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Gold/Acid-Cocatalyzed Regiodivergent Preparation of Bridged Ketals *via* Direct Bis-Oxycyclization of Alkynic Acetonides

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In memory of our colleague and friend José Manuel Concellón.

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Abstract: The regioselective metal/acid co-catalyzed direct bis-oxycyclization of alkynyldioxolanes allows the efficient synthesis of optically pure bi- and tricyclic bridged acetal systems.

Keywords: alkynes; gold; heterocycles; regioselectivity; synthetic methods

Acetals are structural units which have been shown to be the major component of many biologically important natural products and functional molecules. Thus, the synthesis of these heterocycles is of current interest. The use of gold salts has gained a lot of attention in the recent times because of their powerful soft Lewis acidic nature.[1] In particular, activation of alkynes towards attack by oxygen nucleophiles such as carbonyls, carboxylic acids, and alcohols, is an important C–O bond-forming reaction.[2] Although many efforts have been made in these fields, metal-catalyzed heterocyclizations of alkynes bearing a dioxolane ring as nucleophilic moiety have not been mentioned in the literature. Encouraged by our recent results in heterocyclic chemistry,[3] we thought that regioselective metal-catalyzed direct bis-oxycyclization of alkynyldioxolanes may occur by judicious choice of the catalytic system. Herein, we report our findings in this field.

The structures of alkynyldioxolanes **1** that we synthesized and used for bis-oxycyclization are shown in Figure 1.[4] Alkynyldioxolane **1a** was chosen as a model substrate for metal-catalyzed cycloetherification reactions. To screen the reactivity of the alkynyldioxolane moiety, several metal salts were screened. While AgOTf, $FeCl_3$, and $[PtCl_2(CH_2{=}CH_2)]_2$ could not catalyze the heterocyclization reaction alone or in the presence of different additives, the catalytic system $AuCl_3$/PTSA gave the desired ketal **2a** in a low 30% yield. Fortunately, we found that under the appropriate reactions conditions, a gold(I) salt along with a Brønsted (or Lewis) acid could be an excellent cooperative catalytic system for this purpose (Table 1, entries 8 and 9).[5] The Lewis and Brønsted acid co-catalysts, $FeCl_3$ and PTSA, were effective, but the former did not exhibit the wide applicability observed

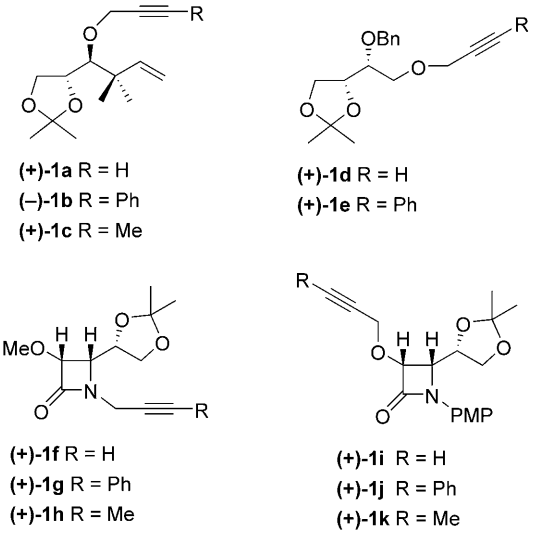
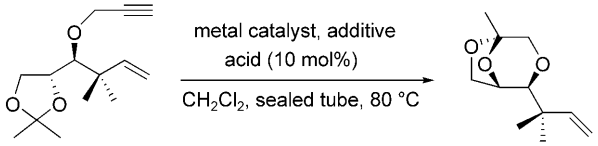


Figure 1. Structures of alkynyldioxolanes **1a–k**. PMP = 4-$MeOC_6H_4$.

