DOI: 10.1002/chem.201102100

Striking Alkenol Versus Allenol Reactivity: Metal-Catalyzed Chemodifferentiating Oxycyclization of Enallenols

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Abstract: An efficient chemodivergent metal-controlled methodology for the generation of different highly functionalized oxygen heterocycles from common enallenol substrates has been developed. Chemoselectivity control in the O−C functionalization of an enallenol can be achieved through the choice of catalyst: $AuCl_3$, $PdCl_2$, and $[PtCl_2(CH_2{=}CH_2)]_2$ exclusively afford dihydrofurans through selective activation of the allenol moiety, whereas $FeCl_3$ solely gives tetrahydrofurans or tetrahydropyrans through selective activation of the alkenol moiety. We have also shown that a combination of metal-mediated hydroalkoxylation and allenic aminocyclization reactions can lead to a useful preparation of the tetrahydrofuro[3,2-b]piperidine core of the antimalarial alkaloid isofebrifugine. These divergent heterocyclization reactions have been developed experimentally and additionally, their mechanisms have been investigated by a theoretical study.

Keywords: allenes · cyclization · gold · iron · selectivity

Introduction

Tetrahydrofuran and pyran rings are present in a wide variety of natural products and biologically relevant compounds, so the development of synthetic methods for their construction has attracted much attention.[1] Of the possible approaches, transition-metal-catalyzed intramolecular addition of oxygen nucleophiles across carbon–carbon double bonds is one of the most rapid and convenient methods for the preparation of oxygen heterocycles.[2] In particular, the heterocyclization of allenes, a class of compounds containing two cumulative carbon–carbon double bonds, is intriguing from the point of view of regioselectivity.[3,4] On the other hand, recent years have seen the dawning of a resplendent age of precious-metal catalysis in the fields of carbon–carbon and carbon–heteroatom bond formation.[5] Iron is the fourth most abundant element on earth, and iron salts have recently emerged as powerful alternatives as a result of their inexpensiveness and environmental friendliness.[6] A process that allows a selective chemical reaction, even if the structure of the substrate suggests numerous possibilities for reactivity, represents an attractive strategy.[7] Such a substrate must have diverse reactive sites at which different transformations can take place. In this context, carbon–heteroatom cyclization is of major interest. Although many efforts have been made in these fields, the chemodivergent metal-catalyzed heterocyclization of alcohols bearing both an allene and an alkene center had not been reported before we entered this field.[8] The selective preparation of different oxygen heterocycles from the same enallenol requires two appropriate catalytic systems that are capable of chemodifferentiating between different alkene functions, thus resulting in dissimilar roles for each partner. Otherwise, a mixture of at least two different products is possible. In continuation of our interest in heterocyclic and allene chemistry,[9] here we report full details of the challenging problem of metal-catalyzed chemodifferentiating (alkene versus allene) cycloetherification of enallenols,[8] together with its application to the synthesis of the tetrahydrofuro-[3,2-b]piperidine core of the antimalarial alkaloid isofebrifugine. In addition, the mechanisms of these divergent heterocyclization reactions have been computationally investigated.

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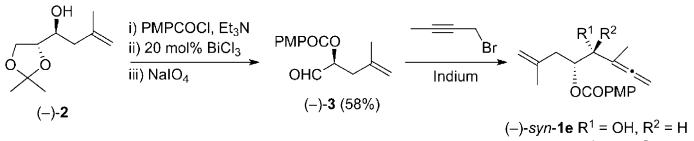
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201102100.

Results and Discussion

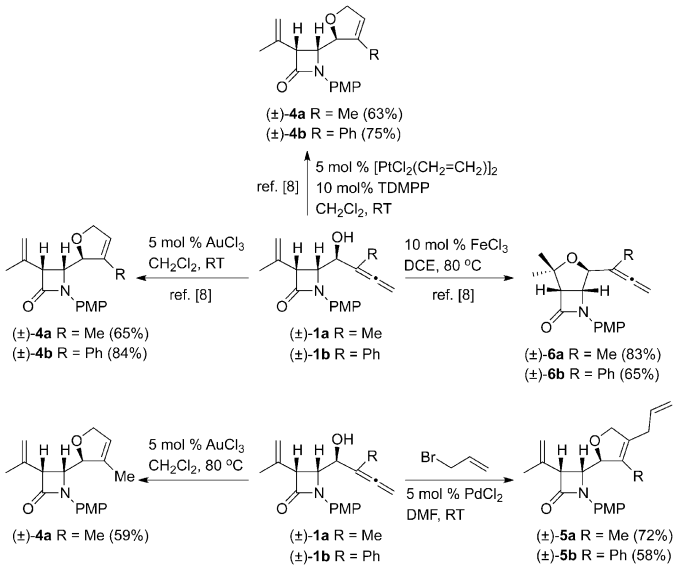
The precursors for oxygen heterocycle formation—the racemic or enantiopure enallenols **1a** and **1b** (Scheme 2, below) and **1c** and **1d** (Scheme 3, below)—were readily prepared

from the appropriate starting 4-oxoazetidine-2-carbaldehydes through regiocontrolled indium-mediated Barbier-type carbonyl–allenylation reactions in aqueous media, as we have previously described.[10a] The optically active precursors *syn*-**1e** and *anti*-**1e** were prepared from homomethallylic alcohol **2** and aldehyde **3**[10b] in a four-step sequence as shown in Scheme 1. Enallenol **1f** was prepared from salicylaldehyde by using our methodology.[10c]



Scheme 1. Preparation of enantiopure enallenols *syn*-**1e** and *anti*-**1e**.

