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Synthesis of Fused-β-Lactams through Selective Gold-Catalyzed Oxycyclization of Dioxolane-Tethered Enynes

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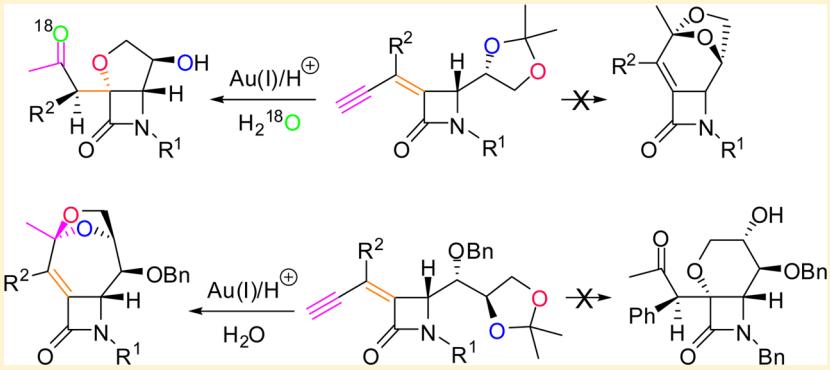
Supporting Information



ABSTRACT: The gold-catalyzed preparation of 2-azetidinone-fused oxacycles was accomplished from β-lactam-linked enynes through heterocyclization reaction taking advantage of the acetonide pendant group. While the synthesis of fused tetrahydrofuran-β-lactams from 1,3-enynes could be considered as an unusual metal-catalyzed cyclization of enynols, α-alkoxy dioxolane-tethered 1,3-enynes exclusively undergo bis-oxycyclization to afford tricyclic bridged acetals.

INTRODUCTION

β-Lactam antibiotics are among the most commonly prescribed antibacterial drugs.[1] In addition, β-lactams further exhibit some other biological activities.[2] 2-Azetidinones are also used as valuable intermediates in organic synthesis.[3] Thus, the search for new syntheses of β-lactam derivatives is of interest because of their important role in synthetic and pharmaceutical chemistry. On the other hand, because of its chemical inertness as a bulk metal, gold has not fascinated chemists working in catalysis until recently. However, the last two decades have witnessed dramatic growth in the number of reactions catalyzed by gold complexes, notably in its homogeneous catalysis manifestation,[4] because of their powerful soft Lewis acidic nature. In particular, activation of alkynes toward attack by oxygen nucleophiles such as carbonyls, carboxylic acids, and alcohols is an important C−O bond-forming reaction.[5] Despite the use of functionalized 1,3-enynes as building blocks for the preparation of bioactive molecules or organic electronic materials,[6] the gold-catalyzed cyclization of enynols has been scarcely reported.[7] In terms of developing a new synthetic method for fused β-lactams based on selective cycloetherification reactions, we hypothesized that a substrate bearing a dioxolane group with a tethered 1,3-enyne moiety should be ideal. We report here an efficient gold-catalyzed fused tetrahydrofuran-β-lactam synthesis from 1,3-enyne β-lactams through tandem addition of tethered dioxolane moieties by use of an equivalent of water.[8] Interestingly, under otherwise identical conditions, α-alkoxy dioxolane-tethered 1,3-enynes exclusively undergo bis-oxycyclization to afford tricyclic bridged acetals.

RESULTS AND DISCUSSION

Starting materials for oxycyclization reactions, functionalized 1,3-enynes **2**, were readily prepared in good yields from the corresponding β-lactam-tethered α-allenols **1** by treatment with the AcCl/NaOH (aqueous) system (Scheme 1).[9] Bromoalkynes **3a** and **3b** were smoothly achieved from enynes **2a** and **2b** in excellent yield by reaction with NBS and AgOAc (Scheme 1). Terminal alkyne **2a** was functionalized as its corresponding aryl alkyne **4** and phenylbuta-1,3-diynyl alkyne **5** under Sonogashira or Cadiot−Chodkiewicz conditions (Scheme 1). Terminally deuterated alkyne [D]-**2a** was accessed through base-promoted deuteration of the enyne **2a** with D_2O, adapting a reported mild protocol to our substrate (Scheme 1).[10]

To validate the concept, an intramolecular hydroalkoxylation of enynic acetonide **2a** was first explored using metal catalysis.

