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An Extremely Facile Synthesis of Furans, Pyrroles, and Thiophenes by the Dehydrative Cyclization of Propargyl Alcohols

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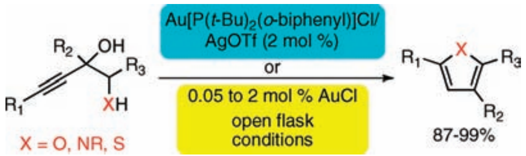
ABSTRACT



Furans, pyrroles, and thiophenes are efficiently prepared by gold-catalyzed dehydrative cyclizations of readily available, heteroatom-substituted propargylic alcohols. The reactions are rapid, high-yielding, and procedurally simple, giving essentially pure aromatic heterocycles in minutes under open-flask conditions with catalyst loadings as low as 0.05 mol %.

Furans, pyrroles, and thiophenes are important compounds found in biologically active natural products, organic materials, pharmaceuticals, and agrochemicals.[1] Additionally, they are synthetically useful building blocks for both heterocyclic and acyclic compounds.[2,3] As such, numerous classical reactions exist[4] and new methods are continually reported for the preparation of these heterocycles,[5] but different strategies are frequently employed for the synthesis of these aromatic systems depending on which heteroatom (O, N, S) is required.[6] The development of new strategies that facilitate rapid access to each of these heterocycles by a single method and provide highly substituted furans, pyrroles, and thiophenes would be extremely useful.

As part of a research program aimed at developing new catalytic reactions, we have been exploring dehydrative transformations of unsaturated alcohols that are catalyzed by simple gold(I) salts.[7] We recently reported that mono-

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(1) For a detailed list of uses of these heterocycles in a multitude of applications, see: Yin, G.; Wang, Z.; Chen, A.; Gao, M.; Wu, A.; Pan, Y. *J. Org. Chem.* **2008**, *73*, 3377–3383.

(2) For pyrroles, see: (a) Trofimov, N. A.; Nedolya, N. A. In *Comprehensive Heterocyclic Chemistry III*; Katritzky, A. R., Ramsden, C. A., Scriven, E. F. V., Taylor, R. J. K., Eds.; Elsevier Ltd.: Oxford, 2008; Vol. 3, pp 45−268. For furans, see: (b) Wong, H. N. C.; Yeung, K. -S.; Yang, Z. In *Comprehensive Heterocyclic Chemistry III*; Katritzky, A. R., Ramsden, C. A., Scriven, E. F. V., Taylor, R. J. K., Eds.; Elsevier Ltd.: Oxford, 2008; Vol. 3, pp 407−496. For thiophenes, see: (c) Rajappa, S.; Deshmunkh, A. R. In *Comprehensive Heterocyclic Chemistry III*; Katritzky, A. R., Ramsden, C. A., Scriven, E. F. V., Taylor, R. J. K., Eds.; Elsevier Ltd.: Oxford, 2008; Vol. 3, pp 741−841.

(3) Maier, M. In *Organic Synthesis Highlights II*; Waldmann, H., Ed.; VCH: Weinheim, 1995; pp 231−242.

(4) Li J. J. In *Name Reactions in Heterocyclic Chemistry*; Wiley-VCH: Weinheim, 2004.

(5) For selected examples, see: (a) Zhang, M.; Jiang, H.-F.; Neumann, H.; Beller, M.; Dixneuf, P. H. *Angew. Chem., Int. Ed.* **2009**, *48*, 1681–1684. (b) Devarie-Baez, N. O.; Kim, W.-S.; SmithI, A. B., III; Xian, M. *Org. Lett.* **2009**, *11*, 1861–1864. (c) Saquib, M.; Husain, I.; Kumar, B.; Shaw, A. K. *Chem.*—*Eur. J.* **2009**, *15*, 6041–6049. (d) Ackermann, L.; Sandmann, R.; Kaspar, L. T. *Org. Lett.* **2009**, *11*, 2031–2034. (e) Dudnik, A. S.; Sromek, A. W.; Rubina, M.; Kim, J. T.; Kel'in, A. V.; Gevorgyan, V. *J. Am. Chem. Soc.* **2008**, *130*, 1440–1452. (f) Liang, F.; Li, D.; Zhang, L.; Gao, J.; Liu, Q. *Org. Lett.* **2007**, *9*, 4845–4848.

