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Synthesis of Functionalized Pyrroles via Gold(I)-Catalyzed aza-Claisen-Type Rearrangement

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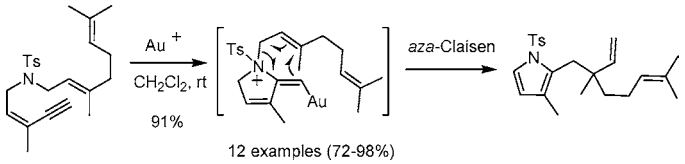
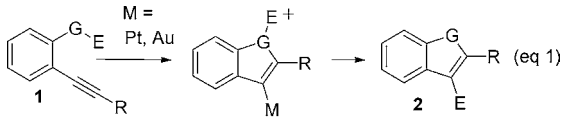
ABSTRACT



Gold(I)-catalyzed cyclization of pentenynyl allyl tosylamides allows the rapid construction of functionalized pyrroles. The concerted aza-Claisen-type mechanism induces a complete selectivity of the process and allows the easy formation of quaternary centers.

Pyrroles are structural motifs which are found in a wide variety of natural products[1] or pharmacologically active substances[2] and are frequently used in materials science.[3] As a consequence, the development of practical synthetic routes to access them remains of major interest. Recently, the groups of Fürstner, Yamamoto and Nakamura have shown that gold and platinum catalysts were highly efficient in converting *o*-alkynyl aryl derivatives of type **1** into a variety of functionalized heterocycles **2** (eq 1).[4] This transformation operates *via* a 5-*endo* cyclization followed by a heteroatom to carbon shift of the electrophilic moiety E.



While this way might be envisaged for the synthesis of pyrroles, the difficult and restricted access to the corresponding substrates represents a severe synthetic limitation. By analogy with the work of Fürstner and co-workers on the rearrangement of allyl pentynyl ether (Scheme 1, eq 2),[5] we rather envisaged that easily accessible substrates of type **3**

(1) (a) Sundberg, R. J. In *Comprehensive Heterocyclic Chemistry II*; Katritsky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Oxford, UK, 1996; Vol. 2. For selected examples, see: (b) Aiello, A.; D'Esposito, M.; Fattorusso, E.; Menna, M.; Mueller, W. E. G.; Perovic-Ottstadt, S.; Schroeder, H. C. *Bioorg. Med. Chem.* **2006**, *14*, 17−24. (c) Lewer, P.; Chapin, E. L.; Graupner, P. R.; Gilbert, J. R.; Peacock, C. *J. Nat. Prod.* **2003**, 143−145. (d) Fürstner, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 3582−3603. (e) Balme, G. *Angew. Chem., Int. Ed.* **2004**, *43*, 6238−6241. (f) Bellina, F.; Rossi, R. *Tetrahedron* **2006**, *62*, 7213−7256.

(2) For selected examples, see: (a) Clark, B. R.; Capon, R. J.; Lacey, E.; Tennant, S.; Gill, J. H. *Org. Lett.* **2006**, *8*, 701−704. (b) Bode, H. B.; Irschik, H.; Wenzel, S. C.; Reichenbach, H.; Mueller, R.; Hoefle, G. *J. Nat. Prod.* **2003**, 1203−1206.

(3) (a) Curran, D.; Grimshaw, J.; Perera, S. D. *Chem. Soc. Rev.* **1991**, *20*, 391−404. For selected examples, see: (b) Ogawa, K.; Rasmussen, S. C. *Macromolecules* **2006**, *35*, 1771−1778. (c) Facchetti, A.; Abbotto, A.; Beverina, L.; van der Boom, M. E.; Dutta, P.; Evmenenko, G.; Pagani, G. A.; Marks, T. J. *Chem. Mater.* **2003**, *15*, 1064−1072.

(4) Migration of allyl group: (a) Fürstner, A.; Davies, P. W. *J. Am. Chem. Soc.* **2005**, *127*, 15024−15025. (b) Shimada, T.; Nakamura, I.; Yamamoto, Y. *J. Am. Chem. Soc.* **2004**, *126*, 10546−10547. (c) Nakamura, I.; Sato, T.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2006**, *45*, 4473−4475. (d) Cacchi, S.; Fabrizi, G.; Pace, P. *J. Org. Chem.* **1998**, *63*, 1001−1011. (e) Arcadi, A.; Cacchi, S.; Rosario, M. D.; Fabrizi, G.; Marinelli, F. *J. Org. Chem.* **1996**, *61*, 9280−9288. Acyl groups: (f) Reference 4b. Alkoxyalkyl groups: (g) Nakamura, I.; Mizushima, Y.; Yamamoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 15022−15023. (h) Reference 4c. (i) Reference 4a. Sulfonyl groups: (j) Nakamura, I.; Yamagishi, U.; Song, D.; Konta, S.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 2284−2287. (k) Fürstner, A.; Heilmann, E. K.; Davies, P. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 4760−4763.