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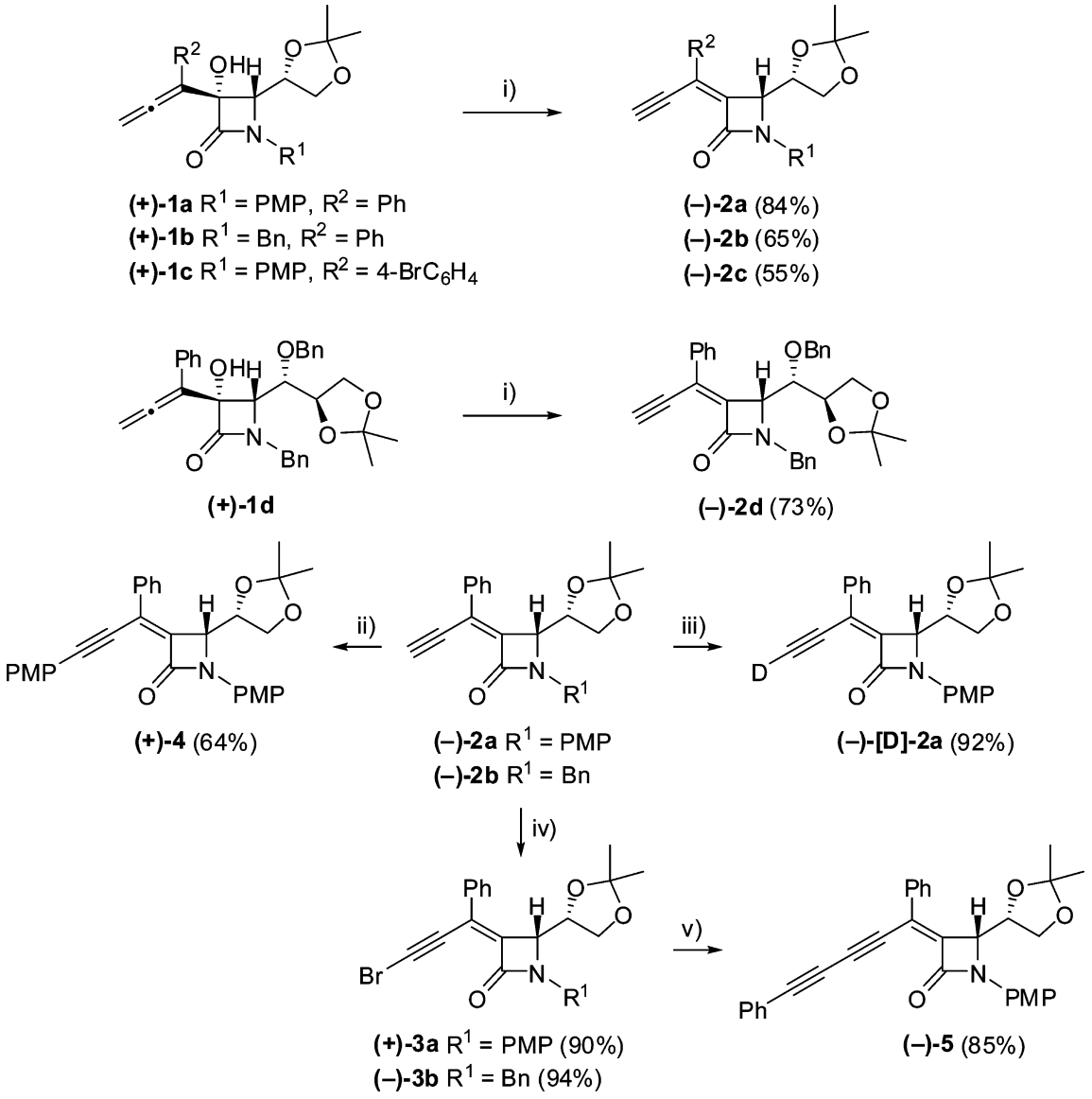
Scheme 1. Preparation of Dioxolane-Tethered 1,3-Enynes 2a–d, [D]-2a, and 3–5[a]



[a]Conditions: (i) CH_3COCl, NaOH, 5 mol % of TBAI, H_2O/CH_2Cl_2 (1:1), rt, 24 h, (ii) 1-iodo-4-methoxybenzene, 1 mol % of $Pd(PPh_3)_2Cl_2$, 2 mol % of CuI, Et_3N, MeCN, rt, 1.5 h, (iii) D_2O, K_2CO_3, MeCN, rt, 1.5 h, (iv) NBS, AgOAc, acetone, darkness, rt, 3 h, (v) phenylacetylene, MeOH/CH_2Cl_2, CuCl, $NH_2OH{\cdot}HCl$, $EtNH_2$, 0 °C, 3 h. PMP = 4-$MeOC_6H_4$. TBAI = tetrabutylammonium iodide.

Initially, the use of $AuCl_3$ and AuCl were tested, but both failed to catalyze the reaction in the presence or absence of any additive. Nicely, it was found that [$AuClPPh_3$] along with AgOTf and a Brønsted acid (PTSA monohydrate) could be a promising cooperative catalytic system for our purpose, even though total conversion was not obtained. Interestingly, enyne **2a** was converted into the bicyclic tetrahydrofuran-fused *β*-lactam **6a** (Scheme 2). Unfortunately, under the above conditions **2a** gave low yields of the reaction products. On the basis of the structure of **2a**, we believed that ambient H_2O in the reaction system was involved in this Au(I)-catalyzed reaction. Obviously, bicycle **2a** could be more easily available if we could directly perform the reaction in the presence of external water as nucleophile. Happily, the addition of 1.0 equiv of H_2O raised the yield of **6a** up to 67% (Scheme 2). This conversion is remarkable as it implies a rare reactivity of the 1,3-enyne moiety. As such, the alkyne functionality would behave as a latent carbonyl group giving a reactive *α*,*β*-unsaturated ketone, while the alkene moiety undergoes metal-catalyzed hydroalkoxylation. As earlier attempts to employ other metal catalysts such as $AuCl_3$ and AuCl met with failure, we switched our attention to $PtCl_2$. We performed the gold-catalyzed reaction of enyne **2a** under otherwise identical conditions, but replaced [$AuClPPh_3$] with $PtCl_2$. The dramatic decrease of yield in the formation of bicycle **6a** (from 67 to 23%) did clearly establish the essential role of the gold salt for this transformation. In addition, the Au-catalyzed reaction afforded **6a** as the sole product, while an epimeric byproduct **7a** was also obtained in the Pt-catalyzed reaction (Scheme 2).[11] The two products obtained from the Pt-catalyzed reaction, **6a** and **7a**, are not identical but rather stand in an epimeric relationship at the *α*-carbonylic position. Interestingly, product **6a** is converted into its epimer **7a** after prolonged treatment with the platinum catalyst.

