-04-9].[10f] yellow solid, 127.2 mg, 69% (isolated yield), mp 65–67 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87 (s, 2H), 7.80 (s, 2H), 7.74

(t, *J* = 6.6 Hz, 4H), 7.40-7.54 (m, 5H), 7.00 (dd, *J* = 7.9, 2.0 Hz, 2H), 3.92 (s, 6H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 160.2, 157.3, 150.3, 141.2, 139.1, 129.8, 129.3, 129.1, 127.3, 119.7, 117.6, 114.9, 112.8, 55.5.

2,6-Bis(4-(tert-butyl)phenyl)-4-phenylpyridine (5g) [CAS: 2070893-06-8].[20] white solid, 157.0 mg, 75% (isolated yield), mp 155–157 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.12 (d, *J* = 8.2 Hz, 4H), 7.83 (s, 2H), 7.72 (d, *J* = 7.7 Hz, 2H), 7.42-7.53 (m, 7H), 1.38 (s, 18H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6): δ 157.6, 152.2, 150.0, 139.4, 137.1, 129.2, 129.0, 127.3, 127.0, 125.8, 116.7, 34.8, 31.5.

2,6-Bis(2-chlorophenyl)-4-phenylpyridine (5h) [CAS: 2056081-58-2].[12a] yellow solid, 115.0 mg, 61% (isolated yield), mp 148–149 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 (s, 2H), 7.73-7.76 (m, 4H), 7.44-7.54 (m, 5H), 7.33-7.41 (m, 4H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 157.3, 148.5, 139.4, 138.4, 132.4, 132.0, 130.3, 129.8, 129.3, 127.4, 127.2, 121.7.

2,6-Bis(4-chlorophenyl)-4-phenylpyridine (5i) [CAS: 72666-43-4].[12a] light yellow solid, 121.3 mg, 64% (isolated yield), mp 190–192 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.14 (d, *J* = 8.6 Hz, 4H), 7.87 (s, 2H), 7.72-7.74 (m, 2H), 7.48-7.57 (m, 7H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 156.5, 150.7, 138.8, 137.9, 135.4, 129.3, 129.1, 128.5, 127.3, 117.3.

2,6-Bis(4-bromophenyl)-4-phenylpyridine (5j) [CAS: 74918-94-8].[12a] light yellow solid, 165.6 mg, 71% (isolated yield), mp 198–199 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07 (d, *J* = 8.6 Hz, 4H), 7.87 (s, 2H), 7.72-7.74 (m, 2H), 7.65 (d, *J* = 8.6 Hz, 4H), 7.49-7.56 (m, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 156.6, 150.8, 138.8, 138.4, 132.0, 129.4, 128.8, 127.3, 123.8, 117.3.

2,6-Bis(4-iodophenyl)-4-phenylpyridine (5k) [CAS: 2103202-38-4]. yellow solid, 141.1 mg, 50% (isolated yield), mp 176–177 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (d, *J* = 8.6 Hz, 4H), 7.83-7.86 (m, 6H), 7.72 (d, *J* = 6.8 Hz, 2H), 7.47-7.55 (m, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz,

$CDCl_3$): δ 156.7, 150.7, 138.9, 138.8, 138.0, 129.3, 128.9, 127.3, 117.3, 95.7; IR (KBr, ν/cm^{-1}): 2348, 1601, 1558, 1544, 1506, 1411, 1004, 816, 762, 692; HRMS (EI) *m*/*z* calcd for $C_{23}H_{15}I_2N$ $[M]^+$: 558.9294, found: 558.9293.

4-Phenyl-2,6-bis(4-(trifluoromethyl)phenyl)pyridine (5l) [CAS: 2056081-57-1].[12a] light yellow solid, 110.0 mg, 50% (isolated yield), mp 152–153 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.30 (d, *J* = 8.2 Hz, 4H), 7.97 (s, 2H), 7.74-7.79 (m, 6H), 7.49-7.58 (m, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 156.4, 151.1, 142.7, 138.5, 131.3 (q, *J* = 32.5 Hz), 129.6, 129.4, 127.6, 127.3, 125.9 (q, *J* = 3.8 Hz), 124.3 (q, *J* = 271.8 Hz), 118.4.

2,6-Di(naphthalen-2-yl)-4-phenylpyridine (5m) [CAS: 3557-63-9].[14a] yellow solid, 157.5 mg, 77% (isolated yield), mp 156–157 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.66 (d, *J* = 0.9 Hz, 2H), 8.39 (dd, *J* = 8.6, 1.8 Hz, 2H), 8.01 (s, 2H), 7.98 (dd, *J* = 8.8, 3.4 Hz, 4H), 7.88 (t, *J* = 4.8 Hz, 2H), 7.77-7.79 (m, 2H), 7.46-7.56 (m, 7H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 157.6, 150.4, 139.2, 137.1, 133.9, 133.7, 129.3, 129.2, 128.9, 128.5, 127.8, 127.4, 126.6, 126.4, 125.1, 117.6.

4-Phenyl-2,6-di(thiophen-2-yl)pyridine (5o) [CAS: 5562-59-4].[14a] yellow solid, 93.0 mg, 58% (isolated yield), mp 113–114 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68-7.71 (m, 6H), 7.47-7.54 (m, 3H), 7.42 (d, *J* = 4.1 Hz, 2H), 7.13-7.15 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 152.7, 150.3, 145.0, 138.7, 129.2, 128.1, 127.9, 127.2, 125.0, 115.2.

4'-Phenyl-2,2':6',2''-terpyridine (5p) [CAS: 58345-97-4].[21] brown solid, 44.5 mg, 29% (isolated yield), mp 203–204 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.72-8.74 (m, 4H), 8.67 (d, *J* = 8.2 Hz, 2H), 7.85-7.91 (m, 4H), 7.43-7.53 (m, 3H), 7.33-7.36 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 156.4, 156.1, 150.5, 149.3, 138.6, 137.0, 129.1, 129.0, 127.5, 123.9, 121.5, 119.1.

2,6-Diphenethyl-4-phenylpyridine (5q) [CAS: 1428423-37-3].[14a] yellow solid, 49.0 mg, 27% (isolated yield), mp 120–121 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49 (d, *J* = 7.7 Hz, 2H),

7.37-7.45 (m, 3H), 7.17-7.30 (m, 10H), 7.09 (s, 2H), 3.08-3.19 (m, 8H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 161.3, 149.1, 141.8, 138.9, 129.1, 128.9, 128.7, 128.5, 127.2, 126.1, 118.8, 40.3, 36.4.

1-(1-Benzyl-1H-pyrrol-2-yl)ethan-1-one (7) [CAS: 100713-02-8].[22] brown oil, 51.9 mg, 26% (isolated yield); ^1H NMR (400 MHz, $CDCl_3$): δ 7.21-7.31 (m, 3H), 7.10 (d, J = 6.8 Hz, 2H), 7.00 (q, J = 2.0 Hz, 1H), 6.90 (t, J = 2.0 Hz, 1H), 6.18 (q, J = 2.1 Hz, 1H), 5.58 (s, 2H), 2.41 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 188.5, 138.4, 130.5, 130.5, 128.7, 127.5, 127.2, 120.5, 108.6, 52.7, 27.4; MS (EI) $[M]^+$ m/z = 199.

General Procedure for the Synthesis of G-Quadruplex Binding Ligands (18).

The desired benzylamine derivative **1** (1.5 mmol), 4-aminoacetophenone (**2r**, 135.17 mg, 1.0 mmol), 4,6-dihydroxysalicylic acid (**3**, 8.5 mg, 0.05 mmol), and DMSO (0.1 mL) were added to a 50 mL round-bottom flask, and then $BF_3{\cdot}Et_2O$ (12.5 μL, 0.1 mmol) was added to the mixture. The reaction mixture was stirred at 100 °C for 18 h under air, and then cooled to 60 °C. 4-Chlorobutyryl chloride (2.0 mL) was added and the resulting mixture was stirred overnight (>16 h) at 60 °C. The dark reaction mixture was cooled in an ice bath and basified to pH > 7 with a saturated $NaHCO_3$ solution (35 mL). A dark oil appeared and was separated from the mixture by pouring out the water. The dark oil was collected and dissolved in methanol (20 mL), concentrated by vacuum, and then pyrrolidine (1.0 mL) was added to the residue. The resulting dark mixture was stirred overnight (>16 h) at room temperature and cooled in an ice bath. Saturated $NaHCO_3$ solution (35 mL) was then added, and the mixture was stirred for 1 h. A gray solid appeared and was collected by filtration. The filter cake was dissolved in methanol/chloroform (30 mL, 1:4) and concentrated by vacuum. The residue was purified by preparative thin-layer chromatography (PTLC, eluent: chloroform/methanol/triethylamine = 15/4/1) to give **18**.

N,N'-((4-Phenylpyridine-2,6-diyl)bis(4,1-phenylene))bis(4-(pyrrolidin-1-yl)butanamide) (18a)

[CAS: 1023617-87-9].[9d] dark yellow solid, 199.1 mg, 65% (isolated yield), mp 123–125 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.95 (br, 2H), 8.16 (d, *J* = 8.7 Hz, 4H), 7.81 (s, 2H), 7.73 (d, *J* = 7.8 Hz, 2H), 7.68 (d, *J* = 8.2 Hz, 4H), 7.44-7.54 (m, 3H), 2.67-2.68 (m, 12H), 2.57 (t, *J* = 6.4 Hz, 4H), 1.90-1.96 (m, 12H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 171.8, 156.8, 150.1, 139.8, 139.1, 134.9, 129.1, 129.0, 127.7, 127.2, 119.7, 116.2, 55.8, 54.0, 36.7, 23.9, 23.6.

N,N'-((4-(p-Tolyl)pyridine-2,6-diyl)bis(4,1-phenylene))bis(4-(pyrrolidin-1-yl)butanamide) (18b). dark yellow solid, 188.0 mg, 60% (isolated yield), mp 102–104 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.93 (br, 2H), 8.14 (d, *J* = 8.7 Hz, 4H), 7.78 (s, 2H), 7.66 (d, *J* = 8.2 Hz, 4H), 7.62 (d, *J* = 7.8 Hz, 2H), 7.31 (d, *J* = 7.8 Hz, 2H), 2.64-2.65 (m, 12H), 2.55 (t, *J* = 6.4 Hz, 4H), 2.43 (s, 3H), 1.87-1.96 (m, 12H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 171.9, 156.7, 149.9, 139.7, 139.0, 136.0, 134.9, 129.8, 127.6, 126.9, 119.7, 115.9, 55.8, 54.0, 36.7, 24.0, 23.6, 21.3; IR (KBr, *v*/cm^{-1}): 2956, 2800, 1661, 1600, 1516, 1423, 1387, 1246, 1181, 811; HRMS (EI) *m*/*z* calcd for $C_{40}H_{47}N_5O_2$ [M]$^+$: 629.3730, found: 629.3729.

N,N'-((4-(4-Methoxyphenyl)pyridine-2,6-diyl)bis(4,1-phenylene))bis(4-(pyrrolidin-1-yl)butanamide) (18c). dark yellow solid, 199.3 mg, 62% (isolated yield), mp 99–101 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.94 (br, 2H), 8.14 (d, *J* = 8.2 Hz, 4H), 7.76 (s, 2H), 7.67 (t, *J* = 8.0 Hz, 6H), 7.03 (d, *J* = 8.2 Hz, 2H), 3.88 (s, 3H), 2.53-2.64 (m, 16H), 1.87-1.94 (m, 12H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 172.0, 160.4, 156.6, 149.4, 139.6, 134.9, 131.2, 128.2, 127.6, 119.7, 115.6, 114.5, 55.8, 55.4, 54.0, 36.7, 24.1, 23.6; IR (KBr, *v*/cm^{-1}): 2933, 2791, 1668, 1602, 1511, 1429, 1390, 1253, 1178, 1117, 1028, 828; HRMS (EI) *m*/*z* calcd for $C_{40}H_{47}N_5O_3$ [M]$^+$: 645.3679, found: 645.3674.

N,N'-((4-(4-(Tert-butyl)phenyl)pyridine-2,6-diyl)bis(4,1-phenylene))bis(4-(pyrrolidin-1-yl)butanamide) (18d). dark yellow solid, 184.0 mg, 55% (isolated yield), mp 113–115 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.94 (br, 2H), 8.16 (d, *J* = 8.7 Hz, 4H), 7.81 (s, 2H), 7.67 (t, *J* = 8.9 Hz, 6H), 7.55 (d, *J* = 8.2 Hz, 2H), 2.64-2.67 (m, 12H), 2.56 (t, *J* = 6.4 Hz, 4H), 1.89-1.95 (m, 12H), 1.39 (s,

9H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 171.9, 156.8, 152.3, 150.0, 139.7, 136.2, 135.0, 127.7, 126.9, 126.1, 119.7, 116.2, 55.9, 54.1, 37.1, 34.8, 31.4, 24.0, 23.7; IR (KBr, *v*/cm^{-1}): 2955, 1684, 1602, 1516, 1423, 1387, 1253, 1180, 1113, 830; HRMS (EI) *m*/*z* calcd for $C_{43}H_{53}N_5O_2$ $[M]^+$: 671.4199, found: 671.4194.

N,N'-((4-(4-Chlorophenyl)pyridine-2,6-diyl)bis(4,1-phenylene))bis(4-(pyrrolidin-1-yl)butanam - ide) (18e). dark yellow solid, 188.3mg, 58% (isolated yield), mp 94–96 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.98 (br, 2H), 8.15 (d, *J* = 8.7 Hz, 4H), 7.76 (s, 2H), 7.67 (d, *J* = 7.3 Hz, 6H), 7.49 (d, *J* = 8.2 Hz, 2H), 2.66-2.67 (m, 12H), 2.57 (t, *J* = 6.4 Hz, 3H), 1.90-1.94 (m, 12H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 171.9, 156.9, 148.8, 139.9, 137.5, 135.1, 134.7, 129.3, 128.5, 127.7, 119.7, 115.9, 55.9, 54.1, 36.8, 24.0, 23.7; IR (KBr, *v*/cm^{-1}): 2934, 2791, 1601, 1516, 1423, 1386, 1252, 1179, 1093, 1014, 823; HRMS (EI) *m*/*z* calcd for $C_{39}H_{44}ClN_5O_2$ $[M]^+$: 649.3184, found: 649.3188.

N,N'-((4-(4-(Trifluoromethyl)phenyl)pyridine-2,6-diyl)bis(4,1-phenylene))bis(4-(pyrrolidin-1-yl)butanamide) (18f). dark yellow solid, 187.3 mg, 55% (isolated yield), mp 105–107 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.00 (br, 2H), 8.16 (d, *J* = 8.7 Hz, 4H), 7.77-7.84 (m, 6H), 7.68 (d, *J* = 8.2 Hz, 4H), 2.55-2.68 (m, 16H), 1.90-1.96 (m, 12H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 172.0, 157.1, 148.7, 142.7, 140.0, 134.5, 130.9 (q, *J* = 32.7 Hz), 127.7, 127.6, 126.1 (q, *J* = 3.8 Hz), 124.1 (q, *J* = 272.1 Hz), 119.8, 116.1, 55.9, 54.1, 36.9, 24.0, 23.7; IR (KBr, *v*/cm^{-1}): 2956, 2800, 2356, 1653, 1601, 1516, 1387, 1324, 1165, 1123, 1067, 1016, 835; HRMS (EI) *m*/*z* calcd for $C_{40}H_{44}F_3N_5O_2$ $[M]^+$: 683.3447, found: 683.3445.

N,N'-((4-(Naphthalen-1-yl)pyridine-2,6-diyl)bis(4,1-phenylene))bis(4-(pyrrolidin-1-yl)butana - mide) (18g). brown solid, 173.3 mg, 52% (isolated yield), mp 115–117 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.95 (br, 2H), 8.17 (d, *J* = 8.2 Hz, 4H), 7.94 (d, *J* = 8.2 Hz, 3H), 7.76 (s, 2H), 7.66 (d, *J* = 8.7 Hz, 4H), 7.46-7.60 (m, 4H), 2.54-2.65 (m, 16H), 1.88-1.95 (m, 12H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 171.8, 156.4, 150.2, 139.8, 138.2, 134.8, 133.9, 131.1, 128.8, 128.6, 127.8, 126.8,

126.7, 126.2, 125.5, 119.7, 119.4, 55.9, 54.1, 37.0, 24.0, 23.7; IR (KBr, ν/cm^{-1}): 2963, 2807, 1652, 1600, 1516, 1418, 1247, 1179, 842, 777; HRMS (EI) *m*/*z* calcd for $C_{43}H_{47}N_5O_2$ $[M]^+$: 665.3730, found: 665.3731.

General Procedure for the Gram-Scale Synthesis of 2,6-Bis(4-methoxyphenyl)-4-phenylpyridine (4a).

Benzylamine (**1a**, 1.6 g, 15 mmol), 4-methoxyacetophenone (**2a**, 1.5 g, 10 mmol), 4,6-dihydroxysalicylic acid (**3**, 85 mg, 0.5 mmol), and DMSO (1.0 mL) were added to a round-bottom flask, and then $BF_3{\cdot}Et_2O$ (187.5 μL, 1.5 mmol) was added to the mixture. The reaction mixture was stirred at 100 °C for 3 days under air, and then cooled to room temperature. The residue was purified by silica gel chromatography (eluent: hexane/ethyl acetate) to give **4a** (1.38 g).

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Chapter 4

4,6-Dihydroxysalicylic Acid-Catalyzed Oxidative Ugi Reactions with Molecular Oxygen via Homo- and Cross-Coupling of Amines

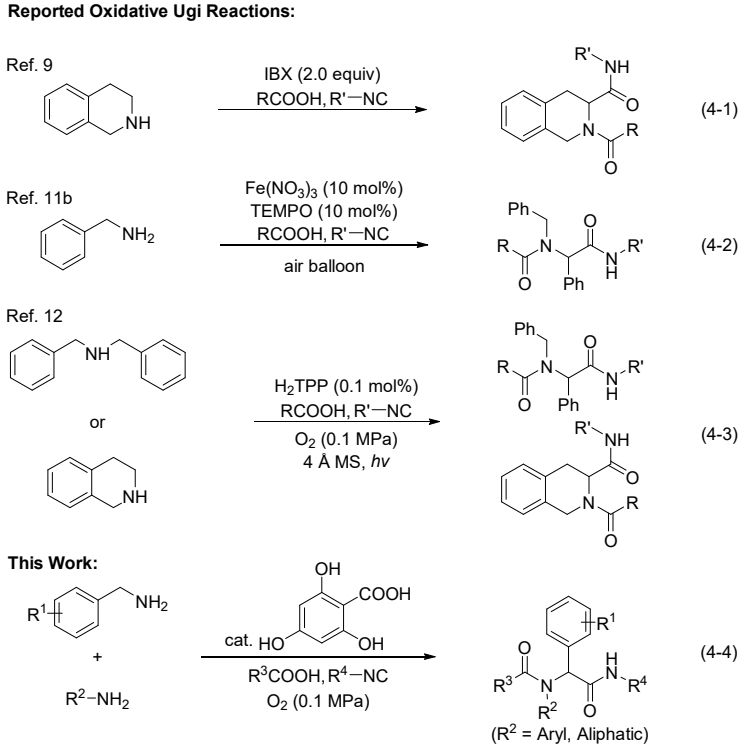
4-1 Introduction

Ugi four-component reactions (U-4CRs) are convergent chemical processes that involve the condensation of an amine, an aldehyde, a carboxylic acid, and an isocyanide with high levels of atom efficiency.[1] As one of the most widely applied multicomponent reactions, the U-4CRs are considered as efficient strategies for the synthesis of different scaffolds, which are usually used in combinatorial,[2] pharmaceutical,[3] and polymer chemistry.[4] Moreover, normal-sized[5] or even medium-sized[6] heterocyclic rings can be constructed via the U-4CRs.

Imines, which are commonly accepted intermediates during the U-4CRs, are generally in situ formed from the aldehydes and the primary amines.[7] Based on this point, the U-4CRs have undergone many modifications involving combination of two substrates together in one molecule or precondensation of the imines.[8] Among them, oxidative Ugi reactions, wherein the imines are formed in situ by oxidation of amines, have recently gained considerable attention.[9-12] The first example was reported by Zhu et al. in 2007, where 2-iodoxybenzoic acid (IBX) was used as an organic oxidant to generate imines from heterocyclic secondary amines (Scheme 4-1, eq 4-1).[9] Since then, several oxidative Ugi reactions have been investigated using different oxidants.[10] In particular, molecular oxygen (O_2) aroused great interest as a green, abundant, and easily available oxidant for the oxidative Ugi reactions. Transition metals are often used as catalysts in

combination with O_2 to accomplish oxidative Ugi reactions (Scheme 4-1, eq 4-2).[11] In sharp contrast, organocatalytic oxidative Ugi reactions with O_2 have remained largely undeveloped; a metal-free method using meso-tetraphenylporphyrin (H_2TPP) as a photosensitizer was reported as the limited protocol to perform oxidative Ugi reactions upon photoirradiation under O_2 atmosphere (Scheme 4-1, eq 4-3).[12] Therefore, the development of organocatalytic oxidative Ugi reactions using O_2 as the terminal oxidant is still strongly desired. Besides, all of these reported oxidation methods for Ugi reactions are based on homo-coupling of amines or oxidation of heterocyclic secondary amines, whereas the cross-coupling of two different primary amines are seldom involved in the oxidative Ugi reactions.[10a]

Scheme 4-1. Oxidative Ugi Reactions



During the course of our studies on green oxidation reactions of amines to imines with O_2,[13] the author has recently succeeded in developed a metal-free oxidative homo-coupling of

benzylamines to imines using salicylic acid derivatives as organocatalysts under O_2 atmosphere.[14] Moreover, this metal-free amine oxidation method could be applied to the synthesis of *N*-containing heterocycles and blue dyes.[15] In the present study, the author has focused their attention on realizing a new and efficient metal-free multicomponent reaction (Ugi reaction) based on the oxidation of amines to imines with O_2 in the presence of an organocatalyst.

