Solvent Effect in Gold(I)-Catalyzed Domino Reaction : Access to Furo-pyrans.

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ABSTRACT: We report an efficient synthesis of furo-pyrans through a gold(I)-catalyzed domino reaction. Starting from the same source, and by changing the solvent of the reaction, two classes of furo-pyrans are accessible. During this one-step process, which takes place in DMF, two bonds and two heterocycles are formed. DFT calculations furnish the mechanistic understanding of this transformation. The sequence includes a 5-*endo*-dig cyclization, a regioselective 8-*endo*-dig cyclization, a retro 8 π and a 6 π electro-cyclization.

Heterocycles are frequently found in biologically active natural and unnatural compounds, and, many drugs and agrochemicals include heterocyclic structures.¹ Among heterocycles, furo-pyran scaffolds are the structural fragments of many natural compounds and synthetic biologically active substances such as hyperaspindiol or coumestrol and derivatives from the pterocarpans family (Scheme 1).²

Scheme 1. Furo-pyran scaffolds.

Significant advances toward the synthesis of heterocyclic scaffolds have been achieved in homogeneous gold catalysis.³ Besides, over the past decade, homogeneous gold catalysis as part of domino processes has been the subject of intense research because of its potential to rapidly build molecular complexity.⁴

In this context, we have previously reported the synthesis of complex furo-pyran derivatives **2** through a gold(I)-catalyzed hetero Diels-Alder (HDA) domino reaction (Scheme 2).⁵ We

have shown that in 1,4-dioxane, the diene and the dienophile are formed simultaneously from **1** by a unique catalyst action. Continuing our exploration in this field, we report herein the synthesis of new furo-pyran derivatives **3**, starting from the same starting material **1**, and only by changing the solvent of the reaction to DMF.

Scheme 2. Gold(I)-catalyzed cascade reaction for the synthesis of furo-pyran derivatives **2 and **3**.**

During this one-step transformation, two bonds, two heterocycles and a quaternary center are formed with 100% atom economy.⁶ DFT calculations furnish the mechanistic understanding of this transformation.

To explain the formation of products **2** and **3** (Scheme 3), we proposed two different pathways (**I** and **II**, Scheme 3). The coordination of compound **1** by the cationic gold(I) complex leads to the π -alkyne complex **4**, permitting a 5-*endo*-dig cyclization of the alcohol to the triple bond producing the vinyl-gold oxonium **5**.⁷ A protodeauration is followed by the formation of a new gold(I) complex by coordination of the residual triple bond, giving the activated intermediate **6**. This intermediate undergoes an 8-*endo*-dig cyclization⁸ of the previously formed enol to the alkyne,⁹ giving complex **7**. From the common intermediate **7**, two pathways are possible, **I** and **II**.¹⁰ As previously described,^{5a} complex **7** undergoes a Grob-type fragmentation, set off by the gold release, forming heterodiene **8** bearing an allene group (Pathway **II**).¹¹ A HDA between heterodiene **8** and dienophile **9** occurs to give the final compound **2** upon a gold(I)-catalyzed hydroarylation.¹² For Pathway **I**, complex **7** undergoes a protodeauration, triggered by the conjugation of the π system, leading to the formation of cyclooctatriene **10**. Then, an 8 π retro-electrocyclization and a subsequent 6 π electrocyclization afford the desired furopyran **3**. As shown below, playing only with solvents, we succeeded to find the optimized conditions in which the protodeauration of **7** is fast enough to give **3**, or sufficiently slow to allow the formation of **2**.

Scheme 3. Proposed mechanism for the formation of 2 and 3.

Solvents play an important role in gold(I) chemistry, especially during the crucial protodeauration step. Indeed, the proton transfer can be assisted by the solvent, the adventitious water it may contain if hygroscopic, the counterion which can be virtually free in a polar environment, or nucleophiles present in

the reaction mixture.¹³ Considering the solvent by itself, depending on its hydrogen-bond basicity (pK_{BHX}), it may act as a proton shuttle, enhancing the efficacy of gold(I)-catalyzed reactions through hydrogen-bonding assisted protodeauration.¹³ In this context, various solvents were tested, and depending on their pK_{BHX} , the pathways **I** or **II** were favored, giving access to compounds **2** or **3** exclusively. In order to optimize the reaction conditions, substrate **1a** was used as model substrate (Table 1).

