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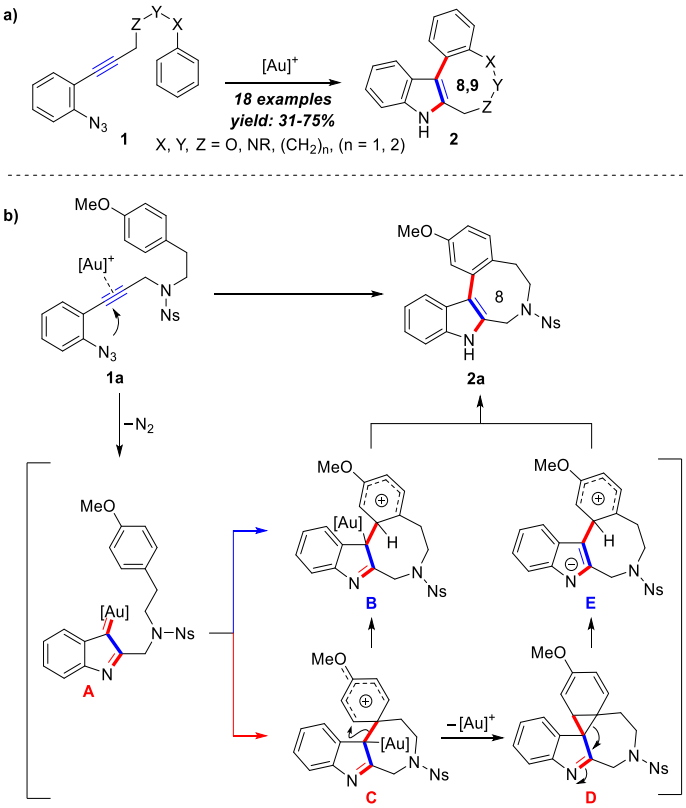
論文題目	**Gold(I)-Catalyzed Reaction of Azido Alkynes for the Synthesis of Indole-Based Polycycles** **(アジドアルキンの金触媒反応によるインドール型多環式化合物の合成)**		

Polycycles based on indole and indoline are common structural motifs found in various biologically-active compounds derived from natural and synthetic heritage. Efficient access to their construction remains challenging and will contribute to the exploration of unknown chemical space relevant for drug discovery. For construction of polycyclic indole and indoline derivatives, transition-metal-catalyzed cascade reactions are beneficial. Particularly, the rise of gold catalysis resulted in a vast toolbox for the rapid build-up of molecular complexity *via* diverse reactivity modes, being frequently exploited for polycyclic indole synthesis. Contemporary, α-imino gold carbenes attract considerable attention, since these are useful synthetic umpolung equivalents for the electrophilic functionalization of indoles, conventionally having the C3 nucleophilic site. In this doctoral study, the author demonstrates new utilities and reactivities of α-imino gold carbenes to access challenging indole- and indoline-fused polycycles from readily available azido alkynes.

