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Au-Catalyzed Piperidine Synthesis via Tandem Acyloxy Migration/Intramolecular [3 + 2] Cycloaddition of Enynyl Esters

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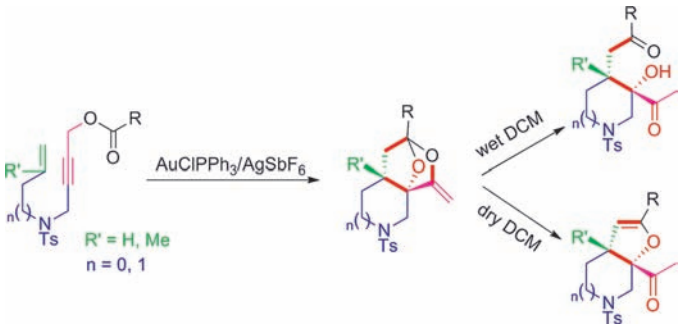
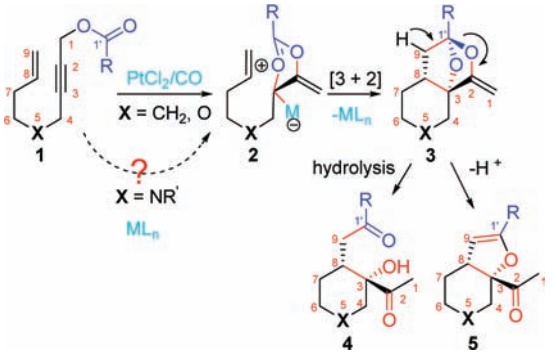
ABSTRACT



An Au-catalyzed tandem protocol involving enynyl ester isomerization and subsequent intramolecular [3 + 2] cyclization has been developed. This strategy provides an efficient approach for the synthesis of polyfunctional piperidines, which are subunits of many bioactive molecules.

The importance of nitrogen heterocycles, especially piperidine and pyrrolidine types, as subunits of bioactive molecules stimulates the development of new synthetic methods.[1] Our recent success in a $PtCl_2$-catalyzed [3 + 2] cycloaddition of enynyl esters[2] led us to wonder whether such a transformation procedure could be applied to nitrogen-containing substrates to further extend the utility of this method, as outlined in Scheme 1.

Scheme 1. $PtCl_2$-Catalyzed [3 + 2] Cycloaddition of Enynyl Esters



In our previous work, harsh conditions (high temperature and an atmosphere of CO[3]) were necessary for such

(1) Trost, B. M.; Pinkerton, A. B.; Kremzow, D. *J. Am. Chem. Soc.* **2000**, *122*, 12007. See also: *The Alkaloids: Chemistry and Biology*; Codell, G. A., Ed.; Academic Press: San Diego, CA, 2000; Vol. 54 and others in this series.

(2) Zheng, H.; Zheng, J.; Yu, B.; Chen, Q.; Wang, X.; He, Y.; Yang, Z.; She, X. *J. Am. Chem. Soc.* **2010**, *132*, 1788. Most recently, a new type of reaction involving [3 + 2] cycloaddition/hydrolytic Michael addition/retro-Aldol reaction of propargylic esters has been reported:Cai, S.; Liu, Z.; Zhang, W.; Zhao, X.; Wang, Z. *Angew. Chem., Int. Ed.* **2011**, *50*, 1.

(3) (a) Lutton, J. M.; Parry, R. W. *J. Am. Chem. Soc.* **1954**, *76*, 4271. (b) Fürstner, A.; Davies, P. W.; Gress, T. *J. Am. Chem. Soc.* **2005**, *127*, 8244.