Table 1. Optimization of the reaction conditions.^[a]

Entry	Catalyst	Solvent (pK_{BHX})	Temp. /Time	Yield (%) ^[b]
1	Cat. A	DCE (-0.6)	RT/3 h	52 ^[b] (2a)
2	Cat. A	THF (1.3)	RT/3 h	41 ^[c] (2a)
3	Cat. A	CH ₂ Cl ₂ (-0.8)	RT/3 h	60 ^[b] (2a)
4	Cat. A	CHCl ₃ (-)	RT/3 h	62 ^[b] (2a)
5	Cat. A	Dioxane (0.7)	RT/3 h	61 ^[c] (2a)
6 ^[g]	Cat. A	Dioxane	60 °C/20 min ^[e]	68 ^[b] (2a)
7	Cat. A	DMF (2.1)	60 °C/20 min ^[e]	77 ^[b] (3a)
8	Cat. A	DMF	RT/3 h	53 ^[b] (10a/3a :1/1)
9	Cat. A	DMF	60 °C/3 h	57 ^[b] (3a)
10	Cat. A	DMSO (2.0)	60 °C/3 h	56 ^[b] (3a)
11	Cat. B	DMSO	60 °C/3 h	55 ^[b] (3a)
12	(Ph ₃ P)AuCl/ AgSbF ₆	DMF	60 °C/3 h	CM ^[d]
13	(Ph ₃ P)AuNTf ₂	DMF	60 °C/3 h	CM ^[d]
14	Cat. C/AgSbF ₆	DMF	60 °C/3 h	CM ^[d]
15	Cat. D/AgSbF ₆	DMF	60 °C/3 h	CM ^[d]

[a] The reactions were performed in the presence of the catalyst (5 mol%) and **1a** in the indicated solvent (0.145 M). [b] Isolated yield. [c] Calculated yield by integration of the ¹H-NMR of the

crude product relatively to the internal reference (caffeine). [d] CM: Complex mixture. [e] With microwave irradiation. [f] No data in the literature. [g] With 1.0 equiv of Et₃N, **9a** (major product) and **3a** (traces).

As previously described,^{5a} the use of solvents such as DCE, DCM, CHCl₃, 1,4-dioxane and THF in the presence of the pre-activated cationic gold(I) complex **A** affords **2a** with at best 68% yield (entries 1-6).⁵ pK_{BHX} of such solvents are between -0.5 and 1.3, seemingly not high enough to favor the proto-deauration, leaving the Grob-type fragmentation prevailing to give **2a**. By using solvents with $pK_{\text{BHX}} \geq 2$, we observed the selective formation of a new product, furopyran **3a** (entry 7, 77% yield in DMF). The structure of **3a** was unambiguously determined by ¹H and ¹³C NMR experiments. During this transformation, two bonds and two heterocycles, including a fused system, were formed, as well as one quaternary carbon. We next screened other reaction conditions. A mixture of cyclooctatriene **10a** and furopyran **3a** was observed at room temperature for 3 h, with 53% overall yield (entry 8). At 60 °C, only the furopyran **3a** was observed with 57% yield (entry 9). A similar result was obtained using DMSO as solvent in the presence of catalyst **A** or **B** (56% and 55% yield, entries 10 and 11). The use of (Ph₃P)AuCl/AgSbF₆ (entry 12), (Ph₃P)AuNTf₂ (entry 13), C/AgSbF₆ (entry 14) and D/AgSbF₆ (entry 15) only gave a complex mixture of not separable compounds. Eventually, the use of DMF with catalyst **A** at 60 °C for 20 min under microwave irradiation were the best conditions to obtain **3a** with good yield.

