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Utility of Ligand Effect in Homogenous Gold Catalysis: Enabling Regiodivergent π-Bond-Activated Cyclization

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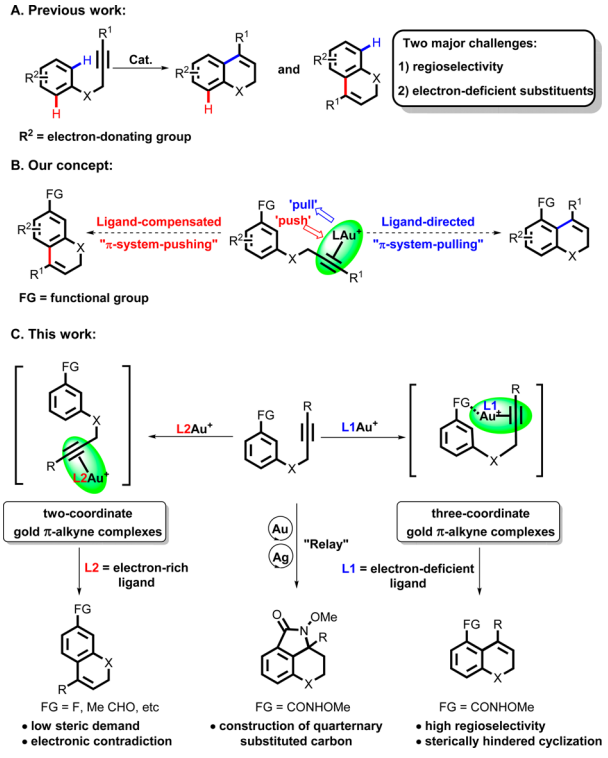
Supporting Information

ABSTRACT: Comprehensive utilization of both electronic and steric properties of ligands in homogeneous gold catalysis is achieved in the regiodivergent intramolecular hydroarylation of alkynes. A flexible electron-deficient phosphite ligand, combined with the readily transformable directing group methoxyl amide, is attached to a cationic Au(I) center in three-coordinate mode, affording sterically hindered *ortho*-position cyclization. Meanwhile, *para*-position cyclization is exclusively achieved with the assistance of a rigid electron-abundant phosphine ligand-based Au(I) catalyst, in which ligands manifest the compensating effect for cyclization through steric hindrance and electronic properties. By combining gold with silver catalysts, tetrahydropyrroloquinolinones possessing a congested tricyclic structure are obtained via a proven Au/Ag relay catalytic process.

Development of homogenous gold catalysis flourished in the past decade, providing an efficient and powerful tool for constructing complex molecules, largely because of its preponderant function as a carbophilic π-acid for activating carbon−carbon multiple bonds.[1] Ligands have played a crucial role in advancing homogeneous gold catalysis because of how they steer the catalysts, leading to a variety of reactions.[2] Intramolecular hydroarylation of alkynes catalyzed by Au has been a useful method for obtaining fused heteroarenes by virtue of its highly efficient atom economy.[3] In 2005, the Echavarren group reported the first Au(I)-catalyzed regioselective intramolecular hydroarylation, with one substrate bearing an electron-rich hydroxyl group.[3c] Next they achieved regiocontrol of intramolecular hydroarylation on indole scaffolds by employing the Au(I) or Au(III) catalysts.[3d] Although massive attention was focused on Au-catalyzed alkyne hydroarylation processes from that point,[3e−j] regioselectivity of substituted aromatics and utilization of electron-deficient substrates remain challenges (Scheme 1A). By utilizing the ligand effect[4] in our research, combined with the directing concept in C−H activation,[5] a solution for the problems mentioned above is envisioned. Electrophilic gold complexes, tuned by electron-deficient ligands, will permit another coordination with a directing group (DG), which simultaneously "pulls" a Au-coordinated π-system to the sterically hindered *ortho*-position on aromatic rings for further cyclization.[6]

Scheme 1. Gold-Catalyzed Intramolecular Hydroarylation of Alkynes and Cascade Cyclization



Alternatively, the rigid, bulky electron-rich ligands supplement steric hindrance and electronic properties, which eventually "push" the π-system to the *para*-position (Scheme 1B). Here we report Au(I)-catalyzed regiodivergent intramolecular hydroarylation of alkynes, in which cyclization to the sterically hindered *ortho*-position is governed by the electron-deficient ligand via three-coordinate gold and the bulky electron-rich ligand satisfies the electronic and steric requirements.