Having established the optimum catalytic system, next we investigated the scope and limitations of the process. Tolerance

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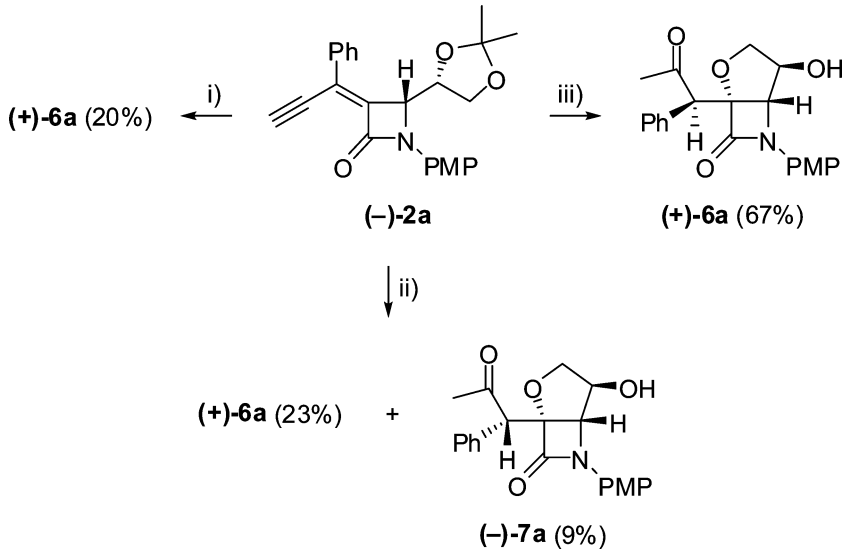
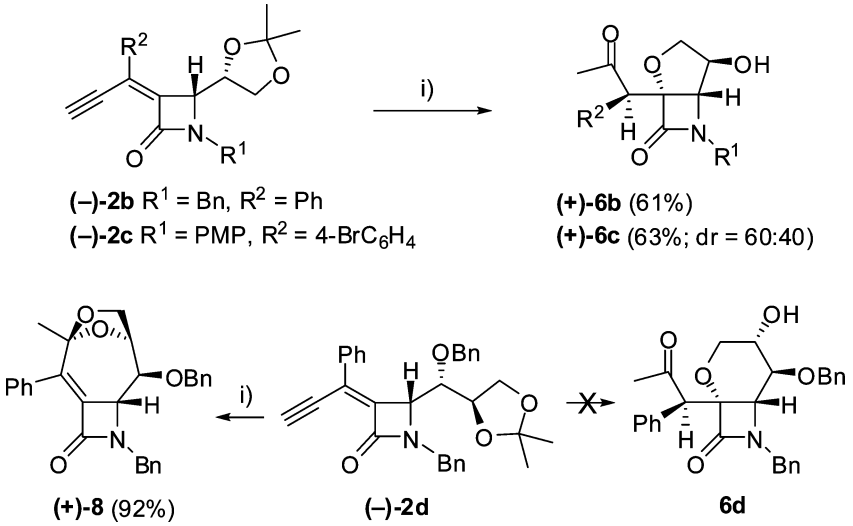
Scheme 2. Hydration/Oxycyclization Reaction of Dioxolane-Tethered 1,3-Enyne 2a under Modified Metal-Catalyzed Conditions[a]



[a]Conditions: (i) 2.5 mol % of [AuClPPh$_3$], 2.5 mol % of AgOTf, 10 mol % of PTSA, CH_2Cl_2, sealed tube, 80 °C, 72 h, (ii) 2.5 mol % of $PtCl_2$, 2.5 mol % of AgOTf, 10 mol % of PTSA, 100 mol % of H_2O, CH_2Cl_2, sealed tube, 80 °C, 4 h, (iii) 2.5 mol % of [AuClPPh$_3$], 2.5 mol % of AgOTf, 10 mol % of PTSA, 100 mol % of H_2O, CH_2Cl_2, sealed tube, 80 °C, 4 h. PMP = 4-MeOC$_6$H$_4$.

