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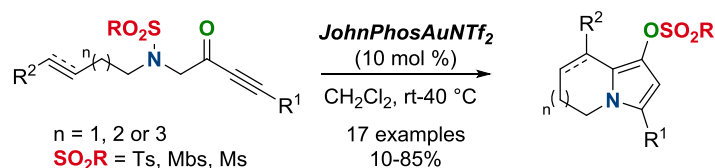
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Synthesis of Indolizine and Pyrrolo[1,2-a]azepine Derivatives via a Gold(I)-Catalyzed 3-Step Cascade

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Supporting Information Placeholder



ABSTRACT: Linear *N*-alkenyl or alkylnyl *N*-sulfonyl 1-aminobut-3-yn-2-ones are converted into bicyclic indolizines and pyrrolo[1,2-*a*]azepine-type alkaloids upon gold(I) catalysis (17 examples, 10-85%). The reaction cascade allowed to form C-N, O-S and C-C bonds via a cycloisomerization/sulfonyl migration/cyclization process using 10 mol % of [(2-biphenyl)di-*tert*-butylphosphine]gold(I) triflimide complex in dichloromethane.

Alkaloids constitute a huge family of natural products. Among them, indolizines and their saturated analogs are commonly distributed in nature, especially in plants (Figure 1).¹ These alkaloids exhibit numerous biological activities and have thus been the focus of various synthetic studies and numerous analogs have been produced.² Rosabulin (STA-5312)³ or rhazinilam⁴ are typical examples, developed as anticancer agents possessing a microtubule inhibitor activity. Isolated from the poison gland secretions of *Myrmecaria* ants, the poisonous myrmecarin alkaloid family represent another example.⁵

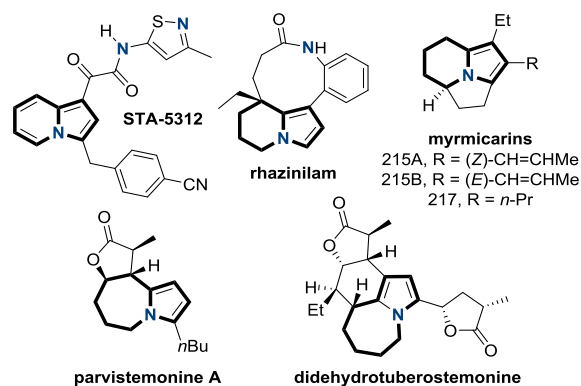


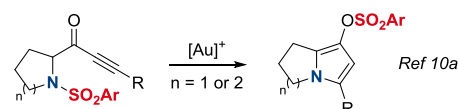
Figure 1. Representative natural and bioactive products with hydroindolizine or pyrrolo[1,2-*a*]azepine scaffolds.

Although analogs to indolizine derivatives, pyrrolo[1,2-*a*]azepine derivatives are far less represented in nature. Such motif can be found in the large family of *Stemona* alkaloids,⁶ isolated from *Stemoneaceae* plants. Used in traditional Chinese medicine to treat bronchitis, tuberculosis

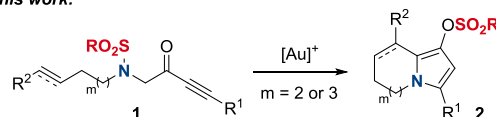
and parasite-induced illness, these alkaloids exhibit diverse physiological properties, as with the antiparasitic parvistemonine **A**⁷ or the insecticidal dihydrotuberostemonine⁸.

Scheme 1. Synthetic Strategies Towards Ring-Fused Pyrroles via Gold-Catalyzed Cyclisation/*N*-to-*O* Sulfonyl Migration.

Previous work:



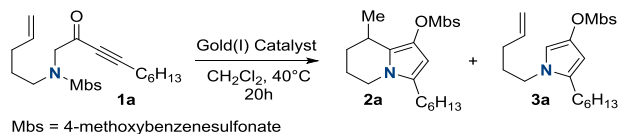
This work:



The gold-catalyzed⁹ cyclization-sulfonyl migration cascade¹⁰ we recently developed offers a unique opportunity to design a new synthetic route to indolizine and azepine type alkaloids. This cascade could indeed provide a mild and efficient access to sulfonylated pyrroles (Scheme 1, top) and if the nitrogen atom of the latter carries an unsaturated chain, gold may promote a third step. A cyclization involving the newly created pyrrole and this activated unsaturation would furnish 1-azabicyclo[*n*.3.0]alkane derivatives ($n = 4$ or 5), depending on the chain length (Scheme 1, bottom). Furthermore, the so-formed motif should carry a sulfonate group, allowing for direct modification through Suzuki-Miyaura-type coupling reaction.^{10b}

We report here the implementation of this gold(I)-catalyzed cascade toward the synthesis of substituted and/or functionalized hydroindolizines or pyrrolo[1,2-a]azepines **2** from linear *N*-alkenyl or alkynyl *N*-sulfonyl 1-aminobut-3-yn-2-ones **1**.

