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学位授与の日付　2021年3月31日
論　文　名　「Studies on the Development of Metal-free Functionalization of Organic Molecules Utilizing the Characteristic Features of Heteroatoms
（ヘテロ原子の特性を活かした有機分子のメタルフリー条件下における官能基化法の開発に関する研究）」

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論文要旨

The function of organic molecules often derives from the presence of heteroatoms such as nitrogen, oxygen, halogens, sulfur, and phosphorus. By taking advantage of the unique properties of heteroatoms, it is possible to impart various functions to organic molecules. Furthermore, it is expected that it will be possible to synthesize these functional organic molecules with high efficiency by properly combining heteroatoms. In recent years, metal catalysts and reagents are often used for the precise synthesis of functional organic molecules, and various novel synthesis methods using metal catalysts and reagents have been developed for this purpose. However, the recent trend toward higher purity in materials and pharmaceuticals has made it difficult for metals to remain. From this point of view, the development of metal-free synthesis methods has recently been strongly demanded. In this thesis, therefore, the author focuses on the development of new synthetic methods for heteroatom chemicals under metal-free conditions using the characteristics of heteroatoms. In particular, organic halides and organophosphorus compounds are becoming increasingly important in organic synthesis, catalyst technology, material chemistry, and medicinal chemistry. Methods for synthesizing these compounds have been developed for high purity, environmental friendliness, and simple operations.

Among organic halides, organic bromide has the appropriate carbon–halogen bond energy; so it has the appropriate stability and reactivity. In addition, organic bromide has the higher selectivity in chemical reactions than organic chlorides, and therefore, the bromide is widely used in organic synthesis as a synthetic intermediate. As to the method for synthesizing organic bromide, the aliphatic bromide can be easily synthesized by various synthetic methods, but the synthetic method of the aromatic bromide is limited. A common bromination method for obtaining aromatic bromides is the conversion of anilines by Sandmeyer reaction. Various bromination reactions with aniline have been developed, but they are limited to methods that use metal-based catalysts under strong basic media or that require tedious workups. To overcome these drawbacks, the development of metal- and base-free synthesis of aryl bromides is strongly desired.

As to the synthesis of phosphorus compounds, one of the simplest methods is the addition of phosphorus compounds to carbon–carbon unsaturated compounds. To avoid the use of metal catalysts and strong bases, radical pathways have recently received considerable interest in C–P formation methodologies. In recent years, phosphine-based organocatalysts have also made great strides in the development of asymmetric catalysis. Furthermore, organophosphorus compounds also served as biophosphate mimics, antibiotics, antivirals, and antitumor agents due to their unique chemical properties and various biological activities. Therefore, there is an increasing demand for efficient, highly regio- and stereoselective preparation of phosphines.

In this thesis, the author has developed the metal-free functionalization of organic molecules utilizing the characteristic features of heteroatoms. Using arylhydrazines as the aryl sources, the author has developed a new synthetic method of aryl bromides that has been attained by the combination of boron tribromide (BBr_3) and dimethyl sulfoxide (DMSO). Moreover, diphenylphosphine oxide ($Ph_2P(O)H$) and tetraphenyldiphosphine monoxide ($Ph_2P(O)–PPh_2$) are used as phosphorus-centered radical sources which successfully add to unsaturated compounds with high regio- and stereoselectivities. All developed reactions can be performed under metal-free conditions to reduce their harmful effects on the environments. This thesis consists of five chapters and the outline of each chapter is summarized as follows.

