ORGANIC LETTERS

2008
Vol. 10, No. 4
669−671

Au-Catalyzed Cyclization of Monoallylic Diols

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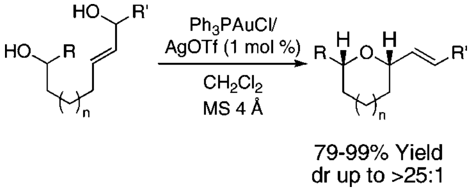
Received December 13, 2007

ABSTRACT



The $Ph_3PAuCl/AgOTf$-catalyzed cyclization of monoallylic diols to form tetrahydropyrans is reported. The reactions proceed rapidly at temperatures as low as −78 °C with catalyst loadings as low as 0.1 mol % to provide the products in 79–99% yield. A broad range of structurally diverse substrates perform well in the reaction. When 2,6-disubstituted tetrahydropyrans are produced, the reaction is highly diastereoselective for the 2,6-cis product.

The use of gold complexes as catalysts has emerged as a powerful synthetic method for the formation of C−C and C−X bonds, characterized by high turnover numbers and turnover frequencies under mild conditions.[1] The reactions are typically based on the activation of π-bonds, and as such, a majority of reports involve the use of alkynes or allenes[1] and to a lesser extent isolated olefins, although these reactions usually require higher temperatures and longer reaction times.[2] The utility of this method could be greatly expanded if new reactions could be developed that employ functional groups not traditionally used. As part of a program aimed at expanding the scope of functional groups used in Au-catalyzed reactions, we began to explore the formation of tetrahydropyrans.

Saturated oxygen heterocycles are a common structural feature found in a broad array of natural products and have therefore been the subject of intense study.[3] Tetrahydropyrans, in particular, are frequently observed in synthetic targets that attract significant attention due to their promising biological activities. Selected examples include spirastrellolide A,[4a] SCH 351448,[4b] psymberin,[4c,d] sorangicin A,[4e] the bryostatins,[4f] and the brevetoxins.[4g,h] Among the strategies developed for preparing tetrahydropyrans,[5] the Au-catalyzed hydroalkoxylation of allenes (**1** → **2**, Scheme 1) has recently been reported as a mild, efficient, and atom-economic approach.[6,7] We envisioned a different strategy that also relies

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[1] For recent reviews on homogeneous Au-catalyzed reactions, see: (a) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180. (b) Gorin, D. J.; Toste, F. D. *Nature* **2007**, *446*, 395. (c) Hashmi, A. S. K. *Catal. Today* **2007**, *122* (3−4), 211. (d) Jimenez-Nunez, E.; Echavarren, A. M. *Chem. Commun.* **2007**, 333. (e) Hashmi, A. S. K.; Hutchings, G. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 7896. (f) Hoffman-Roder, A.; Krause, N. *Org. Biomol. Chem.* **2005**, *3*, 387.

[2] For leading references on Au-catalyzed reactions of isolated alkenes, see: (a) Zhang, J.; Yang, C.-G.; He, C. *J. Am. Chem. Soc.* **2006**, *128*, 1798. (b) Han, X.; Widenhoefer, R. A. *Angew. Chem., Int. Ed.* **2006**, *45*, 1747. (c) Bender, C. F.; Widenhoefer, R. A. *Chem. Commun.* **2006**, 4143. (d) Liu, X.-Y.; Li, C.-H.; Che, C.-M. *Org. Lett.* **2006**, *8*, 2707. (e) Bender, C. F.; Widenhoefer, R. A. *Org. Lett.* **2006**, *8*, 5303. (f) Zhang, X.; Corma, A. *Chem. Commun.* **2007**, 3080. (g) Yang, C.-G.; He, C. *J. Am. Chem. Soc.* **2005**, *127*, 6966 and references cited therein.

