## Synthesis of Fused Bicyclic Aminals through Sequential Gold/Lewis Acid Catalysis

ORGANIC LETTERS XXXX Vol. XX, No. XX 000–000

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## Received March 25, 2013



A novel sequential catalysis by combining gold catalysis with early transition metal catalysis was developed. Biologically important bicyclo[4.n.0] aminals were obtained under very mild conditions.

Bicyclic aminals and a similar structure presented a key structural unit in many bioactive natural products as well as pharmaceuticals (Figure 1). For example, the Nomofungin/Communesin family, a group of eight architecturally intriguing indole alkaloids bearing two fused bicyclic aminal moieties, have attracted much attention in recent years.<sup>1</sup> They show good cytotoxic acitivity. Artemisinin, a polycyclic acetal, is the most effective antimalaria agent.<sup>2</sup> The commercial pharmaceutical Physostigmine, a parasympathomimetic alkaloid, is used to treat myasthenia gravis, glaucoma, and Alzheimer's disease.<sup>3</sup> Perinadine A, the tetracyclic alkaloid bearing fused bicyclic N,Oaminals, is a biologically active secondary metabolite and shows cytotoxicity and antibacterial activity.<sup>4</sup> In addition,



Figure 1. Natural products and pharmaceuticals containg fused bicyclic aminals and acetals.

a rigid spiroketal structure was recently used as an excellent chiral ligand for asymmetric catalysis.<sup>5</sup> Thus efficient synthetic methodology toward this structural target is in great demand. The current access methods mainly include stepwise acetalization from preformed multifunctionlized substrates. Cascade reactions provide an efficient way to construct complex molecular structures from readily available fragments with great operation and step ecconomy.<sup>6a</sup> Recently, an efficient gold-catalyzed tandem reaction

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toward tricyclic cage-like N,O-acetals has been reported by the Hashimi group.<sup>6b</sup> Herein we will report a bimetallic Lewis acid (Au (I) and Ga(III)) sequential catalyzed cascade reaction to access fused bicyclic aminals.

Gold-catalyzed reactions have been intensively investigated and applied in multistep syntheses in the past decade.<sup>7,8</sup> Recently Gong and others developed a series of gold(I)/Bronsted acid relay catalysis and turned out to be a robust strategy to assemble readily available starting materials into structually complex molecules.<sup>9</sup> But the combination of gold catalysis with another metal Lewis acid is still very rare.<sup>9b,10</sup> We can envision that if we can combine the  $\pi$ -acid gold with another  $\sigma$  metal Lewis acid such as early transition metal lanthanide, a dual activation mode of both substrates will be formed and many new reactions and new chemistry can be developed.

Enamine, which is normally generated from the dehydration reaction of an amine with a carbonyl group, played a very important role in the current aminocatalysis.<sup>11</sup> Gold(I)-catalyzed hydroamination of an alkyne will also

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Scheme 1. Concept of the Bimetallic Lewis Acid Catalyzed Intramolecular Hydroamination/Inverse-Electron-Demand Hetero-Diels-Alder Reaction Cascade



generate enamine utilizing an alternative approach. Very recently, Che and Stradiotto reported the intermolecular hydroamination of alkyne with an aromatic amine or aliphatic amine by using a gold catalyst with a bulky phosphine ligand.<sup>12</sup> The produced enamine would isomerize into imine very easily, which was reduced to amine in these two reports. Hammond and Xu reported the tandem intramolecular hydroamination/isomerization into imine/ nucleophilic addition reactions to prepare different N-heterocycles (Scheme 1).<sup>13</sup> We have developed an Inverse-Electron-Demand Hetero-Diels-Alder (IED-HDA) reaction of cyclohexanone with unsaturated  $\beta$ -ketone ester 1 in the presence of an Y(OTf)<sub>3</sub>-primary amine bifunctional catalyst.<sup>14</sup> Ketone ester 1 was greatly activated by the early transition metal Y(OTf)<sub>3</sub> through chelating coordination and thus reacted with the in situ generated enamine from cyclohexanone very rapidly. Therefore we are going to extend this methodology to the bimetallic cooperative catalysis: the alkyne amines 2 underwent a cycloisomerization reaction to afford the enamine by a gold(I) catalyst, and then the enamine was trapped by another Lewis activated electrophile 1 through the IED-HDA reaction to produce the important bicyclic aminals.15

Following this strategy, alkynes 2 and unsaturated  $\beta$ -ketone ester 1a were subjected to this cascade reaction in the presence of AuCl<sub>3</sub> and Y(OTf)<sub>3</sub> in THF at rt (Scheme 2). It was found that the substituent on the amine part played a very important role in this transformation. When it is the primary amine (2a, R = H) and secondary amine (2b, R = Bn), a messy reaction mixture was

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Scheme 2. Initial Formation of the Unexpected Fused Bicyclic Aminals



produced under these conditions. Fortunately, when we use the Ts group ( $\mathbf{R} = 4$ -toluenesulfonyl, 2c), product 3a was isolated in 30% yield. To our great surprise, it is not the expected spiro-aminal 3a', but the fused bicyclo[4.3.0] aminal 3a. The structure was confirmed by single crystal X-ray analysis. More important, only the endo-diastereomer was obtained in this reaction.