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

Chapter 2 describes the bromination of arylhydrazine hydrochlorides using BBr_3 and DMSO. The author's research group has previously reported that the iodination of arylhydrazine hydrochlorides with molecular iodine proceeded by a radical mechanism involving aryl radicals as the key intermediates. Interestingly, the author has found the combination of BBr_3 and DMSO inhibits the radical mechanism, and instead induces an ionic pathway for the bromination. A range of aryl bromides could be synthesized in moderated to excellent yields under metal-free conditions. Several experiments, including the addition of a radical scavenger and Hammett plots (linear free-energy relationship) were also investigated to determine whether this method proceeds via a radical or ionic pathway. The results strongly suggested that the ionic pathway might mainly contribute to the bromination. A species generated from BBr_3 and DMSO plays an important role in the conversion of arylhydrazine hydrochlorides to aryl bromides. Taking advantage of the properties of several heteroatoms such as N, B, S, and Br, a novel metal-free synthesis method of aryl bromides has been successfully attained with a simple handling and high yields. The products, aryl bromides, are important synthetic intermediates for the preparation of a series of functionalized arenes.

Chapter 3 describes photoinduced selective hydrophosphinylation of allylic compounds with $Ph_2P(O)H$ and insights into its mechanism. Phosphines are one of the representative ligands for transition-metal catalysts, and especially, bidentate ligands are very useful for controlling the selectivity of catalytic reactions. The 1,3-bidentate ligand can construct a sterically stable six-membered cyclic metal-containing complex, and therefore, the use of a 1,3-bidentate ligand with two coordination sites composed of different heteroatoms might control catalytic reactivity. Based on this concept, the author investigated the radical addition of $Ph_2P(O)H$ to various allylic compounds leading to γ-heteroatom-functionalized phosphine oxides as 1,3-bidentate *P*-ligand precursors. With allylic alcohol, ether, and ester, the corresponding 1,3-*P*,*O*-ligands were obtained in good yields. Allylic sulfides afforded 1,3-*P*,*S*-ligands, which are expected to preferentially coordinate soft metals. Besides the desired product (namely [*P*]-monomer), a double addition product (namely [*P*]-dimer) was also formed, when allylic ether and ester were employed as substrates. To gain insight into the formation of multiple addition products, reactions of diphenylphosphine oxide with allyl phenyl ether were performed varying the amounts of allyl phenyl ether. The results indicated that the use of excess allylic compound induced further propagations. However, the reaction of [*P*]-monomer with allyl phenyl ether did not give [*P*]-dimer. Therefore, the proposed mechanism suggests that $Ph_2P(O)^\bullet$ adds to two molecules of allyl phenyl ether to afford [*P*]-dimer. Several factors such as electron-withdrawing ability of allylic compounds, steric hindrance, and phosphorus substituent properties could affect to the product selectivity between [*P*]-monomers and [*P*]-dimers. The present photoinduced hydrophosphinylation of allylic compounds could occur with excellent regioselectivity (according to anti-Markovnikov's rule) under simple manipulation in the absence of solvent. Therefore, this method can be accepted as an eco-friendly synthesis of γ-heteroatom-functionalized phosphine oxides as 1,3-bidentate *P*-ligand precursors.

Chapter 4 describes the highly regio- and stereoselective phosphinylphosphination of alkynes with $Ph_2P(O)–PPh_2$. Chapter 3 deals with the radical addition of $Ph_2P(O)H$ to carbon–carbon unsaturated compounds such as allylic compounds by homolysis of P–H bond, while Chapter 4 describes a radical addition of P–P bond compounds to alkynes by homolysis of P–P bonds. The author's research group has found that various P–P bond compounds such as $Ph_2P–PPh_2$, $Ph_2P(O)–PPh_2$, $Ph_2P(S)–PPh_2$, and $Ph_2P(S)–P(S)Ph_2$ could add to carbon–carbon unsaturated compounds upon photoirradiation. By gaining insight into these radical addition reactions, the author noticed that $Ph_2P(O)–PPh_2$ is not advantageous for the photoinduced radical addition to alkynes due to its relatively low absorption. Hence, the author has developed a novel phosphinylphosphination of terminal alkynes with $Ph_2P(O)–PPh_2$ using radical initiators. Cleavage of the $P^{V}(O)–P^{III}$ bond forms two different phosphorus-centered radicals with different reactivities. The P^{V} radical is more reactive toward alkynes compared with the P^{III} radical, and the formed carbon radical is selectively captured by the P^{III} site of $Ph_2P(O)–PPh_2$. Furthermore, the present phosphinylphosphination proceeded stereoselectively to give the *E*-isomers. Both alkyl- and aryl-substituted terminal alkynes tolerated the reaction conditions to selectively afford (*E*)-1-phosphinyl-2-phosphinoalkenes in moderate to good yields. In contrast, internal alkynes could not afford the desired adducts due to the steric hindrance. Noteworthy is that the difference in the oxidation state of heteroatom clearly controls the regioselectivity of the addition.

