Synthetic Methods

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Gold-Catalyzed 1,2-Acyloxy Migration/Intramolecular [3+2] 1,3-Dipolar Cycloaddtion Cascade Reaction: An Efficient Strategy for Syntheses of Medium-Sized-Ring Ethers and Amines**

*Changgui Zhao, Xingang Xie, Shuangshuang Duan, Huilin Li, Ran Fang, and Xuegong She**

Abstract: *A highly efficient strategy for the formation of medium-sized-ring ethers and amines based on a gold-catalyzed cascade reaction, involving enynyl ester isomerization and intramolecular [3+2] cyclization, has been developed. Various multisubstituted medium-sized-ring unsaturated ethers and amines were obtained through this transformation. This method represents one of the relatively few transition metal catalyzed intramolecular cycloaddition reactions for medium-sized ring synthesis.*

Medium-sized rings (eight to ten membered) are prevalent as core motifs in a large number of biologically active natural products or pharmaceutically important compounds.[1] Among them, eight- and nine-membered unsaturated medium-sized-ring ethers and amines are significant structural units which exist in numerous natural products such as otonecine,[2] metabolites of marine red algae of the genus *Laurencia*[3] and many *Lycopodium* alkaloids[4] (Figure 1). However, efficient syntheses of these medium-sized-ring compounds remain a challenge because of entropic factors and transannular interactions.[5,6] To date, there are only a relatively small number of methods for preparing unsaturated medium-sized-ring ether and amines,[7] and ring-closing metathesis (RCM) is the most versatile and efficient method.[8,9] Thus, the development of a new strategy for efficient construction of medium-sized-ring ethers and amines is still in great demand.

In recent years, gold- and platinum-catalyzed, as well as related π-acidic transition-metal-catalyzed cycloadditions and cycloisomerization reactions have witnessed intense developments because of atom economy and the ability to increase molecular complexity in one chemical step.[10,11] In 2010, our group reported a $PtCl_2$-catalyzed 1,2-acyloxy migration/intramolecular [3+2] 1,3-dipolar cycloaddition cascade reaction for preparing a series of useful hexahydropyrans.[12] The reaction was subsequently expanded to its nitrogen series using $AuPPh_3Cl/AgSbF_6$ as catalysts.[13] In 2011, the group of Wang successfully expanded this transformation to propargylic acetate tethered cyclohexadienones for construction of cyclohexenones and dihydrofuran-fused cyclohexenones.[14] However, both methods are restricted to the synthesis of five- to seven-membered rings. Given this background, we wondered whether such a cycloaddition procedure could be extended to 1,10- and 1,11-enynyl esters and thus serve as a powerful and efficient method for the construction of medium-sized rings (Scheme 1). Herein, we show the power

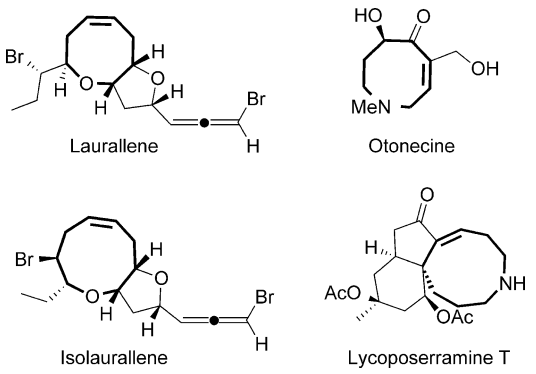
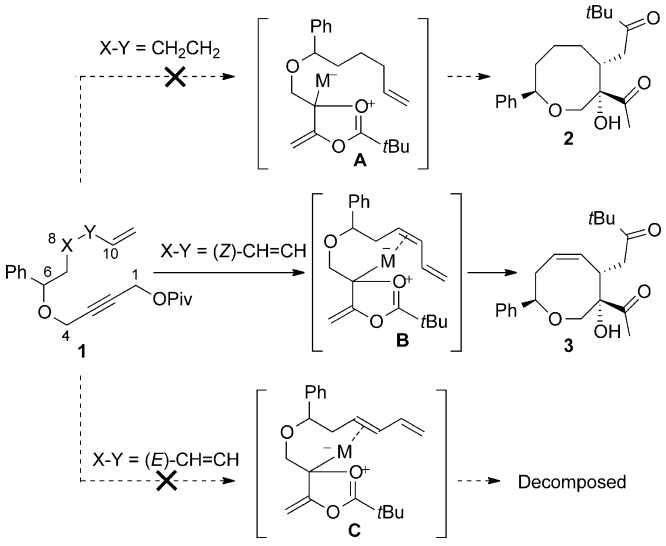


Figure 1. Natural products containing a medium-sized-ring ether or amine.



