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Gold(I)-Catalyzed Hydroaminaloxylation and Petasis–Ferrier Rearrangement Cascade of Aminaloalkynes

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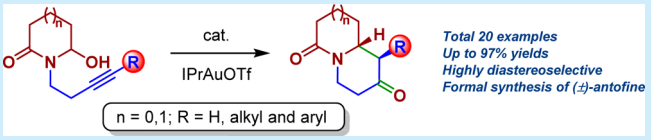
Supporting Information

ABSTRACT: An efficient method has been developed to generate a diverse array of indolizidines and quinolizidines from readily available aminaloalkynes via a gold(I)-catalyzed hydroaminaloxylation and Petasis–Ferrier rearrangement cascade. The method enabled a formal synthesis of (±)-antofine.



The indolizidines and quinolizidines are an important structural motif found in numerous natural products and pharmaceutically important compounds (Figure 1).[1] Accordingly, novel strategies for the stereoselective synthesis of these "izidine"-type alkaloids continue to gain great attention.

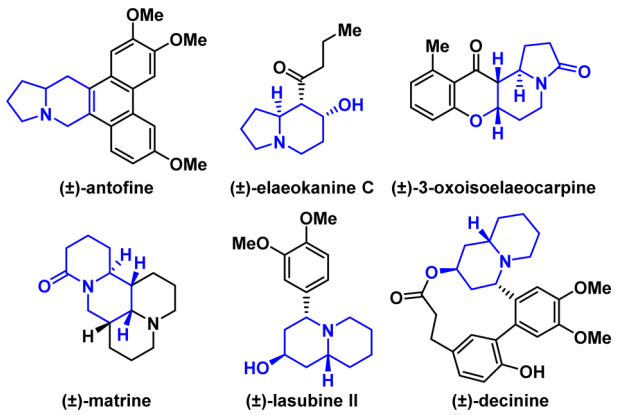
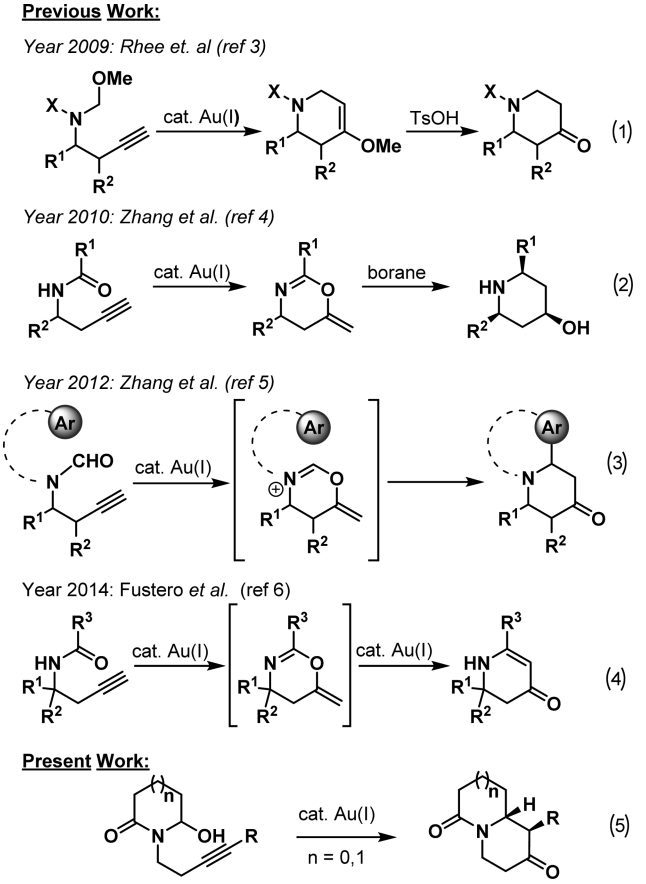


Figure 1. Selected indolizidine and quinolizidine natural products.

