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Gold-Catalyzed One-Pot Cascade Construction of Highly Functionalized Pyrrolo[1,2-*a*]quinolin-1(2*H*)-ones

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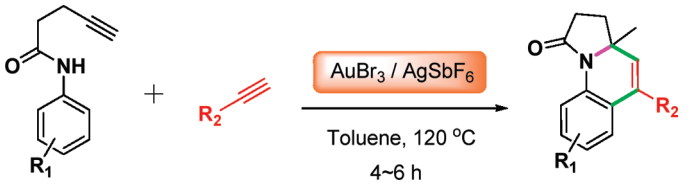

An efficient protocol was developed for the synthesis of fused heterocyclic multiring compounds pyrrolo[1,2-*a*]quinolin-1(2*H*)-ones via a $AuBr_3/AgSbF_6$-catalyzed cascade transformation. Significantly, the strategy affords a straightforward and efficient approach to construction of tricyclic lactam molecular architectures in which two new C−C bonds and one new C−N bond are formed in a one-pot synthetic operation from simple starting materials. Moreover, a broad spectrum of substrates can participate in the process effectively to produce the desired products in good yields and with excellent regio- and chemoselectivities.

Introduction

The development of catalytic cascade reactions for "one-pot" synthesis of complex multiring molecular architectures is fueled by its synthetic efficiency, atom economy, and high selectivity.[1] Recent years have witnessed tremendous growth in the number of gold-catalyzed domino organic transformations.[1b,2] Notably, gold-catalyzed inter- or intramolecular hydroamination of alkynes and inter- or intramolecular hydroarylation of alkynes provide effective avenues for the formation of complex heterocyclic structures.[3] Despite significant progress, several significant limitations remain to be addressed, the vast majority of the reported cascade sequences employed an intramolecular reaction with starting materials containing multiple functional groups strategically positioned along a chain, terminating with alkyne functionality.[2h] Construction of complex fused heterocyclic multiring architectures via an intermolecular union of simple starting materials through a one-pot operation still represents significant synthetic challenges. To our knowledge, the incorporation of less nucloephilic amides for gold-promoted hydroamination/hydroarylation cascade reactions to build tricyclic lactams via one C−N bond and two

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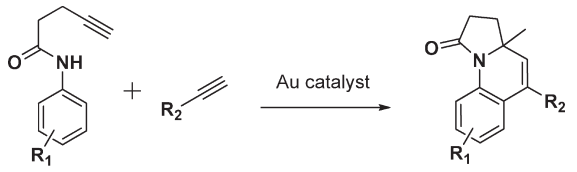
SCHEME 1. Synthesis of Diversely Substituted Pyrrolo[1,2-*a*]quinolin-1(2*H*)-ones

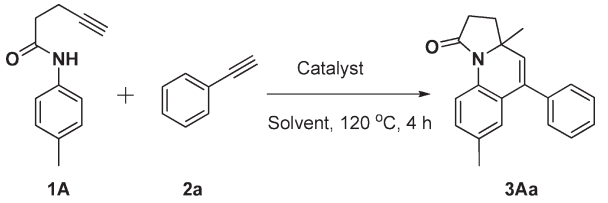


C−C bonds formation in one synthetic operation has not been disclosed. In our effort to develop new methods for synthesizing biologically active heterocycles using transition metal catalysts,[4] we herein report an unprecedented gold-catalyzed hydroamination/hydroarylation cascade process for the construction of fused tricyclic architectures pyrrolo-[1,2-*a*]quinolin-1(2*H*)-ones (Scheme 1), of which analogues are widely distributed in a large collection of biologically interesting natural products and synthetic molecules.[1b,5]

