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学位論文題目	Palladium-Catalyzed Pronucleophile Addition to Alkynes Leading to Optically Active Compounds (パラジウム触媒を利用したアルキンへのプロ求核剤の付加反応・光学活性化合物の合成)
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Introduction

The catalytic addition reaction to C-C multiple bonds is one of the most important process for organic synthesis, because this process can construct new chemical bonds in an efficient and atom-economic manner. In chapter 1, a new transition-metal-catalyzed addition reaction of C-S bond to C-C multiple bonds, that is a palladium-catalyzed intermolecular carbothiolation of alkynes with thioacetals, is described. In chapter 2, the allylation of α-aryl aldehydes with alkynes in the presence of a Pd(0)/PhCOOH combined catalyst system is described. These α-allylated aldehydes are important substances for various transformations in synthetic organic chemistry. The present study provides useful method for the synthesis of α-allylated aldehydes having a quaternary carbon center. In chapter 3, a palladium-catalyzed intramolecular asymmetric addition of oxygen pronucleophiles to alkynes, the so

called hydroalkoxylation, is reported. This methodology allows an easy access to optically active cyclic ethers which are found as framework in several biologically active natural products. In chapter 4, the asymmetric synthesis of tetrahydroquinolines *via* palladium-catalyzed intramolecular hydroamination of alkynes is described. Tetrahydroquinoline derivatives are important synthetic intermediates and biologically active compounds, therefore, this method has a high potential for practical use in organic synthesis. In chapter 5, a CuBr-catalyzed synthesis of furans from 2-(1-alkynyl)-2-alken-1-ones is reported. This methodology allows an easy access to substituted furans which play an important role in organic chemistry, not only as key structural units in many natural products and important pharmaceuticals, but also as useful building blocks in synthesis chemistry.

Chapter 1. Palladium-Catalyzed Intramolecular Carbothiolation of Alkynes with Thioacetals

The C-S bond activation by transition metal complexes has received increasing attention for efficient catalytic and stoichiometric transformations. Our attention was focused to the transition metal-catalyzed addition of a sp^3-C-S bond to a C-C multiple bond. The catalyzed addition of a carbon-sulfur bond to carbon-carbon multiple bonds, so-called carbothiolation, has rarely been investigated before. Herein, a novel transition metal-catalyzed intramolecular carbothiolation of alkynes is reported (eq 1). In this study, thioacetal cleaved products are obtained in high yields.

Chapter 2. Allylation of α-Aryl Aldehydes with Alkynes in the Presence of a Pd(0)/PhCOOH Combined Catalyst System

Pd(0)/benzoic acid catalyzed allylation of α-aryl aldehydes with alkynes was reported (eq 2). To the best of our knowledge, this reaction represents the first example for the coupling of aldehydes with internal alkynes to form α-allylated aldehydes. It should be noted that in the present catalytic system there is no need for pre-activation of the substrates and there is no need for use of any additives. In the absence of any additives, the reaction proceeded smoothly giving the corresponding α-allylated aldehydes in high yields. It is noteworthy that under the reaction conditions the α-hydrogen of aldehydes is easily substituted by allylic groups, without damaging labile aldehyde functionality. The alkynes such as 3-hexyne and 1-phenyl-1-butyne did not react with α-aryl aldehydes under these reaction conditions. In this mechanism (scheme 1), the initial step is the hydropalladation of alkynes **2** with the hydridopalladium species **A** generated from Pd(0) and benzoic acid (catalytic cycle I). The resulting vinyl palladium species **B** would produce phenyl allene **C** and the active catalyst **A** via β-elimination. Hydropalladation of **C** with **A** presumably gives the π-allylpalladium species **D** which react with α-aryl aldehydes to give the allylation products along with the hydridopalladium species **A** (cycle II).

