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論文名	「Studies on the Development of Metal-Free Oxidation Reactions of Amine Derivatives (メタルフリー条件下におけるアミン誘導体の酸化反応の開発に関する研究)」	
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#### 論文要旨

Oxidation is one of the most important organic reactions that has been used in many fields, such as organic synthesis, material science, biology, and industry. Besides, oxidation reactions play important roles in our daily life, including photosynthesis, respiration, combustion, and corrosion. Therefore, the research of oxidation reactions attracts considerable attention in many areas. For the organic chemistry, many oxidation methods have been developed for the demand of industry. Up to today, most of the oxidation methods are based on metal catalysis, organocatalysis, or biocatalysis. Metal catalysis is always associated with drawbacks such as the presence of metal-containing residues, toxic waste water, and complicated purification. From the perspective of green chemistry, scientists pay more attention to the investigation of organocatalysis and biocatalysis. Compared with biocatalysts, organocatalysts feature cheap, simple structure, and easily available.

Amines are the most basic class of nitrogen-containing organic compounds. They are organic derivatives of ammonia, in which one, two, or all three of the hydrogens of ammonia are replaced by organic groups. According to the number of carbon substituents adjacent to the nitrogen, amines are classified to three subcategories: primary, secondary, and tertiary amines. The chemistry of amines was discovered in the nineteenth century by pioneering chemists such as Hofmann and Knoll. At the beginning of the twentieth century, the introduction of the Cyanamide Process and Electric Arc Process made amines commercially available for the first time at low cost. Then, the implementation of the Haber-Bosch Process in Eastern Germany in 1917 marked the beginning of the modern age of amine chemistry. Amines exist widely in nature and are also the major industrial chemicals. Naturally occurring amines include the alkaloids, which are present in certain plants, the catecholamine neurotransmitters, and a chemical mediator, histamine, that occurs in most animal tissues. In industry, amines are used widely in making rubber, dyes, pharmaceuticals, and synthetic resins and fibers.

The oxidation of amines offers great opportunities for the production of key *N*-containing building-blocks for the modern chemical industry. Many important nitrogen-containing compounds, such as oximes, imines, amides, nitriles, amine oxides, and azo compounds, are

obtained from the oxidation of an appropriate amine precursor. Since the beginning of the past century, transition metal complexes and enzymes have been considered to be the main two classes of efficient catalysts for the oxidation of amines. About twenty years ago, from the viewpoint of green and sustainable chemistry, organocatalysis was emerged as an alternative method. However, compared with traditional oxidative methods of amines, the development of metal-free, efficient, and eco-friendly methods for the oxidation of amines is still strongly desired.

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, and this amine oxidation could also be applied to the synthesis of nitrogen-containing heterocycles, bis-amides, and blue dyes. Arylhydrazines could be oxidized by diiodine to form aryl radicals and then combined with iodine radical to afford aryl iodides. 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 using salicylic acid derivatives as organocatalysts under an oxygen atmosphere and its application to synthesis of nitrogen-containing heterocycles. Salicylic acid derivatives are usually used as ligands for metal complexes, but in this study, salicylic acid and its derivatives themselves were found to be efficient organocatalysts and could catalyzed amines oxidation. In particular, 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. For the perspective of the sustainable chemistry, recyclability of the catalyst was also investigated. Silica gel supported with 4.7 wt% of 4,6-dihydroxysalicylic acid was prepared as a recyclable catalyst, which successfully oxidized benzylamines to imines four times. 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*-heterocycles in good yields.

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  $\text{BF}_3\cdot\text{Et}_2\text{O}$ . Pyridines are another kind of important nitrogen-containing heterocycles. In this study, the aforementioned amine oxidation method was successfully applied to the synthesis of 2,4,6-trisubstituted pyridines in good to high yields with a broad substrate scope. During this oxidative coupling reaction, benzylamines play a dual role of providing the aryl moiety at 4-position of pyridines and also acting as the nitrogen donor. 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. To avoid the metal contamination of these precursor drugs, the development of metal-free synthetic method is strongly desired. It is gratifying that this salicylic acid derivatives-catalyzed synthetic method of 2,4,6-trisubstituted pyridines can be applied to the facile synthesis of G-quadruplex binding ligands by the addition of 4-chlorobutyryl chloride and pyrrolidine subsequently. 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 in

moderate yields.

Chapter 4 describes a metal-free organocatalytic oxidative Ugi reaction promoted by 4,6-dihydroxysalicylic acid. The traditional Ugi four-component reactions (U-4CRs) usually combine an amine, an aldehyde, an isocyanide, and a carboxylic acid. During this reaction, imine or iminium, which was considered as the key intermediate, was *in situ* generated by condensation of an amine and aldehyde. As described in Chapter 2, imines were formed efficiently via the homo-coupling of benzylamines in the presence of 4,6-dihydroxysalicylic acid as organocatalyst. Based on the previous work, the oxidative Ugi reaction, wherein the imine intermediate was *in situ* formed by oxidative coupling of amines, was described in this chapter. Catalyzed by 4,6-dihydroxysalicylic acid, bis-amides were synthesized from three components (benzylamines, isocyanides, and carboxylic acids) in good to high yields. Besides, the cross-coupling reaction of benzylamines with aliphatic amines also proceeded successfully using 4,6-dihydroxysalicylic acid as organocatalyst. Therefore, this cross-coupling reaction was involved in the oxidative Ugi reaction, and provides a complementary method for the synthesis of bis-amides bearing aromatic and aliphatic groups simultaneously.

