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An Alternative to Precious Metals: $Hg(ClO_4)_2 \cdot 3H_2O$ as a Cheap and Water-Tolerant Catalyst for the Cycloisomerization of Allenols

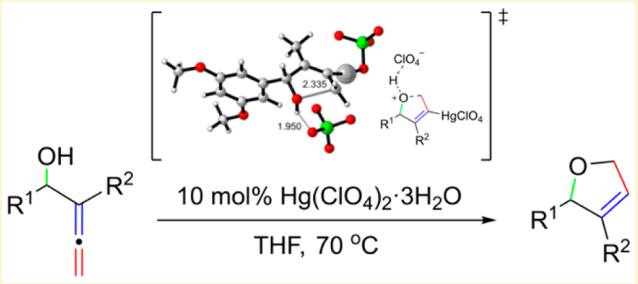
Benito Alcaide,*[,†] Pedro Almendros,*[,‡] Amparo Luna,[†] and Elena Soriano[‡]

[†]Grupo de Lactamas y Heterociclos Bioactivos, Departamento de Química Orgánica I, Unidad Asociada al CSIC, Facultad de Química, Universidad Complutense de Madrid, 28040 Madrid, Spain

[‡]Instituto de Química Orgánica General, CSIC, Juan de la Cierva 3, 28006 Madrid, Spain

Supporting Information

ABSTRACT: $Hg(ClO_4)_2 \cdot 3H_2O$, a cheap, water-tolerant, and stable salt, catalyzes the cycloisomerization reaction or α-allenols to 2,5-dihydrofurans in an efficient and selective manner. The reaction is general and can be applied to differently functionalized substrates, including alkyl-substituted, aryl-substituted, enantiopure, and tertiary allenols. In addition, density functional theory (DFT) calculations were performed to obtain insight into various aspects of the controlled reactivity of α-allenols under mercury catalysis. They suggest a dual activation of the allenol by the Hg complex that drives the reaction to the chemoselective formation of 2,5-dihydrofurans.



INTRODUCTION

The past decade has seen an increasing use of allene derivatives as versatile building blocks in synthetic chemistry, in large part due to their interesting reactivity patterns which allows the preparation of relevant products in a controlled manner.[1] On the other hand, the development of synthetic methods for the preparation of oxacycles is important because they are present in a wide range of natural products and biologically active molecules.[2] Among the possibilities, transition-metal-catalyzed intramolecular nucleophilic addition of the hydroxyl group across the allene moiety in allenols is intriguing from the point of view of regioselectivity as well as it being one of the most rapid and convenient methods for the preparation of oxacycles owing to its atom-economy and efficiency.[1] Despite the fact that that this field was initiated by mercury salts serving as promoters in stoichiometric or substoichiometric amounts,[3] the discovery of platinum- and especially gold-based precatalysts[4,5] has displaced mercury,[6] probably invoking toxicity issues.[7] However, from a scientific point of view, prejudices coming from popularly accepted suppositions must be taken with care[8] because a particular element can be toxic or not depending on the compound considered.[9,10] From an economic point of view, the common practice of using 5% loading in gold catalysis makes its use often impractical on larger scale synthesis in fields such as medicinal chemistry and material science. Compared with noble-metal catalysts, which are extremely expensive and with diminishing reserves, mercury-based methods have obvious economic attractiveness. In light of these facts, we decide to investigate the catalytic profile of $Hg(ClO_4)_2 \cdot 3H_2O$,[11] a cheap, water-tolerant, and stable salt,[12,13] for the cycloisomerization of allenols.

RESULTS AND DISCUSSION

Starting allenols **1a**–**l** were prepared from the appropriate carbonyl derivative via regiocontrolled indium-mediated Barbier-type carbonyl–allenylation reaction in aqueous media adopting our previously reported methodology.[14] Allene **1a** was chosen as a model substrate for Hg(II)-catalyzed cycloetherification reactions. To screen the reactivity of the α-allenol moiety, several conditions were screened. While $Hg(ClO_4)_2 \cdot 3H_2O$ could catalyze the heterocyclization reaction of **1a** to 2,5-dihydrofuran **2a** in several solvents such as 1,2-dichloroethane, acetonitrile, and THF, the mercury-based catalytic system gave the desired product **2a** in low yield when DMF or THF–H_2O (1:1) was used (Table S1, Supporting Information). Treatment of α-allenol **1a** with $Hg(ClO_4)_2 \cdot 3H_2O$ (10 mol %) in THF at 70 °C on a sealed tube afforded the best yield of the corresponding adduct **2a**, from a 5-*endo* oxycyclization, as a single isomer (Scheme 1). Interestingly, under gold catalysis, α-allenol **1a** delivered fused bicycle **3a**, carbocyclization adduct, in addition to 2,5-dihydrofuran **2a** (Scheme 1). A similar reaction course was encountered through the use of α-allenol **1b**. The $AuCl_3$-catalyzed reaction afforded a separable mixture of 2,5-dihydrofuran **2b** and naphthalene **3b**, while the $Hg(ClO_4)_2 \cdot 3H_2O$-catalyzed reaction was totally selective toward the oxycyclization adduct **2b** (Scheme 1). Thus, it has been shown that $Hg(ClO_4)_2 \cdot 3H_2O$ is a more selective cycloetherification catalyst than $AuCl_3$. Different Hg(II) salts such as $HgCl_2$, $Hg(AcO)_2$, and $Hg(TfO)_2$ were also tested. The corresponding dihydrofuran was the major reaction product

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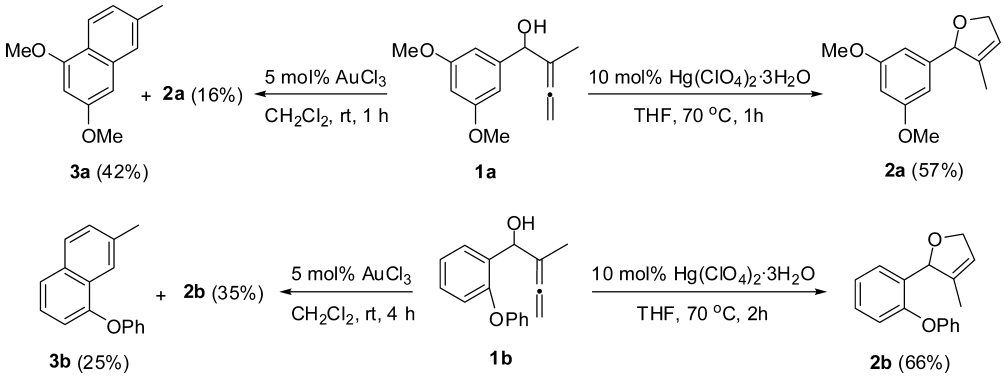
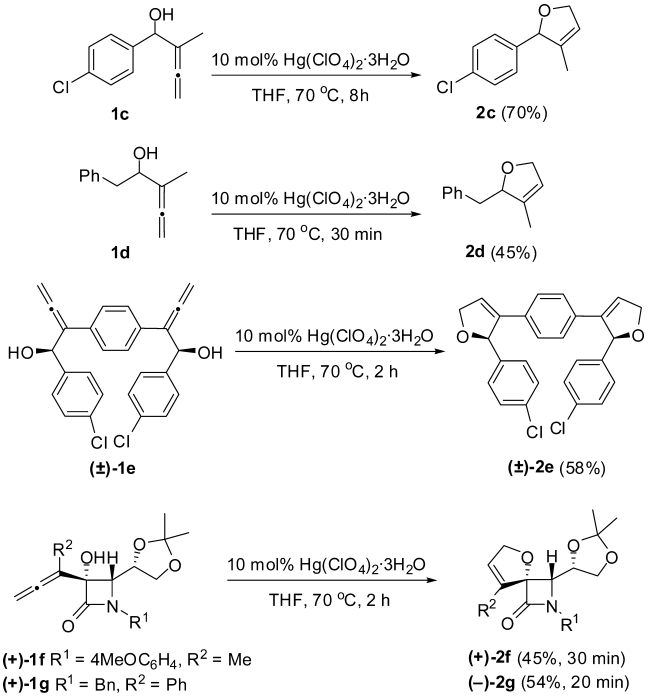
Scheme 1. Gold- versus Mercury-Catalyzed Cyclization Reaction of α-Allenols 1a and 1b