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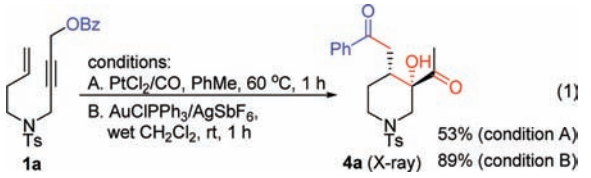
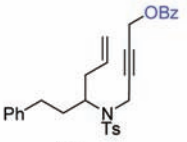
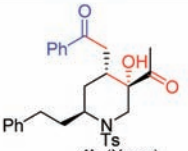
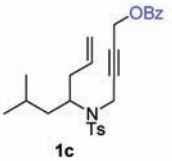
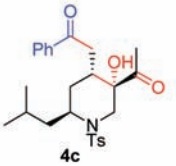
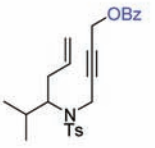
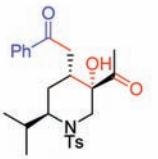
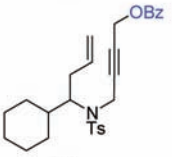
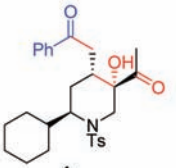
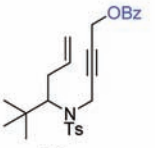
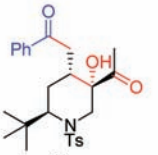
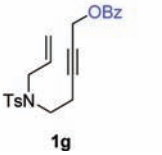
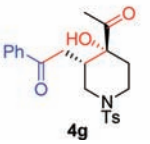
transformations. Therefore, the balance between the stability and the reactivity of nitrogen-tethered substrates needs to be adjusted. In addition, the activity of the catalyst may be significantly affected by the unique nature of nitrogen, which is completely different from oxygen or carbon. Nevertheless, the importance of the target stimulated us to investigate the possibilities of the conversion from nitrogen-containing substrates to the pyrrolidine or piperidine skeleton.



Initially, *p*-toluenesulfonamide **1a** was selected to investigate this transformation (eq 1). Fortunately, piperidine **4a** was formed in 53% yield under $PtCl_2$/CO in toluene at 60 °C for 1 h. Interestingly, the yield was significantly increased to 89% at room temperature via $AuClPPh_3$/$AgSbF_6$ catalysis,[4] which did not serve well in our previous work. In this case, wet dichloromethane[5] was used as solvent for the hydrolysis of ketal intermediate **3** to form **4a**. The relative configuration of the three substituents in the piperidine was consistent with our previous observations (see the X-ray data), which was due to the highly stereospecific control through the cycloaddition reaction.

With this result in hand, a series of substituted enynyl esters joined by a sulfonamide were then investigated via $AuClPPh_3$/$AgSbF_6$ catalysis and various synthetically valuable multisubstituted piperidines were obtained in good to excellent yields (Tables 1 and 2). It was found that this tandem reaction has a wide range of substrate scope, where C4−C8 positions can have various substituent patterns. The substituent effect at the C6 position was first investigated. **1b** possessing a $PhCH_2CH_2$ substituent at C6 was converted to **4b** in excellent yield (entry 1, Table 1). However, this substituent was at the axial position instead of the expected equatorial position. The other two ketone chains preferred equatorial positions, while the hydroxyl group preferred an axial position (see X-ray, Figure 1). Other substituents (e.g., ^{i}Bu, ^{i}Pr, Cy), even the very bulky substituent ^{t}Bu at C6 of the substrate, were also tolerated, and the piperidines (**4c**−**f**) were obtained in good to excellent yield (entries 2−5). The scope of this reaction was also expanded to the homopropargylic amide **1g**, and the structurally differential piperidine **4g** was successfully produced in 73% yield (entry 6). It was noteworthy that **1g** was also tested with the $PtCl_2$/CO system and only the starting material was recovered after 5 h.

Table 1. Piperidines Synthesis through Au-Catalyzed [3 + 2] Cycloaddition of Enynyl Esters[a]

entry	substrate	product	yield[b]
1	 **1b**	 **4b** (X-ray)	91%
2	 **1c**	 **4c**	72%
3	 **1d**	 **4d**	82%
4	 **1e**	 **4e**	93%
5	 **1f**	 **4f**	61%
6	 **1g**	 **4g**	73% trace[c]

[a] Reaction conditions: enynyl ester (0.1 M in wet DCM), 5 mol % of $AuClPPh_3$, 5 mol % of $AgSbF_6$, rt, 1 h. [b] Isolated yields. [c] $PtCl_2$/CO, PhMe, 60 °C, 5 h.