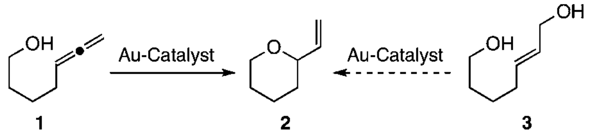
[3] For reviews on the synthesis of marine natural products, see: (a) Morris, J. C.; Nicholas, G. M.; Phillips, A. J. *Nat. Prod. Rep.* **2007**, *24*, 87. (b) Yeung, K.-S.; Paterson, I. *Chem. Rev.* **2005**, *105*, 4237 and references cites therein.

[4] (a) Williams, D. D.; Roberge, M.; Van Soest, R.; Anderson, R. J. *J. Am. Chem. Soc.* **2003**, *125*, 5296. (b) Hegde, V. R.; Puar, M. S.; Dai, P.; Patel, M.; Gullo, V. P.; Das, P. R.; Bond, R. W.; McPhail, A. T. *Tetrahedron Lett.* **2000**, *41*, 1351. (c) Cichewicz, R. H.; Valeriote, F. A.; Crews, P. *Org. Lett.* **2004**, *6*, 1951. (d) Pettit, G. R.; Xu, J. P.; Chapuis, J. C.; Pettit, R. K.; Tackett, L. P.; Doubek, D. L.; Hooper, J. N. A.; Schmidt, J. M. *J. Med. Chem.* **2004**, *47*, 1149. (e) Jansen, R.; Wray, V.; Irschik, H.; Reichenbach, H.; Hofle, G. *Tetrahedron Lett.* **1985**, *26*, 6031. (f) For a recent review, see: Hale, K. J.; Hummersone, M. G.; Manaviazar, S.; Frigerio, M. *Nat. Prod. Rep.* **2002**, *19*, 413. (g) For recent reviews, see: Nakata, T. *Chem. Rev.* **2005**, *105*, 4314. (h) Inoue, M. *Chem. Rev.* **2005**, *105*, 4379.

[5] For leading references, see: (a) Clarke, P. A.; Santos, S. *Eur. J. Org. Chem.* **2006**, 2045. (b) Boivin, T. L. B. *Tetrahedron* **1987**, *43*, 3309 and referenced cited therein.

10.1021/ol703002p CCC: \$40.75

Scheme 1. Allylic Alcohols in Au-Catalyzed Cyclizations

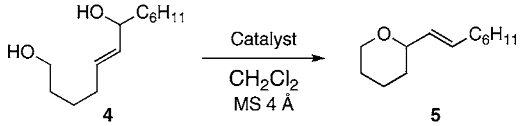


on Au catalysis but instead involves the cyclization of allylic diols (**3** →**2**, Scheme 1). Both Bronsted and Lewis acid catalyzed nucleophilic substitution of allylic alcohols have previously been reported.[8] The reactions usually require strongly acidic conditions[8a−c] or, in the case of late transition metal catalysts, high temperatures or further addition of promoters.[8m] Intramolecular Pd-catalyzed cyclizations are known, but limited examples demonstrating substrate scope and relatively high catalyst loadings are reported.[8i−l]

The development of a catalytic system with the beneficial aspects of homogeneous gold catalysis is highly desirable. Additionally, the potential advantages of using an allylic alcohol in place of an allene include ease of preparation, elimination of the possible endo cyclization pathway, and the potential to form a quaternary carbon by addition to a tri- or tetrasubstituted olefin. Herein, we report that monoallylic diols are highly reactive substrates, forming tetrahydropyrans in high yield with high diastereoselectivity by the action of cationic gold(I) complexes.