Table 1. Optimization of the Reaction Conditions.



entry	catalyst (mol %)	yield 2a+3a (%) ^a	ratio 2a:3a ^b
1	Ph ₃ PAuNTf ₂ (5)	57	0:100
2	(C ₆ F ₅) ₃ PAuNTf ₂ (5)	13	0:100
3	[(2,4- <i>t</i> BuPhO) ₃ P Au(MeCN)]NTf ₂ (5)	18	0:100
4	IPrAuNTf ₂ (5)	44	33:67
5	[IPrAu(MeCN)] [PMO ₁₂ O ₄₀][H ₂] (5)	27	100:0
6	XPhosAuNTf ₂ (5)	19	100:0
7	CyJohnPhosAuNTf ₂ (5)	55	90:10
8	JohnPhosAuNTf ₂ (5)	72	90:10
9	JohnPhosAuCl/AgSbF ₆ (5)	24	100:0
10	JohnPhosAuNTf ₂ (10)	81	100:0

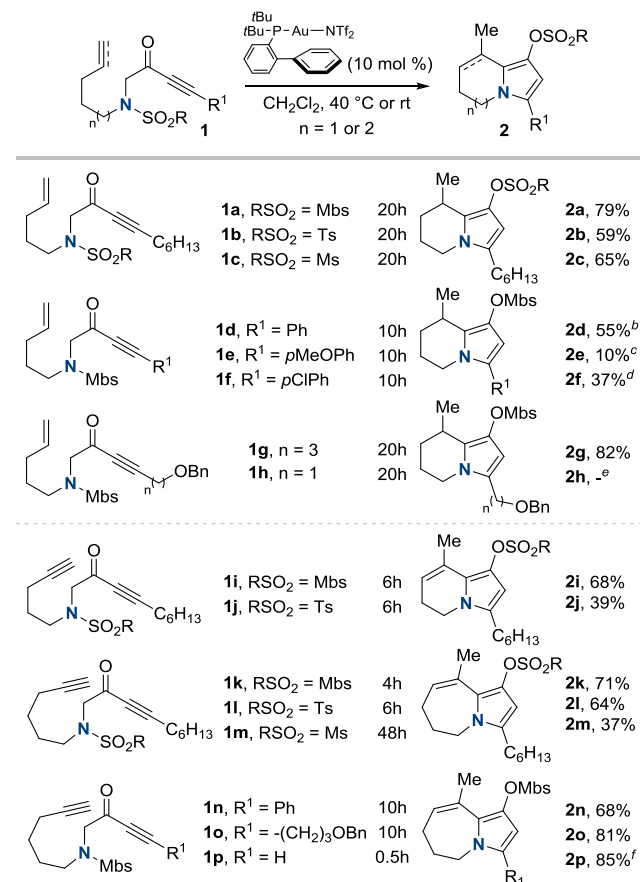
^aCalculated yield from ¹H NMR integration relative to an internal standard (dimethyl terephthalate). ^bThe ratio was determined from the ¹H NMR spectrum of crude reaction.

For the screening of the reaction conditions, we selected the *N*-pent-4-enyl *N*-4-methoxybenzenesulfonyl 1-aminobut-3-yn-2-one **1a**, readily prepared in 4 steps from methyl glycinate (see Supporting Information). **1a** was submitted to different gold complexes as catalyst (Table 1). Previously reported to promote the cyclization-sulfonyl migration reaction,¹⁰ the Gagosz catalyst¹¹ only provided the pyrrole intermediate **3a** in dichloromethane at 40°C (entry 1). The more electron withdrawing tri(phenyl)phosphine analog as well as a phosphite analog also gave the sole pyrrole **3a**, but in low yields (entries 2-3). Gold carbene complexes allowed reversing the selectivity, with a surprisingly dramatic effect of the counterion. Indeed, with a triflimide, a mixture of pyrrole **3a** and the expected bicyclic product **2a** was produced in a 1:2 ratio, while with a polyoxometalate as anion,¹² only the expected bicyclic product was observed, unfortunately in modest yield along with degradation products (entry 4 vs 5). Shifting to Buchwald-type ligand also reversed the selectivity but with more interesting results. The large XPhos ligand promoted the sole formation of the bicyclic product **2a**, but again with modest yield (entry 6). Using the less hindered CyJohnPhos ligand increased the reactivity and the overall yield but with a slightly lower selectivity (entry 7 vs 6). Switching to JohnPhos ligand with different steric parameter¹³ rewardingly provided even higher reactivity and yield, in favor of the expected bicyclic product **2a**, but again not fully selectively (entry 8). Changing the NTf₂ anion to SbF₆ increased the selectivity, with only the