Results and Discussion

To identify optimal reaction conditions for the gold-catalyzed tandem synthesis of pyrrolo[1,2-*a*]quinolinones, various Au(III), Au(I), and Ag(I) catalysts were screened for a model reaction of *N*-*p*-tolylpent-4-ynamide (**1A**) with phenylacetylene (**2a**) in toluene in a sealed tube under argon. As depicted in Table 1, different gold salts such as $AuCl_3$, $AuBr_3$, $AuCl(PPh_3)$, $[Au\{P(t\text{-}Bu)_2(o\text{-biphenyl})\}]Cl$, and $[Au\{P(t\text{-}Bu)_2(o\text{-biphenyl})\}]SbF_6$ were probed at 120 °C in toluene, but the desired products were obtained only in low yields (Table 1, entries 1−5). However, upon activation of these gold complexes with $AgSbF_6$, the yields were increased significantly under otherwise the same reaction conditions (Table 1, entries 1−5). The $AuBr_3/AgSbF_6$ catalytic system seemed slightly better than other gold salts and $AgSbF_6$. In the absence of gold salts, the reaction resulted in a dramatic decrease in the yield of **3Aa** (entry 6). These results indicated that both Au source and $AgSbF_6$ played a crucial role in this tandem cyclization. Subsequently, we screened different solvents, which indicates that CH_2Cl_2, DMF, NMP, dioxane, C_2H_5OH, and CH_3CN are not effective solvents (Table 1, entries 7−12). Nevertheless, treatment of the mixture of **1A** and **2a** with the presence of $AuBr_3/AgSbF_6$ in $ClCH_2CH_2Cl$ and xylene provided the desired product in 30% and 66% yields, respectively (Table 1, entries 13 and 14). It was also found that the reaction solvent plays an important role in this transformation. Furthermore, variations of Ag salts were also probed in the cascade process (Table 1, entries 15−19), and the results revealed that the product **3Aa** was only obtained in 30% yield after 4 h at 120 °C by using 5 mol % of $AgBF_4$ in the presence of 3 mol % of $AuBr_3$. Some protonic acids other than Ag salts, such as TFA and TsOH, were also investigated as a cocatalyst, but no good results were obtained (data were not shown). The yield of **3Aa** was not significantly affected without Ar protection (Table 1, entry 20). It is well-known that the formation of two new carbon−carbon and one new carbon−nitrogen bonds to make two rings in a one-pot reaction is particularly challenging because the region- and chemoselectivity must be well-controlled to avoid formation of intractable mixture of regioisomeric homo- and heterocoupled compounds. However, the current transformation does not require a large excess of either reagent or careful control of reagent addition. As a consequence, a comparable efficiency was

TABLE 1. Optimization of the Reaction Conditions for the Synthesis of 3a,7-Dimethyl-5-phenyl-3,3a-dihydropyrrolo[1,2-*a*]quinolin-1(2*H*)-one[a]



1A 2a 3Aa

entry	Au source	Ag source	solvent	yield (%)
1	$AuCl_3$		toluene	30 (70[b])
2	$AuBr_3$		toluene	55 (81[b])
3	$AuCl(PPh_3)$		toluene	17 (70[b])
4	$[Au\{P(t\text{-}Bu)_2(o\text{-biphenyl})\}]Cl$		toluene	10 (55[b])
5	$[Au\{P(t\text{-}Bu)_2(o\text{-biphenyl})\}]SbF_6$		toluene	15 (75[b])
6		$AgSbF_6$	toluene	45
7	$AuBr_3$	$AgSbF_6$	CH_2Cl_2	0
8	$AuBr_3$	$AgSbF_6$	DMF	0
9	$AuBr_3$	$AgSbF_6$	NMP	0
10	$AuBr_3$	$AgSbF_6$	dioxane	0
11	$AuBr_3$	$AgSbF_6$	C_2H_5OH	0
12	$AuBr_3$	$AgSbF_6$	CH_3CN	0
13	$AuBr_3$	$AgSbF_6$	DCE	30
14	$AuBr_3$	$AgSbF_6$	xylene	66
15	$AuBr_3$	Ag_2CO_3	toluene	0
16	$AuBr_3$	$AgOCOCF_3$	toluene	0
17	$AuBr_3$	$AgBF_4$	toluene	30
18	$AuBr_3$	$AgSO_2CF_3$	toluene	0
19	$AuBr_3$	Ag_2O	toluene	0
20	$AuBr_3$	$AgSbF_6$	toluene	80[c]
21	$AuBr_3$	$AgSbF_6$	toluene	78[d]
22	$AuBr_3$	$AgSbF_6$	toluene	60[e]
23	$AuBr_3$	$AgSbF_6$	toluene	75[f]
24	$AuBr_3$	$AgSbF_6$	toluene	80[g]

[a] **1A** (0.1 mmol), **2a** (0.4 mmol), Au salts (3 mol %)/Ag salts (5 mol %), Ar protection. [b] Reaction performed in the presence of 5 mol % of $AgSbF_6$. [c] Reaction performed without Ar protection. [d] **1A** (0.1 mmol), **2a** (0.15 mmol), $AuBr_3$ (3 mol %)/$AgSbF_6$ (5 mol %). [e] The reaction temperature was below 100 °C. [f] The reaction temperature was 140 °C. [g] The reaction time was prolonged to 10 h.

