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Synthesis of spiroaminals by bimetallic Au/Sc relay catalysis: TMS as a traceless controlling group†

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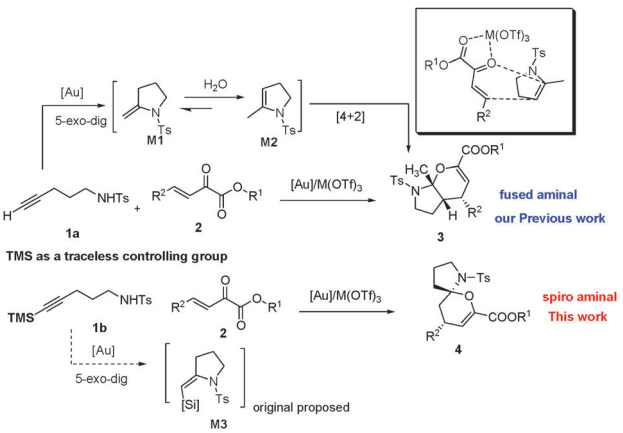
An efficient synthesis of spiroaminals over fused aminals has been successfully developed by bimetallic Au/Sc catalysis by using TMS as a traceless controlling group.

Multicomponent tandem reactions have been developed as the most efficient synthetic strategy to build up molecular complexity and diversity in shortest reaction steps.[1] How to control reaction selectivity, including chemoselectivity and stereoselectivity, to get the target products over undesired isomers, is the most essential issue in these reactions. Thus the switchable synthesis[2] of different products from the same or similar starting materials is very interesting, but very difficult, which not only maximizes the diverse utility of reactants but also benefits the understanding of the reaction mechanism. For example, the Carreira group reported the elegant controllable synthesis of all the four stereoisomers by the rationale of combination of different primary amine catalysts with different iridium complexes.[3] The product distribution, diastereoselectivity, and sometimes even enantioselectivity could be tuned by using different transition metals[4a] or ligands,[4b] adding different additives or bases,[4c–e] and varying the reaction temperatures[4f] or solvents.[4g] In 2013, the Luo group developed the switchable synthesis of *endo*- or *exo*-diastereomers using different Lewis acids in enantioselective [4+2] cycloaddition reactions.[4a] The Tang group reported the tunable carbonyl ylide reactions for the selective synthesis of dihydrofurans and dihydrobenzoxepines by choosing the appropriate ligands.[4b] Apart from the above mentioned control of reaction pathways by catalysts or reaction conditions, we reported another strategy by using a trimethylsilyl (TMS) group as a traceless controlling group,[5]



Scheme 1 Au/M(OTf)$_3$ relay catalysis for the synthesis of aminals.

which not only tuned the reaction to the desired pathway, but also disappeared spontaneously, without further manipulation (Scheme 1).

Recently we reported an efficient gold/Lewis acid relay catalytic methodology toward fused bicyclic aminals by combining π-acid gold catalysis with another σ metal Lewis acid.[6,7] It was a gold-catalyzed intramolecular hydroamination cyclization that generated enamide **M1**, which isomerized into more stabilized internal enamide **M2**, and then reacted with another Lewis-acid activated electrophile through an inverse-electron-demand hetero-Diels–Alder (IED-HDA) reaction to produce the fused bicyclic aminals, instead of the spiroaminals as the original plan. Spiroaminals containing natural products and bioactive molecules show important biological activities, and are of special importance for biological and synthetic chemists. Thus we decided to finely tune the reaction conditions to trap enamide **M1** before its isomerization to get the spiroaminals over its fused isomer. Different π-acid catalysts and σ metal Lewis acids were screened in different solvents. However, all these reactions exhibited poor selectivities for the two isomers. Therefore a silicon protecting group was installed on the terminal alkyne, and it was

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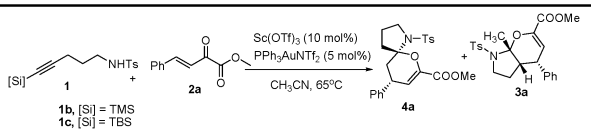
Table 1 Silicon group as the directing group to control reaction pathways



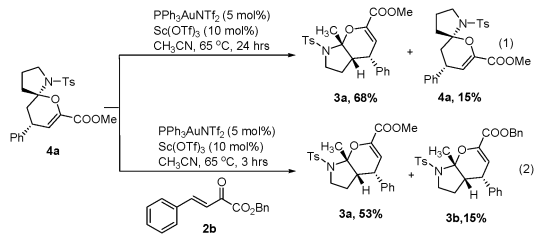
Entry[a]	Substrate	Time	Conversion%	Yield%[b] (**4a**)	Yield%[b] (**3a**)
1	**1b**	3 hours	100	40	34
2	**1c**	3 hours	0	0	0
3	**1b**	**10 min**	**100**	**83**	**8**
4	**1b**	48 hours	100	22	56
5[c]	**1b**	10 min	100	0	0
6[d]	**1b**	10 min	0	0	0

[a] Reaction conditions: alkyne **1** (0.2 mmol), **2a** (0.22 mmol), PPh_3AuNTf_2 (5 mol%), $Sc(OTf)_3$ (10 mol%), CH_3CN (1 mL). [b] Isolated yield. [c] Only PPh_3AuNTf_2 (5 mol%). [d] Only $Sc(OTf)_3$ (10 mol%).

anticipated that the electronic effect of silicon could stabilize the derived enamide **M3** to inhibit its isomerization (Scheme 1).

