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A Highly Efficient Access to Spiroketals, Mono-unsaturated Spiroketals, and Furans: Hg(II)-Catalyzed Cyclization of Alkyne Diols and Triols

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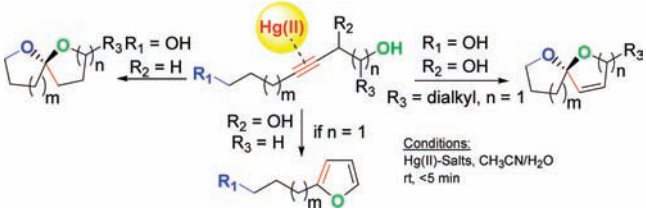
ABSTRACT



Hg(II) salts are identified as highly efficient catalysts for the versatile construction of spiroketals from alkyne diols in aqueous conditions. Monounsaturated spiroketals and furans were accessed with equal ease when propargylic triols (or propargylic diols) were subjected to similar conditions. Even the semiprotected alkyne diols gave the corresponding spiroketals with the same ease in a cascade manner. The reactions are instant and high yielding at ambient temperatures. Regioselectivity issues are well addressed.

Many natural products contain the spiroketal motif.[1] Various categories of biologically important molecules with this motif include insect pheromones,[1c,2] polyether antibiotics,[1b,3] and spongistatins/altohyrtins.[4] In addition to the fully saturated analogues, a number of families of natural products with an unsaturation in the spiroketal unit have been reported. Selected examples include azaspiracid,[5a] okadaic acid,[5b] avermectin,[5c] aigialospirol,[5d] and the spirastrellolides.[5e] In light of this, there has been an increased pursuit in the development of methodologies for the efficient construction of spiroketals. For many decades, the conventional strategy for this construction involved the formation of keto and hydroxyl functions separately with protection and deprotection sequence and subsequent acid-mediated ketalization.[1c] This method had several limitations such as multiple steps, purification of mixtures, and sensitivity of the substrates in highly acidic reaction conditions. Recent developments in oxy-functionalization of internal alkynes using mild acidic metal catalysts became potentially attractive approaches to overcome many of the problems mentioned above.[6] Using alkyne diols for the construction of the spiroketal unit has opened several

(1) For reviews on spiroketals, see: (a) Kluge, A. F. *Heterocycles* **1986**, *24*, 1699–1740. (b) Boivin, T. L. B. *Tetrahedron* **1987**, *43*, 3309–3362. (c) Perron, F.; Albizati, K. F. *Chem. Rev.* **1989**, *89*, 1617–1661. (d) Jacobs, M. F.; Kitching, W. B. *Curr. Org. Chem.* **1998**, *2*, 395–436. (e) Mead, K. T.; Brewer, B. N. *Curr. Org. Chem.* **2003**, *7*, 227–256. (f) Aho, J. E.; Pihko, P. M.; Rissa, T. K. *Chem. Rev.* **2005**, *105*, 4406–4440.

(2) Hintzer, K.; Weber, R.; Schurig, V. *Tetrahedron Lett.* **1981**, *22*, 55–58.

(3) Brasholz, M.; Sörgel, S.; Azap, C.; Reibig, H.-U. *Eur. J. Org. Chem.* **2007**, 3801–3814.

(4) (a) Yeung, K.-S.; Paterson, I. *Chem. Rev.* **2005**, *105*, 4237–4313. (b) Brimble, M. A.; Liu, Y.-C.; Trzoss, M. *Synthesis* **2007**, 1392–1402.

(5) (a) Ito, E.; Satake, M.; Ofuji, K.; Kurita, N.; McMahon, T.; James, K.; Yasumoto, T. *Toxicon.* **2000**, *38*, 917–930. (b) Tachibana, K.; Scheuer, P. J.; Tsukitani, Y.; Kikuchi, H.; Van Engen, D.; Clardy, J.; Gopichand, Y.; Schmitz, F. J. *J. Am. Chem. Soc.* **1981**, *103*, 2469–2471. (c) Miller, T. W.; Chaiet, L.; Cole, D. J.; Cole, L. J.; Flor, J. E.; Goegelman, R. T.; Gullo, V. P.; Joshua, H.; Kempf, A. J.; Krellwitz, R. L.; Monaghan, R. L.; Ormond, R. E.; Wilson, K. E.; Albers, S.; Putter, I. *Antimicrob. Agents Chemother.* **1979**, *15*, 368–371. (d) Vongvilai, P.; Isaka, M.; Kittakoop, P.; Srikitikulchai, P.; Kongsaeree, P.; Thebtaranonth, Y. *J. Nat. Prod.* **2004**, *67*, 457–460. (e) Warabi, K.; Williams, D. E.; Patrick, B. O.; Roberge, M.; Andersen, R. J. *J. Am. Chem. Soc.* **2007**, *129*, 508–509.