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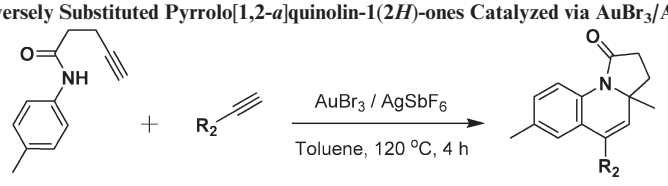
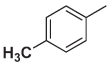
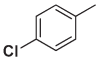
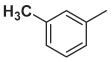
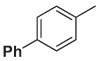
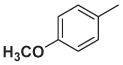
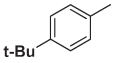
TABLE 2. Tandem Synthesis of Diversely Substituted Pyrrolo[1,2-*a*]quinolin-1(2*H*)-ones Catalyzed via $AuBr_3/AgSbF_6$[a]



1A 2a-2l 3Aa-3Al

Entry	R_2	Product	Yield (%)	Entry	R_2	Product	Yield (%)
1		**3Aa**	81	7		**3Ag**	52
2		**3Ab**	77	8		**3Ah**	55
3		**3Ac**	77	9		**3Ai**	69[b]
4		**3Ad**	73	10		**3Aj**	0
5		**3Ae**	68[b]	11		**3Ak**	trace
6		**3Af**	67	12		**3Al**	0

[a] **1A** (0.1 mmol), **2** (0.4 mmol), $AuBr_3$ (3 mol %)/$AgSbF_6$ (5 mol %), toluene (2 mL), Ar protection. [b] The reaction time was prolonged from 4 to 6 h to complete substrate conversion.

achieved even with 1.5 equiv of **2a** (Table 1, entry 21 and Table 3, entry 7) without homocoupled product.[6] On the other hand, the reaction temperature was found to be an important factor for this tandem transformation. For example, compound **3Aa** was obtained in 60% yield when the temperature was reduced to 100 °C (Table 1, entry 22), whereas increasing reaction temperature to 140 °C resulted in a decreased yield (Table 1, entry 23). In addition, longer reaction time (10 h) did not improve the yield in this tandem process (Table 1, entry 24).

Under our optimized reaction conditions (0.1 mmol of **1A**, 0.4 mmol of **2a**, 3 mol % of $AuBr_3$/5 mol % of $AgSbF_6$,[7] 2 mL of toluene, Ar protection, 120 °C, 4 h), we examined the substrate scope of this tandem cyclization reaction. A variety of aromatic alkynes can participate in the process to afford products **3Aa**−**3Ai** in moderate to good yields (52−81%) (Table 2, entries 1−9), and a relatively longer reaction time was needed to complete substrate conversion in the cases of *p*-*t*-Bu- and *p*-Ph-substituted phenylacetylenes, presumably due to the steric effect (Table 2, entries 5 and 9). However, limitation of the reaction was also realized. No desired products **3Aj** and **3A*l*** were obtained under the optimized condition when 2-ethynylpyridine and 1-octyne, respectively, were used (Table 2, entries 10 and 12); and only a trace amount of **3Ak** was observed for ethynylcyclopropane, presumably due to charge effects (Table 2, entry 11).

We further probed the substrate scope in variation of *N*-aryl-4-ynamides. As shown in Table 3, *N*-aryl-4-ynamides with substituents bearing steric and electronic properties are tolerant of the cascade reactions. (Table 3, entries 1−27). Relatively higher yields were obtained in the case of treatment of *p*-COOEt-substituted *N*-aryl-4-ynamides with different aromatic alkynes (Table 3, entries 6−9).