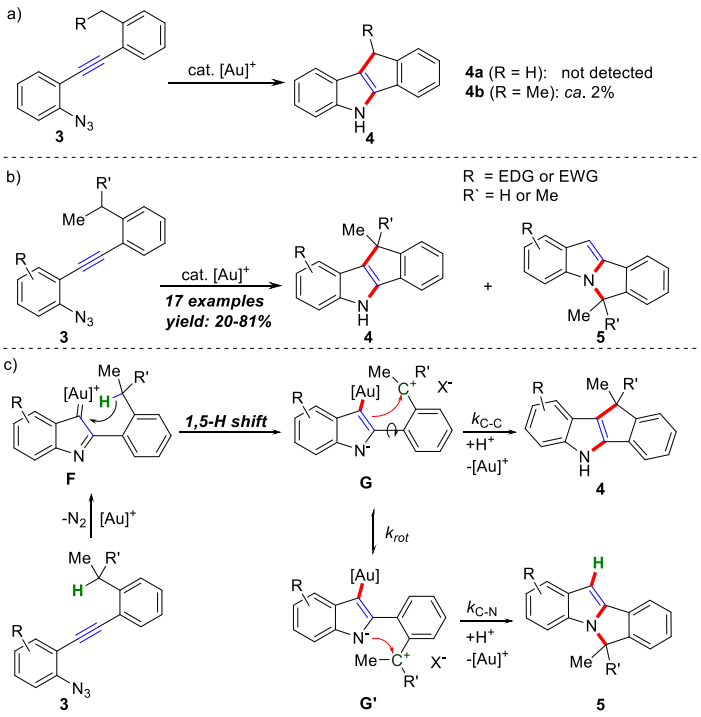
In **Chapter 1**, the author showcases access to challenging and biologically-relevant benzannulated indole-fused medium-sized rings *via* gold-catalyzed cascade cyclization of azido alkynes **1**. A preliminary investigation demonstrated that introduction of an electron-withdrawing 2-nitrobenzenesulfonyl (Ns) group at the propargylamine functionality significantly decreases impeding polymerization, while increasing the reactivity of the substrate. When optimizing the reaction conditions, the polymerization was suppressed by dilution of the substrate concentration to 2 mM. Additionally, the author identified that *t*-$Bu_3PAuCl/AgSbF_6$ represents the best catalytic system for the eight-membered ring formation. Subsequently, the reaction scope was investigated and yields in the range of 31–75% were registered (**Scheme 1a**). Notably, *ipso*-activation with an electron-donating group *para*-positioned to the alkyl tether tremendously accelerated the cyclization reaction, while in stark contrast introduction of an electron-withdrawing group made the reaction sluggish. Based on the result of anisole derivatives, the author proposed a mechanism which proceeds *via* a less strained *ipso* cyclization to form the intermediate **C** followed by ring-expansion (**Scheme 1b**). A thermodynamically more challenging nine-membered ring was obtained under employment of a highly congested semi-hollow shaped C-dtbm ligand. This ligand was also effective for an alkoxylative eight-membered ring formation.

Scheme 1: a) General Scheme for Gold(I)-Catalyzed Cascade Cyclization to Indole-Fused Benzannulated-Medium-Sized Rings **b)** Proposed Mechanism for the Eight Membered Ring Formation



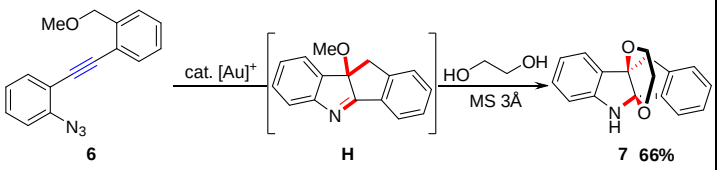
In **Chapter 2**, the author verifies that C(sp^3)-H functionalization is operational in a gold(I)-catalyzed cyclization of azido alkynes through electrophilic functionalization of α-imino gold carbenes. The carbocation originating from a 1,5-H shift from gold carbene undergoes product bifurcation triggered by the ambident nucleophilic character of indole C3 and N1 positions (**Scheme 2**). The chemoselectivity can be controlled by substrate and counteranion modulations. In a preliminary experiment, the author used azido alkyne bearing an *ortho*-tolyl group **3a** (R = H), which did not exhibit sufficient hydride character and resulted in a complex mixture (**Scheme 2a**). Increasing the stabilization of the corresponding carbocation with an additional methyl group employing ethyl substituted azido alkyne **3b** (R = Me) gave the desired product **4b** in *ca*. 2% yield. Subjecting the substrate to JohnPhos(MeCN)SbF_6 in non-coordinating tetrachloroethane (TCE) as a solvent at 90 °C with a 2 mM substrate concentration for 30 min represents the optimized conditions for the C–C bond formation in good yields (63%). Consecutive investigation of the substrate scope gave a range of yields between 20 and 81%, suggesting an emerging substrate-dependent product bifurcation (**Scheme 2b**). Electron-withdrawing groups on the aryl azide moiety tend to accelerate the aza-cyclization to **5**, while electron-rich groups facilitate carbo-cyclization to **4**, suggesting that lowering the reactivity of the vinyl gold intermediate results in increased time for aryl indole bond rotation as depicted in **G** and increases the probability for aza-cyclization (**Scheme 2c**). Iterative stabilization of the carbocation *via* further methylation (R' = Me) increased the ratio towards C–N bond formation. This chemoselectivity can also be shifted towards aza-cyclization if NaBARF is used as a counteranion. Through combined effects using the isopropylated derivative as substrate and the BARF counteranion, absolute chemoselectivity for the aza-cyclization was established (>99:1).

