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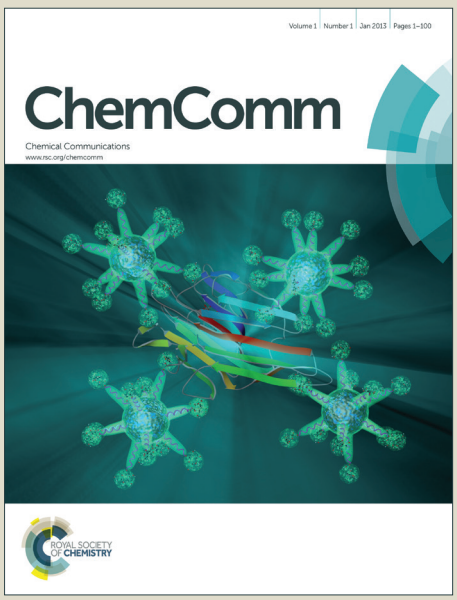

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ARTICLE TYPE

Synthesis of Spiroaminals with Bimetallic Au/Sc Relay Catalysis: TMS as a Traceless Controlling Group

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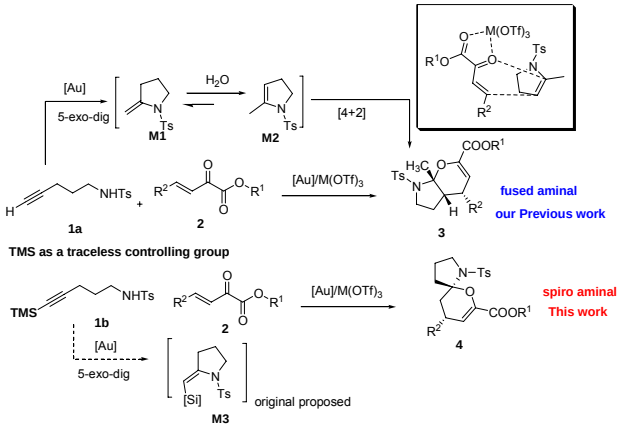
An efficient synthesis of spiroaminals over fused aminals has been successfully developed with bimetallic Au/Sc catalysis by using TMS as a traceless controlling group.

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 a very interesting, but very difficult problem, which not only maximizes the diverse utility of reactants but also benefits the understanding of reaction mechanism. For example, the Carreira group reported the elegant controllable synthesis of all the four stereo isomers by the rational of combination of different primary amine catalyst with different iridium complex.[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 endo or exo diastereomers with varing different Lewis acids in enantioselective [4+2] cycloaddition reactions[4a]. 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 report another strategy by using a trimethylsilyl (TMS) group as a traceless controlling group,[5] 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 is a gold-catalyzed intramolecular hydroamination cyclization to generate an 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 showed important biological activities, and are of special importance for biological and synthetic chemists. Thus we decided to fine tune the reaction conditions to trap the 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 gave poor selectivities on the two isomers. Therefore a silicon protecting group was installed on the terminal alkyne, and it was anticipated that the electronic effect of silicon could stabilize the derived enamide **M3** to inhibit its isomerization (Scheme 1).



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

To test this hypothesis, two silicon protected alkyne amines **1b** and **1c** were synthesized according 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 supporting information).The alkyne amine **1b** bearing a TMS group was subjected to this cascade reaction at 60 °C for 3 hrs. To our surprize, we did not get any silicon containing products, but a mixture of spiro isomer **4a** and fused isomer **3a** in 40% and 34% isolated yield respectively (Table 1, entry 1). The reaction with only $Sc(OTf)_3$ catalyst showed no desilylation product and the starting **1b** remained unreactive (entry 6). These results

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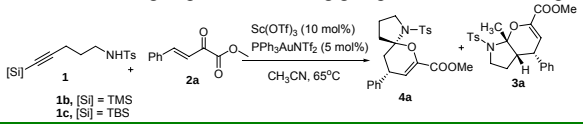
†Electronic Supplementary Information (ESI) available : Detailed experimental procedures and analytical data. CCDC Number: 1013254 for compound **4a**. See DOI: 10.1039/b000000x.

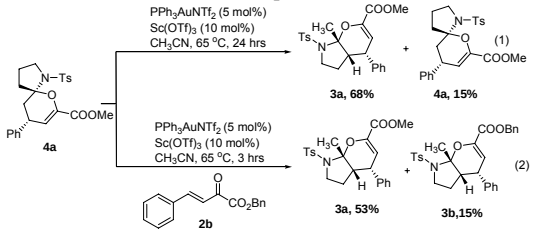
Table 1. Silicon group as the directing group to control reaction pathways



Entry[a]	Substrate	time	Conver-sion%	Yield% (**4a**)[b]	Yield% (**3a**)[b]
1	**1b**	3 hrs	100	40	34
2	**1c**	3 hrs	0	0	0
3	**1b**	**10 min**	**100**	**83**	**8**
4	**1b**	48 hrs	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%)