We then investigated the scope of this new gold(I)-catalyzed domino reaction. The optimized conditions were tested on a wide range of substrates **1** and yields between 29% and 77% were obtained (Scheme 4). The use substrates bearing aromatic or heteroaromatic groups at the alkyne terminus is a requirement as the presence of a hydrogen atom or an aliphatic group at this position, lead to complex mixtures. Aryl groups displaying electron-donating or -withdrawing groups at the *meta* or *para* positions were well accepted (**3b-3j**). The use of *ortho*-substituted aryl groups inhibits the reaction because of the steric hindrance. Thiophene and benzothiophene derivatives gave as well good results (**3k** and **3l**). On the other hand, no conversion was observed with a 2-pyridyl substituent, the catalytic activity might be inhibited by the strong coordinative power of pyridines towards gold(I).¹⁵ Finally, with a phenyl group and a CF₃ group on the central aromatic ring, compounds **3m** and **3n** were isolated in 68% and 44% yield respectively. In some cases, traces of cyclooctatrienes **10** was observed and was not separable from products (**3k**, **3l**, **3m**, **3n**, less than 10% of impurity).

All of these compounds (**3a-3n**) undergo slow degradation once isolated. This instability is due to the presence of the bisallylic ether. Partial hydrogenation of **3a** was accomplished with platinum oxide in 1 h at room temperature in 99% yield (Scheme 5). Reduction of the exocyclic alkene renders the resulting compound **12** stable for months.

DFT computations were performed in order to support the mechanistic hypothesis formulated in Scheme 3 regarding the formation of type **3** products (see the Supporting Information for details). The formation of type **2** compounds was already computed in our previous paper.^{5a}

Scheme 4. Synthesis of furopyran derivatives **3**.

Scheme 5. Reduction of furopyran **3a**.

Compound **1a** and (2-biphenyl)dimethylphosphine were used as models (Scheme 6). The combination of LAu⁺ and **1a** leads to the π -alkyne complex **A**, releasing 11.8 kcal/mol of free energy. The latter undergoes a 5-*endo*-dig cyclization through the transition state **TS_{AB}**, located at 2.6 kcal/mol on the potential energy surface (PES), to form the protonated dihydrofuran **B**. This complex is less stable than **A**, but the protodemetalation leading to **C** is strongly exergonic by 26.6 kcal/mol. The dihydrofuran moiety of **C** then reacts with the coordinated alkyne via the 8-*endo*-dig transition state **TS_{CD}**, lying at -16.0 kcal/mol on the PES. This step liberates 3.7 kcal/mol of free energy. The formation of **E** by intramolecular protodemetalation would represent an unlikely symmetry-forbidden 1,3-H shift. It thus requires a proton shuttle, such as solvents (DMF or DMSO), counterion, trace of water, etc. In any case, this process is markedly exergonic in DMF, placing **E** at -41.1 kcal/mol on the surface (i.e. a gain of 11.3 kcal/mol, compared to only 4.0 kcal/mol

in dioxane). Ring-opening of **E** is achieved through the retro- 8π transition state **TS_{EF}** at the expense of 20.4 kcal/mol. The obtained furodienone **F** is less stable than **E** by 9.2 kcal/mol, by is easily converted into the final product **G** by 6π -electrocyclization, occurring via the transition state **TS_{FG}**, which lies at -24.5 kcal/mol. Furopyrane **G** is more stable than cyclooctatriene **E** by 2.0 kcal/mol only, thus it is not surprising that **10a** could be detected at lower temperatures.

Scheme 6. Computed free energy profile (ΔG_{298} , kcal/mol; M06/def2-QZVP(Au),6-311+G(2d,p)) of the formation of the furopyran **G and geometries of **TS_{EF}** and **TS_{FG}**.**

In conclusion, we have developed a new domino reaction giving access to furopyran derivatives of type 4*H*-furo[3,2-*c*]pyran **3**. During this work, we have studied the solvent effect on a gold catalyzed domino reaction and we have shown that, depending on the solvent of the reaction, two classes of furopyran derivative are accessible: 4*H*-furo[2,3-*b*]pyrans **2** which are formed in 1,4-dioxane and 4*H*-furo[3,2-*c*]pyrans **3** which are obtained in DMF. DFT calculations support the mechanistic hypothesis of a consecutive 5-*endo*-dig and 8-*endo*-dig cyclizations, followed by a retro 8π and finally a 6π electrocyclicization.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, compound characterization data, ^1H and ^{13}C spectra of the products, coordinates and energies of the computed structures (PDF). The Supporting Information is available free of charge on the ACS Publications website. The Supporting Information is available free of charge on the ACS Publications website.