In our previous communication[8] we studied the cyclization of olefinic α-allenol **1a** under different metal catalysis conditions. In a first series of runs, the cyclization of enallenol **1a** was catalyzed by precious metal salts—$[PtCl_2(CH_2{=}CH_2)]_2$ and $AuCl_3$—to afford the allene cycloisomerization adduct **4a** as the sole isomer (Scheme 2). AgOTf was not effective as a catalyst, whereas to achieve reasonable yields of dihydrofuran **4a** one equivalent of $AgNO_3$ was needed. Here the $PdCl_2$-catalyzed cyclizative coupling reaction of enallenol **1a** with allyl bromide to give the functionalized dihydrofuran **5a** is described. The above results indicate that palladium- and noble-metal-based catalysts exclusively activate the allenyl group of the enallenol. One of the challenges for modern synthesis is to create distinct types of complex molecules from identical starting materials solely on the basis of catalyst selection. Having found a solution for the selective hydroalkoxylation of the allene moiety (previous communication[8] for Au and current work for Pd), the more intricate heterocyclizative problem associated with tuning of the chemoselectivity of enallenols towards alkenol activation was examined. The metal-catalyzed cyclization of unsaturated alcohol **1a** in the presence of other metallic chlorides,



Scheme 2. Iron-, gold-, platinum-, and palladium-catalyzed chemodivergent preparations of dihydrofurans **4** and **5** and tetrahydrofurans **6**.

such as bismuth trichloride, hafnium tetrachloride, and iron trichloride, was also studied in our previous communication.[8] The reactivities of $BiCl_3$, $InCl_3$, and $HfCl_4$ in catalytic quantities (20 mol%) in dichloromethane at reflux were examined. However, complete conversion of enallenol **1a** was not observed by TLC or ^1H NMR analysis of the crude reaction mixtures. Complete conversion was, however, observed on heating of a solution of enallenol **1a** in dichloromethane at 70 °C in a sealed tube in the presence of 1.5 equivalents of the metallic chlorides, selectively affording tetrahydrofuran **6a** in 70% yield. However, these reactions require stoichiometric amounts of the metallic reagents. Similar results were obtained with use of a Brønsted acid (HCl).

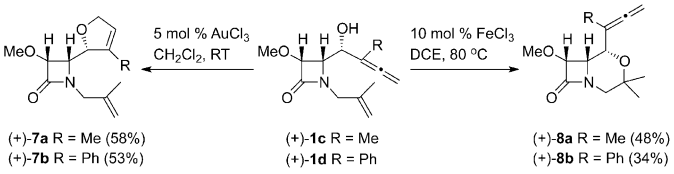
Iron-catalyzed reactions have recent attracted much attention because of the low cost, ready availability, and environmentally benign character of iron, and so we decided to test the catalytic efficiency of $FeCl_3$. To our delight, as we have communicated previously,[8] use of 10 mol% of the Fe^{III} salt was able to catalyze the cyclization chemospecifically in favor of the alkene component to afford the β-lactam-tetrahydrofuran hybrid **6a** exclusively and in 83% yield of the isolated product (Scheme 2). Another important feature is that the allene moiety is not altered under the iron-catalyzed oxycyclization reaction conditions. As far as we know, the chemocontrolled hydroalkoxylation of an olefin moiety in the presence of the more reactive allene functionality was unprecedented until we entered this field.[8] A special mention should be made of the fact that the chemoselectivity can be switched by changing the metal component in the metallic trichloride catalyst from gold to iron. In addition to the total chemocontrol, the reaction was regiospecific and only the five-membered ring ether was formed, with no trace of the isomeric six-membered ring. The Au-, Pt-, and Pd-catalyzed reactions of phenyl enallenol **1b** furnished the corresponding dihydrofurans **4b** and **5b**; the same starting

Abstract in Spanish: *Se ha investigado la quimiodiferenciación en las reacciones de oxiciclación entre los grupos alqueno y aleno de un mismo sustrato, observándose que ésta puede controlarse mediante la elección adecuada del catalizador. Se ha demostrado que catalizadores tales como el tricloruro de hierro y las sales de metales nobles son capaces de discriminar entre ambos centros reactivos. También se ha mostrado que la combinación de reacciones de hidroalcoxilación e hidroaminación catalizadas por metales da lugar a la preparación del núcleo heterocíclico del alcaloide antimalárico isofebrifugina. Estas reacciones de heterociclación se han desarrollado experimentalmente y sus mecanismos se han investigado por métodos computacionales.*

material also underwent a chemodivergent Fe-catalyzed alkene cycloetherification resulting in the formation solely of the isomeric tetrahydrofuran **6b** (Scheme 2). Because of their dual alkenol/allenol character, the enallenols **1** show remarkably distinct, metal-tunable reaction behavior toward both electrophilic sites.

Because the best results for iron-catalyzed reactions had been obtained at 80 °C, it was decided to conduct the reaction with $AuCl_3$ under the same conditions (higher temperature). In the event, no remarkable changes were detected when starting from enallenol **1a** (Scheme 2).