During the past decade, gold catalysis has emerged as a powerful tool in the area of organic synthesis.[2] Based on the intrinsic π-activation property of gold catalysts, a great number of novel transformations for the synthesis of heterocyclic cores have appeared in the literature. Recently, gold-catalyzed cascade reactions, involving Petasis–Ferrier cyclization as one of the elementary steps, has emerged as a new area. As far as azaheterocycles are concerned, Rhee and co-workers were the first one to report a gold(I)-catalyzed Petasis–Ferrier type cyclization for the synthesis of piperidine enol ethers which after hydroalysis afforded piperidones (Scheme 1, eq 1).[3] A year later, Zhang and co-workers reported the one-pot synthesis of piperidin-4-ols by sequential gold(I)-catalyzed cyclization, chemoselctive reduction, and spontaneous Petasis–Ferrier rearrangement (Scheme 1, eq 2).[4] Subsequently, the same group successfully developed gold(I)-catalyzed Petasis–Ferrier

Scheme 1. Aza-heterocycles through Gold-Catalyzed Cascade Reactions Involving Petasis–Ferrier Cyclizations



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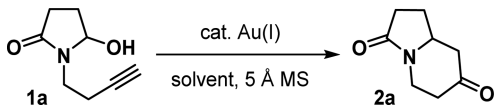
cyclization triggered by amide cyclization for the synthesis of arene-fused hexahydroquinolizinones (Scheme 1, eq 3).[5] Recently, Fustero and Pozo reported a slightly different cyclization cascade of homopropargyl amides for the synthesis of dihydropyridones (Scheme 1, eq 4).[6]

Although a few reports exist on gold-catalyzed cascade reactions involving Petasis–Ferrier cyclization[7] as mentioned above,[3−6] a new approach is necessary because of following reasons: (a) all the reported methods utilize only terminal alkynes; (b) all the methods generate piperidines except the work reported by Zhang and co-workers wherein quinolizidines were accessible (Scheme 1, eq 3). Although the latter report deals with quinolizidine synthesis, the appended aromatic ring was necessary and therefore the method limits it application in the synthesis of natural products. These pitfalls encouraged us to initiate a research project oriented toward the development of a new methodology for the synthesis of indolizidines and quinolizidines that will allow the rapid assembly of both bicyclic scaffolds through a common mechanistic pathway. Our approach is based on the direct utilization of aminaloalkynes as the starting material, and the details of the work are outlined herein.

At the onset of our investigation, we tested our hypothesis using 1-(but-3-yn-1-yl)-5-hydroxypyrrolidin-2-one **1a** as starting material (Table 1). Initially, the planned reaction was performed

Table 1. Optimization of the Reaction Conditions[a]



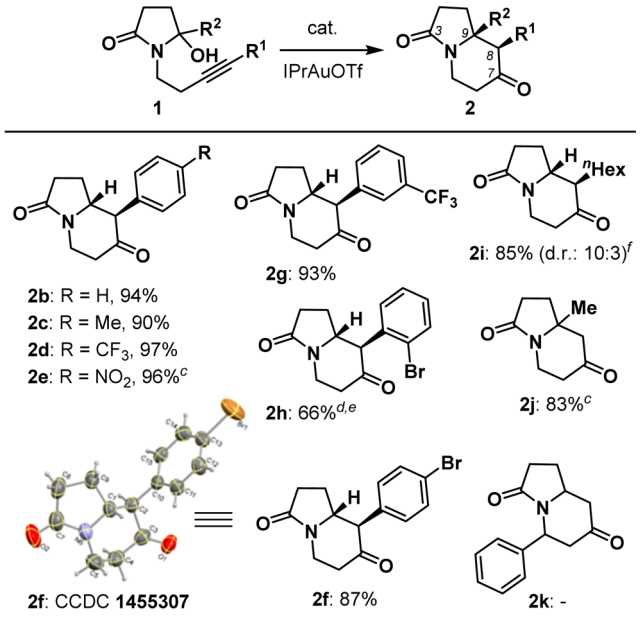
entry	catalyst	solvent	time (h)	yield[b]
1	AuCl	toluene	12	–
2	$Ph_3PAuOTf$	toluene	12	–
3	JohnPhosAuOTf	toluene	12	22
4	IPrAuOTf	toluene	12	80
5	$IPrAuNTf_2$	toluene	12	72
6	IPrAuOTf	1,4-dioxane	12	67
7	IPrAuOTf	THF	12	83
8	IPrAuOTf	CH_3CN	12	trace
9	IPrAuOTf	$CHCl_3$	12	77
10	IPrAuOTf	DCM	12	87
11	IPrAuOTf	DCE	12	93
12[c]	IPrAuOTf	DCE	6	90
13[c,d]	IPrAuOTf	DCE	12	95
14[c,e]	IPrAuOTf	DCE	12	92
15[c,f]	IPrAuOTf	DCE	12	75
16	AgOTf	DCE	12	–
17	–	DCE	12	–