Scheme 3. Oxycyclization Reactions of Dioxolane-Tethered 1,3-Enynes 2b–d under Gold-Catalyzed Conditions[a]



[a]Conditions: (i) 2.5 mol % of [AuClPPh$_3$], 2.5 mol % of AgOTf, 10 mol % of PTSA, 100 mol % of H_2O, CH_2Cl_2, sealed tube, 80 °C, **2b**: 2.5 h; **2c**: 3 h; **2d**: 1 h. PMP = 4-MeOC$_6$H$_4$.

toward different substituents at the alkene and β-lactam moieties was demonstrated starting from enynes **2b** and **2c** (Scheme 3). While adduct **6b** was formed as the sole product, reaction of **2c** afforded an inseparable mixture (60:40) of diastereomers **6c**/**7c**. The reason for the poor diastereoselectivity moving from phenyl derivative **2b** to the 4-bromophenyl derivative **2c** may be the presence of the bulkier bromoaryl substituent, which makes the approach of the incoming nucleophile to the less hindered face difficult. Surprisingly, the cationic gold-catalyzed reaction of α-alkoxy dioxolane-tethered 1,3-enyne **2d** proceeded smoothly but gave adduct **8** with no expected bicycle **6d** (Scheme 3). Formation of tricyclic bridged acetal **8** implies cycloketalization of the acetonide group toward the alkyne. The structure of fused tetrahydrofuran-β-lactam **6b** was unambiguously assigned through its X-ray structure (Figure 1, see the Supporting Information).[12] X-ray analysis of **6b** reveals that there exist intramolecular hydrogen bonds between hydroxyl group on the tetrahydrofuran ring and carbonyl from the newly created ketone moiety, helping to further stabilize the structure of the products.

We also tested the reactivity of 1,3-enynes **3**–**5** bearing an additional substituent at the distal alkyne position. The results, reported in Scheme 4, show that these substrates could not be all converted into the corresponding tetrahydrofuran-β-lactam. Tetrahydrofuran-β-lactams **6e** and **6f** were formed from bromoalkynes **3a** and **3b** as major or exclusive products. Adduct **6e** was accompanied by tricyclic bridged acetal **9a** along with fused 3,6-dihydro-2*H*-pyran **10**. The skeletal reorganiza-

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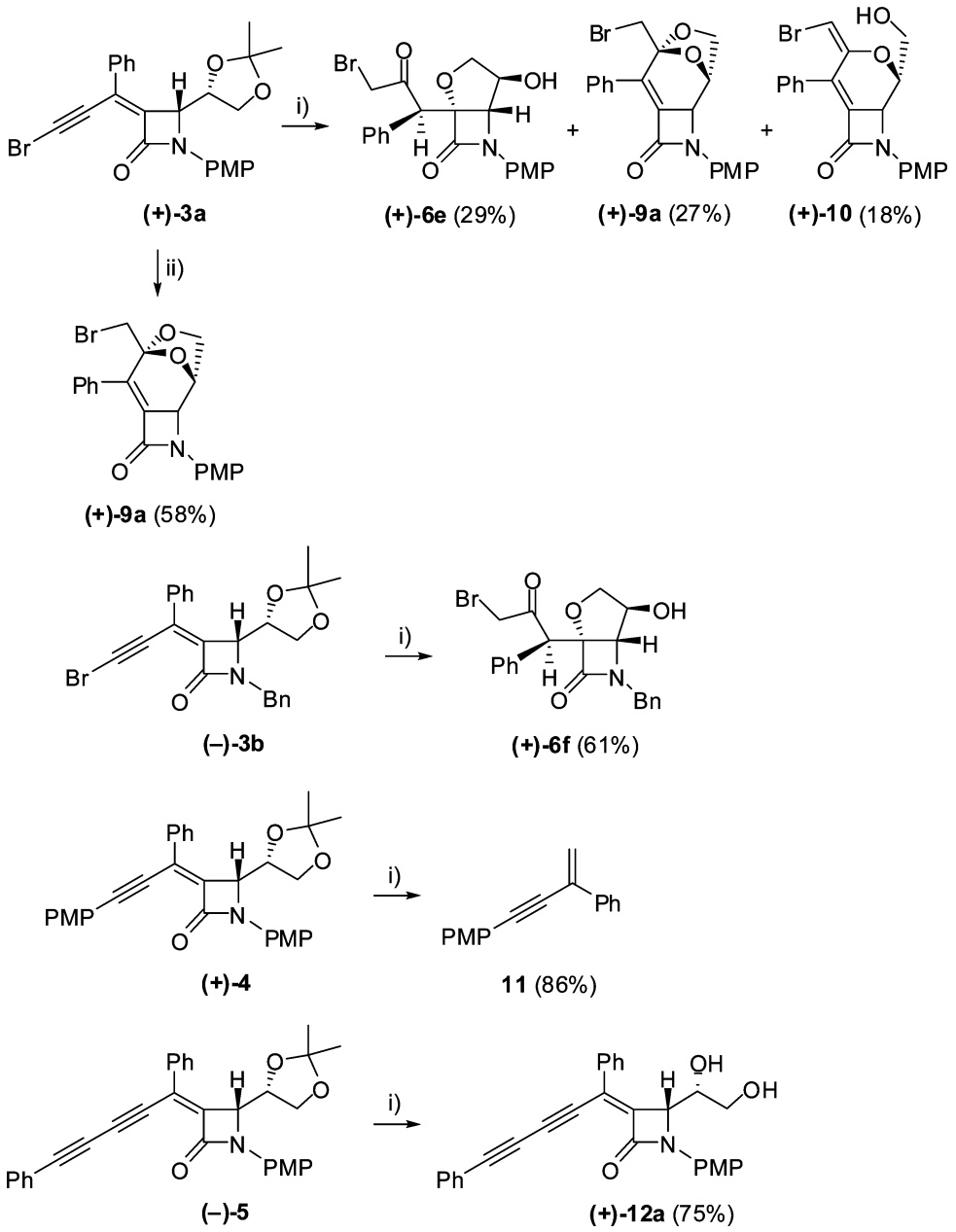
Scheme 4. Reactions of Dioxolane-Tethered 1,3-Enynes 3−5 under Gold-Catalyzed Conditions[a]