(6) (a) Liu, B.; Brabander, J. K. D. *Org. Lett.* **2006**, *8*, 4907–4910. (b) Aponick, A.; Li, C. Y.; Palmes, J. A. *Org. Lett.* **2009**, *11*, 121–124. (c) Selvaratnam, S.; Ho, J. H. H.; Huleatt, P. B.; Messerle, B.; Chai, C. L. L. *Tetrahedron Lett.* **2009**, *50*, 1125–1127. (d) Antoniotti, S.; Genin, E.; Michelet, V.; Genet, J. P. *J. Am. Chem. Soc.* **2005**, *127*, 9976–9977. (e) Ramana, C. V.; Suryawanshi, S. B.; Gonnade, R. G. *J. Org. Chem.* **2009**, *74*, 2842–2845.

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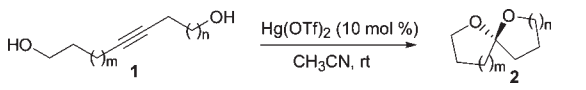
options for the increased convergence in the total synthesis of natural products[7] because of the availability of several methods to synthesize alkyne motifs. Also, alkynes are relatively inert toward many reaction conditions, making it a safe way for higher functionality order construction.

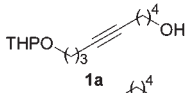
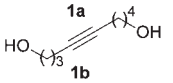
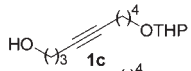
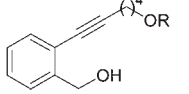
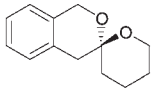
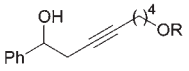
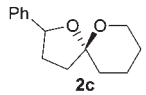
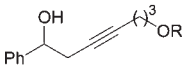
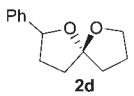
So far, Au(I), Au(III), Pt(II), Pd(II), Ir(I), and Rh(I) have been used for the synthesis of spiroketals from alkynediol motifs.[6,7a,8] There is still a great need for the development of a new catalytic system to address several issues together, viz. expensive catalysts, low yields, long reaction times, poor regioselectivities, elevated temperatures, and need of additional Bronsted acid catalysts and additives. In our recent paper on the synthesis of the natural product hippuristanol and its analogues,[9] we have reported the identification of $Hg(OTf)_2$-catalyzed transformation of semiprotected alkyne diol to the corresponding spiroketal unit in a cascade manner. Herein, we describe the scope and limitations of this new catalytic system,[10] addressing all of the issues mentioned above to make it a highly generalized method.

We began our investigations with a representative example **1a** (Table 1, entry 1). This substrate was selected by Brabander et al.[6a] to compare the efficiency of several catalysts and conditions regarding the yield, time, and regioselectivity. We considered this a good beginning to evaluate our catalyst system. Brabander reported that $PdCl_2$ and $AuCl_3$ yielded 6-*exo* and 7-*endo* products in an almost 2:1 ratio in 52% and 41% yields, respectively. Other Au catalysts, which needed other additive or Bronsted acid support, gave lower yields and regioselectivities.

