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Gold(I)-Catalyzed Synthesis of Furopyrans: Insight into Hetero Diels-Alder Reactions.

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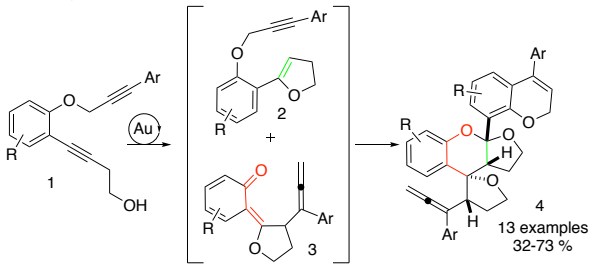
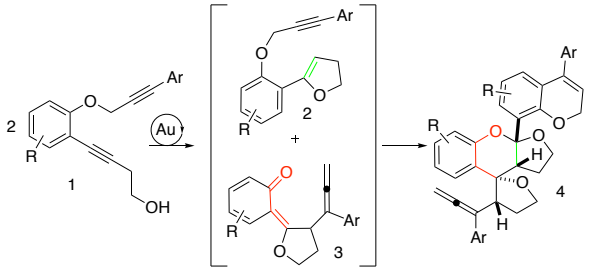


ABSTRACT: We report herein the synthesis of complex molecules containing furopyran cores through a gold(I)-catalyzed hetero Diels-Alder cascade reaction. During this process, the diene and the dienophile are produced concomitantly by the action of a single catalyst from a single starting material. Moreover, six bonds, four heterocycles and four controlled stereogenic centers are formed in a one-step operation. DFT calculations provide the mechanistic basis of this unprecedented reaction.

The last 30 years have witnessed an upsurge in the development of methodologies enabling the synthesis of intricate molecular scaffolds from simple precursors. In addition to these new synthetic strategies, the quest for molecular complexity has often resulted in important fundamental insight into selectivity principles.[1] A particularly promising strategy to rapidly construct complex molecules is to trigger domino reactions that convert simple starting materials into highly sophisticated targets by creating several bonds in a one-pot operation.[2] Achieving complexity with brevity is indeed a key to ideal synthesis. The use of transition metal-catalyzed transformations as part of a domino process considerably decreases the energy cost of the overall transformation and favors highly selective reactions due to the pre-organization of the reactive intermediates around the metallic center. In particular, homogeneous gold(I)-catalyzed reactions have attracted much attention because of the great diversity of original and complex molecules that can be obtained from adequately designed substrates, under mild reaction conditions.[3] Recently, few methodologies have been developed using gold(I)-catalysis in domino processes, including hetero Diels-Alder reactions. The hetero Diels-Alder reaction (HDA) is among the most efficient methods for the synthesis of functionalized heterocycles with control of regio-, diastereo- and enantioselectivity.[4] Most of the gold(I)-triggered HDA reported so far rely on the in situ generation of the diene and/or of the dienophile, starting with two different reagents.[5] However, HDA between diene and dienophile obtained from single starting substrate using gold-catalyst remains elusive.

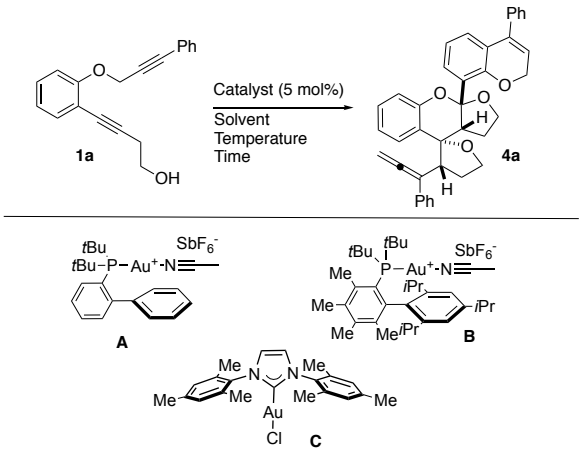
We report herein the synthesis of complex polycyclic molecules **4** containing furopyran cores of interest[6] through a gold(I)-catalyzed domino reaction involving HDA (Scheme 1). During this process, both of the dienophile **2** and the diene **3** are produced concomitantly by the action of a single catalyst from a single starting material **1**. To our knowledge, this concept has never been exploited. Moreover, during this transformation, six bonds, four heterocycles and four controlled stereogenic centers are formed in a one-step operation with 100% atom economy. DFT calculations provide the mechanistic insight of this unprecedented reaction.

