Gold-catalyzed synthesis of nitrogen-containing heterocycles from ε-*N*-protected propargylic esters†

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Received 4th March 2010, Accepted 14th April 2010
First published as an Advance Article on the web 27th April 2010
DOI: 10.1039/c003734f

A mild and efficient gold-catalyzed tandem cyclization to piperidinyl enol esters has been developed with facilely available ε-*N*-Boc-protected propargylic esters.

Nitrogen-containing heterocycles are extensively distributed in nature with various biological activities.[1] Specifically, α-piperidinyl ketone is a ubiquitous structure motif in natural alkaloids (Fig. 1). A variety of synthetic strategies have been advanced to achieve this substructure, including intra-molecular S_N2 aza-cyclization,[2] intramolecular aza-Michael addition,[3] dearomatization of pyridine[4] and nucleophilic addition of cyclic *N*-acyliminium ions[5] *etc.* However, there is continuous demanding for developing new processes to produce such functionalized azacycles.

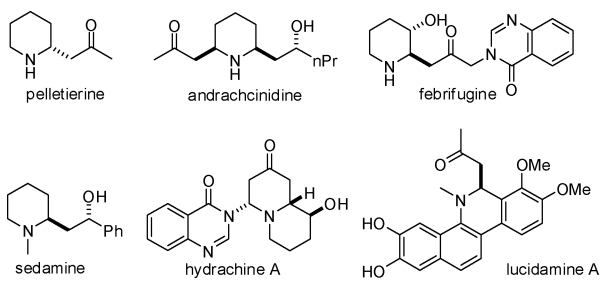
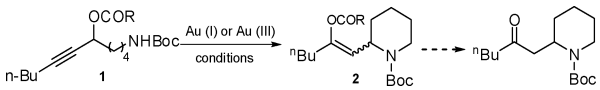


Fig. 1 Structures of selected natural alkaloids.

Gold-catalyzed reactions of alkynes have drawn much attention from the synthetic community in recent years, mainly rooting from the interesting π acid property of gold catalysts and the resultant formidable molecular diversity.[6] Although gold-catalyzed carbon–nitrogen bond formation has been broadly investigated,[7] few examples were reported on piperidine cyclization. Recently, gold-catalyzed tandem reactions of alkynyl amines were elegantly explored as effective protocols to achieve α-piperidinyl ketone structure motifs, *via* a facile enone-forming and intramolecular aza-Michael sequence,[8] an effective formal [4+2] synthesis,[9] or a formal alkyne aza-Prins cyclization.[10] So new catalysts leading to piperidine formation, which are active in a mild reaction atmosphere, are still worth searching for, especially for synthetically significant internal alkynes. We envisioned that piperidinyl enol ester, a variation of α-piperidinyl ketone, could be achieved *via* tandem [3,3]-rearrangement/allene hydroamination from ε-*N*-protected propargylic ester (Scheme 1), in an extension of our interest in gold-catalyzed synthesis.[11] Herein we would like to present our results on this project.



Scheme 1 Gold-catalyzed synthesis of α-piperidinyl enol ester.

With compound **1a** as the test substrate, different catalysts were investigated to evaluate their activity of catalyzing the desired tandem rearrangement/azacycle formation (Table 1). Simple gold salts, both AuCl and $AuCl_3$, prompted this transformation smoothly in moderate yield (entries 1–2). Although $AuCl(PPh_3)$ or AgOTf did not show any catalytic activity respectively, the combined use of these two noble metal salts afforded the desired product in 76% yield (entries 3–5). A comparable yield was obtained with AuCl/AgOTf (1 : 1), but in a greater reaction rate (120 min *vs.* 60 min; entry 5 *vs.* entry 6), which was exceeded by $AuCl_3$/AgOTf combination achieving a rather better yield in shorter time (entry 7).[12] The data indicated that polar solvents should be favorable for this catalytic transformation (entries 7–12). Interestingly, the catalytic systems including gold(III) chloride, combined with other silver salts than AgOTf, did not provide

Table 1 Optimization of reaction conditions toward α-piperidinyl enol ester[a]

Entry	*R*	Catalyst[b]	Solvent	Time/min	Yield (%)[c]
1	Me(**1a**)	AuCl	MeCN	120	69
2	Me(**1a**)	$AuCl_3$	MeCN	120	62
3	Me(**1a**)	$AuCl(PPh_3)$	MeCN	60	\[d]
4	Me(**1a**)	AgOTf	MeCN	60	\[d]
5	Me(**1a**)	$AuCl(PPh_3)$/AgOTf	MeCN	120	76
6	Me(**1a**)	AuCl/AgOTf	MeCN	60	78
7	**Me(1a)**	$AuCl_3$AgOTf	**MeCN**	**45**	**84**
8	Me(**1a**)	$AuCl_3$AgOTf	DCM	120	trace
9	Me(**1a**)	$AuCl_3$/AgOTf	PhMe	120	\[d]
10	Me(**1a**)	$AuCl_3$/AgOTf	THF	120	trace
11	Me(**1a**)	$AuCl_3$/AgOTf	Et_2O	120	trace
12	Me(**1a**)	$AuCl_3$/AgOTf	$MeNO_2$	120	67
13	Me(**1a**)	$AuCl_3$/$AgBF_4$	MeCN	80	83
14	Me(**1a**)	$AuCl_3$/$AgSbF_6$	MeCN	120	62
15	OEt(**1b**)	$AuCl_3$/AgOTf	MeCN	60	72
16	^{t}Bu(**1c**)	$AuCl_3$/AgOTf	MeCN	45	83
17	**Ph(1d)**	**$AuCl_3$/AgOTf**	**MeCN**	**30**	**92**