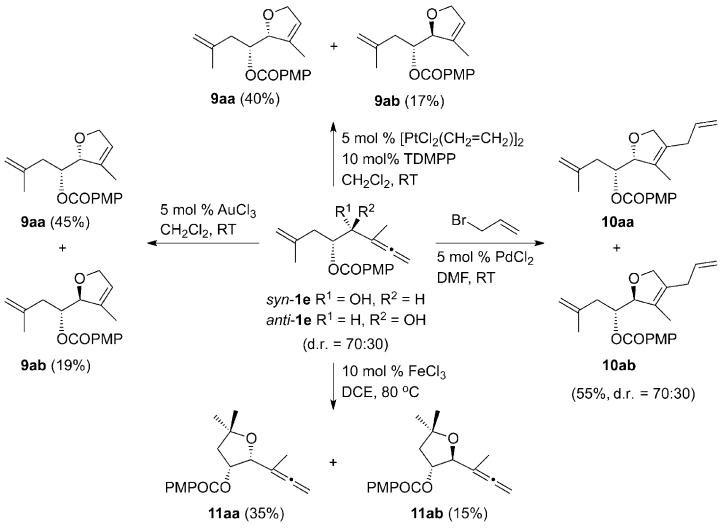
We next investigated the generality of the metal-catalyzed enallenol chemodivergence. The synthetic power of the process can best be demonstrated by application of the enantiopure olefinic α-allenols **1c** and **1d** in the preparations both of the dihydrofurans **7a** and **7b** and of the isooxacephams **8a** and **8b** (Scheme 3).[11,12] Interestingly, when the alkene



Scheme 3. Iron- and gold-catalyzed chemodivergent preparations of the attached-ring dihydrofurans **7** and the fused tetrahydropyrans **8**.

substituent was moved from position C3 to N1, as in the 1,4-tethered β-lactam enallenes **1c** and **1d**, the corresponding fused adducts **8a** and **8b** were furnished in fair yields and exclusively as single isomers in the reactions conducted in the presence of the iron catalytic system. In contrast, the precious-metal-catalyzed 5-*endo* heterocyclization of enallenols **1c** and **1d** gave the dihydrofurans **7a** and **7b** (Scheme 3). Scheme 3 shows how the mild conditions of iron and gold catalysis remarkably allow the chemoselective formation of attached-ring or anellated β-lactams without disruption of the sensitive four-membered ring systems. Although complete conversion was observed by TLC and ^{1}H NMR analysis of the crude reaction mixtures, some decomposition of the sensitive fused azaoxacycles **8** during purification by flash chromatography was observed, and this might be responsible for the moderate isolated product yields.

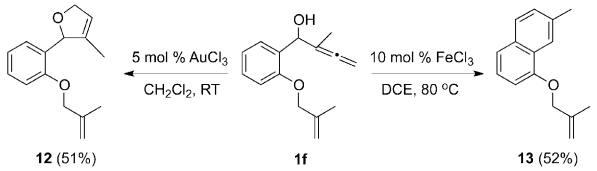
To check whether the structurally different non-β-lactam allenols **1e** (prepared as an inseparable 70:30 *syn*/*anti* mixture) are good substrates for the chemodivergent metal-catalyzed oxycyclizations, reactions of **1e** were also carried out (Scheme 4). Under similar conditions, the reactions do take the same chemodifferentiating course, with the corresponding dihydrofurans **9** and **10** and tetrahydrofurans **11** being chemospecifically obtained in good yields by precious-metal (or palladium) and iron catalysis, respectively. Fortunately, the diastereomeric adducts **9aa**, **9ab**, **11aa**, and **11ab**, obtained from the Au- (or Pt-) and Fe-catalyzed selective cyclizations of allenols *syn*-**1e** and *anti*-**1e**, could be easily sepa-



Scheme 4. Iron-, gold-, platinum-, and palladium-catalyzed chemodivergent preparations of dihydrofurans **9** and **10** and tetrahydrofurans **11**. PMP = 4-MeOC$_6$H$_4$; TDMPP = tris(2,6-dimethoxyphenyl)phosphine.

rated by gravity flow chromatography. In contrast, the bench chromatographic separation of diastereomers **10aa** and **10ab**, obtained through Pd catalysis, failed. Full chirality transfer from the starting enallenols *syn*-**1e** and *anti*-**1e** had been accomplished.

It was interesting at this point to test the reactivity of an enallenol moiety tethered to an aromatic ring under chemodivergent metal-catalyzed conditions. We found that treatment of enallenol **1f** (Scheme 5), bearing an aromatic sub-

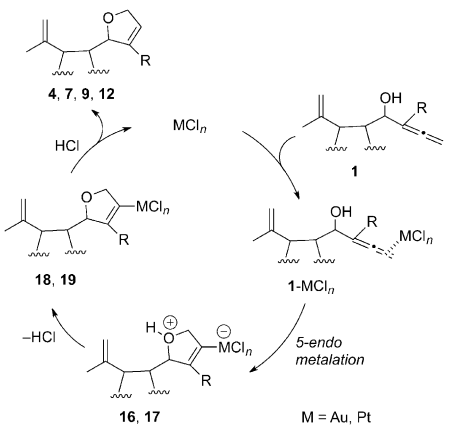


Scheme 5. Iron- and gold-catalyzed chemodivergent preparation of dihydrofuran **12** and naphthalene **13**.

stituent, with gold trichloride selectively led to the cycloetherification product **12**, resulting from 5-*endo-trig* cyclization, in a reasonable isolated product yield. We also tested the reactivity of phenyl-substituted enallenol **1f** under iron catalysis conditions. To our surprise, in contrast with the oxycyclization reaction of enallenols **1a–e** that had led to dihydrofuran or dihydropyran rings, treatment of enallenol **1f** under identical conditions afforded naphthalene **13** through a chemo- and regioselective 6-*endo* carbocyclization/dehydration sequence by attack of the aromatic ring on the distal allene carbon (Scheme 5).