[a]Reaction conditions: 0.2 mmol of **1a**, 10 mol % catalyst, solvent (1 mL), rt, 5 Å MS (45 mg). [b]Isolated yields. [c]Reaction was carried out at 80 °C. [d]5 mol % of catalyst was used. [e]3 mol % of catalyst was used. [f]Reaction performed without 5 Å MS.

in toluene using various gold(I) complexes (10 mol %). Initial screening of AuCl and PPh_3AuOTf catalysts did not lead to the formation of product (entries 1 and 2). However, to our delight, desired product **2a** was obtained in 22% yield with the use of JohnPhosAuOTf as a catalyst (entry 3). When NHC gold complexes such as IPrAuOTf and $IPrAuNTf_2$ were employed, **2a** was obtained in 80% and 72% yields, respectively (entries 4 and 5). Further extensive screening of solvents revealed that DCE is the solvent of choice (entries 6–11). When the temperature of the reaction increased to 80 °C, the reaction was faster and **2a** was obtained 90% yield in just 6 h (entry 12). Next, the effect of catalyst loading on the reaction outcome in terms of yield was studied (entries 13 and 14). At 80 °C, there was no substantial effect on product yield when 5 mol % (95%) and 3 mol % (92%) of catalyst were used. Therefore, we considered the optimal catalyst loading for further study to be 3 mol %. A significant decrease in yield was observed when the reaction was carried out without 5 Å MS (entry 15). It should be noted that substrate **1a** was inert either in the presence of AgOTf or in the absence of a gold catalyst (entries 16 and 17).

With the optimized reaction conditions (Table 1, entry 14) in hand, the scope of the reaction was examined with various aminaloalkynes. As shown in Table 2, the reaction is applicable to

Table 2. Access to Indolizidines[a,b]



[a]Reaction conditions: 0.2 mmol of **1**, 3 mol % IPrAuOTf, DCE (1 mL), 80 °C, 45 mg of 5 Å MS, 12 h. [b]Isolated yields. [c]Reaction time 6 h. [d]5 mol % catalyst was used. [e]Reaction time 24 h. [f]Inseparable mixture of diasteriomers (d.r. determined by ^1H NMR).

a range of aminaloalkynes giving indolizidines in excellent yields. The reaction proceeds smoothly to furnish various 8-arylhexahydroindolizine-3,7-diones, as single diastereomer. For instance, 8-phenylhexahydroindolizine-3,7-dione (**2b**) was obtained in 94% yield. Similarly *para*- and *meta*-substituted 8-arylhexahydroindolizine-3,7-diones (**2c–2g**) were obtained in excellent yields (87–97%). Even in the case of a highly electron-withdrawing group such as $-NO_2$ on the aryl ring (**2e**), the product was isolated in high yield (96%). 8-(*o*-Bromophenyl)hexahydroindolizine-3,7-dione (**2h**) was obtained in 66% yield; however, the reaction required 24 h to complete even when 5 mol % of catalyst was used. In the case of 8-hexylhexahydroindolizine-3,7-dione (**2i**), the product was isolated in 85% yield; however, the diastereoselectivity was found to be poor (d.r. = 10:3).[8] Interestingly, the introduction of a methyl substitution at the hemiaminal carbon increased the rate of reaction and **2j** was isolated in 83% yield. Unfortunately the reaction did not work with α-aryl aminaloalkyne to produce **2k**. The relative stereochemistry of **2f** was established by X-ray crystallographic analysis,[8] and other indolizidines were assigned by analogy.

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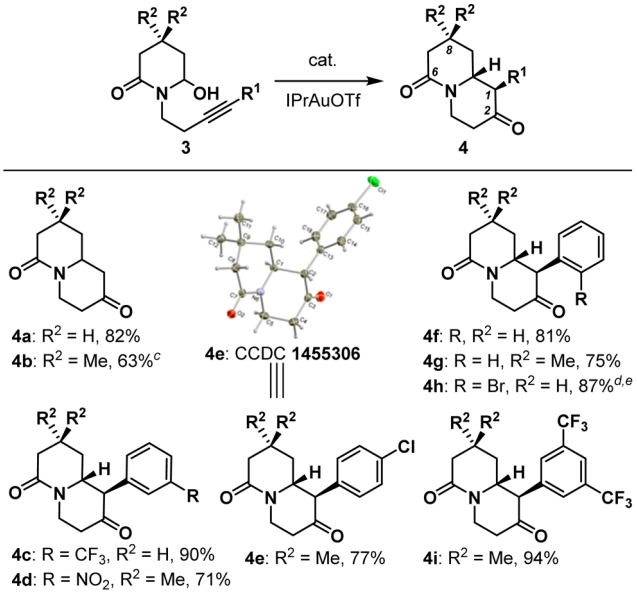
We next examined the scope of the reaction to access quinolizidine scaffolds (Table 3) by treating 1-(but-3-yn-1-yl)-6-