A catalytic cycle for the above transformation, which is similar to the gold-catalyzed tandem reactions reported by Che and Li,[1b,8] is shown in Scheme 2. The terminal alkyne moiety of **1** is first activated by the $AuBr_3/AgSbF_6$ catalyst system to generate intermediate **A**, which then converts to enamine intermediate **B** via intramolecular hydroamination. Attack of enamine **B** by alkynes **2** in the presence of $AuBr_3/AgSbF_6$ generates a propargylamine **C**. Finally, the propargylamine is also activated by gold-/silver-salt catalyst to generate **D**, which undergoes intramolecular hydroarylation to yield the final product **3**.

(6) The byproducts of this reaction were also investigated by treatment of *N*-*p*-tolylpent-4-ynamide (**1A**) with phenylacetylene (**2a**) in toluene in a sealed tube at 120 °C for 4 h, and only intermediate propargylamine **4Aa** was obtained. (see the Supporting Information, Table S1). Characterization data for **4Aa**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.39 (m, 2H), 7.33 (m, 3H), 7.29 (d, J = 8.0 Hz, 2H), 7.23 (d, J = 8.0 Hz, 2H), 2.81 (m, 1H), 2.61 (m, 2H), 2.36 (s, 3H), 2.22 (m, 1H), 1.55 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 174.4, 137.6, 133.6, 131.5, 129.7, 128.5, 128.4, 128.0, 122.4, 90.8, 84.3, 59.8, 36.3, 30.5, 27.8, 21.2; LRMS (EI) m/z 289 (M^+); HRMS (EI) m/z calcd $C_{20}H_{19}NO$ (M^+) 289.1467, found 289.1464.

(7) The amount of $AuBr_3/AgSbF_6$ catalyst was also optimized in this cascade reaction, and these results showed that 3 mol % of $AuBr_3$ and 5 mol % of $AgSbF_6$ is the optimum reaction condition. In addtion, increasing the amount of $AgSbF_6$ can accelerate this transformation. (see the Supporting Information, Table S2).

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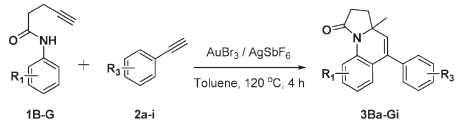
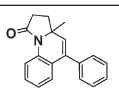
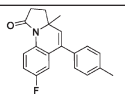
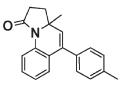
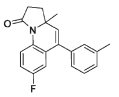
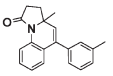
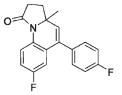
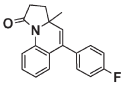
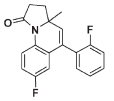
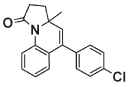
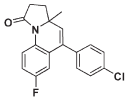
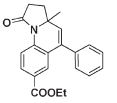
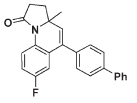
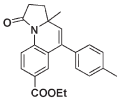
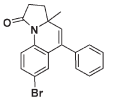
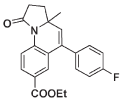
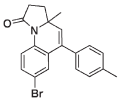
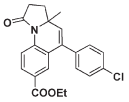
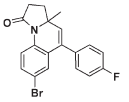
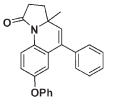
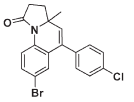
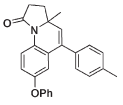
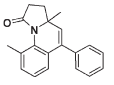
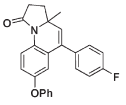
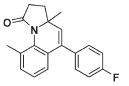
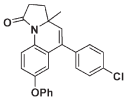
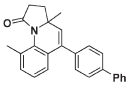
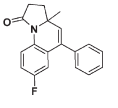
TABLE 3. Tandem Synthesis of a Broad Spectrum of Pyrrolo[1,2-*a*]quinolin-1(2*H*)-ones Catalyzed by $AuBr_3/AgSbF_6$[a]