(5) (a) Fürstner, A.; Stelzer, F.; Szillat, H. *J. Am. Chem. Soc.* **2001**, *123*, 11863−11869. (b) Fürstner, A.; Szillat, H.; Stelzer, F. *J. Am. Chem. Soc.* **2000**, *122*, 6785−6786.

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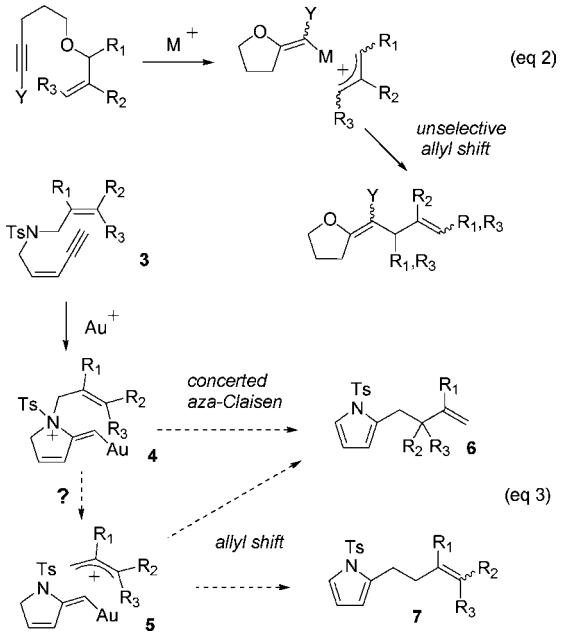
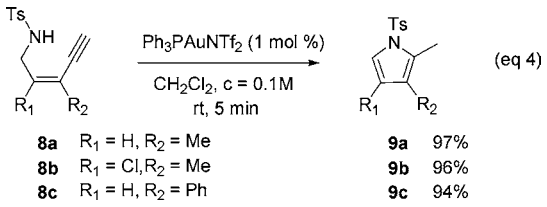
Scheme 1. Synthetic Approach to Functionalized Pyrroles



could be valuable precusors for a gold(I) catalyzed synthesis of pyrroles (Scheme 1, eq 3).[6,7]

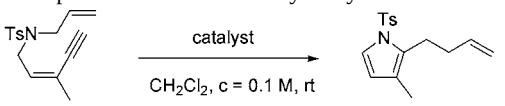
Moreover, we were particularly intrigued by the mechanistic aspect of this transformation which should determine the selectivity of the rearrangement. Indeed, an N to C allyl shift from intermediate **4** and **5** should lead to a mixture of pyrroles **6** and **7**[8] while a concerted aza-Claisen type rearrangement of intermediate **4** should lead to a selective formation of **6**.

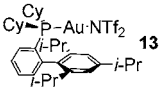
Following our recent success in using the air-stable crystalline $Ph_3PAuNTf_2$ catalyst[9] for the formation of C−C or C−O bonds, we first chose this catalytic system to validate our approach. Treatment of tosylamides **8a**−**c** with 1 mol % of $Ph_3PAuNTf_2$ in CH_2Cl_2 at room temperature rapidly led to the expected pyrroles **9a**−**c** (eq 4).[10]



However, more surprisingly, allyl tosylamide **10a** reacted more slowly under the same reaction conditions to give rearranged pyrrole **11a** in a moderate 62% yield (Table 1, entry 1). Increasing the catalyst loading led to a complete conversion of **10a** and improved the yield (entry 2). However, a rapid screening of various catalytic systems led to the conclusion that the use of the more electrophilic (*p*-$CF_3Ph)_3PAuNTf_2$ **12** was ideal, leading to the rapid formation of **11a** which was isolated in nearly quantitative yield (entry 3). Other catalysts such as biphenylphosphine-based catalyst **13**, $AuBr_3$, or $AgNTf_2$ were less efficient or did not promote the reaction (entries 4−6).

Table 1. Optimization of the Catalytic System



entry	catalyst		time	conversion [a]	yield [b]
1	PPh_3AuNTf_2	1 mol %	6 h	84%	62%
2	PPh_3AuNTf_2	2 mol %	2 h	100%	80%
3	**(*p*$CF_3Ph)_3PAuNTf_2$ 12**	**2 mol %**	**30 min**	**100%**	**94%**
4	 **13**	2 mol %	16 h	51%	42%
5	$AuBr_3$	5 mol %	16 h	60%	21%
6	$AgNTf_2$	10 mol %	16 h	14%	0%

[a] Determined by ^1H NMR of the crude reaction mixture. [b] Isolated yield.