Table 3. Access to Quinolizidines[a,b]

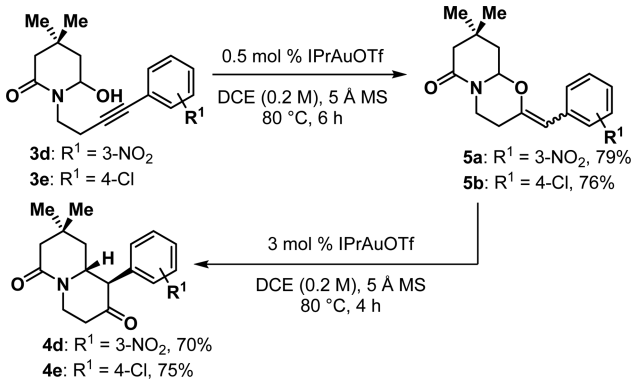


[a]Reaction conditions: 0.2 mmol of **3**, 3 mol % IPrAuOTf, DCE (1 mL), 80 °C, 45 mg 5 Å MS, 8−12 h. [b]Isolated yields. [c]Cyclic enamine **6** was isolated in 33% yield. [d]5 mol % catalyst was used. [e]Reaction time 24 h.

hydroxypiperidin-2-ones under the optimized reaction conditions. As expected, quinolizidine **4a** was obtained in 82% yield. Note that compound **4a** is synthetically important, as it can be transformed into natural products such as Matrine and Leontine.[9] Similarly, **4b** was obtained, albeit, in a slightly lower yield (63%) because in this case cyclic enamine **6** was obtained as a side product in 33% yield (vide infra). Likewise, 1-arylhexahydro-2*H*-quinolizine-2,6(1*H*)-diones (**4c−i**) were obtained in 71−94% yield as a single diastereomer. The relative stereochemistry of **4e** was established by X-ray crystallographic analysis,[8] and that of others were assigned by analogy.

Interestingly, we found that when aminaloalkynes **3d** and **3e** were treated with IPrAuOTf under a very low catalyst loading (0.5 mol %), oxazinanes **5a** and **5b** were isolated in 79% and 76% yields, respectively (Scheme 2). Further treatment of these oxazinanes under standard reaction conditions (IPrAuOTf, 3

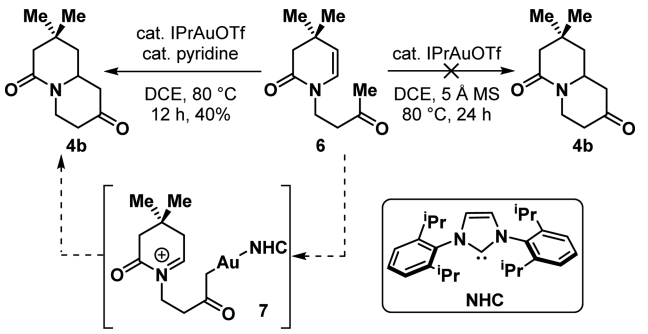
Scheme 2. Control Experiments: Isolation of Oxazinane



mol %) resulted in the gold catalyzed aza-Petasis−Ferrier rearrangement to obtain requisite products **4d** and **4e** in 70% and 75% yields, respectively. This observation clearly indicated that the oxazinanes are the potential intermediate for the reaction. Both the reaction, i.e. oxazinane formation, and its transformation into products are catalyzed by the gold catalysts in a relay manner.[10]

