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Access to Divergent Benzo-Heterocycles via a Catalyst-Dependent Strategy in the Controllable Cyclization of *o*-Alkynyl-*N*-methoxyl-benzamides

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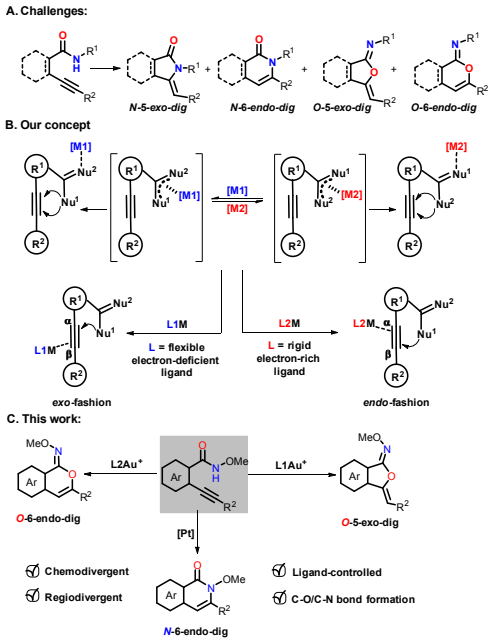
A chemo- and regio- selectively controllable approach for construction of diverse benzo-heterocycles is established. A new strategy of utility of ligand effect in gold catalysis to control the regioselectivity in the cyclization of *o*-alkynylbenzamides is successfully achieved. Meanwhile, chemoselectivity between nitrogen and oxygen nucleophiles is precisely switched by gold and platinum catalysts.

Gold complexes have received a great deal of attention during the past decade, owing to their prominent performances in the electrophilic activation of carbon-carbon π-bonds.[1] Gold-catalyzed intramolecular cyclization of alkynes bearing an adjacent nucleophilic group has been proven useful methods for facile construction of various heterocycles.[1c-g, 1o] In contrast to the tremendous growth of gold-catalyzed intramolecular nucleophilic additionto alkynes, addition of amide to alkynes has been scarcely reported.[2] Amides behave as peculiar ones compared to other nucleophiles, due to their ambident form[3] resulting in two different nucleophilic sites which diversify the reaction processes and simultaneously enhance the difficulty of controlling the selectivities. In 2004, Hashmi and coworkers reported the first gold(III)-catalyzed intramolecular cyclization of propargylic amides for the synthesis of oxazoles, in which O-cyclization was favored via 5-*exo-dig* pathway rather than 4-*endo-dig* N-cyclization.[2a] *o*-Alkynylbenzamide,[4] different from propargylic amide, challenges four different possibilities in cyclization of N- and O-attack mode with 5-*exo-dig* and 6-*endo-dig* pathways (Scheme 1A). Inspired by the ligand effect in gold catalysis,[5] we envisioned that ligands containing various electronic and steric properties might bring about different regioselectivity of alkynes. For chemoselectivity, we envisaged different "soft" and "hard" transition metals[6] possess distinct coordinations and ambident forms toward different heteroatoms, which brings chance to differentiate nucleophilic sites (Scheme 1B). Herein, we present our success in controlling the cyclization of *o*-alkynyl-*N*-methoxybenzamide, in which ligand is in command of regioselectivity and metal is in charge of chemoselectivity (Scheme 1C). It should be noted there are no precedents on ligand-controlled regioselectivity in cyclization of *o*-alkynyl-*N*-methoxybenzamide.



Scheme 1 Selectivity challenge on cyclization of *o*-Alkynylbenzamide.

We commenced our investigation with *o*-alkynyl-*N*-methoxybenzamide **1a** in which the methoxy group could afford another coordination site and increase the nucleophilicity of amide, subjecting to diversely "soft" and "hard" transition-metal catalysts (Table S1).[7] Delightedly, N-6-*endo-dig* cyclization product **5a** was obtained as the sole isomer in 82% yield with $PtCl_4$ as catalyst. However, $PtCl_2$