Next, we found that substitutions at C7−C8 positions, which were close to the C−C double bonds, inevitably led to the formation of hydrolyzed and partially hydrolyzed bicyclic products. Therefore, by using dry CH_2Cl_2 as solvent to prevent the occurrence of hydrolysis, dihydrofurans **5h**−**k** were successfully obtained as single product in good yield (entries 1−4, Table 2). In contrast, such enol

(4) For recent work on gold-catalyzed [3 + 2] cycloadditions, see: (a) Melhado, A. D.; Amarante, G. W.; Wang, Z. J.; Luparia, M.; Toste, F. D. *J. Am. Chem. Soc.* **2011**, *133*, 3517. (b) Yang, C.-Y.; Wang, C.-D.; Tian, S.-F.; Liu, R.-S. *Adv. Synth. Catal.* **2010**, *352*, 1605. (c) Li, C.-W.; Lin, G.-Y.; Liu, R.-S. *Chem.—Eur. J.* **2010**, *16*, 5803. (d) Zhang, G.; Zhang, L. *J. Am. Chem. Soc.* **2008**, *130*, 12598. (e) Melhado, A. D.; Luparia, M.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 12638. (f) Huang, X.; Zhang, L. *J. Am. Chem. Soc.* **2007**, *129*, 6398. (g) Partyka, D. V.; Updegraff, J. B., III; Zeller, M.; Hunter, A. D.; Gray, T. G. *Organometallics* **2007**, *26*, 183. (h) Kusama, H.; Miyashita, Y.; Takaya, J.; Iwasawa, N. *Org. Lett.* **2006**, *8*, 289. (i) Kim, N.; Kim, Y.; Park, W.; Sung, D.; Gupta, A. K.; Oh, C. H. *Org. Lett.* **2005**, *7*, 5289. (j) Adè, A.; Cerrada, E.; Contel, M.; Laguna, M.; Merino, P.; Tejero, T. *J. Organomet. Chem.* **2004**, *689*, 1788. (k) For the use of gold ctalysis in total synthesis, see: Hashmi, A. S. K.; Rudolph, M. *Chem. Soc. Rev.* **2008**, *37*, 1766.

(5) Generated by shaking distilled CH_2Cl_2 with deionized water in a separatory funnel. See: (a) Hashmi, A. S. K.; Molinari, L.; Rominger, F.; Oeser, T. *Eur. J. Org. Chem.* **2011**, 2256. (b) Zhang, L.; Wang, S. *J. Am. Chem. Soc.* **2006**, *128*, 1442.

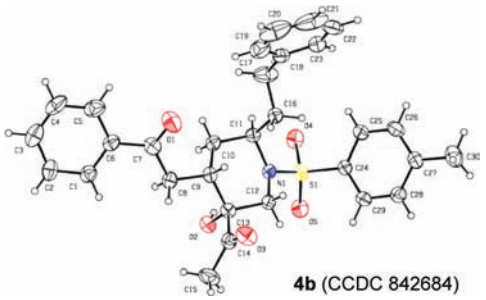
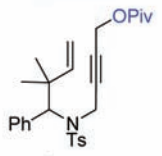
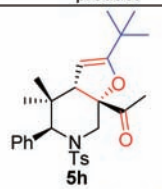
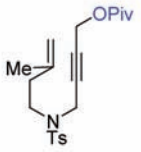
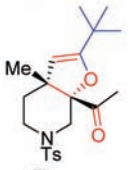
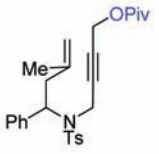
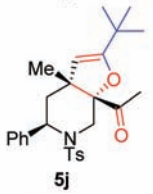
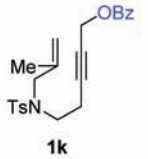
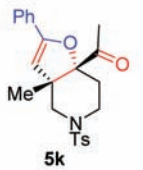
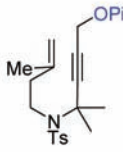
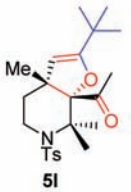
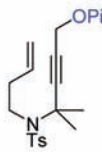
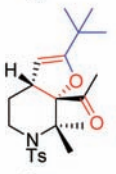


Figure 1. X-ray of **4b**.

