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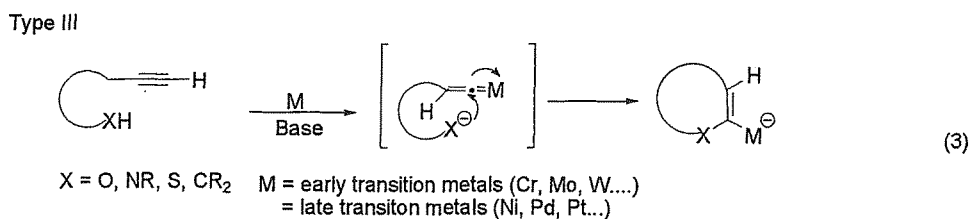
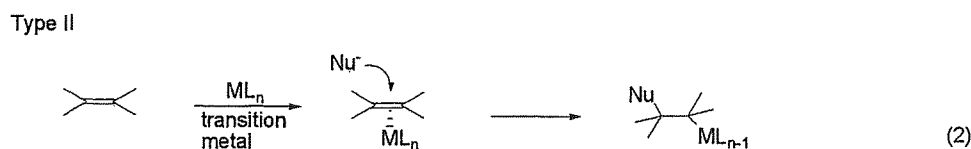
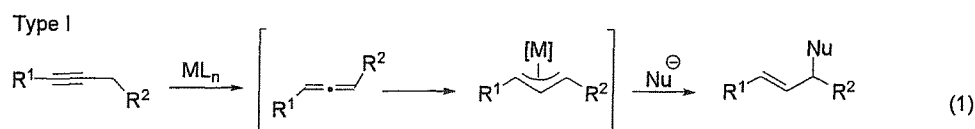
論 文 內 容 要 旨

Introduction:

Over the last decades, our laboratory focused on the use of Lewis acid catalysts including the transition metal complex to invent the new chemical transformation reactions. Among them, we are generally interested in the reaction catalyzed by "Palladium" which is a pivotal techniques for chemist to generate carbon-carbon and carbon-hetero bond forming reactions. During the course of investigation, we have recently discovered some of very interesting reactions which I would like to describe my work in the three different categories (Scheme 1): First category involves the palladium-catalyzed reaction of alkynes/allenes with carbon and heteroatom nucleophiles, leading to the formation of carbon-carbon and carbon-heteroatom bonds which generally proceeds *via* π -allylpalladium intermediate (Type I, eq 1). Second category involved the transition-metal making the complex with π -electron of alkenes or alkynes multiple bonds, which makes feasible the attack of Nu^- to an electron deficient carbon to give an organometal intermediate having a C-Nu bond (Type II, eq 2). Third category involves the direct simple formation of metal vinylidene intermediates from the terminal alkynes has made possible the transfer from stoichiometric to catalytic reactions, and now organometallic vinylidenes are at the heart of selective transformation of terminal alkynes with atom economy (Type III, eq 3).

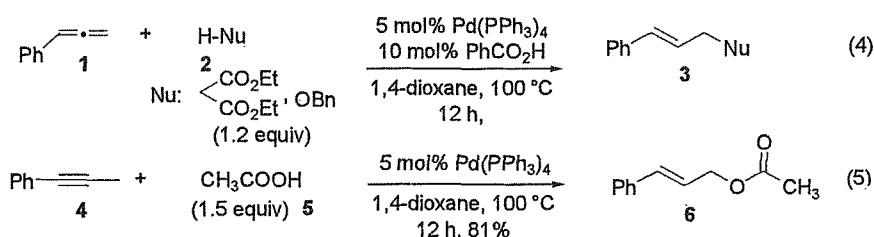
Scheme 1.

General Scheme for the Transition-Metal-Catalyzed Addition of nucleophiles to a Carbon-Carbon Multiple Bonds