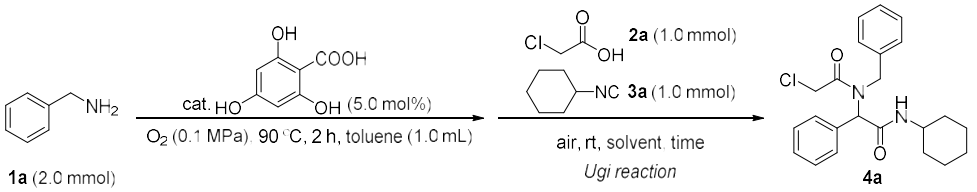
This chapter describes an oxidative Ugi reaction with O_2 catalyzed by 4,6-dihydroxysalicylic acid. It is noteworthy that not only homo-coupling of benzylamines but also cross-coupling of benzylamines with other aliphatic or aromatic amines could proceed in this catalytic system, which provided a very rare example of the oxidative Ugi four-component reactions with two different amines, a carboxylic acid, and an isocyanide (Scheme 4-1, eq 4-4).

4-2 4,6-Dihydroxysalicylic Acid-Catalyzed Oxidative Ugi Reactions

Initially, the homo-coupling reaction of benzylamine (**1a**) was conducted according to the previous work,[14] and then to the reaction mixture was added 2-chloroacetic acid (**2a**), isocyanocyclohexane (**3a**), and toluene (2.0 mL) at 90 °C. The resulting mixture was stirred under O_2 atmosphere (using O_2 balloon) to obtain 11% of bis-amides **4a** (Table 4-1, entry 1). Encouraged by this result, the reaction conditions of this oxidative Ugi reaction were continued to be optimized. When the Ugi reaction was performed at room temperature, the yield of **4a** was improved to 52% (Table 4-1, entry 2). Prolonging the reaction time of this Ugi reaction hindered the formation of **4a** under O_2 atmosphere (Table 4-1, entry 3). Removing the O_2 balloon and conducting the reaction in air could improve the yield of **4a** (60%) in 24 h (Table 4-1, entry 4). Thus, the Ugi reaction conditions were further optimized in air. Shorten the reaction time of the Ugi reaction led to the decreased yield of product **4a** (Table 4-1, entry 5). Using CH_3OH as the solvent instead of toluene during the Ugi reaction was favorable for the formation of **4a** (Table

4-1, entry 6), whereas the homo-coupling of benzylamine was suppressed totally in CH_3OH (Table 4-1, entry 7). When the homo-coupling reaction of benzylamine under neat condition was combined with the Ugi reaction in CH_3OH, **4a** was formed in slightly decreased yield (Table 4-1, entry 8). Increasing the amount of benzylamine (3.0 mmol) afforded the product **4a** in 93% yield (Table 4-1, entry 9). Therefore, the optimal conditions for this one-pot oxidative Ugi reaction were as follows: 3.0 mmol of **1a** was oxidized in toluene promoted by 4,6-dihydroxysalicylic acid as organocatalyst at 90 °C under O_2 atmosphere for 2 h, after removed the O_2 balloon, the reaction mixture was cooled to room temperature and directly used for the Ugi reaction with **2a** (1.0 mmol) and **3a** (1.0 mmol) in CH_3OH (2.0 mL) for 24 h.

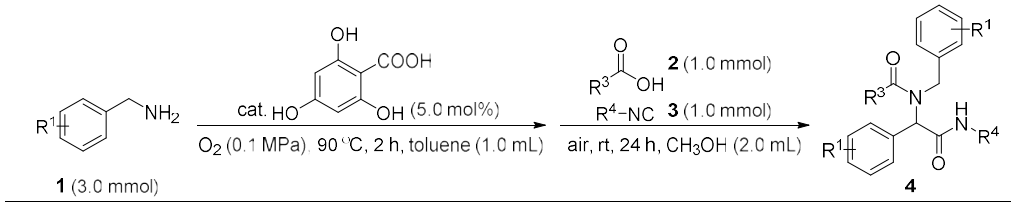
Table 4-1. Optimization of Oxidative Ugi Reactions via Homo-Coupling of Benzylamines

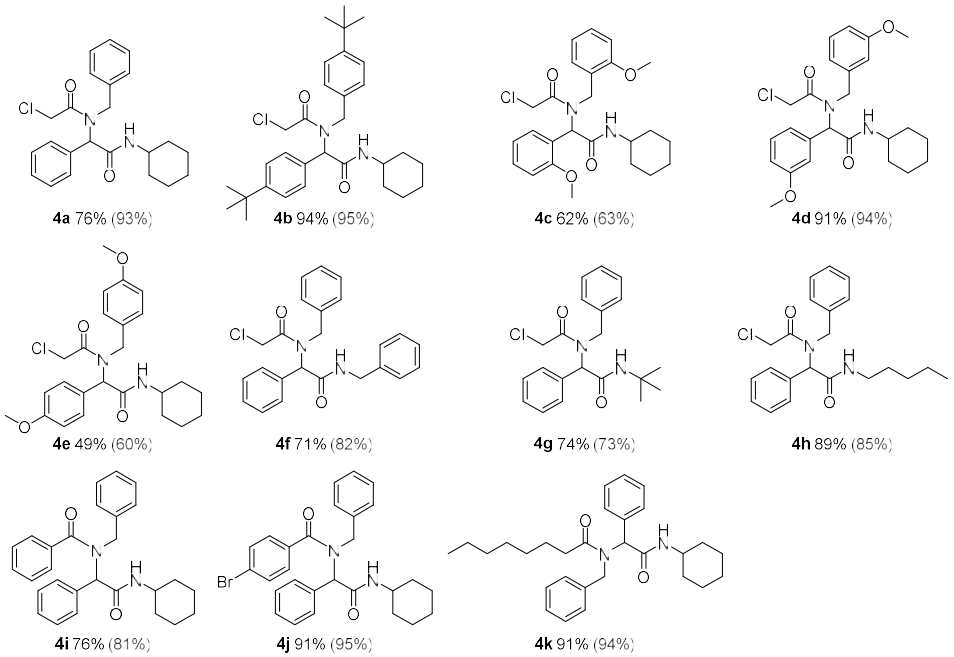


entry	solvent (mL)	time (h)	yield (%)[a]
1[b,c]	toluene (2.0)	22	11
2[b]	toluene (2.0)	22	52
3[b]	toluene (2.0)	36	40
4	toluene (2.0)	24	60
5	toluene (2.0)	18	50
6	CH_3OH (2.0)	36	65
7[d]	CH_3OH (2.0)	92	no reaction
8[e]	CH_3OH (2.0)	36	62
9[f]	CH_3OH (2.0)	24	93 (76)

[a]Determined by ^1H NMR using bibenzyl as the internal standard (isolated yield); the yields of products are based on **2a**. [b]Ugi reactions were conducted under O_2 atmosphere. [c]Ugi reaction was conducted at 90 °C. [d]Homo-coupling of benzylamine was conducted in 1.0 mL of CH_3OH. [e]Homo-coupling of benzylamine was conducted under neat condition. [f]Benzylamine **1a** (3.0 mmol) was used.

Scheme 4-2. Oxidative Ugi Reaction via Homo-Coupling of Benzylamines[a]



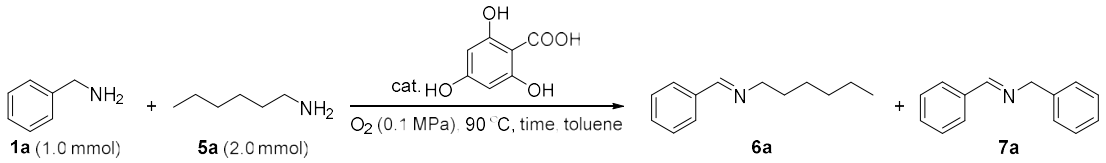


[a]Isolated yield (determined by ^{1}H NMR using bibenzyl as the internal standard); the yields of products are based on **2**.

Under the optimized reaction conditions (Table 4-1, entry 9), the scope of this oxidative Ugi reaction was examined (Scheme 4-2). A variety of benzylamine derivatives such as *para*-*tert*-butyl, *ortho*-methoxy, *meta*-methoxy, and *para*-methoxybenzylamines could be oxidized, and then successfully involved in the Ugi reaction with 2-chloroacetic acid and isocyanocyclohexane, affording the corresponding bis-amides **4b**–**4e** in good to excellent yields. Isocyanide derivatives and carboxylic acid derivatives were also examined under the standard reaction conditions. The oxidative Ugi reactions of benzyl isocyanide (**3f**), *tert*-butyl isocyanide (**3g**), or 1-isocyanopentane (**3h**) proceeded well to form the products **4f**–**4h** efficiently. When aromatic carboxylic acid, i.e., benzoic acid (**2i**) or 4-bromobenzoic acid (**2j**), as well as aliphatic

carboxylic acid (**2k**) were employed, the bis-amides **4i**–**4k** were obtained in high yields.

Table 4-2. Optimization of Cross-Coupling of Benzylamine with Other Amines



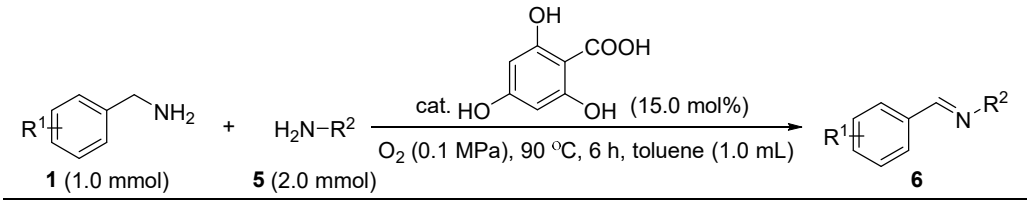
entry	cat. (mol %)	toluene (mL)	time (h)	yield (%)[a]	
				6a	**7a**
1	5	1.0	6	47	21
2	15	1.0	6	79 (71)	trace
3	15	neat	6	21	trace
4	15	1.5	6	61	6
5	15	1.5	24	64	trace
6	15	1.5	2	52	27

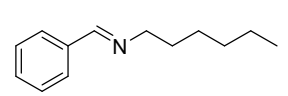
[a]Determined by ^{1}H NMR using 1,3,5-trioxane as the internal standard (isolated yield); the yields of products are based on **1a**.

Until now, the oxidative Ugi reaction via cross-coupling of amines is still unexplored. The cross-coupling imine products are usually synthesized from the condensation of amines with aldehydes, alcohols, or additional amines.[16] Although metal[17] and metal-free[18] methods have been researched widely for the cross-coupling of amines, metal-free methods based on organocatalysis[19] are still rarely reported. Thus, the cross-coupling of amines was next investigated and tried to involved into the Ugi reaction. First, the cross-coupling reaction conditions were optimized using benzylamine (**1a**, 1.0 mmol) and hexylamine (**5a**, 2.0 mmol) as the model substrates in the presence of 4,6-dihydroxysalicylic acid as an organocatalyst (Table 4-2). 4,6-Dihydroxysalicylic acid (5 mol%) catalyzed the cross-coupling reaction of **1a** with **5a** to generate 47% of cross-coupling product **6a** and 21% of homo-coupling product **7a** (Table 4-2, entry 1). Increasing the load of catalyst to 15 mol% led to the formation of **6a** in 79% yield with trace of **7a** (Table 4-2, entry 2). The reduced yields of **6a** were obtained by conducting the

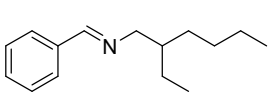
reaction in neat condition, lower concentration, longer or shorter reaction time (Table 4-2, entries 3–6).

Scheme 4-3. Cross-Coupling of Benzylamines with Other Amines[a]

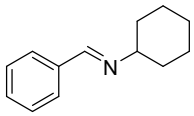




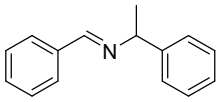
6a 71% (79%)



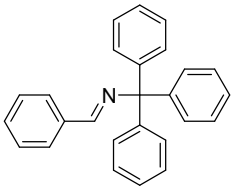
6b 83% (95%)



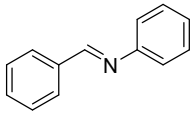
6c 80% (74%)



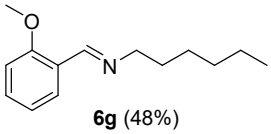
6d 79% (76%)



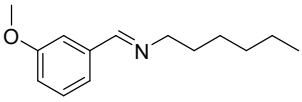
6e (11%)[b]



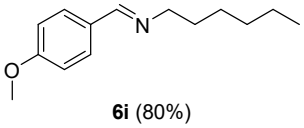
6f (51%)



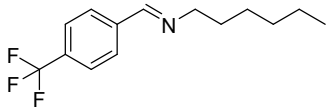
6g (48%)



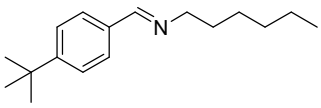
6h 66% (53%)



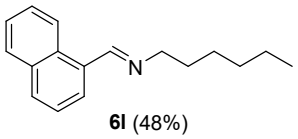
6i (80%)



6j 61% (60%)



6k (61%)



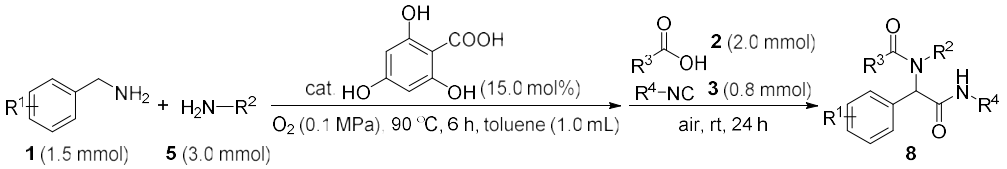
6l (48%)

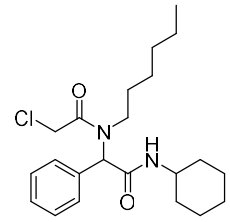
[a]Isolated yield (determined by ^{1}H NMR using bibenzyl as the internal standard); the yields of products are based on **1**; **6e**, **6f**, **6g**, **6i**, **6k**, and **6l** were difficult to purify because of hydrolysis. [b]CH_3CN was used as solvent.

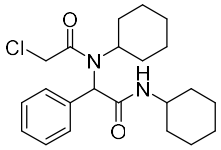
With the optimized reaction conditions in hand (Table 4-2, entry 2), benzylamine derivatives were examined to couple with a series of amines (Scheme 4-3). Benzylamine could be coupled with aliphatic and aromatic amines, affording the cross-coupling products **6a**–**6f** successfully. When benzylamines with a methoxy substituent at *ortho*, *meta*, and *para* positions were used as substrates, the corresponding imines **6g**–**6i** were formed in good yields.

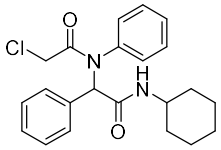
Electron-withdrawing and -donating groups at *para* positions of benzylamines were also examined, affording **6j** and **6k** in satisfactory yields. Besides, the reaction of 1-naphthylmethylamine **1l** could proceed smoothly under the standard reaction conditions.

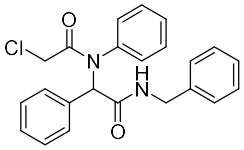
Scheme 4-4. Oxidative Ugi Reaction via Cross-Coupling of Benzylamines[a]

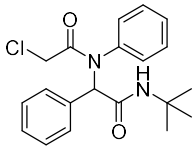


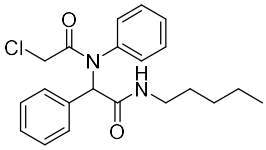

8a 39% (62%)

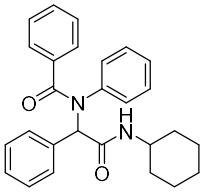

8b 37% (53%)

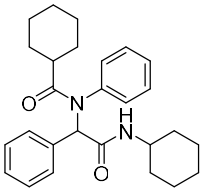

8c 61% (77%)[b]

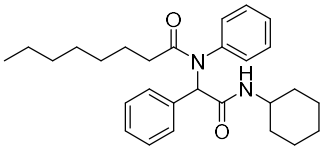

8d 48% (59%)


8e 78% (82%)


8f 63% (46%)[b]


8g 41% (42%)


8h 33% (46%)


8i 38% (69%)

[a]Isolated yield (determined by ^{1}H NMR using bibenzyl as the internal standard); the yields of products are based on **3**. [b]1.0 mL of CH_3OH was used as solvent.

As the cross-coupling of amines succeeded, the oxidative Ugi reactions based on the cross-coupling of amines promoted by 4,6-dihydroxysalicylic acid were investigated. After the cross-coupling reactions of two different amines were conducted, 2.0 mmol of carboxylic acids and 0.8 mmol of isocyanides were added. Successfully, the Ugi reactions were performed smoothly (Scheme 4-4). Aliphatic amines, such as hexylamine and cyclohexanamine, could be

converted to the corresponding bis-amides **8a** and **8b** successfully. When aromatic amine, i.e., aniline, was examined under this oxidative Ugi reaction conditions, the product **8c** was formed in moderate yield. Additionally, a series of isocyanide derivatives and carboxylic acid derivatives were examined. When the oxidative Ugi reactions of isocyanide derivatives, such as benzyl isocyanide, *tert*-butyl isocyanide, and 1-isocyanopentane, were performed, the corresponding products **8d**–**8f** were generated in moderate to good yields. Both of aromatic and aliphatic carboxylic acids were tolerated under this oxidative Ugi reaction conditions, affording bis-amides **8g**–**8i** successfully.

4-3 Conclusion

In summary, the author has developed a facile oxidative Ugi reaction promoted by 4,6-dihydroxysalicylic acid as an organocatalyst under O_2 atmosphere. Pseudo-four-component oxidative Ugi reactions were performed efficiently via homo-coupling of benzylamines and subsequently condensation with carboxylic acids and isocyanides. Catalyzed by 4,6-dihydroxysalicylic acid, the cross-coupling reactions of two different amines also proceed smoothly with O_2, which subsequently involved in the Ugi reactions with carboxylic acids and isocyanides successfully. This organocatalytic oxidative Ugi four-component reaction of a carboxylic acid and an isocyanide with the imine *in situ* formed form the cross-coupling of two different amines under O_2 atmosphere was demonstrated as a very rare example of oxidative Ugi reactions.

4-4 Experimental Section

General Comment

Unless otherwise stated, all starting materials and catalysts were purchased from commercial sources and used without further purification. All solvents were distilled and degassed with nitrogen before use. ^{1}H NMR spectra were recorded on JEOL JNM-ECS400 (400 MHz) FT NMR system or JEOL JNM-ECX400 (400 MHz) FT NMR system in $CDCl_3$ with Me_4Si as an internal standard. ^{13}C NMR spectra were recorded on JEOL JNM-ECX400 (100 MHz) FT NMR or JEOL JNM-ECS400 (100 MHz) FT NMR in $CDCl_3$. IR spectra were reported in wave numbers (cm^{-1}).

General Procedure for the Synthesis of Bis-Amides (4).

Benzylamines **1** (3.0 mmol), 4,6-dihydroxysalicylic acid (25.5 mg, 0.15 mmol), and toluene (1.0 mL) were added to a two-necked flask equipped with O_2 balloon at room temperature, and stirred at 90 °C under O_2 atmosphere for 2 h. Then O_2 balloon was removed, the reaction mixture was cooled to room temperature. To the mixture were added methanol (2.0 mL), carboxylic acids **2** (1.0 mmol), and isocyanides **3** (1.0 mmol), and the resulting solution was stirred at room temperature in air for 24 h. After the reaction was finished, the resulting mixture was transferred into round-bottom flask using methanol (5 mL) and concentrated under reduced pressure. Finally, the residue was purified by gel permeation chromatography (eluent: chloroform) to give product **4**.

N-Benzyl-2-chloro-N-(2-(cyclohexylamino)-2-oxo-1-phenylethyl)acetamide (4a). white solid, 303.2 mg, 76%, mp 139-141 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28-7.36 (m, 5H), 7.15-7.23 (m, 3H), 7.03 (d, J = 6.9 Hz, 2H), 5.93 (s, 1H), 5.76 (d, J = 7.8 Hz, 1H), 4.79 (d, J = 17.9 Hz, 1H), 4.59 (d, J = 17.9 Hz, 1H), 4.04 (d, J = 12.8 Hz, 1H), 3.92 (d, J = 12.8 Hz, 1H), 3.78 (s, 1H), 1.88 (s, 2H),

1.55-1.67 (m, 3H), 1.28-1.37 (m, 2H), 1.06-1.12 (m, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 168.4, 168.0, 136.8, 134.6, 129.7, 129.0, 128.9, 128.7, 127.5, 126.1, 63.4, 50.1, 48.8, 42.3, 32.8, 25.5, 24.9, 24.8; IR (KBr, ν/cm^{-1}): 3271, 2927, 2854, 1647, 1552, 1451, 1219, 731, 698.

N-(4-(tert-Butyl)benzyl)-N-(1-(4-(tert-butyl)phenyl)-2-(cyclohexylamino)-2-oxoethyl)-2-chloro-acetamide (4b). yellow solid, 480.5 mg, 94%, mp 104-105 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27-7.33 (m, 4H), 7.20 (d, J = 8.2 Hz, 2H), 6.90 (d, J = 7.3 Hz, 2H), 5.91 (s, 1H), 5.72 (d, J = 8.2 Hz, 1H), 4.74 (d, J = 17.9 Hz, 1H), 4.54 (d, J = 17.4 Hz, 1H), 4.07 (d, J = 12.8 Hz, 1H), 3.95 (d, J = 12.8 Hz, 1H), 3.79-3.81 (m, 1H), 1.86-1.93 (m, 2H), 1.56-1.67 (m, 4H), 1.20-1.33 (m, 20H), 1.10-1.11 (m, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 168.2, 151.9, 150.3, 133.8, 131.6, 129.5, 125.9, 125.8, 125.5, 63.0, 49.8, 48.8, 42.4, 34.6, 34.5, 32.8, 31.4, 31.3, 25.5, 24.9, 24.8; IR (KBr, ν/cm^{-1}): 3312, 2933, 2858, 1645, 1515, 1455, 1363, 1274, 819, 559.

2-Chloro-N-(2-(cyclohexylamino)-1-(2-methoxyphenyl)-2-oxoethyl)-N-(2-methoxybenzyl)acet-amide (4c). white solid, 284.3 mg, 62%, mp 197-199 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 (d, J = 7.7 Hz, 1H), 7.10-7.21 (m, 3H), 6.85 (t, J = 7.5 Hz, 1H), 6.77 (t, J = 7.5 Hz, 1H), 6.68 (t, J = 7.9 Hz, 2H), 6.03 (s, 1H), 5.56 (d, J = 8.2 Hz, 1H), 4.55-4.67 (m, 2H), 4.19 (d, J = 12.7 Hz, 1H), 4.07 (d, J = 12.7 Hz, 1H), 3.73-3.79 (m, 7H), 1.87 (s, 2H), 1.55-1.66 (m, 3H), 1.27-1.38 (m, 2H), 0.97-1.14 (m, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 168.4, 168.0, 157.7, 156.5, 130.4, 130.1, 128.4, 127.2, 124.7, 122.6, 120.6, 120.3, 110.1, 109.7, 58.5, 55.2, 48.5, 46.2, 42.2, 32.9, 32.8, 25.6, 24.9, 24.8; IR (KBr, ν/cm^{-1}): 3279, 2934, 2853, 1645, 1561, 1495, 1467, 1242, 1110, 1032, 949, 751, 540.