Table 2. Modified Au-Catalyzed Cycloaddition of Enynyl Esters[a]

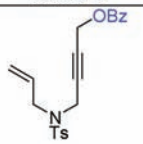
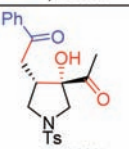
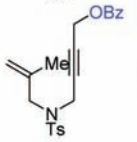
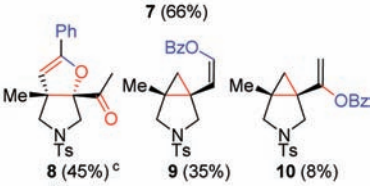
entry	substrate	product	yield [b]
1	 **1h**	 **5h**	85%
2	 **1i**	 **5i**	79%
3	 **1j**	 **5j**	62%
4	 **1k**	 **5k**	73%
5	 **1l**	 **5l**	65%
6	 **1m**	 **5m**	35%

[a] Reaction conditions: enynyl ester (0.1 M in dry DCM), 5 mol % of $AuClPPh_3$, 5 mol % of $AgSbF_6$, rt, 1 h. [b] Isolated yields.

ether products were converted to aromatic ketones by an aromatization/elimination process.[6] Through this method, the C4 dimethyl-substituted substrates **1l** and **1m** were converted to cyclized product **5l** and **5m**, respectively, although the substituents were very close to the C−C triple bonds (entries 5 and 6).[7]

On the basis of the success of piperidine synthesis, we then turned our attention to the synthesis of pyrrolidines. Many reactions involving cycloisomerization of 1,6-enynes to form cyclized products including pyrrolidines were reported,[8] but 1,6-enynes with a propargylic ester moiety in one substrate have not been fully studied yet since the competition between cycloisomerization of enynes and 1,2-acyloxy or 1,3-acyloxy migration[9] of propargylic esters may lead to the complicated products.[10]

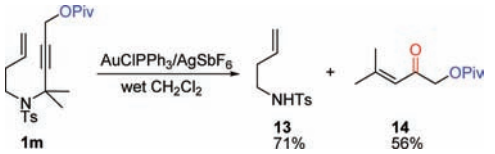
Table 3. Pyrrolidine Synthesis in the Au-Catalyzed Reactions of Enynyl Esters[a]

entry	substrate	product [b]
1	 **6a**	 **7** (66%)
2	 **6b**	 **8** (45%) [c] (X-ray), **9** (35%), **10** (8%)

[a] Reaction conditions: enynyl ester (0.1 M in wet DCM), 5 mol % of $AuClPPh_3$, 5 mol % of $AgSbF_6$, rt, 1 h. [b] Isolated yields. [c] Dry DCM was used.

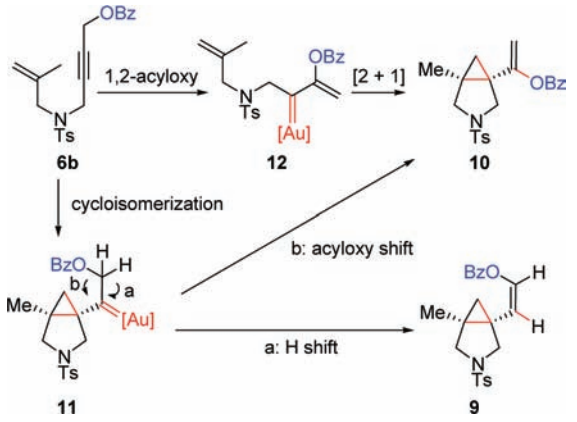
(6) Hashmi, A. S. K.; Pankajakshan, S.; Rudolph, M.; Enns, E.; Bander, T.; Rominger, F.; Frey, W. *Adv. Synth. Catal.* **2009**, *351*, 2855.

