# <u>Creanic</u> LETTERS

## Gold-Catalyzed Cycloisomerization/1,5-H Migration/Diels—Alder Reaction Cascade: Synthesis of Complex Nitrogen-Containing Heterocycles

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**Supporting Information** 

**ABSTRACT:** An unprecedented gold-catalyzed cycloisomerization/1,5-H migration/Diels—Alder reaction cascade has been developed that enables the rapid construction of complex nitrogen polycyclic compounds. This one-pot, three-step cascade reaction offers good yields of the products and is promoted by a single gold catalyst under very mild conditions.

pplications of homogeneous gold catalysis have witnessed Aexponential growth in recent years. Gold catalysts serving as  $\pi$ -acids can activate C–C multiple bonds and trigger subsequent cascade reactions to assemble complex structures.<sup>1</sup> Lewis acid promoted [1,5]-H migration has been developed as an important strategy with which to functionalize sp<sup>3</sup> C-H bonds adjacent to heteroatoms, and it has been widely used in organic synthesis.<sup>2–4</sup> Gold catalyst can also catalyze this reaction by activating an alkyne moiety to participate as a hydride acceptor in subsequent cascade reactions (Scheme 1). In 2010, Gagosz and co-workers reported that C(2)-alkynetethered tetrahydrofurans can undergo [1,5]-hydride migration to the gold(I)-activated alkyne, followed by the intramolecular cyclization between the vinylgold species and oxonium intermediate, generating spirodihydropyran structures (Scheme 1A).<sup>5</sup> Gold-catalyzed [1,5]-hydride migration and subsequent elimination reactions can produce allene products, and this has been developed as an important method for the synthesis of chiral allenes (Scheme 1B).<sup>6</sup> Recently, the group of Gong reported a gold-catalyzed [1,5]-hydride shift generating isoindole intermediate, subsequent Diels-Alder reaction provided bridged-ring heterocycles in one-pot reaction (Scheme 1C).<sup>7</sup> In this paper, we report an unexpected goldcatalyzed cycloisomerization/1,5-H migration/Diels-Alder reaction cascade, generating structurally complex nitrogen bridged-ring polycyclic compounds in one step from readily available starting materials (Scheme 1D). This efficient, onepot, three-step cascade reaction is promoted by a single gold catalyst at room temperature in 1 h.

Recently, we used a gold-catalyzed 5-*exo-dig* cyclization of an alkynyl amide generating an active exocyclic enamide



Scheme 1. Gold-Catalyzed [1,5]-H Migration Reactions









D) Cycloisomerization / 1,5-H Migration / Diels-Alder Reaction (this work)



intermediate (M<sup>1</sup>). This is followed by  $\sigma$  metal Lewis acid catalyzed [4 + 2] or [3 + 2] cycloaddition reactions giving complex spiroheterocycles efficiently (Scheme 2).<sup>8</sup> During our continuing studies of this reaction, which combines  $\pi$ -acid and

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 $\sigma$ -acid catalysis, we investigated the reaction of 1a with *N*-phenylmaleimide (2a) in the presence of Ph<sub>3</sub>PAuNTf<sub>2</sub> and La(OTf)<sub>3</sub> to determine if it is possible to develop a [2 + 2] cascade reaction generating a push–pull four-membered ring. However, the target spirocyclobutane was not detected in this reaction, but a different nitrogen bridged-ring polycycle (3a) was isolated in 94% yield (Scheme 2), and its structure was unambiguously characterized by X-ray crystallography.<sup>9</sup> In contrast with our previous reports, this electron-rich enamide ( $\mathbf{M}^1$ ) isomerizes into an isoindole ( $\mathbf{M}^2$ ) and serves as the diene component in a subsequent Diels–Alder reaction with a dienophile.<sup>10</sup> Interestingly, only the *endo* isomer of 3a was observed in this reaction.

These findings encouraged us to explore this reaction further (Table 1). We discovered that various Lewis acids such as  $Al(OTf)_3$ ,  $Yb(OTf)_3$ , and  $La(OTf)_3$  all undergo very clean reactions, giving the product (**3a**) in 91–95% yield (entries 1–



<sup>*a*</sup>Reaction conditions: **1a** (0.1 mmol), **2a** (0.2 mmol), [Au] (5 mol %), solvent (2 mL), N<sub>2</sub> atmosphere. <sup>*b*</sup>Isolated yields were reported. <sup>*c*</sup>The reaction mixture was messy, and no **3a** was observed. <sup>*d*</sup>1 mol % of gold catalyst.

3). These results prompted us to examine the possible role of the Lewis acid in this cascade reaction. It was found that this reaction proceeded equally well in the absence of the Lewis acid. With only 5 mol % of Ph<sub>3</sub>PAuNTf<sub>2</sub> as catalyst, the reaction was complete in 1 h at room temperature, and the target product (3a) was isolated in 93% yield (entry 4). Other commonly used gold catalysts were screened (entries 5-8), and it was found that PPh<sub>3</sub>AuCl/AgOTf gave an acceptable yield (89%), but other gold catalysts such as AuCl, AuCl<sub>3</sub>, and Me<sub>2</sub>SAuCl gave much lower yields. The solvent effect was also investigated, and it was found that similar yields were obtained in THF solution (entry 9) but no reaction was observed in acetonitrile (entry 10). When the gold catalyst level was decreased to 1 mol %, the product was obtained in 85% isolated yield within 2 h, illustrating the efficiency of this gold-catalyzed cascade reaction.