We commenced the study with the model substrate **1a**, equipped with a methoxyl amide, to test Au(I) catalysts with diverse electronic and steric properties (Table S1, S2). As assumed, the electron-deficient tris(2,4-di-*tert*-butylphenyl)

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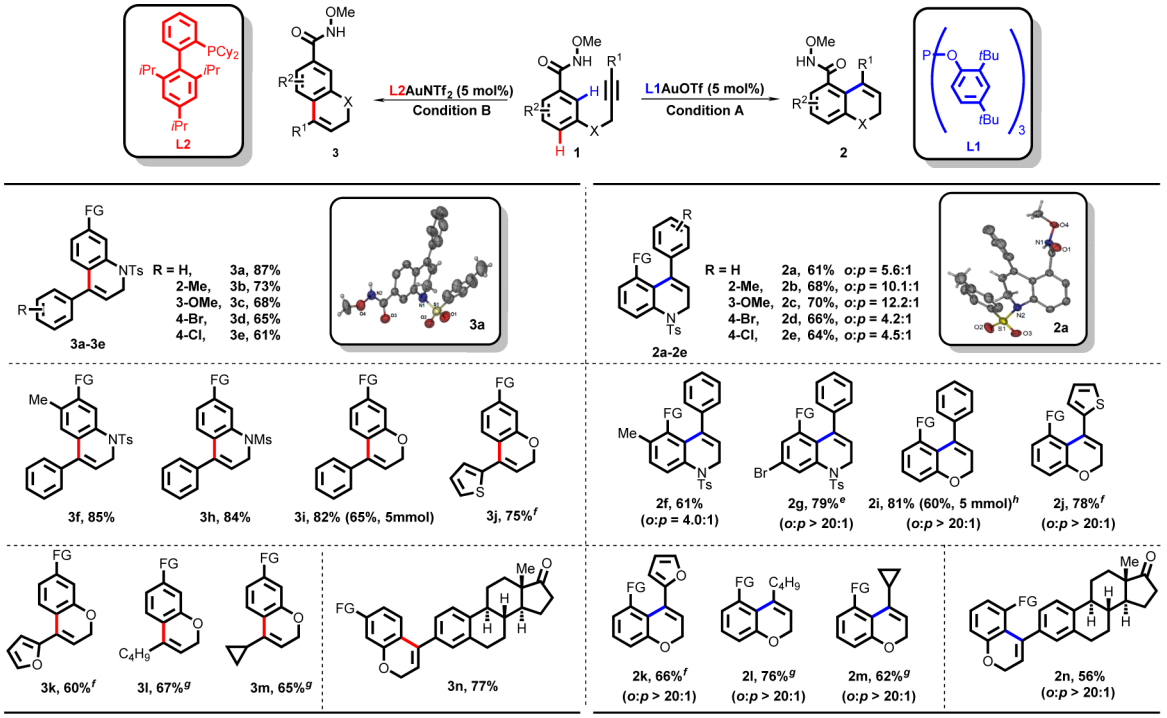
Table 1. Scope of Both *Ortho*- and *Para*-Position Cyclization[a–d]



[a]FG = CONHOMe. [b]Condition A: **1a** (0.1 mmol), $(2,4\text{-}t\text{Bu}_2\text{PhO})_3\text{PAuOTf}$ (5 mol%) in DCE (1.0 mL) at 80 °C for 8 h. Condition B: **1a** (0.1 mmol), XphosAuNf_2 (5 mol%) in DCE at 80 °C for 8 h. [c]Isolated yields of pure product; on right side, isolated yields refer to the yields of *ortho*-cyclized products. [d]Ratios determined by ^{1}H NMR. [e]$(2,4\text{-}t\text{Bu}_2\text{PhO})_3\text{PAuNTf}_2$ was used, and 1 equiv of acetic acid was added. [f]3 h. [g]5 h. [h]*o*:*p* = 10.8:1