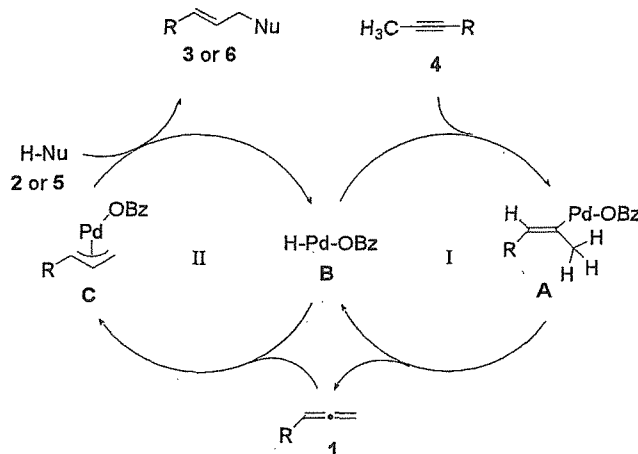


Chapter 1. Palladium/Benzoic Acid Combined Catalytic System for the Allylation of C- and O- Pronucleophiles with Allenes and Internal Alkynes

Pd(0)-benzoic acid combined catalytic system for the addition of carbon and oxygen pronucleophiles to allenens and internal alkynes, respectively, is described (eqs 4 & 5). For example, phenyl allene **1** undergoes smooth addition with diethyl malonate and benzyl alcohol to give the corresponding products **3** in 90% and 71%, respectively. On the other hand, mixture of 1-phenyl-1-propyne **4** and acetic acid **5** also furnished the allylated product **6** in 81% yield. The addition of a catalytic amount of carboxylic acid is crucial, in this palladium catalyzed reaction, for obtaining the allylation products in high yields with regio- and stereoselective manner. The proposed mechanism for the present reaction is depicted in scheme 2.



Scheme 2. Proposed mechanism for the addition of C- and O-nucleophiles with allenens and alkynes

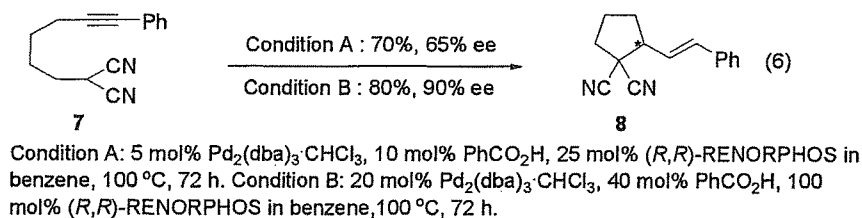


The initial step is the hydrometallation of alkynes **4** with the hydridopalladium species **B** generated from Pd(0) and benzoic acid (catalytic cycle I). The resulting vinyl palladium species **A** would produce phenyl allene **1** and the active catalyst **A** via β -elimination. Hydrometallation of **1** with **B** presumably gives the π -allylpalladium species **C** which reacts with nucleophiles to give allylation products along with the hydridopalladium species **B** (cycle II). In case of allene only, another conceivable pathway is that the Pd-catalyzed addition of benzoic acid to allene **1** takes place first and then the resulting cinnamyl benzoate reacts with H-Nu in the Tsuji-Trost allylation manner to give the products **3**. In short, in case of alkynes cycle I and II operates while in the case of allenens only cycle II operates.

Chapter 2. Palladium-Catalyzed Intramolecular Asymmetric Hydrocarbonation of Alkynes

Palladium-catalyzed intramolecular asymmetric addition of carbon pronucleophiles with alkynes tethered by carbon chain having diacyanomethine at the terminus of carbon chain, leading to the formation of optically active five and six members carbocycles with good to high enantioselectivities and good to high yields, is reported. In the

presence of 5 mol% Pd₂(dba)₃·CHCl₃ and 25 mol% (*R,R*)-RENORPHOS in benzene at 100°C, substrate **7** undergoes the smooth cyclization to afford the product **8** in 70% yield with 65% enantiomeric excess (eq 6). On the other hand, when the amounts of palladium precursors and ligands were increase from 20 to 100 mol%, respectively (condition B), better chemical and optical yields were obtained. This represents the first example of the asymmetric addition of carbon pronucleophiles to alkynes.