under catalytic $Hg(TfO)_2$ conditions. However, the use of either 10 mol % of $HgCl_2$ or 10 mol % of $Hg(AcO)_2$ did not get the reaction to completion. Dihydrofuran adducts **2** were afforded as minor products along with degradation products. Comparatively, the use of mercurium salts different to $Hg(ClO_4)_2{\cdot}3H_2O$ led to limited reactivity.

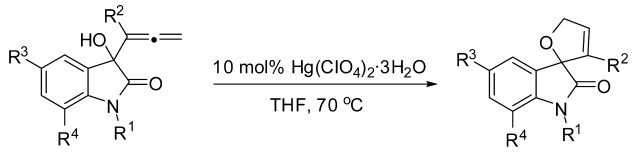
Under the optimized reaction conditions, we investigated the generality of the mercury-catalyzed transformation of differently substituted α-allenols **1c–m**. As shown in Schemes 2 and 3, the

Scheme 2. Controlled Mercury-Catalyzed Oxycyclization of α-Allenols 1c–g



above process serves as a general approach to 2,5-dihydrofurans **2c–m**. Nicely, bis(α-allenol) **1e** undergoes the double transformation to give bi(2,5-dihydrofuran) **2e**. To assess scope, the even more challenging enantiopure allenyl-tethered 2-azetidinones **1f** and **1g** were tested as cyclization precursors, giving the desired spirocyclic dihydrofuran-β-lactams **2f** and **2g**. Notably, despite the fact that Lewis acids are well known for their ability to promote acetonide cleavage, no traces of diols were detected from tertiary α-allenols **1f** and **1g** (Scheme 2).[15]

Scheme 3. Controlled Mercury-Catalyzed Oxycyclization of 2-Indolinone-Tethered α-Allenols 1h–m

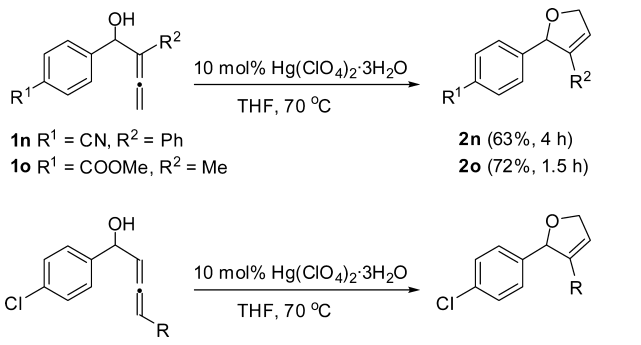


1h R^1 = H, R^2 = Me, R^3 = R^4 = H — **2h** (80%; 1.5 h)
1i R^1 = H, R^2 = 4-MeOC_6H_4, R^3 = R^4 = H — **2i** (56%; 1.5 h)
1j R^1 = Me, R^2 = Me, R^3 = R^4 = H — **2j** (75%; 3 h)
1k R^1 = Me, R^2 = Ph, R^3 = R^4 = H — **2k** (67%; 3 h)
1l R^1 = Me, R^2 = Me, R^3 = Cl, R^4 = H — **2l** (73%; 2 h)
1m R^1 = Me, R^2 = Me, R^3 = H, R^4 = Cl — **2m** (87%; 1 h)

Encouraged by the above results, 3-allenyl 3-hydroxyoxindoles **1h–m** were studied to determine the applicability of the Hg(II)-catalyzed method (Table S2 in the Supporting Information) for the preparation of the spiroindolinone framework,[16] which is an important structural motif in biologically relevant compounds.[17] Nicely, 2-indolinone-tethered allenic alcohols **1h–m** responded well to the oxycyclization reaction, affording reasonable yields of spiroindolinones **2h–m** (Scheme 3).

Since the above examples bear either electron-donating or weakly electron-withdrawing groups, we prepared cyano- and carboxyethylallenol derivatives **1n** and **1o**. Pleasingly, exposure of each of these electron-poor substrates to the mercury salt gave the corresponding 2,5-dihydrofurans **2n** and **2o** in good yields (Scheme 4). By contrast, if an ester group is placed at the terminal carbon of the allene, such as in allenol **1p**, the

Scheme 4. Mercury-Catalyzed Reaction of α-Allenols 1n–q



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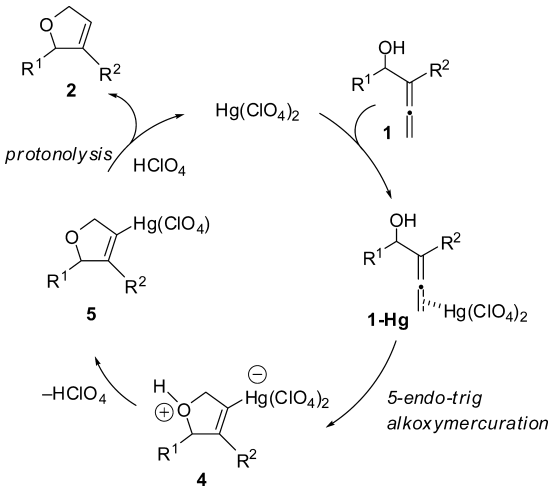
cycloetherification reaction did not proceed (Scheme 4). Likewise, exposure of allenol **1q** with a monosubstituted allene moiety under the optimized conditions did not give rise to the expected heterocycle (Scheme 4). It should be noted that we observed a similar unselective process for the $AuCl_3$-catalyzed reaction of unsubstituted allenol **1q**.

A possible mechanism for the catalytic achievement of dihydrofurans **2** involving a mercury-based carbophilic π-acid may proceed through initial η-coordination of the metal to the distal double bond of allenols **1** leading to species **1-Hg**. Next, 5-*endo-trig* alkoxymercuration forms zwitterionic dihydrofurans **4**. Loss of $HClO_4$ in intermediates **4** generates neutral vinylmetal species **5**. Protonolysis of the carbon−mercury bond of **5** liberates dihydrofurans **2** with concomitant regeneration of the Hg(II) catalytic species (Scheme 5).

Scheme 5. Initially Proposed Mechanistic Explanation for the Mercury-Catalyzed Cycloetherification of Allenols 1



Density functional theory (DFT) calculations have been carried out to rationalize the divergent chemoselectivity observed for the Hg- and Au-catalyzed reactions of α-allenols **1a** and **1b**.