Pt catalysts improved the yields and regioselectivities, but again needed Bronsted acid catalyst for both deprotection of THP ether and spiroketalization. When we subjected the same substrate to the catalytic system, 10 mol % of $Hg(OTf)_2$ in aqueous CH_3CN at ambient temperature, the 6-*exo* product **2a** was formed exclusively in 90% yield in a cascade manner. No further acid catalysts were needed for deprotection of THP acetal or to ensure cyclization. With this interesting result, we prepared various starting materials and subjected to the same conditions to get similar results which are summarized in Table 1. In entry 2, though the diol **1b** has the possibilities for both 5-*exo*- and 6-*exo-dig* cyclizations to give the corresponding 5,7- and 6,6-spiroketals, respectively, we observed only the later possibility to get 6,6-spiroketal **2a** in 92% yield. The same result was observed with substrate **1d** (entry 4) which gave exclusively 6-*exo* product **2b** in 94% yield. Then we

Table 1. Hg(II)-Catalyzed Spiroketalization of Various Internal Alkyne Diols



entry	substrate	product[a]	time	yield[b] (%)
1	 **1a**	 **2a**	45 min	90[c]
2	 **1b**	**2a**	45 min	92[d]
3	 **1c**	**2a**	45 min	90[c]
4	 R = H, **1d**	 **2b**	45 min	94[d]
5	R = THP, **1e**	**2b**	45 min	90[c]
6	 R = H,**1f**	 **2c**	10 min	92[d]
7	R = THP, **1g**	**2c**	10 min	90[c]
8	 R = H, **1h**	 **2d**	10 min	94[d]
9	R = THP, **1i**	**2d**	10 min	90[c]

[a] All the products were prepared as racemic mixture. [b] Isolated yields. [c] General procedure A used; see the Supporting Information. [d] General procedure B used; see the Supporting Information.

performed the reaction on **1c** (with the reversal of protection in **1a**) (entry 3) anticipating the 5-*exo-dig* cyclization either in full or part, but we observed the exclusive formation of 6,6-spiroketal **2a** in 90% yield. The same was ascertained with compound **1e** in entry 5 to furnish 6,6-spiroketal **2b** in 90% yield. This implies that the kinetics of the reaction favors the 6-*exo-dig* cyclization rather than 6-*endo*- or 5-*exo-dig* cyclizations.

Having found a solution for the 6-*exo* selective hydroalkoxylation, we next wanted to examine the 5-*endo-dig* cyclization. Thus, on exposure to the same reaction conditions, substrates **1f** and **1g** produced 5,6-spiroketal **2c** in 92% and 90% respectively. This could be either through 6-*exo-dig* or 5-*endo-dig* cyclizations. But interestingly, substrates **1h** and **1i** gave 5,5-spiroketal **2d** in 94% and 90% yields respectively implying that in all cases from **1f** to **1i** the reactions might have taken place through 5-*endo-dig* cyclization. Notably, the cyclization of substrates **1f**–**i** are faster than the other examples listed above implying that the transition state energy of 5-*endo-dig* cyclization is quite lower than 6-*exo-dig* cyclization.

Our next study was aimed at the evaluation of other mercury catalysts and conditions. We selected example **1h**

(7) (a) Li, Y.; Zhou, F.; Forsyth, C. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 279–282. (b) Trost, B. M.; O'Boyle, B. M.; Hund, D. *J. Am. Chem. Soc.* **2009**, *131*, 15061–15074. (c) Trost, B. M.; O'Blyle, B. M. *J. Am. Chem. Soc.* **2008**, *130*, 16190–16192. (d) Fang, C.; Pang, Y.; Forsyth, C. J. *Org. Lett.* **2010**, *12*, 4528–4531.

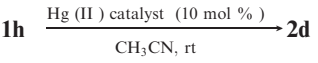
(8) (a) Zhang, Y.; Xue, J.; Xin, Z.; Xie, Z.; Li, Y. *Synlett.* **2008**, 940–944. (b) Li, X.; Chianese, A. R.; Vogel, T.; Crabtree, R. H. *Org. Lett.* **2005**, *7*, 5437–5440.

(9) (a) Ravindar, K.; Reddy, M. S.; Lindqvist, L.; Pelletier, J.; Deslongchamps, P. *Org. Lett.* **2010**, *12*, 4420–4423. (b) Ravindar, K.; Reddy, M. S.; Lindqvist, L.; Pelletier, J.; Deslongchamps, P. *J. Org. Chem.* **2011**, *76*, 1269–1284.