[a]Conditions: (i) 2.5 mol % of [$AuClPPh_3$], 2.5 mol % of AgOTf, 10 mol % of PTSA, 100 mol % of H_2O, CH_2Cl_2, sealed tube, 80 °C, **3a**: 1.5 h; **3b**: 2.5 h; **4**: 4.5 h; **5**: 21 h, (ii) 2.5 mol % of [$AuClPPh_3$], 2.5 mol % of AgOTf, 10 mol % of PTSA, CH_2Cl_2, sealed tube, 80 °C, 2 h. PMP = 4-$MeOC_6H_4$.

tion of **3a** under gold catalysis but in absence of water resulted in total selectivity with the exclusive formation of tricycle **9a**. While aryl-substituted enyne **4** underwent *β*-lactam cleavage, alkynyl-substituted enyne **5** was nearly inert. This study demonstrated that a subtle structural variation of dioxolane-tethered 1,3-enyne *β*-lactams could result in completely different product patterns in their gold-catalyzed cyclizations. The above studied reaction makes use of starting enynes. These enyne substrates have three points of diversity. Notably, substituted and unsubstituted alkynes at the terminal position followed different reactivity patterns. The presence of an aryl or ethynylbenzene substituent at the terminal alkyne position does not allow the oxycyclization reaction to proceed. Normally, changing from an aryl to a benzyl substituent at the N1-*β*-lactam nitrogen has little effect in the reactivity. By examining the influence of the R^2 substituent on the alkene side chain, we found that substrates which contain bulky aryl groups were smoothly transformed into tetrahydrofuran-*β*-lactam products but with diminished stereoselectivity. In addition, when applicable the presence of water favored the formation of bicycles of type **6**, while the absence of water directed the reaction to the cycloketalization path.

Several experiments were performed to gain a mechanistic insight into the present reaction. When $H_2{}^{18}O$ was added to the gold-catalyzed reaction of enyne **2b**, product [^{18}O]-**6b** with 100% ^{18}O content was formed in 62% yield (Scheme 5). A similar trend was observed for compound [^{18}O]-**6a**, but the efficiency of the labeling process was lower (Scheme 5). $H_2{}^{18}O$-

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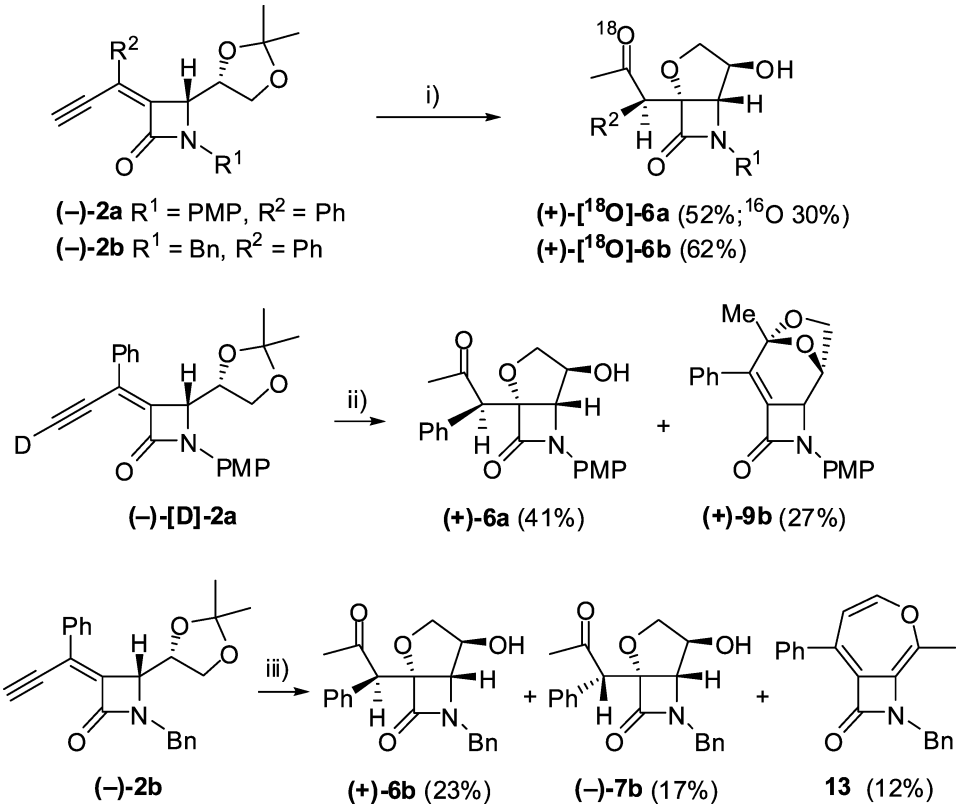
Scheme 5. Control and ^{18}O-Labeling Experiments of Dioxolane-Tethered 1,3-Enynes under Gold-Catalyzed Conditions[a]