Scheme 1. Strategy for the synthesis of medium-sized rings. Piv = pivaloyl.

[*] C. Zhao, Dr. X. Xie, S. Duan, H. Li, Dr. R. Fang, Prof. Dr. X. She
State Key Laboratory of Applied Organic Chemistry
College of Chemistry and Chemical Engineering
Lanzhou University, Lanzhou, Gansu, 730000 (P. R. China)
E-mail: shexg@lzu.edu.cn
Prof. Dr. X. She
State Key Laboratory for Oxo Synthesis and Selective Oxidation
Lanzhou Institute of Chemical Physics, Chinese Academy of Sciences, Lanzhou, Gansu, 730000 (P. R. China)

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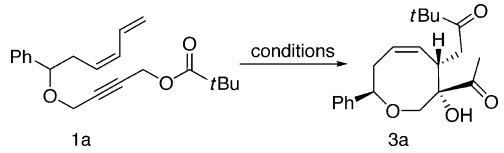
of the gold-catalyzed 1,2-acyloxy migration/intramolecular [3+2] cycloaddtion reaction, which provides access to various functionalized unsaturated medium-sized-ring ethers and amines.

Initially, the enynyl ester **1** was selected to investigate this transformation (Scheme 1). However, various attempts to achieve this cyclization reaction failed. We thought the 1,3-dipolar synthon could not approach the terminal olefin in intermediate **A**. To solve this problem, we envisaged the *Z*-conjugated diene to be suitable for this reaction, since the complexation properties of a transition metal with the *Z*-olefinic bond should place the 1,3-dipolar synthon and the terminal olefin in close proximity to each other (**B**).[15] In contrast, we anticipated that the *E*-olefinic bond would not undergo reaction since the 1,3-dipolar synthon could not approach the terminal olefin (**C**).[16] However, two critical issues must be considered: a) Gold- and platinum-catalyzed intramolecular cycloaddition and cycloisomerization reactions mainly involve the formation of five- to seven-membered-ring systems, and cyclization strategies to make medium-sized rings are often challenging;[17] b) regioselectivity of the two olefinic bonds and competition between [3+2] and [4+3] cycloaddition reactions.

With this consideration in mind, we began to test our designed system for the synthesis of medium-sized rings using the *Z*-diene **1a**. The reaction was run in toluene with 10 mol% $PtCl_2$ at room temperature under an atmosphere of CO (1 atm) for 24 hours; however, no reaction was observed (Table 1, entry 1). Then after heating this reaction at 60 °C for 2 hours, **3a** was observed in 10% yield (entry 2). Increasing the reaction temperature to 80 °C did not improve the yield, but only resulted in decomposition of the starting material (entry 3). Pleasingly, when $PPh_3AuCl/AgSbF_6$ (5 mol%/5 mol%) in CH_2Cl_2 was employed under mild reaction conditions, **3a** was isolated in 73% yield (entry 4). Further study of the influence of different reaction media showed that $ClCH_2CH_2Cl$ was a less effective solvent (entry 4 versus entry 5). Replacing $AgSbF_6$ with AgOTf did not deliver the desired product (entry 6). Among the various gold catalysts, PPh_3AuCl turned out to be the most effective one (entries 4–8). Remarkably, this cycloaddition reaction occurred selectively with the terminal olefin, and we did not observe the cycloaddition product from either the internal *Z*-olefinic bond or the [4+3] cycloaddition. The configuration of the olefinic bond has an influence on this transformation, that is, the *E*-olefinic bond did not undergo this reaction and only resulted in decomposition of the starting material (entry 9).

With the optimized reaction conditions in hand, we set out to define the scope of this cascade protocol (Table 2). It was found that this cascade reaction has a wide substrate scope, where the C6-position can possess various substitution patterns. Both aryl- and alkyl-substituted (e.g., Cy, *i*Pr,

Table 1: Optimization of reaction conditions.

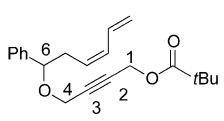
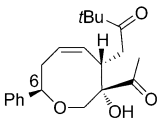
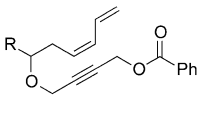
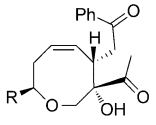
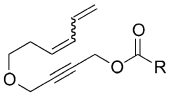
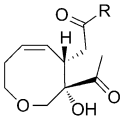
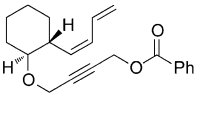
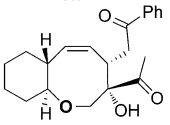
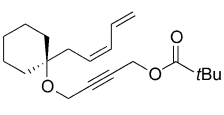
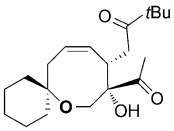