[a] All reactions were carried out at room temperature. [b] 5 mol% of catalyst loading was used for all entries. As for Au/Ag combined catalyst, $Au^I/Ag^I = 1/1$ or $Au^{III}/Ag^I = 1/3$. [c] Isolated yield. The *Z*/*E* ratios range from 1/1 to 2/3. [d] No desired product could be detected.

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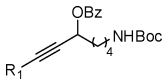
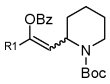
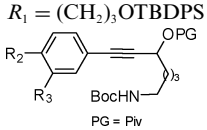
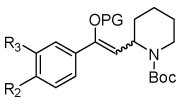
† Electronic supplementary information (ESI) available: Experimental details and characterization data for the new compounds. See DOI: 10.1039/c003734f

Table 2 Gold-catalyzed cyclization of ε-*N*-Boc-protected propargylic esters to afford piperidinyl enol esters[a]

Entry	Substrate	Time/min	Product; Yield/%[b] ($Z:E$)[c]
			
1	**1d**; R_1 = ^{n}Bu	30	**2d**; 92 (2 : 3)
2	**3a**; R_1 = isopentyl	30	**4a**; 83 (2 : 3)
3	**3b**; $R_1 = (CH_2)_3Ph$	30	**4b**; 85 (2 : 3)
4	**3d**; $R_1 = (CH_2)_3OBz$	60	**4d**; 55 (3 : 7)[d]
5	**3e**; $R_1 = (CH_2)_3OTBDPS$	60	**4e**; 81 (2 : 3)
			
6	**3f**; [e]R_2 = H, R_3 = H	60	**4f**; 50 (1 : 1)
7	**3g**; [e]R_2 = Ph, R_3 = H	60	**4g**; 53 (1 : 1)
8	**3h**; R_2 = Me, R_3 = H	60	**4h**; 64 (1 : 2)
9	**3i**; R_2 = Me, R_3 = Me	60	**4i**; 75 (1 : 2)
10	**3j**; R_2 = OMe, R_3 = H	60	**4j**; 61 (3 : 2)
11	**3k**; R_2 = OTBDPS, R_3 = H	60	**4k**; 65 (1 : 1)
12	**3l**; R_2 = CO_2Et, R_3 = H	60	**4l**; trace

[a] All reactions were carried out at 0.2 mmol scale in acetonitrile (2 ml) with $AuCl_3$ (5 mol%) and AgOTf (15 mol%) as the combined catalyst at room temperature. [b] Isolated yield. [c] The Z/E ratios were determined by ^{1}H NMR spectra. [d] The Z/E ratio is based on the isolated yields of two isomers. [e] PG = Bz.

superior results (entries 13–14). Taking the efficiency and the expense into account, we selected $AuCl_3$/AgOTf as the preferred catalyst combination. Other propargylic esters were also tested to acquire the optimal reaction result. To our delight, the benzoate **1d**, as an excellent substrate, affords the top yield, while the pivaloate **1c** behaves as well as the acetate **1a** (entries 15–17).[13]

To explore the scope of this catalytic tandem transformation, a variety of propargylic esters were surveyed in the optimized conditions (Table 2). Acyclic aliphatic alkynes were firstly examined and internal alkynes (**1d**, **3a** and **3b**), are found to be suitable substrates in satisfactory yields (entries 1–3).[14] A distal TBDPS ether in compound **3e** was found to be compatible with the catalyst very well, while the benzoate at γ position of the triple bond in **3d** seemingly affects the reaction efficiency unfavorably (entries 4 and 5). Aromatic alkynes were also tested to be appropriate substrates. Compounds **3f** and **3g** produce comparable yields, indicating that a phenyl substitution at *para* position has minute influence (entries 6 and 7).[15] However, the pivaloates **3h–3k**, with electron-donating groups, such as alkyl, methoxyl and TBDPS ether at the *para* position of the benzene ring, show better reactivity than compound **3l** with electron-withdrawing group (entries 7–13).