Chapter 3. Palladium-Catalyzed Asymmetric Intramolecular Hydroalkoxylation of Alkynes

Oxygen heterocyclic compounds have attracted considerable attention owing to their biological activities. In particular, the synthesis of oxygen heterocyclic compounds, such as tetrahydrofurans, tetrahydropyrans, isochromans and their saturated derivatives are very important because their skeletons are found in a variety of natural products. The intramolecular addition of the O-H bond of an alcohol to C-C multiple bonds has been considered as one of the most efficient methods for the synthesis of cyclic ethers, because the addition process does not produce any waste elements in contrast to nucleophilic substitution or addition reactions which inevitably afford useless by-products such as organic or inorganic salts. Recently, palladium-catalyzed inter- and intramolecular hydroalkoxylation of C-C multiple bonds such as alkenes, allenes and alkynes has been developed by our group and others. Because catalytic asymmetric synthesis is a field of great importance in its practical usefulness as well as its scientific interest. It promoted us to investigate the asymmetric version of hydroalkoxylation. In 2004, our group reported the intramolecular asymmetric hydroamination of alkynes catalyzed by palladium, using the diphosphine ligand (*R,R*)-RENORPHOS as the chirality inducing agent. We were pleased to find that this catalytic system was also operative

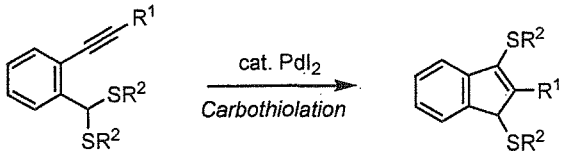
in the case of intramolecular hydroalkoxylation of alkynes (eq 3). By this methodology, a variety of optically active oxygen heterocyclic compounds can be obtained in good yields.

Chapter 4. Asymmetric Synthesis of Tetrahydroquinolines *via* Palladium-Catalyzed Intramolecular Hydroamination of Alkynes

Substituted tetrahydroquinolines are the core structures in many important pharmacological agents and drug molecules, such as anti-arrhythmic and cardiovascular agents, anti-cancer drugs, immunosuppressants, ligands for 5-HT1A and NMDA receptors. For these reasons, many efforts have been made to synthesize tetrahydroquinoline derivatives. Here, we investigated a new method for construction of 1,2,3,4-tetrahydroquinoline rings using palladium-catalyzed intramolecular hydroamination of alkynes (eq 4). As we succeeded for developing the tetrahydroquinoline skeletons as shown in eq 4, we believed that this procedure could be applied to the synthesis of natural products such as (-)-Angustureine, (-)-Galipeine, (-)-Cuspareine and (-)-Galipinine, after hydrogenation of key step products.

Chapter 5. CuBr-Catalyzed Synthesis of Furans from 2-(1-Alkynyl)-2-alken-1-ones

Substituted furans play an important role in organic chemistry, not only as key structural units in many natural products and important pharmaceuticals, but as useful building blocks in synthetic chemistry. Considerable efforts have been directed towards the development of new and efficient methodologies for the synthesis of furans. Previous work in our laboratories has showed that CuI catalyst in DMF is a highly effective catalytic system for the synthesis of cyclic alkenyl ethers from acetylenic aldehydes. The conceivable mechanism is that the resonance stabilized oxonium ion, formed by the nucleophilic attack of the aldehydic oxygen to the copper coordinated alkynes, and is being trapped by alcohols to give the desired products. With this in mind, we hypothesized that cyclization of 2-(1-alkynyl)-2-alken-1-ones might also proceed under our previously developed catalytic system i.e Cu(I) in DMF. Indeed, our hypothesis proved factual and we report herein detailed study on the Cu(I) salts catalyzed cyclization of 2-(1-alkynyl)-2-alken-1-ones which lead to the formation of highly functionalized furans (eq 5).



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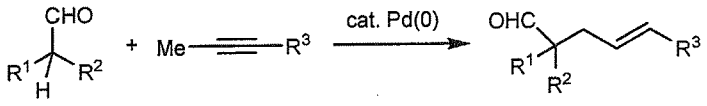

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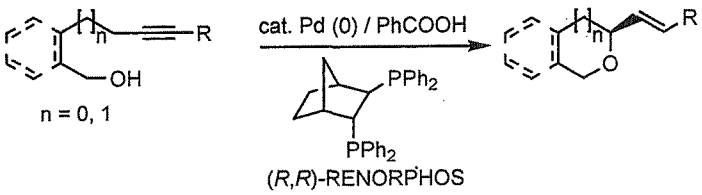

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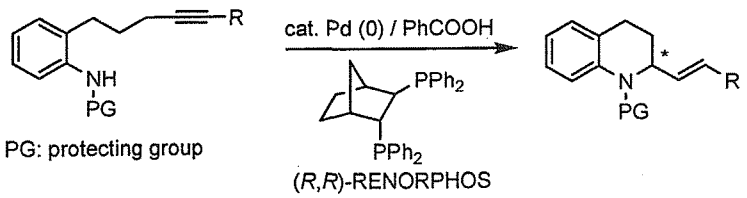