1a 3a

Entry	Catalyst	Solvent	*T* [°C]	*t* [h]	Yield [%][a]
1	$PtCl_2$/CO (10 mol%/1 atm)	toluene	0	24	n.r.
2	$PtCl_2$/CO (10 mol%/1 atm)	toluene	60	2	10
3	$PtCl_2$/CO (10 mol%/1 atm)	toluene	80	24	trace
4	**$PPh_3AuCl/AgSbF_6$ (5 mol%/5 mol%)**	**CH_2Cl_2**	**RT**	**2**	**73**
5	$PPh_3AuCl/AgSbF_6$ (5 mol%/5 mol%)	DCE	RT	2	60
6	PPh_3AuCl/AgOTf (5 mol%/5 mol%)	CH_2Cl_2	RT	12	n.r.
7	AuCl (5 mol%)	CH_2Cl_2	RT	6	8
8	$AuCl_3$ (5 mol%)	CH_2Cl_2	RT	6	trace
9	*E* olefin $PPh_3AuCl/AgSbF_6$ (5 mol%/5 mol%)	CH_2Cl_2	RT	6	complex

[a] Yields of isolated products. DCE = 1,2-dichloroethane, n.r. = no reaction.

Table 2: Gold-catalyzed 1,2-acyloxy migration/intramolecular [3+2] cycloaddition cascade reaction for construction of medium-sized unsaturated ring ethers.[a]

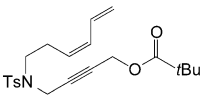
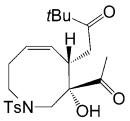
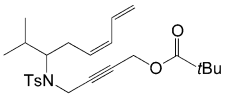
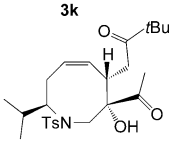
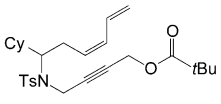
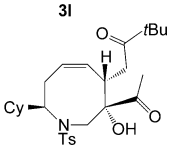
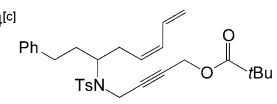
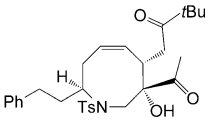
Entry	Substrate	Product	Yield [%][b]
1	 **1a** (6*S*)-**1a** (98% *ee*)	 **3a** (6*S*)-**3a** (98% *ee*)	73
2[c]	 **1b** R = Cy	 **3b**	70
3[c]	**1c** R = *i*Pr	**3c**	72
4[c]	**1d** R = diethyl	**3d**	61
5[c]	**1e** R = *t*Bu	**3e**	83
6	 *Z*/*E* = 1:1 **1f** R = Me	 **3f**	35
7	**1g** R = Ph	**3g**	38
8	**1h** R = *t*Bu	**3h**	45
9[c,d]	 **1i**	 **3i** (X-ray)	81
10[c]	 **1j**	 **3j**	80

[a] Reaction conditions: enynyl ester (0.1 M in CH_2Cl_2), 5 mol% $AuPPh_3Cl$, 5 mol% $AgSbF_6$, RT, 3 h. [b] Yields of isolated products. [c] Reaction time of 6 h. [d] Relative configuration.

diethyl, *t*Bu) substrates were suitable for this reaction (Table 2, entries 2–5). Nonsubstituted substrates which were a mixture of isomers ($Z/E = 1{:}1$) were also tolerated, and the ester group could be varied from proargylic acetate to benzoate and pivaloate (entries 6–8). Notably, the *E*-olefinic substrates decomposed completely under these reaction conditions. Both fused- and spiro-bicyclic skeletons were efficiently made by this method, when using the enynyl esters **1i** and **1j**, in satisfactory yield (entries 9 and 10). The relative configuration of the substituents in the medium-sized-ring was consistent with our previous observations (see X-ray data and NOESY experiments). We also prepared the optically active substrate **1a** (98% *ee*) which gave the expected product **3a** (98% *ee*) with excellent chirality transfer under the above reaction conditions (entry 1).

To further demonstrate the utility of this remarkable reaction, we examined a series of nitrogen-containing substrates. To our delight, the reaction worked well and smoothly afforded multisubstituted medium-sized-ring unsaturated amines in moderate yield (Table 3). The relative configuration of the three substituents was established by NOESY experiments (see the Supporting Information for details).

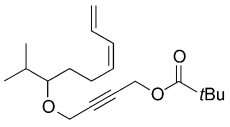
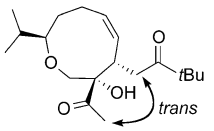
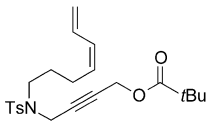
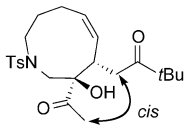
Table 3: Gold-catalyzed 1,2-acyloxy migration/intramolecular [3+2] cycloaddition cascade reaction for construction of unsaturated medium-sized-ring amines.