2-Chloro-N-(2-(cyclohexylamino)-1-(3-methoxyphenyl)-2-oxoethyl)-N-(3-methoxybenzyl)acet-amide (4d). white solid, 417.8 mg, 91%, mp 144-145 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22 (t, J = 8.0 Hz, 1H), 7.14 (t, J = 8.0 Hz, 1H), 6.92-6.97 (m, 2H), 6.83 (dd, J = 8.2, 1.8 Hz, 1H), 6.67-6.73 (m, 2H), 6.58 (s, 1H), 5.90 (s, 1H), 5.78 (d, J = 7.3 Hz, 1H), 4.75 (d, J = 17.9 Hz, 1H), 4.58 (d, J =

17.4 Hz, 1H), 4.05 (d, *J* = 12.8 Hz, 1H), 3.92 (d, *J* = 13.3 Hz, 1H), 3.75-3.80 (m, 1H), 3.72 (s, 3H), 3.70 (s, 3H), 1.86-1.92 (m, 2H), 1.56-1.67 (m, 3H), 1.28-1.37 (m, 2H), 1.06-1.12 (m, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 168.4, 167.9, 159.9, 138.6, 136.2, 130.0, 129.8, 121.9, 118.4, 115.0, 114.8, 113.2, 111.5, 63.4, 55.3, 55.3, 50.1, 48.7, 42.3, 32.8, 25.5, 24.9, 24.8; IR (KBr, *v*/cm^{-1}): 3276, 2933, 2836, 2360, 1645, 1602, 1490, 1456, 1260, 1042, 872, 692.

2-Chloro-N-(2-(cyclohexylamino)-1-(4-methoxyphenyl)-2-oxoethyl)-N-(4-methoxybenzyl)acetamide (4e). yellow solid, 225.1 mg, 49%, mp 103-104 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30 (d, *J* = 8.7 Hz, 2H), 6.99 (d, *J* = 8.2 Hz, 2H), 6.83 (d, *J* = 8.7 Hz, 2H), 6.76 (d, *J* = 8.7 Hz, 2H), 5.78 (s, 1H), 5.63 (d, *J* = 7.8 Hz, 1H), 4.68 (d, *J* = 17.4 Hz, 1H), 4.50 (d, *J* = 16.9 Hz, 1H), 4.04 (d, *J* = 12.8 Hz, 1H), 3.92 (d, *J* = 12.8 Hz, 1H), 3.80-3.83 (m, 1H), 3.78 (s, 3H), 3.75 (s, 3H), 1.88 (s, 2H), 1.56-1.67 (m, 3H), 1.28-1.37 (m, 2H), 1.08-1.12 (m, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 168.3, 159.9, 159.0, 131.1, 128.8, 127.5, 126.7, 114.4, 114.2, 63.2, 55.4, 55.3, 49.6, 48.7, 42.4, 32.9, 25.5, 24.9, 24.8; IR (KBr, *v*/cm^{-1}): 3265, 2924, 2833, 2356, 1645, 1615, 1514, 1419, 1250, 1179, 1036, 796.

N-Benzyl-2-(N-benzyl-2-chloroacetamido)-2-phenylacetamide (4f). white solid, 288.9 mg, 71%, mp 113-114 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33 (s, 2H), 7.22-7.27 (m, 5H), 7.15-7.20 (m, 6H), 6.97 (d, *J* = 7.7 Hz, 2H), 6.67-6.70 (m, 1H), 6.09 (s, 1H), 4.76 (d, *J* = 17.2 Hz, 1H), 4.61 (d, *J* = 17.7 Hz, 1H), 4.33-4.45 (m, 2H), 3.98 (d, *J* = 13.1 Hz, 1H), 3.86 (d, *J* = 13.1 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 169.1, 168.4, 138.0, 136.7, 134.3, 129.7, 128.9, 128.9, 128.7, 128.6, 127.6, 127.4, 126.1, 63.1, 49.9, 43.6, 42.3; IR (KBr, *v*/cm^{-1}): 3247, 3072, 2356, 1645, 1557, 1455, 1404, 1222, 1075, 794, 696.

N-Benzyl-N-(2-(tert-butylamino)-2-oxo-1-phenylethyl)-2-chloroacetamide (4g) [CAS: 1370472-34-6].[20] yellow solid, 276.2 mg, 74%, mp 146-147 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 (s, 2H), 7.27-7.28 (m, 3H), 7.13-7.20 (m, 3H), 6.97 (d, *J* = 6.3 Hz, 2H), 5.97 (s, 1H), 5.73 (s,

1H), 4.78 (d, *J* = 17.7 Hz, 1H), 4.61 (d, *J* = 17.7 Hz, 1H), 4.04 (d, *J* = 12.7 Hz, 1H), 3.91 (d, *J* = 13.1 Hz, 1H), 1.33 (s, 9H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 168.4, 168.3, 136.9, 134.7, 129.7, 128.9, 128.8, 128.6, 127.3, 126.0, 63.4, 51.8, 49.8, 42.4, 28.6.

N-Benzyl-2-chloro-N-(2-oxo-2-(pentylamino)-1-phenylethyl)acetamide (4h). white solid, 344.5 mg, 89%, mp 73-74 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.17-7.36 (m, 8H), 7.01 (d, *J* = 6.8 Hz, 2H), 6.19 (s, 1H), 6.02 (s, 1H), 4.79 (d, *J* = 18.1 Hz, 1H), 4.63 (d, *J* = 17.7 Hz, 1H), 4.04 (d, *J* = 12.7 Hz, 1H), 3.92 (d, *J* = 12.7 Hz, 1H), 3.18-3.26 (m, 2H), 1.45 (s, 2H), 1.22-1.33 (m, 4H), 0.86 (t, *J* = 6.8 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 168.9, 168.4, 136.8, 134.6, 129.6, 128.9, 128.8, 128.7, 127.4, 126.1, 63.2, 50.0, 42.3, 39.8, 29.0, 22.3, 14.0; IR (KBr, ν/cm^{-1}): 3270, 3091, 2932, 2857, 1645, 1557, 1496, 1455, 1404, 1189, 940, 798, 733, 694, 532.

N-Benzyl-N-(2-(cyclohexylamino)-2-oxo-1-phenylethyl)benzamide (4i) [CAS: 189077-35-8].[10a] light yellow solid, 324.0 mg, 76%, mp 71-73 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47 (d, *J* = 6.9 Hz, 2H), 7.29-7.35 (m, 8H), 7.14-7.20 (m, 3H), 7.08 (d, *J* = 6.4 Hz, 2H), 5.71 (s, 1H), 5.49 (s, 1H), 4.46-4.70 (m, 2H), 3.77-3.85 (m, 1H), 1.80-1.90 (m, 2H), 1.54-1.66 (m, 3H), 1.27-1.38 (m, 2H), 1.04-1.13 (m, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 173.3, 168.3, 136.3, 135.2, 129.9, 129.7, 128.9, 128.7, 128.6, 128.4, 127.1, 126.8, 64.8, 52.9, 48.7, 32.8, 25.6, 24.9, 24.8.

N-Benzyl-4-bromo-N-(2-(cyclohexylamino)-2-oxo-1-phenylethyl)benzamide (4j). light yellow solid, 460.2 mg, 91%, mp 83-85 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26-7.42 (m, 10H), 7.11-7.18 (m, 3H), 7.02 (d, *J* = 6.0 Hz, 2H), 5.70 (s, 1H), 5.54 (s, 1H), 4.69 (d, *J* = 16.5 Hz, 1H), 4.45 (s, 1H), 3.76-3.84 (m, 1H), 1.81-1.88 (m, 2H), 1.54-1.64 (m, 3H), 1.27-1.37 (m, 2H), 1.03-1.12 (m, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 172.2, 168.1, 137.3, 137.1, 135.1, 134.9, 131.6, 129.7, 128.9, 128.8, 128.4, 127.1, 126.9, 124.1, 64.3, 52.2, 48.7, 32.7, 25.5, 24.8, 24.7; IR (KBr, ν/cm^{-1}): 3287, 2930, 2851, 2356, 1622, 1590, 1496, 1455, 1409, 1069, 1013, 832, 696, 554.

N-Benzyl-N-(2-(cyclohexylamino)-2-oxo-1-phenylethyl)octanamide (4k). yellow solid, 408.3 mg,

91%, mp 107-108 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 (s, 2H), 7.12-7.22 (m, 6H), 6.99 (d, *J* = 7.3 Hz, 2H), 6.02 (s, 1H), 5.94 (d, *J* = 7.8 Hz, 1H), 4.75 (d, *J* = 17.9 Hz, 1H), 4.56 (d, *J* = 17.9 Hz, 1H), 3.78-3.80 (m, 1H), 2.16-2.36 (m, 2H), 1.02-1.89 (m, 20H), 0.85 (t, *J* = 6.6 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 175.2, 168.9, 137.9, 135.5, 129.7, 128.6, 128.4, 128.3, 126.8, 126.1, 62.7, 50.1, 48.5, 34.1, 32.8, 31.7, 29.3, 29.0, 25.5, 25.3, 24.9, 24.8, 22.6, 14.1; IR (KBr, ν/cm^{-1}): 3282, 2924, 2853, 1647, 1558, 1496, 1451, 1419, 1196, 948, 725, 698, 569.

General Procedure for the Synthesis of Imines (6).

Benzylamines **1** (1.0 mmol), aromatic amines or aliphatic amines **5** (2.0 mmol), 4,6-dihydroxysalicylic acid (25.5 mg, 0.15 mmol), and toluene (1.0 mL) were added to a two-necked flask equipped with O_2 balloon at room temperature, and the mixture was stirred at 90 °C under O_2 atmosphere for 6 h. After the reaction was finished, the resulting mixture was transferred into round-bottom flask using ethyl acetate (5 mL) and concentrated under reduced pressure. The residue was purified by gel permeation chromatography (eluent: chloroform) to give product **6**.

N-Hexyl-1-phenylmethanimine (6a) [CAS: 19340-96-6].[21] colorless oil, 134.6 mg, 71%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.26 (s, 1H), 7.69-7.74 (m, 2H), 7.37-7.41 (m, 3H), 3.60 (td, *J* = 7.0, 1.4 Hz, 2H), 1.66-1.73 (m, 2H), 1.28-1.39 (m, 6H), 0.89 (t, *J* = 6.8 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 160.8, 136.4, 130.8, 130.5, 128.6, 128.3, 128.1, 127.1, 61.9, 31.8, 31.0, 27.1, 22.7, 14.2.

N-(2-Ethylhexyl)-1-phenylmethanimine (6b) [CAS: 69375-86-6].[19b] colorless oil, 180.6 mg, 83%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.24 (s, 1H), 7.71-7.74 (m, 2H), 7.38-7.39 (m, 3H), 3.51-3.53 (m, 2H), 1.68-1.71 (m, 1H), 1.32-1.41 (m, 8H), 0.89 (t, *J* = 7.3 Hz, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 160.8, 136.6, 130.4, 128.6, 128.1, 65.2, 40.6, 31.5, 29.1, 24.7, 23.2, 14.2, 11.1.

N-Cyclohexyl-1-phenylmethanimine (6c) [CAS: 2211-66-7].[21] colorless oil, 149.8 mg, 80%; ^{1}H

NMR (400 MHz, $CDCl_3$): δ 8.30 (s, 1H), 7.71-7.73 (m, 2H), 7.37-7.38 (m, 3H), 3.14-3.21 (m, 1H), 1.54-1.84 (m, 7H), 1.21-1.41 (m, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 158.6, 136.7, 130.4, 128.6, 128.1, 70.1, 34.6, 34.4, 25.7, 24.9.

1-Phenyl-N-(1-phenylethyl)methanimine (6d) [CAS: 3129-98-4].[19b] colorless oil, 165.4 mg, 79%; ^1H NMR (400 MHz, $CDCl_3$): δ 8.35 (s, 1H), 7.76-7.78 (m, 2H), 7.30-7.43 (m, 7H), 7.19-7.24 (m, 1H), 4.52 (q, *J* = 6.6 Hz, 1H), 1.58 (d, *J* = 6.3 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 159.5, 145.3, 136.5, 130.7, 128.6, 128.5, 128.4, 126.9, 126.7, 69.8, 25.0.

N-Hexyl-1-(3-methoxyphenyl)methanimine (6h) [CAS: 2122325-36-2].[21] colorless oil, 144.9 mg, 66%; ^1H NMR (400 MHz, $CDCl_3$): δ 8.24 (s, 1H), 7.29-7.33 (m, 2H), 7.23-7.26 (m, 1H), 6.95-6.98 (m, 1H), 3.85 (s, 3H), 3.60 (td, *J* = 7.1, 1.2 Hz, 2H), 1.66-1.73 (m, 2H), 1.30-1.38 (m, 6H), 0.89 (t, *J* = 7.0 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 160.8, 160.0, 138.0, 129.7, 121.5, 117.3, 111.5, 61.9, 55.5, 31.8, 31.0, 27.2, 22.8, 14.2.

N-Hexyl-1-(4-(trifluoromethyl)phenyl)methanimine (6j) [CAS: 1153620-92-8].[22] colorless oil, 157.1 mg, 61%; ^1H NMR (400 MHz, $CDCl_3$): δ 8.31 (s, 1H), 7.83 (d, *J* = 7.8 Hz, 2H), 7.66 (d, *J* = 8.2 Hz, 2H), 3.64 (t, *J* = 6.9 Hz, 2H), 1.67-1.74 (m, 2H), 1.30-1.38 (m, 6H), 0.89 (t, *J* = 6.6 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 159.3, 139.6, 132.2 (q, *J* = 32 Hz), 125.7 (q, *J* = 3.8 Hz), 123.9 (q, *J* = 247 Hz), 62.0, 31.8, 30.9, 27.2, 22.7, 14.2.

1-(4-(Tert-butyl)phenyl)-N-hexylmethanimine (6k). colorless oil; ^1H NMR (400 MHz, $CDCl_3$): δ 8.24 (s, 1H), 7.66 (d, *J* = 8.2 Hz, 2H), 7.43 (d, *J* = 8.2 Hz, 2H), 3.59 (t, *J* = 6.6 Hz, 2H), 1.67 (q, *J* = 7.2 Hz, 2H), 1.29-1.37 (m, 15H), 0.88 (t, *J* = 6.8 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 160.7, 153.9, 133.8, 127.9, 125.6, 62.0, 35.0, 31.8, 31.3, 31.1, 27.1, 22.8, 14.2.

N-Hexyl-1-(naphthalen-1-yl)methanimine (6l). colorless oil; ^1H NMR (400 MHz, $CDCl_3$): δ 8.93 (s, 1H), 8.86 (d, *J* = 8.6 Hz, 1H), 7.87-7.90 (m, 3H), 7.49-7.59 (m, 3H), 3.73 (t, *J* = 6.8 Hz, 2H),

1.75-1.82 (m, 2H), 1.33-1.44 (m, 6H), 0.91 (d, J = 6.8 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 160.3, 133.9, 132.0, 131.4, 130.8, 128.7, 128.4, 127.1, 126.1, 125.4, 124.4, 62.9, 31.8, 31.2, 27.3, 22.8, 14.2.

General Procedure for the Synthesis of Bis-Amides (8).

Benzylamines **1** (1.5 mmol), aliphatic or aromatic amines **5** (3.0 mmol), 4,6-dihydroxysalicylic acid (38.3 mg, 0.225 mmol), and toluene (1.0 mL) were added to a two-necked flask equipped with O_2 balloon at room temperature, and the mixture was stirred at 90 °C under O_2 atmosphere for 6 h. Then O_2 balloon was removed, the reaction mixture was cooled to room temperature. To the resulting mixture were added carboxylic acids **2** (0.8 mmol) and isocyanides **3** (1.0 mmol), and the solution was stirred at room temperature in air for 24 h. After the reaction was finished, the resulting mixture was transferred into round-bottom flask using methanol (5 mL) and concentrated under reduced pressure. Finally, the residue was purified by gel permeation chromatography (eluent: chloroform) to give product **8**.

2-Chloro-N-(2-(cyclohexylamino)-2-oxo-1-phenylethyl)-N-hexylacetamide (8a). light yellow solid, 122.7 mg, 39%, mp 109-110 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.37 (s, 5H), 5.89 (d, J = 7.3 Hz, 1H), 5.78 (s, 1H), 4.11-4.19 (m, 2H), 3.78-3.80 (m, 1H), 3.32 (t, J = 7.4 Hz, 2H), 1.02-1.99 (m, 18H), 0.80 (t, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 168.2, 167.4, 135.0, 129.5, 128.9, 128.7, 63.2, 48.7, 47.5, 41.6, 32.8, 31.1, 29.9, 26.5, 25.5, 24.8, 24.8, 22.4, 14.0; IR (KBr, ν/cm^{-1}): 3260, 3088, 2926, 2853, 2348, 1647, 1558, 1419, 1252, 700, 529.

2-Chloro-N-cyclohexyl-N-(2-(cyclohexylamino)-2-oxo-1-phenylethyl)acetamide (8b). white solid, 115.0 mg, 37%, mp 155-157 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.27-7.36 (m, 5H), 6.26 (d, J = 6.3 Hz, 1H), 4.87 (s, 1H), 4.07-4.21 (m, 2H), 3.67-3.80 (m, 2H), 1.52-2.02 (m, 11H), 1.26-1.43 (m, 5H), 1.07-1.17 (m, 4H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 169.3, 167.2, 136.2, 128.8, 128.0, 127.5, 63.6, 59.9, 48.5, 42.2, 32.7, 32.6, 31.8, 31.7, 25.9, 25.6, 25.2, 24.7, 24.6; IR (KBr, ν/cm^{-1}):

3297, 2929, 2855, 1616, 1539, 1451, 1221, 1151, 1032, 895, 697.

2-Chloro-N-(2-(cyclohexylamino)-2-oxo-1-phenylethyl)-N-phenylacetamide (8c). white solid, 187.8 mg, 61%, mp 227-228 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.11-7.27 (m, 10H), 6.00 (s, 1H), 5.54 (d, *J* = 7.7 Hz, 1H), 3.79-3.88 (m, 3H), 1.95 (d, *J* = 9.1 Hz, 1H), 1.84 (d, *J* = 11.3 Hz, 1H), 1.56-1.68 (m, 3H), 1.26-1.40 (m, 2H), 0.97-1.18 (m, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 168.2, 166.9, 138.8, 134.1, 130.5, 129.3, 128.9, 128.8, 128.6, 128.5, 65.9, 49.0, 42.7, 33.0, 32.9, 25.6, 24.9, 24.9; IR (KBr, *ν*/cm^{-1}): 3265, 2928, 2853, 2357, 1675, 1646, 1557, 1490, 1456, 1244, 699, 668, 554.

N-Benzyl-2-(2-chloro-N-phenylacetamido)-2-phenylacetamide (8d). white solid, 151.1 mg, 48%, mp 196-197 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.11-7.30 (m, 15H), 6.07 (s, 2H), 4.43-4.54 (m, 2H), 3.79-3.88 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 169.2, 167.0, 138.7, 138.0, 133.7, 130.6, 129.3, 129.0, 128.9, 128.8, 128.7, 127.7, 127.5, 66.0, 44.0, 42.7; IR (KBr, *ν*/cm^{-1}): 3296, 3068, 1652, 1557, 1493, 1454, 1394, 1245, 1077, 699, 544.

N-(tert-Butyl)-2-(2-chloro-N-phenylacetamido)-2-phenylacetamide (8e). white solid, 224.1 mg, 78%, mp 170-171 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.11-7.29 (m, 10H), 5.93 (s, 1H), 5.58 (s, 1H), 3.79-3.88 (m, 2H), 1.34 (s, 9H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 168.3, 166.8, 138.7, 134.2, 130.5, 130.4, 129.2, 128.8, 128.7, 128.5, 66.2, 51.8, 42.7, 28.7; IR (KBr, *ν*/cm^{-1}): 3295, 3064, 2971, 1674, 1647, 1595, 1544, 1496, 1453, 1431, 1394, 1359, 1222, 1149, 764, 702, 628, 540.

2-Chloro-N-(2-oxo-2-(pentylamino)-1-phenylethyl)-N-phenylacetamide (8f). white solid, 137.2 mg, 46%, mp 137-138 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.11-7.27 (m, 10H), 6.02 (s, 1H), 5.80 (s, 1H), 3.80-3.89 (m, 2H), 3.24-3.30 (m, 2H), 1.43-1.50 (m, 2H), 1.20-1.30 (m, 4H), 0.85 (t, *J* = 6.8 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 169.1, 166.9, 138.7, 134.0, 130.5, 129.3, 128.9, 128.8, 128.6, 65.9, 42.7, 40.0, 29.2, 29.1, 22.4, 14.1; IR (KBr, *ν*/cm^{-1}): 3272, 2933, 1678, 1652, 1557, 1492, 1455, 1373, 1242, 700, 551.

N-(2-(Cyclohexylamino)-2-oxo-1-phenylethyl)-N-phenylbenzamide (8g) [CAS: 1266385-49-2].[23] white solid, 135.4 mg, 41%, mp 160-161 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22-7.32 (m, 7H), 7.09-7.19 (m, 3H), 7.00 (s, 5H), 6.17 (s, 1H), 5.88 (d, *J* = 7.7 Hz, 1H), 3.83-3.93 (m, 1H), 1.89-1.98 (m, 2H), 1.55-1.70 (m, 3H), 1.29-1.41 (m, 2H), 1.03-1.21 (m, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 171.4, 168.7, 141.5, 136.2, 135.0, 130.3, 130.2, 129.5, 128.6, 128.6, 128.5, 127.7, 127.2, 66.9, 48.8, 32.9, 25.6, 24.9, 24.8; IR (KBr, *v*/cm^{-1}): 3285, 2923, 2853, 1645, 1557, 1490, 1447, 1348, 1232, 754, 698, 540.