A possible mechanism for the gold- and platinum-catalyzed formation of dihydrofurans **4**, **7**, **9**, and **12** from enallenols **1** could initially involve the formation of complexes **14** (**1**·$AuCl_3$) or **15** (**1**·$PtCl_2L$) through selective coordination of

the gold trichloride or platinum dichloride to the distal double bond of the 1,2-diene moiety (Scheme 6). Next, specific 5-*endo* oxyauration or 5-*endo* oxyplatination could



Scheme 6. Mechanistic explanation for the gold- or platinum-catalyzed oxycyclization of enallenols **1**.

form species **16** (M = Au) or **17** (M = Pt). Loss of HCl followed by protonolysis of the carbon–gold or carbon–platinum bonds in the neutral species **18** (M = Au) or **19** (M = Pt) could afford the products **4**, **7**, **9**, and **12** and regenerate the gold or platinum catalyst. It should be mentioned that $[PtCl_2(CH_2{=}CH_2)]_2$ has been used for the cycloetherification both of γ- and of δ-hydroxy alkenes and allenes,[13] but not for the oxycyclization of α-allenols.[14] The platinum atom of the catalyst could thus be complexed either to the olefinic or the allenic double bonds in enallenols **1**.

Density functional theory (DFT) calculations[15] were carried out at the dispersion-corrected M06L/def2-SVP level to gain more insight into the mechanism of the gold-catalyzed divergent oxycyclization reaction discussed above. The corresponding computed reaction profile of the model system **1M**, in which the OCOPMP group attached to the sp^3 carbon of enallenol **1e** has been replaced by a hydrogen atom, is illustrated in Figure 1, which shows the corresponding free energies in CH_2Cl_2 solution (PCM-M06L/def2-SVP level).

As initially envisaged, two different coordination modes of the metal fragment to **1M**—that is, alkene or distal allene—are possible. Our calculations indicate that the alkene-coordinated complex **1-Au-B** is 8.2 kcal mol^{-1} more stable than the allene-coordinated species **1-Au-A**. This is consistent with the computed molecular orbitals depicted in Figure 2, which clearly shows that the HOMO is mainly located in the alkene moiety whereas the HOMO−1 (which lies 0.23 eV below the HOMO) corresponds to the π molecular orbital of the allenic fragment. Both complexes **1-Au-A** and **1-Au-B** can undergo easy oxyauration cyclization in view of the quite low computed activation barriers ($\Delta G^{\ddagger}_{298}$ = +3.5 and +5.6 kcal mol^{-1}, respectively) to produce the cor-

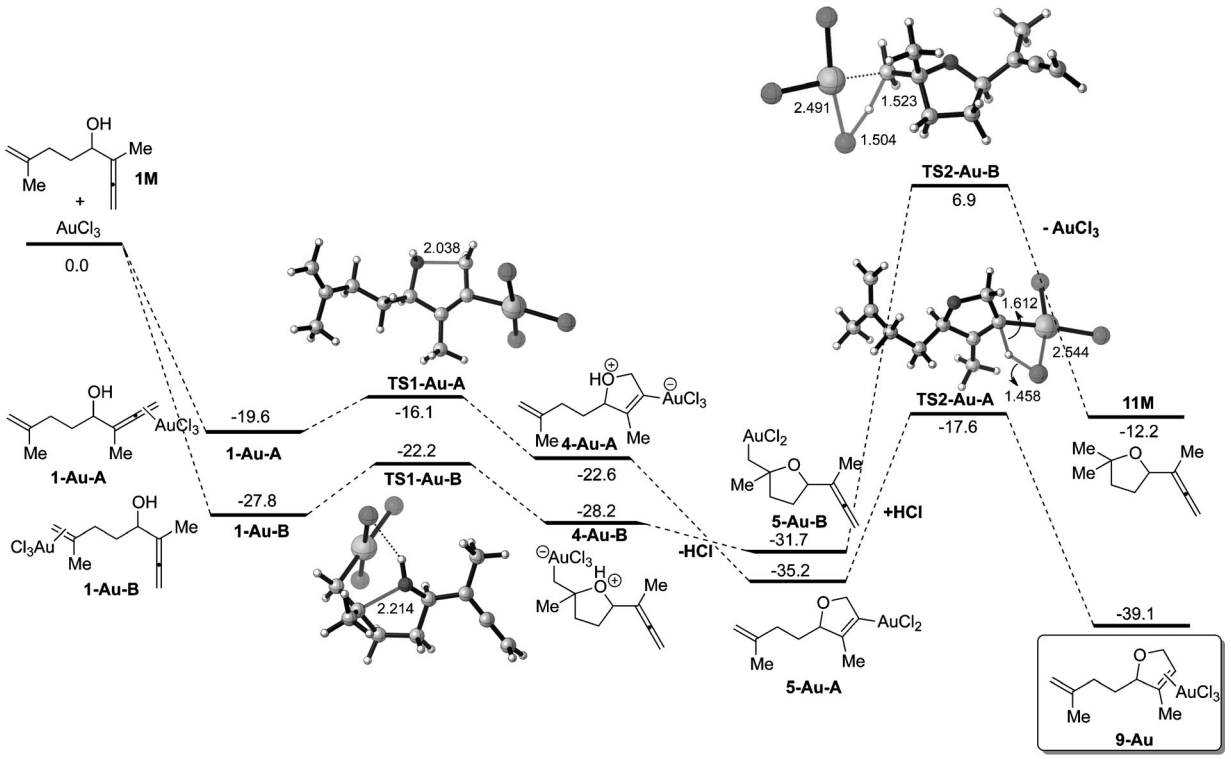


Figure 1. Computed reaction profile for the reaction of **1M** and $AuCl_3$. Numbers indicate the corresponding PCM-corrected ΔG_{298} energies (in kcal mol^{-1}) in dichloromethane. Interatomic distances in the corresponding transition states are given in Ångstroms. All values were computed at the M06L/def2-SVP level.