Scheme 1. Gold(I)-catalyzed hetero Diels-Alder cascade reaction for the synthesis of furopyrans derivatives 4.



By the strategic positioning of two triple bonds and a nucleophilic hydroxyl group around a benzene core, we have designed a pre-organized system for successive cyclization reactions. Our initial investigation was performed with **1a** as model substrate for optimization of the reaction conditions (Table 1). The first experiment was carried out in dichloroethane (DCE) as solvent and in the presence of a pre-activated cationic gold(I) complex, the commercially available catalyst [(JohnPhos)Au(MeCN)][SbF_6] (**A**), at room temperature for 3 h (entry 1). Pleasingly, these reaction conditions afforded the furopyran compound **4a** in 52% yield. A remarkable diastereoselectivity and regioselectivity were obtained as only one compound was isolated. The configuration of **4a** was unambiguously determined by ^{1}H and ^{13}C NMR experiments. During this transformation, four heterocycles, including a spiro and a fused system, and four stereogenic centers were formed, two of them being quaternary carbons. With this promising result in hand, we next optimized the reaction conditions. A complex mixture of inseparable compounds was obtained with (Ph_3P)AuCl/AgOTf (entry 2), (PPh_3)$AuNTf_2$ (entry 3), [(Me_4*t*BuXPhos)Au(MeCN)][SbF_6] (**B**, entry 4) and IMesAuCl/$AgSbF_6$ (**C**/$AgSbF_6$, entry 5).

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



Entry	Catalyst	Solvent	Temp. /Time	Yield of **4a** (%)[b]
1	**A**	DCE	RT/3 h	52[b]
2	(Ph_3P)AuCl/ AgOTf	DCE	RT/3 h	CM[d]
3	(Ph_3P)$AuNTf_2$	DCE	RT/3 h	CM[d]
4	**B**	DCE	RT/3 h	CM[d]
5	**C**/$AgSbF_6$	DCE	RT/3 h	CM[d]
6	**A**	THF	RT/3 h	41[c]
7	**A**	CH_2Cl_2	RT/3 h	60[b]
8	**A**	$CHCl_3$	RT/3 h	62[b]
9	**A**	Dioxane	RT/3 h	61[c]
10	**A**	Dioxane	60°C/20 min[e]	68[b]
11	**A**	Toluene	RT/3 h	CM[d]
12	**A**	*i*PrOH	RT/3 h	CM[d]