Scheme 2: a) Initial Attempts for the Gold(I)-Catalyzed C(sp^3)-H functionalization **b)** General Scheme for the Scope of Bifurcative Gold(I)-Catalyzed C(sp^3)-H Functionalization c) Proposed Mechanism



In **Chapter 3**, to explore the diverse reactivity modes of α-imino gold carbenes derived from azido alkynes, the author shed light on a cascade process that is capable of rapid buildup of molecular complexity in a sequential manner *via* an alkoxy migration/nucleophilic addition sequence to give oxygenated and sp^3-enriched tetracyclic indoline scaffolds (**Scheme 3**). Exposure of benzyl methoxymethyl-substituted arylalkynes **6** to *t*BuXPhosAuCl/ $AgSbF_6$ in TCE at 140 °C gave the indoline **7** in 66% yield (**Scheme 3**). This reaction would proceed through the generated α-imino gold carbene, methoxy migration, and carbo-cyclization. Interception of the resulting iminium **H** *via* injection of glycol in the presence of MS 3Å resulted in the corresponding indoline derivative **7**.

Scheme 3: Gold(I)-Catalyzed Cascade Cyclization of Azido Alkynes towards Indolines via Methoxy Mirgation



As described, the author presented an efficient and novel gold-catalyzed cascade reaction towards highly functionalized indoles and indolines based on α-imino gold carbenes. This study will contribute to rapid generation of molecular complexity to expand the chemical space of biologically relevant polycyclic indole/indolines.

（続紙 ２ ）

（論文審査の結果の要旨）

本博士論文は、α-イミノ金カルベンの反応性を活用した含窒素複素環の新規構築反応について述べている。第一章では、アルキン末端にフェニルアルキル基を有するアジドアルキンの金触媒反応により、八員環縮環型インドールの合成に成功した。置換基効果の検討により、本反応がイプソ置換に引き続く環拡大によって進行していることが示唆された。さらに、C-dtbm リガンドを用いることにより、九員環形成反応が可能となることも示している。本反応は、金カルベンを用いた中員環形成反応として学術的な価値が高い。

第二章において著者は、金カルベンへのヒドリド転位によってベンジルカチオンを発生させ、続くインドール 3 位または 1 位からの環化反応によって縮環インドールを合成している。興味深いことに、カルボカチオンを安定化する基質を用いた際には 1 位からの環化（N 環化）反応が高い選択性で進行することを見出した。さらに、カウンターアニオンが環化の選択性を大きく変化させることを明らかにした。本反応は、金カルベンに対する 1,5-ヒドリド転位のはじめての例であり、ベンジル位 C-H 官能基化に成功している点においても高い価値がある。

第三章では、1,5-アルコキシ転位を経由する多環式インドリンの合成について述べている。第二章の検討の過程において、カルボカチオンを安定化する目的でメトキシ基を導入すると、ヒドリドではなくアルコキシ基が転位することを著者は新たに見出した。この反応性を利用して、生成するイミン中間体をエチレングリコール等の求核剤で処理することで、五環性インドリンの合成に展開できることを示した。

各章とも、Luca Can Greiner 氏が中心となって実施した実験結果をもとに、有機合成化学および医薬品化学の観点で新規性が高く興味深い実験結果がまとめられている。よって、本論文は博士（薬科学）の学位論文として価値あるものと認める。また、令和５年２月１７日、論文内容とそれに関連した事項について試問を行った結果、合格と認めた。

要旨公表可能日：２０２３年6月２３日以降