In the light of these preliminary results, experimental conditions as mentioned in entry 3 were finally retained for the study of the scope of this transformation Secondary tosylamides **8a**−**c** were functionalized with various substituted allylating agents and the corresponding products isomerized (Table 2). As for substrate **10a**, simple allylated tosylamides **10b** and **10c** furnished the desired products **11b** and **11c** in good yields while methallyl derivative **10d** gave pyrrole **11d** in 89% yield (entries 1−3). Examples compiled in entries 4−11 are in agreement with the concerted aza-Claisen type mechanism since *the exclusive formation of branched products was observed*. Indeed, no linear product resulting from a formal N to C shift of the allylic moiety

(6) For recent reviews on gold catalysis, see: (a) Gorin, D. J.; Toste, F. D. *Nature* **2007**, *46*, 395−403. (b) Fürstner, A.; Davies, P. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 2−42. (c) Hashmi, S. A.; Huchings, G. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 7896−7936. For selected recent examples of gold-(I)-catalyzed reactions, see: (d) Lee, J. H.; Toste, F. D. *Angew. Chem., Int. Ed.* **2007**, *46*, 912−914. (e) Witham, C. A.; Mauleon, P.; Shapiro, N. D.; Sherry, B. D.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 5838−5839. (f) Hashmi, S. A.; Salathé, R.; Frey, W. *Eur. J. Org. Chem.* **2007**, 1648−1652. (g) Zhang, Z.; Widenhoefer, R. A. *Angew. Chem., Int. Ed.* **2007**, *45*, 283−285. (h) Binder, J. T.; Crone, B.; Kirsch, S. F.; Liébert, C.; Menz, H. *Eur. J. Org. Chem.* **2007**, 1636−1647. (i) Huang, X.; Zhang, L. *J. Am. Chem. Soc.* **2007**, *129*, 6398−6399. (j) López, S.; Herrero-Gómez, E.; Pérez-Galán, P.; Nieto-Oberhuber, C.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2006**, *44*, 6029−6032. (k) Sun, J.; Conley, M. P.; Zhang, L.; Kozmin, S. A. *J. Am. Chem. Soc.* **2006**, *128*, 9705−9710.

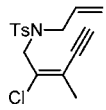
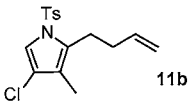
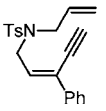
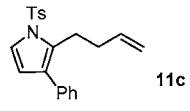
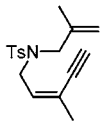
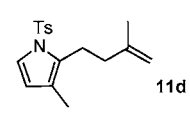
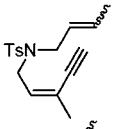
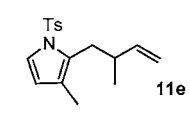
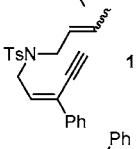
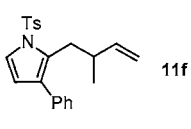
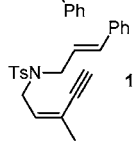
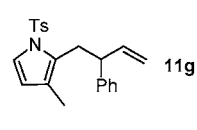
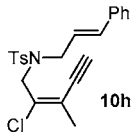
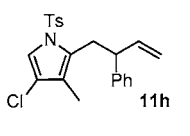
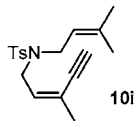
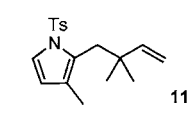
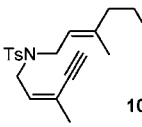
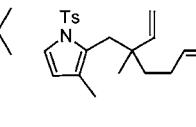
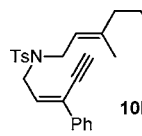
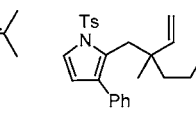
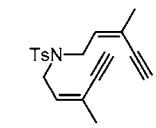
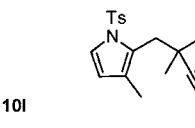
(7) For a similar rearrangement leading to indoles, see: (a) Cariou, K.; Ronan, B.; Mignani, S.; Fensterbank, L.; Malacria, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1881−1884. For an other gold(I)-catalyzed synthesis of pyrroles, see: (b) Binder, J. T.; Kirsch S. F. *Org. Lett.* **2006**, *8*, 2151−2153. For an analogous gold(I)-catalyzed formation of furans from (*Z*)-2-en-4-yn-1-ols, see: (c) Liu, Y.; Song, F.; Song, Z.; Liu, M.; Yan, B. *Org. Lett.* **2005**, *7*, 5409−5412.