N-(2-(Cyclohexylamino)-2-oxo-1-phenylethyl)-N-phenylcyclohexanecarboxamide (8h). yellow solid, 110.7 mg, 33%, mp 140-141 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.10-7.28 (m, 10H), 6.01 (s, 1H), 5.86 (d, *J* = 7.7 Hz, 1H), 3.78-3.87 (m, 1H), 2.04-2.12 (m, 1H), 1.84-1.95 (m, 2H), 1.48-1.77 (m, 10H), 1.28-1.40 (m, 2H), 0.85-1.17 (m, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 177.0, 169.0, 140.3, 135.0, 130.3, 130.3, 128.8, 128.3, 128.2, 128.0, 65.1, 48.6, 42.2, 32.9, 29.6, 29.2, 25.7, 25.6, 25.5, 25.4, 24.9, 24.8; IR (KBr, *v*/cm^{-1}): 3327, 2931, 2854, 1634, 1594, 1544, 1492, 1450, 1398, 1339, 1267, 1220, 754, 697, 556.

N-(2-Cyclohexylamino)-2-oxo-1-phenylethyl)-N-phenyloctanamide (8i). white solid, 132.4 mg, 38%, mp 175-176 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.11-7.27 (m, 10H), 6.02 (s, 1H), 5.74 (d, *J* = 7.2 Hz, 1H), 3.79-3.86 (m, 1H), 1.84-2.10 (m, 4H), 1.56-1.69 (m, 5H), 0.99-1.40 (m, 13H), 0.83 (t, *J* = 6.4 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 174.0, 169.0, 140.5, 135.0, 130.6, 130.4, 128.9, 128.4, 128.0, 65.3, 48.8, 35.0, 33.0, 31.7, 29.3, 29.1, 25.6, 25.5, 24.9, 24.9, 22.7, 14.2; IR (KBr, *v*/cm^{-1}): 3267, 2923, 2852, 1645, 1557, 1493, 1451, 1394, 1241, 699, 565.

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Chapter 5

Metal-Free Blue Dye Synthesis: Oxidation Coupling of Benzylamines and *N*,*N*-Dimethylanilines to Yield 4,4′-Diaminotriarylmethanes in the Presence of Salicylic Acid as a Co-oxidant

5-1 Introduction

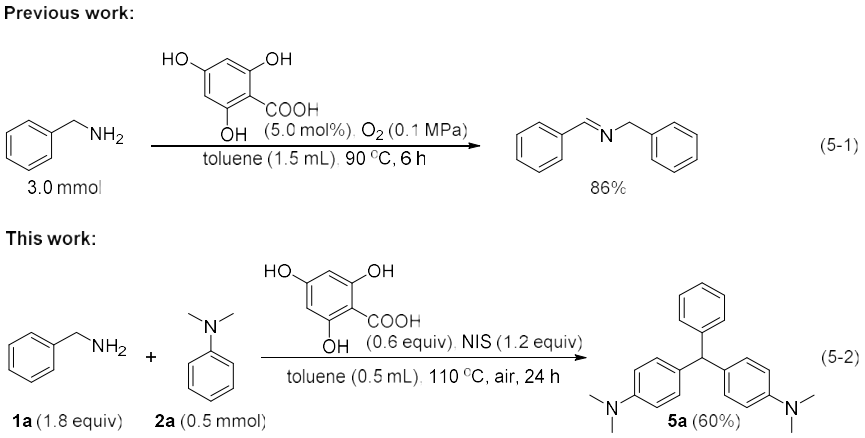
Dyes play important roles in modern materials science applications, such as display, imaging, and memory technologies, and are also often employed in both the analytical and biological sciences.[1] Dyes are generally classified on the basis of their chemical structures, with typical structural motifs including the spiropyran, quinone, thiazine, oxazine, phenazine, phthalide, triarylmethane, fluoran, and tetrazolium salt skeletons.[2] Among these structures, triarylmethane dyes are of particular importance due to their practical value, and these dyes are employed mainly for nontextile purposes, in novel types of colorless copying papers and in pressure-sensitive, thermal, and photographic recording materials. They are also extensively used in analytical and biological applications.[3] To render such structures valuable dye precursors, a minimum of two amino groups or a combination of hydroxyl and amino groups at the para-positions of the phenyl rings are required.[4]

Owing to the importance of triarylmethane compounds, considerable attention has been paid to the development of efficient methods for the synthesis of triarylmethane derivatives, and a variety of chemical transformations have been reported recently. Typically, triarylmethanes are synthesized by the reaction of functionalized diarylmethane derivatives, such as benzhydrols,[5]

diarylmethyl carbocations,[6] diarylmethyl carbonates,[7] diphenylacetonitriles,[8] sulfonyl diarylamines,[9] *N*-tosylhydrazones,[10] diphenylmethyl phenyl sulfones,[11] diarylmethyl ethers,[12] diarylketones,[13] and secondary alkyl halides,[14] in addition to the direct C-H arylation of diarylmethanes.[15] In addition, synthetic methods toward triarylmethanes based on the coupling of aromatic aldehydes[16] or one-carbon synthons[17] and the dehydroxylation of triarylmethanol derivatives[18] have also been developed. However, to the best of the author's knowledge, the synthesis of triarylmethanes from benzylamine substrates has not yet been reported.

Typically, the reported routes to 4,4′-diaminotriarylmethanes (DTMs) require the use of catalysts, which are commonly based on metals,[19] Brønsted acids such as sulfonic acid, sulfuric acid, and HCl, or Lewis acids such as zeolite and montmorillonite K-10.[20] As such, these routes suffer from various drawbacks, including the presence of metal-containing residues and the use of corrosive acids or hazardous reagents, which can lead to serious issues in their application.

Scheme 5-1. Oxidation of Benzylamines by 4,6-Dihydroxysalicylic Acid



Oxidation of amines to imines under metal-free conditions have been investigated extensively.[21] As shown in eq 5-1 (Scheme 5-1), the author recently also developed the 4,6-dihydroxysalicylic acid-catalyzed homo-coupling of benzylamines to imines,[22] and during this work, the author found that 4,6-dihydroxysalicylic acid can also assist the synthesis of DTMs

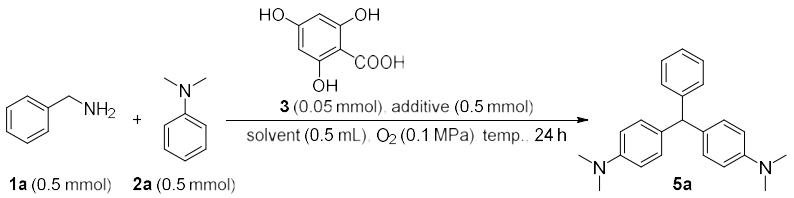
from benzylamines and *N*,*N*-dimethylanilines (Scheme 5-1, eq 5-2). Thus, this chapter deal with the coupling of benzylamines (**1**) and *N*,*N*-dimethylanilines (**2**) in the presence of 4,6-dihydroxysalicylic acid as a catalyst and *N*-iodosuccinimide (NIS) as a co-oxidant to yield a novel, safe, facile, and metal-free strategy for the synthesis of DTMs.

5-2 Oxidative Coupling of Benzylamines and *N*,*N*-Dimethylanilines

Initially, 4,6-dihydroxysalicylic acid (**3**), which was used as an organocatalyst in the oxidation of benzylamines to imines in the previous work,[22] was employed for the coupling of benzylamine (**1a**) and *N*,*N*-dimethylaniline (**2a**) under an O_2 atmosphere. When NIS (**4**) was selected as an additive, 4,4′-diaminotriarylmethane (**5a**) was formed, albeit in a low yield (Table 5-1, entry 1). Encouraged by this interesting result, the author further optimized the reaction conditions through variation in the additives and solvents employed (Table 5-1, entries 2–5). More specifically, *N*-bromosuccinimide (NBS) was less effective as an additive in this coupling reaction, and the absence of an additive or the use of tetrabutylammonium iodide (TBAI) or tetrabutylammonium bromide (TBAB) failed to generate the desired product **5a**. Among the various solvents examined (Table 5-1, entries 6–10), toluene emerged as the optimal solvent, as CH_3CN and benzene (i.e., the only other solvents that yielded the desired product) exhibited higher toxicities.

The author then attempted to increase the yield of this coupling reaction using 4,6-dihydroxysalicylic acid as the co-oxidant, NIS as the oxidant, and toluene as the solvent, and the results are shown in Table 5-2. Thus, in the presence of benzylamine (**1a**, 2.0 equiv) and 4,6-dihydroxysalicylic acid (**3**, 0.2 equiv), an increased yield of **5a** (26%) was achieved (Table 5-2, entry 1). In addition, a slight alteration of the procedure, where a toluene solution (0.1 mL) of **1a**, **3**, and **4** was stirred for 20 min at 110 °C prior to the addition of **2a** and an additional

Table 5-1. Optimization of the Reaction Conditions for the Coupling of Benzylamine and *N*,*N*-Dimethylaniline[a]



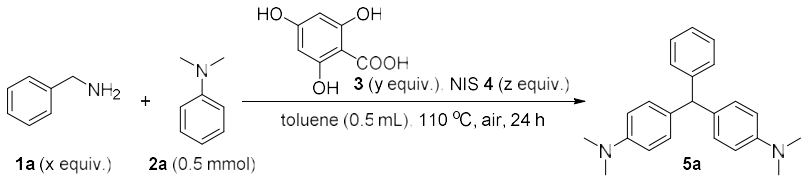
entry	additive	solvent	temp. (°C)	yield[b] (%)
1	NIS	toluene	110	8
2	NBS	toluene	110	5
3	TBAI	toluene	110	0
4	TBAB	toluene	110	0
5	none	toluene	110	0
6	NIS	DMSO	110	0
7	NIS	CH_3CN	80	7
8	NIS	benzene	80	5
9	NIS	THF	55	0
10	NIS	$CHCl_3$	55	0

[a]Conditions: **1a**, **2a**, **3**, additive, and solvent (0.5 mL) were stirred under O_2 at the desired temperature for 24 h. [b]Determined by ^1H NMR spectroscopy of the crude mixture using 1,3,5-trioxane as an internal standard.

aliquot of toluene (0.4 mL), resulted in the formation of **5a** in 43% yield (Table 5-2, entry 2). Although the use of a N_2 atmosphere decreased the yield of **5a**, removal of the O_2 balloon (i.e., the reaction in the air) afforded **5a** in 46% yield (Table 5-2, entries 3 and 4). Furthermore, considering that I_2 could be generated during this reaction, 4,6-dihydroxysalicylic acid (**3**) and NIS (**4**) were mixed in toluene (0.5 mL), and the mixture was stirred for 20 min at 110 °C to observe and confirm the formation of I_2. Subsequently, benzylamine (**1a**) and *N*,*N*-dimethylaniline (**2a**) were added, and the resulting mixture was allowed to stir for 24 h. As a result, the desired product **5a** was obtained in an improved yield of 50% (Table 5-2, entry 5), which indicated that I_2 plays an important role in the synthesis of DTMs. Interestingly, upon decreasing the quantity of **1a** to 1.2 equiv, the yield of **5a** was slightly improved (i.e., 54%, Table

5-2, entry 6). The author then examined the influence of the 4,6-dihydroxysalicylic acid (**3**) and NIS (**4**) molar ratios on the yield of **5a** (Table 5-2, entries 6–9) and found that a 1:2 ratio of **3**/**4** afforded **5a** in a similar yield (51%, Table 5-2, entry 8). Further optimization of the reaction

Table 5-2. Optimization of the Coupling Reaction between Benzylamine and *N*,*N*-Dimethylaniline[a]



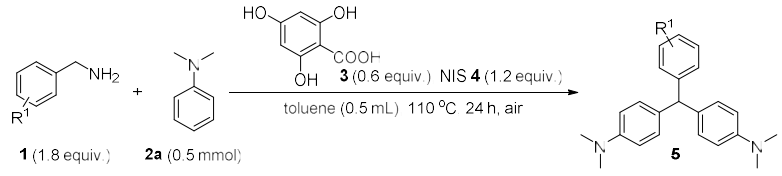
entry	x	y	z	y:z	yield[f] (%)
1[bd]	2.0	0.2	1.0	1:5	26
2[cd]	2.0	0.2	1.0	1:5	43
3[ce]	2.0	0.2	1.0	1:5	20
4[c]	2.0	0.2	1.0	1:5	46, 33[g], 30[h], 22[i], 20[j]
5	2.0	0.2	1.0	1:5	50
6	1.2	0.2	1.0	1:5	54
7	1.2	0.3	0.9	1:3	53
8	1.2	0.3	0.6	1:2	51
9	1.2	0.3	0.3	1:1	41
10	0.9	0.3	0.6	1:2	53
11	0.7	0.3	0.6	1:2	30
12	0.6	0.2	0.4	1:2	34
13	1.5	0.5	1.0	1:2	58
14	**1.8**	**0.6**	**1.2**	**1:2**	**60 (58)**
15	2.4	0.8	1.6	1:2	50

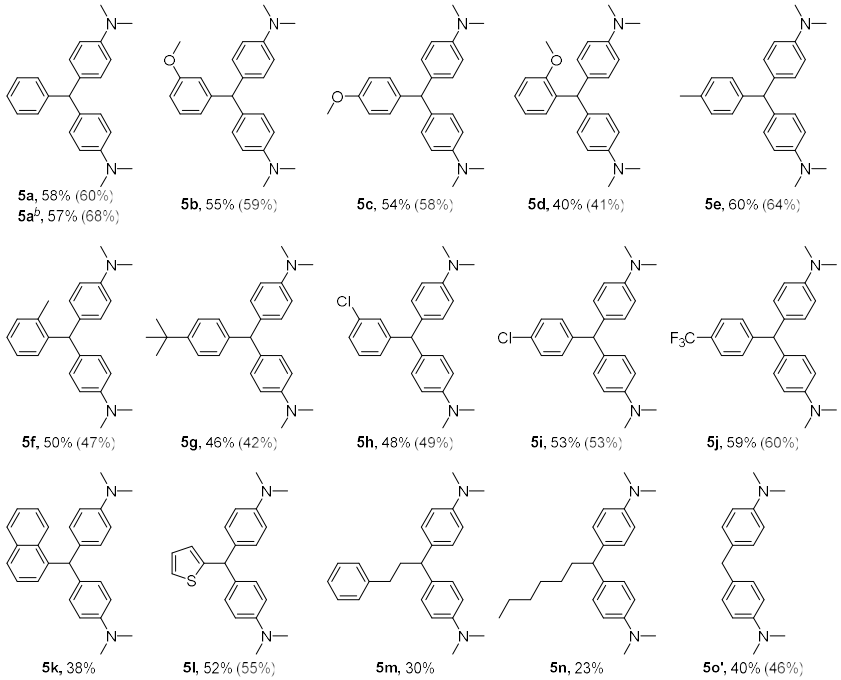
[a]Conditions: **3**, NIS (**4**), and distilled toluene (0.5 mL) were stirred at 110 °C for 20 min prior to the addition of benzylamine (**1a**) and *N*,*N*-dimethylaniline (**2a**). The reaction was allowed to continue for 24 h. [b]All reagents were mixed in distilled toluene prior to commencing the reaction. [c]Conditions: benzylamine (**1a**), **3**, NIS (**4**), and distilled toluene (0.1 mL) were stirred at 110 °C for 20 min prior to the addition of **2a** in distilled toluene (0.4 mL). The reaction was allowed to continue for 24 h. [d]Under O_2. [e]Under N_2. [f]Yield of **5a** is based on substrate **2a** and determined by ^{1}H NMR spectroscopy using 1,3,5-trioxane as the internal standard (isolated yield). [g]4,6-Dimethoxysalicylic acid was used instead of **3**. [h]Acetic acid was used instead of **3**. [i]*p*-TSA was used instead of **3**. [j]PPTS was used instead of **3**.

conditions revealed that the use of **1a** (1.8 equiv), **3** (0.6 equiv), and **4** (1.2 equiv) led to the formation of **5a** in 60% yield (Table 5-2, entry 14). Although 4,6-dimethoxysalicylic acid (an effective organocatalyst in the oxidation of benzylamines to imines),[21] acetic acid, *p*-toluenesulfonic acid (*p*-TSA), and pyridinium toluene-4-sulfonate (PPTS) were examined in this coupling reaction, lower yields of **5a** were obtained in all cases (Table 5-2, entry 4, footnotes g, h, i, and j).

With the optimized reaction conditions in hand (Table 5-2, entry 14), the scope of this coupling reaction was examined using **2a** and a range of substituted benzylamines (Table 5-3). As indicated, 4-substituted benzylic amines, including the 4-methoxyl, 4-methyl, 4-*tert*-butyl, 4-chloro, and 4-trifluoromethyl derivatives, were successfully coupled with **2a** to afford the corresponding DTMs in moderate to good yields (Table 5-3, **5c**, **5e**, **5g**, **5i**, and **5j**). Moreover, 2- and 3-substituted benzylamines also led to the formation of the desired products in moderate yields (Table 5-3, **5b**, **5d**, **5f**, and **5h**). Interestingly, despite its steric hindrance, *o*-methoxybenzylamine afforded the desired triarylmethane derivative in a moderate yield (**5d**), and similar results were achieved with para- and ortho-methylbenzylamines (**5e** and **5f**). It is noteworthy that 1-naphthylmethylamine (**1k**), 2-thiophenemethylamine (**1l**), 3-phenylpropylamine (**1m**), and heptylamine (**1n**) were also tolerated under these coupling conditions to afford DTMs in acceptable yields, although furfurylamine and 2-pyridinemethylamine were unsuitable in the reaction with *N*,*N*-dimethylaniline (data not shown). Furthermore, the gram-scale synthesis of DTMs was also successful under the optimized reaction conditions (Table 5-3, **5a**^{b}), giving a 57% yield of **5a** from **2a** (0.97 g, 8 mmol scale) after increasing the reaction time to 49 h. The author also investigated the use of the activated *N*,*N*-disubstituted *para*-aminobenzylamine substrate, but in this case, the diarylmethane derivative was generated instead of the desired product (Table 5-3, **5o′**).

Table 5-3. Substrate Scope for Coupling of the Benzylamine Derivatives with *N*,*N*-Dimethylaniline[a]

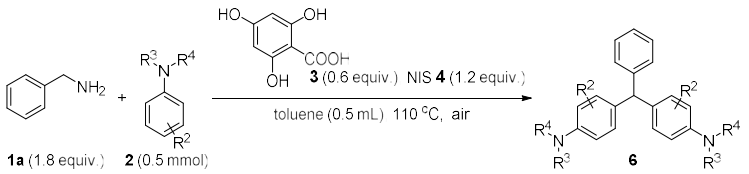


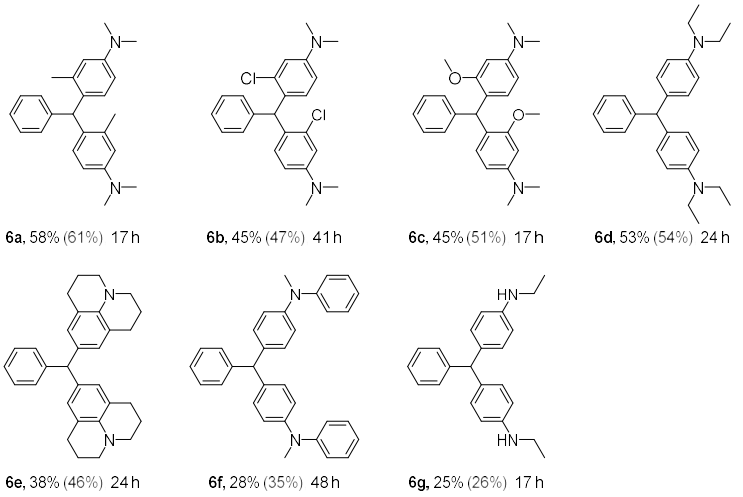


[a]Yields of **5** are based on **2a** (^{1}H NMR yield using a 1,3,5-trioxane internal standard). [b]Gram-scale synthesis, **2a** (0.97 g, 8 mmol), 49 h reaction time.

The substrate scope was further investigated using a series of *N*,*N*-dimethylaniline derivatives under the optimized reaction conditions (Table 5-4). More specifically, *N*,*N*-dimethylanilines bearing electron-donating and moderately electron-withdrawing groups at the 3-position of the phenyl ring proceeded smoothly to furnish the corresponding DTMs over 17-41 h (Table 5-4, **6a**–**c**). Furthermore, symmetrically and unsymmetrically substituted amino groups on the aniline structures were also successfully converted under these metal-free conditions (Table 5-4, **6d**–**g**).

Table 5-4. Substrate Scope for Coupling of Benzylamine with *N*,*N*-Dimethylaniline Derivatives[a]





[a]Yields of **6** are based on **2** (^{1}H NMR yield using a 1,3,5-trioxane internal standard).

5-3 Oxidation of DTMs to Blue Dyes

As dye precursors, DTMs can be oxidized to produce malachite green derivatives. Thus, as outlined in Figure 5-1, the author examined the oxidation of several DTM products using tetrachloro-1,4-benzoquinone (chloranil), prior to dissolution of the obtained products in $CHCl_3$. With the exception of the 4-*tert*-butyl-substituted DTM, which produced a light green color, the other malachite green derivatives gave dark or light blue solutions. Besides, the absorption maxima of the malachite green derivatives **A-F** were detected by UV-vis absorption spectroscopy (Table 5-5 and Figure 5-2), which more or less corresponded with literature data.[23]

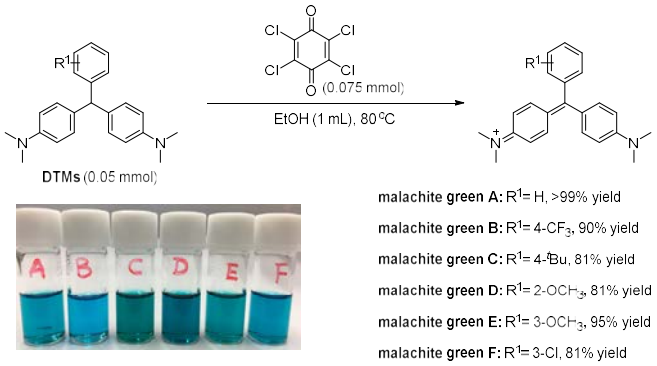


Figure 5-1. (a) Synthesis of malachite green derivatives by the oxidation of DTMs, and subsequent dissolution in $CHCl_3$ (50 μg/mL). Yields were determined by ^1H NMR spectroscopy using 1,3,5-trioxane as the internal standard.