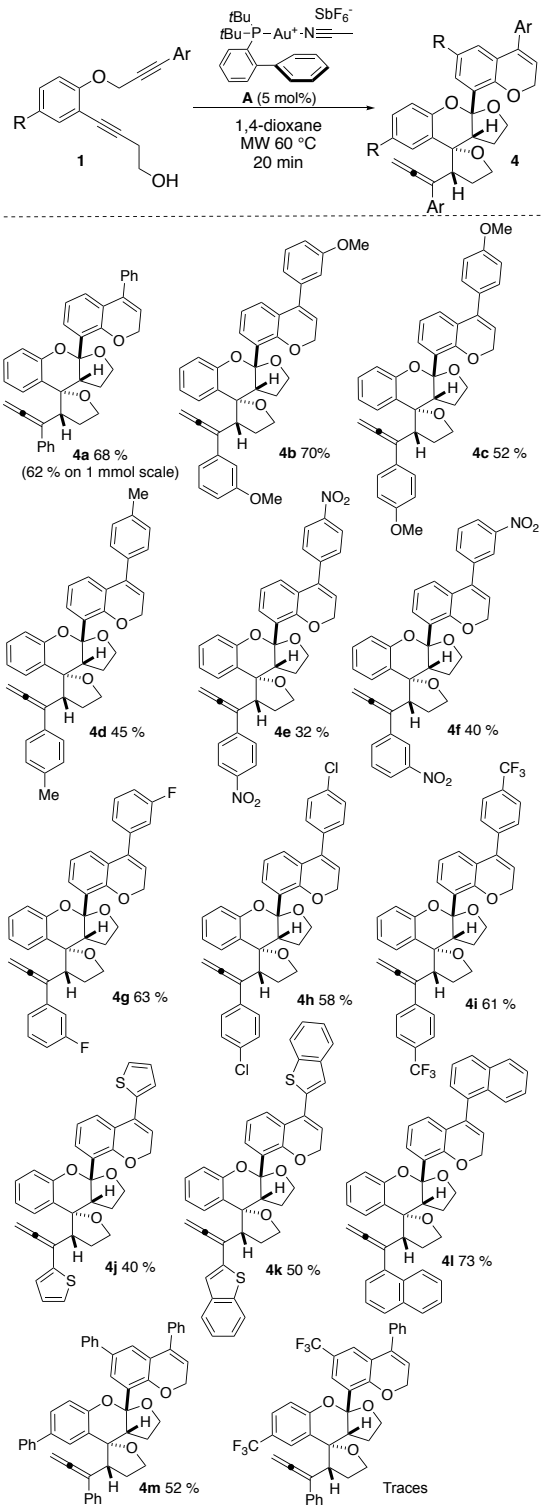
[a] The reactions were performed by adding catalyst (5 mol%) to a solution of **1a** in the solvent (0.145 M). [b] Isolated yield. [c] Calculated yield by integration of the ^{1}H-NMR of the crude product relative to the internal reference (caffeine) [d] CM: Complex mixture. [e] With microwave irradiation.

Then, several solvents were tested with the use of **A** as the best catalyst (entries 6-11). Tetrahydrofuran (entry 6), dichloromethane (entry 7), chloroform (entry 8) and 1,4-dioxane (entry 9) at room temperature for 3 h afforded compound **4a** with a slight increase in yield (~ 60%) except in THF (~ 40%). The use of 1,4-dioxane under microwave irradiation (60 °C) led to **4a** with the highest yield (68%, entry 10). The other solvents tested, toluene (entry 10) and *i*PrOH (entry 11) gave only complex mixtures. Eventually, the use of catalyst **A** in 1,4-dioxane under microwave irradiation proved to be the conditions of choice. We then examined the scope of this new gold(I)-catalyzed polycyclization process. As illustrated in Scheme 2, this transformation is efficient on a broad range of substrates **1** with yields between 32% and 73%. As in the case of **1a**, all of these reactions proved remarkably regio- and diastereoselective, as only one compound was obtained in each case.

A requirement is to use substrates bearing aromatic or heteroaromatic groups at the alkyne terminus. With a hydrogen atom or an aliphatic group at this position, complex mixtures were obtained. A wide range of aryls exhibiting electron-donating or -withdrawing groups at the *meta* or *para* positions are well tolerated (**4b-4i**). With *ortho*-substituted aryl groups, the steric hindrance hampers the reaction. Heteroaromatics such as thiophene and benzothiophene gave good results (**4j** and **4k**). On the other hand, with 2-pyridine derivative, no conversion was observed, which might be due to the strong coordinative power of pyridines towards gold(I) inhibiting its catalytic activity.[7] The substitution of the central aromatic ring bearing both peripheral chains was briefly examined. With a phenyl group, compound **4m** was isolated in 52% yield. However, with a CF_3 group, the desired product was obtained only as traces. All of these compounds (**4a-4m**) are stable once isolated.