Table 1. Selective cyclo-ketalization reaction of alkynyldioxolane **1a** under modified metal/Brønsted (or Lewis) acid-cocatalyzed conditions.[a]



(+)-**1a** (–)-**2a**

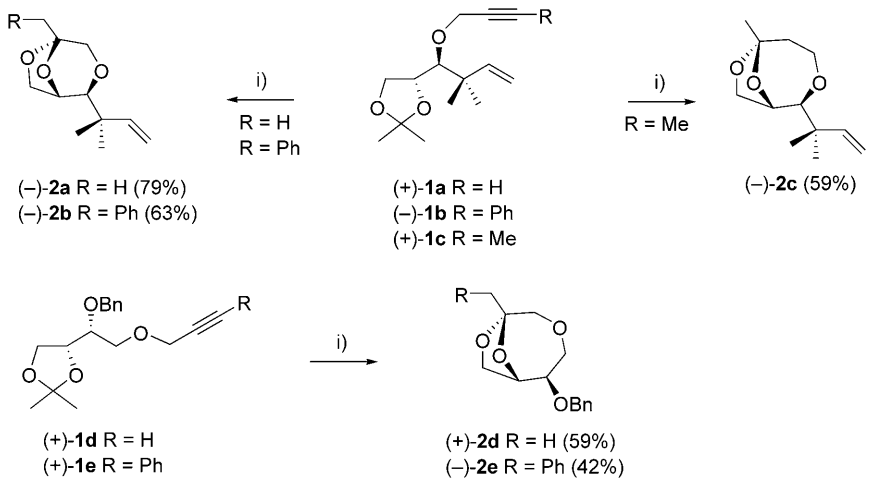
Entry	Metal catalyst (mol%)	Additive (mol%)	Time [h]	Acid	Conversion, yield [%]
1	$[PtCl_2(CH_2{=}CH_2)]_2$ (1)	TDMPP (2)	24	–	–
2	AgOTf (5)	–	24	PTSA	–[b]
3	$FeCl_3$ (10)	–	24	–	–[b,c]
4	$AuCl_3$ (2.5)	–	24	PTSA	100, 30
5	AuCl (2.5)	–	24	PTSA	100, 40
6	$[AuClPPh_3]$/AgOTf (2.5)	–	24	$FeCl_3$	90, 35
7	$[AuClPPh_3]$/AgOTf (2.5)	–	24	PTSA	95, 46
8	$[AuClPPh_3]$/AgOTf (2.5)	H_2O (100)	15	$FeCl_3$	100, 55
9	$[AuClPPh_3]$/AgOTf (2.5)	H_2O (100)	3	PTSA	100, 79

[a] Yield of pure, isolated product with correct analytical and spectral data; conversion = ^{1}H NMR conversions.
[b] Quantitative conversion to the corresponding uncyclized alkynyldiol was observed.
[c] No methyl ketone formation was observed despite it has been recently reported the iron chloride-catalyzed hydration of terminal alkynes.[14] TDMPP = tris(2,6-dimethoxyphenyl)phosphine, PTSA = *p*-toluenesulfonic acid.