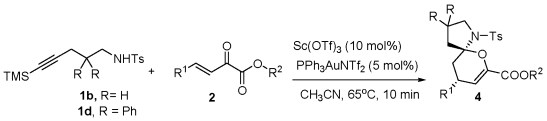
To test this hypothesis, two silicon protected alkyne amines **1b** and **1c** were synthesized according to the known procedure. After a detailed screening of different gold catalysts and different σ metal Lewis acids, PPh_3AuNTf_2 and $Sc(OTf)_3$ were found to be the best partners in this reaction (for details, see ESI†).The alkyne amine **1b** bearing a TMS group was subjected to this cascade reaction at 60 °C for 3 h. To our surprise, we did not get any silicon containing products, but a mixture of spiro-isomer **4a** and fused isomer **3a** in 40% and 34% isolated yields, respectively (Table 1, entry 1). The reaction with only the $Sc(OTf)_3$ catalyst showed no desilylation product and the initial **1b** remained unreactive (entry 6). These results demonstrated that there was a fast gold-catalyzed desilylation or silicon–gold transmetalation process[9] under these conditions and the original proposal on the formation of enamide **M3** was not possible. Then we carried out the cyclization of silicon amine **1b** using PPh_3AuNTf_2; no cyclization product **M3** was produced, but the enamide dimerization or oligomerization products acted as amine **1a** in previous reactions.[6,8] Switching from the labile TMS group to the more stable TBS group (*tert*-butyldimethyl silyl), alkyne **1c** became very inert and remained intact under these conditions (Table 1, entry 2). During optimization, we noted that the distribution of products was greatly influenced by reaction time, and actually the reaction was very fast and completed in 10 minutes. The reaction was quenched rapidly and the target spiroaminal **4a** was isolated in 83% yield with a very good ratio of **4a**/**3a** (10.5/1, entry 3). For comparison, a 48 hours reaction was conducted and the ratio of **4a**/**3a** changed to 1/2.6 and fused isomer **3a** was the major product (entry 4). Further studies showed that **4a** could be transformed into **3a** in 68% yield with **4a** recovered in 15% yield (Scheme 2, eqn (1)). The reaction of **4a** with another ketone ester **2b** gave the fused products **3a** and **3b** in 53% and 15% yields, respectively (Scheme 2, eqn (2)). These results clearly indicate that spiro-isomer **4a** is the kinetic product and fused isomer **3a** is the thermodynamic product, and **4a** could convert into **3a** through retro Diels–Alder reaction, isomerization, and the Diels–Alder reaction sequence.

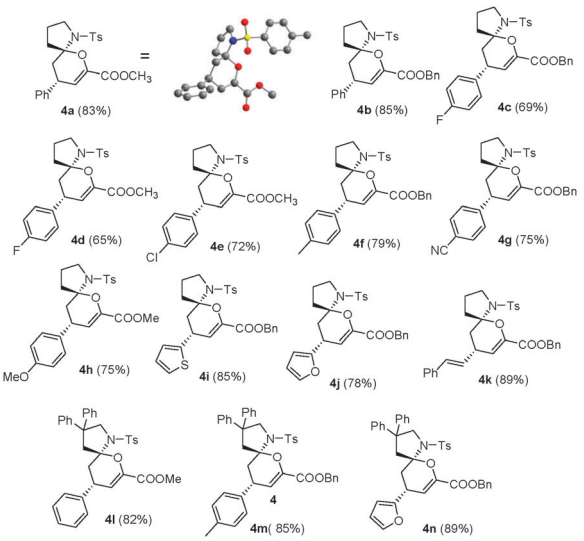
With the optimal conditions established, we examined the scope of this transformation and the results are summarized in



Scheme 2 Kinetic and thermodynamic balance experiments.

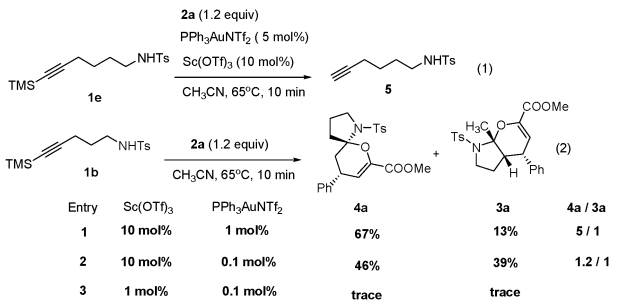
Table 2 Substrate scope of the selective synthesis of spiroaminals[a]





[a] Reaction conditions: alkyne **1** (0.2 mmol), **2** (0.22 mmol), PPh_3AuNTf_2 (5 mol%), $Sc(OTf)_3$ (10 mol%), CH_3CN (1 mL); isolated yield of spiroaminals **4** is indicated in parentheses.