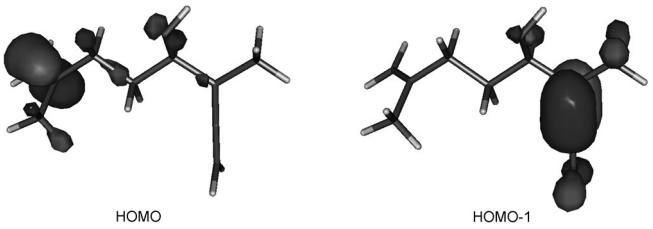
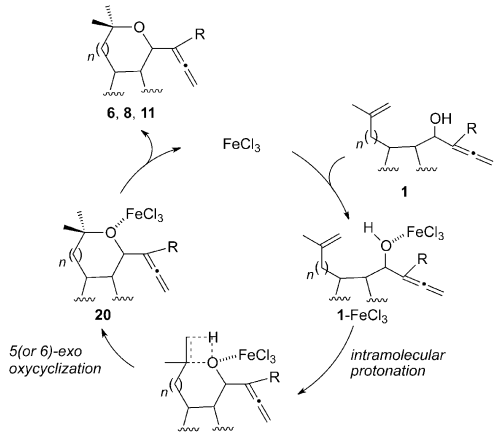


Figure 2. Molecular orbitals of enallenol **1M**.

responding five-membered zwitterionic intermediate **4-Au** in an exergonic transformation ($\Delta G_{R,298} = -6.5$ and -6.0 kcal mol^{-1}, respectively). The loss of HCl then produces neutral complexes **5-Au** in an process that is highly exergonic for **5-Au-A** ($\Delta G_{R,298} = -12.6$ kcal mol^{-1}) and only slightly exergonic for **5-Au-B** ($\Delta G_{R,298} = -3.5$ kcal mol^{-1}). Finally, protonolysis of the carbon-gold bond produces the final products **9-Au** and **11M** through the transition states **TS2-Au-A** and **TS2-Au-B**, respectively. From the values shown in Figure 1, it becomes obvious that this step constitutes the bottleneck of the process in view of the computed higher barrier energies relative to the initial cyclization processes involving **TS1-Au-A** and **TS1-Au-B**. Strikingly, whereas the process leading to **9-Au** occurs with an activation energy of $\Delta G^{\ddagger}_{298} = +17.6$ kcal mol^{-1}, the transformation involving **TS2-Au-B** has a much higher barrier energy ($\Delta G^{\ddagger}_{298} = +38.6$ kcal mol^{-1}), which makes the latter Au–C protonolysis unfeasible under the reaction conditions used in the experiment (room temperature). The formation of the five-membered compound originating from the cyclization involving the allenic moiety of **1** (i.e., compounds **9** and **10** versus **11**) should therefore be exclusive, which is in good agreement with the experimental findings.

Scheme 7 outlines a mechanistic proposal for the formation of compounds **6**, **8**, and **11**. The Lewis acid $FeCl_3$ should strongly enhance the Brønsted acidities of the hydroxy protons of the enallenols **1** through Fe^{III} coordination to the oxygen. A hydroxy-iron complex **1**-$FeCl_3$ should thus be formed initially. Species **1**-$FeCl_3$ could undergo intramolecular protonation (stepwise or concerted) accompanied by 5-*exo* or 6-*exo* oxycyclization reactions to give the intermediates **20**. Finally, deferration could afford oxygen heterocycles **6**, **8**, and **11** and regenerate the iron catalyst (Scheme 7). The cycloetherification involves a chemo- and regiospecific Markonikov-type addition of the hydroxy group to the alkene moiety. An alternative pathway involving coordination of $FeCl_3$ to the olefinic double bond cannot be ruled out at the moment.



Scheme 7. Mechanistic explanation for the iron-catalyzed oxycyclization of enallenols **1**.

Chemoselectivity similar to that observed with $FeCl_3$ is achieved when enallenols **1** react in the presence of HCl (albeit in lower yields; see above). Our calculations (Figure 3) indicate that the formation of dihydrofuran **11-H**,

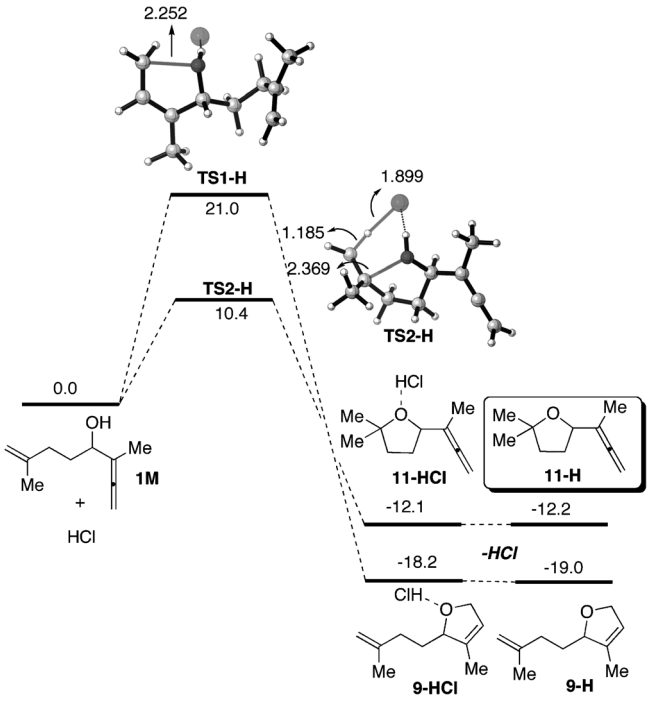
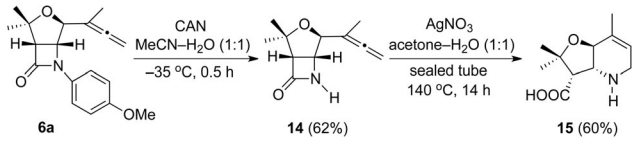