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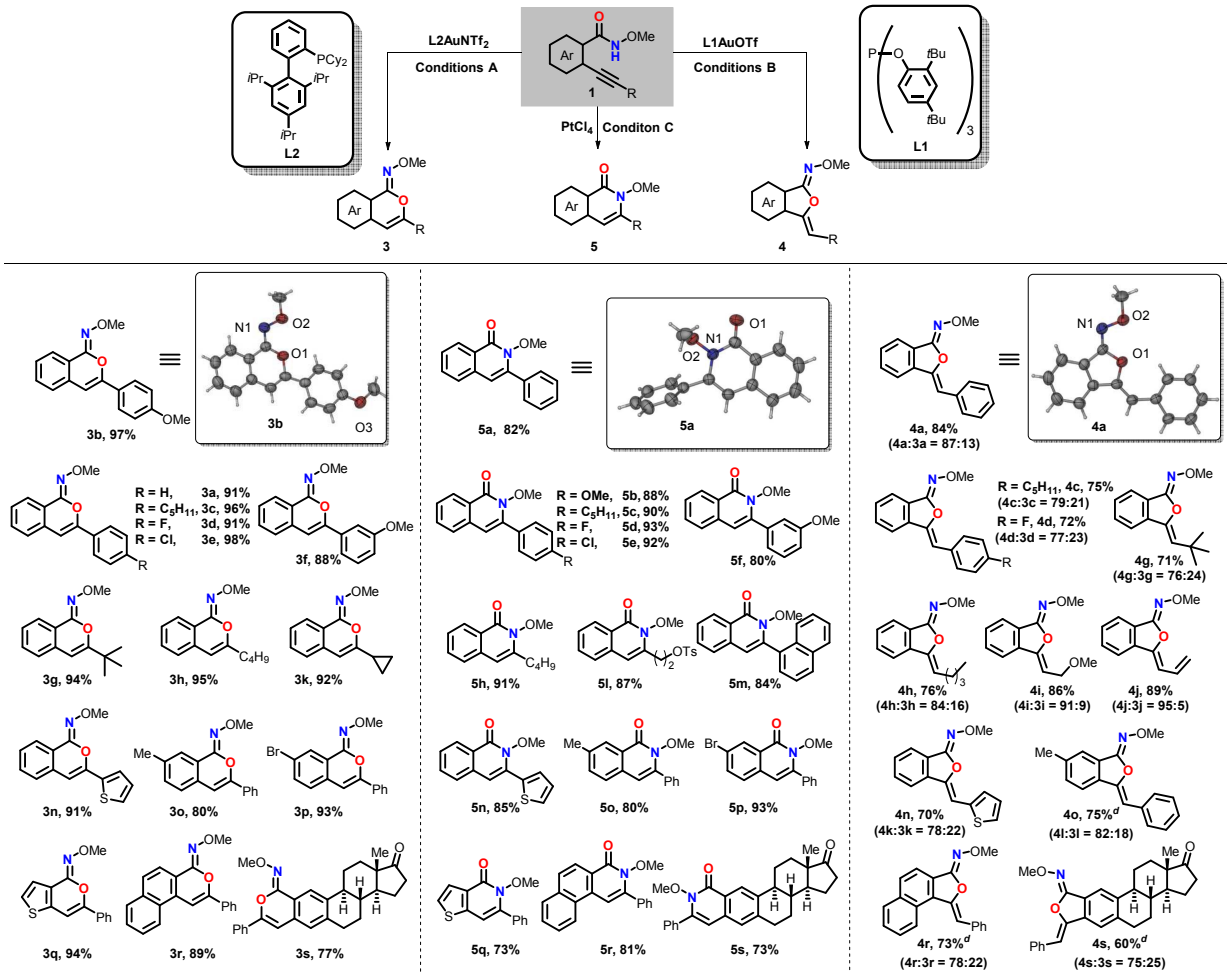
Table 1 Scope of regioselective and chemoselective cyclization[a, b, c]



[a]Condition A: **1** (0.1 mmol), XphosAuNTf$_2$ (5 mol%) in DCE (1.0 mL) at room temperature for 10 min. Condition B: **1** (0.1 mmol), (ArO)$_3$PAuOTf (5 mol%) in ethylbenzene (1 mL) at room temperature for 10 min. Condition C: **1** (0.1 mmol), $PtCl_4$ (5 mol%) in EtOH (1 mL) at 60 ^{o}C for 6 h. [b] Isolated yields of pure product. [c]Values in brackets are determined by ^{1}H NMR of the crude reaction mixture. [d]The concentration was decreased to 0.02 M.