Table 2. Various unsaturated keto-esters bearing different aromatic substituents at the γ-position reacted smoothly with alkyne amine **1b** to give the spiro-N,O-aminal **4** in good to excellent yields in less than 10 minutes. In these reactions, the chemoselectivity and diastereoselectivity are very good. There were very trace amounts of fused isomers on TLC and only *endo*-isomers of spiroaminal **4** were detected. The structure and the relative configuration of **4a** were confirmed by X-ray analysis. Substrates with different ester groups, either electron-withdrawing or electron-donating groups, are all suitable substrates, giving the spiro-aminals in good yields (**4a–4e**). Different functional groups such as halogens, CN, styryl, and OMe are all tolerated under these conditions. The extention of this reaction to heterocyclic substrates was also successful, and 2-thienylaminal **4i** and 2-furylaminal **4j** in 85% and 78% yields were obtained, respectively. Another gem-diphenyl alkyne amine **1d** was also synthesized to test its reactivity. It also reacted efficiently with different electrophiles with great chemoselectivity and stereoselectivity to furnish the corresponding spiroaminals in 82–89% yield (**4l–n**). However, the

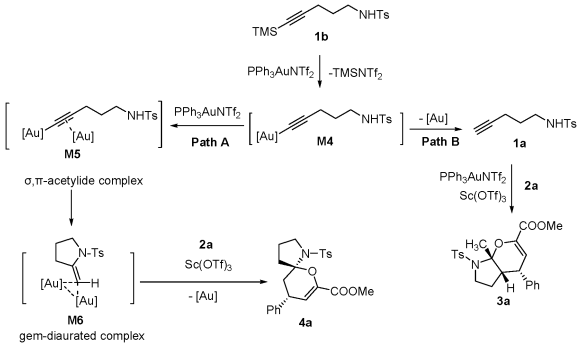


Scheme 3 Experiments at low catalyst loading.

reaction of alkyne amine **1e** with one more carbon was not successful; the desilylation product **5** was isolated in 80% yield in 10 minutes (Scheme 3, eqn (1)).

All the above reactions were completed in 10 minutes, thus making us to consider whether we could lower the catalyst loading. The elegant work from Nolan[10] and Shi[7e] has demonstrated that the homogeneous gold catalyst could be decreased to the ppm level. At the outset, keeping the loading of $Sc(OTf)_3$ constant, when the loading of the Au catalyst decreased to 1 mol%, the spiro-aminal **4a** was isolated in 67% yield in 10 min; however the chemoselectivity decreased from previous 10.5/1 to 5/1 (Scheme 3, eqn (2), entry 1). Upon further decreasing the loading to 0.1 mol%, amazingly, the reaction still completed in 10 min, but the chemoselectivity further decreased to 1.2/1 (Scheme 3, entry 2). In addition, trying to reduce the amount of $Sc(OTf)_3$ was not successful (entry 3).

Based on these experiments and previous reports, a dinuclear gold catalysis mechanism is proposed in Scheme 4. Since Houk and Toste proposed the dinuclear gold catalysis for the first time in 2008,[11] many digold σ,π-acetylide complexes and gem-diaurated complexes have been synthesized and characterized by X-ray analysis.[12] Recently the Hashmi group and others have developed a series of elegant chemistry based on digold catalysis.[13] In this reaction, at the relatively elevated temperature, the gold catalyst serve as the σ acid first to form the gold acetylide **M4** through silicon gold transmetalation. When there are more gold catalysts, they would coordinate with the alkyne to form the digold σ,π-acetylide complex **M5**, and lead to intramolecular nucleophilic attack forming the gem-diaurated intermediate **M6**, and subsequent slow proton deauration and fast cyclization would form spiro-isomer **4** (path A). However when



Scheme 4 Proposed digold participated mechanism.

the reaction was performed at very low catalyst loading, the desilylation intermediate **M4** did not form a digold complex, but went through protodeauration to form the desilylation product **1a**, which would generate fused products through the **M1**–**M2** sequence as our previous reaction (path B). The relative inert reactivity of gem-diaurated species have been proved by Gagné,[12a] and in this work, it was utilized to stabilize the exocyclic double bond to tune the selectivity.

In summary, a highly efficient selective synthesis of spiroaminals was developed by introducing a small TMS group. More importantly, the directing group disappeared *in situ* without a further deprotection step. A very interesting kinetic–thermodynamic balance was observed in this reaction and a binuclear gold catalysis was proposed to explain the reaction mechanism. A detailed study of the mechanism such as isolation of gold intermediates is underway in our laboratory.

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