Table 5-5. Visible Absorption Data for Malachite Green A-F.

entry	R	λ_{max}/nm[a]	λ_{max}/nm[b]
1	H	619; 427	622; 428
2	4-CF_3	631; 420[c]	635; 422
3	4-*t*Bu	616; 439	617; 442
4	2-OCH_3	622; 441	625; 443
5	3-OCH_3	621; 435	623; 436
6	3-Cl	627; 425	631; 426

[a]In acetic acid; [b]In $CHCl_3$; [c]In EtOH.

To gain an improved understanding of the role of 4,6-dihydroxysalicylic acid (**3**) and NIS (**4**) in this coupling reaction, a 1:2 molar ratio of **3** and **4** was mixed in distilled toluene and stirred for 1 h under air. The ^1H and $^{13}C\{^1H\}$ NMR spectra of the resulting crude mixture and of 4,6-dihydroxysalicylic acid (**3**) alone were then recorded in CD_3OD, as shown in Figure 5-3. Upon comparison of Figure 5-3(a) (**3**) and 5-3(b) (the crude mixture), it was apparent that a diagnostic signal at 5.86 ppm, which corresponds to the phenyl protons of **3**, disappeared after 1 h. This result indicates that the reaction between **3** and **4** takes place at the phenyl ring of **3**. This conclusion was further confirmed by the $^{13}C\{^1H\}$ NMR spectra shown in Figure 5-3(c) and

5-3(d). More specifically, the signal corresponding to the C(d) atoms of **3** shifted from 96.12 to 63.51 ppm following the reaction, while the positions of the other carbon signals remained essentially unchanged after 1 h, and the C(d) atom at 63.51 ppm has no resonance position according to the HSQC spectroscopy. It is interesting that this crude reaction mixture can be detected by ESR spectroscopy after being stored at room temperature for 3 h, and a narrow very strong signal with g = 2.00336 occurred (Figure 5-4).[24] These results strongly indicated that radical species were generated between **3** and **4**. The author therefore speculated that radical complex **A** was formed, and that this radical complex initiates the coupling reaction between benzylamines and *N*,*N*-dimethylanilines.

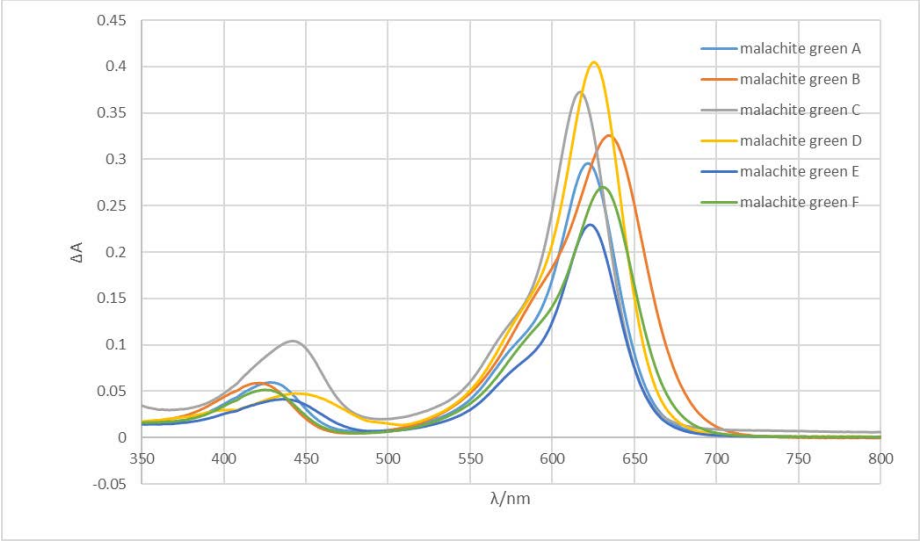


Figure 5-2. Visible Absorption of Malachite Green **A–F** in $CHCl_3$.

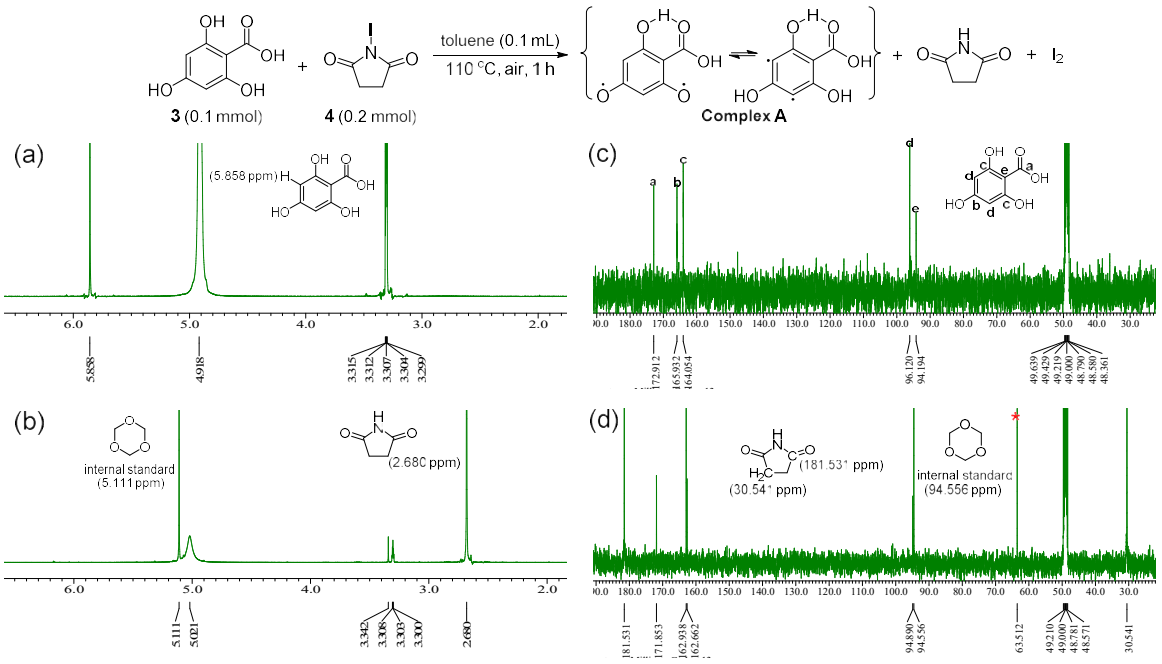


Figure 5-3. The *in situ* Generation of I_2 from 4,6-Dihydroxysalicylic Acid (**3**) and NIS (**4**). (a) ^{1}H NMR spectrum of **3** in CD_3OD. (b) ^{1}H NMR spectrum of the crude reaction mixture in CD_3OD. (c) $^{13}C\{^1H\}$ NMR of **3** in CD_3OD. (d) $^{13}C\{^1H\}$ NMR spectrum of the crude reaction mixture in CD_3OD.

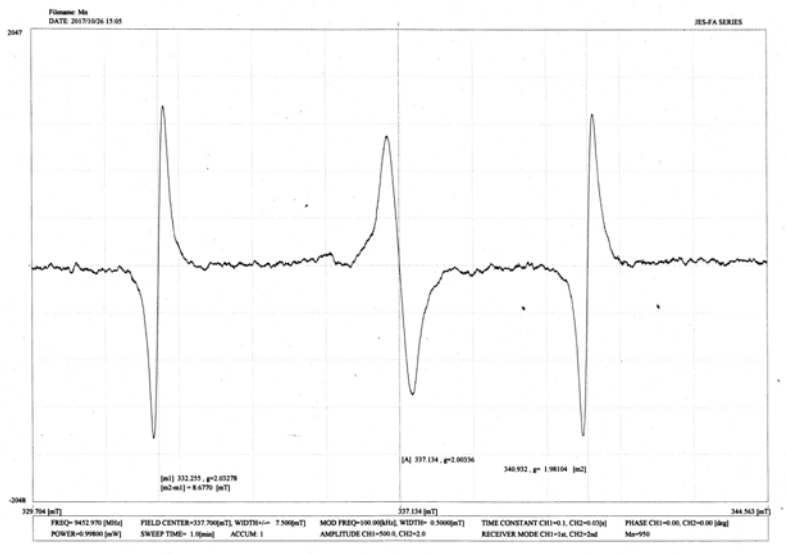
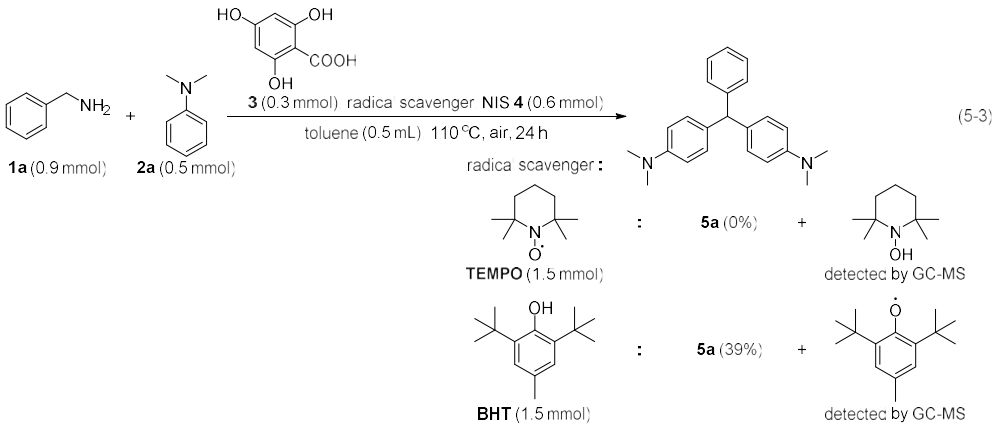


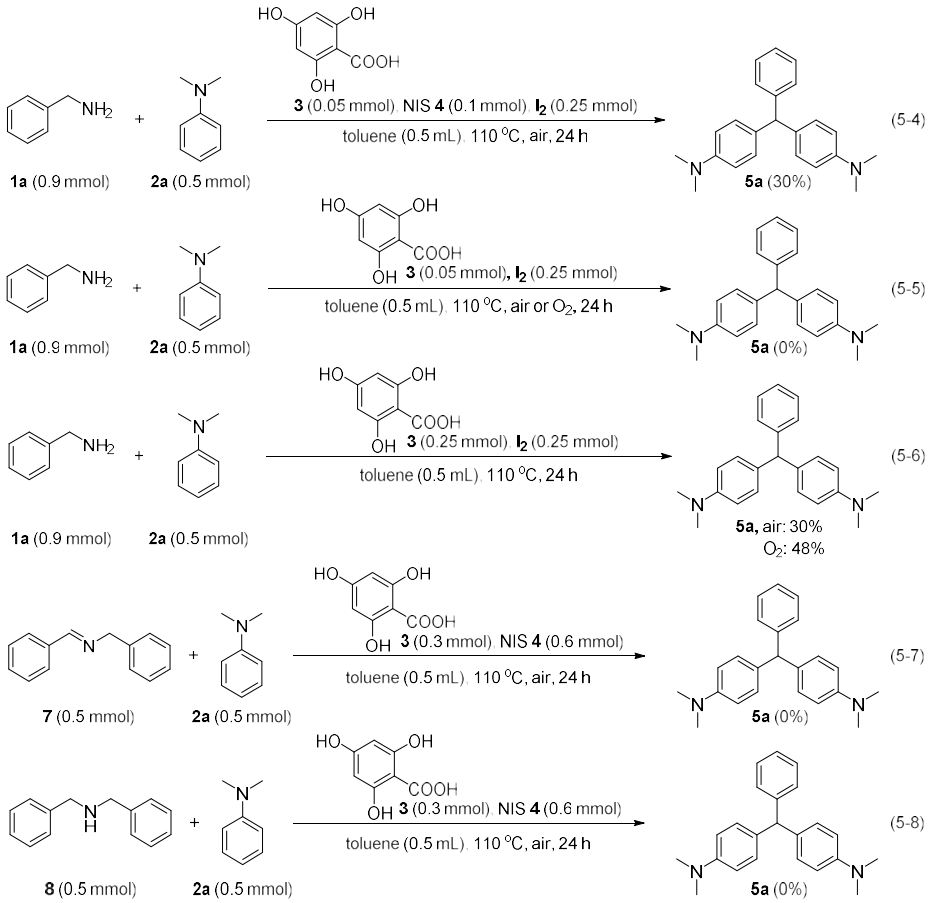
Figure 5-4. ESR Spectroscopy of Crude Complex **A** in Acetone.

To clarify the mechanism of this coupling reaction, several other control experiments were also performed, as outlined in Scheme 5-2 (eq 5-3) and Scheme 5-3. First, the radical scavengers TEMPO ((2,2,6,6-tetramethylpiperidin-1-yl)oxyl) and BHT (2,6-di-*tert*-butyl-4-methylphenol) were added to the reaction mixture under the optimized conditions, respectively (Scheme 5-2, eq 5-3). TEMPO suppressed the coupling reaction totally, and the phenomenon of a H· captured by TEMPO was detected by GC-MS (*m*/*z* 157). Triarylmethane derivative **5a** was obtained in 39% yield in the presence of the radical scavenger BHT, and the corresponding phenoxyl radical was detected by GC-MS (*m*/*z* 219). These results indicated that the phenoxyl radical species is positive for this coupling reaction. In addition, when I_2 was added in combination with catalytic amounts of **3** and **4**, the desired product **5a** was obtained in 30% yield, suggesting that the in situ generation of I_2 is favorable for this coupling reaction (Scheme 5-3, eq 5-4). However, under equivalent conditions but in the absence of **4** (Scheme 5-3, eq 5-5), product **5a** was not generated under either air or O_2. Interestingly, increasing the quantity of **3** addressed this deficiency, leading to the formation of **5a** in 30% yield under air and 48% yield under O_2 (Scheme 5-3, eq 5-6). As determined in the previous study,[22] a phenoxyl radical species can also be generated from **3** upon oxidation by O_2. The author can therefore assume that the reactivity of the corresponding phenoxyl radical is critical for this coupling reaction, and this species generated from **3** and **4** exhibits a higher reactivity than that generated from the oxidation of **3** by O_2. In addition, *N*-(benzylidene)benzylamine (**7**) and dibenzylamine (**8**), which may also be formed under these reaction conditions, were employed as substrates in the reaction with **2a** under the optimized reaction conditions (Scheme 5-3, eqs 5-7 and 5-8). As the corresponding product **5a** was not obtained, it became apparent that neither of these two compounds are intermediates in this coupling reaction.

Scheme 5-2. Radical-Trapping Experiments

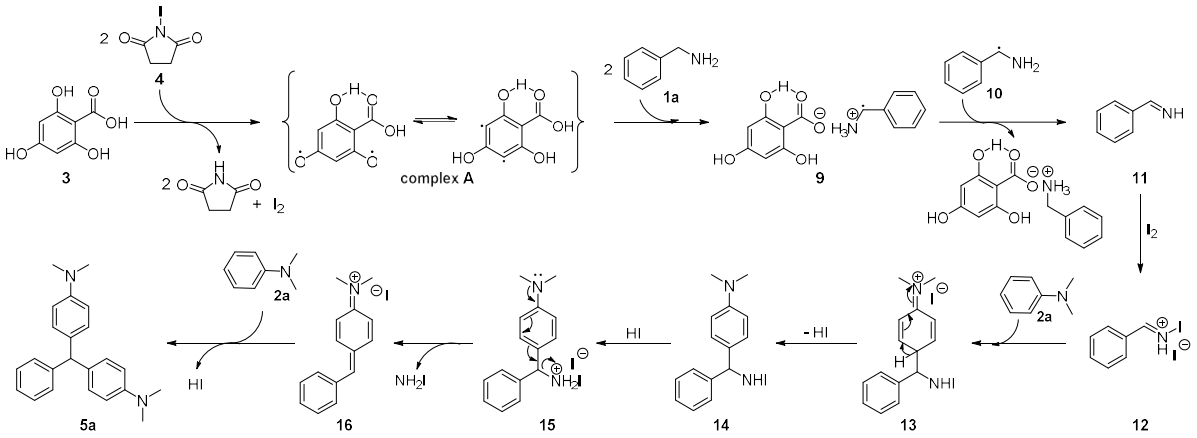


Scheme 5-3. Control Experiments



On the basis of these control experiments, a proposed mechanism for the transformation from benzylamine and aniline to triarylmethane derivative is shown in Scheme 5-4. More specifically, in the reaction containing a 1:2 molar ratio of **3** and **4**, phenol radical complex **A** is formed along with the generation of I_2. Complex **A** then abstracts hydrogen from **1a** to afford phenylmethanimine (**11**), which reacts readily with I_2 to generate **12**. Electrophilic aromatic substitution then takes place between **2a** and **12** to form intermediate **13**. Subsequent dehydroiodination of **13** leads to **14**, which reacts with HI to afford electrophilic species **15**. Charge transfer of **15** leads to **16**, which is attacked by an additional molecule of **2a** to afford the desired product **5a**.

Scheme 5-4. Proposed Reaction Mechanism for the Synthesis of 4,4′-Diaminotriarylmethanes



5-4 Conclusion

In summary, the author successfully developed a novel metal-free method for the synthesis of 4,4′-diaminotriarylmethanes (DTMs) from benzylamine and *N*,*N*-dimethylaniline derivatives in the presence of 4,6-dihydroxysalicylic acid as the co-oxidant and *N*-iodosuccinimide as the oxidant. Compared to previously reported methods for the synthesis of DTMs, this approach tolerates a range of benzylamine and *N*,*N*-dimethylaniline derivatives and provides the first example of DTM synthesis from benzylamines without the necessity for metal

catalysts. A selection of the resulting DTM products were then further oxidized to malachite green derivatives upon treatment with tetrachloro-1,4-benzoquinone (chloranil), although the majority of the produced dyes exhibited a blue color. Due to the successful gram-scale synthesis of 4,4′-diaminotriarylmethane and the wide substrate scope of our procedure, the author therefore expect that it will be suitable for the preparation of various DTMs and the corresponding dye species without the use of metal catalysts, corrosive acids, or hazardous reagents. This work will make it possible to develop new coupling reactions of various benzylamines with other nucleophilic reagents.

5-5 Experimental Section

General Comment

Unless otherwise stated, all starting materials and catalysts were purchased from commercial sources and used without further purification. All solvents were distilled and degassed with nitrogen before use. ^{1}H NMR spectra were recorded on a JEOL JNM-ECS400 (400 MHz) FT NMR system or JEOL JNM-ECX400 (400 MHz) FT NMR system in $CDCl_3$ and CD_3OD with Me_4Si as an internal standard. $^{13}C\{^{1}H\}$ NMR spectra were recorded on a JEOL JNM-ECX400 (100 MHz) FT NMR or JEOL JNM-ECS400 (100 MHz) FT NMR in $CDCl_3$ and CD_3OD. IR spectra were reported in wave numbers (cm^{-1}). ESI and EI mass spectra were obtained by employing double focusing mass spectrometers

General Procedure for the Synthesis of 4,4'-Diaminotriarylmethanes (5).

4,6-Dihydroxysalicylic acid **3** (51.0 mg, 0.3 mmol), NIS **4** (135.0 mg, 0.6 mmol), and distilled toluene (0.5 mL) were added to a round-bottom flask, and the reaction mixture was stirred at 110 °C under air for 20 min; then the desired benzylamine derivative **1** (0.9 mmol) and

N,*N*-dimethylaniline **2a** (60.6 mg, 0.5 mmol) were added to the above mixture. The reaction mixture was continued to stir at 110 °C under air for 24 h. After this time, the resulting mixture was diluted with acetone (5.0 mL) and concentrated under reduced pressure. Finally, the residue was purified by silica gel chromatography (basified with 25 wt % Et_3N) using ethyl acetate (5-10%) in hexane (containing 1 vol % Et_3N) as the eluent to give product **5**.

4,4'-(Phenylmethylene)bis(N,N-dimethylaniline) (5a) [CAS: 129-73-7].[25a] white solid, 49.5 mg, 58%, mp 91-92 °C (lit. mp 92-93 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26-7.21 (m, 2H), 7.17-7.12 (m, 3H), 6.98 (d, *J* = 8.8 Hz, 4H), 4.66 (d, *J* = 8.8 Hz, 4H), 5.37 (s, 1H), 2.89 (s, 12H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 148.9, 145.4, 132.8, 129.9, 129.3, 128.0, 125.7, 112.5, 55.0, 40.7; IR (KBr, ν/cm^{-1}): 2803, 1612, 1519, 1443, 1351; MS (EI) $[M]^+$ *m*/*z* = 330.

4,4'-((3-Methoxyphenyl)methylene)bis(N,N-dimethylaniline) (5b) [CAS: 57751-99-2]. pale green solid, 49.6 mg, 55%, mp 120-121 °C (lit.[25b] mp 123 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21-7.14 (m, 1H), 6.98 (d, *J* = 8.8 Hz, 4H), 6.73-6.69 (m, 3H), 6.65 (d, *J* = 8.8 Hz, 4H), 5.33 (s, 1H), 3.71 (s, 3H), 2.89 (s, 12H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 159.4, 148.9, 147.1, 132.7, 129.9, 128.9, 121.9, 115.3, 112.5, 110.9, 55.0, 55.0, 40.7; IR (KBr, ν/cm^{-1}): 2803, 1604, 1519, 1482, 1349, 1265, 1046; MS (EI) $[M]^+$ *m*/*z* = 360.

4,4'-((4-Methoxyphenyl)methylene)bis(N,N-dimethylaniline) (5c) [CAS: 641-59-8].[20f] blue solid, 48.6 mg, 54%, mp 95-96 °C (lit.[23c] mp 100-101 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.03 (d, *J* = 8.8 Hz, 2H), 6.97 (d, *J* = 8.8 Hz, 4H), 6.79 (d, *J* = 8.8 Hz, 2H), 6.65 (d, *J* = 8.8 Hz, 4H), 5.32 (s, 1H), 3.76 (s, 3H), 2.89 (s, 12H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 157.6, 148.9, 137.6, 133.2, 130.2, 129.8, 113.4, 112.5, 55.2, 54.1, 40.7; IR (KBr, ν/cm^{-1}): 2795, 1609, 1509, 1347, 1245, 1178, 1033; MS (EI) $[M]^+$ *m*/*z* = 360.

4,4'-((2-Methoxyphenyl)methylene)bis(N,N-dimethylaniline) (5d) [CAS: 26455-19-6]. yellow solid, 35.1 mg, 40%, mp 140-141 °C (lit.[25d] mp 147-149 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ

7.19-7.14 (m, 1H), 6.97-6.94 (m, 4H), 6.93-6.90 (m, 1H), 6.86-6.82 (m, 2H), 6.66-6.63 (m, 4H), 5.76 (s, 1H), 3.72 (s, 3H), 3.90 (s, 12H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 157.1, 148.8, 134.0, 132.9, 130.3, 130.0, 127.0, 120.2, 112.5, 110.6, 55.7, 47.4, 40.8; IR (KBr, ν/cm^{-1}): 2795, 1612, 1519, 1487, 1339, 1239, 1028; MS (EI) $[M]^+$ m/z = 360.