(6) To prepare furans, pyrroles, and thiophenes by the same method, in addition to the Paal−Knorr synthesis, several methods have been reported, but these methods generally require specific substrates. For select examples, see: (a) Yadav, J. S.; Reddy, B. V. S.; Eeshwaraiah, B.; Gupta, M. K. *Tetrahedron Lett.* **2004**, *45*, 5873–5876. (b) Shindo, M.; Yoshimura, Y.; Hayashi, M.; Soejima, H.; Yoshikawa, T.; Matsumoto, K.; Shishido, K. *Org. Lett.* **2007**, *9*, 1963–1966. (c) Metwally, N. H. *Synth. Commun.* **2007**, *37*, 4227–4237. (d) Kaniskan, N.; Elmali, D.; Civcir, P. U. *ARKIVOC* **2008**, *xii*, 17–29.

(7) (a) Aponick, A.; Li, C.-Y.; Palmes, J. A. *Org. Lett.* **2009**, *11*, 121–124. (b) Aponick, A.; Biannic, B. *Synthesis* **2008**, *20*, 3356–3359. (c) Aponick, A.; Li, C.-Y.; Biannic, B. *Org. Lett.* **2008**, *10*, 669–671.

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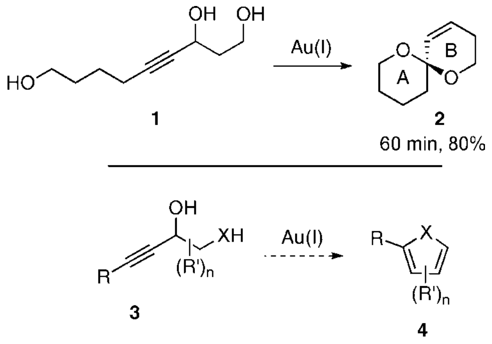
propargylic triols undergo a dehydrative spiroketalization with concomitant loss of the propargylic hydroxyl group to form unsaturated spiroketals (**1** → **2**, Scheme 1).[7a] Since four atoms in the B-ring of **2** are in the correct oxidation state, we reasoned that the desired aromatic heterocycles **4** should be produced when truncated substrates such as **3** are employed. Additionally, since gold complexes are known to perform well in the presence of a variety of different functional groups,[8] it seemed likely that the requisite heteroatoms and functionalized substituents would be tolerated. Oxidative reactions employing iodine to produce 3-iodofurans[9] and metal-catalyzed reactions have been reported,[10] but these methods suffer from having specific substitution requirements and the necessity for high catalyst loadings, elevated temperatures, and prolonged reaction times. Herein we report an extremely facile catalytic dehydrative cyclization reaction that proceeds rapidly under mild conditions and provides furans, pyrroles, and thiophenes in high yields with exceedingly low catalyst loadings.

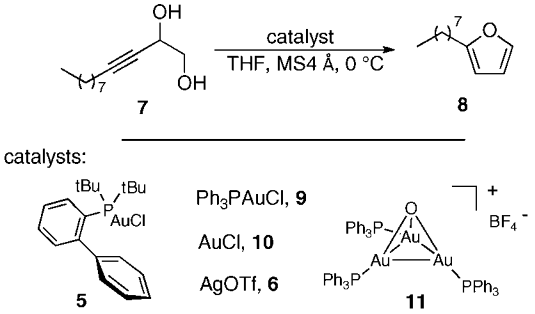
Scheme 1. Initial Hypothesis



The synthesis of heterocycles is an active area for developing new Au-catalyzed reactions.[11] Although pioneering work in this area has focused on the cycloisomerization epoxyalkynes,[12−14] no such methods have been reported for the cyclodehydration of substituted propargyl alcohols such as **3**. If successful, a broad range of substrates would be readily accessible by numerous staightforward synthetic strategies.

To test the feasibility of this idea, the diol **7** was prepared and treated with gold salts (Table 1). To our delight, when **7** was subjected to reaction conditions employing 2 mol % of Au[P(*t*-Bu)$_2$(*o*-biphenyl)]Cl **5** and AgOTf **6** at 0 °C in the presence of molecular sieves, the furan **8** was obtained in 96% yield (Table 1, entry 1). Using Ph$_3$PAuCl **9** in place of **5**, the product was also easily produced; however, a slightly longer reaction time was required and a lower yield was obtained (entry 3). No reaction was observed with catalyst **11** (entry 2), and control experiments (entries 4, 5) indicated that the cationic gold complex generated in situ was the catalytically active species.

Table 1. Catalyst Optimization



entry	catalyst system	loading (mol %)	time (min)	yield[a] (%)
1	**5** + **6**	2	10	96
2	**11**	0.75	60	0
3	**9** + **6**	2	15	80
4	**6**	2	30	0
5	TfOH	2	30	0
6	**10**	2	10	88
7[b]	**10**	2	10	87
8[c]	**10**	2	15	83
9[d]	**10**	2	30	0

[a] Isolated yield of pure product. [b] Reaction conducted without molecular sieves. [c] Reaction conducted without molecular sieves in an open vessel that had not been dried. [d] Solvent = water.