The desired cyclization was envisioned to proceed by an S_N2' or cationic mechanism and initial experiments employed $AuCl_3$ since gold(III) salts are known to be somewhat more oxophilic than gold(I).[9] Gratifyingly, treatment of diol **4** with as low as 1 mol % $AuCl_3$ cleanly provided the cyclized product **5** in excellent yield (Table 1, entries 1 and 2). Using $Ph_3PAuCl/AgOTf$ (entries 3 and 4), tetrahydropyran **5** was isolated in greater than 90% yield, and this catalyst system was deemed optimal vide infra. While AuCl provided **5** in 41% yield, there was no conversion employing Ph_3PAuCl without AgOTf. Additional control experiments (entries 7−9) provide evidence that in the presence of silver salts or potentially TfOH,[1c,10] the cationic gold(I) complex is the catalytically active species.

Table 1. Optimization and Control Experiments



entry	catalyst	loading (mol %)	time	yield (%)
1	$AuCl_3$	2	30 min	96
2	$AuCl_3$	1	100 min	87
3	$Ph_3PAuCl/AgOTf$	5	20 min	91
4	$Ph_3PAuCl/AgOTf$	1	40 min	96
5[a]	AuCl	1	16 h	41
6	Ph_3PAuCl	5	16 h	0
7	AgOTf	5	16 h	0
8	AgCl	5	48 h	0
9[b]	TfOH	1	40 min	9

[a] 49% diol **4** recovered. [b] 46% diol **4** recovered.

Using the conditions from entry 4 of Table 1, the reaction of substituted diols was investigated to determine substrate scope (Table 2). In general, the reactions are rapid and high yielding at room temperature. Substituting C-7 (entry 2) gives rise to the 2,6-disubstituted product **9** which was obtained in 95% yield and 11:1 dr, favoring the cis diastereomer. The ratio could be improved to >25:1 by reducing the temperature to −50 °C (entry 3). Additional experiments focused on obtaining potentially useful synthons (entries 6−13). When the aldol adduct **12** was subjected to the standard conditions, **13** was obtained in high yield without any elimination product. Surprisingly, this substrate failed to react at −50 °C, but a 12:1 dr was obtained at −10 °C (entry 7). The reaction was also attempted with $AuCl_3$ but was found to require extremely long reaction times (entry 8), making $Ph_3PAuCl/AgOTf$ the preferred catalyst system.

Further studies were designed to test the effects of substitution on the allylic alcohol moiety. Interestingly, when *cis*-olefin **18** was subjected to the standard conditions, the trans product **5** was isolated (entry 14) with similar yield and reaction time to **4**. Tertiary allylic alcohols also performed quite well, providing the trisubstituted olefin **20** in 91% yield (entry 15). This substrate was then used to test the lower limit of the catalyst loading. We were pleased to

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(6) (a) Zhang, Z.; Liu, C.; Kinder, R. E.; Han, X.; Qian, H.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2006**, *128*, 9066. (b) Zhang, Z.; Widenhoefer, R. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 283. (c) Hamilton, G. L.; Kang, E. J.; Mba, M.; Toste, F. D. *Science* **2007**, *317*, 496. (d) Zhang, Z.; Bender, C. F.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2007**, *129*, 14148.

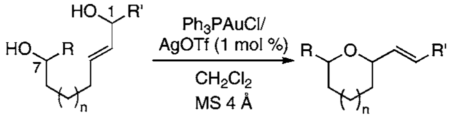
(7) Au-catalyzed heterocycle formation by hydration of homopropargylic ethers with subsequent elimination and Michael addition to the resultant α,*β*-unsaturated ketone has also been reported: (a) Jung, H. H.; Floreancig, P. E. *Org. Lett.* **2006**, *8*, 1949. (b) Jung, H. H.; Floreancig, P. E. *J. Org. Chem.* **2007**, *72*, 7359.