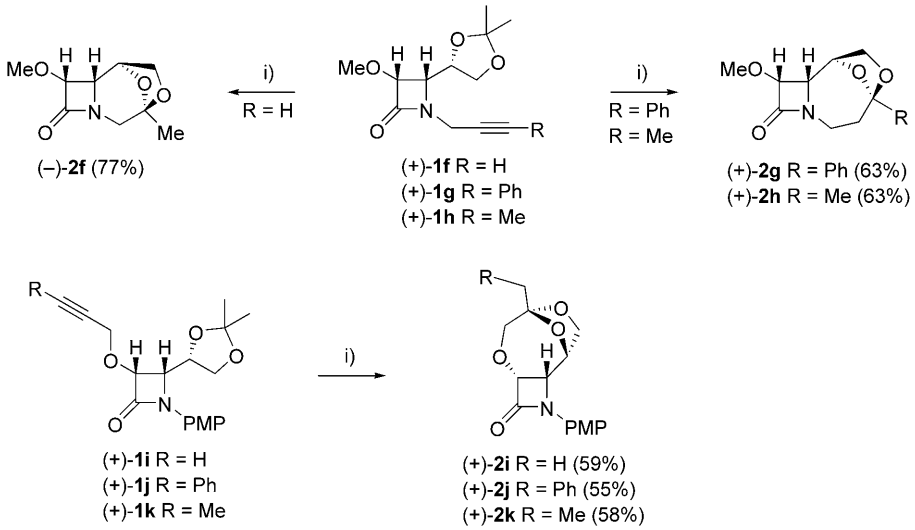
in the case of *p*-toluenesulfonic acid. Adding a stoichiometric amount of water into the reaction system did improve the yield of **2a**. Treatment of alkynyldioxolane **1a** with $[AuClPPh_3]$ (2.5 mol%)/AgOTf (2.5 mol%)/PTSA (10 mol%)/H_2O (100 mol%) in dichloromethane at 80 °C on a sealed tube afforded the best yield of the 6-*exo*/5-*exo* bis-oxycyclization to afford the corresponding bicyclic ketal as a single regio- and diastereomer (Table 1).

With these optimal conditions in hand, we applied them to the precious metal-catalyzed bis-oxycyclization reaction of alkynyldioxolanes **1b–e**. The synthetic power of the process can be best demonstrated by application of phenyl-substituted alkynyldioxolane **1b** to the preparation of bridged acetal **2b**. By contrast, and to our delight, the exposure of methyl-substituted alkynyl dioxolane **1c** to these reactions conditions exclusively afforded the 7-*endo*/5-*exo* bis-oxycyclization bridged acetal **2c** with not even a trace of the corresponding 6-*exo*/5-*exo* adduct; thus indicating that the nature of the alkyne side chain is crucial to the regioselectivity of the cyclization. At present, we have no explanation for this behaviour. The bis-cycloetherification was also accomplished on increasing the distance between the dioxolane group and the alkyne moiety, such as in the analogous homologue substrates **1d** and **1e**. The related bridged acetals **2d** and **2e** (proximal adducts) were formed as single isomers in reasonable yields following the same regiochemical pattern as for **1a** and **1b**. All the reactions were complete in 3 h as monitored by TLC, providing trioxabicyclo[3.2.1]octanes or trioxabicyclo[4.2.1]nonanes exclusively. The results are shown in Scheme 1. It was desirable to scale-up the procedure to obtain gram quantities of the ketal derivatives. Nicely, it quickly became clear that scale-up was possible. Thus, an isolated 75% yield of adduct **2a** was obtained when the reaction was carried out on a gram scale.

Given the interest in β-lactams and aiming to extend the methodology beyond bicyclic acetals, 2-azetidinone-tethered alkynyldioxolanes **1f–k** were explored as substrates.[6] Using the terminal alkyne **1f**, the catalytic system $AuCl_3$/PTSA gave the desired ketal **2f** accompanied by appreciable amounts of a polar ketone, arising from alkyne hydration.[7] Again, the $[AuClPPh_3]$/AgOTf/PTSA system demonstrated better activity. Interestingly, reaction times for complete conversion were similar to those for the simpler alkynyldioxolanes **1a–e**. Worthy of note, in contrast to the precious metal/acid-cocatalyzed reaction of terminal alkynyl dioxolane **1f** which leads to the 6,8-dioxabicyclo[3.2.1]octane derivative **2f** (proximal adduct), the reactions of substituted at the terminal end alkynyl dioxolanes **1g** and **1h** under identical conditions gave the 7,9-dioxabicyclo[4.2.1]nonane derivatives **2g** and **2h** (distal adducts) as the sole products (Scheme 2), through an exclusive 7-*endo*/5-*exo* bis-oxycyclization by initial attack of the oxygen atom to the external alkyne carbon. The competition between the initial 6-*exo* and 7-*endo* oxycyclizations is gained by the latter, in spite of the *a priori* fact that it should be energetically more demanding. The structure and stereochemistry of the tricyclic acetal **2g** were deter-



Scheme 1. Controlled precious metal/Brønsted acid-cocatalyzed preparation of bridged bicyclic acetals **2a–e**. *Reagents and conditions:* i) 2.5 mol% $[AuClPPh_3]$, 2.5 mol% AgOTf, 10 mol% PTSA, 100 mol% H_2O, CH_2Cl_2, sealed tube, 80 °C, **2a**: 3 h; **2b**: 3 h, **2c**: 2 h; **2d**: 3 h; **2e**: 3 h. PTSA = *p*-toluenesulfonic acid.