(8) As previously reported by Fürstner and co-workers (see ref 5).

(9) (a) Buzas, A.; Istrate, F.; Gagosz, F. *Org. Lett.* **2006**, *8*, 1957−1959. (b) Buzas, A.; Gagosz, F. *Org. Lett.* **2006**, *8*, 515−518. (c) Mezailles, N.; Ricard, L.; Gagosz, F. *Org. Lett.* **2005**, *7*, 4133−4136. (d) Buzas, A.; Gagosz, F. *Synlett.* **2006**, 2727−2730.

(10) For Pd- and Cu-catalyzed formation of pyrroles from 1-alkylamino (*Z*)-2-en-4-ynes, see: (a) Gabriele, B.; Salerno, G.; Fazio, A.; Bossio, M. R. *Tetrahedron Lett.* **2001**, *42*, 1339−1342. (b) Gabriele, B.; Salerno, G.; Fazio, A. *J. Org. Chem.* **2003**, *68*, 7853−7861. See also ref 7b.

Table 2. Scope of Au(I)-Catalyzed Synthesis of Pyrroles[a]

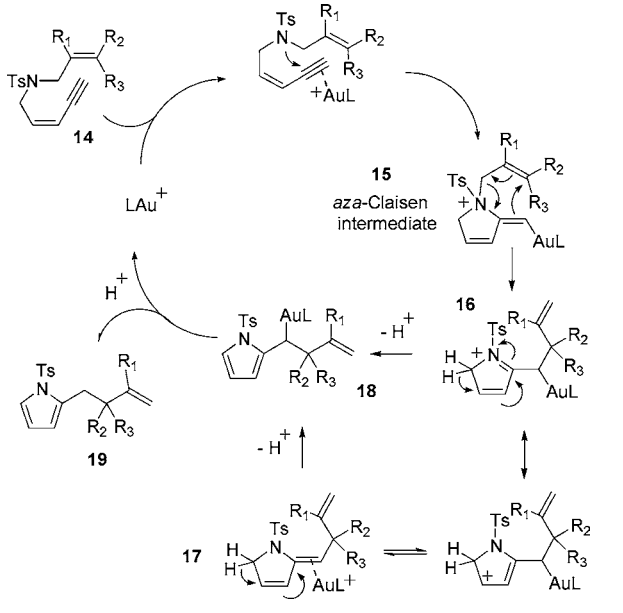
entry	substrate	product	time	yield[b]
1	 **10b**	 **11b**	30 min	88%
2	 **10c**	 **11c**	45 min	72%
3	 **10d**	 **11d**	45 min	89%
4	 **10e**[c]	 **11e**	15 min	91%
5	 **10f**[d]	 **11f**	15 min	89%
6	 **10g**	 **11g**	15 min	97%
7	 **10h**	 **11h**	5 min	98%
8	 **10i**	 **11i**	15 min	90%
9	 **10j**	 **11j**	15 min	91%
10	 **10k**	 **11k**	15 min	93%
11	 **10l**	 **11l**	15 min	84%

[a] Reaction conditions: 0.1 M of substrate in CH_2Cl_2 with 2 mol % of **12** at rt. [b] Isolated yields. [c] Z/E = 1:3.5. [d] Z/E = 1:2.6.

could be observed whatever the substrate used.[11] Crotyl derivatives **10e**,**f** and cinnamyl derivatives **10g**,**h** were thus efficiently isomerized into the corresponding pyrroles **11e**,**f** and **11g**,**h** in yields ranging from 89% to 98%. More interestingly, tosylamides **10i**−**l** bearing allylic moieties disubstituted at the terminal vinylic position reacted with no observable difference in rate even if the steric hindrance in the postulated aza-Claisen intermediate was increased. This behavior strongly contrasts with the generally less efficient classical Claisen or aza-Claisen reaction of substrates possessing the same substitution pattern. To the best of our knowledge, metal-catalyzed isomerization of such substituted allyl substrates has never been reported before.[12] It is also noteworthy that the isomerizations of tosylamides **10i**−**l** bearing a prenyl, a geranyl, or a pentenynyl moiety operate under mild conditions at room temperature and produce pyrroles possessing *a new quaternary center* on the side chain in high yields (84−93%). Interestingly, in the case of substrate **10l**, the second alkyne moiety remains unchanged with no detectable products derived from a possible cyclization onto the pyrrole ring. From a reactivity point of view, allylic substrates bearing substituents at the terminal position tend to react more rapidly as the consequence of a probable higher stabilization of the incipient positive charge in the postulated aza-Claisen intermediate.