delivered the mixture of N-6-*endo-dig* (60%), O-5-*exo-dig* (11%) and O-6-*endo-dig* (18%) cyclization products. Application of phosphine- or pyridine-derived platinum catalyst could not afford the cyclization at all. Unexpectedly, N-5-*exo-dig* cyclization could be promoted in high yields with only catalytic amount of sodium carbonate which indicated that 5-*exo-dig* N-cyclization might be thermaldynamically favored. Switching the catalyst from platinum (IV) to gold(I) displayed completely distinct cyclization style, which preferred the O-attack mode.[2a-f] Combining the ligand effect in gold catalysis, the regioselectivity could be perfectly achieved. Application of rigid and electron-rich Xphos based gold(I) as catalyst and dichloroethane as solvent, iminoisocoumarin **3a** was selectively delivered in high yield (91%). When flexible and electron-deficient phosphite derived gold(I) complex was employed, O-5-*exo-dig* pathway proceeded smoothly and iminoisobenzofuran **4a** was generated in 87% yield and 87/13 regioselectivity.

With optimized reaction conditions in hand, then we set out for the benzoheterocycle library construction with catalyst-dependent divergent cyclizations (Table 1). Subjecting *o*-alkynyl-*N*-methoxybenzamide to XphosAuNTf$_2$, *O*-6-*endo-dig* cyclization was prosperously achieved to provide iminoisocoumarins with excellent yields and sole regioselectivity. Both electron-donating and electron-deficient aromatic substituents of alkynes could furnish corresponding iminoisocoumarin **3b**-**3f** in high yields (88%-98%). Gratifyingly, this transformation proceeded well with excellent efficiency even with bulky *t*-butyl group (94%, **3g**). Additionally, aliphatic chains and small rings were all effecently converted to iminoisocoumarin **3h** and **3k** with 95% and 92% yield respectively. Thiophene substituted alkyne also performed well in this cyclization (91%, **3n**). Employing phosphite coordinated gold(I) catalyst, previouly unaccessible *O*-5-*exo-dig* cyclization dominantly occured and varieties of isobenzofuran-1-one oximes were obtained in good to

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excellent yields and selectivities, which was shown in the right column of Table 1. Alkynes substituted with electron-donating and -withdrawing groups all delivered products in good yields and selectivities (**4a**-**4d**). Alkynes bearing aliphatic groups successfully afforded the reactions as well (**4g** and **4h**). Notably, weak coordinating group such as methoxyl (**4i**) and alkene (**4j**) substituent promoted higher regioselectivity, revealing that coordinated and conjugated effect assisting the regioselectivity during the process. Altering the benzo-ring backbone to naphthalenes successfylly afforded the corresponding fused heterocycle as well (**4r**). Last, *N*-6-*endo*-*dig* cyclization via platinum(IV) catalysis was further surveyed. As shown in the middle column of Table 2, *o*-alkynyl-*N*-methoxybenzamides **1a**-**1f** bearing multiple types of substituents delivered corresponding products **5a**-**5f** in excellent yields ranging from 80% to 93% and sole regioselectivity. Terminal alkynes substituted with alkyl groups (**5h** and **5l**), fused rings (**5m**) and heterocycles (**5n**) demonstrated successful transformation. Noteworthily, readily transformed OTs group remained intact during the cyclization, which could be applied for further S_N2 substitution (**5l**). *tert*-Butyl substituted alkynylbenzamide was subjected to $PtCl_4$ with 89% starting material recovery, indicating that bulky *tert*-butyl group prevented coordination from platinum to alkynes. Moreover, thiophene and naphthalene derived backbones provided the desired thienopyridinone and benzoisoquinolinone in 73% and 81% yields respectively (**5q** and **5r**). Furthermore, in order to further demonstrate the praticality and generality of the controllable divergent cyclizations, natural product estrone was installed with cyclizing precursor. Three different estrone-based benzoheterocycles were facilely obtained in good yields (**3s**, **4s** and **5s**).

Isochromenone and isobenzofuranone are featured structures due to their wide existence in a variety of natural products and pharmaceuticals, which possess significant biological activities, such as anticancer[8a], antibacterial[8b] and anti-inflammatory[8c]. Based on our controllable divergent cyclizations, four different isochromenone- and isobenzofuranone-containing natural products were efficiently acheieved (Figure 1). Xyridine A[9], Olivetonide[10], thunberginol A[11] and (Z)-3-butylidenephthalide[12] were readily prepared in 85%, 75%, 64% and 65% respectively via this ligand controlled O-attack cyclization.