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REFERENCES

- ¹ *Heterocycles in Natural Product Synthesis: MAJUMDAR: HETEROCYCLES O-BK*; Majumdar, K. C.; Chattopadhyay, S. K., Eds.; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany, 2011. <https://doi.org/10.1002/9783527634880>.
- ² He, J.; Chen, L.; Heber, D.; Shi, W.; Lu, Q.-Y. Antibacterial Compounds from *Glycyrrhiza u. Ralensis*. *Journal of Natural Products* **2006**, *69*, 121–124. <https://doi.org/10.1021/np058069d>.
- ³ a) Rudolph, M.; Hashmi, A. S. K. Heterocycles from Gold Catalysis. *Chem. Commun.* **2011**, *47*, 6536. <https://doi.org/10.1039/c1cc10780a>. b) Avato, P. A Survey on the Hypericum Genus: Secondary Metabolites and Bioactivity. In *Studies in Natural Products Chemistry*; Elsevier, 2005; Vol. 30, pp 603–634. [https://doi.org/10.1016/S1572-5995\(05\)80043-2](https://doi.org/10.1016/S1572-5995(05)80043-2). c) Tanaka, N.; Kashiwada, Y.; Kim, S. Y.; Hashida, W.; Sekiya, M.; Ikeshiro, Y.; Takaishi, Y. Acylphloroglucinol, Biyouyanagiol, Biyouyanagin B, and Related Spiro-Lactones from *Hypericum chinense*. *J. Nat. Prod.* **2009**, *72*, 1447–1452. <https://doi.org/10.1021/np900109y>. d) Aramaki, Y.; Chiba, K.; Tada, M. Spiro-Lactones, Hyperolactone A-D from *Hypericum chinense*. *Phytochemistry* **1995**, *38*, 1419–1421. [https://doi.org/10.1016/0031-9422\(94\)00862-N](https://doi.org/10.1016/0031-9422(94)00862-N). e) Abe, S.; Tanaka, N.; Kobayashi, J. Prenylated Acylphloroglucinols, Chipericumins A–D, from *Hypericum chinense*. *J. Nat. Prod.* **2012**, *75*, 484–488. <https://doi.org/10.1021/np200741x>.
- ⁴ a) Ohno, H. Gold-Catalyzed Cascade Reactions of Alkynes for Construction of Polycyclic Compounds. *Isr. J. Chem.* **2013**, *53*, 869–882. <https://doi.org/10.1002/ijch.201300054>. b) Sugimoto, K.; Matsuya, Y. Recent Applications of Gold-Catalyzed Cascade Reactions in Total Synthesis of Natural Product. *Tetrahedron Letters* **2017**, *58*, 4420–4426. <https://doi.org/10.1016/j.tetlet.2017.10.029>. c) Michelet, V. Gold-Catalyzed Domino Reactions. In *Homogeneous Gold Catalysis*; Slaughter, L. M., Ed.; Topics in Current Chemistry; Springer International Publishing: Cham, 2014; Vol. 357, pp 95–132. https://doi.org/10.1007/128_2014_595. d) Kirsch, S. Construction of Heterocycles by the Strategic Use of Alkyne π -Activation in Catalyzed Cascade Reactions. *Synthesis* **2008**, *2008*, 3183–3204. <https://doi.org/10.1055/s-0028-1083164>. e) Ohno, H.; Oishi, S.; Fujii, N. Gold-Catalyzed Atom-Economical Cascade Reactions of Alkynes for Ring Formation. *J. Synth. Org. Chem. Jpn.* **2014**, *72*, 1218–1227. <https://doi.org/10.5059/yukigoseikyokaishi.72.1218>. f) Qian, D.; Zhang, J. Gold-Catalyzed Cascade Reactions for Synthesis of Carbo- and Heterocycles: Selectivity and Diversity: Gold-Catalyzed Cascade Reactions. *The Chemical Record* **2014**, *14*, 280–302. <https://doi.org/10.1002/tcr.201300039>. g) Gu, Y.; Tan, C.; Gong, J.; Yang, Z. Diversity-Oriented Synthesis of Natural Products via Gold-Catalyzed Cascade Reactions. *Synlett* **2018**, *29*, 1552–1571. <https://doi.org/10.1055/s-0037-1610126>.
- ⁵ a) Pertschi, R.; Wagner, P.; Ghosh, N.; Gandon, V.; Blond, G. Gold(I)-Catalyzed Synthesis of Furopyrans: Insight into Hetero-Diels–Alder Reactions. *Org. Lett.* **2019**, *21*, 6084–6088. <https://doi.org/10.1021/acs.orglett.9b02228>. b) Blond, G.; Gulea, M.; Mamane, V. Recent Contributions to Hetero Diels–Alder Reactions. *Curr. Org. Chem.* **2016**, *20*, 2161–2210. <https://doi.org/10.2174/1385272820666160216000401>.
- ⁶ Trost, B. The Atom Economy—a Search for Synthetic Efficiency. *Science* **1991**, *254* (5037), 1471–1477. <https://doi.org/10.1126/science.1962206>.
- ⁷ Zhdanko, A.; Maier, M. E. The Mechanism of Gold(I)-Catalyzed Hydroalkoxylation of Alkynes: An Extensive Experimental Study. *Chem. Eur. J.* **2014**, *20*, 1918–1930. <https://doi.org/10.1002/chem.201303795>.
- ⁸ a) Kong, X.-F.; Guo, X.-Y.; Gu, Z.-Y.; Wei, L.-S.; Liu, L.-L.; Mo, D.-L.; Pan, C.-X.; Su, G.-F. Silver(I)-Catalyzed Selective Hydroalkoxylation of C2-Alkynyl Quinazolinones to Synthesize Quinazolinone-Fused Eight-Membered N,O-Heterocycles. *Org. Chem. Front.* **2020**, *7*, 2055–2062. <https://doi.org/10.1039/D0QO00437E>. b) Choury, M.; Basilio Lopes, A.; Blond, G.; Gulea, M. Synthesis of Medium-