Inspired by the observed results, we continued to optimize the reaction conditions to develop an efficient bimetallic Lewis acid catalyzed system toward fused bicyclic aminals (Table 1). Solvent screening showed that toluene was the optimal solvent, and the reaction yield increased to 76% yield in 1.5 h (for details, see the Supporting Information). During this process, we found that there is certain amount of the spiro-aminals by careful analysis of <sup>1</sup>H NMR spectra of the mixture (3a/3a' = 2.3/1, entry 2). Then a variety of different  $\pi$ -acid metal catalysts with  $Y(OTf)_3$  were examined. Different gold catalysts,  $Pd(OAc)_2$ , and CuOTf all displayed very high activity toward the bicyclic aminals (entries 3-11), and AuCl(CH<sub>3</sub>SCH<sub>3</sub>) afforded the products in the highest yield (96%), although the chemoselectivity is still only 2.3/1 (3a/3a', entry 7). In order to improve the chemoselectivity, we investigated different early transition metals such as In(OTf)<sub>3</sub>, Sc(OTf)<sub>3</sub>, Ga(OTf)<sub>3</sub>, La(OTf)<sub>3</sub>, and Bi(OTf)<sub>3</sub> together with AuCl(CH<sub>3</sub>SCH<sub>3</sub>) as the  $\pi$ -acid (entries 12–16). Among all of them, Ga(OTf)<sub>3</sub> was the best choice and resulted in the formation of the fused bicyclic aminal 3a in 81% yield with good chemoselectivity (f/s = 6.6/1, entry 14), although a trace amount of another exo-diastereomer of **3a** was detected from <sup>1</sup>H NMR.

With the optimized conditions in hand, the substrate scope was examined (Scheme 3). Different halogen groups on the *para* or *ortho* position of the phenyl ring and different ester groups favored the reaction, providing corresponding products in good to excellent yields (3a-3f, 3l). Substrates bearing an electron-donating group such as methyl and methoxyl were also suitable substrates, giving the desired aminals in 65% yield (3g, 3h). Electron-withdrawing groups favored this IED-HDA reaction greatly and affored the product 3n in the highest 90% yield. In addition, more sensitive substituents such as styryl, 2-furyl, and 2-thienyl were well tolerated in this mild transformation and the corresponding products were obtained in 62-65% yield (3i, 3j, 3k).

In order to further probe the scope of this reaction, different alkynyl amines were investigated. Substrate **2d** bearing one more carbon chain reacted smoothly with **1** to Table 1. Optimization of Reaction Conditions<sup>a</sup>



Entry -	Catalyst		S a la sant	c(_b	Yield
	А	В	Solvent	I/S°	%°
1	AuCl <sub>3</sub>	Y(OTf) <sub>3</sub>	THF	/	30
2	AuCl	Y(OTf) <sub>3</sub>	Toluene	2.3/1	77
3	AuCl·PPh <sub>3</sub> / AgOTf	Y(OTf) <sub>3</sub>	Toluene	2.1/1	79
4	PPh <sub>3</sub> AuNTf <sub>2</sub>	Y(OTf) <sub>3</sub>	Toluene	1.3/1	86
5	iPrAuCl/Ag(OTf)	Y(OTf) <sub>3</sub>	Toluene	2.3/1	78
6	NaAuCl <sub>4</sub> ·2H <sub>2</sub> O	Y(OTf) <sub>3</sub>	Toluene	2.5/1	78
7	AuCl(CH <sub>3</sub> SCH <sub>3</sub> )	Y(OTf) <sub>3</sub>	Toluene	1.2/1	96
8		Y(OTf) <sub>3</sub>	Toluene	3.4/1	81
9	$Pd(OAc)_2$	Y(OTf) <sub>3</sub>	Toluene	1/3.5	70
10	CuOTf·1/2PhH	Y(OTf) <sub>3</sub>	Toluene	1/1.6	92
11	AgOTf	Y(OTf) <sub>3</sub>	Toluene	1.8/1	45
12	AuCl(CH <sub>3</sub> SCH <sub>3</sub> )	In(OTf) <sub>3</sub>	Toluene	2/1	90
13	AuCl(CH <sub>3</sub> SCH <sub>3</sub> )	Sc(OTf) <sub>3</sub>	Toluene	1/1.4	93
$14^{d}$	AuCl(CH <sub>3</sub> SCH <sub>3</sub> )	Ga(OTf) <sub>3</sub>	Toluene	6.6/1	93(81)
15	AuCl(CH <sub>3</sub> SCH <sub>3</sub> )	La(OTf) <sub>3</sub>	Toluene	1/1.1	70
16	AuCl(CH <sub>3</sub> SCH <sub>3</sub> )	Bi(OTf) <sub>3</sub>	Toluene	1/1	78