(7) The most common side reaction was decomposed to sulfonamide and propargylic ester moieties. This phenomenon was more obvious in **1m** when wet CH_2Cl_2 was used, see below:



(8) For the first conversion of an enyne-type substrate in gold catalysis, see: Hashmi, A. S. K.; Frost, T. M.; Bats, J. W. *J. Am. Chem. Soc.* **2000**, *122*, 11553. For reviews on enyne cycloisomerization, see: (a) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Rev.* **2008**, *108*, 3326. (b) Michelet, V.; Toullec, P. Y.; Genêt, J.-P. *Angew. Chem., Int. Ed.* **2008**, *47*, 4268. (c) Nieto-Oberhuber, C.; López, S.; Jiménez-Núñez, E.; Echavarren, A. M. *Chem.—Eur. J.* **2006**, *12*, 5916. (d) Zhang, Z.; Zhu, G.; Tong, X.; Wang, F.; Xie, X.; Wang, J.; Jiang, L. *Curr. Org. Chem.* **2006**, *10*, 1457. (e) Zhang, L.; Sun, J.; Kozmin, S. A. *Adv. Synth. Catal.* **2006**, *348*, 2271. (f) Ma, S.; Yu, S.; Gu, Z. *Angew. Chem., Int. Ed.* **2006**, *45*, 200. (g) Bruneau, C. *Angew. Chem., Int. Ed.* **2005**, *44*, 2328. (h) Diver, S. T.; Giessert, A. J. *Chem. Rev.* **2004**, *104*, 1317. (i) Echavarren, A. M.; Nevado, C. *Chem. Soc. Rev.* **2004**, *33*, 431. (j) Añrbe, L.; Domínguez, G.; Pérez-Castells, J. *Chem.—Eur. J.* **2004**, *10*, 4938. (k) Méndez, M.; Mamane, V.; Fürstner, A. *Chemtracts* **2003**, *16*, 397. (l) Echavarren, A. M.; Méndez, M.; Muñoz, M. P.; Nevado, C.; Martín-Matute, B.; Nieto-Oberhuber, C.; Cárdenas, D. J. *Pure Appl. Chem.* **2004**, *76*, 453. (m) Lloyd-Jones, G. *Org. Biomol. Chem.* **2003**, *1*, 215. (n) Aubert, C.; Buisine, O.; Malacria, M. *Chem. Rev.* **2002**, *102*, 813.

Scheme 2. Mechanistic Possibilities for the Rearrangements of 1,6-Enynyl Esters



Thus 1,6-enynyl ester **6a** without any substituent on the side chain was first selected to test this process, and pyrrolidine **7** was obtained as the main product in 66% yield (entry 1, Table 3). However, methyl-substituted olefin offered severe disadvantages to the anticipated reaction. For substrate **6b**, the desired [3 + 2] cycloaddition product **8** was isolated in 45% yield in dry CH_2Cl_2 along with the formation of **9** and **10** (entry 2). The generation of **9** and **10** probably experienced the same intermediate **11**, which was derived from cycloisomerization of enyne (Scheme 2).[11] Then a 1,2-shift of H (path a) or OBz (path b) lead to **9** or **10**. An alternative route for the formation of **10** was the intramolecular [2 + 1] cycloaddition of **12**, which was derived from **6b** through 1,2-acyloxy migration.

In conclusion, we have developed an Au-catalyzed new type of tandem reaction involving enynyl ester isomerization and subsequent intramolecular [3 + 2] cyclization. This methodology has broad applications, providing the corresponding cyclized products in good yields and with excellent stereoselectivities. Here the Au(I)-catalyzed cycloisomerization of nitrogen-containing enynyl esters strategy provides an efficient approach for the synthesis of polyfunctional piperidines and pyrrolidines. Further studies that take advantage of this tandem protocol to address complex synthetic issues are ongoing.

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Supporting Information Available. Experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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