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Gold(I)-Catalyzed Cyclization/Nucleophilic Substitution of 1-(*N*-Sulfonylazetidin-2-yl) Ynones into *N*-Sulfonylpyrrolin-4-ones

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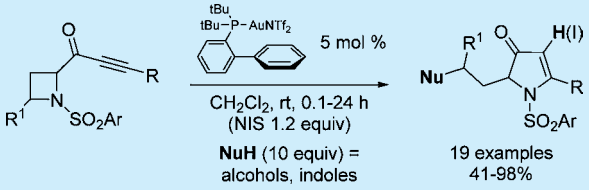
Supporting Information

ABSTRACT: Polysubstituted pyrrolin-4-ones have been efficiently synthesized from readily available 1-(*N*-sulfonylazetidin-2-yl) ynones via gold(I)-catalyzed cyclization/nucleophilic substitution in the presence of various nucleophiles, such as water, alcohols, or indoles. Additionally, 3-iodopyrrolin-4-one derivatives have also been obtained under the same reaction conditions upon addition of 1.2 equiv of *N*-iodosuccinimide.



The pyrrolin-4-one motif constitutes the core of naturally occurring or synthetic derivatives presenting various interesting biological properties, such as HIV-1 protease inhibition[1] and antibiotic[2] or antimalarial[3] activities (Figure 1). However, only a few efficient syntheses of such *N*-heterocyclic compounds have been described in the literature to date.[4] They rely on two main strategies (Scheme 1), the cycloisomerization of 1-amino ynones catalyzed or mediated by late transition metals[5] and the dimerization of enaminone derivatives[6] and related compounds.

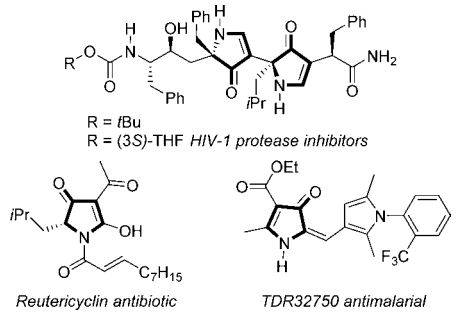
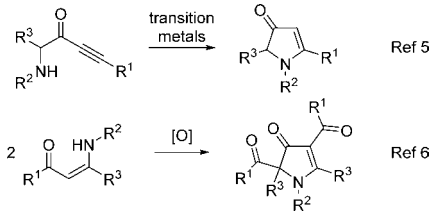


Figure 1. Natural products and some bioactive non-natural compounds exhibiting the pyrrolin-4-one motif.

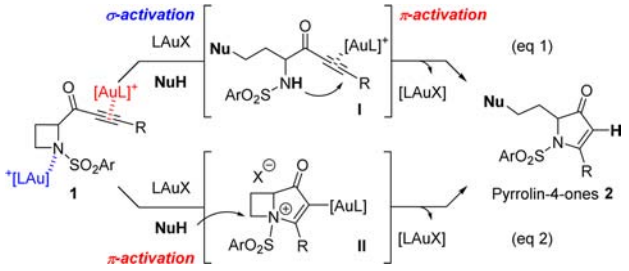
Exploiting the well-known π-activation of gold cations[7] as well as their dual π and σ Lewis acidities,[8] we have successfully developed various gold(I)-catalyzed rearrangements of α-alkynyl strained heterocyclic compounds bearing nucleophilic moieties and/or in the presence of external nucleophiles. Therefore, we have been able to efficiently construct sophisticated and added-value (hetero)cyclic derivatives such as polysubstituted furans and pyrroles,[9] spiro[isochroman-4,2′-pyrrolines],[10] or cyclopentenones[11] from small oxo- or aza-rings. Among them, functionalized α-alkynyl azetidines have proven to be powerful substrates for the preparation of tricyclic pyrrolo[1,2-*a*]indoles.[12] As the azetidine scaffold remains scarcely used as a starting material in homogeneous gold catalysis,[13] we further investigated the reactivity of α-alkynyl azetidines, and we report here their gold-catalyzed conversion to polysubstituted pyrrolin-4-ones.