4,4'-(p-Tolylmethylene)bis(N,N-dimethylaniline) (5e) [CAS: 641-58-7].[25e] green solid, 51.0 mg, 60%, mp 89-91 °C (lit. mp 85-87 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.05 (d, J = 8.0 Hz, 2H), 7.01 (d, J = 8.4 Hz, 2H), 6.98-6.96 (m, 4H), 6.66-6.64 (m, 4H), 5.33 (s, 1H), 2.88 (s, 12H), 2.29 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 148.9, 142.4, 135.1, 133.0, 129.9, 129.2, 128.7, 112.5, 54.6, 40.7, 21.0; IR (KBr, ν/cm^{-1}): 2795, 1616, 1520, 1476, 1349, 1223; MS (EI) $[M]^+$ m/z = 344.

4,4'-(o-Tolylmethylene)bis(N,N-dimethylaniline) (5f) [CAS: 4601-64-3]. yellow solid, 42.8 mg, 50%, mp 78-79 °C (lit.[25c] mp 96-97 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.12-7.06 (m, 3H), 6.93-6.90 (m, 4H), 6.87-6.85 (m, 1H), 6.66-6.64 (m, 4H), 5.48 (s, 1H), 2.90 (s, 12H), 2.22 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 148.8, 143.7, 136.5, 132.2, 130.1, 129.4, 129.3, 125.8, 125.5, 112.5, 51.6, 40.7, 19.9; IR (KBr, ν/cm^{-1}): 2798, 1612, 1517, 1346, 1163; MS (EI) $[M]^+$ m/z = 344.

4,4'-((4-(tert-Butyl)phenyl)methylene)bis(N,N-dimethylaniline) (5g) [CAS: 196206-96-9]. yellow solid, 44.5 mg, 46%, mp 149-150 °C ; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27-7.24 (m, 2H), 7.05 (d, J = 8.0 Hz, 2H), 6.99 (d, J = 8.8 Hz, 4H), 6.66 (d, J = 8.8 Hz, 4H), 5.33 (s, 1H), 2.89 (s, 12H), 1.29 (s, 9H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 148.9, 148.3, 142.2, 133.1, 129.9, 128.8, 124.9, 112.5, 54.5, 40.7, 34.3, 31.4; IR (KBr, ν/cm^{-1}): 2957, 1612, 1558, 1517, 1472, 1339; MS (EI) $[M]^+$ m/z = 386; HRMS (EI) m/z calcd for $C_{27}H_{34}N_2$ $[M]^+$: 386.2722, found: 386.2721.

4,4'-((3-Chlorophenyl)methylene)bis(N,N-dimethylaniline) (5h) [CAS: 26455-20-9].[20f] green oil, 44.1 mg, 48%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.16-7.12 (m, 3H), 7.02-7.00 (m, 1H), 6.96-6.94

(m, 4H), 6.66-6.64 (m, 4H), 5.32 (s, 1H), 2.90 (s, 12H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 149.0, 147.6, 131.9, 129.8, 129.3, 129.2, 127.6, 126.0, 112.5, 54.7, 40.6; IR (NaCl, ν/cm^{-1}): 2798, 1611, 1517, 1340, 1201, 1164; MS (EI) $[M]^+$ m/z = 364.

4,4'-((4-Chlorophenyl)methylene)bis(N,N-dimethylaniline) (5i) [CAS: 6310-51-6]. purplish blue solid, 48.5 mg, 53%, mp 77-79 °C (lit.[25c] mp 98-100 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22-7.19 (m, 2H), 7.06-7.03 (m, 2H), 6.96-6.93 (m, 4H), 6.66-6.64 (m, 4H), 5.33 (s, 1H), 2.90 (s, 12H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 149.0, 144.0, 132.2, 131.5, 130.6, 129.8, 128.1, 112.5, 54.3, 40.6; IR (NaCl, ν/cm^{-1}): 2798, 1612, 1518, 1349, 1163; MS (EI) $[M]^+$ m/z = 364.

4,4'-((4-(Trifluoromethyl)phenyl)methylene)bis(N,N-dimethylaniline) (5j). pale yellow solid, 59.2 mg, 59%, mp 106-107 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49 (d, J = 8.4 Hz, 2H), 7.24 (d, J = 8.4 Hz, 2H), 6.95 (d, J =8.4 Hz, 4H), 6.68-6.64 (m, 4H), 5.40 (s, 1H), 2.90 (s, 12H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 149.7, 149.1, 131.7, 129.9, 129.6, 129.4, 128.0 (q, J = 32.6 Hz), 125.0 (q, J = 3.9 Hz), 112.5, 54.8, 40.6; IR (KBr, ν/cm^{-1}): 2799, 1613, 1521, 1323, 1159, 1067; MS (EI) $[M]^+$ m/z = 398; HRMS (EI) m/z calcd for $C_{24}H_{25}F_3N_2$ $[M]^+$: 398.1970, found: 398.1966.

4,4'-(Naphthalen-1-ylmethylene)bis(N,N-dimethylaniline) (5k) [CAS: 36429-95-5]. white solid, 35.6 mg, 38%, mp 162-163 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03 (d, J = 8.0 Hz, 1H), 7.83-7.81 (m, 1H), 7.70 (d, J = 8.4 Hz, 1H), 7.42-7.32 (m, 3H), 6.99-6.96 (m, 4H), 6.66-6.63 (m, 4H), 6.10 (s, 1H), 2.89 (s, 12H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 148.9, 141.4, 133.8, 132.6, 132.0, 130.1, 128.5, 127.3, 126.7, 125.8, 125.2, 125.2, 124.6, 112.5, 51.2, 40.7; IR (KBr, ν/cm^{-1}): 2802, 1616, 1520, 1349, 1227, 1166; MS (EI) $[M]^+$ m/z = 380; HRMS (EI) m/z calcd for $C_{27}H_{28}N_2$ $[M]^+$: 380.2252, found: 380.2258.

4,4'-(Thiophen-2-ylmethylene)bis(N,N-dimethylaniline) (5l) [CAS: 6339-91-9]. dark green solid, 43.4 mg, 51%, mp 69-70 °C (lit.[25c] mp 84-85 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.14 (d, J = 5.6 Hz, 1H), 7.07 (d, J = 8.8 Hz, 4H), 6.91-6.89 (m, 1H), 6.68-6.65 (m, 5H), 5.49 (s, 1H), 2.90 (s,

12H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 150.1, 149.2, 132.7, 129.3, 126.3, 125.6, 123.9, 112.4, 50.3, 40.7; IR (KBr, ν/cm^{-1}): 2795, 1611, 1519, 1350, 1227, 1167; MS (EI) $[M]^+$ m/z = 336.

4,4'-(3-Phenylpropane-1,1-diyl)bis(N,N-dimethylaniline) (5m). green solid, 26.9 mg, 30%, mp 62-63 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27-7.24 (m, 2H), 7.18-7.14 (m, 3H), 7.11-7.10 (m, 4H), 6.69-6.66 (m, 4H), 3.75 (t, J = 7.8 Hz, 1H), 2.89 (s, 12H), 2.57 (t, J = 7.8 Hz, 2H), 2.33-2.27 (m, 2H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 148.9, 142.6, 134.0, 128.5, 128.3, 128.2, 125.6, 112.9, 48.7, 40.8, 37.7, 34.3; IR (KBr, ν/cm^{-1}): 2795, 1612, 1517, 1339, 1165; HRMS (ESI) m/z calcd for $C_{25}H_{31}N_2^+$ $[M+H]^+$: 359.2482, found: 359.2479; HRMS (EI) m/z calcd for $C_{25}H_{30}N_2$ $[M]^+$: 358.2409, found: 358.2404.

4,4'-(Heptane-1,1-diyl)bis(N,N-dimethylaniline) (5n) [CAS: 7597-98-0]. yellow oil, 19.6 mg, 23%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.10-7.06 (m, 4H), 6.69-6.65 (m, 4H), 3.70 (t, J = 7.8 Hz, 1H), 2.88 (s, 12H), 1.94 (q, J = 7.5 Hz, 2H), 1.33-1.20 (m, 8H), 0.85 (t, J = 7.0 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 148.8, 134.5, 128.3, 112.8, 49.3, 40.8, 36.2, 31.8, 29.4, 28.1, 22.7, 14.1; IR (NaCl, ν/cm^{-1}): 2796, 1613, 1517, 1344, 1163; MS (EI) $[M]^+$ m/z = 338; HRMS (EI) m/z calcd for $C_{23}H_{34}N_2$ $[M]^+$: 338.2722, found: 338.2719.

4,4'-Methylenebis(N,N-dimethylaniline) (5o') [CAS: 101-61-1].[25f] pale blue solid, 50.9 mg, 40%, mp 85-86 °C (lit. mp 86-89 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.05 (d, J = 8.8 Hz, 4H), 6.68 (d, J = 8.8 Hz, 4H), 3.80 (s, 2H), 2.90 (s, 12H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 149.0, 130.3, 129.4, 113.1, 40.9, 39.9.

General Procedure for the Synthesis of 4,4'-Diaminotriarylmethanes (6).

4,6-Dihydroxysalicylic acid **3** (51.0 mg, 0.3 mmol), NIS **4** (135.0 mg, 0.6 mmol), and distilled toluene (0.5 mL) were added to a round-bottom flask, and the reaction vessel was stirred at 110 °C under air for 20 min; then benzylamine **1a** (96.5 mg, 0.9 mmol) and the desired

N,*N*-dimethylaniline derivative **2** (0.5 mmol) were added to the above mixture. The reaction mixture was continued to stir at 110 °C under air for 17-48 h. After this time, the resulting mixture was diluted with acetone (5.0 mL) and concentrated under reduced pressure. Finally, the residue was purified by silica gel chromatography (basified with 25 wt % Et_3N) using ethyl acetate (5–10%) in hexane (containing 1 vol % Et_3N) as the eluent to give product **6**.

4,4'-(Phenylmethylene)bis(N,N,3-trimethylaniline) (6a) [CAS: 69183-96-6]. yellow solid, 56.0 mg, 58%, mp 107-108 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23 (t, *J* = 7.2 Hz, 2H), 7.15 (t, *J* = 7.4 Hz, 1H), 7.04 (d, *J* = 7.2 Hz, 2H), 6.61-6.56 (m, 4H), 6.46 (dd, *J* = 8.8, 2.8 Hz, 2H), 5.52 (s, 1H), 2.89 (s, 12H), 2.14 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 148.9, 144.4, 137.0, 131.1, 129.9, 129.6, 128.0, 125.7, 114.7, 109.9, 48.9, 40.7, 20.1; IR (KBr, *v*/cm^{-1}): 2795, 1610, 1558, 1349, 1198; MS (EI) $[M]^+$ *m*/*z* = 358; HRMS (EI) *m*/*z* calcd for $C_{25}H_{30}N_2$ $[M]^+$: 358.2409, found: 358.2413.

4,4'-(Phenylmethylene)bis(3-chloro-N,N-dimethylaniline) (6b) [CAS: 57752-08-6]. yellow solid, 46.5 mg, 45%, mp 180-181 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29-7.24 (m, 2H), 7.21-7.18 (m, 1H), 7.04 (d, *J* = 7.6 Hz, 2H), 6.73 (d, *J* = 2.8 Hz, 2H), 6.68 (s, 1H), 6.66 (s, 1H), 6.49 (dd, *J* = 8.8, 2.4 Hz, 2H), 6.04 (s, 1H), 2.90 (s, 12H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 149.8, 143.0, 135.1, 130.9, 129.4, 128.5, 128.1, 126.1, 113.2, 110.6, 49.0, 40.4; IR (KBr, *v*/cm^{-1}): 2879, 1608, 1540, 1442, 1355, 1223, 1173, 1027; MS (EI) $[M]^+$ *m*/*z* = 398; HRMS (EI) *m*/*z* calcd for $C_{23}H_{24}Cl_2N_2$ $[M]^+$: 398.1317, found: 398.1316.

4,4'-(Phenylmethylene)bis(3-methoxy-N,N-dimethylaniline) (6c) [CAS: 6310-53-8]. yellow solid, 45.3 mg, 45%, mp 133-134 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21-7.17 (m, 2H), 7.13-7.10 (m, 1H), 7.07-7.05 (m, 2H), 6.66 (d, *J* = 8.8 Hz, 2H), 6.28 (d, *J* = 2.8 Hz, 2H), 6.21 (dd, *J* = 8.8, 2.8 Hz, 2H) 5.99 (s, 1H), 3.68 (s, 6H), 2.91 (s, 12H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 157.9, 150.3, 145.6, 130.5, 129.1, 127.6, 125.1, 121.8, 104.4, 96.7, 55.7, 41.7, 40.8; IR (KBr, *v*/cm^{-1}): 2795,

1611, 1565, 1436, 1349, 1237, 1107; MS (EI) $[M]^+$ *m*/*z* = 390; HRMS (EI) *m*/*z* calcd for $C_{25}H_{30}N_2O_2$ $[M]^+$: 390.2307, found: 390.2310.

4,4'-(Phenylmethylene)bis(N,N-diethylaniline) (6d) [CAS: 82-90-6].[25g] dark green oil, 58.6 mg, 54%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26-7.23 (m, 2H), 7.16-7.13 (m, 3H), 6.95 (d, *J* = 8.8 Hz, 4H), 6.59 (d, *J* = 8.8 Hz, 4H), 5.32 (s, 1H), 3.30 (q, *J* = 7.2 Hz, 8H), 1.12 (t, *J* = 7.0 Hz, 12H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 146.1, 145.7, 131.7, 130.1, 129.4, 128.0, 125.6, 111.6, 54.9, 44.3, 12.6; IR (NaCl, *v*/cm^{-1}): 2969, 1612, 1517, 1374, 1265, 1198, 1075; MS (EI) $[M]^+$ *m*/*z* = 386.

9,9'-(Phenylmethylene)bis(2,3,6,7-tetrahydro-1H,5H-pyrido[3,2,1-ij]quinoline) (6e). pale red solid, 39.7 mg, 38%, mp 175-176 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25-7.22 (m, 2H), 7.16-7.13 (m, 3H), 6.52 (s, 4H), 5.12 (s, 1H), 3.07 (t, *J* = 5.6 Hz, 8H), 2.67 (t, *J* = 6.4 Hz, 8H), 1.97-1.91 (m, 8H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 145.7, 141.1, 132.1, 129.4, 127.9, 127.8, 125.5, 121.3, 55.5, 50.1, 27.6, 22.3; IR (KBr, *v*/cm^{-1}): 2926, 2773, 1495, 1306, 1206, 1182; HRMS (ESI) *m*/*z* calcd for $C_{31}H_{35}N_2^+$ $[M+H]^+$: 435.2795, found: 435.2779; HRMS (EI) *m*/*z* calcd for $C_{31}H_{34}N_2$ $[M]^+$: 434.2722, found: 434.2711.

4,4'-(Phenylmethylene)bis(N-methyl-N-phenylaniline) (6f) [CAS: 136369-92-1].[25h] yellow oil, 31.1 mg, 28%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31-7.15 (m, 9H), 7.04-6.99 (m, 8H), 6.96-6.90 (m, 6H), 5.43 (s, 1H), 3.29 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 149.0, 147.1, 144.5, 137.1, 130.1, 129.3, 129.1, 128.2, 126.1, 121.0, 120.3, 120.1, 55.5, 40.2; IR (NaCl, *v*/cm^{-1}): 3025, 1594, 1496, 1340, 1254, 1131.

4,4'-(Phenylmethylene)bis(N-ethylaniline) (6g) [CAS: 134170-69-7]. yellow oil, 20.5 mg, 25%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26-7.23 (m, 2H), 7.18-7.11 (m, 3H), 6.91 (d, *J* = 8.4 Hz, 4H), 6.54-6.50 (m, 4H), 5.33 (s, 1H), 3.12 (q, *J* = 7.2 Hz, 4H), 1.23 (t, *J* = 7.0 Hz, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 146.6, 145.4, 133.5, 130.1, 129.3, 128.0, 125.7, 112.5, 55.2, 38.6, 14.9; IR (NaCl, *v*/cm^{-1}): 2967, 1613, 1516, 1319, 1260, 1180; MS (EI) $[M]^+$ *m*/*z* = 330; HRMS (EI) *m*/*z*

calcd for $C_{23}H_{26}N_2$ $[M]^+$: 330.2096, found: 330.2091.

***General Procedure for the Synthesis of Malachite Green Dyes A–F.*[26]**

The desired 4,4′-diaminotriarylmethane **5** (0.05 mmol), tetrachloro-1,4-benzoquinone (18.5 mg, 0.075 mmol), and 95% EtOH (1.0 mL) were added to a round-bottom flask, and the reaction vessel was stirred at 80 °C until the reaction was judged complete by TLC (SiO_2, MeOH/$CHCl_3$ = 1:5). After completion of the reaction (1-3 h), the resulting mixture was concentrated under reduced pressure, and the obtained residue was purified by gel permeation chromatography using chloroform as the eluent to give malachite green dyes **A**–**F** as purple-red solids.

N-(4-((4-(Dimethylamino)phenyl)(phenyl)methylene)cyclohexa-2,5-dien-1-ylidene)-N-methylmethanaminium (malachite green A) [CAS: 10309-95-2]. mp 147-148 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67 (t, *J* = 7.6 Hz, 1H), 7.53 (t, *J* = 7.6 Hz, 2H), 7.37 (d, *J* = 8.8 Hz, 4H), 7.31 (t, *J* = 6.4 Hz, 2H), 6.93 (d, *J* = 9.2 Hz, 4H), 3.35 (s, 12H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 177.4, 156.9, 141.1, 139.3, 134.8, 133.0, 128.6, 127.2, 114.3, 42.1; IR (KBr, *v*/cm^{-1}): 3354, 1615, 1584, 1361, 1173; HRMS (ESI) *m*/*z* calcd for $C_{23}H_{25}N_2^+$ $[M]^+$: 329.2013, found: 329.2013.

N-(4-((4-(Dimethylamino)phenyl)(4-(trifluoromethyl)phenyl)methylene)cyclohexa-2,5-dien-1-ylidene)-N-methylmethanaminium (malachite green B) [CAS: 34101-55-8]. mp 137-138 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79 (d, *J* = 7.6 Hz, 2H), 7.46 (d, *J* = 8.0 Hz, 2H), 7.35 (d, *J* = 7.2 Hz, 4H), 6.98 (d, *J* = 6.4 Hz, 4H), 3.38 (s, 12H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 173.7, 157.0, 142.8, 141.0, 138.6, 134.6, 133.9, 128.6, 127.9, 127.1, 125.5, 114.9, 42.4; IR (KBr, *v*/cm^{-1}): 3388, 1615, 1585, 1372, 1169; HRMS (ESI) *m*/*z* calcd for $C_{24}H_{24}F_3N_2^+$ $[M]^+$: 397.1887, found: 397.1878.

N-(4-((4-(tert-Butyl)phenyl)(4-(dimethylamino)phenyl)methylene)cyclohexa-2,5-dien-1-ylidene)-N-methylmethanaminium (malachite green C). mp 152-153 °C; ^{1}H NMR (400 MHz, $CDCl_3$):

δ 7.55 (d, *J* = 8.4 Hz, 2H), 7.39 (d, *J* = 8.4 Hz, 4H), 7.27 (d, *J* = 8.0 Hz, 2H), 6.95 (d, *J* = 9.2 Hz, 4H), 3.36 (s, 12H), 1.41 (s, 9H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 178.0, 157.6, 156.7, 141.0, 136.4, 135.0, 127.1, 125.6, 113.7, 41.6, 35.2, 31.0; IR (KBr, *v*/cm^{-1}): 3407, 1616, 1585, 1373, 1170; HRMS (ESI) *m*/*z* calcd for $C_{27}H_{33}N_2^+$ $[M]^+$: 385.2639, found: 385.2632.

N-(4-((4-(Dimethylamino)phenyl)(2-methoxyphenyl)methylene)cyclohexa-2,5-dien-1-ylidene)-N-methylmethanaminium (malachite green D) [CAS: 42297-72-3]. mp 149-150 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61-7.56 (m, 1H), 7.38 (d, *J* = 8.8 Hz, 4H), 7.08-7.02 (m, 3H), 6.88 (d, *J* = 8.4 Hz, 4H), 3.63 (s, 3H), 3.35 (s, 12H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 174.0, 158.9, 156.7, 140.2, 134.7, 133.9, 127.9, 127.6, 120.4, 113.7, 111.7, 55.9, 41.3; IR (KBr, *v*/cm^{-1}): 3395, 1617, 1583, 1362, 1168; HRMS (ESI) *m*/*z* calcd for $C_{24}H_{27}N_2O^+$ $[M]^+$: 359.2118, found: 359.2114.

N-(4-((4-(Dimethylamino)phenyl)(3-methoxyphenyl)methylene)cyclohexa-2,5-dien-1-ylidene)-N-methylmethanaminium (malachite green E) [CAS: 42297-52-9]. mp 149-151 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 (t, *J* = 8.0 Hz, 1H), 7.38 (d, *J* = 8.8 Hz, 4H), 7.21 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.93 (d, *J* = 9.2 Hz, 4H), 6.90 (s, 1H), 6.83 (s, 1H), 3.83 (s, 3H), 3.36 (s, 12H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 177.2, 159.3, 156.9, 140.9, 140.7, 129.4, 127.2, 119.6, 118.7, 113.8, 55.6, 41.2; IR (KBr, *v*/cm^{-1}): 3391, 1615, 1585, 1361, 1171; HRMS (ESI) *m*/*z* calcd for $C_{24}H_{27}N_2O^+$ $[M]^+$: 359.2118, found: 359.2112.