[a]Conditions: (i) 2.5 mol % of [AuClPPh$_3$], 2.5 mol % of AgOTf, 10 mol % of PTSA, 200 mol % of $H_2{}^{18}O$, CH_2Cl_2, sealed tube, 80 °C, 2.5 h, (ii) 2.5 mol % of [AuClPPh$_3$], 2.5 mol % of AgOTf, 10 mol % of PTSA, 100 mol % of H_2O, CH_2Cl_2, sealed tube, 80 °C, 2 h, (iii) 10 mol % of PTSA, 100 mol % of H_2O, CH_2Cl_2, sealed tube, 80 °C, 5 h. PMP = 4-MeOC$_6$H$_4$.

labeling experiments unambiguously established that the oxygen atom in the resulting ketone carbonyl group of adducts **6** originated from water.[13] When [D]-**2a**, a deuterated alkyne, reacted under otherwise identical gold-catalyzed reaction conditions to those for **2a**, nondeuterated tetrahydrofuran-β-lactam **6a** and tricyclic bridged acetal **9b** were obtained (Scheme 5). This absence of deuteration may be due to a fast hydrogen–deuterium exchange on the enolic form of intermediate species. A control experiment that would clarify the participation of the gold species as the active catalyst in the oxycyclization reaction was undertaken. A marked difference of reactivity using gold salts or PTSA as catalysts was observed because when enyne **2b** was treated with PTSA under metal-free reaction conditions bicycles **13** and **7b** were obtained along with the major component **6b**. Unfortunately, diol **12c** was not available by acid treatment (PTSA or AcOH) of enyne **3a** because the reactions were not clean. However, taking into account that the reaction of acetonide **3a** under gold catalysis in the absence of water proceeded to afford the corresponding ketal **9a** as the exclusive product (see Scheme 4) would suggest that water is not necessarily needed for the cycloketalization reaction to proceed.

There is general agreement that the role of the silver salt just consists in the activation of the precatalyst through formation of cationic gold species by anion exchange.[14] AgOTf alone does not catalyze the reaction, thus indicating that a gold complex is the active catalyst. Consequently, AgOTf cannot be considered a cocatalyst, and in our case the catalytic system may consist of [Au(OTf)PPh$_3$], generated in situ from [AuClPPh$_3$] and AgOTf.[15] The reaction of 1,3-enynes to yield tetrahydrofuran-β-lactams may be catalyzed by the Au(I) salt. The catalytic reaction is likely divided into six parts. The initial formation of the 1,2-diol **14** assisted by the Brønsted acid is followed by coordination of the carbon–carbon triple bond of enyne diol **14** to the Au(I) salt, giving gold-π-alkynyl complex **15**. Regioselective nucleophilic addition of water to the alkyne triple bond in gold-enynyl complex **15** provides the α,β-unsaturated ketonic gold complex **16**. Species **16** evolves through a chemo- and regioselective 5-*exo*-*dig* oxyauration of the diol moiety to form oxonium **17**.[16] Loss of proton generates neutral species **18**, which followed by protonolysis of the carbon–gold bond afforded tetrahydrofuran-β-lactams **6** with concurrent regeneration of the gold catalyst (Scheme 6).

A possible pathway for the gold-catalyzed formation of bridged acetals **8** and **9** from dioxolane-tethered 1,3-enynes may or may not involve an α,β-unsaturated ketone intermediate. Using [D]-**2a** as starting material (Scheme 5), we argued that it would be possible to determine wheter the reaction occurs through an α,β-unsaturated ketone intermediate or direct bis-oxycyclization of the acetonide group toward the alkyne. The direct bis-oxycyclization pathway would lead to formation of deuterated tricyclic bridged acetal [D]-**9b**. The absence of deuteration in compound **9b** may be due to a fast hydrogen–deuterium exchange on the enolic form of the α,β-unsaturated ketone intermediate. This leads us to propose a mechanism that is exemplified in Scheme 7 by the obtention of adduct **8** from enyne **2d**. The reaction may tentatively be classified as cooperative concurrent catalysis, involving a