Further experimentation demonstrated that similar results could be obtained using AuCl **10** (entry 6), which was advantageous for both economic reasons and procedural simplicity. Using this salt, the nonpolar reaction products

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(8) For reviews on Au-catalyzed reactions, see: (a) Hashmi, A. S. K.; Rudolph, M. *Chem. Soc. Rev.* **2008**, *37*, 1766–1775. (b) Li, Z.; Brouwer, C.; He, C. *Chem. Rev.* **2008**, *108*, 3239–3265. (c) Arcadi, A. *Chem. Rev.* **2008**, *108*, 3366–3325. (d) Jimenez-Nunez, E.; Echavarren, A. M. *Chem. Rev.* **2008**, *108*, 3326–3350. (e) Gorin, D. J.; Sherry, B. D.; Toste, F. D. *Chem. Rev.* **2008**, *108*, 3351–3378.

(9) Bew, S. P.; El-Taeb, G. M. M.; Jones, S.; Knight, D. W.; Tan, W.-F. *Eur. J. Org. Chem.* **2007**, 5759–5770.

(10) (a) Hayes, S. J.; Knight, D. W.; Menzies, M. D.; O'Halloran, M.; Tan, W.-F. *Tetrahedron Lett.* **2007**, *48*, 7709–7712. (b) McDonald, F. E.; Connolly, C. B.; Gleason, M. M.; Towne, T. B.; Treiber, K. D. *J. Org. Chem.* **1993**, *58*, 6952–6953. (c) Yada, Y.; Miyake, Y.; Nishibayashi, Y. *Organometallics* **2008**, *27*, 3614–3617. (d) Wakabayashi, Y.; Fukuda, Y.; Shiragami, H.; Utimoto, K.; Nozaki, H. *Tetrahedron* **1985**, *41*, 3655–3661.

(11) For leading references on Au-catalyzed reactions in heterocycle synthesis, see: (a) Shen, H. C. *Tetrahedron* **2008**, *64*, 3885–3903. (b) Shen, H. C. *Tetrahedron* **2008**, *64*, 7847–7870. (c) Patil, N. T.; Yamamoto, Y. *Chem. Rev.* **2008**, *108*, 3395–3442.

(12) For leading references on isomerization of epoxyalkynes using Hg, Au, Pt, and Ag salts, see the following. Hg: (a) Miller, D. *Chem. Soc. C* **1969**, 12–15. Au: (b) Hashmi, A. S. K.; Sinha, P. *Adv. Synth. Catal.* **2004**, *346*, 432–438. (c) Shu, X.-Z.; Liu, X.-Y.; Xiao, H.-Q.; Ji, K.-G.; Guo, L.-N.; Qi, C.-Z.; Liang, Y.-M. *Adv. Synth. Catal.* **2007**, *349*, 2493–2498. (d) Dai, L.-Z.; Shi, M. *Tetrahedron Lett.* **2008**, *49*, 6437–6439. (e) Ji, K.-G.; Shen, Y.-W.; Shu, X.-Z.; Xiao, H.-Q.; Bian, Y.-J.; Liang, Y-M *Adv. Synth. Catal.* **2008**, *350*, 1275–1280. (f) Hashmi, A. S. K.; Buhrle, M.; Salathe, R.; Bats, J. W. *Adv. Synth. Catal.* **2008**, *350*, 2059–2064. Pt: (g) Yoshida, M.; Al-Amin, M.; Matsuda, K. S. *Tetrahedron Lett.* **2008**, *49*, 5021–5023. (h) Yoshida, M.; Al-Amin, M.; Shishido, K. *Synthesis* **2009**, 2454–2466. Ag: (i) Blanc, A.; Tenbrink, K.; Weibel, J. -M.; Pale, P. *J. Org. Chem.* **2009**, *74*, 4360–4363.

(13) For isomerization of alkynylaziridines to form pyrroles, see: Davies, P. W.; Martin, N. *Org. Lett.* **2009**, *11*, 2293–2296.