Sized Heterocycles by Transition-Metal-Catalyzed Intramolecular Cyclization. *Molecules* **2020**, *25* (14), 3147 and references inside. <https://doi.org/10.3390/molecules25143147>. c) Scully, S. S.; Zheng, S.-L.; Wagner, B. K.; Schreiber, S. L. Synthesis of Oxazocenones via Gold(I)-Catalyzed 8- Endo -Dig Hydroalkoxylation of Alkynamides. *Org. Lett.* **2015**, *17* (3), 418–421. <https://doi.org/10.1021/ol503273v>.

⁹ For example of gold (I)-catalyzed vinyl ether addition on propargyl ether: a) (1) Sherry, B. D.; Maus, L.; Laforteza, B. N.; Toste, F. D. Gold(I)-Catalyzed Synthesis of Dihydropyrans. *J. Am. Chem. Soc.* **2006**, *128*, 8132–8133. <https://doi.org/10.1021/ja061344d>. b) Staben, S. T.; Kennedy-Smith, J. J.; Huang, D.; Corkey, B. K.; LaLonde, R. L.; Toste, F. D. Gold(I)-Catalyzed Cyclizations of Silyl Enol Ethers: Application to the Synthesis of (+)-Lycopladiene A. *Angew. Chem. Int. Ed.* **2006**, *45*, 5991–5994. <https://doi.org/10.1002/anie.200602035>. c) Kusama, H.; Karibe, Y.; Onizawa, Y.; Iwasawa, N. Gold-Catalyzed Tandem Cyclization of Dienol Silyl Ethers for the Preparation of Bicyclo[4.3.0]Nonane Derivatives. *Angewandte Chemie International Edition* **2010**, *49*, 4269–4272. <https://doi.org/10.1002/anie.201001061>. d) Chen, Y.; Chen, M.; Liu, Y. Gold-Catalyzed Cascade Cyclizations of 1,6-Diynyl Carbonates to Benzo[b]Fluorenes Involving Arylation of Oxocarbenium Ion Intermediates and Decarboxylative Etherification. *Angew. Chem. Int. Ed.* **2012**, *51*, 6493–6497. <https://doi.org/10.1002/anie.201201799>. e) Iwai, T.; Okochi, H.; Ito, H.; Sawamura, M. Construction of Eight-Membered Carbocycles through Gold Catalysis with Acetylene-Tethered Silyl Enol Ethers. *Angew. Chem. Int. Ed.* **2013**, *52*, 4239–4242. <https://doi.org/10.1002/anie.201300265>. f) Jin, S.; Jiang, C.; Peng, X.; Shan, C.; Cui, S.; Niu, Y.; Liu, Y.; Lan, Y.; Liu, Y.; Cheng, M. Gold(I)-Catalyzed Angle Strain Controlled Strategy to Furopyran Derivatives from Propargyl Vinyl Ethers: Insight into the Regioselectivity of Cycloisomerization. *Org. Lett.* **2016**, *18*, 680–683. <https://doi.org/10.1021/acs.orglett.5b03641>.