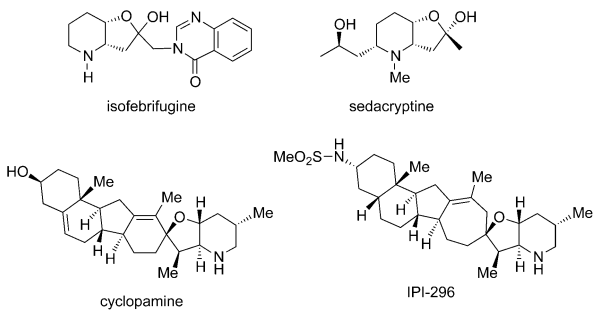
Figure 3. Computed reaction profile for the reaction of **1M** and HCl. Numbers indicate the corresponding PCM-corrected ΔG_{298} energies (in kcal mol^{-1}) in dichloromethane. Interatomic distances in the corresponding transition states are given in Ångstroms. All values were computed at the M06L/def2-SVP level.

a model compound for the experimentally observed species **11aa** and **11ab**, takes place under kinetic control via the saddle point **TS2-H**, in view of the considerably higher activation energy required for the cyclization involving the allenic moiety via **TS1-H** ($\Delta\Delta G^{\ddagger}_{298} = +9.6$ kcal mol^{-1}). Interestingly, a close inspection of **TS2-H** indicates that the protonation of the alkene and the 5-*exo*-oxycyclization occur simultaneously in a concerted way, assisted by the chloride counteranion. The final loss of HCl, which is weakly bonded (by a hydrogen bond) to the oxygen atom of the five-membered ring in both **9-HCl** and **11-HCl**, affords the final products **9-H** and **11-H** (the latter obtained exclusively in the experiment).

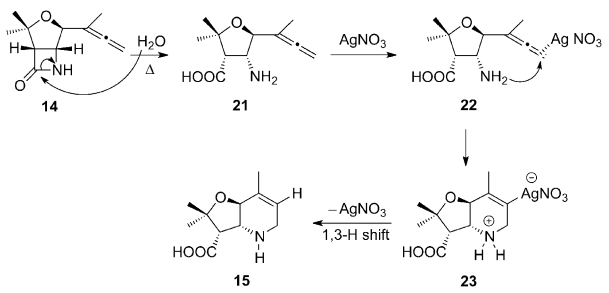
To capitalize on the above findings for the preparation of different products, a stereocontrolled route from the allenyl β-lactam-tetrahydrofuran **6a** to the tetrahydrofuro[3,2-b]piperidine core, which appears in several natural products of biological interest, was envisioned. This fused tetrahydrofuran substructure is present both in the antimalarial alkaloids isofebrifugine and sedacryptine[16] and in the plant-derived steroid cyclopamine and its semisynthetic analogue IPI-926.[17] Firstly, the deprotection of the β-lactam nitrogen was achieved through oxidative cleavage (ceric ammonium nitrate) of the activated aromatic functionality attached to the azetidin-2-one nitrogen to give the *NH*-β-lactam **14** (Scheme 8). To achieve the desired conversion to the alkaloid framework, selective addition of the β-lactam nitrogen to the terminal allenic carbon is essential. Fortunately, the transformation of the allene-β-lactam moiety into the piperidine ring was carried out through a silver(I)-promoted regioselective aminocyclization reaction. The formation of the furo[3,2-b]piperidine-3-carboxylic acid **15** (Scheme 8)[18,19] presumably involves the selective amide bond cleavage of the four-membered ring to give the corresponding β-amino ester,[20] followed by intramolecular N–H addition to the allene group.



Scheme 8. Preparation of the heterocyclic core of the antimalarial alkaloids isofebrifugine and sedacryptine from precursor **6a**. CAN = ceric ammonium nitrate.

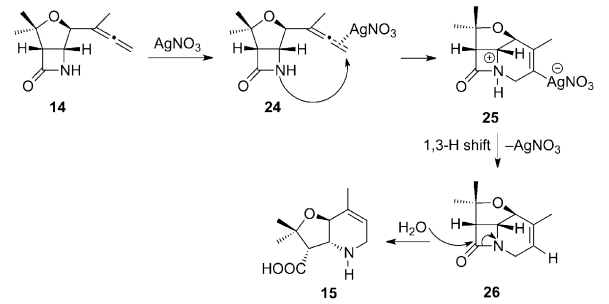


A possible reaction course for the rearrangement process from **14** to **15** is shown in Scheme 9. Initially, the relief of the strain associated with the four-membered ring in bicycle **14** through β-lactam hydrolysis could afford β-amino ester **21**. Next, the silver salt could coordinate to the allenic double bond of the substrate **21** and form π complex **22**. As a consequence of the increased electrophilicity, cyclization via a S_N2 type transition state could produce the intermediate **23**, which could transform into the bicycle **15** through subsequent demetalation.



Scheme 9. Mechanistic explanation for the silver-promoted rearrangement of β-allenic lactam **14**.