Starting from the 1-(*N*-sulfonylazetidin-2-yl) ynones **1**, two mechanistic hypotheses could be envisaged for the formation of polysubstituted *N*-sulfonyl pyrrolin-4-ones **2** in the presence of external nucleophiles (Scheme 2).[14] First, upon σ-activation of the substrate by a gold catalyst, a regioselective nucleophilic opening of the azetidine ring could occur, affording an amino ynone **I** intermediate that could then cyclize upon π-activation

Scheme 1. Known Strategies toward Pyrrolin-4-ones



Scheme 2. Hypotheses for Gold(I)-Catalyzed Cyclization/Nucleophilic Substitution of 1 toward Pyrrolin-4-ones 2



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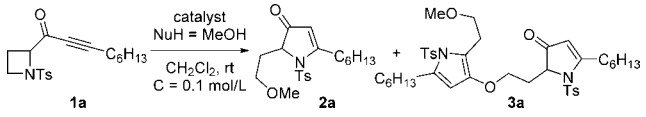
(Scheme 2, eq 1). Based on the gold-catalyzed ammoniumation of alkynes described by Bertrand,[15] another possible process could also be envisaged. Indeed, the azetidinium intermediate **II** could be formed upon direct addition of the nitrogen atom on the ynone motif (Scheme 2, eq 2).[16] The selective addition of an external protic nucleophile on the ammonium **II** would then open the aza-ring and provide the required proton for the final demetalation step.

We started our investigation by submitting 1-(*N*-tosylazetidin-2-yl) ynone **1a** to various gold catalysts in the presence of methanol as nucleophile (Table 1). Such azetidinyl ynones are

Table 1. Screening of Reaction Conditions for the Formation of *N*-Tosylpyrrolin-4-one 2a from Azetidine 1a



				yield[a] (%)	
entry	catalyst (5 mol %)	MeOH (equiv)	time (min)	**2a**	**3a**
1	PPh_3AuNTf_2	5	24 h	39[b]	11
2	Cy_2JohnPhosAuSbF$_6$ (MeCN)	5	10	77	19
3	Cy_2JohnPhosAuSbF$_6$ (MeCN)	10	5	80	10
4	JohnPhosAuSbF$_6$ (MeCN)	10	5	79	10
5	JohnPhosAuNTf$_2$	10	5	84	5
6	JohnPhosAuCl/AgBF$_4$	10	24 h	70[c]	
7	JohnPhosAuCl/AgOTf	10	24 h	65[c]	
8	*t*BuXPhosAuNTf$_2$	10	1	72	10
9	JohnPhosAuNTf$_2$ (2.5 mol %)	10	5 h	68[b]	8
10	JohnPhosAuNTf$_2$		5	*d*	
11		10	48 h	*e*	

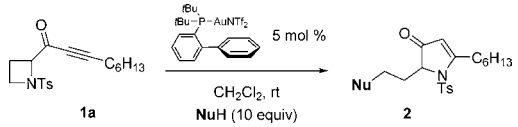
[a]Calculated yield from crude ^{1}H NMR spectrum. [b]Starting material was recovered. [c]Reaction run in the presence of 3 Å molecular sieves. [d]Degradation occurred leading to unidentified byproducts. [e]No conversion.

conveniently synthesized in two steps from α-carbonylated *N*-sulfonylazetidine building blocks available on grams scale[17] after Weinreb's amide formation followed by alkynylation.

When mixed with 5 mol % of Gagosz's catalyst and 5 equiv of methanol at room temperature for 24 h, the azetidine **1a** afforded two pyrrolin-4-one derivatives **2a** and **3a**, despite the low conversion (50%) (Table 1, entry 1). As expected, the pyrrolin-4-one **2a**, bearing a methoxy group, was formed as the major product, while the minor one **3a** was identified as a dimeric pyrrolinone/pyrrole compound. The slow reaction rate probably allowed **2a** to accumulate and, via its enol form, act as a competitive nucleophile. Switching from triphenylphosphine to Buchwald-type ligands enhanced the reactivity, leading to the consumption of **1a** in less than 10 min (Table 1, entries 2−4). Moreover, the yield of pyrrolin-4-one **2a** was improved (Table 1, entry 1 vs 2). Unexpectedly, compound **3a** was still observed, but its formation was limited to some extent by increasing the quantity of methanol from 5 to 10 equiv (Table 1, entry 2 vs 3). With JohnPhos ligand as the best compromise (Table 1, entry 4), we then examined the influence of the counterion on the reaction (Table 1, entries 4−7). Compared to hexafluoroantimonate, the triflimidate anion slightly increased the yield of **2a** to 84% while further decreasing the amount of **3a** (Table 1, entry 4 vs 5). The use of other counterions, such as BF_4^- or TfO^-, was detrimental to the formation of **2a**, although the complete absence of unwanted **3a** has to be noticed (Table 1, entries 6 and 7).[18] Increasing the ligand bulkiness using *t*-BuXPhos or decreasing the catalyst loading to 2.5 mol % did not give satisfactory results (Table 1, entries 8 and 9). Control experiments without nucleophile or gold catalyst confirmed the requirement of both reagents in this transformation (Table 1, entries 10 and 11).