phosphite ligand (**L1**) resulted in smooth *ortho*-position cyclization, generating dihydroquinoline **2a** in 61% isolated yield. The ligand compensating effect was demonstrated when Au(I) complexes coordinated with the rigid, bulky electron-rich Xphos ligand, leading to the exclusive formation of dihydroquinoline **3a** in 87% yield via *para*-position cyclization. As shown in the right side of Table 1, R^1 substituted with electron-donating groups provided better yields and higher regioselectivity than in the case of substitution with electron-withdrawing groups, probably owing to the poorer coordination of electron-deficient alkynes with a gold catalyst (Table 1, **2b–e**). Particularly, when the aromatic ring contained a *meta*-substituted Br group, *ortho*-position cyclization occurred with great regioselectivity (>20:1, **2g**). In addition, when an O-atom was employed as a linker in the substrate, a 20:1 selectivity ratio was attained for *ortho*-position cyclization, since O-linkage gives open and flexible space for facile coordination of the ligand (**2i–n**). Substrates bearing heterocycles such as thiophene and furan also worked well for *ortho*-position cyclization (**2j,k**). An alkyne substituted with a three-membered ring was compatible, and the strained ring remained intact (**2m**). Remarkably, natural product estrone could be equipped with alkynes and underwent *ortho*-position cyclization with moderate yield and excellent regioselectivity (**2n**). The corresponding *para*-position cyclization is shown in the left section of Table 1. In general, both electron-rich and -deficient substituents of R^1 and R^2 successfully achieved this transformation, generating the desired products as a single regioisomer (**3b–f**). Notably, *para*-position cyclization was equally tolerated with heterocycles, aliphatic groups, and complex steroids as well (**3i–n**). Gratifyingly, gram-scale operations were feasible in both *ortho*- and *para*-cyclization, affording **2i** and **3i** in moderate yields. Moreover, to demostrate the facile removal of the DG, dihydroquinolines **2a** and **3a** were readily transformed into the corresponding aldehyde and ketone with high yields (for details, see SI). In an attempt to explore the catalyst efficiencies, turnover numbers (TON) were studied. When 0.5 mol% phosphite Au(I) catalyst was applied, TON = 60 for *ortho*-cyclization, while the Xphos-based Au(I) catalyst for *para*-cyclization gave TON = 164. However, the regioselectivity values of the corresponding products decreased dramatically in both cyclizations when the catalyst loading was lowered.

Interestingly, tetrahydropyrrolo[2,3,4-*de*]quinolin-5(1*H*)-one (**4a**) was obtained directly by subjecting **1a** to the Au/Ag mixture (Table S1, entry 10), which was further confirmed by X-ray analysis (Table 2, **4a**). Testing the ratio of the Au(I) catalyst and a Ag additive identified 5 mol% of Au(I) catalyst and 10 mol% of silver salt as the best proportions. The substrate scope of this cascade cyclization was consequently evaluated under optimized conditions (Table 2). Both electron-donating and -withdrawing substituents of R^1 and R^2 accomplished this transformation efficiently, affording products with a quaternary substituted C-center in good to excellent yields (**4c–g**). Comparatively, cyclization of substrates with an O-atom linker delivered the oxygenated products in excellent yields and >20:1 *o*:*p* regioselectivity (**4i–n**).

Control experiments were subsequently conducted (Scheme 2). There was no formation of **4a**, resulting in a 77% recovery of **2a** when cationic gold catalyst $(2,4\text{-}t\text{Bu}_2\text{PhO})_3\text{PAuOTf}$ was utilized alone. Combining $(2,4\text{-}t\text{Bu}_2\text{PhO})_3\text{PAuCl}$ with an excess catalytic amount of AgOTf afforded the desired product in 80% yield. **4a** could be obtained in 85% yield with complete consumption of **2a**, even when AgOTf was applied alone, demonstrating that silver was the authentic catalyst in the second cyclization step. These results showed the different phenomena