A mechanism involving i) initial coordination of the silver salt to the allenic double bond of compound **14** to form π complex **24**, ii) aminocyclization to produce tricyclic β-lactam **26** via intermediate **25**, and iii) β-lactam ring opening to afford compound **15** may also be considered (Scheme 10).



Scheme 10. Alternative mechanistic explanation for the silver-promoted rearrangement of β-allenic lactam **14**.

This mechanism was deemed unlikely, however, because of the great formation energy presumably associated with the highly strained tricyclic azetidin-2-one intermediate **25**. Furthermore, if this mechanism was in operation, the absence of H_2O should lead to formation of the tricyclic β-lactam adduct **26** by 6-*endo-trig* aminometallation. However, no such product was observed in silver- and gold-catalyzed reactions of **14** under anhydrous conditions.[21]

Conclusion

In conclusion, the chemodivergent metal-controlled cycloetherification of enallenol substrates into different oxygen heterocycles has been developed. The scope of these protocols has been investigated and clearly demonstrates their utility for the selective preparation of several cyclic ethers from structurally related substrates.[22] Chemoselectivity control in the O–C functionalization of enallenols can be achieved through the choice of catalyst: $AuCl_3$, $PdCl_2$, and $[PtCl_2(CH_2{=}CH_2)]_2$ exclusively afford dihydrofurans through selective activation of the allenol moiety, whereas $FeCl_3$ solely gives tetrahydrofurans or tetrahydropyrans through selective activation of the alkenol moiety. We have also

shown that a combination of metal-mediated hydroalkoxylation and allenic aminocyclization reactions can lead to a useful preparation of the tetrahydrofuro[3,2-b]piperidine core of the antimalarial alkaloid isofebrifugine. These divergent heterocyclization reactions have been developed experimentally and their mechanisms have additionally been investigated by a computational study that showed that the protonolysis of the Au–C bond constitutes the step on which the chemoselectivity is based.

Experimental Section

General methods: ^{1}H NMR and ^{13}C NMR spectra were recorded with Bruker AMX 500, Bruker Avance 300, Varian VRX 300S, or Bruker AC 200 instruments. NMR spectra were recorded in $CDCl_3$ solutions unless otherwise stated. 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 with a HP5989A spectrometer and use of the electronic impact (EI) or electrospray modes (ES) unless otherwise stated. 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 (see the Supporting Information). All commercially available compounds were used without further purification.

General procedure for Au-catalyzed cyclizations of enallenols 1: $AuCl_3$ (0.05 mmol) was added under argon to a stirred solution of the appropriate enallenol **1** (1.0 mmol) in dichloromethane (1.0 mL). The resulting mixture was stirred at room temperature until disappearance of the starting material (TLC). The reaction was then quenched with brine (1.0 mL), the mixture was extracted with ethyl acetate (3×5 mL), and the combined extracts were washed twice with brine. The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue with elution with ethyl acetate/hexanes mixtures gave analytically pure dihydrofuran adducts **4**, **7**, **9**, and **12**.[23]

Dihydrofuran (±)-4a: This compound was obtained from enallenol **1a** (55 mg, 0.18 mmol). Chromatography of the residue with hexanes/ethyl acetate 3:1 as eluent gave compound **4a** (35 mg, 65%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.38 and 6.87 (d, J = 9.0 Hz, each 2H), 5.48 (m, 1H), 5.22 (d, J = 1.0 Hz, 1H), 5.15 (t, J = 1.3 Hz, 1H), 5.06 (m, 1H), 4.52 (m, 2H), 4.41 (dd, J = 6.1, 3.3 Hz, 1H), 4.01 (d, J = 6.1 Hz, 1H), 3.79 (s, 3H), 1.83 (br s, 1H), 1.68 ppm (t, J = 1.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 165.7, 156.3, 136.4, 134.8, 131.1, 123.9, 119.3, 116.3, 114.3, 84.0, 75.0, 59.3, 57.7, 55.5, 23.1, 13.4 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 1746 cm^{-1}; HRMS (EI): m/z calcd (%) for $C_{18}H_{21}NO_3$ $[M]^+$: 299.1521; found: 299.1515.

General procedure for Pd^{II}-catalyzed cyclizations of enallenols 1 in the presence of allyl bromide: Palladium(II) chloride (0.005 mmol) was added to a stirred solution of the appropriate enallenol **1** (0.10 mmol) and allyl bromide (0.50 mmol) in *N*,*N*-dimethylformamide (0.6 mL). The reaction mixture was stirred under argon until disappearance of the starting material (TLC). Water (0.5 mL) was added before extraction with ethyl acetate (3×4 mL). The organic phase was washed with water (2× 2 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue with elution with hexanes/ethyl acetate mixtures gave analytically pure adducts **5** and **10**.

Dihydrofuran (±)-5a: This compound was obtained from enallenol **1a** (55 mg, 0.18 mmol). Chromatography of the residue with hexanes/ethyl acetate 3:1 as eluent gave compound **5a** (44 mg, 72%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.36 (d, J = 9.0 Hz, 2H), 6.86 (d, J = 9.3 Hz, 2H), 5.58 (m, 1H), 5.20 (br s, 1H), 5.13 (m, 2H), 5.02 (m, 1H), 4.95 (dd, J = 2.2, 1.5 H, 1H), 4.46 (m, 2H), 4.42 (dd, J = 5.9, 3.2 Hz, 1H), 3.98 (d, J = 5.9 Hz, 1H), 3.78 (s, 3H), 2.72 (d, J = 6.6 Hz, 2H), 1.80 (s, 3H), 1.58 ppm (d, J = 1.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 165.7, 156.3, 136.4, 134.0, 132.6, 131.1, 127.1, 119.2 (2C), 116.2, 116.1, 114.3 (2C), 85.5, 77.2, 59.7, 57.6, 55.5, 29.6, 23.0, 10.8 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 1741 cm^{-1}; MS (ES): m/z (%): 340 (100) $[M+H]^+$, 339 (19) $[M]^+$.