Scheme 2. Controlled precious metal/Brønsted acid-cocatalyzed preparation of bridged tricyclic acetals **2f–k**. *Reagents and conditions:* i) 2.5 mol% $[AuClPPh_3]$, 2.5 mol% AgOTf, 10 mol% PTSA, 100 mol% H_2O, CH_2Cl_2, sealed tube, 80 °C, **2f**: 2 h; **2g**: 3 h; **2h**: 2 h; **2i**: 2 h; **2j**: 3 h; **2k**: 3 h. PMP = 4-$MeOC_6H_4$, PTSA = *p*-toluenesulfonic acid.

mined by X-ray crystallography,[8] as it is shown in Figure 2. Although we suspected that on the β-lactam series the regioselectivity for the phenyl- or methyl-substituted alkynyldioxolanes **1j** and **1k** would be the same as for the previous set of experiments for substituted alkynyldioxolanes **1g** and **1h**, we found that in this case bridged tricyclic acetals **2j** and **2k** (proximal adducts) were obtained as single regio- and diastereomers. Thus, by using a related alkynyldioxolane homologue (**1j** *versus* **1g** or **1k** *versus* **1h**), the regioselectivity can be reversed, favouring the 7-*exo*/5-*exo* bis-oxycyclization of the acetonide group towards the internal alkyne carbon (proximal adduct) over the 8-*endo*/5-*exo* bis-oxycyclization towards the external alkyne carbon (distal adduct). The exclusive formation of proximal adducts **2j** and **2k** would be interpreted by considering the ring size of the intermediates (7-membered *versus* 8-membered rings). Probably, the combination of developing ring strain and the requirement to restrict rotations around flexible bonds in the fused 8,10-dioxabicyclo[5.2.1]decane system ensures unfavourable enthalpic and entropic contributions to ΔG, avoiding its formation.

The reaction may tentatively be classified as cooperative concurrent catalysis, involving a catalytic action by the Au(I) salt on the alkynic site, and by the Brønsted (or Lewis) acid on the activation of the transient methylenic intermediate.[9] AgOTf cannot be considered as a cocatalyst because its action is generally assumed to be restricted to forming cationic gold species by anion exchange.[10] A possible pathway for the gold/acid-cocatalyzed alkynyldioxolane cyclization