Entry	Substrate	Product	Yield [%][b]
1[c]	 **1k**	 **3k**	61
2[c]	 **1l**	 **3l**	73
3[c]	 **1m**	 **3m**	74
4[c]	 **1n**	 **3n**	67

[a] Reaction conditions: enynyl ester (0.1 M in CH_2Cl_2), 5 mol% $AuPPh_3Cl$, 5 mol% $AgSbF_6$, RT, 6 h. [b] Yields of isolated products. [c] Relative configuration. Ts = 4-toluenesulfonyl.

Moreover, the reaction could also be extended to the preparation of nine-membered-ring compounds. As shown in Table 4, starting from the enynyl esters **1o** and **1p**, the expected nine-membered unsaturated cyclic ether **3o** (60%) and amine **3p** (57%), respectively, were formed (entries 1 and 2). The stereochemical assignment of **3o** was established by NOESY experiments and the structure of **3p** was assigned by X-ray analysis (see the Supporting Information for details).

Table 4: Gold-catalyzed 1,2-acyloxy migration/intramolecular [3+2] cycloaddition cascade reaction for the construction of nine-membered rings.

Entry	Substrate	Product	Yield [%][b]
1	 **1o**	 **3o**	60
2	 **1p**	 **3p** (X-ray)	57

[a] Reaction conditions: enynyl ester (0.1 M in CH_2Cl_2), 5 mol% $AuPPh_3Cl$, 5 mol% $AgSbF_6$, RT, 6 h. [b] Yields of isolated products.

However, it should be mentioned that the two ketone-bearing moieties of **3p** were *cis*, which was different from the other examples. The different diastereoselectivity could be explained by the two possible transition states depicted in Figure 2. DFT calculations suggest that the activation free energy for **TS1** and **TS2** are 15.5 and 18.1 kcal mol^{-1}, respectively. This result implies that the *cis* product will be generated exclusively and is in good agreement with our experimental results (see the Supporting Information for details).

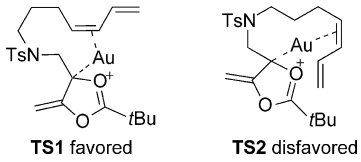
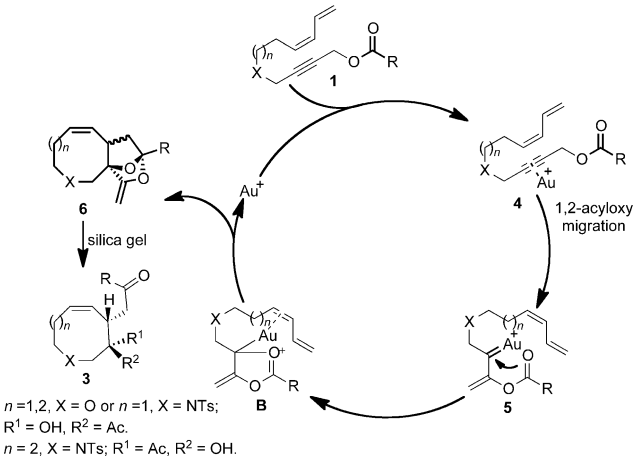


Figure 2. Transition states for the reaction.

To account for these observations, a mechanistic manifold is proposed in Scheme 2. Gold(I) activation of the triple bond in **1** promotes the formation of the gold carbene intermediate **5** through a 1,2-acyloxy migration. A nucleophilic attack of the carbonyl results in the formation of the 1,3-dipolar intermediate **B**, which undergoes a [3+2] cycloaddition to afford the enol ketal **6** and regenerates the catalyst. Finally, hydrolysis of **6** on silica gel provides the desired product **3**.

In conclusion, we have developed a highly efficient procedure for the formation of medium-sized-ring ethers and amines by a gold-catalyzed cascade reaction involving enynyl ester isomerization/intramolecular [3+2] cyclization. We have successfully demonstrated the power of the gold-catalyzed cycloaddition reaction for the preparation of various functionalized medium-sized rings. The method represents one of the few transition-metal-catalyzed intramolecular cycloaddition reactions for the synthesis of medium-sized rings. We believe that this transformation will provide new insights into gold- and platinum-catalyzed intramolecular cycloaddtion reactions. Further studies that



Scheme 2. Plausible mechanism.

take advantage of this tandem protocol to address the synthesis of laurallene, isolaurallene, and some of the fawcettimine-type *Lycopodium* alkaloids are ongoing.

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Keywords: cycloaddition · gold · heterocycles · medium-ring compounds · synthetic methods

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