The scope of this cascade reaction was then investigated by using the optimal reaction conditions. We first studied the cascade reaction of *N*-phenylmaleimide (2a) with various alkynyl amides. As shown in Scheme 3, a large variety of

Scheme 3. Scope of Alkynyl Amides<sup>a</sup>



<sup>*a*</sup>Reaction conditions: 1 (0.1 mmol), 2a (0.15 mmol), Ph<sub>3</sub>PAuNTf<sub>2</sub> (5 mol %), and dry DCM (2 mL) were stirred at room temperature under an  $N_2$  atmosphere. Isolated yields are reported.

bridged-ring polycyclic compounds were synthesized as a single diastereomer and in good to excellent yield by these simple gold-catalyzed cascade reactions. Substituents at the  $\alpha$  position of nitrogen atom have no effect on the reaction. Substrates with aliphatic groups such as methyl and benzyl react smoothly to afford the target products in good yields (3b,c). A tosylamide bearing a vinyl group was also suitable for this transformation, giving the product 3d in 56% yield. Substrates with various aromatic groups as substituents are all amenable to this transformation, giving the corresponding products (3e-k) in 51-96% yields. Electron-donating groups such as CH<sub>3</sub> and CH<sub>3</sub>O or electron-withdrawing groups such as CF<sub>3</sub> at the paraor meta-position of the aromatic ring are well tolerated in this reaction. Unfortunately, when the internal nucleophile NHTs was replaced with an OH group, the reaction under standard condition was messy and no major product could be isolated.

Various dienophiles were investigated to further explore the generality of the above reaction (Scheme 4). Maleimides with a





<sup>*a*</sup>Reaction conditions: **1b** (0.1 mmol), **2** (0.15 mmol),  $Ph_3PAuNTf_2$  (5 mol %), and dry DCM (2 mL) were stirred at room temperature under an N<sub>2</sub> atmosphere. Isolated yields are reported.

methyl group (2b) or a benzyl group (2c) reacted with 1b efficiently, and the corresponding products (3l,m) were isolated as the single *endo*-isomer in 57% and 70% yields, respectively. The reaction of dimethyl acetylenedicarboxylate (2e) with 1b provided the unsaturated bridged polycycle (3o) in 86% yield. Dienophiles 2d and 2f also reacted with 1b, affording the corresponding products in moderate yields. Notably, methyleneindolinone (2g) was an excellent partner in this reaction, delivering the corresponding product (3q) as a single diastereomer in excellent yield.

The reaction of the thiophene-substituted alkyne (11) gave the bridged polycyclic 3r, which is unstable and isomerized into the thienyl naphthalene (4a) in 80% yield (Scheme 5a). Simply heating product 3a in the presence of 10 mol % of Cu(OTf)<sub>2</sub> leads to formation of the polyaromatic compound (4b) in 92% yield by the elimination of one molecule of TsNH<sub>2</sub> (Scheme 5b). Compound 3s can be transformed into the 1-naphthylamine derivative (4c) in 81% yield in the presence of TfOH

#### Scheme 5. Synthetic Applications



(Scheme 5c). These kinds of multisubstituted naphthalene compounds are difficult to prepare by other methods.

In an effort to understand the mechanism of this reaction, we conducted deuterium-labeling experiments (Scheme 6). When

### Scheme 6. Deuterium-Labeling Experiments



5 equiv of  $D_2O$  was added to the standard reaction, the newly formed angular methyl group was 30% deuterated (eq 1). The reaction of deuterated  $[D_2]$ -**1a** under standard conditions led to product  $[D_2]$ -**3a** with a 20% deuterium content at the methyl group (eq 2). If 5 equiv of  $D_2O$  was added to this reaction of  $[D_2]$ -**1a**, the methyl group in the product had a deuterium content of 55% (eq 3). These results clearly indicate a [1,5]-D migration mechanism. On the other hand, [1.5]-H migration followed by cyclization can also generate the isoindole intermediate  $M^2$ , but the first [1,5]-H migration step breaks the aromaticity of benzene ring and is therefore unlikely. Goldcatalyzed *5-exo-dig* cyclization and a [1,5]-H migration sequence are more probable.

In summary, we have developed a highly efficient gold(I)catalyzed cascade reaction to build bridged-ring polycyclic compounds. This approach provides an atom-economical synthesis of structurally complex polycyclic heterocycles from readily available starting materials. This cascading cycloisomerization/1,5-H migration/Diels–Alder reaction is triggered by a gold catalyst under mild conditions. This type of gold(I)-catalyzed cascade reaction to construct complex structures will find applications in organic synthesis.

### ASSOCIATED CONTENT

### **S** Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.or-glett.7b00090.

Experimental details, crystal structure of 3a, and characterization data (PDF) X-ray data for compound 3a (CIF)

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#### Notes

The authors declare no competing financial interest.

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