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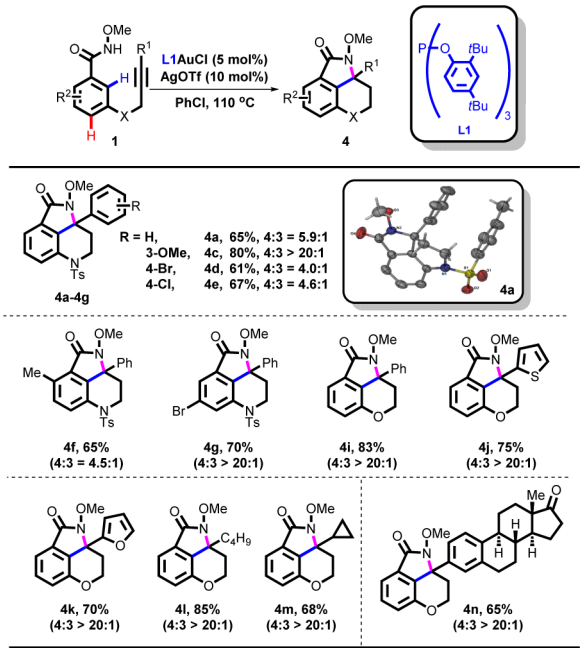
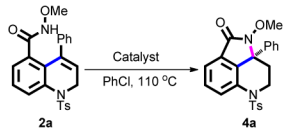
Table 2. Au/Ag Relay Cascade Cyclization[a,b]



[a]Reaction conditions: **1a** (0.1 mmol), $(2,4\text{-}t\text{Bu}_2\text{PhO})_3$PAuCl (5 mol %), AgOTf (10 mol%), PhCl (1.0 mL), 110 °C, 12 h. [b]Isolated yields.

Scheme 2. Control Experiments of Au/Ag Relay Cyclization



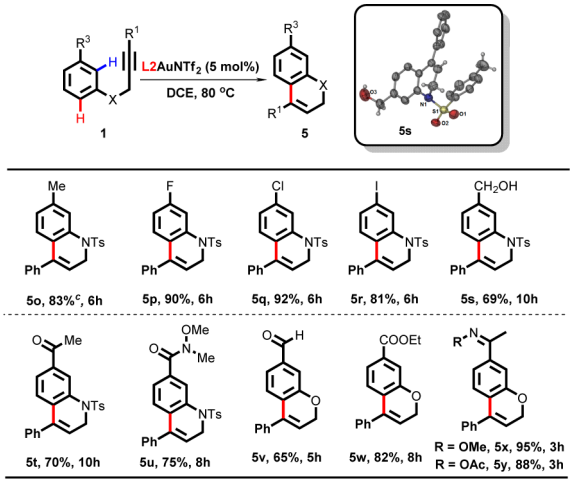
Cat.	Yield
$(2,4\text{-}t\text{Bu}_2\text{PhO})_3$AuOTf (5 mol%)	0%
$(2,4\text{-}t\text{Bu}_2\text{PhO})_3$AuCl(5 mol%) /AgOTf (10 mol%)	80%
AgOTf (10 mol%)	**85%**

in gold chemistry, indicating the catalytic effect of silver toward double bonds rather than simply as an additive for precipitating halide anions.[7]

To further demonstrate the ligand compensating effect, we investigated aromatic nucleophiles bearing electron-deficient and substituted functional groups with subtle steric hindrance (Table 3). Notably, dihydroquinoline **5o** was exclusively obtained with only a methyl group substituted on the *meta*-position, assisted by the tBuXphos-based Au(I) catalyst. Furthermore, the substrate bearing a F-atom, which barely possesses steric hindrance, also afforded solely the corresponding product in high yield (**5p**). Moreover, this transformation could be compatible with the H-bond-containing hydroxyl group generating the corresponding product **5s**. We were delighted to find that electron-withdrawing substituents such as ketone (**5t**), Weinreb amide (**5u**), aldehyde (**5v**), ester (**5w**), and sensitive imines (**5x,y**) were all well tolerated in good to excellent yields.