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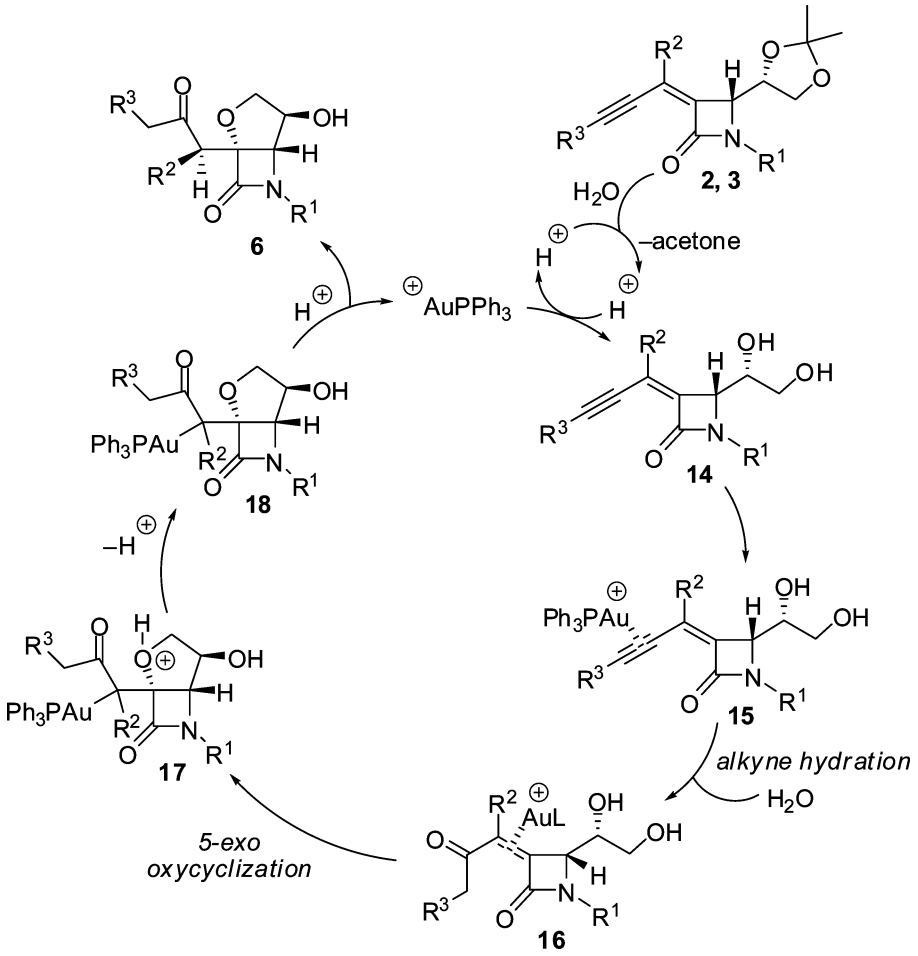
Scheme 6. Mechanistic Explanation for the Gold-Catalyzed Oxycyclization Reaction of Dioxolane-Tethered 1,3-Enynes into Fused Tetrahydrofuran-β-lactams



catalytic action by the Au(I) salt on the alkynic site (Scheme 7, right catalytic cycle) and by the Brønsted acid on the activation of the transient ketonic intermediate (Scheme 7, left catalytic cycle).

CONCLUSION

In conclusion, a hydrative oxycyclization of dioxolane-tethered enynes has been developed for the preparation of fused tetrahydrofuran-β-lactams under gold catalysis. By contrast, under otherwise identical conditions, α-alkoxy dioxolane-tethered 1,3-enynes exclusively undergo bis-oxycyclization to afford tricyclic bridged acetals.

EXPERIMENTAL SECTION

General Methods. NMR spectra were recorded at 25 °C on a 300 MHz instrument: ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz). 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.

Previously Unreported α-Allenic Alcohol 1d. α-Allenol (+)-**1d** was prepared according to the general prcedure.[9a] From 200 mg (0.51 mmol) of the corresponding azetidine-2,3-dione and after chromatography of the residue using hexanes/ethyl acetate (2:1) as eluent compound (+)-**1d** (166 mg, 64%) was obtained as a colorless oil: $[\alpha]_D$ = +156.3 (c 0.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.62 (m, 2H), 7.32 (m, 11H), 6.97 (m, 2H), 5.13 (d, 1H, J = 12.3 Hz), 5.00 (d, 1H, J = 12.1 Hz), 4.86 (d, 1H, J = 6.3 Hz), 4.82 (d, 1H, J = 2.6 Hz), 4.64 (d, 1H, J = 11.3 Hz), 4.13 (m, 3H), 3.92 (dd, 1H, J = 8.0, 6.1 Hz), 3.84 (d, 1H, J = 8.0 Hz), 3.76 (d, 1H, J = 8.2 Hz), 1.38 (s, 3H), 1.32 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 207.4, 168.4, 137.8, 135.3, 132.6, 131.7, 128.7 (2C), 128.6 (2C), 128.5 (2C), 128.3 (2C), 127.8 (2C), 109.2, 106.0, 84.3, 80.1, 79.2, 76.7, 74.5, 66.2, 62.3, 45.5, 31.6, 31.0, 26.3, 25.2, 22.7, 14.2; IR ($CHCl_3$) ν 3339, 2987, 1940, 1739 cm^{-1}; HRMS (ES) calcd for $C_{32}H_{33}NO_5$ $[M]^+$ 511.2359, found 511.2381.