bicycle formed, but to the detriment of yields (entry 9). Unfortunately, the compounds **2a** and **3a** were inseparable by chromatography. Therefore, we tried to improve the selectivity by performing the reaction with 10 mol % of JohnPhosAuNTf₂ catalyst (entry 10) and we were pleased to obtain **2a** with a total selectivity and with high yield. This catalyst was thus used for exploring the scope of this reaction.

With the optimized conditions in hand, various substrates carrying *N*-alkenyl or *N*-alkynyl chain were prepared **1a-p** (see Supporting Information) and engaged in the new gold-catalyzed cycloisomerization-sulfonyl migration-cyclisation cascade (Scheme 2).

Scheme 2. Reaction Scope of the Cascade with Terminal *N*-Alkenyl or Alkynyl *N*-Sulfonyl 1-Aminobut-3-yn-2-one Derivatives **1**.^a



^aReactions run at 40°C for *N*-alkenyl derivatives or at room temperature for *N*-alkynyl derivatives, *c* = 0.1 mol/L. ^bIsolated along 10% of pyrroles intermediate **3d** (See Supporting Information). ^cCalculated yield from ¹H NMR integration relative to an internal standard (dimethyl terephthalate). ^dPartial degradation occurs during purification. ^eDegradation occurs. ^fCumulative yield with the exo-methylene product.

Considering the importance of the sulfonyl group for the migration step,^{10a,14} its influence was first examined. As shown with *N*-pent-4-enyl substrates **1a-c**, the *para*-methoxybenzenesulfonate (Mbs) gave the best result, providing the expected bicycle **2a** in high yield. In contrast, the tosylate (Ts) and mesylate (Ms) derivatives **1b-c** furnished, after 20 h at 40 °C, mostly the bicyclic products **2b**

and **2c** in an average yield of 60% but together with 5% of pyrrole intermediates **3**. The Mbs sulfonate was thus used to explore functional compatibility.

With a phenyl group as substituent of the alkyne, the cascade proceeded as well, but the conjugation of this group to the formed pyrrole **3d** lowered the nucleophilicity of this pyrrole, and thus some pyrrole was left, lowering the yield of the expected bicyclic product **2d**. The substrates **1e** and **1f**, possessing respectively electron withdrawing (Cl) or donating (OMe) groups on the aryl part, were more problematic. Indeed, the tetrahydroindolizine **2e** was only obtained in low yield along with many degradation products, while compound **2f** proved highly unstable and could only be isolated in modest yield, despite a clean reaction observed by NMR.

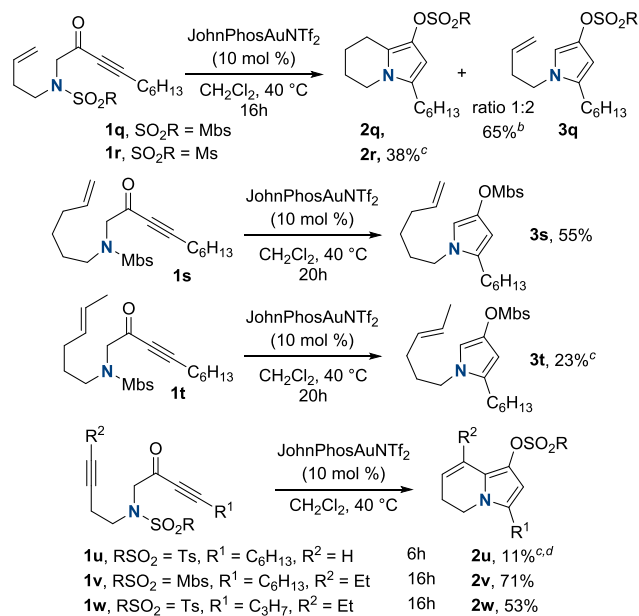
With a protected hydroxy group, the cascade was very effective, only giving the corresponding bicycle **2g** in high yield, but only when this functional group is remote from the alkyne moiety. When such functional group is at the propargylic position, degradation occurred (**2h** vs **2g**).