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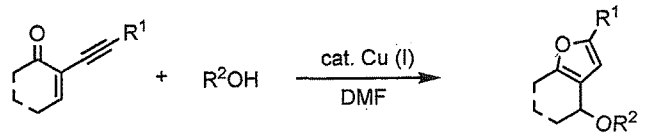
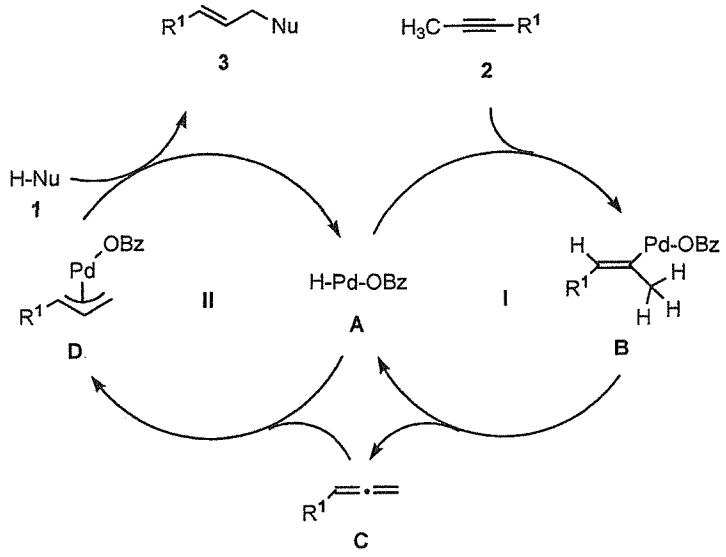


(5)

Scheme 1



論文審査の結果の要旨

炭素—炭素多重結合へのプロ求核剤の付加反応は，原子効率的及び環境負荷の少ないプロセスであることから，炭素—炭素結合や炭素ヘテロ原子結合の構築手法として注目されている。また，医薬品では光学活性な化合物が大半を占めるため，不斉合成の重要性が年々高まってきている。今回創薬研究の一環として光学活性体の新規合成法，即ち，不斉反応の開発を目指すことにした。また，開発された新手法の応用として実際に天然物や生理活性物質の不斉全合成を行った。

第一章では，パラジウム触媒存在下，オルトアルキニルベンズアルデヒドチオアセタール化合物のＣ－Ｓ結合が触媒的に炭素—炭素多重結合に付加する反応，即ち，カルボチオレーション反応を見出しました。本反応ではパラジウム触媒を用いることで，C-S結合の開裂が進行し，アルキル基が転移せずに，生成物として１，３－ビスースルファニルーインデン誘導体が得られると考えられる。

第二章では，酸性条件下，パラジウム触媒を用いることでα-アリールアルデヒドのアリル化反応を見出した。本反応では，アルキンからアレンを経てπ－allylパラジウムを形成し，その後，炭素求核剤の位置選択的攻撃により生成物が得られると考えられる。

第三章では，炭素—炭素多重結合へのアルコール類のエナンチオ選択的付加する反応，即ちヒドロアルコキシル化反応を検討した。本反応は遷移金属触媒によるアルコールのアルキンへのエナンチオ選択的付加反応の初めての例である。また，本反応により得られた80%eeの生成物を用いて還元反応を経て既知化合物へと変換し絶対配置を決めることができた。

第四章では，不斉配位子を有するパラジウム触媒を用いた分子内環化反応により，多様な光学活性テトラヒドロキノリン化合物の合成反応に関して述べられている。この方法により有用な天然物(-)-Angustureineの不斉全合成が可能となった。

第五章では，より安価及び取り扱いの容易な銅触媒を用いてフラン誘導体の合成を行った。特に多置換フラン化合物は合成中間体として重要であることからその効率的合成手法として期待される。

以上，本研究は反応有機化学，有機合成化学の分野に貢献するものであり，著者が自立して研究活動を行うには必要な高度の研究能力と学識を有することを示している。したがって，吴 煥友提出の博士論文は，博士（理学）の学位論文として合格と認める。