Based on the yields and stereoselectivities listed above, we speculate a mechanism as illustrated in Fig. 2. At first, the gold catalyst acts as a π-acid to activate the triple bond in substrates and then initiates an intramolecular rearrangement to afford intermediates **II** and **III**, which coexist in a fast equilibrium.[16,17] Secondly, the corresponding reactive sites in intermediates **II** and **III** are captured by Boc-protected nitrogen atom, providing intermediate *E*-**IV** and *E*/*Z*-**V** respectively *via path a* and *path b*.[18] The following protonation of carbon–gold bond converts these

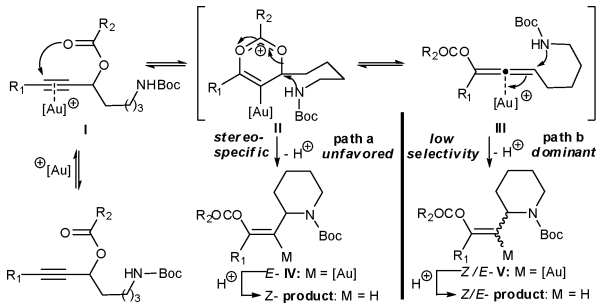
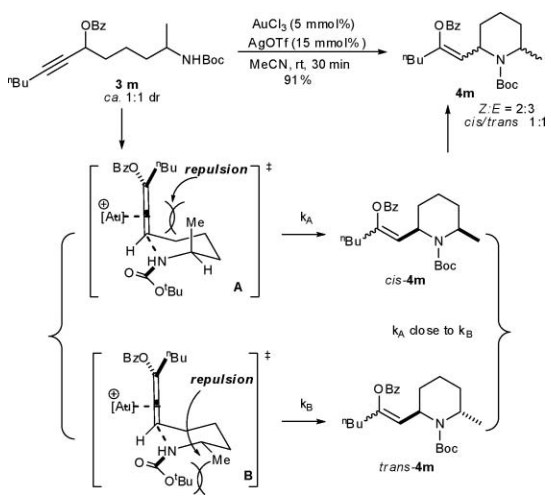


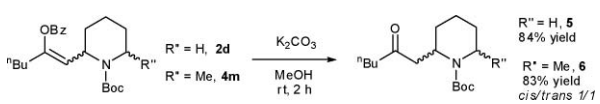
Fig. 2 Tentative mechanism for gold-catalyzed piperidine ring cyclization.

intermediates to the final *E*- or *E*/*Z*- products. Indeed, in view of the weak nucleophilicity of carbamate, it seems reasonable that the direct S_N2 attack by Boc-protected nitrogen through *path a*, affording *E*-IV stereospecifically, should not be dominant. Thus the cyclization through gold-activated allenyl ester **III** might be considered as the preferred pathway, albeit without a favored stereochemical bias, which is consistent with the data in Table 2.

Furthermore, 2° amine **3m** exhibits excellent reactivity as well in 91% yield, though without any diastereoselectivity. We suspect that it might be the imperceptible energy difference between the two respective transition states (**A** & **B**) that accounts for the insignificant selectivity ($k_A \approx k_B$, Scheme 2).[19] To elucidate the applicability of our methodology, the facile conversion of piperidinyl enol esters to piperidinyl ketones was confirmed by transforming compounds **2d** and **4m** to the corresponding ketones **5** and **6** smoothly using potassium carbonate in methanol (Scheme 3).



Scheme 2 Transition states to compound **4m**.



Scheme 3 Conversion to piperidinyl ketone.

In summary, we have developed an efficient method achieving piperidinyl enol esters and piperidinyl ketones in mild reaction conditions. Compared to intermolecular catalyzed propargylic substitution[20] and nucleophilic addition to propargyl

carboxylates,[21] this intramolecular piperidine cyclization methodology shows different reactivity and different substrate applicability. The tandem cyclization is potentially useful and its application in total synthesis of natural product is under way in our laboratory.

Acknowledgements

We appreciate the financial support from the National Natural Science Foundation of China (20702032, 20872098), the Ministry of Education of China (NCET-08-0365), and National Basic Research Program of China (973 Program, 2010CB833200). We also thank Analytical & Testing Center of Sichuan University for NMR recording and State Key Laboratory of Biotherapy for HRMS determination.

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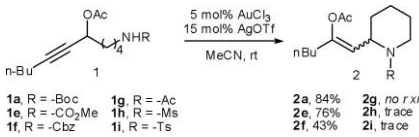
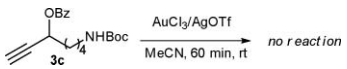
13 It is interesting to note that different substituents on nitrogen, ranging from Boc to Ac, Ms, Ts, Cbz and methyl carbamate, appear to have different influence on the reaction, but *N*-Boc-protected substrate behaves best. For the detail, please see the following scheme.



14 No reaction occurs with terminal alkyne **3c** in the standard condition within an hour. Prolonged reaction time or heating the reaction mixture makes no improvement.



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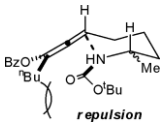

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