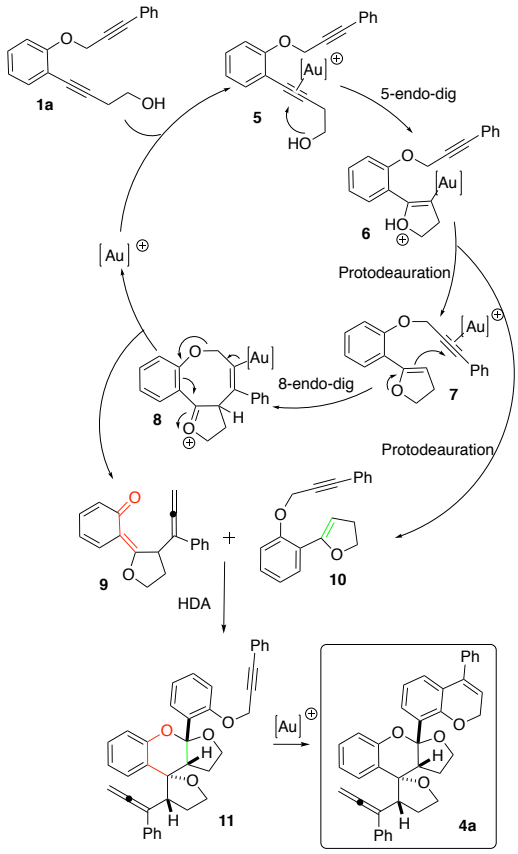
The mechanism proposed to explain the formation of product **4** and its diastereoselectivity is shown in Scheme 3. The coordination of the homopropargyl alcohol moiety of **1a** by the cationic gold(I) complex leads to complex **5**, allowing a 5-*endo*-dig addition of the alcohol to the triple bond to form the vinyl-gold oxonium species **6**,[8] which undergoes a protodeauration leading to dienophile **10**. While **10** can become an off-cycle species, part of it can stay as a new gold(I) complex by coordination of the remaining triple bond, generating the activated intermediate **7**. This latter cyclizes via an 8-*endo*-dig addition of the previously formed enol to the alkyne leading to complex **8**.[9] This intermediate undergoes a ring-opening, triggered by the gold release, leading to the formation of heterodiene **9** displaying an allene group.[10] A HDA between heterodiene **9** and dienophile **10** occurs to give adduct **11**. It is noteworthy that all the stereogenic centers are controlled during this step. The last step is a well-known gold(I)-catalyzed hydroarylation of the alkyne leading to the final compound **4a.**[11] In support of this mechanistic proposal, we have been able to isolate product **11** when the reaction of **1a** is performed with catalyst **A** at room temperature in acetonitrile.

Scheme 2. Synthesis of furopyran derivatives 4.