With the optimized reaction conditions in hand (Table 1, entry 5), we screened different nucleophiles in the cyclization/nucleophilic substitution of **1a** affording various pyrrolin-4-one derivatives **2** (Table 2).

Table 2. Screening of Nucleophiles in the Rearrangement of 1a into *N*-Tosylpyrrolin-4-ones 2



entry	nucleophile	pyrrolin-4-one **2**	time (h)	yield[a] (%)
1	MeOH	**2a**	0.1	81
2	EtOH	**2b**	0.1	81
3	$C_5H_{11}OH$	**2c**	0.1	84
4	*i*-PrOH	**2d**	0.1	74
5	*t*-BuOH	**2e**	3	75
6	benzyl alcohol	**2f**	0.1	81
7	allyl alcohol	**2g**	0.1	74
8	propargyl alcohol	**2h**	24	61[b]
9	hept-2-yn-1-ol	**2i**	24	89
10	H_2O	**2j**	24	*c*
11	H_2O	**2j**	3.5	71[d]
12	indole	**2k**	0.75	41[b]
13	1,2-dimethylindole	**2l**	0.5	68[b]
14	benzylamine	**2m**	24	90[e]
15	aniline	**2n**	24	57[e]
16	EtSH		24	*c*

[a]Isolated yield of pure product. [b]Reaction run in DCE at 70 °C. [c]No reaction. [d]JohnPhosAuCl/hydrated AgOTf. [e]Product resulting from amine addition on the triple bond was observed.

Primary alcohols, such as ethanol or pentanol, were as effective as methanol in the rearrangement, furnishing the pyrrolin-4-ones **2b** and **2c**, respectively, in 81 and 84% isolated yield (Table 2, entries 2 and 3 vs 1). Secondary or more hindered tertiary alcohols were also suitable for the transformation, despite the longer reaction time using 2-methyl-2-propanol (Table 2, entries 4 and 5). Valuable benzyl or allyl ether moieties could also easily be introduced on the side chain of the pyrrolin-4-one motif (Table 2, entries 6 and 7). Propargyl alcohols were more difficult to incorporate. Indeed, the reaction had to be stirred for 24 h or heated at 70 °C to reach full conversion, presumably due to the complexation of the gold catalyst to such type of nucleophiles. Nevertheless, pyrrolin-4-ones **2h** and **2i** have been obtained in good to high yields (Table 2, entries 8 and 9). The direct addition of water (10 equiv) in the reaction mixture did not promote the transformation, and the starting material was entirely recovered. However, the pyrrolin-4-one **2j** bearing a hydroxyl group could be easily obtained using the combination of JohnPhosAuCl (5 mol %) with hydrated silver triflate (AgOTf·xH$_2$O) as gold

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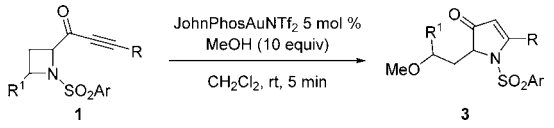
activator and source of water (Table 2, entry 10 vs 11). Carbon nucleophiles such as indoles proved to be compatible with the reaction conditions, furnishing pyrrolin-4-ones **2k** and **2l** in modest to good yields (Table 2, entries 12 and 13). Not surprisingly, the addition of Lewis basic protic nucleophiles such as amines, anilines, or thiols failed to promote the formation of the corresponding pyrrolin-4-ones (Table 2, entries 14−16).

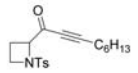
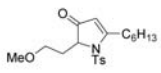
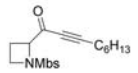
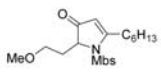
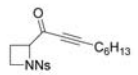
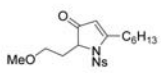
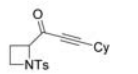
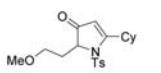
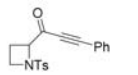
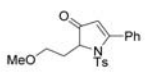
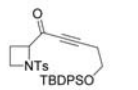
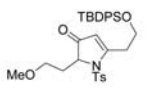
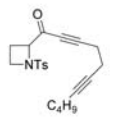
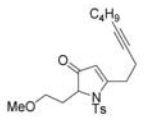
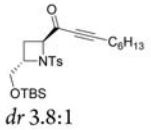
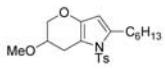
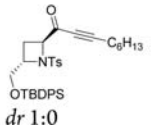
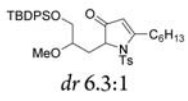
We then examined the scope of the gold−catalyzed rearrangement with various 1-(*N*-sulfonylazetidin-2-yl) ynones **1** in the presence of methanol (Table 3). We focused our attention on the role of the sulfonyl moiety, the alkyne substitution, and the behavior of 2,4-disubstituted azetidinyl derivatives.