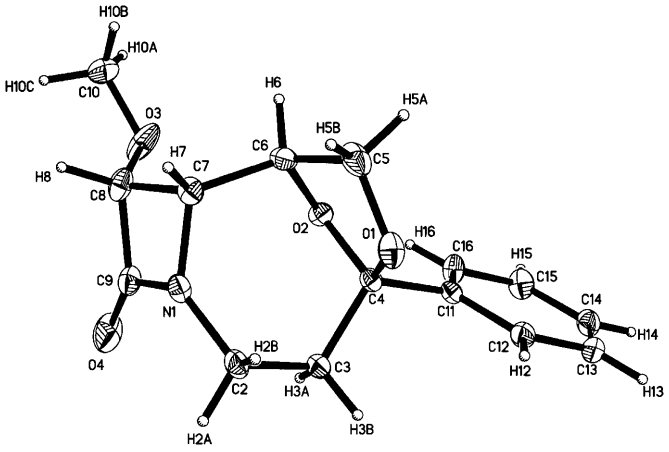
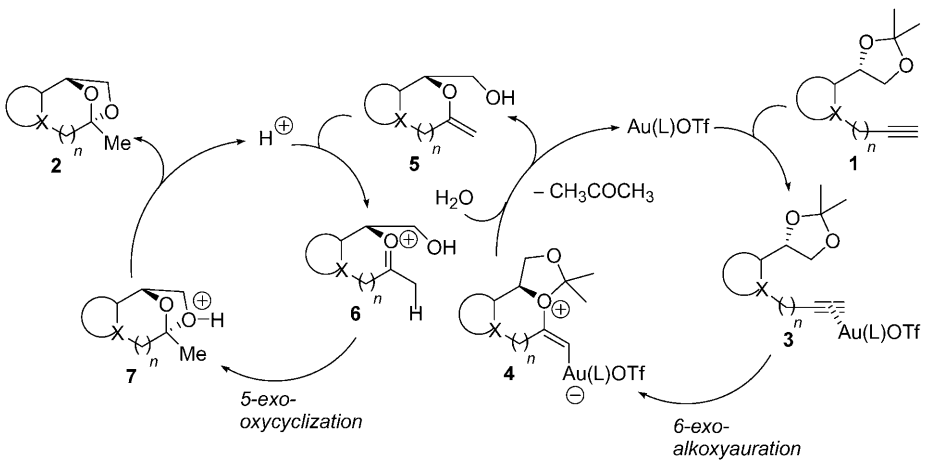


Figure 2. X-ray diffraction analysis of tricyclic bridged acetal **2g**.

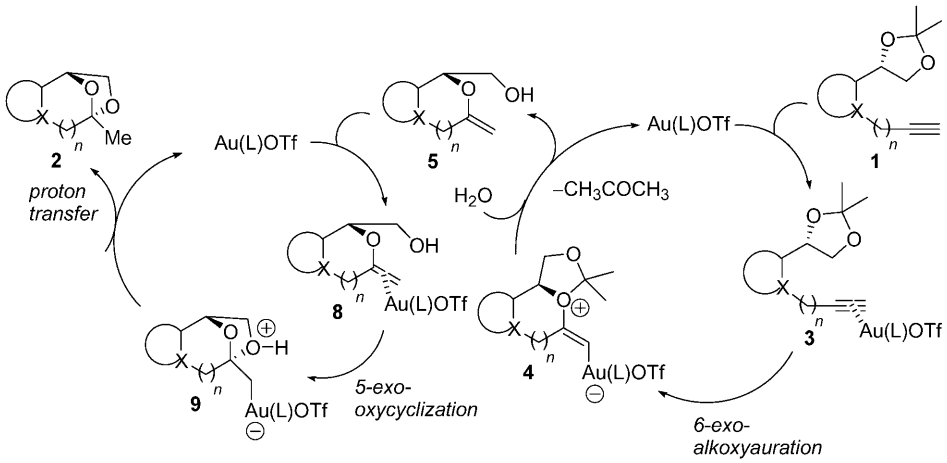
may initially involve the formation of a π-complex **3** through coordination of the gold salt to the triple bond of alkynyldioxolanes **1**.[11] Next, 6-*exo* oxymetalation forms the zwitterionic enol vinylmetal species **4**. Intermediates **4** would evolve through demetalation and acetonide hydrolysis forming methylenic oxacycles **5** and releasing the metal catalyst into the first catalytic cycle. Methylenic oxacycles **5** enter the second catalytic cycle generating species **6** by protonation of the alkene group, thus, enhancing the electrophilicity of the resulting carbonyl carbon. Subsequent intramolecular nucleophilic attack of the primary alcohol to the carbonylic-like position would form oxoniums **7**. Deprotonation liberates adduct **2** with concomitant regeneration of the acid catalyst, closing the second catalytic cycle (Scheme 3).