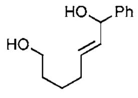
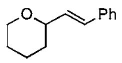
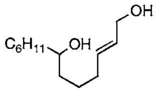
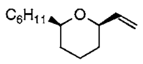
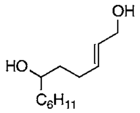
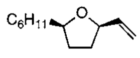
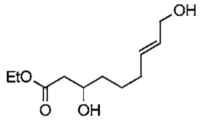
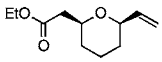
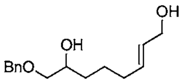
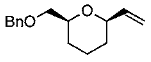
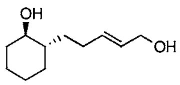
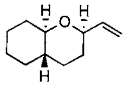
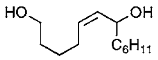
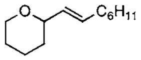
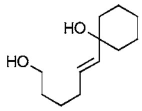
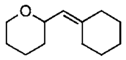
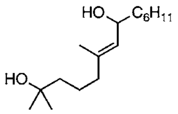
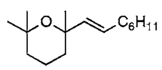
(8) For leading references involving Brønsted acids, see: (a) Bras, J. L.; Muzart, J. *Tetrahedron* **2007**, *63*, 7942. (b) Sanz, R.; Martínez, A.; Miguel, D.; Álvarez-Gutiérrez, J. M.; Rodríguez, F. *Adv. Synth. Catal.* **2006**, *348*, 1841. (c) Young, J.-J.; Jung, L.-J.; Cheng, K.-M. *Tetrahedron Lett.* **2000**, *41*, 3415. Pd-intermolecular: (d) Muzart, J. *Eur. J. Org. Chem.* **2007**, 3077. (e) Trost, B. M.; Quancard, J. *J. Am. Chem. Soc.* **2006**, *128*, 6314. (f) Kimura, M.; Futamata, M.; Mukai, R.; Tamaru, Y. *J. Am. Chem. Soc.* **2005**, *127*, 4592. (g) Kayaki, Y.; Koda, T.; Ikariya, T. *J. Org. Chem.* **2004**, *69*, 2595. (h) Ozawa, F.; Okamoto, H.; Kawagishi, S.; Yamamoto, S.; Minami, T.; Yoshifuji, M. *J. Am. Chem. Soc.* **2002**, *124*, 10968. Pd-intramolecular: (i) Kawai, N.; Lagrange, J.-M.; Ohmi, M.; Uenishi, J. *J. Org. Chem.* **2006**, *71*, 4530. (j) Uenishi, J.; Ohmi, M.; Ueda, A. *Tetrahedron: Asymmetry* **2005**, *16*, 1299. (k) Miyazawa, M.; Hirose, Y.; Narantsetseg, M.; Yokoyama, H.; Yamaguchi, S.; Hirai, Y. *Tetrahedron Lett.* **2004**, *45*, 2883. (l) Yokoyama, H.; Otaya, K.; Kobayashi, H.; Miyazawa, M.; Yamaguchi, S.; Hirai Y. *Org. Lett.* **2000**, *2*, 2427. Other metals: (m) Qin, H.; Yamagiwa, N.; Matsunaga, S.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 409. (n) Guo, S.; Song, F.; Liu, Y. *Synlett* **2007**, 964. (o) Yasuda, M.; Somyo, T.; Baba, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 793. (p) Nay, B.; Collet, M.; Lebon, M.; Cheze, C.; Vercauteren, J. *Tetrahedron Lett.* **2002**, *43*, 2675.

(9) (a) Reich, N. W.; Yang, C.-G.; Shi, Z.; He, C. *Synlett* **2006**, 1278. (b) Sromek, A. W.; Rubina, M.; Gevorgyan, V. *J. Am. Chem. Soc.* **2005**, *127*, 10500.

(10) For reports on reactions employing TfOH in comparison to metal triflates, see: (a) Li, Z.; Zhang, J.; Brouwer, C.; Yang, C.-G.; Reich, N. W.; He, C. *Org. Lett.* **2006**, *8*, 4175. (b) Rosenfeld, D. C.; Shekhar, S.; Takemiya, A.; Utsunomiya, M.; Hartwig, J. F. *Org. Lett.* **2006**, *8*, 4179 and references cited therein.