These metals are known as excellent π-activators and, more generally, soft Lewis acids. These properties make them superior as catalysts to other transition and non-transition metals for the addition of carbon and heteroatom nucleophiles to unsaturated C−C bonds.[18] Au(III) complexes form $16e^-$ square-planar structures, which is typical of a metal complex with a d^8 electron count, with a vacant coordination site that easily admits extra-coordination to a new molecule (to give an $18e^-$ species). In contrast, the Hg(II) species is a d^{10} that prefers to form $14e^-$ linear complexes. The existence of these linear complexes is explained by the high stabilization of the 6s orbital compared to the 6p: since the LUMO is exclusively composed by the 6s and the 6p orbitals, it has more s-character. Thus, sp-hybridization occurs, giving the linear structure for the metal center. In this case, the access of the reactants must be preceded by the release of the ligands since (a) no oxidative addition is possible and (b) associative addition hardly occurs since π-back-donation from the Hg(II) cation is disfavored.[10] These general trends make important differences in the catalytic behavior of both metal complexes in the cycloisomerization of α-allenols **1**.

Thus, the activation of the allene moiety of **1a** by $Hg(ClO_4)_2$ proceeds with the release of ClO_4^- species from a metal coordination site which is occupied by η^2-coordination of the distal double bond of the allene to give a linear complex, **1a**−Hg (Figure 1). Remarkably, the inspection of the transition structure for the 5-*endo-trig* alkoxymercuration (**TS1**) reveals that the released counteranion ClO_4^- forms a hydrogen bond with the nucleophile. It suggests a dual activation by the catalyst, as both the electrophile and nucleophile are activated for the intramolecular heterocyclization. This effect is supported by the low computed activation barrier ($\Delta G^{\ddagger}$ = 2.6 kcal/mol). Moreover, it should be noted that **TS1** leads to **5**, not to **4**, as proposed in Scheme 4, since the hydroxylic proton is captured by the counteranion to form $HClO_4$ simultaneously to the formation of the C−O bond. Thus, the vinylmetal **5** is H-bonded to $HClO_4$ through the ether oxygen. The formation of this intermediate structure is highly exothermic (ΔG = −23.2 kcal/mol), so this step is probably irreversible. The subsequent protonolysis step of the carbon−mercury bond of **5** liberates dihydrofuran **2a** with regeneration of the linear $Hg(ClO_4)_2$ catalytic species. This step takes place through **TS2**, −12.9 kcal/mol below **1a**−Hg, and it is strongly exothermic (ΔG = −31.1 kcal/mol). Therefore, this cycloetherification proceeds through a two-step mechanism involving dual activation of the precursor by the catalyst.

In order to verify the ability of the Hg counteranion to H-bond and its role onto selectivity, we have performed further calculations with $Hg(OTf)_2$ and $Hg(BF_4)_2$. In the former case, slightly higher barriers than for $Hg(ClO_4)_2$ have been computed for the two possible cyclizations (3.3 and 5.9 kcal/mol, for **TS1** and **TS1′**, respectively), which suggest a lower reactivity and the same selectivity. For the catalyst with the less basic anion BF_4^-, however, both barriers are similarly higher (5.9 and 6.5 kcal/mol, for **TS1** and **TS1′**, respectively). Moreover, the evolution of **TS1** leads to an intermediate where the H remains partially attached to the oxygen (1.167 Å vs 1.568 for $Hg(OTf)_2$ and 1.722 Å for $Hg(ClO_4)_2$).

The plausible hydroarylation to form naphthalene should take place probably via initial 6-*endo-trig* cyclization of **1a**−Hg following a Friedel−Crafts-type mechanism.[19] This carbocyclization step affords the Wheland-type intermediate **I1′** through the transition structure **TS1′** (Figure 1), 2.5 kcal/mol higher in energy than **TS1**. In addition, the intermediate **I1′** is 2.1 kcal/mol less stable than **5**. Hence, the 5-*endo-trig* oxycyclization is the preferred cyclization mode from kinetic and thermodynamic viewpoints, and these energy differences clearly support the chemoselective formation of the 2,5-dihydrofuran skeleton under $Hg(ClO_4)_2$ catalysis.

On the other hand, the $AuCl_3$ complex presents a vacant coordination site that can be occupied by the allene moiety to form a square-planar complex, **1a**−Au. Thus, the 5-*endo-trig* oxycyclization step takes place with an activation barrier of 4.9 kcal/mol and leads to a zwitterionic intermediate, $\mathbf{I1}_{Au}$, 6.2 kcal/mol more stable than the reactant complex **1a**−Au (Figure 2). Amazingly, the calculations show that the nucleophilic addition of the arene to the gold(III)-activated allene is more favorable, requiring an activation free energy of only 1.5 kcal/mol via transition state $\mathbf{TS1'}_{Au}$. Moreover, the formation of the Wheland-type intermediate $\mathbf{I1'}_{Au}$ is strongly exothermic (by 27.7 kcal/mol) and, hence, likely irreversible. This step leads to a C−C bond formation between the allene and the aromatic core. The formation of the naphthalene framework **3a** then takes place via stepwise rearomatization. Thus, calculations

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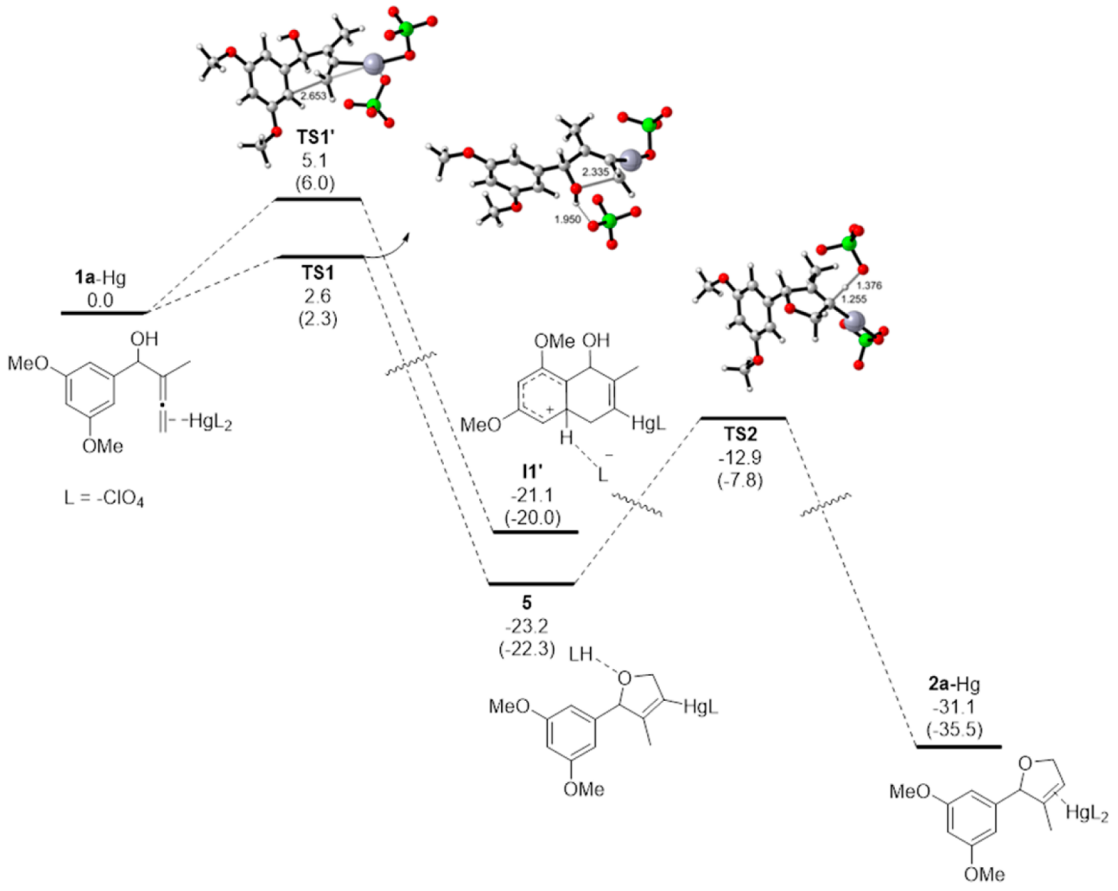