On the basis of the experimental results, an alternative mechanism for the observed catalytic cyclo-ketalization of alkynyldioxolanes to produce ketals could be proposed (Scheme 4). Accordingly, it is also possible that a catalytic action by the Au(I) salt, with the collaboration of the Brønsted (or Lewis) acid would exhibit a benefitial influence.[5,9] Mechanistically, this gold-catalyzed reaction might also proceed in a tandem sequence involving as the first step the formation of the π-complex **3** through coordination of the gold salt to the triple bond of alkynyldioxolanes **1**.[11,12] As above in Scheme 3, species **3** evolves through 6-*exo* alkoxyauration to intermediates **4**, which after sequential demetalation and acetonide hydrolysis lead to methylenic oxacycles **5**, releasing the gold catalyst into the first catalytic cycle. Next, methylenic oxacycles **5** enter the second catalytic cycle, which is also gold-catalyzed, generating species **8** by coordination of the alkene group with the metal, thus enhancing the electrophilicity of the resulting enol ether. Subsequent intramolecular nucleophilic attack of the primary alcohol to the internal alkene position would form the ate complex **9**. Demetalation linked to proton transfer liberates adduct **2** with concomitant regeneration of the gold catalyst, closing the second catalytic cycle (Scheme 4).

In order to confirm the mechanistic proposals of Scheme 3 and Scheme 4, we performed in substrate **1g** both a control experiment as well as labeling studies with deuterium oxide. A mechanistic experiment was carried out, namely, the reaction of acetonide **1g** under gold catalysis in the absence of acid additive. In this event, the reaction proceeded to afford the corresponding ketal **2g** in just a slightly lower 58% yield. Even more important, the gold catalyst alone did not produce an observable intermediate of type **5**. This would suggest that the acid is not necessarily needed for the second step of the proposed catalytic cycle to proceed, because this latter step may also be catalyzed by gold. However, the comparative studies of ketal formation with addition of PTSA demonstrated that the presence of the Brønsted acid gives higher yields. On the basis of the above results, Scheme 4 should be the more plausible reaction mechanism.



Scheme 3. Mechanistic explanation for the metal/acid-cocatalyzed controlled preparation of bridged ketals.



Scheme 4. Mechanistic explanation for the gold-catalyzed controlled preparation of bridged ketals.

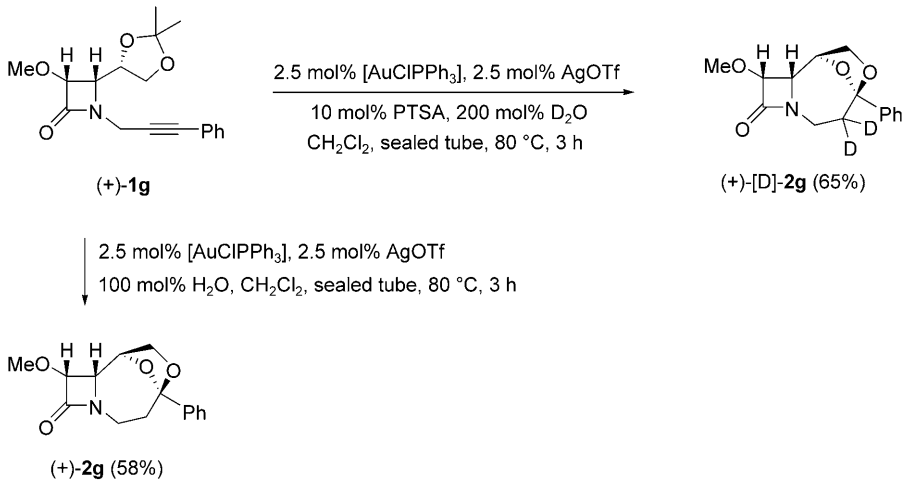
When alkynyldioxolane **1g** was treated under cycloketalization conditions employing D_2O (200 mol%) instead of H_2O, adduct **2g** with incorporation of two deuterium atoms at the methylenic group was achieved (Scheme 5). This double deuteration caused both the modification of the peaks at 3.10 and 3.87 ppm, which are the signals of the NC*HH* protons, and the disappearance of the peaks at 1.94 and 2.34 ppm, which are the signals of the NCH_2CHH protons, on the 7,9-dioxabicyclo[4.2.1]nonane **2g**. The fact that the gold-catalyzed conversion of alkynyldioxolane **1g** into tricycle **2g** in the presence of 2 equiv. of D_2O afforded double deuterated product [D]-**2g** as judged by ^1H NMR spectroscopy and mass spectrometry (see Supporting Information), suggests that deuterolysis of the carbon-gold bond in species **4** as well as deuteration of species of type **9** have occurred (Scheme 4).