(10) Nishizawa, M.; Imagawa, H.; Yamamoto, H. *Org. Biomol. Chem.* **2010**, *8*, 511–521.

from Table 1 and the results are shown in Table 2. $HgCl_2$ was almost equally efficient for the spiroketalization of alkyne diols. Thus, when **1h** was treated with $HgCl_2$, 5,5-spiroketal **2d** was formed in 85% yield in 45 min compared to 94% yield in 10 min with $Hg(OTf)_2$. HgO was found to be very less reactive, whereas no product was observed with $Hg(OAc)_2$ even on prolonged reaction times. No considerable decrease in yield and no diminished reactivity were observed when **1h** was subjected to the spiroketalization in nonaqueous to aqueous conditions.

Table 2. Hg(II)-Catalyst Screening for Spiroketalization



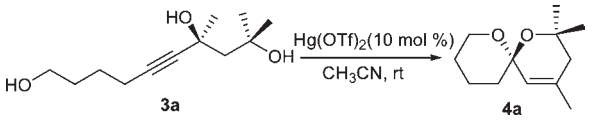
entry	Hg(II) catalyst	time	yield[a] (%)/yield[b] (%)
1	$Hg(OTf)_2$	10 min	94[a]/90[b]
2	HgCl2	45 min	85[a]/82[b]
3	HgO	3.5 h	15[a]/10[b]
4	$Hg(OAc)_2$	3.5 h	no product

[a] Isolated yield using general procedure B. See the Supporting Information for general procedures. [b] Isolated yield using general procedure A. See the Supporting Information for general procedures.

Having identified a good catalytic system for the spiroketalization of alkyne diols, we were interested in studying the reactivity pattern of a propargylic alcohol system which could lead to monounsaturated spiroketal motifs. This was previously reported by Aponick and coworkers[6b] using Au(I) catalysts, the use of additives, and in highly anhydrous conditions. Compound **3a** was prepared to explore the feasibility of our catalytic system toward this end. The reason for selecting this system is that the feasible 6-*exo-dig* (rather than 5-*exo-dig*) cyclization will lead to an intermediate with Hg and hydroxyl groups on adjacent carbons which is mandatory for the elimination process. Compound **3a** was then subjected to the catalytic system ($Hg(OTf)_2$, CH_3CN, rt) to get the expected product **4a** in excellent yield (96%) in a very quick reaction span (10 min). Other Hg catalysts were also evaluated for the same reaction where $HgCl_2$ was found to be equally efficient. $Hg(OAc)_2$ was very weakly effective while HgO showed no reactivity (Table 3). The interesting point here is that no care needs to be taken for maintaining anhydrous conditions in stark contrast with the Aponick's method.

With the optimal conditions established, we prepared other propargylic triols which were subjected to the standard reaction conditions. The results are summarized in Table 4. Substrates **3a** to **3e** produced the corresponding monounsaturated products **4a** to **4e** smoothly, whereas **3f** yielded hydroxyl ketal **4f** rather than dehydrated product **4g** likely because of a preferred 5-*endo* or 5-*exo* cyclization pathway. A mechanistic hypothesis consistent with the available data is presented in the Supporting Information.

Table 3. Hg(II) Catalyst Screening for Mono-unsaturated Spiroketals

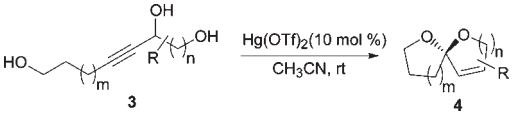


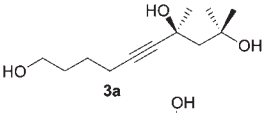
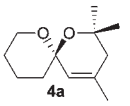
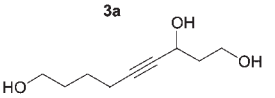
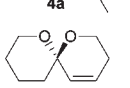
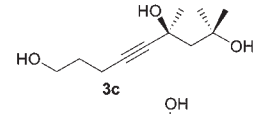
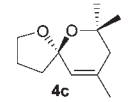
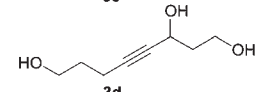
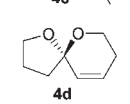
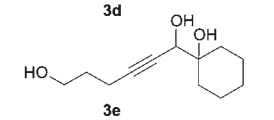
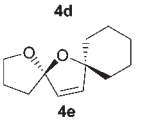
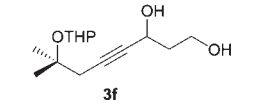
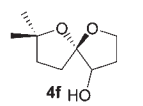
entry	Hg(II) catalyst	time	yield[a], [b] (%)
1	$Hg(OTf)_2$	5 min	96
2	$HgCI_2$	5 min	90
3	$Hg(OAc)_2$	2.5 h	10
4	HgO	2.5 h	no product

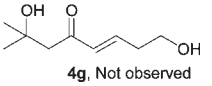
[a] Isolated yields. [b] General procedure C; see the Supporting Information.