Figure 1. Computed reaction profile (PCM(THF)-M06/6-31+G(2d,p)/SDD(Hg)//M06/6-31+G(2d,p)/SDD(Hg) level) for the cycloisomerization of allenol **1a** catalyzed by $Hg(ClO_4)_2$. Gas-phase results are shown in parentheses. Relative free energies are given in kcal/mol and bond lengths in the transition states in angstroms.

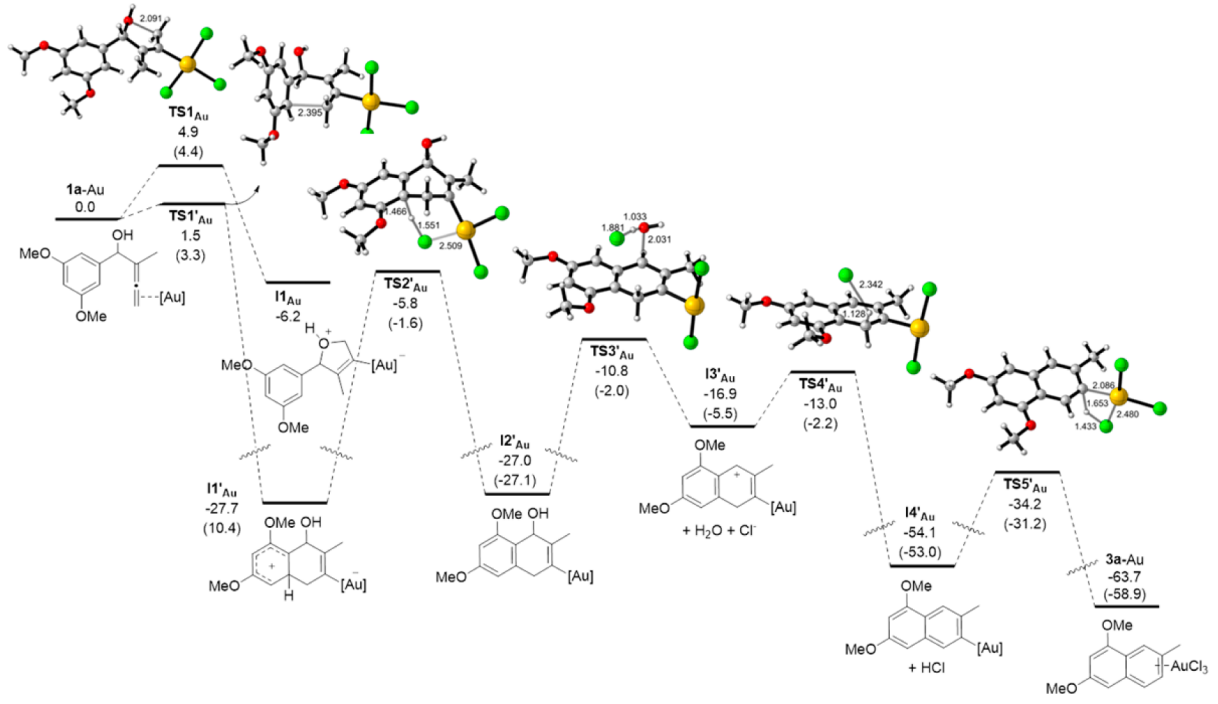

Figure 2. Computed reaction profile (PCM(CH_2Cl_2)-M06/6-31+G(2d,p)/SDD(Au)//M06/6-31+G(2d,p)/SDD(Au) level) for the cycloisomerization of allenol **1a** catalyzed by $AuCl_3$. Gas-phase results are shown in parentheses. Relative free energies are given in kcal/mol and bond lengths in the transition states in angstroms.

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suggest that $\mathbf{I1'}_{Au}$ drives to $\mathbf{I2'}_{Au}$ (ΔG = −27.0 kcal/mol) through a deprotonation process assisted by a chloride ligand via $\mathbf{TS2'}_{Au}$ ($\Delta G^{‡}$ = −5.8 kcal/mol). Then, the released HCl promotes the protonation of the hydroxylic substituent and formation of a water molecule. This step proceeds through $\mathbf{TS3'}_{Au}$ ($\Delta G^{‡}$ = −10.8 kcal/mol), which shows the advanced formation of the O−H bond (1.033 Å) and breaking of the O−C bond (2.031 Å). The subsequent step is the aromatization through a deprotonation process assisted by the chloride anion. The transition state $\mathbf{TS4'}_{Au}$ for this step needs a low activation energy ($\Delta G^{‡}$ = −13.0 kcal/mol) and drives to the formation of the aromatic intermediate $\mathbf{I4'}_{Au}$ and HCl in a strongly exothermic step (ΔG = −54.1 kcal/mol) due to the high stability of the aromatic bicycle.[20] Finally, this intermediate undergoes demetalation by protonolysis to yield the hydroarylation product and regenerates the gold(III) catalyst. This transformation occurs via $\mathbf{TS5'}_{Au}$ ($\Delta G^{‡}$ = −34.2 kcal/mol) and leads to the expected formation of naphthalene **3a**−Au (ΔG = −63.7 kcal/mol). Therefore, the favored reaction of α-allenols **1** under Au(III) catalysis proceeds through initial π-complexation of the allene moiety, which triggers the nucleophilic attack of the arene via an *endo-trig* carbocyclization pathway in a Friedel−Crafts-type mechanism.

CONCLUSIONS

In conclusion, $Hg(ClO_4)_2{\cdot}3H_2O$, a cheap, water-tolerant, and stable salt,[21] catalyzes the heterocyclization reaction or α-allenols.[22] Thus, differently functionalized 2,5-dihydrofurans can be obtained in an efficient and selective manner. The possibility of using optically active substrates as well as substrates of increased steric demand, such as tertiary α-allenols, expands the attractiveness of the method. In addition, density functional theory (DFT) calculations were performed to obtain insight into various aspects of the controlled reactivity of α-allenols under mercury catalysis. They suggest a dual activation of the allenol by the Hg complex that drives the reaction to the chemoselective formation of 2,5-dihydrofurans.