(14) For other seminal reports on Au-catalyzed furan synthesis, see: (a) Hashmi, A. S. K.; Schwarz, L.; Choi, J.-H.; Frost, T. J. *Angew. Chem., Int. Ed.* **2000**, *39*, 2285–2288. (b) Yao, T.; Zhang, X.; Larock, R. C. *J. Am. Chem. Soc.* **2004**, *126*, 11164–11165. (c) Yao, T.; Zhang, X.; Larock, R. C. *J. Org. Chem.* **2005**, *70*, 7679–7685. (d) Sromek, A. W.; Rubina, M.; Gevorgyan, V. *J. Am. Chem. Soc.* **2005**, *127*, 10500–10501.

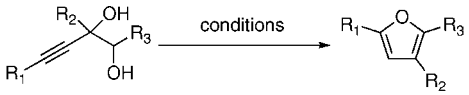
are readily obtained in high purity after filtration of the crude reaction mixture over silica gel to remove the catalyst residue.

Since only a minimal effect was observed after changing the catalyst to AuCl, additional experiments focused on further simplifying the procedure. Omission of molecular sieves (entry 7) afforded **8** in 87% yield, demonstrating that the water produced in the reaction could be tolerated by the catalyst system. *Furthermore, conducting the reaction in an open vessel that had not been dried and without molecular sieves also rapidly provided* **8**, albeit in slightly lower yield (entry 8, 83%). When water was used as the solvent, no reaction was observed, likely due to solubility issues (entry 9). From these data, it is apparent that the best yield is obtained using Au[P(*t*-Bu)$_2$(*o*-biphenyl)]Cl **5** and AgOTf **6** (entry 1), while the simplest procedure employs AuCl **10** with no precautions taken to exclude water (entry 8).[15]

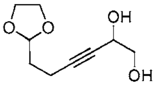
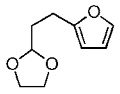
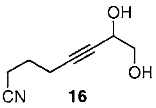
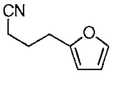
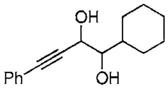
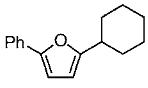
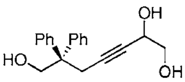
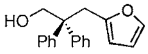
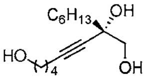
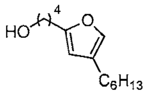
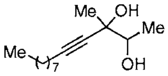
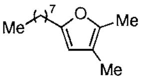
The reaction scope was next explored using substituted diols to produce furans with substituents at the 2-, 3-, and 5-positions (Table 2). Employing reaction conditions A (complexes **5**/**6**, MS 4 Å, N$_2$ atmosphere) and B ("open flask conditions" using AuCl with no precautions taken to exclude air or moisture), the target furans were obtained in excellent yield after 10−25 min. Using substrates **14** and **16**, comparison between the conditions demonstrated that the procedurally simple "open flask" conditions B could function as well as (entries 1 vs 2), if not better than the more rigorous conditions A (entries 3 vs 4). In addition to acetals and cyano groups, additional alcohol moieties were also tolerated (entry 6) and tertiary alcohols (entry 7) were readily dehydrated to form the products in excellent yield. Using diol **24**, the 2,3,5-trisubstituted furan was easily prepared in 95% yield. Further substitution is limited by the nature of the propargyl alcohol substrates, but electrophilic substitution should provide the 2,3,4,5-tetrasubstituted furans if desired.[16]

We next focused our attention on the preparation of pyrroles and thiophenes. For comparison, 2-phenylfuran **29** was first prepared from the requisite diol in 93% using conditions A and 75% using conditions B (Table 3, entries 1,2). Since introducing potentially coordinating heteroatoms into the substrates may be detrimental to the reaction, the more rigorous conditions A were employed with the nitrogen and sulfur analogues. In the event, when the *N*-tosylamino alcohol **30** was subjected to the reaction conditions, the pyrrole **31** was obtained in 89% yield after 10 min (entry 3), and cyclization of the alkyne **32** demonstrated that the phenyl group is not required for the reaction to proceed (entry 4). Basic amines also perform well in the reaction (entries 5,6), but increased reaction times (50 and 40 min, respectively) were required.

Table 2. Optimization Studies



12 **13**

entry	substrate	product	conditions^a	time (min)	yield (%)^b
1 2	 **14**	 **15**	A B	10 10	90 85
3 4	 **16**	 **17**	A B	10 5	87 91
5	 **18**	 **19**	B	10	88
6	 **20**	 **21**	A	20	99
7	 **22**	 **23**	A	25	99
8	 **24**	 **25**	B	10	95

^{a} Conditions A: Au[P(*t*-Bu)$_2$(*o*-biphenyl)]Cl (2 mol %), AgOTf (2 mol %), MS4 Å, THF, 0 °C. Conditions B: AuCl (2 mol %), THF, 0 °C, open flask.[15] ^{b} Isolated yield of pure product.