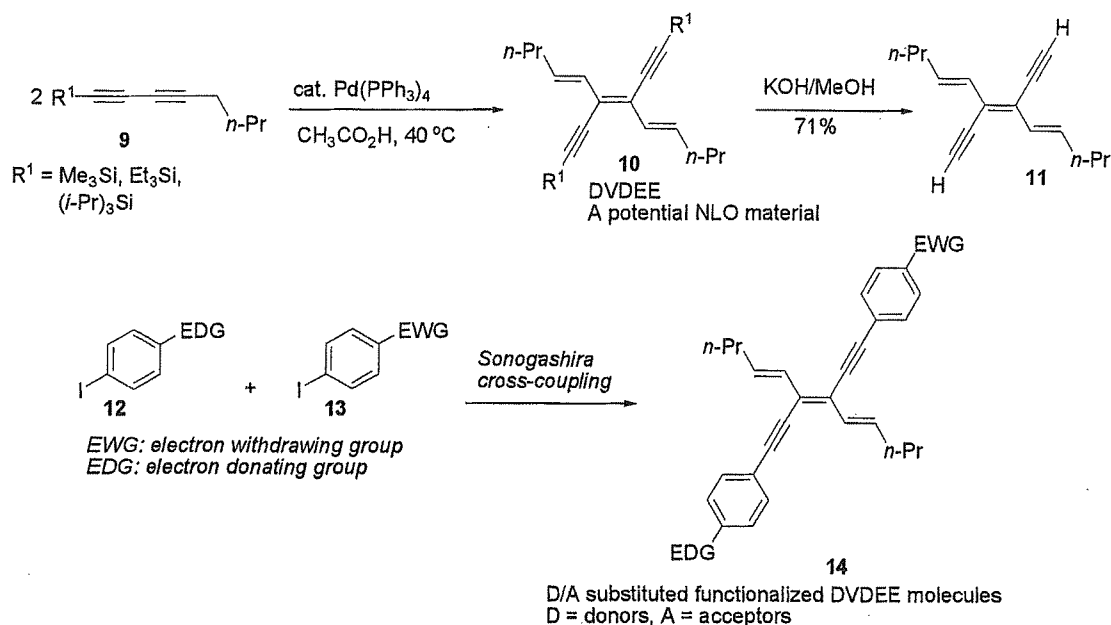


The general mechanism of this reaction is believed to proceed in similar way as described in Scheme 2.

Chapter 3. Palladium-Catalyzed Dimerization of Conjugated Diynes: Synthesis of (*E*)-1,2-Divinyl-diethynylethenes (DVDEEs) having Donor and Acceptor Chromophores at the Terminus of Alkyne

(*E*)-1,2-Divinyl-diethynylethenes (DVDEEs) having donor and acceptor chromophores at the terminus of alkyne unit **14** were synthesized by the palladium/HOAc catalyzed dimerization of the conjugated diynes **9** bearing an Si-group at the terminus of alkyne (R¹ position) followed by desilylation and subsequent Sonogashira reaction of the resulting terminal alkyne **11** with aryl iodides (Scheme 3) is described.

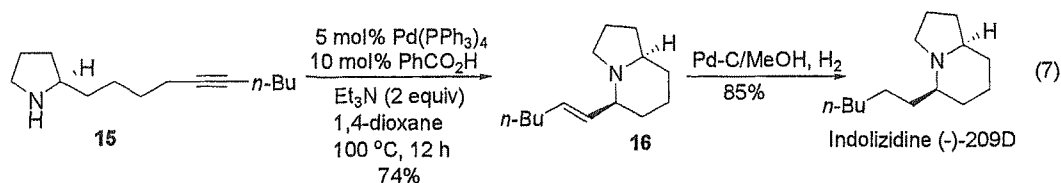
Scheme 3.



Chapter 4. Total Synthesis of Indolizidine (-)-209D: An Application of the Intramolecular Hydroamination Reaction

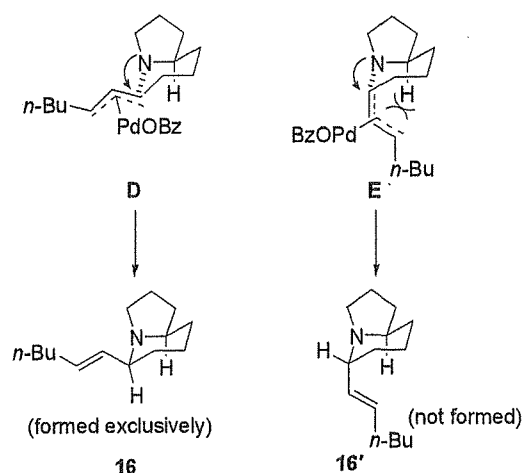
Palladium-catalyzed highly efficient synthesis of indolizidine (-)-209D *via* the intramolecular hydroamination of ϵ -amino alkyne **15** has been accomplished. The alkyne **15** in the presence of 5 mol % Pd(PPh₃)₄ and 10 mol %

benzoic acid and 2 equiv of triethylamine in 1,4-dioxane at 100 °C for 12 h led to the formation of cyclized product **16** as a single diastereomer which on further hydrogenation gave the natural product indolizidine (-)-209D in 85% yield (eq 7).