EXPERIMENTAL SECTION

General Methods. NMR spectra were recorded at 25 °C on a 300 or a 700 MHz instrument. Chemical shifts are given in ppm relative to TMS (^{1}H, 0.0 ppm) or $CDCl_3$ (^{13}C, 76.9 ppm). Low- and high-resolution mass spectra were taken on a QTOF LC/MS spectrometer using the electronic impact (EI) or electrospray modes (ES). Specific rotation $[\alpha]_D$ is given in 10^{-1} deg cm^2 g^{-1} at 20 °C, and the concentration (c) is expressed in g per 100 mL. All commercially available compounds were used without further purification.

Preparation of α-Allenic Alcohols 1b and (±)-1e via Our General Procedure.[14] *2-Methyl-1-(2-phenoxyphenyl)buta-2,3-dien-1-ol (**1b**).* From 235 mg (2.19 mmol) of 2-phenoxybenzaldehyde and after chromatography of the residue using hexanes/ethyl acetate (8:1) as eluent, compound **1b** (337 mg, 61%) was obtained as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ 7.49 (dd, J = 7.5, 1.8 Hz, 1H), 7.33 (t, J = 7.6 Hz, 2H), 7.25 (td, J = 8.0, 1.8 Hz, 1H), 7.16 (td, J = 7.4, 1.2 Hz, 1H), 7.10 (t, J = 7.4 Hz, 1H), 6.98 (d, J = 7.6 Hz, 2H), 6.88 (dd, J = 8.0, 1.2 Hz, 1H), 5.42 (m, 1H), 4.74 (qu, J = 3.1 Hz, 2H), 2.56 (d, J = 6.0 Hz, 1H), 1.65 (t, J = 3.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ 205.0, 157.4, 154.3, 133.0, 129.7 (2C), 128.8, 128.3, 123.7, 123.0, 119.1, 118.3 (2C), 102.1, 77.7, 70.0, 15.0; IR ($CHCl_3$, cm^{-1}): ν 3419, 3065, 1483, 1230, 751, 691; HRMS (ES) calcd for $C_{17}H_{16}O_2$ $[M]^+$ 252.1150, found 252.1147.

*(SR)-1-(4-Chlorophenyl)-2-(4-((RS)-1-(4-chlorophenyl)-1-hydroxybuta-2,3-dien-2-yl)phenyl)buta-2,3-dien-1-ol ((±)-**1e**).* From 169 mg (1.2 mmol) of 4-chlorobenzaldehyde and after chromatography of the residue using hexanes/ethyl acetate (2:1) as eluent, compound (±)-**1e** (120 mg, 45%) was obtained as a yellow oil: ^{1}H NMR (300 MHz, acetone-d_6, 25 °C) δ 7.48 (d, J = 8.5 Hz, 4H), 7.31 (d, J = 8.5 Hz, 4H), 5.77 (d, J = 5.0 Hz, 2H), 5.11 (m, 4H), 4.96 (d, J = 5.0 Hz, 2H); ^{13}C NMR (75 MHz, acetone-d_6, 25 °C) δ 210.0 (2C), 143.4 (2C), 133.9 (2C), 133.0 (2C), 129.3 (4C), 128.8 (4C), 128.0 (4C), 110.2 (2C), 80.0, 79.9, 72.8 (2C); IR ($CHCl_3$, cm^{-1}) ν 3397, 1937, 1701, 1089, 1014; HRMS (ES) calcd for $C_{26}H_{20}Cl_2O_2$ $[M]^+$ 434.0840, found 434.0829.

*4-(1-Hydroxy-2-phenylbuta-2,3-dienyl)benzonitrile (**1n**).* From 200 mg (1.5 mmol) of 4-formylbenzonitrile and after chromatography of the residue using hexanes/ethyl acetate (4:1) as eluent, compound **1n** (157 mg, 44%) was obtained as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ 7.62 (d, J = 8.4 Hz, 2H), 7.55 (d, J = 8.4 Hz, 2H), 7.30 (m, 5H), 5.80 (s, 1H), 5.22 (m, 2H), 2.44 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ 207.9, 147.2, 133.2, 132.0, 128.6, 127.5, 127.3, 126.8, 118.7, 111.4, 109.3, 81.3, 72.1; IR ($CHCl_3$, cm^{-1}) ν 3455, 2230, 1711, 853; HRMS (ES) calcd for $C_{17}H_{13}NO$ $[M]^+$ 247.0997, found 247.0992.

*Methyl 4-(1-hydroxy-2-methylbuta-2,3-dienyl)benzoate (**1o**).* From 330 mg (2.0 mmol) of methyl 4-formylbenzoate, and after chromatography of the residue using hexanes/ethyl acetate (5:1) as eluent, compound **1o** (284 mg, 65%) was obtained as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ 7.98 (d, J = 8.2 Hz, 2H), 7.42 (d, J = 8.2 Hz, 2H), 5.18 (s, 1H), 4.84 (m, 2H), 3.88 (s, 3H), 2.77 (br s, 1H) 1.54 (t, J = 3.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ 205.0, 166.9, 147.0, 129.5, 129.2, 126.3, 101.9, 77.4, 74.3, 51.9, 13.9; IR ($CHCl_3$, cm^{-1}) ν 3471, 1720, 1279, 1112; HRMS (ES) calcd for $C_{13}H_{14}O_3$ $[M]^+$ 218.0943, found 218.0939.

General Procedure for the $Hg(ClO_4)_2{\cdot}3H_2O$-Catalyzed Reaction of Allenols 1. Preparation of Dihydrofurans 2. $Hg(ClO_4)_2{\cdot}3H_2O$ (0.014 mmol) was added to a solution of the appropriate allenol **1** (0.14 mmol) in THF (2.5 mL). The reaction mixture was stirred at 70 °C oinn a sealed tube until the starting material disappeared as indicated by TLC. The mixture was concentrated under vacuum and purified by flash column chromatography eluting with ethyl acetate/hexanes mixtures. Spectroscopic and analytical data for pure forms of compounds **2** follow.

*2-(3,5-Dimethoxyphenyl)-3-methyl-2,5-dihydrofuran (**2a**).* From 34 mg (0.15 mmol) of allenol **1a** and after chromatography of the residue using hexanes/ethyl acetate (6:1) as eluent, compound **2a** (19 mg, 57%) was obtained as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ 6.44 (d, J = 2.2 Hz, 2H), 6.40 (m, 1H), 5.63 (m, 1H), 5.41 (m, 1H), 4.84 (m, 1H), 4.70 (m, 1H), 3.79 (s, 6H), 1.58 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ 160.9(2C), 143.9, 138.4, 120.8, 104.7 (2C), 99.8, 90.5, 75.4, 55.3 (2C), 12.5; IR ($CHCl_3$, cm^{-1}) ν 1596, 1153; HRMS (ES) calcd for $C_{13}H_{17}O_3$ $[M + H]^+$ 221.1178, found 221.1175.