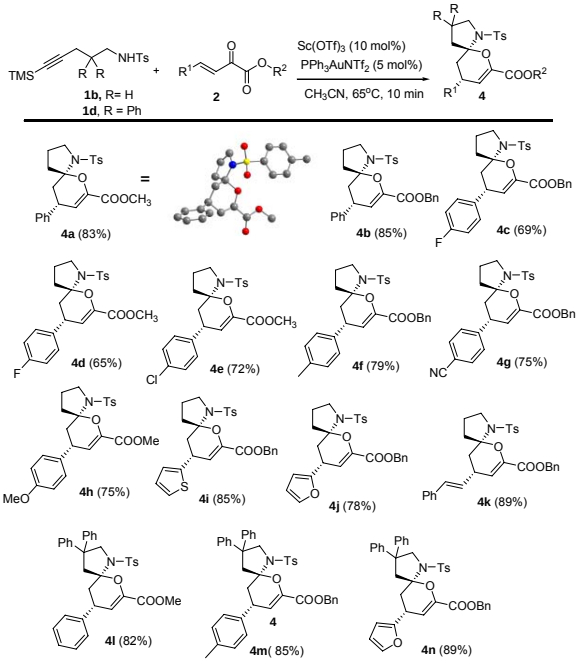
demonstrated that there is a fast gold-catalyzed desilylation or silicon-gold transmetalation process[9] under this condition and the original proposal on the formation of enaminde **M3** was not possible. Then we carried out the cyclization of silicon amine **1b** with PPh_3AuNTf_2, no cyclization product **M3** was produced, but the enamide dimerization or oligomerization products as amine **1a** behaved in previous reactions.[6,8] Switching from the labile TMS group to the more stable TBS group (tert-butyldimethyl silyl), the alkyne **1c** became very inert and remained intact under this condition (Table 1, entry 2). During the optimization, we noticed 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** could be 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** is the major product (entry 4). Further studies showed **4a** could transform into **3a** in 68% yield with 15% **4a** recovered (Scheme 2, eq. 1). The reaction of **4a** with another ketone ester **2b** gave the fused product **3a** and **3b** in 53% and 15% yield respectively (Scheme 2, eq. 2). These results clearly indicated 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 Diels-Alder reaction sequence.



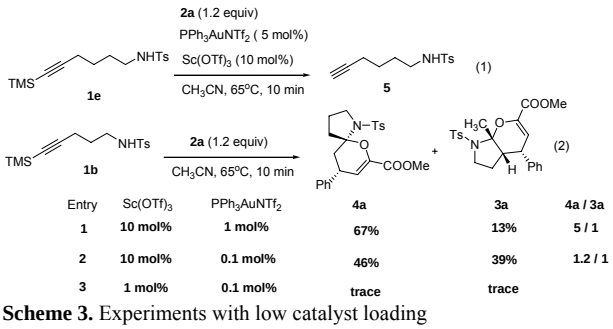
Scheme 2. Kinetic and thermodynamic balance experiments

With the optimal condition established, we examined the scope of this transformation and the results were summarized in 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 are very trace amount of fused isomers observed on TLC and only endo isomers of spiro aminal **4** detected. The structure and the relative configuration of **4a** was 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 halogen, CN, styryl, and OMe are all tolerated under this condition. The extention of this reaction to heterocyclic substrates was also successful, and achieving the 2-thienylaminal **4i** and 2-furylaminal **4j** in 85% and 78% yield respectively. Another gem-diphenyl alkyne amine **1d** was also synthesized to test its reactivity. It also reacted with different electrophiles efficiently with great chemoselectivity and stereoselectivity to furnish the corresponding spiroaminals in 82-89% yield (**4l-n**). However, the 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, eq. 1).

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



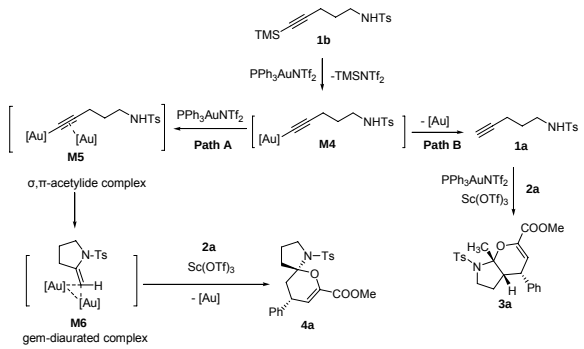
[a] Reaction conditions: alkyne **1** (0.2 mmol), **2** (0.22 mmol), PPh_3AuNTf_2 (5 mol%), $Sc(OTf)_3$ (10 mol%), CH_3CN (1 mL); isolated yield of the spiroaminals **4** indicated in the parentheses.



Scheme 3. Experiments with low catalyst loading

All the above reactions were completed in 10 minutes, thus making us consider whether we could lower the catalyst loading. The elegant work from Nolan[10] and Shi[7e] have demonstrated that the homogeneous gold catalyst could be decreased to ppm level. At the outset, keeping the loading of $Sc(OTf)_3$ constant, when the loading of Au catalyst decreased to 1 mol%, the spiro-aminal **4a**

could be isolated in 67% yield in 10 min, however the chemoselectivity decreased from previous 10.5/1 to 5/1 (Scheme 3, eq. 2, entry 1). Further decreasing 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).



Scheme 4. Proposed digold participated mechanism**.**

Based on these experiments and previous reports, a dinuclear gold catalysis mechanism was 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 charaterized by X-ray analysis.[12] Recently Hashmi group and others have developed a series of elegant chemistry based on digold catalysis.[13] In this reaction, at the relatively elevated temperature, gold catalyst serve the σ acid first to form the gold acetylide **M4** through silicon gold transmetalation. When there are extra gold catalyst, it would coordinate with the alkyne to form the digold σ,π-acetylide complex **M5**, intramolecular nucleophilic attack forming the gem-diaurated intermediate **M6**, subsequent slow proton deauration and fast cyclization would form the spiro-isomer **4** (Path A). However when the reaction was performed at very low catalyst loading, the desilyation intermediate **M4** would not form digold complex, but went through protodeauration to form the desilylation product **1a**, which would generate fused products through **M1**-**M2** sequence as our previous reaction (Path B). The relative inert reactivity of gem-diaruated species have been proved by Gagné,[12a] and in this work, it was utilized to stablize the exocyclic double bond to tune the selectivity.

In summary, a highly efficient selective synthesis of spiro aminals was developed by introducing a small TMS group. More important, the directing group disappeared in situ without 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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