¹⁰ For example of protodeauration versus Grob-type fragmentation competition process: Ferrer, C.; Echavarren, A. M. Gold-Catalyzed Intramolecular Reaction of Indoles with Alkynes: Facile Formation of

Eight-Membered Rings and an Unexpected Allenylation. *Angew. Chem. Int. Ed.* **2006**, *45*, 1105–1109. <https://doi.org/10.1002/anie.200503484>.

¹¹ For example of gold(I)-catalyzed rearrangement and allene formation: Sherry, B. D.; Toste, F. D. Gold(I)-Catalyzed Propargyl Claisen Rearrangement. *J. Am. Chem. Soc.* **2004**, *126*, 15978–15979. <https://doi.org/10.1021/ja044602k>.

¹² Lau, V. M.; Pfalzgraff, W. C.; Markland, T. E.; Kanan, M. W. Electrostatic Control of Regioselectivity in Au(I)-Catalyzed Hydroarylation. *J. Am. Chem. Soc.* **2017**, *139* (11), 4035–4041. <https://doi.org/10.1021/jacs.6b11971>.

¹³ a) Lu, Z.; Han, J.; Okoromoba, O. E.; Shimizu, N.; Amii, H.; Tormenta, C. F.; Hammond, G. B.; Xu, B. Predicting Counterion Effects Using a Gold Affinity Index and a Hydrogen Bonding Basicity Index. *Org. Lett.* **2017**, *19* (21), 5848–5851. <https://doi.org/10.1021/acs.orglett.7b02829>. b) BabaAhmadi, R.; Ghanbari, P.; Rajabi, N. A.; Hashmi, A. S. K.; Yates, B. F.; Ariafard, A. A Theoretical Study on the Protodeauration Step of the Gold(I)-Catalyzed Organic Reactions. *Organometallics* **2015**, *34* (13), 3186–3195. <https://doi.org/10.1021/acs.organomet.5b00219>.

¹⁴ a) Wang, W.; Kumar, M.; Hammond, G. B.; Xu, B. Enhanced Reactivity in Homogeneous Gold Catalysis through Hydrogen Bonding. *Org. Lett.* **2014**, *16* (2), 636–639. <https://doi.org/10.1021/ol403584e>. b) Laurence, C.; Brameld, K. A.; Graton, J.; Le Questel, J.-Y.; Renault, E. The pK_{BHX} Database: Toward a Better Understanding of Hydrogen-Bond Basicity for Medicinal Chemists. *J. Med. Chem.* **2009**, *52*, 4073–4086. <https://doi.org/10.1021/jm801331y>.

¹⁵ Schiefl, J.; Stein, P. M.; Stirn, J.; Emler, K.; Rudolph, M.; Rominger, F.; Hashmi, A. S. K. Strategic Approach on *N*-Oxides in Gold Catalysis - A Case Study. *Adv. Synth. Catal.* **2019**, *361*, 725–738. <https://doi.org/10.1002/adsc.201801007>.