Finally, we were curious to know the reactivity of 1, 2-dihydroxy-3-alkynes which would react through the 5-*endo-dig* cyclization mode to yield a 5-membered ring containing two unsaturations which could lead to the formation

Table 4. Synthesis of Mono-unsaturated Spiroketals Using $Hg(OTf)_2$

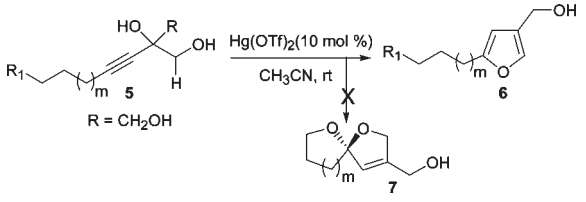


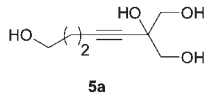
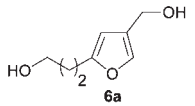
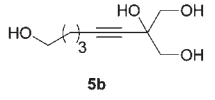
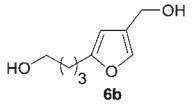
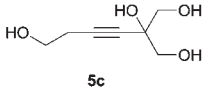
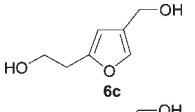
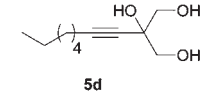
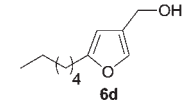
entry	substrate	product[a]	time	yield (%)[b]
1			5 min	96
2			5 min	90
3			5 min	96
4			5 min	95
5			5 min	95
6			5 min	95



[a] All of the products were prepared as a racemic mixture. [b] Isolated yield. General procedure C was used; see the Supporting Information.

Table 5. Synthesis of Substituted Furans Using $Hg(OTf)_2$



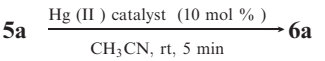
entry	substrate	product	time	yield (%)[a]
1	 **5a**	 **6a**	5 min	98
2	 **5b**	 **6b**	5 min	95
3	 **5c**	 **6c**	5 min	96
4	 **5d**	 **6d**	5 min	96

[a] Isolated yield. General procedure D was used; see the Supporting Information.

of the furan ring rather than hydrolysis to corresponding ketones or unsaturated spiroketals **7**. Accordingly, tetrol **5a** was prepared and upon subjection to the standard conditions gave directly the furan **6a** in excellent yield of 98%. To test the generality of this method, substrates **5b**–**d** were evaluated and the results are shown in Table 5. We are convinced that this is an excellent general method for the synthesis of furans some of which are biologically important and naturally occurring.[11]

Efficiency of various Hg(II) catalysts on this furan formation is presented in Table 6. As observed for other reactions, $HgCl_2$ was equally efficient, but $Hg(OAc)_2$ and HgO showed moderate and no reactivities, respectively.

Table 6. Hg(II) Catalyst Screening for the Synthesis of Substituted Furans



entry	Hg(II) catalyst	time	yield[a] (%)
1	$Hg(OTf)_2$	5 min	98
2	$HgCl_2$	5 min	96
3	$Hg(OAc)_2$	4 h	5
4	HgO	5 h	no product

[a] Isolated yields.

In conclusion, we have demonstrated that the Hg(II) catalysts are highly efficient and economical ($HgCl_2$) utilizing a simple experimental procedure for the synthesis of various saturated and unsaturated spiroketals, and furans. The regioselectivity issues are well addressed, and different products can be obtained by appropriate modification of the substitution pattern.

Acknowledgment. We thank NSERCC for funding.

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

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