*3-Methyl-2-(2-phenoxyphenyl)-2,5-dihydrofuran (**2b**).* From 123 mg (0.49 mmol) of allenol **1b**, and after chromatography of the residue using hexanes/ethyl acetate (7:1) as eluent, compound **2b** (82 mg, 66%) was obtained as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ 7.30 (dd, J = 7.5, 1.7 Hz, 1H), 7.23 (t, J = 8.0 Hz, 2H), 7.15 (t, J = 7.7 Hz, 1H), 7.06 (t, J = 7.4 Hz, 1H), 6.98 (d, J = 6.9 Hz, 1H), 6.89 (d, J = 7.7 Hz, 2H), 6.80 (d, J = 8.0 Hz, 1H), 5.90 (br s, 1H), 5.51 (m, 1H), 4.74 (m, 1H), 4.60 (m, 1H), 1.55 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ 157.7, 154.1, 138.5, 133.0, 129.6 (2C), 128.9, 128.5, 124.1, 122.8, 120.7, 119.2, 118.0 (2C), 84.1, 75.4, 12.6; IR ($CHCl_3$, cm^{-1}) ν 3067, 1757, 1483, 1231, 753, 693; HRMS (ES) calcd for $C_{17}H_{16}O_2$ $[M]^+$ 252.1150, found 252.1147.

*2-(4-Chlorophenyl)-3-methyl-2,5-dihydrofuran (**2c**).* From 35 mg (0.18 mmol) of allenol **1c**, and after chromatography of the residue using hexanes/ethyl acetate (5:1) as eluent, compound **2c** (25 mg, 70%) was obtained as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ 7.32 (d, J = 8.5 Hz, 2H), 7.21 (d, J = 8.5 Hz, 2H), 5.65 (m, 1H), 5.46 (m, 1H), 4.84 (m, 1H), 4.71 (m, 1H), 1.55 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ 140.0, 138.1, 133.5, 128.5 (2C), 128.2 (2C), 121.0, 89.8, 75.5, 12.4; IR ($CHCl_3$, cm^{-1}) ν 1730, 1684, 1091; HRMS (ES) calcd for $C_{11}H_{12}ClO$ $[M + H]^+$ 195.0577, found 195.0579.

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*2-Benzyl-3-methyl-2,5-dihydrofuran (**2d**).* From 43 mg (0.24 mmol) of allenol **1d**, and after chromatography of the residue using hexanes/ethyl acetate (9:1) as eluent, compound **2d** (19 mg, 45%) was obtained as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ 7.27 (m, 5H), 5.44 (q, J = 1.6 Hz, 1H), 4.88 (m, 1H), 4.46 (m, 2H), 3.01 (dd, J = 14.2, 3.9 Hz, 1H), 2.72 (dd, J = 14.2, 6.8 Hz, 1H), 1.74 (q, J = 1.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ 138.2, 137.5, 129.4 (2C), 128.0 (2C), 126.0, 121.3, 88.1, 74.4, 40.4, 12.7; IR ($CHCl_3$, cm^{-1}) ν 1759, 1081, 1027; HRMS (ES) calcd for $C_{12}H_{14}O$ $[M]^+$ 174.1045, found 174.1041.

*1-((RS)-2-(4-Chlorophenyl)-2,5-dihydrofuran-3-yl)-4-((SR)-2-(4-chlorophenyl)-2,5-dihydrofuran-3-yl)benzene (**(±)-2e**).* From 41 mg (0.09 mmol) of allenol (±)-**1e**, and after chromatography of the residue using hexanes/ethyl acetate (4:1) as eluent, compound (±)-**2e** (23 mg, 58%) was obtained as a colorless solid: mp 78−80 °C; ^{1}H NMR (700 MHz, $CDCl_3$, 25 °C) δ 7.27 (m, 8H), 7.09 (s, 4H), 6.45 (d, J = 1.7 Hz, 1H), 6.42 (d, J = 1.7 Hz, 1H), 6.00 (m, 2H), 4.92 (m, 2H), 4.84 (m, 2H); ^{13}C NMR (175 MHz, $CDCl_3$, 25 °C) δ 139.9 (2C), 139.2 (2C), 134.0 (2C), 131.8, 131.6, 129.0 (2C), 128.9 (2C), 128.8 (4C), 126.5 (2C), 126.4 (2C), 123.7, 123.6, 87.3, 87.2, 75.3 (2C); IR ($CHCl_3$, cm^{-1}) ν 1720, 1091, 1014; HRMS (ES) calcd for $C_{26}H_{20}Cl_2O_2$ $[M]^+$ 434.0840, found 434.0842.

*(3S,4R)-3-((S)-2,2-Dimethyl-1,3-dioxolan-4-yl)-2-(4-methoxyphenyl)-8-methyl-5-oxa-2-azaspiro[3.4]oct-7-en-1-one (**(+)-2f**).* From 30 mg (0.087 mmol) of allenol (+)-**1f**, and after chromatography of the residue using hexanes/ethyl acetate (1:1) as eluent, compound (+)-**2f** (15 mg, 45%) was obtained as a yellow solid: mp 95−97 °C; $[\alpha]_D$ +6.0 (c 0.53 in $CHCl_2$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ 7.72 (d, J = 9.1 Hz, 2H), 6.88 (d, J = 9.1 Hz, 2H), 5.80 (q, J = 1.5 Hz, 1H), 4.82 (dt, J = 13.0, 1.9 Hz, 1H), 4.61 (dt, J = 13.0, 1.9 Hz, 1H), 4.46 (m, 1H), 4.26 (dd, J = 8.6, 7.1 Hz, 1H), 4.08 (d, J = 8.6 Hz, 1H), 3.80 (s, 3H), 3.55 (dd, J = 8.6, 6.3 Hz, 1H), 1.76 (q, J = 1.9 Hz, 3H), 1.54 (s, 3H), 1.34 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ 165.9, 156.5, 132.7, 130.9, 124.8, 119.7 (2C), 114.0 (2C), 109.8, 99.6, 77.2, 76.3, 66.5, 66.3, 55.4, 26.6, 24.6, 10.9; IR ($CHCl_3$, cm^{-1}) ν 1752; HRMS (ES) calcd for $C_{19}H_{24}NO_5$ $[M + H]^+$ 346.1654, found 346.1665.

*(3SR,4RS)-2-Benzyl-3-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)-8-phenyl-5-oxa-2-azaspiro[3.4]oct-7-en-1-one (**(−)-2g**).* From 29 mg (0.074 mmol) of allenol (+)-**1g**, and after chromatography of the residue using hexanes/ethyl acetate (2:1) as eluent, compound (−)-**2g** (16 mg, 54%) was obtained as a colorless oil: $[\alpha]_D$ −22.2 (c 0.5 in $CHCl_2$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ 7.20 (m, 10 H), 6.23 (t, J = 1.8 Hz, 1H), 4.97 (dd, J = 14.1, 1.8 Hz, 1H), 4.83 (d, J = 14.4 Hz, 1H), 4.69 (dd, J = 14.1, 1.8 Hz, 1H), 4.46 (m, 1H), 4.25 (d, J = 14.4 Hz, 1H), 4.13 (dd, J = 8.5, 7.0 Hz, 1H), 3.47 (d, J = 7.9 Hz, 1H), 3.43 (dd, J = 8.5, 6.0 Hz, 1H), 1.33 (s, 3H), 1.31 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ 167.9, 158.2, 134.8, 131.2, 129.1, 128.6, 128.4, 128.3, 127.5, 126.9, 126.5, 109.7, 99.8, 77.2, 76.0, 66.3, 64.4, 45.3, 26.5, 24.8; IR ($CHCl_3$, cm^{-1}) ν 1753; HRMS (ES) calcd for $C_{24}H_{26}NO_4$ $[M + H]^+$ 392.1862, found 392.1875.