p-Methoxybenzenesulfonyl (Mbs) and nosyl (Ns) protecting groups were evaluated by submitting ynones **1b** and **1c** to our reaction conditions. If the Mbs group was fully compatible with our conditions (Table 3, entry 1 vs 2), the nosylated azetidine **1c** afforded the pyrrolin-4-one **3c** in a modest yield of 50% along with the formation of denosylated azabicyclo[3.2.0]-heptenone derivative **4c**. The latter arose from the scavenging of the nosyl group by methanol on the azetidinium intermediate **II** (Table 3, entry 3).[19] This result clearly suggests the direct π-activation mechanism for the formation of pyrrolin-4-ones (Scheme 2, eq 2). Substituents at the propargylic position were perfectly tunable as demonstrated by the formation of functionalized pyrrolin-4-ones **3d−g** bearing alkyl, aryl, alkynyl, or protected hydroxyl groups (Table 3, entries 4−7). Effects of substituents on the azetidine moiety were also studied with compounds **1h,i** bearing a silyloxymethyl group (Table 3, entries 8 and 9). Under our reaction conditions, compound **1h** (R^1 = CH_2OTBS) afforded exclusively the bicyclic pyrano[3,2-*b*]pyrrole **3h** incorporating a methoxy group, likely through in situ deprotection of the *tert*-butyldimethylsilyl group of the pyrrolin-4-one formed followed by intramolecular cyclization and dehydration. Starting from substrate **1i** carrying the more robust *tert*-butyldiphenylsilyl group (TBDPS), we obtained the expected pyrrolin-4-one **3i** in correct yield.

The reaction could also be performed in the presence of an electrophilic halogen source, such as *N*-iodosuccinimide (NIS), in order to supplant the protodeauration by a halodeauration.[20] Using our optimal conditions in the presence of 1.2 equiv of NIS, we were pleased to isolate *N*-tosyl 3-iodopyrrolin-4-ones **5a** and **5f**, suitable substrates for further palladium cross-coupling reactions, respectively, in 74% and 68% yield from **1a** and **1f** (Scheme 3).

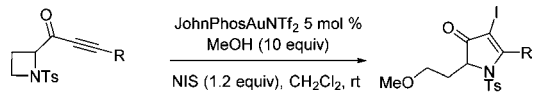
Table 3. Synthesis of Various *N*-Sulfonylpyrrolin-4-ones 3 from 1-(*N*-sulfonylazetidin-2-yl) Ynones 1 Using Methanol as Nucleophile



entry	azetidine		product		yield[a] (%)
1		**1a**		**2a**	81
2		**1b**		**3b**	77
3		**1c**		**3c**	50[b]
4		**1d**		**3d**	98
5		**1e**		**3e**	94
6		**1f**		**3f**	73
7		**1g**		**3g**	83
8	 *dr* 3.8:1	**1h**		**3h**	49
9	 *dr* 1:0	**1i**	 *dr* 6.3:1	**3i**	45

[a]Isolated yield of pure product. [b]Along with 49% of 2-hexyl-1-azabicyclo[3.2.0]hept-2-en-4-one **4c**.

Scheme 3. Gold-Catalyzed Formation of *N*-Tosyl-3-iodopyrrolin-4-ones 5 in the Presence of *N*-Iodosuccinimide from 1a and 1f



In conclusion, we have developed convenient access to polysubstituted pyrrolin-4-ones from 1-(*N*-sulfonylazetidin-2-yl) ynones in high yields in the presence of water, alcohols, or indoles. Such unprecedented gold-catalyzed rearrangement probably occurs via an intramolecular cyclization of *N*-sulfonylated azetidine on the ynone part followed by a nucleophilic substitution and opening of the so-formed azetidinium (**II** in Scheme 2). Further investigations on the role of this type of ammonium intermediates in gold catalysis are ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00135.

Complete experimental procedures, characterization data, and spectral data (PDF)

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Notes

The authors declare no competing financial interest.

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(18) Reactions run with 5 mol % of JohnPhosAuNTf$_2$ catalyst *with and without* molecular sieves (3 Å) afforded comparable yields of **2a**, e.g., respectively, 81 vs 84% under entry 5 conditions. Molecular sieves were added when the reaction required long duration (entries 6 and 7) to avoid the formation of **2j** (see Table 2, entry 11).

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