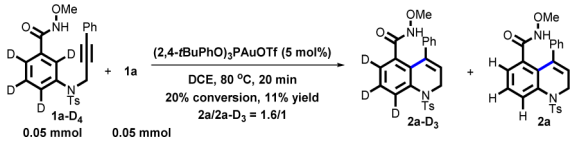
An intermolecular kinetic isotope effect (KIE) experiment including *ortho*-position cyclization resulted in the value 1.6:1. This demonstrated a secondary KIE for this transformation, which indicated that cleavage of the C−H bond was not the rate-determining step (Scheme 3). Based on these results, pathway mechanisms tunable by the ligand effect are shown in Scheme 4. Both the flexible electron-deficient phosphite ligand **L1** and the weakly coordinating OTf^- anion would increase the electrophilicity of the gold center. The Au(I) catalyst then must be trapped by lone-pair electrons on the amide group, allowing for the formation of three-coordinate Au(I) π-alkyne intermediate **A**.[6] Additionally, flexible, bulky aryl moieties on the phosphite

Table 3. *Para*-Position Cyclization of Subtly Sterically Hindered and Electron-Deficient Aromatic Nucleophiles[a,b]

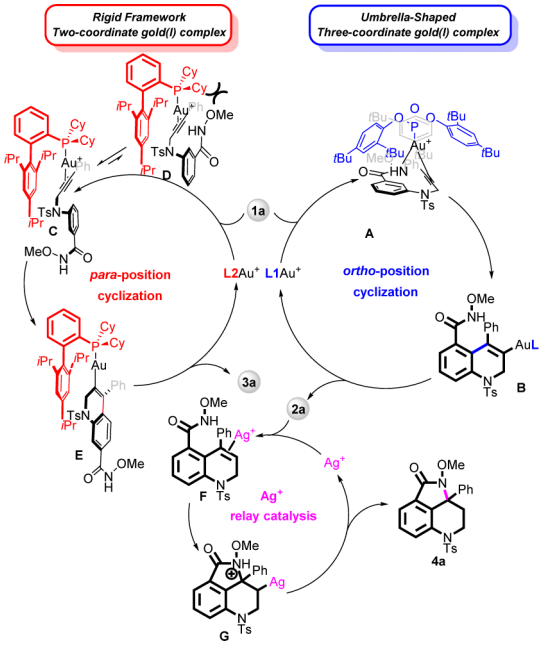


[a]Reaction conditions: **1a** (0.1 mmol), XphosAuNTf$_2$ (5 mol%), DCE (1.0 mL), 80 °C. [b]Isolated yields. [c]*t*BuXphosAuNTf$_2$ was used instead of XphosAuNTf$_2$.

Scheme 3. KIE Experiments



Scheme 4. Proposed Mechanism



ligand offer umbrella-shaped protection, further stabilizing intermediate **A**. Through Friedel−Crafts-type addition, intermediate **B** was generated and subsequently followed by protonation, affording sterically hindered *ortho*-position cyclization to form dihydroquinoline product **2a**. The C−C double bond in **2a** is subsequently activated by the silver catalyst, giving rise to intermediate **F**, which undergoes nucleophilic addition to obtain the congested tricyclic product **4a**. Moreover, the rigid,

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bulky electron-abundant Xphos ligand (**L2**) and slightly more strongly coordinated NTf_2^- could jointly lower the electrophilicity of the gold center to increase the stability of intermediate **C** and minimize the conformation leading to *ortho*-position cyclization. The electron-rich tri-isopropylphenyl ring on the ligand compensates for the electron-deficient phenyl moiety of the substrate through $\pi-\pi$ interaction, which affords the smooth cyclization of electron-deficient aromatics. Finally, sequential *para*-position-selective cyclization and protonation are successfully achieved.

In conclusion, we have developed a ligand-controlled Au(I)-catalyzed regiodivergent intramolecular hydroarylation of alkynes. *Ortho*- and *para*-position cyclization are successfully established respectively through fine-tuning electronic and steric effects of the ligands derived from gold complexes. Altering three-coordinate Au(I) complexes plays a key role in the adjacent cyclization, and using a rigid electron-rich ligand allows *para*-position cyclization exclusively, in which aromatic nucleophiles bearing electron-deficient functional groups and a subtle steric difference could afford the cyclization highly selectively. Moreover, a silver instead of a gold catalyst proved to be the prior activator of double bonds in the second cyclization of the cascade cyclization. Further synthetic applications of these tunable transformations are under investigation by our group.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b01707.

Experimental procedures and NMR spectral, X-ray, and analytical data for all new compounds (PDF)
Crystallographic data for 2a, 3a, 4a, and 5s (CIF)

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

This paper is dedicated to Professor K. C. Nicolaou on the occasion of his 70th birthday.

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