The preparation of thiophene **39** necessitated further modification to the standard procedure. When the standard conditions were employed, **39** was only isolated in 19% yield. Raising the temperature to room temperature and using 5 mol % catalyst, the yield increased to 63%. Finally, carrying out the reaction at 40 °C (Table 3, entry 7) afforded the thiophene in 90% yield.

It was also important to determine the lower limit of catalyst loading. To study this, the sterically demanding diol **24** was employed using AuCl as catalyst. When the loading was reduced to 0.5 mol % (Table 4, entry 1), the furan **25** was isolated in 82% yield. This reduced yield (cf. 95%, Table 2, entry 8) seemed to indicate that catalyst loadings lower than 2 mol % could be problematic. We reasoned that by increasing the temperature to shorten the reaction time and by excluding water lower loadings may be successful. Inclusion of activated molecular sieves and conducting the reaction in refluxing THF, with 0.1 mol % of AuCl, a nearly quantitative yield of **25** was isolated (Table 4, entry 2). Decreasing the catalyst loading to 0.05 mol % also resulted in high yield (91%, entry 3), but this was significantly diminished (entries 4 and 5) after further reduction in the

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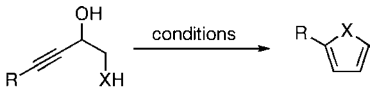
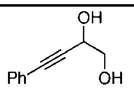
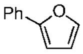
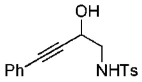
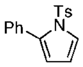
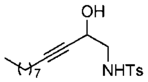
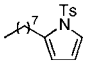
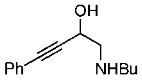
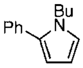
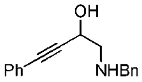
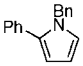
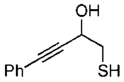
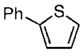
(15) **General Procedure for Dehydrative Cyclization under "Open Flask" Conditions.** THF (1 M relative to substrate) was added to an unstoppered, open test tube containing AuCl (2 mol %), and the mixture was cooled to 0°C. A solution of substrate (0.13 M in THF; overall concentration of substrate: 0.1 M) was added. After TLC analysis showed the reaction to be complete, the mixture was filtered through a short plug of silica with hexanes, and the solvents were removed in vacuo to afford the desired product in high purity.

(16) (a) Baily, P. S.; Nowlin, G. *J. Am. Chem. Soc.* **1949**, *71*, 732–735. (b) Dominguez, C.; Csaky, A. G.; Plumet, J. *Tetrahedron* **1992**, *48*, 149–158.

Table 3. Heteroatom Studies



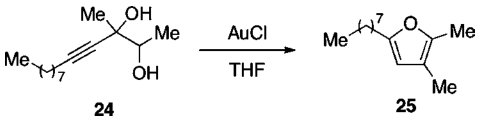
26 **27**

entry	substrate	product	time (min)	yield (%)
1[a] 2[b]	 **28**	 **29**	10 10	93 75
3[a]	 **30**	 **31**	10	89
4[a]	 **32**	 **33**	10	91
5[a]	 **34**	 **35**	50	91
6[a]	 **36**	 **37**	40	92
7[c]	 **38**	 **39**	80	90

[a] Au[P(*t*-Bu)$_2$(*o*-biphenyl)]Cl (2 mol %), AgOTf (2 mol %), THF, MS4 Å, 0 °C. [b] AuCl (2 mol %), THF, 0 °C, open flask.[15] [c] **5** (5 mol %), **6** (5 mol %), THF, MS4 Å, 40 °C.

loadings. It is likely that this is due to trace amounts of impurity below NMR detection limits in diol **24** as a reaction with 0.01 mol % requires an extremely small amount of AuCl.

Table 4. Catalyst Loading



24 **25**

entry	catalyst loading (mol %)	time (min)	yield[a] (%)
1[b]	0.5	35	82
2[c]	0.1	10	99
3[c]	0.05	15	91
4[c]	0.02	20	34
5[c]	0.01	20	4

[a] Isolated yield. [b] 0 °C. [c] 65 °C, MS4 Å.

In conclusion, we have developed an extremely mild and efficient method for the preparation of furans, pyrroles, and thiophenes. The reaction employs very simple and readily available substrates, tolerates a range of functional groups to produce highly substituted heteroaromatics, and is typically complete in minutes with high yield. Although care must be taken to exclude water when loadings below 0.5 mol % are utilized, the use of AuCl as a catalyst under "open-flask conditions" in combination with facile purification makes this method highly practical.

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

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