*3-Methyl-5H-spiro[furan-2,3′-indolin]-2′-one (**2h**).* From 30 mg (0.15 mmol) of allenol **1h**, and after chromatography of the residue using hexanes/ethyl acetate (2:1) as eluent, compound **2h** (24 mg, 80%) was obtained as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ 8.76 (br, 1H), 7.25 (td, J = 7.7, 1.3 Hz, 1H), 7.19 (m, 1H), 7.05 (td, J = 7.5, 1.0 Hz, 1H), 6.89 (d, J = 7.8 Hz, 1H), 5.98 (m, 1H), 5.03 (dquin, J = 12.4, 2.0 Hz, 1H), 4.94 (dquin, J = 12.4, 2.0 Hz, 1H), 1.50 (q, J = 2.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ 178.3, 141.0, 135.8, 130.0, 128.7, 124.8, 124.7, 123.2, 110.4, 93.0, 76.5, 11.1; IR ($CHCl_3$, cm^{-1}) ν 3256, 1726, 1619; HRMS (ES) calcd for $C_{12}H_{11}NO_2$ $[M]^+$ 201.0790, found 201.0793.

*3-(4-Methoxyphenyl)-5H-spiro[furan-2,3′-indolin]-2′-one (**2i**).* From 30 mg (0.10 mmol) of allenol **1i**, and after chromatography of the residue using hexanes/ethyl acetate (2:1) as eluent, compound **2i** (16.5 mg, 56%) was obtained as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ 8.28 (br, 1H), 7.25 (m, 2H), 7.02 (m, 2H), 6.89 (d, J = 7.7 Hz, 1H), 6.68 (d, J = 8.8 Hz, 1H), 6.54 (t, J = 1.8 Hz, 1H), 5.15 (dd, J = 13.5, 1.8 Hz, 1H), 5.06 (dd, J = 13.5, 1.8 Hz, 1H), 3.70 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ 177.5, 159.4, 140.9, 138.4, 130.3, 129.2, 127.4 (2C), 125.6, 125.3, 124.1, 123.4, 113.9 (2C), 110.5, 91.0, 76.0, 55.1; IR ($CHCl_3$, cm^{-1}) ν 1725; HRMS (ES) calcd for $C_{18}H_{15}NO_3$ $[M]^+$ 293.1052, found 293.1061.

*1′,3-Dimethyl-5H-spiro[furan-2,3′-indolin]-2′-one (**2j**).* From 30 mg (0.14 mmol) of allenol **1j**, and after chromatography of the residue using hexanes/ethyl acetate (4:1) as eluent, compound **2j** (22 mg, 75%) was obtained as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ 7.32 (td, J = 7.7, 1.2 Hz, 1H), 7.20 (d, J = 6.3 Hz, 1H), 7.07 (t, J = 7.5 Hz, 1H), 6.82 (d, J = 7.7 Hz, 1H), 5.96 (q, J = 1.5 Hz, 1H), 5.01 (dt, J = 12.4, 1.9 Hz, 1H), 4.90 (dt, J = 12.4, 1.9 Hz, 1H), 3.20 (s, 3H), 7.07 (m, 2H), ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ 175.6, 144.0, 135.8, 130.0, 128.3, 124.9, 124.4, 123.1, 108.2, 92.4,76.3, 26.3, 11.1; IR ($CHCl_3$, cm^{-1}) ν 1715; HRMS (ES) calcd for $C_{13}H_{14}NO_2$ $[M + H]^+$ 216.1025, found 216.1031.

*1′-Methyl-3-phenyl-5H-spiro[furan-2,3′-indolin]-2′-one (**2k**).* From 25 mg (0.09 mmol) of allenol **1k**, and after chromatography of the residue using hexanes/ethyl acetate (2:1) as eluent, compound **2k** (17 mg, 67%) was obtained as a yellow solid: mp 144−146 °C;^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ 7.26 (td, J = 7.7, 1.1 Hz, 1H), 7.19 (m, 2H), 7.07 (m, 2H), 6.97 (td, J = 7.5, 0.8 Hz, 1H), 6.91 (m, 2H), 6.78 (d, J = 7.9 Hz, 1H), 6.57 (q, J = 1.8 Hz, 1H), 5.09 (dd, J = 13.6, 1.8 Hz, 1H), 4.99 (dd, J = 13.6, 1.8 Hz, 1H), 3.15 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ 175.1, 144.0, 139.0, 131.7, 130.4, 128.7, 128.4 (2C), 128.0, 127.5, 126.1 (2C), 124.9, 123.4, 108.5, 90.7, 75.8, 26.4; IR ($CHCl_3$, cm^{-1}) ν 1725, 1612; HRMS (ES) calcd for $C_{18}H_{16}NO_2$ $[M + H]^+$ 278.1181, found 278.1180.

*5′-Chloro-1′,3-dimethyl-5H-spiro[furan-2,3′-indolin]-2′-one (**2l**).* From 30 mg (0.12 mmol) of allenol **1l**, and after chromatography of the residue using hexanes/ethyl acetate (2:1) as eluent, compound **2l** (22 mg, 73%) was obtained as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ 7.29 (dd, J = 8.3, 2.2 Hz, 1H), 7.18 (d, J = 2.2 Hz, 1H), 6.75 (d, J = 8.3 Hz, 1H), 5.97 (q, J = 1.5 Hz, 1H), 5.00 (dt, J = 12.4, 2.0 Hz, 1H), 4.90 (dt, J = 12.4, 2.0 Hz, 1H), 3.18 (s, 3H), 1.44 (q, J = 2.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ 175.2, 142.4, 135.2, 130.0, 129.9, 128.6, 125.3, 124.9, 109.2, 92.3, 76.5, 26.4, 11.1; IR ($CHCl_3$, cm^{-1}) ν 1729, 1487; HRMS (ES) calcd for $C_{13}H_{13}ClNO_2$ $[M + H]^+$ 250.0635, found 250.0612.

*7′-Chloro-1′,3-dimethyl-5H-spiro[furan-2,3′-indolin]-2′-one (**2m**).* From 31 mg (0.12 mmol) of allenol **1m**, and after chromatography of the residue using hexanes/ethyl acetate (4:1) as eluent, compound **2m** (26 mg, 87%) was obtained as a yellow solid: mp 81−83 °C;^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ 7.25 (m, 1H), 7.09 (dd, J = 7.2, 1.1 Hz, 1H), 6.99 (t, J = 7.7 Hz, 1H), 5.97 (q, J = 1.5 Hz, 1H), 5.00 (dt, J = 12.4, 1.9 Hz, 1H), 4.90 (dt, J = 12.4, 1.9 Hz, 1H), 3.57 (s, 3H), 1.44 (q, J = 1.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ 175.9, 139.7, 135.5, 132.2, 131.2, 125.1, 123.9, 123.0, 115.7, 91.8, 76.5, 29.7, 11.1; IR ($CHCl_3$, cm^{-1}) ν 1734, 1461; HRMS (ES) calcd for $C_{13}H_{12}ClNO_2$ $[M]^+$ 249.0557, found 249.0551.