To account for these observations, a mechanistic manifold for the formation of the pyrroles is proposed in Scheme 2.

Scheme 2. Proposed Mechanism



In contrast with what was previously observed by Fürstner and co-workers for the rearrangement of allyl pentynyl ether,[5] the results obtained in this study strongly suggest that no

(11) Within the limits of detection by ^{1}H NMR.

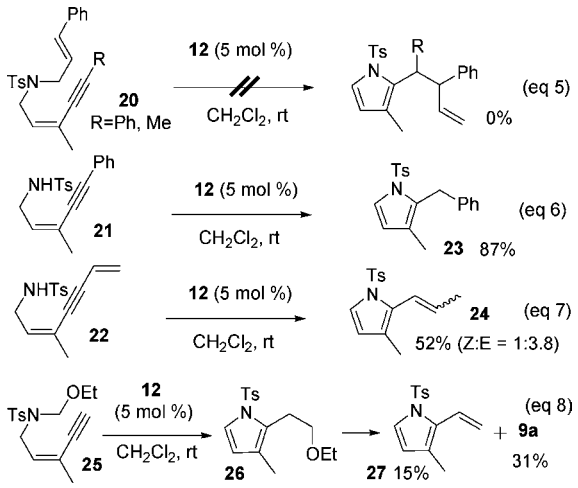
(12) Examples reported by Fürstner and coworkers dealt with the rearrangement of substrates bearing allylic moieties monosubstituted at the terminal vinylic position.

allyl cation is formed during the reaction. The results shown in entries 4−11 (Table 2) serve as a mechanistic probe indicating a more concerted mechanism in the present case and tend to exclude the possibility of a simple N to C allyl shift. The key step of this transformation may therefore be seen as a gold-catalyzed aza-Claisen type reaction. The following reaction pathway is therefore envisaged: gold(I) activation of the triple bond in substrate **14** promotes the nucleophilic addition of the tosylamide and leads to the formation of the cationic vinyl gold intermediate **15**. A subsequent aza-Claisen-type rearrangement furnishes intermediate **16**, which is presumably in equilibrium with the gold(I) tosylenamide complex **17**. A proton loss from one of these two intermediates allows the aromatization of the system and the formation of a new gold intermediate **18**. This latter is subsequently protodemetalated to finally give pyrrole **19**.

This mechanism is partly supported by a crossover experiment in which an equimolar mixture of tosylamides **10f** and **10g** was reacted under standard conditions. As a probe of the internal delivery of the allylic fragment, pyrroles **11f** and **11g** were the only products formed in this reaction with no detectable products derived from a crossover of these fragments.[11]

To further highlight the synthetic potential of this transformation, reactions of tosylamides bearing an internal alkyne were attempted. Unfortunately, cinnamyl derivative **20** possessing either a phenyl or a methyl group at the terminal position of the alkyne did not lead to the corresponding pyrrole even in the presence of 5 mol % of the catalyst (eq 5). This lack of reactivity might be attributed to an increased steric hindrance during the nucleophilic addition step of the tosylamide moiety onto the gold(I)-activated alkyne (from **14** to **15**, Scheme 2).

Tosylamides **21** and **22** lacking the allyl fragment were, however, transformed into pyrroles **23** and **24** under the same conditions (eqs 6 and 7).[13] Finally, by analogy with the work



of Fürstner and Yamamoto,[4a,c] migration of an ethoxymethyl group was attempted. Even if this reaction proved to be very sensitive, vinyl pyrrole **27**, presumably derived from the intermediate ethoxy pyrrole **26**, could, however, be obtained in a poor 15% yield along with 31% of pyrrole **9a** (eq 8).[14]

In summary, we have developed a new gold(I)-catalyzed formation of functionalized pyrroles, which is characterized by its efficiency, the mild conditions employed and the easy formation of quaternary centers. The complete selectivity observed in the structure of the final product is in agreement with the postulated aza-Claisen type rearrangement. Further studies of this new gold(I)-catalyzed process and its application to the synthesis of other heterocycles are underway.

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

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(13) Formation of pyrrole **24** might be the result of a gold(I) or proton catalyzed isomerization of the intermediate allyl pyrrole which seems to be unstable under the reaction conditions. Such a behavior was already observed for the gold catalyzed formation of furans (see ref 7b).

(14) Elimination of ethanol from intermediate **26** might be a gold(I)- or a proton-catalyzed reaction.