N-(4-((3-Chlorophenyl)(4-(dimethylamino)phenyl)methylene)cyclohexa-2,5-dien-1-ylidene)-N-methylmethanaminium (malachite green F) [CAS: 42297-44-9]. mp 147-148 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62 (d, *J* = 6.8 Hz, 1H), 7.50 (t, *J* = 8.0 Hz, 1H), 7.35 (d, *J* = 8.0 Hz, 4H), 7.29 (s, 1H), 7.23 (d, *J* = 7.2 Hz, 1H), 6.95 (d, *J* = 8.8 Hz, 4H), 3.37 (s, 12H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 174.3, 156.9, 141.1, 140.8, 134.6, 133.6, 132.6, 132.5, 129.9, 127.0, 114.3, 41.6; IR (KBr, *v*/cm^{-1}): 3397, 1616, 1583, 1363, 1170; HRMS (ESI) *m*/*z* calcd for $C_{23}H_{24}ClN_2^+$ $[M]^+$: 363.1623, found: 363.1618.

General Procedure for the Gram-Scale Synthesis of 4,4'-(Phenylmethylene)bis(N,N-dimethylaniline) (5a).

4,6-Dihydroxysalicylic acid **3** (0.82 g, 4.8 mmol), NIS **4** (2.16 g, 9.6 mmol), and distilled toluene (8.0 mL) were added to a round-bottom flask, and the resulting mixture was stirred at 110 °C under air for 1 h; then benzylamine **1a** (1.55 g, 14.4 mmol) and *N*,*N*-dimethylaniline **2a** (0.97 g, 8.0 mmol) were added to the above mixture. The reaction vessel was continued to stir at 110 °C under air for 49 h. After the reaction was finished, the resulting mixture was diluted with acetone (50.0 mL) and concentrated under reduced pressure. Finally, the residue was purified by silica gel chromatography (basified with 25 wt % Et_3N) using ethyl acetate (5–10%) in hexane (containing 1 vol % Et_3N) as the eluent to give product **5a**.

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Chapter 6

Synthesis of Aryl Iodides from Arylhydrazines and Iodine

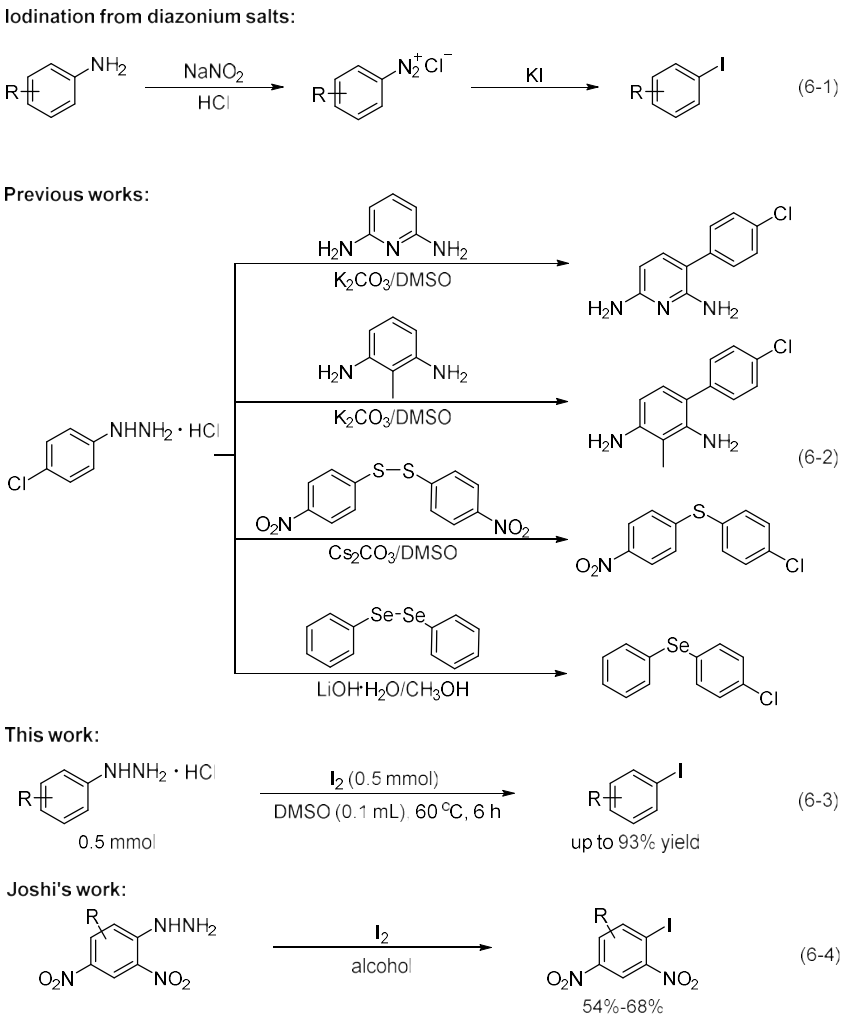
6-1 Introduction

Aryl iodides are important synthetic building blocks in organic chemistry that are mainly used for cross-coupling and related reactions,[1] such as the Mizoroki-Heck reaction,[2] Sonogashira coupling,[3] Suzuki-Miyaura cross-coupling,[4] and Ullmann condensation.[5] Besides, aryl iodides are employed in metal-iodine exchange using organometallic reagents such as Grignard reagents[6] and in halogen exchange via the halogenation of diaryliodonium salts with cuprous halides.[7] In addition, hypervalent iodine compounds, which are important oxidizing agents, are usually synthesized from aryl iodides.[8] Furthermore, arenes bearing radioactive iodine isotopes (^{123}I, ^{124}I, ^{125}I, and ^{131}I) play an important role in labeling biomacromolecules, such as proteins, nucleic acids, and cell surfaces in nuclear medicine and radiotherapy science.[9]

Over the past several decades, many methodologies for aromatic iodination have been developed: (1) direct aromatic iodination with I_2 or other iodination reagents such as *N*-iodosuccinimide;[10] (2) aromatic iodination by using activated precursors such as aryl boronic acid,[11] aryl triflates,[12] phenylazocarboxylates,[13] aryl carboxylic acids,[14] potassium aryltrifluoroborates,[15] and aryl diazonium salts;[16] (3) halogen exchange via an aromatic Finkelstein reaction.[17] Among these, the Sandmeyer reaction is a classical reaction that proceeds via the diazotization of aromatic amines, followed by iodination with iodides (Scheme 6-1, eq 6-1). This method does not require transition metals; however, nitrous acid, which is highly

corrosive, and a strongly acidic medium, such as sulfuric acid, hydrochloric acid, or tetrafluoroboric acid are inevitable for the diazotization step.[18] Therefore, developing a facile approach to generate diazonium salts without transition metals, corrosive acids, and harsh oxidants or reductants is highly desirable.

Scheme 6-1. Aromatic Iodination



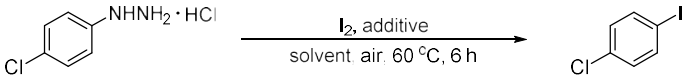
Recently, the author used commercially available arylhydrazine hydrochlorides as the source of aryl radicals and successfully achieved the arylation of aminoheterocycles and aromatic diamines, as well as the synthesis of unsymmetrical diaryl sulfides and selenides (Scheme 6-1, eq

6-2).[19] Inspired by the results, the author explored the reaction of arylhydrazines with iodine to synthesize aryl iodides (Scheme 6-1, eq 6-3). Joshi's group reported a similar method (Scheme 6-1, eq 6-4), but it is applicable only to nitrophenylhydrazines and afforded the corresponding products in moderate yields (54-68%).[20] By contrast, the author's method requires mild conditions, has a much broader substrate scope, and tolerates a wide range of functional groups; further, the desired aryl iodides are formed in good to excellent yields (74-95%). Besides, compared to the Sandmeyer reaction, this protocol is safer, easier to execute, involves simpler work-up, and has higher efficiency.

6-2 Iodination of Arylhydrazines

Initially, the cesium carbonate (Cs_2CO_3)/dimethyl sulfoxide (DMSO) system, which was used for the generation of aryl radicals in the previous work,[19] was employed for the present iodination reaction. 4-Chlorophenylhydrazine hydrochloride (**1a**, 0.5 mmol) was chosen as the model substrate for reaction with I_2 (1.0 equiv) in the presence of Cs_2CO_3 (1.0 equiv) as the base and DMSO as the solvent in the air, and 1-chloro-4-iodobenzene **2a** was obtained in 63% yield (Table 6-1, entry 1). A lower or higher reaction temperature (40 or 80 °C) gave **2a** in reduced yield (Table 6-1, entry 1, footnotes c and d). Screening of the solvent effects demonstrated that DMSO was the best solvent for this iodination (Table 6-1, entries 2-8). Increasing the amount of I_2 (2.0 equiv) failed to improve the yield of **2a** (Table 6-1, entry 9). A higher concentration of reactants led to the slightly improved yield of **2a** (Table 1, entry 10), but the exorbitant reaction concentration with the same equivalent of Cs_2CO_3 was sluggish for the generation of **2a** (Table 6-1, entry 11). Interestingly, a greater amount of Cs_2CO_3 hindered the formation of **2a** (Table 6-1, entry 12), and conversely, the reaction without the base afforded **2a** in 54% yield (Table 6-1, entry 13). Encouraged by this result, the author hypothesized that no additional base was required for the generation of aryl radicals in this reaction, as opposed to the previous work.[19]

Table 6-1. Optimization of Reaction Conditions for Iodination of Arylhydrazines and Iodine [a]



1a (0.5 mmol) **2a**

entry	I_2 (mmol)	additive (mmol)	solvent (mL)	yield[b] (%)
1[g]	0.5	Cs_2CO_3 (0.5)	DMSO (1.5)	63, 43[c], 57[d]
2	0.5	Cs_2CO_3 (0.5)	DMF (1.5)	50
3	0.5	Cs_2CO_3 (0.5)	DMA (1.5)	38
4	0.5	Cs_2CO_3 (0.5)	CH_3CN (1.5)	35
5	0.5	Cs_2CO_3 (0.5)	Acetone (1.5)	29
6	0.5	Cs_2CO_3 (0.5)	MeOH (1.5)	28
7	0.5	Cs_2CO_3 (0.5)	$CHCl_3$ (1.5)	13
8	0.5	Cs_2CO_3 (0.5)	toluene (1.5)	14
9	1.0	Cs_2CO_3 (0.5)	DMSO (1.5)	61
10	0.5	Cs_2CO_3 (0.5)	DMSO (0.5)	68
11	0.5	Cs_2CO_3 (0.5)	DMSO (0.25)	58
12	0.5	Cs_2CO_3 (0.75)	DMSO (0.5)	36
13	0.5	none	DMSO (0.5)	54
14[h]	1.0	none	DMSO (0.5)	84, 83[e], 78[f]
15	1.0	none	DMSO (0.1)	92
16	0.5	none	DMSO (0.1)	92 (87)
17	0.3	none	DMSO (0.1)	82

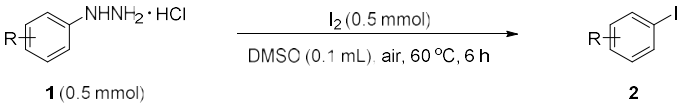
[a]Conditions: **1a**, I_2, additive, and solvent were stirred at 60 °C for 6 h in the air. [b]Determined by ^{1}H NMR using an internal standard 1,3,5-trioxane (isolated yield). [c]Reaction temperature was 40 °C. [d]Reaction temperature was 80 °C. [e]Reaction time was 4 h. [f]Reaction time was 8 h. [g]In this reaction, azide and aniline, besides of the aryl iodide, were generated as byproducts. After the reaction, aryl hydrazine was already consumed but I_2 was not consumed. Most probably, air acted as an oxidant for this iodination. [h]Iodine not only acts as iodination reagent, but also oxidizes phenylhydrazines to diazonium salt, and therefore excessive iodine is more beneficial to the iodination.

Hence, the author further optimized the iodination conditions in the absence of the base. As expected, the use of 2.0 equiv of I_2 gave **2a** in 84% yield (Table 6-1, entry 14). A shorter reaction time furnished **2a** in a similar yield (Table 6-1, entry 14, footnote e), whereas a longer reaction time lowered the yield of **2a** slightly (Table 6-1, entry 14, footnote f). Moreover, upon reducing

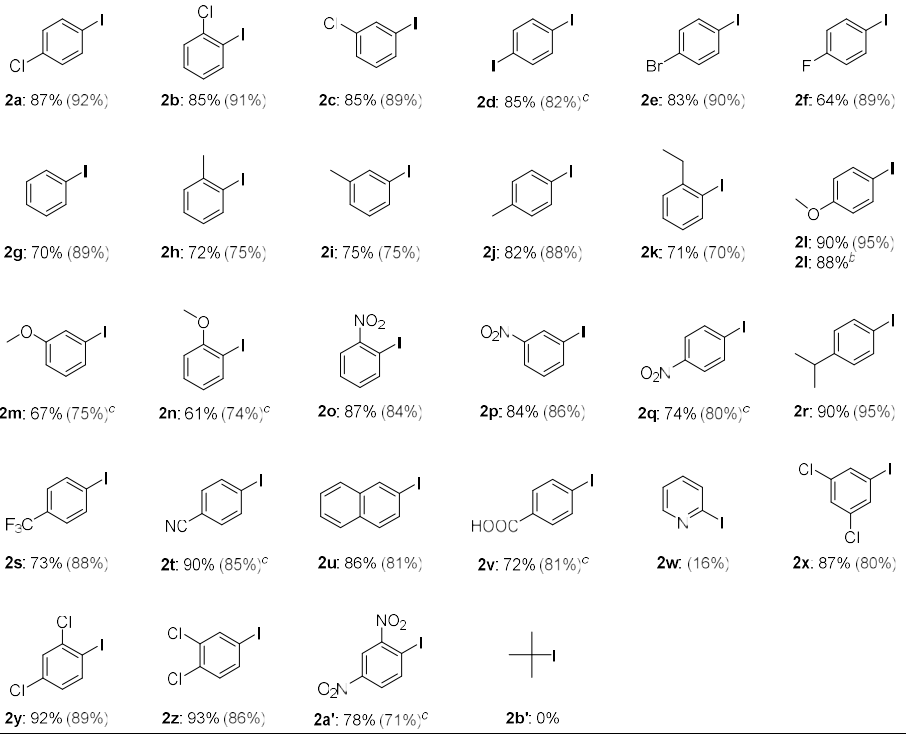
the amount of DMSO to 0.1 mL, the desired product **2a** was furnished in 92% yield (Table 6-1, entry 15). With this substrate concentration, the use of the same equivalent of iodine gave **2a** in 92% yield (Table 6-1, entry 16), which was chosen as the optimized condition for this iodination reaction. Under the optimized condition, a clear dark red solution was formed and gas bubbles appeared. After the reaction was finished, the color of iodine does not disappear and the resulting mixture caused a foul odor, suggests the formation of dimethyl sulfide. Further decreasing the concentration (equivalents) of iodine gave **2a** in a slightly reduced yield (Table 6-1, entry 17).

With the optimized reaction conditions in hand (Table 6-1, entry 16), the author next investigated a series of phenylhydrazine hydrochlorides to synthesize aryl iodides (Table 6-2). First, substrates with a chloro-substituent at the *para*-, *ortho*-, and *meta*-positions were examined and the corresponding aryl iodides were isolated in high yields (Table 6-2, **2a**–**2c**). Substrates with other halo-substituents (iodo, bromo, and fluoro) at the *para*-position were also examined under these reaction conditions; **2d** and **2e** were formed in high yields, but the volatile product **2f** was generated in somewhat low isolated yield. A similar scenario was encountered during the purification of iodobenzene, which decreased the yield of the isolated product **2g** (70% yield). Substrates with a methyl-substituent at the *ortho*-, *meta*-, and *para*-position, and an ethyl-substituent at the *ortho*-position gave the corresponding aryl iodides **2h**–**2k** in good to excellent yields. The reaction of 4-methoxyphenylhydrazine hydrochloride gave the product **2l** in 90% yield. Besides, a gram-scale iodination of 4-methoxyphenylhydrazine hydrochloride was performed under the standard conditions (Table 6-2, **2l**^{b}) and 1.44 g (6.15 mmol, 88% isolated yield) of **2l** was formed from 7 mmol of the starting compound (1.22 g). 3-Methoxy- and 2-methoxy substituents were also tolerated under these reaction conditions (Table 6-2, **2m** and **2n**). Substrates with electron-withdrawing groups such as the nitro group at the *ortho*-, *meta*-, and *para*-positions (**1o**–**1q**), as well as 4-trifluoromethyl (**1s**), 4-cyano (**1t**), and 4-carboxyl (**1v**) moieties could be iodinated to afford the corresponding products in good to excellent yields.

Table 6-2. Substrate Scope[a]



1 (0.5 mmol) **2**



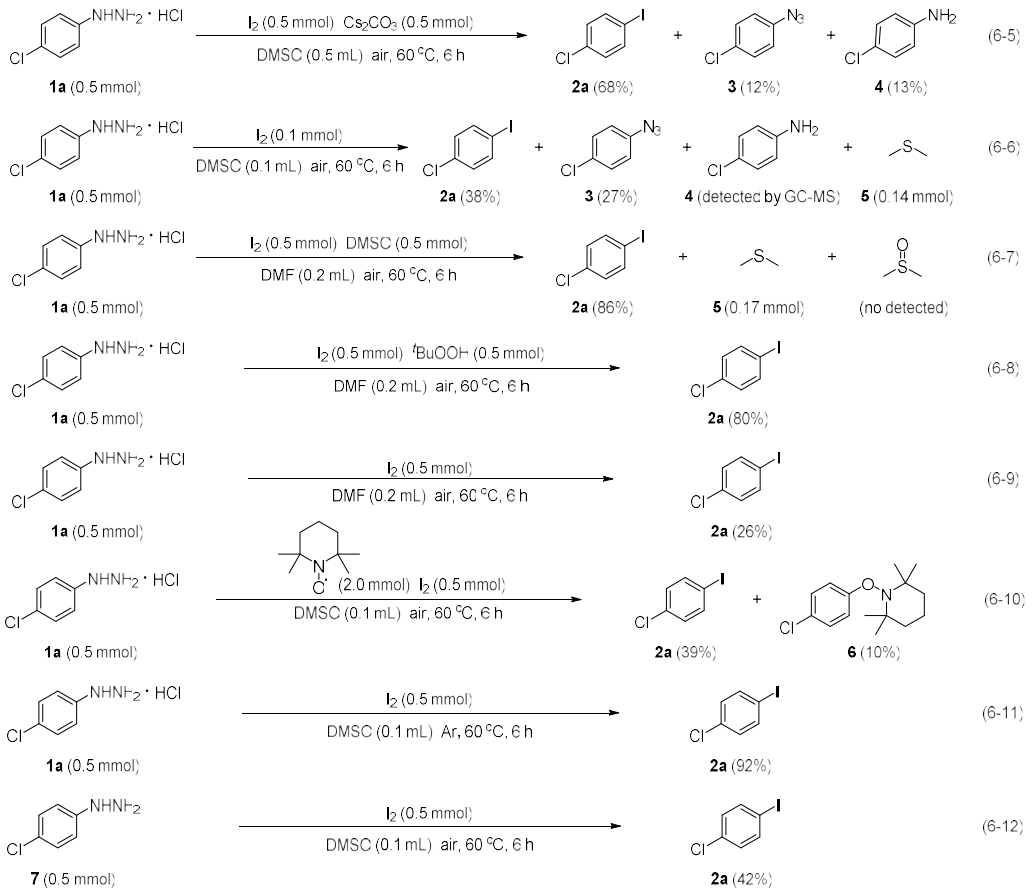
[a]Yield of isolated product is based on **1** ([1]H NMR yield using an internal standard 1,3,5-trioxane). [b]Gram scale. [c]DMSO (0.2 mL) was used.

4-Isopropylphenylhydrazine hydrochloride also afforded **2r** in excellent yield. Furthermore, 2-iodonaphthalene **2u** was generated in good yield under these iodination conditions but the formation of 2-iodopyridine **2w** did not proceed well probably due to the presence of the basic pyridyl group. Disubstituted substrates, i.e., hydrazines with 3,5-dichloro-, 2,4-dichloro-, 3,4-dichloro-, and 2,4-dinitro substituents, could be employed under the standard reaction conditions to afford the desired products in good to excellent yields (Table 6-2, **2x**–**2a′**). Unfortunately, when an aliphatic hydrazine such as *tert*-butylhydrazine hydrochloride was employed as substrate, **2b′** was not formed under the standard condition.

For a better understanding of this iodination reaction, several control experiments were

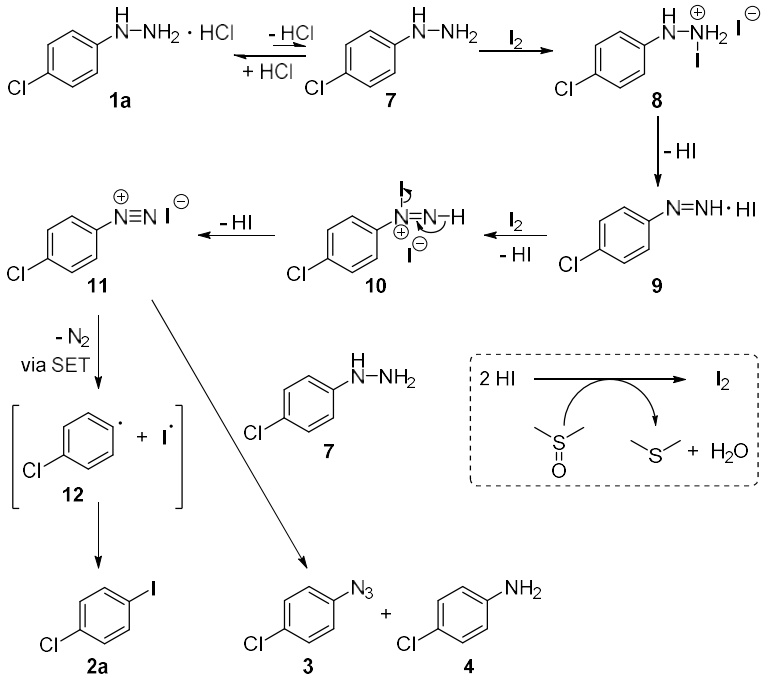
conducted, as shown in Scheme 6-2. During the optimization of the reaction conditions, the author found that 1-azido-4-chlorobenzene **3** and 4-chloroaniline **4** were generated as byproducts in the presence of a base (Scheme 6-2, eq 6-5). Under the standard reaction conditions, when the amount of I_2 was decreased to 0.1 mmol, aryl iodide **2a**, azide **3**, aniline **4**, and dimethyl sulfide **5** were detected by ^{1}H NMR analysis of the crude mixture. Besides, the formation of azide **3** and aniline **4** could be further confirmed by gas chromatography-mass spectrometry (Scheme 6-2, eq 6-6). As well known, DMSO can oxidize hydrogen iodide to iodine, whereas dimethyl sulfide is generated as the reduction product.[21] Therefore, the author speculated that hydrogen iodide may be generated during this iodination, which further confirms that acidic conditions favor this reaction. To clarify the role of DMSO in the iodination reaction, dimethylformamide was used as the solvent in combination with 0.5 mmol DMSO (Scheme 6-2, eq 6-7); 86% of **2a** was formed along with 0.17 mmol of dimethyl sulfide **5** (which was detected by the crude ^{1}H NMR spectra), whereas DMSO was not detected after the iodination reaction was finished. The reaction with 0.5 mmol of *tert*-butyl hydroperoxide (^{t}BuOOH) as an oxidant instead of DMSO also afforded **2a** in 80% yield (Scheme 6-2, eq 6-8). In contrast, the iodination in the absence of DMSO only yielded 26% of **2a** (Scheme 6-2, eq 6-9). These results suggest that DMSO acted as not only solvent but also co-oxidant during the iodination reaction: comparing the results of eqs 6-7, 6-9, and 6-11, DMSO seems to be the major oxidant in this iodination reaction. In addition, when the radical scavenger (2,2,6,6-tetramethylpiperidin-1-yl)oxyl was added to the reaction mixture under the standard conditions (Scheme 6-2, eq 6-10), **2a** was formed in a low yield with 10% of **6**, which implies that the iodination proceeds through a free-radical pathway. Besides, this reaction can proceed well under argon protection (Scheme 6-2, eq 6-11), suggesting that the oxidation of arylhydrazine to aryl radical can proceed not only with molecular oxygen but also iodine itself. Free 4-chlorophenylhydrazine **7** was also employed as a substrate for the iodination reaction but only to generate 42% of **2a**, which implied that acidic condition is essential for stabilizing arylhydrazine under this iodination reaction (Scheme 6-2, eq 6-12).