*4-(3-Phenyl-2,5-dihydrofuran-2-yl)benzonitrile (**2n**).* From 40 mg (0.16 mmol) of allenol **1n**, and after chromatography of the residue using hexanes/ethyl acetate (7:1) as eluent, compound **2n** (24 mg, 63%) was obtained as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ 7.35 (s, 4H), 7.14 (m, 3H), 7.09 (d, J = 3.0 Hz, 2H), 6.05 (td, J = 4.6, 1.8 Hz, 1H), 5.98 (q, J = 1.9 Hz, 1H), 4.76 (d, J = 1.9 Hz, 1H), 4.74 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ 146.7, 141.3, 133.0, 132.7, 129.0, 128.6, 128.5, 127.2, 124.2, 119.0, 112.8, 87.9, 76.1; IR ($CHCl_3$, cm^{-1}) ν 2230, 1758, 843; HRMS (ES) calcd for $C_{17}H_{13}NO$ $[M]^+$ 247.0997, found 247.1005.

*Methyl 4-(3-Methyl-2,5-dihydrofuran-2-yl)benzoate (**2o**).* From 40 mg (0.18 mmol) of allenol **1o**, and after chromatography of the residue using hexanes/ethyl acetate (6:1) as eluent, compound **2o** (28 mg, 72%) was obtained as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ 8.16 (d, J = 8.4 Hz, 2H), 7.17 (m, 2H), 5.38 (m, 1H), 5.13 (q, J = 1.6 Hz, 1H), 4.61 (m, 2H) 3.50 (s, 3H), 1.23 (t, J = 1.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ 137.0, 147.9, 138.8, 130.7, 130.5, 127.3, 121.7, 90.5, 76.1, 51.9, 12.6; IR ($CHCl_3$, cm^{-1}) ν 1723, 1281, 1112; HRMS (ES) calcd for $C_{13}H_{14}O_3$ $[M]^+$ 218.0943, found 218.0938.

$AuCl_3$-Catalyzed Reaction of Allenol 1a. $AuCl_3$ (2 mg, 0.0065 mmol) was added to a solution of allenol **1a** (30 mg, 0.13 mmol) in

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dichloromethane (3 mL). The reaction mixture was stirred at rt until the starting material disappeared as indicated by TLC. Saturated aqueous sodium bicarbonate (1 mL) was added before the mixture was partitioned between dichloromethane and water. The organic extract was washed with brine, dried ($MgSO_4$), and concentrated under vacuum. Chromatography of the residue using hexanes/ethyl acetate (6:1) as eluent gave 12 mg (42%) of the less polar compound **3a** and 5 mg (16%) of the more polar compound **2a**.

*1,3-Dimethoxy-6-methylnaphthalene (**3a**):* colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ 8.02 (d, J = 8.5 Hz, 1H), 7.46 (s, 1H), 7.14 (dd, J = 8.5, 1.2 Hz, 1H), 6.66 (d, J = 1.9 Hz, 1H), 6.44 (d, J = 1.9 Hz, 1H), 3.96 (s, 3H), 3.90 (s, 3H), 2.48 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ 158.2, 156.5, 136.7, 135.2, 125.6, 125.0, 121.7, 119.7, 97.4. 96.7, 55.4, 55.2, 21.6; IR ($CHCl_3$, cm^{-1}) ν 2934, 1633, 1154; HRMS (ES) calcd for $C_{13}H_{14}O_2$ $[M]^+$ 202.0994, found 202.0998.

$AuCl_3$-Catalyzed Reaction of Allenol 1b. $AuCl_3$ (4 mg, 0.013 mmol) was added to a solution of allenol **1b** (62 mg, 0.24 mmol) in dichloromethane (6 mL). The reaction mixture was stirred at rt until the starting material disappeared as indicated by TLC. Saturated aqueous sodium bicarbonate (2 mL) was added before the mixture was partitioned between dichloromethane and water. The organic extract was washed with brine, dried ($MgSO_4$), and concentrated under vacuum. Chromatography of the residue using hexanes/ethyl acetate (10:1) as eluent gave 22 mg (35%) of the less polar compound **2b** and 14 mg (25%) of the more polar compound **3b**.

*7-Methyl-1-phenoxynaphthalene (**3b**):* colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ 7.66 (s, 1H), 7.45 (d, J = 7.6 Hz, 1H), 7.32 (m, 3H), 7.16 (m, 3H), 6.97 (m, 3H), 2.36 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ 157.2, 155.0, 138.6, 134.9, 130.6, 130.0 (2C), 129.8 (2C), 127.7, 123.3 (2C), 119.3, 119.1, 118.3 (2C), 25.7; IR ($CHCl_3$, cm^{-1}) ν 3065, 1483, 1235, 752, 693; HRMS (ES) calcd for $C_{17}H_{14}O$ $[M]^+$ 234.1045, found 234.1041.

■ ASSOCIATED CONTENT

Supporting Information

Copies of NMR spectra of new compounds and computational details. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b00887.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: alcaideb@quim.ucm.es.

*E-mail: palmendros@iqog.csic.es.

Notes

The authors declare no competing financial interest.

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(9) Today, the use of mercury-based compounds is widespread (barometers, batteries, electrical switches, electrodes, extraction of

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(16) A potentially promising subset of the spirooxindole alkaloids are the oxa-spirooxindoles, joining two privileged motifs, the oxacycle, and oxindole substructures through a unique spiro-quaternary carbon. Unfortunately, approaches for this interesting hybrid scaffold remain limited. For selected examples, see: (a) Liu, R.; Yu, C.; Xiao, Z.; Li, T.; Wang, X.; Xie, Y.; Yao, C. *Org. Biomol. Chem.* **2014**, *12*, 1885. (b) Xie, X.; Peng, C.; He, G.; Leng, H.-J.; Wang, B.; Huang, W.; Han, B. *Chem. Commun.* **2012**, *48*, 10487. (c) Wang, X.-N.; Zhang, Y.-Y.; Ye, S. *Adv. Synth. Catal.* **2010**, *352*, 1892. (d) Alcaide, B.; Almendros, P.; Martínez del Campo, T.; Quirós, M. T. *Chem.—Eur. J.* **2009**, *15*, 3344.

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(21) **CAUTION!** Perchlorates are potentially explosive compounds and should be handled very carefully. We used $Hg(ClO_4)_2{\cdot}3H_2O$ for our experiments, and we encountered no problems during handling. $Hg(ClO_4)_2{\cdot}3H_2O$ is a stable salt because (a) 0.006 M solutions (around 22 mg) in different organic solvents (THF, DCE, acetonitrile, and DMF) can be safely heated at 70 °C for several hours; (b) 10 mg of $Hg(ClO_4)_2{\cdot}3H_2O$ (neat product) can be heated at 200 °C with decomposition but not explosion; and (c) it did not decompose during storage at room temperature for several weeks. No explosions occurred during our work, but this salt should be handled with care.

(22) The unpurified reaction mixture of allenol **1j** under catalytic $HClO_4$ conditions contained the corresponding rearranged α,β-unsaturated ketone as the major reaction product, along with unidentified impurities. This result should rule out the possibility of Brønsted acid catalysis through adventitious perchloric acid with the use of $Hg(ClO_4)_2{\cdot}3H_2O$.

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