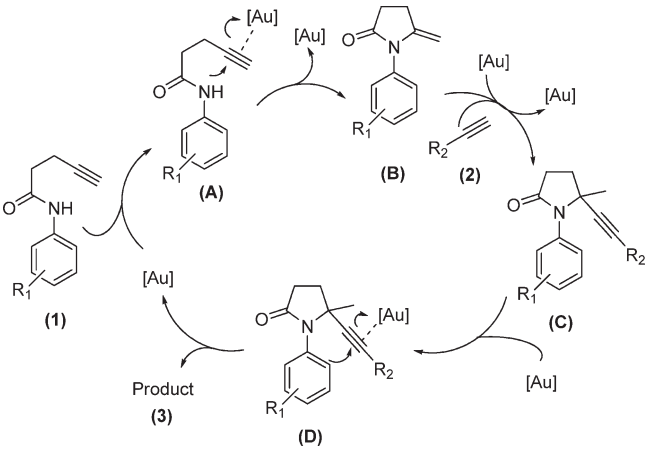


1B-G 2a-i 3Ba-Gi

Entry	Product		Yield (%)	Entry	Product		Yield (%)
1		**3Ba**	70	15		**3Eb**	81
2		**3Bb**	75	16		**3Ec**	75
3		**3Bc**	66	17		**3Ef**	77
4		**3Bf**	59	18		**3Eg**	61
5		**3Bh**	44	19		**3Eh**	58
6		**3Ca**	85	20		**3Ei**	85
7		**3Cb**	90 (84[b])	21		**3Fa**	74
8		**3Cf**	67	22		**3Fb**	77
9		**3Ch**	64	23		**3Ff**	62
10		**3Da**	63	24		**3Fh**	54
11		**3Db**	72	25		**3Ga**	66
12		**3Df**	57	26		**3Gf**	65
13		**3Dh**	57	27		**3Gi**	70
14		**3Ea**	65				

[a] **1** (0.1 mmol), **2** (0.4 mmol), $AuBr_3$ (3 mol %)/$AgSbF_6$ (5 mol %), toluene (2 mL), Ar protection. [b] **1** (0.1 mmol), **2** (0.15 mmol), $AuBr_3$ (3 mol %)/$AgSbF_6$ (5 mol %), toluene (2 mL).

SCHEME 2. A Plausible Mechanism



Conclusion

In summary, we have developed an efficient method for the synthesis of fused heterocyclic building blocks pyrrolo-[1,2-*a*]quinolin-1(2*H*)-ones via a $AuBr_3/AgSbF_6$-catalyzed tandem reaction in good yields and with excellent regio- and chemoselectivities. Significantly, the strategy affords a straightforward and efficient construction of tricyclic lactam molecular architectures in which several carbon−carbon and carbon−nitrogen bonds are formed in a one-pot reaction from simple starting materials. It is our expectation that the biologically interesting compound can be found from the pool of these products. Further investigation of this powerful cascade reaction and its application to our medicinal chemistry program will be reported in the future.

Experimental Section

General Procedure for the Gold-Catalyzed Tandem Reaction for the Synthesis of Pyrrolo[1,2-*a*]quinolin-1(2*H*)-ones (Compound 3Aa, for Example). To a solution of 0.1 mmol of *N*-*p*-tolylpent-4-ynamide and 0.4 mmol of phenylethyne in 2 mL of toluene was added 0.003 mmol of $AuBr_3$ and 0.005 mmol of $AgSbF_6$. The reaction tube was sealed under Ar protection and the mixture was stirred under argon in a sealed tube and at 120 °C for 4 h. After the starting materials were completely consumed, the solvent was removed under reduced pressure, and the residue was purified by a flash column chromatography (petroleum ether/ethyl acetate = 4/1, v/v, as an eluent) to yield the desired product **3Aa** in 81% yield. The characterization data obtained are as follows: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.07 (d, J = 8.1 Hz, 1H), 7.39 (m, 3H), 7.32 (m, 2H), 7.13 (d, J = 8.1 Hz, 1H), 6.87 (s, 1H), 5.82 (s, 1H), 2.64 (m, 1H), 2.50 (m, 1H), 2.23 (s, 3H), 2.20 (m, 2H), 1.29 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.2, 138.8, 135.5, 133.7, 131.8, 130.9, 129.0, 128.9, 128.3, 127.7, 126.8, 126.3, 121.4, 60.6, 32.4, 29.9, 24.0, 21.1; LRMS (EI) m/z 289 (M^+); HRMS (EI) m/z calcd for $C_{20}H_{19}NO$ (M^+) 289.1467, found 289.1466.

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Supporting Information Available: Part of the experimental details, general information, and ^{1}H and ^{13}C NMR spectra for all products. This material is available free of charge via the Internet at http://pubs.acs.org.