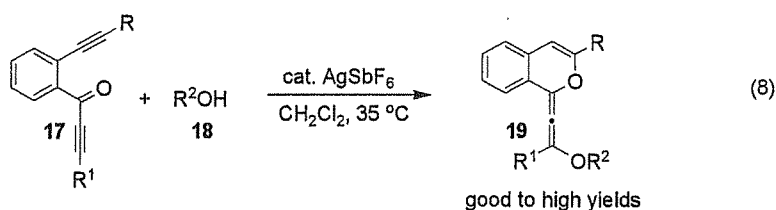
A plausible explanation for the observed diastereoselectivity in the intramolecular hydroamination reaction is made on the basis of 1,3-diaxial interactions. As depicted in Scheme 4, two transition states A and B are conceivable. In the model E, the π -allyl palladium complex would be in an axial position, therefore it suffers from a severe 1,3-diaxial interaction. On the other hand such a 1,3-diaxial interaction is not present in the transition state D, as the π -allyl palladium complex is oriented in an equatorial position. This explains the exclusive formation of the desired diastereomer.

Scheme 4. Proposed transition states for the observed diastereoselectivity

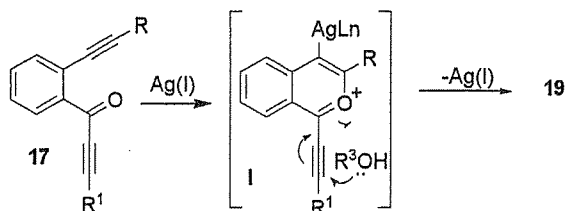


Chapter 5. Silver(I)-Catalyzed Cyclization of Alkynes: Incorporation of Allenes into the Isochromenes

The silver(I)-catalyzed reaction of alkynes with alcohols represents a general tool for the synthesis of 1-allenyl isochromenes. The reaction of **17** with various alcohol **18** (2 equivs) in CH_2Cl_2 in the presence of AgSbF_6 , (5 mol %) at 35 °C gave the desired product **19** in good to high yields (eq 8). The reaction most probably proceeds through the benzopyrylium cation **I**, which would be formed by the nucleophilic attack of carbonyl oxygen to the silver coordinated alkynes. The benzopyrylium ion formed in this way would undergo subsequent trapping with alcohols. The protonation and regeneration of the Ag(I) catalyst produce the annulation products (Scheme 5).

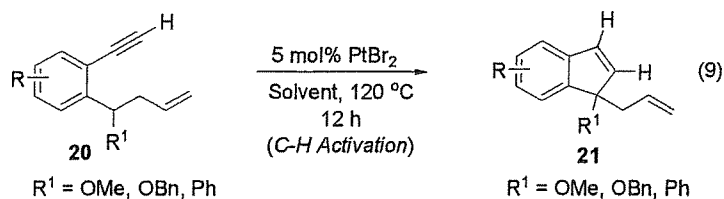


Scheme 5. Proposed mechanism for cyclization reaction



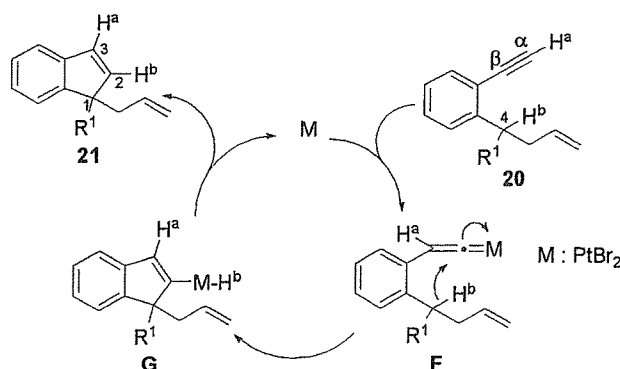
Chapter 6. PtBr₂-Catalyzed Transformation of Allyl(*ortho*-ethynylaryl)carbinol Derivatives into Functionalized Indenes. Sp³ C-H Bond Activation

The PtBr₂-catalyzed transformation of 1-ethynyl-2-(1-alkoxy-but-3-enyl)-benzene **20** into functionalized indenes **21** in good to moderate yields is described. The reaction proceeds most probably sp³ C-H activation by Pt-vinylidene complex (eq 9).