Table 2. Reaction Scope

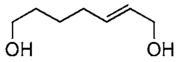


entry	substrate	product	time (h)	temp (°C)	yield (%)	dr[a]
1[b]	 **6**	 **7**	0.5	rt	89	-
2	 **8**	 **9**	0.33	rt	95	11:1
3			8	-50	80	>25:1
4	 **10**	 **11**	0.5	rt	89	5:1
5			10	-50	79	7:1
6	 **12**	 **13**	0.5	rt	96	6:1
7			9	-10	99	12:1
8[c,d]			21	rt	80	5:1
9	 **14**	 **15**	1	0	96	4:1
10			24	-50	97	8:1
11	 **16**	 **17**	0.33	rt	87	4:1
12			10	-50	76	5:1
13[e]			10	-78	79	10:1
14	 **18**	 **5**	0.66	rt	92	-
15	 **19**	 **20**	2.5	rt	91	-
16[f]			48	rt	82	-
17	 **21**	 **22**	6	rt	89	-

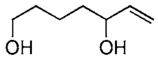
[a] Diastereomeric ratios were determined by ^{1}H NMR of the crude reaction mixtures and by isolated yields when separable. [b] A trace amount of the cis olefin was observed with **7**. [c] 1 mol % $AuCl_3$ used as catalyst. [d] 10% unreacted diol **12** recovered. [e] 5 mol % $Ph_3PAuCl/AgOTf$. [f] 0.1 mol % $Ph_3PAuCl/AgOTf$.

find complete consumption of **19** in 48 h using *0.1 mol %* $Ph_3PAuCl/AgOTf$ to give **20** in 82% yield (entry 16). More highly substituted olefins are also tolerated. Reaction of **21** cleanly provided **22**, demonstrating that sterically demanding 2,2,6,6-tetrasubstituted tetrahydropyrans can efficiently be formed (entry 17). To the best of our knowledge, no examples of Au-catalyzed exo-hydroalkoxylations of 3,3-disubstituted allenes to yield quaternary centers have been reported to date.

Several mechanistic scenarios are possible. Considering the fact that the *trans*-olefin **5** was obtained from the *cis*-allylic alcohol **18**, the possibility of forming an allyl cation followed by cyclization of the pendent hydroxyl group seemed likely. To test this hypothesis, compounds **23** and **24** were prepared, both of which would be predicted to yield the same cationic intermediate and product. When **23** was treated under the standard conditions, complete conversion to 2-vinyltetrahydropyran was effected in 20 min.[11] Diol **24** failed to react under both standard conditions or more forcing conditions with up to 5 mol % $Ph_3PAuCl/AgOTf$, temperatures up to 83 °C (DCE), or with $AuCl_3$. This disparity seems to rule out a cationic mechanism.



23



24

These data are consistent, however, with a mechanism that proceeds by an S_N2' pathway with gold(I) activating the allylic alcohol by coordination to the oxygen. What remains unclear is if the metal instead coordinates the olefin, which then undergoes hydroxyauration followed by elimination of Ph_3PAuOH to provide the product.

In summary, a highly efficient Au-catalyzed cyclization of monoallylic diols has been reported. The reaction tolerates a structurally diverse set of substrates and generates 2-vinyltetrahydropyrans in high yield with high diastereoselectivity. The reactions proceed at low temperatures with catalyst loadings as low as 0.1 mol %. Further investigation of the mechanism and application of the method to natural product synthesis is ongoing and will be reported in due course.

Acknowledgment. We gratefully acknowledge the University of Florida for startup funds and the Herman Frasch Foundation (647-HF07) and the donors of the Petroleum Research Fund (47539-G1) for their generous support of our programs.

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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(11) Cyclization of **23** smoothly provides 2-vinyltetrahydropyran, but the yield is not reported due to its volatility.