Chapter 5 describes a convenient, novel, and metal-free method for the synthesis of 4,4'-diaminotriarylmethanes (DTMs). As dye precursors, DTMs can be oxidized to produce malachite green derivatives, which are one of the most important dyes. Owing to the importance of triarylmethane compounds, considerable attention has been paid to the development of efficient methods for the synthesis of DTMs and a variety of chemical transformations have been reported. However, the synthesis of DTMs from benzylamine substrates has not yet been reported. In this study, 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 was investigated. 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. During this oxidation reaction, radical derived from 4,6-dihydroxysalicylic acid was confirmed by ESR spectroscopy ( $g = 2.00336$ ). 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.

Chapter 6 describes a metal- and base-free method for the synthesis of aryl iodides from arylhydrazine hydrochlorides and iodine. Arylhydrazine hydrochlorides are usually used as the source of aryl radicals, and most of the oxidative methods for arylhydrazine hydrochlorides to aryl radicals need additional oxidants or additives such as base. The Sandmeyer reaction is a classic method to synthesize 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. In this study, a wide variety of aryl iodides can be conveniently synthesized by an equimolar reaction of arylhydrazine hydrochlorides and  $I_2$  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 single-electron transfer (SET) to form aryl radicals; (2) an iodination reagent to afford aryl iodides. Compared to the Sandmeyer reaction, this protocol is safer, easier to execute, involves simpler work-up, and has higher efficiency.

Chapter 7 describes the conclusion of this thesis.

In conclusion, this thesis describes 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-heterocycles (i.e., benzimidazoles, benzoxazoles, benzothiazoles, and triarylpyridines), bis-amides, and blue dyes have been developed successfully. The author believes that these works will open up a new field for eco-friendly oxidation of amines by organocatalysis.

#### 審査結果の要旨

本論文は、メタルフリー条件下でベンジルアミン類およびアリールヒドラジン類を酸化する手法を開発し、この酸化手法に基づいて、含窒素複素環化合物、ジペプチド、青色色素、およびヨウ化アリールを合成する研究について述べたものであり、以下の成果を得ている。

- (1) サリチル酸誘導体を有機触媒として用いることにより、ベンジルアミン類からイミン類への酸素酸化反応が効率良く進行することを明らかにしている。サリチル酸誘導体をシリカゲルに固定化した触媒が、本アミン酸化反応において回収・再使用できることも見出している。さらに、本酸化手法に基づいて、ベンジルアミン類と *o*-置換アニリン誘導体から含窒素複素環化合物を合成することにも成功している。これらの反応は、安価なサリチル酸誘導体を有機触媒として、温和な条件下、簡便な操作で進行するという優位性を有している。
- (2) ベンジルアミン類とアセトフェノン類の酸化的カップリング反応が、サリチル酸誘導体を有機触媒に用いたメタルフリー条件下で進行し、2,4,6-三置換ピリジン類が生成することを見出している。さらに、本ピリジン合成法を応用して、グアニン四重鎖結合性リガンドの簡便合成も達成している。
- (3) サリチル酸触媒によるメタルフリーな酸化的 Ugi 反応に成功している。本反応では、ベンジルアミン類の酸化的ホモカップリングだけではなく、ベンジルアミン類と脂肪族アミン類との酸化的クロスカップリングも進行し、芳香族基および脂肪族基を有する様々なジペプチドのメタルフリー合成が可能である。
- (4) サリチル酸誘導体を共酸化剤とし、*N*-ヨードスクシンイミドを酸化剤として用いたベンジルアミン類と *N,N*-ジメチルアニリン誘導体のワンポット縮合反応により、4,4'-ジアミノトリアリールメタン類 (DTMs) が得られることを明らかにしている。本手法は、ベンジルアミン類を基質として DTMs を合成した最初の例である。さらに、得られた DTMs をクロラニルで酸化することにより、青色色素を合成することにも成功している。これらの研究成果は、有毒な重金属、腐食性の酸、および危険性のある試薬を必要とせず、メタルフリーかつ直截的に一連の青色色素を合成できるという点で有用である。
- (5) アリールヒドラジン類とヨウ素の反応により、アリールヨージド類をメタルフリーかつ塩基フリーで合成することに成功している。アリールヒドラジン類を酸化するとアリールラジカルが発生するが、その一般的な酸化手法としては酸化剤や塩基を必要としている。また、アリールヨージドを合成する古典的な手法に Sandmeyer 反応があるが、ジアゾ化に腐食性のある強酸が用いられる。これらに対して、本手法は安全、簡便、かつ高効率な合成手法である。

以上の諸成果はメタルフリー条件下でアミン誘導体の酸化を達成し、この酸化手法を応用して、グアニン四重鎖結合性リガンド、ジペプチド、青色色素などの合成にも成功しており、有機合成化学の分野に大きく貢献するものである。また、申請者が自立して研究活動を行うにあたり、十分な能力と学識を有することを証するものである。