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論文名	「Development of Novel Synthesis Methods Using Isocyanides by Transition-Metal-Catalyzed or Photoinduced Reactions (遷移金属触媒または光誘起反応によるイソシアニドを用いた新規合成手法の開発)」	
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### 論文要旨

Isocyanides are useful C1 units in organic synthesis due to their versatility in the construction of imine derivatives and nitrogen-containing heterocyclic compounds, leading to a variety of significant applications such as ligands for metal complexes, pharmaceuticals, pesticides, dyes, organic electronic devices, and so on. Indeed, insertion reaction of isocyanides has been shown as a powerful strategy to prepare various nitrogen-containing organic compounds. A number of significant progresses have been made in transition-metal-mediated or -catalyzed insertion reaction of isocyanides as well as the radical reactions involving imidoyl radical intermediates. However, synthetic transformations of isocyanides sometimes require excess amounts of strong base, acid, and oxidants under harsh reaction conditions, resulting in the formation of a complex mixture involving isocyanide oligomers. Thus, the development of highly atom-economic and efficient synthetic methods using isocyanides is strongly desired.

Because of the unique properties of group 16 heteroatoms (especially, S and Se), the use of chalcogen compounds including organic chalcogenides and thiols has been attracted much attention. For example, it has been proven that a lot of chalcogen compounds exhibit novel bioactivities as well as superior properties in materials science. Therefore, investigations of the pharmaceutical compounds such as antibacterial, antitumor, and hypotensive agents bearing sulfur and selenium have been extensively developed in recent years. For example, chalcogenated quinoxalines have been reported to exhibit antioxidant activities. However, the current synthetic methods of them still suffer from the narrow substrate range. Therefore, new synthetic approaches are strongly desired to extend the substrate scope of the reaction to afford chalcogenated quinoxalines.

In this thesis, the author has developed transition-metal-catalyzed arylation reactions of isocyanides. Using tetraarylleads as arylating reagents, isocyanides could be transformed into imines and/or  $\alpha$ -diimines under a catalytic amount of palladium catalysts. In addition, the diarylation of isocyanides with triarylbismuthines as aryl sources has been investigated using various catalytic transition metal systems. The synthesis of various chalcogenated, nitrogen-

containing compounds has also been established under the photoirradiation conditions. In particular, the photoinduced chalcogenated cyclization of *o*-diisocynoarenes with organic diselenides and thiols provides a useful, straightforward tool to chalcogenated quinoxalines. All the reported reactions are carried out under additive-free conditions. This thesis consists of five 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 a palladium-catalyzed arylation of isocyanides using tetraarylleads as arylating reagents to synthesize imines and/or  $\alpha$ -diimines. During the investigation of arylating reagents of heavy elements, the author found that, unlike triarylbismuthines which afforded only  $\alpha$ -diimines under a catalytic amount of palladium catalyst, the use of tetraarylleads provided the formation of imines as the major product in the case of some aliphatic isocyanides. On the other hand,  $\alpha$ -diimines were found to be formed primarily when electron-rich aromatic isocyanides were applied to the diarylation. The mechanistic investigation indicated that the selectivity and yield of products depended on the nature structure of isocyanides used. Electron-rich aromatic isocyanides stabilized the imidoyl-metal complex; thus, secondary insertion of isocyanide happened and  $\alpha$ -diimine was formed as the result. Meanwhile, unstable imidoyl-metal complexes preferred to undergo reductive elimination, affording the corresponding imines. The reaction proceeded under additive-free and base-free conditions without formation of polymers or oligomers of isocyanides. Even though the use of organoleads in organic synthesis is very limited because of the toxicity of lead compounds, this work demonstrates a very interesting organic transformation using organoleads. It is also worth noting that  $\alpha$ -diimines are useful synthetic precursors for a variety of *N*-heterocyclic carbenes (NHCs) as special ligands for transition-metal-catalyzed reactions. The author believes that the present research provides an efficient synthetic tool for the preparation of NHCs.

Chapter 3 describes a transition-metal-catalyzed diarylation of isocyanides with triarylbismuthines and its synthetic application. Organobismuth compounds are well-known to be environmentally friendly reagents and have been used as unique synthetic reagents in organic chemistry. Indeed, the synthetic applications of triarylbismuthines have been investigated, and various arylation reactions have been reported using triarylbismuthines as arylating reagents. In this study, the author investigated the diarylation of isocyanides with triarylbismuthines in the presence of the palladium and rhodium catalysts; namely, condition parameters such as solvent, temperature, type of catalyst, and inert atmosphere were optimized in detail. As the results, the palladium-catalyzed diarylation afforded  $\alpha$ -diimines as the major products, whereas the rhodium-catalyzed reaction gave imines selectively. Besides, amides as by-product was formed under some certain conditions. In addition, the present diarylation was successfully applied to the synthesis of quinoxaline derivatives in moderate to good yields. The synthesis of *N*-heterocyclic carbenes (NHCs) in one reaction bath was also carried out and the desired *N*-heterocyclic carbene precursor was obtained.