General procedure for Fe^{III}-catalyzed cyclizations of enallenols 1: $FeCl_3$ (0.10 mmol) was added to a stirred solution of the appropriate enallenol **1** (1.0 mmol) in 1,2-dichloroethane (1.0 mL). The resulting mixture was heated at 80 °C in a sealed tube until complete disappearance (TLC) of the starting material. The reaction mixture was allowed to cool to room temperature and was then quenched with aqueous saturated NH_4Cl (1.0 mL). The mixture was extracted with ethyl acetate (3×5 mL), and the combined extracts were washed twice with brine. The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue with elution with ethyl acetate/hexanes mixtures gave analytically pure tetrahydrofuran adducts **6**, **8**, **11**, and **13**.

Tetrahydrofuran (±)-6a: This compound was obtained from enallenol **1a** (122 mg, 0.5 mmol). Chromatography of the residue with hexanes/ethyl acetate 3:1 as eluent gave compound **6a** (101 mg, 83%) as a colorless solid. M.p.: 107–108 °C (hexanes/ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.26 and 6.87 (d, J = 9.3 Hz, each 2H), 4.88 (m, 3H), 4.62 (t, J = 4.5 Hz, 1H), 3.79 (s, 3H), 3.55 (d, J = 4.4 Hz, 1H), 1.83 (td, J = 3.2, 0.7 Hz, 3H), 1.55 and 1.31 ppm (s, each 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 204.3, 163.1, 156.2, 130.9, 117.8, 114.6, 100.3, 80.5, 76.7, 76.5, 63.2, 60.8, 55.5, 28.3, 25.4, 16.5 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 2995, 1945, 1750 cm^{-1}; MS (ES): m/z (%): 300 (100) $[M+H]^+$, 299 (18) $[M]^+$; elemental analysis calcd (%) for $C_{18}H_{21}NO_3$ (299.4): C 72.22, H 7.07, N 4.68; found: C 72.34, H 7.04, N 4.71.

Procedure for the silver-induced reaction of bicyclic *NH*-β-lactam 14—preparation of tetrahydrofuro[3,2-b]piperidine 15: Silver nitrate (0.30 mmol) was added to a stirred solution of the bicyclic *NH*-β-lactam **14** (60 mg, 0.30 mmol) in acetone/water (1:1, 1.0 mL). The reaction mixture was heated in a sealed tube at 140 °C until disappearance of the starting material (TLC). The mixture was allowed to reach room temperature, after which brine (3 mL) was added and it was then extracted with ethyl acetate (4×5 mL). The organic extract was washed with brine and dried ($MgSO_4$). Removal of solvent under reduced pressure yielded the adduct **15** (38 mg, 60%) in analytically pure form.

Tetrahydrofuro[3,2-b]piperidine 15: Pale orange oil; ^{1}H NMR ($CDCl_3$, 300 MHz, $CDCl_3$, 25 °C): δ = 12.17 (br s, 1H), 5.34 (s, 1H), 5.09 (d, J = 10.6 Hz, 1H), 4.33 (d, J = 19.0 Hz, 1H), 3.97 (m, 2H), 3.59 (d, J = 6.8 Hz, 1H), 1.90 (s, 3H), 1.54 and 1.26 ppm (s, each 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 172.3, 138.7, 113.7, 84.8, 77.1, 63.3, 53.4, 45.2, 31.7, 25.2, 17.3 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 3370, 1718 cm^{-1}; MS (EI): m/z (%): 211 (20) $[M]^+$, 110 (100) $[M-101]^+$; elemental analysis calcd (%) for $C_{11}H_{17}NO_3$ (211.3): C 62.54, H 8.11, N 6.63; found C 62.41, H 8.15, N 6.60.

Computational details

All the calculations reported in this paper were performed with the GAUSSIAN 09 suite of programs.[24] All species were optimized with Truhlar's dispersion-corrected meta hybrid exchange-correlation functional M06L, which has been recommend for species involving transition metals,[25] in combination with double-ξ-quality def2-SVP basis sets.[26] All minima were characterized by frequency calculations and have positive definite Hessian matrices. Transition structures (TSs) each show only one negative eigenvalue in their diagonalized force constant matrices, and their associated eigenvectors were confirmed to correspond to the motion along the reaction coordinate under consideration. Solvents effects were taken into account by use of the Polarizable Continuum Model (PCM).[27] Single-point calculations (PCM-M06L/def2-SVP) on the gas-phase optimized geometries were performed to estimate the changes in the Gibbs energies in the presence of dichloromethane as solvent.

Acknowledgements

Support for this work by the MICINN [CTQ2009–09318, CTQ2010–20714-C02–01, and Consolider-Ingenio 2010 (CSD2007–00006)], the Comunidad Autónoma de Madrid (Projects S2009/PPQ-1752 and S2009/PPQ-1634), and SANTANDER-UCM (Project GR35/10) is gratefully acknowledged. I.F. is a Ramón y Cajal fellow.

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[23] Experimental procedures as well as full spectroscopic and analytical data for compounds not included in this Experimental Section are described in the Supporting Information. It contains compound characterization data and experimental procedures for compounds *syn*-**1e**, *anti*-**1e**, **1c**, **1d**, **1f**, and **3**. It contains as well copies of NMR spectra for all new compounds.
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Received: September 19, 2011
Published online: December 1, 2011