Chapter 5 describes the summary of this thesis.

In conclusion, this thesis describes a series of metal-free functionalizations of organic molecules that take advantage of the characteristics of heteroatoms. By using of a system of BBr_3 and DMSO, arylhydrazine hydrochlorides are successfully converted to aryl bromides. These products play an important role in organic synthesis. Furthermore, the author has succeeded in developing a new synthetic method under metal-free conditions for functional phosphorus compounds being useful as ligands. In the radical addition of $Ph_2P(O)H$ to the allylic compounds, γ-heteroatom-functionalized phosphine oxides as 1,3-bidentate *P*-ligand precursors can be easily synthesized. On the other hand, in the radical addition reaction of $Ph_2P(O)–PPh_2$ to alkynes, 1-phosphinyl-2-phosphinoalkenes are obtained regio- and stereoselectively by utilizing the characteristics of phosphorus having different oxidation states.

As described above, the author succeeded in highly selective functionalization of organic molecules under metal-free conditions by utilizing the characteristics of heteroatoms. These developed synthetic methods are expected to be effective for the powerful synthesis of functional materials and pharmaceuticals.

審査結果の要旨

本論文は、ヘテロ原子の特性を活かしたメタルフリー条件下での有機分子の官能基化法の開発、およびこの手法に基づく臭素化芳香族化合物や有機リン化合物の合成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）アリールヒドラジンの臭素化が、三臭化ホウ素とジメチルスルホキシドを用いた置換型反応として効率良く進行し、アリールブロミドを選択的に合成することに成功している。さらに、ヨウ素分子を用いたアリールヒドラジンのヨウ素化反応がラジカル機構で進行するのに対して、本臭素化反応がイオン機構で進行することを明らかにしている。本反応で得られるアリールブロミドは、芳香族化合物の重要な合成中間体であることから、本研究は多様な芳香族化合物の調製のための効率的な合成ツールを提供するものである。

（２）ジフェニルホスフィンオキシドを用いたアリル化合物の光誘起ヒドロホスフィニレーションにより、γ 位に各種ヘテロ原子を有するホスフィンオキシドを合成することに成功している。本手法は、メタルフリーかつ無溶媒条件下での付加型反応により、アリル化合物に対してリンを位置選択的に導入可能であるという特長を有する。さらに、本反応で得られるヘテロ原子官能基化ホスフィンオキシドを還元すれば、金属との安定な錯形成が可能な1,3-二座配位子に誘導できるため、本手法は様々な 1,3-二座ホスフィン配位子前駆体の環境調和型合成手法を提供するものである。

（３）ラジカル開始剤存在下で、テトラフェニルジホスフィンモノオキシドの末端アルキンへの付加型反応がメタルフリー条件下で位置および立体選択的に進行することを明らかにしている。本反応では、Ⅴ価およびⅢ価リンのラジカル反応特性の違いを解明することにより、選択性の制御に成功している。本手法で得られた *E* 型アルケンは、複数の金属を架橋して階層構造を構築できる架橋配位子の前駆体として有用である。

以上の諸成果は、ヘテロ原子の特性を活かしたメタルフリーでの有機分子の官能基化法を開発し、これらの手法を応用して、芳香族化合物の官能基化に有用なアリールブロミドや、ホスフィン配位子前駆体の合成に成功しており、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。