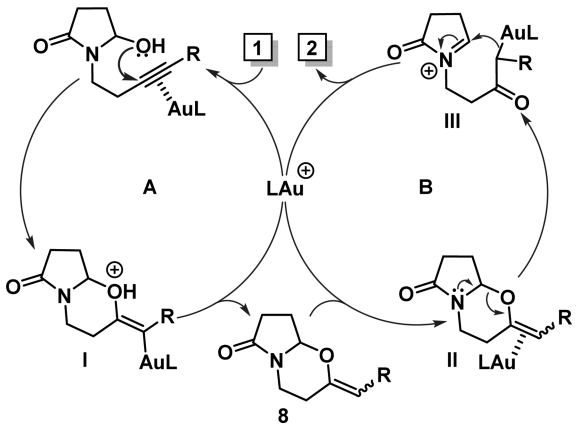
Since in one of the cases (Table 3, **4b**) cyclic enamines **6** was isolated, we were curious to know the intermediacy of **6** as a potential intermediate. Accordingly, when cyclic enamines **6** were subjected to standard reaction conditions, the formation of product **4b** was not observed at all even with heat for 24 h. This observation clearly ruled out the intermediacy of cyclic enamines. However, when **6** was subjected to gold-catalyzed reactions using a catalytic amount of pyridine, the reaction proceeded and product **4b** was isolated in 40% yield (Scheme 3). This results account for the involvement of gold−acetonyl complex **7**[11] as an intermediate.

Scheme 3. Control Experiments: Proof for Intermediacy of Gold−Acetonyl Complex



Based on these observations and previous reports for gold-mediated Petasis−Ferrier rearrangement, the mechanism has been proposed as outlined in Scheme 4. In catalytic cycle A, the

Scheme 4. A Plausible Reaction Mechanism



intramolecular hydroalkoxylation of aminaloalkynes would occur to generate oxazinanes (**8**) via protodeauration of transient intermediate **I**. The isolable intermediate **8** would then undergo Petasis−Ferrier rearrangement[12] via π-intermediate[13] **II** and gold−acetonyl complexes[11] **III** to form products with the regeneration of the gold catalyst.

Next, the utility of the reaction was demonstrated in the formal synthesis of (±)-antofine (Scheme 5). The requisite precursor, 2-

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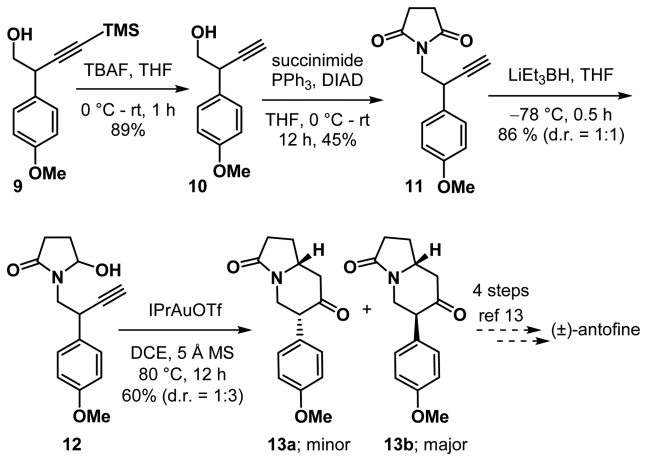
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 5. Formal Synthesis of (±)-Antofine



(4-methoxyphenyl)-4-(trimethylsilyl)but-3-yn-1-ol (**9**), was synthesized readily in two steps from *p*-anisaldehyde.[14] The deprotection of the −TMS group with TBAF in THF (cf. **10**) followed by Mitsunobu reaction with succinimide led to the formation of imide **11**. The selective reduction of imide **11** was then performed with $LiEt_3BH$ at −78 °C to afford aminaloalkyne **12** as 1:1 mixture of diastereomers. When aminaloalkyne **12** was treated with IPrAuOTf under standard conditions, the hydroaminaloxylation and Petasis−Ferrier rearrangement cascade proceeded smoothly to give appropriately substituted indolizidines **13a** (*anti*) and **13b** (*syn*) as a diastereomeric mixture (**13a**:**13b** = 1:3). Since the conversion of **13b** into antofine is known,[15] this work represents the formal synthesis of this structurally intriguing molecule.

In summary, we have developed a new approach for the synthesis of indolizidines and quinolizidines from aminaloalkynes via a gold(I)-catalyzed hydroaminaloxylation and Petasis−Ferrier rearrangement cascade. The functionality embedded in these structures would enable their facile elaboration into more complex structures of biological relevance. For instance, the application of this methodology in the formal synthesis of (±)-antofine has been described. Studies addressing the enantioselective version with merged gold/chiral Brønsted acid catalysis are currently under investigation.[16]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00585.

All experimental procedure, analytical data, and copies of ^1H, ^{13}C NMR spectra for all newly synthesized products (PDF)

X-ray data for **2f** (CIF)

X-ray data for **4e** (CIF)

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Notes

The authors declare no competing financial interest.

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