Scheme 6-2. Control Experiments



On the basis of these control experiments, a mechanism for the iodination is proposed, as shown in Scheme 6-3. Specifically, the starting material **1a** produces the free 4-chlorophenylhydrazine **7**, which reacts with iodine to afford intermediate **8**. Dehydroiodination of **8** leads to **9**, which further reacts with iodine to form **10**. Charge transfer of **10** affords diazonium salt **11**, which upon single-electron transfer (SET) and nitrogen release, generates phenyl radical **12** and an iodine radical. The combination of the phenyl and iodine radicals leads to the formation of aryl iodide **2a**. Excess amount of **7** (free form) may react with diazonium salt **11** to generate byproducts **3** and **4**.[22] During this iodination, hydrogen iodide can be oxidized to iodine by DMSO with the release of dimethyl sulfide.[21]

Scheme 6-3. Possible Pathway for the Synthesis of Aryl Iodides



6-3 Conclusion

In summary, the author has developed a facile and efficient method to synthesize aryl iodides from arylhydrazine hydrochlorides and iodine in the absence of any metal catalysts and additives. During this iodination, iodine plays a dual role: (1) an oxidant for converting arylhydrazines to arenediazonium salts, which subsequently undergo SET to form aryl radicals; (2) an iodination reagent to afford aryl iodides. Arylhydrazine hydrochlorides with a diverse range of functional groups are tolerated under these iodination conditions, and the corresponding aryl iodides are obtained in good to excellent yields. The present work is expected to lead to development of halogenation of the arylhydrazine hydrochlorides using other halogenation reagents.

6-4 Experimental Section

General Comment

Unless otherwise stated, all starting materials and solvents were purchased from commercial sources and used without further purification. ^{1}H NMR spectra were recorded on JEOL JNM-ECS400 (400 MHz) FT NMR system or JEOL JNM-ECX400 (400 MHz) FT NMR system in $CDCl_3$ with Me_4Si as an internal standard. ^{13}C NMR spectra were recorded on JEOL JNMECX400 (100 MHz) FT NMR or JEOL JNM-ECS400 (100 MHz) FT NMR in $CDCl_3$.

General Procedure for the Synthesis of Aryl Iodides (2).

The desired arylhydrazine hydrochloride derivatives **1** (0.5 mmol), I_2 (126.9 mg, 0.5 mmol), and DMSO (0.1 mL) were added to a round-bottomed flask, and the reaction mixture was stirred at 60 °C for 6 h under air. The resulting mixture was cooled to room temperature and then sat. $Na_2S_2O_8$ (aq, 5 mL) and water (10 mL) were added. The mixture was extracted with $CHCl_3$ (4 × 5 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. Finally, the residue was purified by silica gel chromatography (eluent: hexane/ethyl acetate) to give **2** (eluent for **2v**: chloroform/methanol).

1-Chloro-4-iodobenzene (2a) [CAS: 637-87-6].[23] white solid, 103.7 mg, 87% (isolated yield), mp 52-53 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 (d, J = 8.8 Hz, 2H), 7.08 (d, J = 8.8 Hz, 2H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 138.9, 134.6, 130.7, 91.3; MS (EI) $[M]^+$ m/z = 238.

1-Chloro-2-iodobenzene (2b) [CAS: 615-41-8].[23] light yellow oil, 101.6 mg, 85% (isolated yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 (d, J = 8.0 Hz, 1H), 7.45 (d, J = 8.0 Hz, 1H), 7.29 (t, J = 8.4 Hz, 1H), 6.96 (t, J = 8.0 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 140.4, 138.6, 129.5, 128.0, 98.2; MS (EI) $[M]^+$ m/z = 238.

1-Chloro-3-iodobenzene (2c) [CAS: 625-99-0].[23] light yellow oil, 102.0 mg, 85% (isolated yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72 (t, *J* = 1.8 Hz, 1H), 7.59 (dq, *J* = 7.6, 0.9 Hz, 1H), 7.32 (dq, *J* = 8.4, 1.1 Hz, 1H), 7.03 (t, *J* = 8.2 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 137.3, 135.8, 135.2, 131.1, 128.1, 94.1; MS (EI) $[M]^+$ *m*/*z* = 238.

1,4-Diiodobenzene (2d) [CAS: 624-38-4].[12] white solid, 145.3 mg, 85% (isolated yield), mp 126-127 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 (s, 4H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 139.5, 93.5; MS (EI) $[M]^+$ *m*/*z* = 330.

1-Bromo-4-iodobenzene (2e) [CAS: 589-87-7].[24] white solid, 117.2 mg, 83% (isolated yield), mp 87-88 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55 (dt, *J* = 8.8, 2.4 Hz, 2H), 7.23 (dt, *J* = 8.8, 2.4 Hz, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 139.2, 133.6, 122.3, 92.2; MS (EI) $[M]^+$ *m*/*z* = 282.

1-Fluoro-4-iodobenzene (2f) [CAS: 352-34-1].[11] colorless oil, 71.2 mg, 64% (isolated yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60-7.65 (m, 2H), 6.84 (tt, *J* = 8.8, 2.6 Hz, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 162.8 (d, *J* = 249.1 Hz), 139.1 (d, *J* = 7.6 Hz), 117.9 (d, *J* = 23.0 Hz), 87.1 (d, *J* = 2.9 Hz), ; MS (EI) $[M]^+$ *m*/*z* = 222.

Iodobenzene (2g) [CAS: 591-50-4].[12] colorless oil, 71.5 mg, 70% (isolated yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (d, *J* = 7.6 Hz, 2H), 7.33 (t, *J* =7.4 Hz, 1H), 7.11 (t, *J* =7.8 Hz, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 137.6, 130.4, 127.6, 94.5; MS (EI) $[M]^+$ *m*/*z* = 204.

1-Iodo-2-methylbenzene (2h) [CAS: 615-37-2].[23] colorless oil, 78.6 mg, 72% (isolated yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 (d, *J* = 7.6 Hz, 1H), 7.25-7.22 (m, 2H), 6.84-6.88 (m, 1H), 2.43 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 141.5, 139.1, 129.9, 128.3, 127.5, 101.6, 28.3; MS (EI) $[M]^+$ *m*/*z* = 218.

1-Iodo-3-methylbenzene (2i) [CAS: 625-95-6].[23] colorless oil, 80.9 mg, 75% (isolated yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55 (s, 1H), 7.49 (d, *J* = 7.6 Hz, 1H), 7.12 (d, *J* = 7.6 Hz, 1H), 6.98

(t, J = 8.0 Hz, 1H), 2.29 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 140.4, 138.2, 134.6, 130.1, 128.5, 94.5, 21.1; MS (EI) $[M]^+$ m/z = 218.

1-Iodo-4-methylbenzene (2j) [CAS: 624-31-7].[12] white solid, 90.1 mg, 82% (isolated yield), mp 31-32 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56 (d, J = 8.0 Hz, 2H), 6.92 (d, J = 8.4 Hz, 2H), 2.29 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 137.6, 137.4, 131.3, 90.3, 21.2; MS (EI) $[M]^+$ m/z = 218.

1-Ethyl-2-iodobenzene (2k) [CAS: 18282-40-1].[25] colorless oil, 82.1 mg, 71% (isolated yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 (dd, J = 8.3, 1.6 Hz, 1H), 7.21-7.30 (m, 2H), 6.87 (td, J = 8.3, 1.6 Hz, 1H), 2.73 (q, J = 7.5 Hz, 2H), 1.21 (t, J = 7.5 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 146.6, 139.5, 128.7, 128.5, 100.6, 34.3, 14.7; MS (EI) $[M]^+$ m/z = 232.

1-Iodo-4-methoxybenzene (2l) [CAS: 696-62-8].[12] white solid, 106.5 mg, 90% (isolated yield), mp 48-49 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55 (d, J = 9.2 Hz, 2H), 6.68 (d, J = 9.2 Hz, 2H), 3.77 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 159.6, 138.3, 116.5, 82.8, 55.4; MS (EI) $[M]^+$ m/z = 234.

1-Iodo-3-methoxybenzene (2m) [CAS: 766-85-8].[23] light yellow oil, 78.3 mg, 67% (isolated yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25-7.29 (m, 2H), 7.00 (t, J = 8.1 Hz, 1H), 6.87 (dd, J = 8.3, 1.6 Hz, 1H), 3.78 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 160.3, 130.9, 129.9, 123.1, 113.9, 94.5, 55.5; MS (EI) $[M]^+$ m/z = 234.

1-Iodo-2-methoxybenzene (2n) [CAS: 529-28-2].[23] light yellow oil, 71.5 mg, 61% (isolated yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 (d, J = 7.7 Hz, 1H), 7.29-7.33 (m, 1H), 6.83 (d, J = 8.2 Hz, 1H), 6.71 (t, J = 7.6 Hz, 1H), 3.88 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 158.2, 139.6, 129.7, 122.6, 111.1, 86.1, 56.4; MS (EI) $[M]^+$ m/z = 234.

1-Iodo-2-nitrobenzene (2o) [CAS: 609-73-4].[26] yellow solid, 108.6 mg, 87% (isolated yield), mp

48-49 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05 (d, *J* = 8.3 Hz, 1H), 7.87 (d, *J* = 8.3 Hz, 1H), 7.50 (t, *J* = 7.7 Hz, 1H), 7.25-7.29 (m, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 153.1, 142.0, 133.5, 129.2, 125.6, 86.3; MS (EI) $[M]^+$ *m*/*z* = 249.

1-Iodo-3-nitrobenzene (2p) [CAS: 645-00-1].[27] colorless oil, 106.5 mg, 84% (isolated yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.57 (t, *J* = 2.0 Hz, 1H), 8.21 (dq, *J* = 8.8, 1.1 Hz, 1H), 8.03 (dt, *J* = 7.6, 1.1 Hz, 1H), 7.30 (t, *J* = 8.2 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 148.7, 143.6, 132.6, 130.8, 122.9, 93.6; MS (EI) $[M]^+$ *m*/*z* = 249.

1-Iodo-4-nitrobenzene (2q) [CAS: 636-98-6].[28] yellow solid, 92.4 mg, 74% (isolated yield), mp 171-172 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 (d, *J* = 9.6 Hz, 2H), 7.91 (d, *J* = 9.6 Hz, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 147.9, 138.8, 125.0, 102.8; MS (EI) $[M]^+$ *m*/*z* = 249.

1-Iodo-4-isopropylbenzene (2r) [CAS: 17356-09-1].[12] light yellow oil, 111.0 mg, 90% (isolated yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 (d, *J* = 7.9 Hz, 2H), 6.98 (d, *J* = 8.7 Hz, 2H), 2.80-2.90 (m, 1H), 1.23 (s, 3H), 1.21 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 148.6, 137.4, 128.8, 90.8, 33.9, 24.0; MS (EI) $[M]^+$ *m*/*z* = 246.

1-Iodo-4-(trifluoromethyl)benzene (2s) [CAS: 455-13-0].[29] colorless oil, 99.0 mg, 73% (isolated yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85 (d, *J* = 7.7 Hz, 2H), 7.35 (d, *J* = 8.2 Hz, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 138.2, 130.3 (q, *J* = 33.0 Hz), 127.0 (q, *J* = 3.8 Hz), 124.1 (q, *J* = 272.2 Hz), 98.7; MS (EI) $[M]^+$ *m*/*z* = 272.

4-Iodobenzonitrile (2t) [CAS: 3058-39-7].[28] white solid, 103.4mg, 90% (isolated yield), mp 124-125 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85 (d, *J* = 7.9 Hz, 2H), 7.37 (d, *J* = 7.9 Hz, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 138.6, 133.3, 118.3, 111.9, 100.4,; MS (EI) $[M]^+$ *m*/*z* = 229.

2-Iodonaphthalene (2u) [CAS: 612-55-5].[28] light yellow solid, 110.7 mg, 86% (isolated yield), mp 49-50 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.24 (s, 1H), 7.80 (q, *J* = 3.2 Hz, 1H), 7.72 (dt, *J* = 9.6,

1.6 Hz, 2H), 7.58 (d, *J* = 8.8 Hz, 1H), 7.51-7.47 (m, 2H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 136.7, 135.1, 134.5, 132.2, 129.6, 128.0, 126.9, 126.8, 126.6, 91.6; MS (EI) $[M]^+$ *m*/*z* = 254.

4-Iodobenzoic acid (2v) [CAS: 619-58-9].[23] white solid, 89.1 mg, 72% (isolated yield), mp 269-270 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.04 (br, 1H), 7.88 (d, *J* = 8.3 Hz, 2H), 7.69 (d, *J* = 8.7 Hz, 2H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6): δ 166.9, 137.6, 131.1, 130.3, 101.2; MS (EI) $[M]^+$ *m*/*z* = 248.

1,3-Dichloro-5-iodobenzene (2x) [CAS: 3032-81-3].[27] white solid, 119 mg, 87% (isolated yield), mp 49-50 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61 (d, *J* = 1.6 Hz, 2H), 7.34 (t, *J* = 2.0 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 135.7, 128.5, 93.8; MS (EI) $[M]^+$ *m*/*z* = 272.

2,4-Dichloro-1-iodobenzene (2y) [CAS: 29898-32-6].[30] colorless oil, 125.1 mg, 92% (isolated yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, *J* = 8.2 Hz, 1H), 7.46 (d, *J* = 2.3 Hz, 1H), 6.96 (dd, *J* = 8.7, 2.3 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 140.9, 139.6, 135.2, 129.4, 128.5, 95.6; MS (EI) $[M]^+$ *m*/*z* = 272.

1,2-Dichloro-4-iodobenzene (2z) [CAS: 20555-91-3].[27] white solid, 126.6 mg, 93% (isolated yield), mp 30-31 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79 (d, *J* = 1.8 Hz, 1H), 7.51 (dd, *J* = 8.5, 2.1 Hz, 1H), 7.16 (d, *J* = 8.7 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 138.9, 136.9, 133.8, 132.8, 131.9, 91.1; MS (EI) $[M]^+$ *m*/*z* = 272.

1-Iodo-2,4-dinitrobenzene (2a') [CAS: 709-49-9].[24] yellow solid, 114.4 mg, 78% (isolated yield), mp 83-84 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.68 (d, *J* = 2.4 Hz, 1H), 8.31 (d, *J* = 8.8 Hz, 1H), 8.11 (dd, *J* = 8.8, 2.4 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 153.3, 148.1, 143.5, 127.1, 120.5, 94.9; MS (EI) $[M]^+$ *m*/*z* = 294.

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Chapter 7

Conclusion

In this research work, metal-free oxidative methods of benzylamines and arylhydrazines has been developed.

Chapter 2 described a metal-free oxidative coupling of benzylamines using salicylic acid derivatives as organocatalysts under an oxygen atmosphere, affording the corresponding *N*-benzylidenebenzylamines in high yields. Electron-rich salicylic acid derivatives such as 4,6-dimethoxysalicylic acid and 4,6-dihydroxysalicylic acid exhibit excellent catalytic activities for the oxidative coupling of benzylamines to give the corresponding imines. This amine oxidation can also be applied to the synthesis of nitrogen-containing heterocycles such as benzimidazoles, benzoxazoles, and benzothiazoles via the oxidative cyclization of benzylamines with *o*-phenylenediamines, *o*-aminophenols, and *o*-aminothiophenols. Furthermore, to recycle the catalyst, silica gel supported with 4.7 wt % of 4,6-dihydroxysalicylic acid is prepared, which acts as a recyclable catalyst, oxidizing benzylamine to imine four times successfully.

Chapter 3 described 4,6-dihydroxysalicylic acid-catalyzed oxidative coupling of benzylic amines and aromatic ketones for the preparation of 2,4,6-trisubstituted pyridines. 4,6-Dihydroxysalicylic acid was activated under air to catalyze the one-pot oxidative coupling reaction of benzylamines with acetophenones in the presence of $BF_3{\cdot}Et_2O$, affording 2,4,6-trisubstituted pyridines in yields of 59 to 91%. During this metal-free oxidative coupling reaction, the benzylamines not only provided the aryl moiety at the 4-position of the pyridines, but also acted as the nitrogen donor. This method can be applied to the metal-free synthesis of G-quadruplex binding ligands by the sequential addition of 4-chlorobutyryl chloride and pyrrolidine to the reaction system of the 2,4,6-trisubstituted

pyridine synthesis.

Chapter 4 described a metal-free oxidative Ugi reaction for the synthesis of bis-amides. Pseudo-four-component oxidative Ugi reactions are conducted to synthesize bis-amides from benzylamines, isocyanides, and carboxylic acids in the presence of 4,6-dihydroxysalicylic acid as an organocatalyst. The cross-coupling of benzylamines with other aliphatic or aromatic amines also proceeds efficiently under this organocatalytic oxidation conditions. Thus, the cross-coupling reactions are subsequently involved in the oxidative Ugi reaction with isocyanides and carboxylic acids, affording the corresponding bis-amides successfully.

Chapter 5 described a convenient, novel, and metal-free method for the synthesis of 4,4′-diaminotriarymethanes (DTMs). This process is based on a one-pot condensation of benzylamines with *N*,*N*-dimethylaniline derivatives using 4,6-dihydroxysalicylic acid as a co-oxidant and *N*-iodosuccinimide as an oxidant. To the best of the author's knowledge, the present method provides the first reported synthesis of DTMs from benzylamines via oxidative C–N bond cleavage and subsequent double C–C bond formations. The obtained DTMs were then easily converted into a series of blue dyes upon treatment with tetrachloro-1,4-benzoquinone (chloranil). Although the production of triarylmethane dyes tends to require the use of toxic heavy metals, the present method is advantageous in that it is a metal-free and straightforward process.

Chapter 6 described a metal- and base-free method for the synthesis of aryl iodides from arylhydrazine hydrochlorides and iodine. A wide variety of aryl iodides can be conveniently synthesized by an equimolar reaction of arylhydrazine hydrochlorides and I_2 in dimethyl sulfoxide at 60 ºC for 6 h. In the iodination step, arylhydrazines are oxidized by iodine to form arenediazonium salts, which undergo single-electron transfer from iodide anion to give aryl and iodine radicals; subsequent combination of them affords the corresponding aryl iodides.

In summary, a series of benzylamines and arylhydrazines were oxidized by metal-free methods, and based on this oxidation of nitrogen compounds, the organocatalyzed oxidative

coupling method of benzylamines to synthesis of nitrogen-containing heterocycles, bis-amides, and blue dyes have been developed successfully. The author believes that this unprecedented research work will make a great contribution for the development of metal-free oxidation chemistry.

List of Publications

1. Metal-Free Oxidative Coupling of Benzylamines to Imines under an Oxygen Atmosphere Promoted Using Salicylic Acid Derivatives as Organocatalysts

   Dong, C-p.; Higashiura, Y.; Marui, K.; Kumazawa, S.; Nomoto, A.; Ueshima, M.; Ogawa, A.

   ACS Omega **2016**, *1*, 799–807.

   (Chapter 2)

2. Metal-Free Synthesis of *N*-Containing Heterocycles from *o*-Substituted Aniline Derivatives via 2,4,6-Trihydroxybenzoic Acid-Catalyzed Oxidative Dehydrogenation of Benzylamines under Oxygen Atmosphere

   Kumazawa, S.; Uematsu, A.; Dong, C-p.; Kodama, S.; Nomoto, A.; Ueshima, M.; Ogawa, A.

   Heterocycles **2018**, *97*, Published online, DOI:10.3987/COM-18-S(T)60.

   (Chapter 2)

3. 4,6-Dihydroxysalicylic Acid-Catalyzed Oxidative Coupling of Benzylic Amines and Aromatic Ketones for the Preparation of 2,4,6-Trisubstituted Pyridines and Its Application to Metal-Free Synthesis of G-quadruplex Binding Ligands

   Dong, C-p.; Kodama, S.; Nomoto, A.; Ueshima, M.; Ogawa, A.

   J. Org. Chem. Submitted.

   (Chapter 3)

4. 4,6-Dihydroxysalicylic Acid-Catalyzed Oxidative Ugi Reactions with Molecular Oxygen via Homo- and Cross-Coupling of Amines

   Dong, C-p.; Uematsu, A.; Kumazawa, S.; Yamamoto, Y.; Kodama, S.; Nomoto, A.; Ueshima, M.; Ogawa, A.

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5. Metal-Free Blue Dye Synthesis: Oxidative Coupling of Benzylamines and *N*,*N*-Dimethylanilines to Yield 4,4'-Diaminotriarylmethanes in the Presence of Salicylic Acid as a Co-oxidant

   Dong, C-p.; Kodama, S.; Uematsu, A.; Nomoto, A.; Ueshima, M.; Ogawa, A.

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6. Synthesis of Aryl Iodides from Arylhydrazines and Iodine

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