<sup>*a*</sup> Reaction conditions: **2c** (0.2 mmol), **1a** (0.24 mmol), catalyst **A** (5 mol %), catalyst **B** (10 mol %), solvent (2 mL) at 40 °C for 1.5 h. <sup>*b*</sup> Determined by crude <sup>1</sup>H NMR; "f" represents a fused product, and "s" represents a spiro product. <sup>*c*</sup> Isolated yield of combined products. <sup>*d*</sup> Diastereoselectivity ratio: endo/exo = 13/1.

generate the corresponding bicyclo[4.4.0] aminals (4a-4c) in moderate yield in the presence of PPh<sub>3</sub>AuNTf<sub>2</sub> (5 mol %) and Ga(OTf)<sub>3</sub> (10 mol %) (eq 1). Substrate **2e** bearing one less carbon also proceeded smoothly giving the bicyclo[4.3.0] aminal **5** in 65% yield with very moderate diastereoselectivity (endo/exo = 1/1, eq 2). Besides, the alkynyl alcohol **2f** was also effective, affording the bicyclo-[4.3.0] ketal **6** as the major product in 55% yield (eq 3).



**Scheme 3.** Scope of the Au(I)–Ga(III) Catalyzed Cascade Reaction<sup>*a*</sup>



<sup>*a*</sup> Reaction conditions: **2c** (0.2 mmol), **1** (0.24 mmol), Au(CH<sub>3</sub>SCH<sub>3</sub>)Cl (5 mol %), Ga(OTf)<sub>3</sub> (10 mol %), toluene (2 mL) at 40 °C for 1.5 h. Isolated yield of combined products and the number in parentheses represent the isolated yield of fused bicyclic aminals. <sup>*b*</sup> The crude <sup>1</sup>H NMR was complicated, making determination of the selectivity difficult.

To gain insights into the reaction mechanism, we conducted deuteration experiments. The reaction was performed under standard conditions with an additional 5 equiv of D<sub>2</sub>O, and the newly formed methyl group was 30% deuterated (eq 4). We also prepared 2c-d, which was deuterated 100% at the alkyne terminus, and the reaction led to **2c**-*d* having a 33% deuterium content at the methyl position (eq 5). If 5 equiv of D<sub>2</sub>O were added into the reaction of 2c-d, the methyl group was 60% deuterated (eq 6). More important, during the reactions, the proton at the methylene group adjacent to the triple bond was deuterated in the presence of D<sub>2</sub>O and lost a D atom in the absence of  $D_2O$  (eqs 5 and 6). These data indicated that there is an equilibrium between enamide M1 and M2, and M2 is favored (Scheme 4).<sup>11</sup> Thus we proposed the possible mechanism: the gold catalyzed 5-exo-dig cyclization affording the enaminde M1, followed by isomerization into the more stable enamide M2, followed by the [4 + 2] Scheme 4. Proposed Mechanism



cycloaddition with the Lewis acid activated electrophile generating the final product.



In summary, we have described a new synthetic strategy based upon a one-pot sequential gold-catalysis/Lewis acid catalysis. The biologically important bicyclo[4.*n*.0] aminals were synthesized in high efficiency under very mild conditions. This type of combination of a  $\pi$ -acid with another  $\sigma$ metal Lewis acid will find more applications in organic synthesis.

Acknowledgment. We are grateful for financial support from the Natural Science Foundation of China (Grant No. 21102085), Science Foundation of Ministry of Education of China (No. 20110131120049), and Natural Science Foundation of Shandong Province (BS2012-YY006). We thank Dr. Prof. Daofeng Sun and Dr. Di Sun for the X-ray structure analysis.

**Supporting Information Available.** Experimental procedures, characterization data, and NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.