In summary, a novel method was developed for the regio- and stereocontrolled synthesis of enantiopure bridged bi- and tricyclic ketals *via* a selective cycloketalization reaction of alkynyldioxolanes under precious metal/Brønsted (or Lewis) acid-cocatalyzed conditions. Further studies on the scope and synthetic applications of these reactions are currently in progress.

Experimental Section

Typical Procedure for the Metal/Acid Co-Catalyzed Cyclization to Bridged Acetals using Alkynyldioxolane 1g

[$AuClPPh_3$] (0.0040 mmol), AgOTf (0.0040 mmol), *p*-toluenesulfonic acid (0.016 mmol), and water (0.16 mmol) were sequentially added to a stirred solution of the alkynyldioxolane (+)-**1g** (49 mg, 0.16 mmol) in dichloromethane



Scheme 5. Au(I)-catalyzed bis-oxycyclization reaction of alkynyldioxolane derivative **1g** both in the presence of D_2O and in the absence of acid.

(0.16 mL). The resulting mixture was heated in a sealed tube at 80 °C for 3 h. The reaction was allowed to cool to room temperature and filtered through a pack of celite. The filtrate was extracted with ethyl acetate (3×3 mL), and the combined extracts were washed twice with brine. The organic extract was washed with brine, dried ($MgSO_4$), concentrated under reduced pressure, and purified by flash column chromatography on silica gel (hexanes/ethyl acetate = 1:1) to afford the product (+)-**2g** as a colorless solid; yield: 26 mg (63%); mp 150–152 °C; $[\alpha]_D$: +5.0 (*c* 1.1 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.44 (m, 5H), 4.66 and 4.57 (d, J = 4.8 Hz, each 1H), 4.09 (m, 1H), 4.01 (dd, J = 8.1, 4.9 Hz, 1H), 3.87 (ddd, J = 14.4, 5.4, 1.5 Hz, 1H), 3.79 (d, J = 4.6 Hz, 1H), 3.63 (s, 3H), 3.10 (ddd, J = 14.6, 12.0, 4.2 Hz, 1H), 2.34 (ddd, J = 14.4, 12.2, 5.4 Hz, 1H), 1.94 (ddd, J = 14.4, 3.9, 1.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 168.2, 142.5, 128.2, 128.1, 124.7, 111.8, 83.5, 72.2, 71.2, 63.0, 59.2, 38.6, 36.5; IR ($CHCl_3$): ν = 1748, 1190, 1044 cm^{-1}; HR-MS (ES): m/z = 276.1232, calcd (%) for $C_{15}H_{18}NO_4$ $[M+H]^+$: 276.1236.