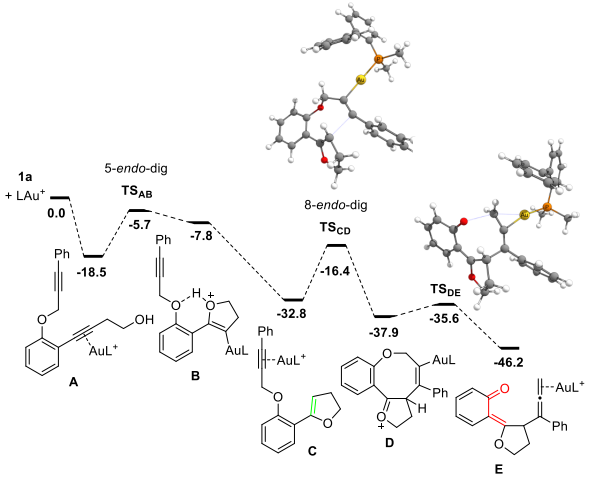


In order to corroborate this hypothesis, DFT computations were carried out. All structures were optimized using the Gaussian 09 software package at the B3LYP level of density functional theory (DFT). The effective-core potential of Hay and Wadt with a double-ξ valence basis set (LANL2DZ) was used to describe Au. The other atoms were described by the 6-31G(d,p) basis set. Thermal corrections to the Gibbs free energy were obtained at the same level of theory. Single-point energy calculations were carried out at the M06 level with the quadruple-ζ valence def2-QZVP basis set on Au and the 6-311+G(2d,p) basis set on other elements. This level was also chosen to obtain the solvation energy in dioxane using the CPCM model. The values presented herein are Gibbs free energies (ΔG_{298}, kcal/mol). Compound **1a** was used as model substrate and (2-biphenyl)dimethylphosphine as model ligand (Scheme 4). The energy profile of the formation of the gold complexes **C** and **E** at the origin of the dienophile and the diene is shown in Scheme 4. Coordination of LAu^+ to the starting material **1a** delivers 18.5 kcal/mol of free energy. The resulting complex **A** can then be transformed into the protonated dihydrofuran species **B** though a low lying 5-*endo*-dig cyclization transition state located at -5.7 kcal/mol on the potential energy surface (PES). This step is endergonic, but the subsequent protodemetalation is a strongly exergonic process, as shown by the low free energy of **C** (-32.8 kcal/mol).

Scheme 3. Proposed mechanism for the formation of 4.

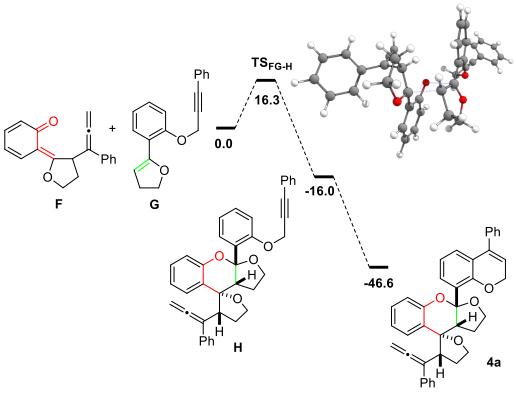


Scheme 4. Free Energy Profile (ΔG_{298}, kcal/mol) of the Formation of the Diene and the Dienophile; Geometries of TS_{CD} and TS_{DE}



No transition state was sought after for this step since it corresponds to a symmetry forbidden 1,3-H shift that actually requires an unknown proton shuttle. Complex **C**, which corresponds to the putative dienophile of the HAD reaction, can be transformed in two steps into the required diene **E**. First, the dihydrofuran core reacts with the coordinated alkyne in **C** through an 8-*endo*-dig transition state lying at -16.4 kcal/mol on the PES. The resulting complex **D** is more stable than C by 5.1 kcal/mol. Cleavage of the C-O bond of the 8-membered ring is then achieved through the low-lying transition state TS_{DE}. This step yields complex **E**, located at -46.2 kcal/mol. The HDA was then modelled (Scheme 5). The [4+2] cycloaddition between diene **F** and dienophile **G** is achieved through the *endo* transition state $\mathbf{TS_{FG\text{-}H}}$, lying at only 16.3 kcal/mol on the PES. No *exo* transition state could be found, which is likely due to the steric hindrance. Introduction of the bulky LAu^+ fragment did not have a positive effect on the barrier. The forming bonds in the transition state of this asynchronous step are 2.08 and 2.65 Å long for the C-C and C-O bonds respectively. Cycloadduct **H**, which is more stable than the reagents by 16.0 kcal/mol displays the experimentally observed stereochemistry. The hydroarylation step, which is a process that has been already well-described computationally, [12] was thus not computed, but the isolated product **4a** was placed on the PES, at -46.6 kcal/mol.

Scheme 5. Free Energy Profile (ΔG_{298}, kcal/mol) of the HAD, Geometry of $\mathbf{TS_{FG\text{-}H}}$.



Overall, the computations support the proposed mechanism and justify the stereochemistry of the products. Both the diene and the dienophile can be obtained from the same substrate, the diene deriving from the dienophile by an 8-*endo*-dig/ring opening sequence. The HAD reaction between the two promotes an important increase of the molecular complexity, while ensuring the stereoselectivity.

ASSOCIATED CONTENT

Supporting Information

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

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Author Contributions

All authors approved the final version of the manuscript.

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