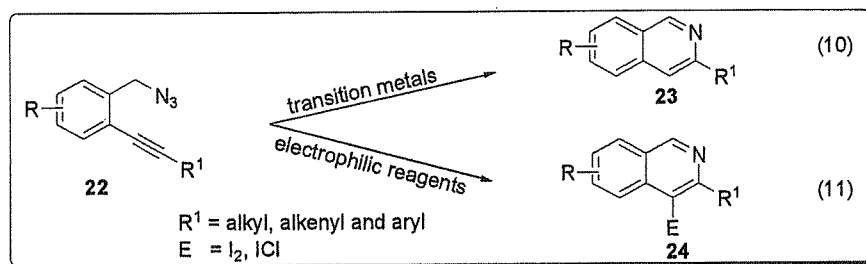
A plausible mechanism is outlined in Scheme 6. The interaction of PtBr₂ with the terminal alkyne of substrate **20** gives an alkyne-PtBr₂ π-complex, which gradually isomerizes *via* the migration of the terminal hydrogen from α-carbon to the adjacent internal β-carbon atom, as observed in the other metal alkylidene complexes, to form the platinum vinylidene intermediate **F**. It is most probable that the *endo*-carbocyclization of intermediate **F** takes place *via* a second H transfer (or *via* C-H activation/C=M mtathesis) to form the five membered metal vinyl species **G**. Finally, reductive elimination of PtBr₂ forms final product **21**.

Scheme 6. Proposed mechanism for the *endo*-carbocyclization *via* sp³ C-H bond activation



Chapter 7. Synthesis of Isoquinolines via Electrophilic Cyclization from Azido-Alkynes

This chapter describes completely new method for the synthesis of isoquinoline derivatives **23** via the transition metal catalyzed cyclization of alkynylazide **22** (eq 10). On the other hand, this result encouraged us to examine the electrophilic cyclization of alkynylazide **10** by electrophiles other than organopalladium compounds in order to obtain 3,4-substituted isoquinoline **24** (eq 11).



論文審査の結果の要旨

近年パラジウム触媒を用いた遷移金属触媒による炭素-炭素結合及び炭素-ヘテロ原子結合構築反応が盛んに研究されているが、これらの反応は効率性が高いのみならずアトムエコノミーの観点からも優れた反応であるといえる。本論文においてNirmal Kumar Pahadiはパラジウム触媒を用いた新規反応を開発し、これらの手法を用いた有用天然物の合成を行った。

第1章では、パラジウム-安息香酸の共触媒系を用いることにより、炭素および酸素プロ求核体がアレンや分子内アルキンへ付加することを見いだしている。アリル化生成物は従来置換型反応である辻-Trost反応により合成されていたが、今回開発された反応は付加反応であることからより原子効率的なアリルエステルの合成手法であるといえる。

第2章では、パラジウム触媒を用いたアルキンの分子内不斉ヒドロカルボ化反応の開発について述べられている。RENORPHOSを不斉配位子として添加することにより不斉収率90%でキラル炭素環化合物が得られることを明らかにした。

第3章では、パラジウム触媒を用いた共役ジインの二量化反応を用いた電子供与及び受容クロモフォアを有するジビニルジエチニルエテンの合成について述べられている。これらの分子群は2次非線形光学活性を有することから、その簡便合成法として注目に値する。

第4章では、分子内ヒドロアミノ化反応を用いたIndolizidine (-)-209Dの全合成を達成している。詳細なメカニズムの解析により高ジアステレオ選択性の発現の機構を明らかにしている。

第5章では銀触媒によるアルキノンの環化反応によりアレン部位を有するイソクロメンの合成反応について述べられている。反応の適応範囲を検討した結果、種々のアルコールが酸素求核体として用いることが可能であることを明らかにした。

第6章では白金触媒によるインデン化合物の合成反応に関して述べられている。詳細なメカニズムの検討によりこの反応は白金ビニリデン錯体を鍵中間体として経由すると提案されている。

第7章ではアジドアルキン化合物の求電子的環化反応によるイソキノリンの合成について報告している。特に4-ハロイソキノリン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。よって、Nirmal Kumar Pahadi 提出の論文は博士（理学）の学位論文として合格と認める。