N-Alkynyl chains were then evaluated. Substrates carrying such chain proved more reactive and the reactions were conducted at room temperature. The *N*-pent-4-ynyl chain induced a 6-*exo-dig* cyclization in good yield with the Mbs derivative **1i**, but in modest yield with the *N*-tosyl analog **1j**. Structural analysis of these products revealed that the resulting double bond in such products was internal to the newly created cycle, despite *exo*-cyclization. This could be the result of double bond migration, probably assisted by the catalyst. Interestingly, the longer *N*-hex-4-ynyl chain also allowed *exo-dig* cyclization, which provided in good yields dihydropyrrolo[1,2-*a*]azepine compounds **2k-p**, here again after double bond migration. As in the *N*-alkenyl series, changing the tosylate or mesylate for the *para*-methoxybenzenesulfonate improved the cyclization efficiency and yield (**2k** vs **2l-m**). Modification of the ynone was perfectly tolerated as attested by the good yields obtained for bicyclic products **2n-p**. It is worth noticing that in this *N*-alkynyl series, the bicyclic products contain a double bond, which can be further functionalized.

The influence of the chain length as well as the substitution of the alkene or alkyne function were then investigated (Scheme 3). With a shorter *N*-but-4-enyl chain, the substrates **1q** and **1r** still provide the tetrahydroindolizine system, although in modest yields. The cyclization still proceeded, but in a 6-*endo-trig* process instead of the 6-*exo-trig* cyclisation observed with the *N*-pent-4-enyl chain. With the longer *N*-hex-4-enyl chain (**1s**) or with substituted alkene such as in the (*E*)-*N*-(hex-4-en-1-yl) chain (**1t**), the cascade stopped at the pyrrole stage and no bicyclic product could be detected.

The *N*-but-4-ynyl chain (**1u**) also allowed a 6-*endo-dig* cyclization, but in very low yield mostly due to the high instability of the so-formed dihydroindolizine **2u**. However, the cascade was efficiency restored with internal alkynes (**1v-w**), as showed by the formation of the expected dihydroindolizines **2v** and **2w** in good yields.

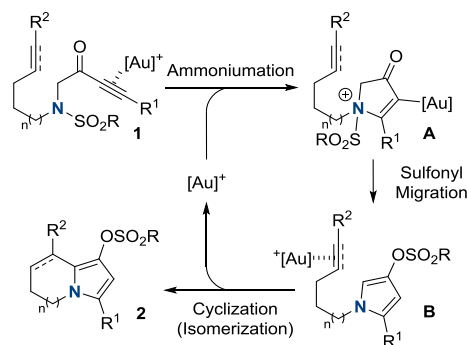
Scheme 3. Synthesis of Indolizine Derivatives from Linear *N*-Enyl or Ynyl *N*-Sulfonyl 1-Aminobut-3-yn-2-ones **1q-v** and Limitations.^a



^a*c* = 0.1mol/L. ^bCumulative yield of inseparable **2q** and **3q** derivatives. ^cDegradation occurs. ^dCalculated yield from ¹H NMR integration relative to an internal standard (dimethyl terephthalate).

The mechanism of this cascade was postulated to begin by the π -activation of the ynone substrate **1** by gold(I) catalyst (Scheme 4). Intramolecular ammonium formation of the alkyne¹⁵ could then occur leading to the transient vinylgold ammonium intermediate **A**. At this stage, the intramolecular sigmatropic *N*-to-*O* migration of the sulfonyl group took place affording the sulfonylated pyrrole intermediate **B**.¹⁰ Finally, the nucleophilic addition of the electron-rich pyrrole motif to the remaining unsaturation activated by gold furnished the bicyclic product **2**.¹⁶ Further isomerization of the double bond also occurred when starting from *N*-alkynyl substrates.

Scheme 4. Proposed Mechanism for the Formation of Indolizine and Pyrrolo[1,2-*a*]azepine via Gold(I)-Catalyzed Cascade.



In conclusion, we developed a new 3 step gold-catalyzed cascade from readily available compounds derived from glycine. The cycloisomerization of *N*-alkenyl or alkynyl *N*-sulfonyl 1-aminobut-3-yn-2-ones followed by a *N*-to-*O* sulfonyl migration provided *N*-alkenyl or alkynyl pyrrolyl sulfonates and a further cyclization afforded functionalized

indolizines or pyrrolo[1,2-a]azepines in good to high yields.

ASSOCIATED CONTENT

The Supporting Information is available free of charge on the ACS Publications website.
Experimental details, copies of spectra (PDF).

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Notes

The authors declare no competing financial interest.

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