Acknowledgements

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[8] X-ray data of **2g**: crystallized from ethyl acetate/*n*-hexane at 20 °C; $C_{15}H_{17}NO_4$ (M_r = 275.30); monoclinic; space group = *P*21; a = 11.3463(16) Å, b = 5.8344(8) Å.; c = 11.4061(16) Å; β = 112.014(2) deg.; V = 700.02(17) Å^3; Z = 2; density (calc.) = 1.306 mg m^{-3}; μ = 0.095 mm^{-1}; F(000) = 292. A transparent crystal of 0.45×0.19×0.10 mm^3 was used. 2990 [R(int) = 0.0930] independent reflections were collected on a Bruker Smart CCD difractomer using graphite-monochromated Mo-Kα radiation (λ = 0.71073 Å) operating at 50 kV and 30 mA. Data were collected over a hemisphere of the reciprocal space by combination of three exposure sets. Each exposure of 20 s covered 0.3 in ω. The cell parameters were determined and refined by a least-squares fit of all reflections. The first 100 frames were recollected at the end of the data collection to monitor crystal decay, and no appreciable decay was observed. The structure was solved by direct methods and Fourier synthesis. It was refined by full-matrix least-squares procedures on F^2 (SHELXL-97). All non-hydrogen atoms were refined anisotropically. All hydrogen atoms were included in calculated positions and refined riding on the respective carbon atoms. Final R(Rw) values were $R1$ = 0.0863 and $wR2$ = 0.1696. CCDC 711398 contains the supplementary crystallographic data for this

paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif (or from The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB21EZ, UK; Fax (+44)-1223-336033; or deposit@cccdc.cam.ac.uk).

[9] Control experiments have ruled out the hypothesis of Brønsted acid catalysis; although competition between gold and Brønsted acids has been described, see: a) G. Dyker, E. Muth, A. S. K. Hashmi, L. Ding, *Adv. Synth. Catal.* **2003**, *345*, 1247; b) D. Kadzimirsz, D. Hildebrandt, K. Merz, G. Dyker, *Chem. Commun.* **2006**, 661; c) W.-J. Shi, Y. Liu, P. Butti, A. Togni, *Adv. Synth. Catal.* **2007**, *349*, 1619, no conversion to acetal **2a** was observed from the reaction of alkynyldioxolane **1a** in the absence of gold salt.

[10] A. Duschek, S. F. Kirsch, *Angew. Chem.* **2008**, *120*, 5787; *Angew. Chem. Int. Ed.* **2008**, *47*, 5703.

[11] A mechanistic scenario involving the initial formation of the 1,2-diol followed by bis-hydroalkoxylation is less likely. A control experiment showed that the diol derived from acetonide **1f** did react in dichloromethane at 80 °C on a sealed tube in the presence of [AuClPPh$_3$] (2.5 mol%)/AgOTf (2.5 mol%)/FeCl$_3$ (10 mol%)/H$_2$O (100 mol%) to afford a complex mixture of products, in which the tricyclic acetal **2f** was not detected. No reaction occurred on heating a solution of the above diol in dichloromethane at 80 °C on a sealed tube in the presence of [AuClPPh$_3$] (2.5 mol%)/AgOTf (2.5 mol%)/FeCl$_3$ (10 mol%). The fact that the reaction of acetonide **1g** catalyzed by the π-philic gold complex [Au(OTf)PPh$_3$] alone, in the absence of acid additive, proceeded to afford the corresponding ketal **2g**, may also support this order of steps: the ketal in species **3** attacks the alkyne and the resulting oxonium then is hydrolyzed.

[12] For the the synthesis of acetals by gold-catalyzed attack of diols onto alkynes, see: a) S. Antoniotti, E. Genin, V. Michelet, J.-P. Genêt, *J. Am. Chem. Soc.* **2005**, *127*, 9976; b) A. Diéguez-Vázquez, C. C. Tzschucke, J. Crecente-Campo, S. McGrath, S. V. Ley, *Eur. J. Org. Chem.* **2009**, 1698; c) L.-P. Liu, G. B. Hammond, *Org. Lett.* **2009**, *11*, 5090.

[13] It has been demonstrated that an ether oxygen atom can serve as an excellent nucleophile in reacting with gold-coordinated alkynes, leading to an ether transfer: H. J. Bae, B. Baskar, S. E. An, J. Y. Cheong, D. T. Thangadurai, I.-C. Hwang, Y. H. Rhee, *Angew. Chem.* **2008**, *120*, 2295; *Angew. Chem. Int. Ed.* **2008**, *47*, 2263.

[14] X.-F. Wu, D. Bezier, C. Darcel, *Adv. Synth. Catal.* **2009**, *351*, 367.