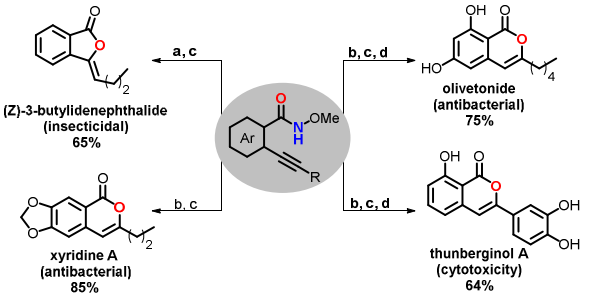
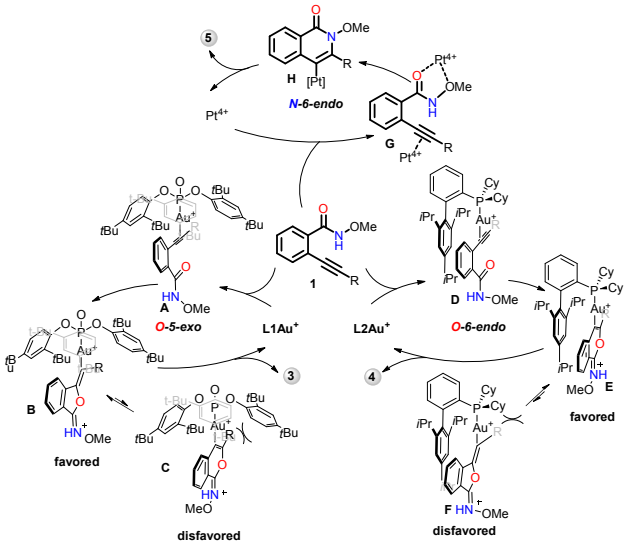


Figure 1 Divergent natural products synthesis via catalyst-tuning. a. Conditions A. b. Conditions B. c. 6N HCl, dioxane, room temperature. d. BBr_3, DCM, 0 °C to room temperature.



Scheme 2 Proposed mechanism cycles.

Based on experimental results obtained, plausible mechanism cycles are proposed (Scheme 2). The oxygen of amide **1** behaves as the nucleophile in the gold-catalyzed processes. Through direct coordination to alkynes from gold, electron-deficient phosphite ligand makes the alkyne become more polarized, simultaneously combining with the flexibly steric properties of the ligand, which resulted in the 5-*exo*-*dig* cyclization pathway. By contrast, rigid and electron-rich biphenyl phosphine might turn the alkyne less polarized combing with the steric hindrance at the same time, thus resulting in spatially accessible 6-endo-dig cyclization. Meanwhile, two cyclizations might be reversible when protodeauration is the rate determining step. Applying electron-rich ligand would make the intermediate less positively charged, in which the proton is released slower during protodeauration. Hence, six-membered cyclization would be preferred owing to its aromatic character, which makes it thermodynamically stable. Employing electron-deficient ligand makes the intermediate more positively charged, in which the proton is released faster. Therefore, kinetically favored 5-exo-dig cyclization is preferred. For platinum(IV) catalysis, it inclines to chelate with both oxygen atoms of amide and exposed the nitrogen atom to attack the carbon carbon triple bond forming intermediate **G**, next delivering the stable six membered intermediate **H**. Followed by protonation step, isoquinolinone **5** is obtained and regenerating the platinum(IV) catalyst.

In conclusion, we have developed a divergent, efficient and atom-economic protocol for facile construction of benzo-heterocycles. In the reaction processes, gold(I) catalyst prefers O-attack and platinum(IV) complex favors the N-attack in the cyclization of *o*-alkynyl-*N*-methoxybenzamide. Meanwhile, 5-*exo*-*dig* and 6-*endo*-*dig* mode selectivity of alkynes could be simply and accurately controlled via utilizing the ligand effect in gold catalysis. Further efforts of probing the details of mechanism are ongoing in our laboratory.

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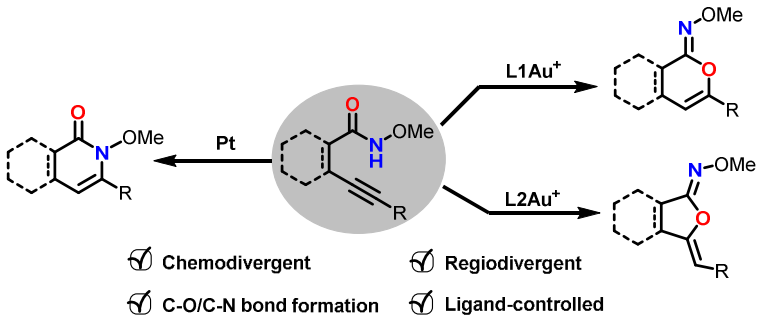

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