Chapter 4 describes a photoinduced radical cyclization of *o*-diisocynoarenes with organic diselenides and thiols that successfully afford chalcogenated quinoxalines. The chalcogenated quinoxalines have been known to exhibit unique bioactivities, which have been proven in many reports. Conventionally, chalcogenated quinoxalines have been synthesized by the nucleophilic substitution reaction of thiols (or selenides) with the corresponding chlorinated quinoxalines. However, the methods significantly suffer from the substrate scope of quinoxalines derivatives. It has been known that organic thiols, diselenides, and *o*-diisocynoarenes are activated upon visible light irradiation. This is because their absorptions are observed in a range of 300-500

nm. The author expected that the photoinduced reaction of the above compounds must efficiently provide the corresponding quinoxaline products. Hence, the photoinduced reaction of *o*-diisocyanoarenes with thiols or diselenides provided an effective synthetic approach to the construction of chalcogenated quinoxaline derivatives. Some mechanistic investigations indicated that the reaction proceeded via a radical cyclization pathway initiated by the attack of chalcogeno radicals to isocyanides. The transformation is featured by a high conversion, a broad substrate scope, and mild reaction conditions. Moreover, the cyclization reaction is scalable to gram-scale of the starting *o*-diisocyanoarenes, which demonstrates the practicability of the present cyclization reaction.

Chapter 5 describes the conclusion of this thesis.

In conclusion, this thesis describes a series of organic transformations of isocyanides under very diverse transition-metal-catalyzed conditions. With the careful choice of catalysts (e.g., palladium or rhodium) and arylating reagent (organolead or organobismuth compounds), the desired imine or  $\alpha$ -diimine can selectively be synthesized. The reported reactions provide very powerful synthetic methods to various useful nitrogen-containing molecules including *N*-heterocyclic carbenes. The photoinduced reactions of *o*-diisocyanoarenes with chalcogenides (e.g., thiols and diselenides) contribute to very efficient and interesting synthetic methods for thio- or seleno-substituted quinoxalines with promising bioactivities. Other potential reactions of *o*-diisocyanoarenes with radical sources are also expected to happen. For example, diphenyl ditelluride or iodine are known to be very good radical trapping reagents. Thus, a new generation of quinoxalines can be created in this methodology. The author believes that these works will open up a new route to construct various bioactive and pharmaceutical compounds.

#### 審査結果の要旨

本論文は、16族ヘテロ原子を有する官能基と他の有用官能基の高選択的複合導入によるアセチレン類の多官能基化反応の開発を目的として、直截的かつ効率的な有機反応の開発に関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) アセチレンアルコール類を出発物質とし、コバルト触媒またはパラジウム触媒を用いることで、通常では反応が生じにくい内部アルキンに対して、硫黄官能基と一酸化炭素を高収率かつ高選択的に導入できることを明らかにしている。本反応を用いると、硫黄官能基を有するビニリデンラクトンを効率良く合成することが可能である。これらのラクトン誘導体は有用な合成中間体であり、ビニル基、エステル基、または硫黄官能基を反応点とする様々な分子変換反応に利用できる。
- (2) 内部アルキンに対するシアノチオレーションがパラジウム触媒存在下、効率的に進行することを明らかにしている。本反応は、内部アルキンに対してジスルフィドおよび *tert*-ブチルイソシアニドを用いることで進行する。特に、シアノ源として安全な *tert*-ブチルイソシアニドを用いており、有毒なシアン化物を用いることなくシアノ化を達成している点で有用である。
- (3) ベンゾイルペルオキシドとジセレニドを組み合わせることで、内部アルキンに対してベンゾイルオキシセレネーションが進行することを明らかにしている。また、内部アルキンではなく、末端アルキンを用いることでアルキンの末端水素がセレン官能基に置換されたアルキニルセレニドが選択的に得られることも明らかにした。また、本反応はラジカル反応と求電子付加を組み合わせた反応機構で進行することを見出している。

以上の諸成果は16族ヘテロ元素である硫黄、セレンと、カルボニル基、シアノ基またはエステル基などの有用官能基を直截的かつ高選択的に有機分子に導入する新規な付加反応群であり、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。