Previously unreported 1,3-enyne 2d. (*E*)-1,3-Enyne (−)-**2d** was prepared according to the generalprocedure.[9b] From 80 mg (0.16 mmol) of the α-allenol (+)-**1d** and after chromatography of the residue using hexanes/ethyl acetate (3:1) as eluent compound (−)-**2d** (63 mg, 50%) was obtained as a colorless oil: $[\alpha]_D$ = −75.4 (c 0.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 8.06 (dd, 2H, J = 8.2, 1.9 Hz), 7.32 (d, 2H, J = 7.6 Hz), 7.21 (m, 11H), 4.91 (d, 1H, J = 15.6 Hz), 4.64 (d, 1H, J = 11.4 Hz), 4.46 (m, 2H), 4.26 (d, 1H, J = 15.3 Hz), 4.08 (d, 1H, J = 6.7 Hz), 3.96 (m, 2H), 3.62 (m, 1H), 3.33 (s, 1H), 1.28 (s, 3H), 1.20 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 161.0, 144.4, 136.6, 135.0, 132.2, 128.7, 127.8 (2C), 127.6 (2C), 127.4 (2C), 127.3 (2C), 127.2 (2C), 127.0 (2C), 126.9, 126.5, 120.1, 108.5, 83.8, 79.2, 76.1, 74.8, 73.8, 67.0, 59.3, 45.6, 25.7, 24.2; IR ($CHCl_3$) ν 3030, 1735, 1607 cm^{-1}; HRMS (ES) calcd for $C_{32}H_{31}NO_4$ $[M]^+$ 493.2253, found 493.2276.

Procedure for the Synthesis of Deutero-enyne (−)-[D]-2a. Deuterium oxide (36 mmol) was added at room temperature under argon atmosphere to a stirred solution of the (*E*)-1,3-enyne (−)-**2a** (280 mg, 0.72 mmol) and K_2CO_3 (1.08 mmol) in acetonitrile (0.15 mL). The reaction was stirred for 1 h before being partitioned between dichloromethane and water. The aqueous phase was extracted with dichloromethane (3 × 10 mL). The organic extract was washed with

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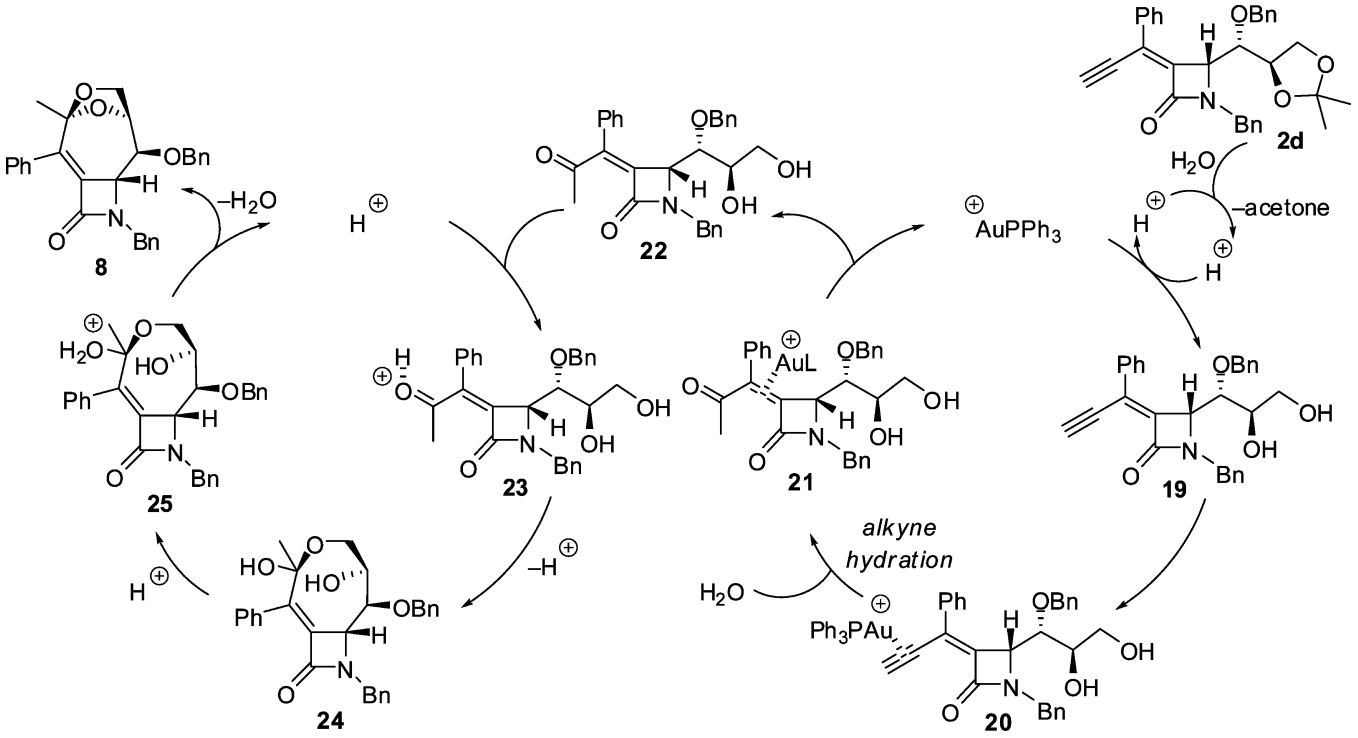
Scheme 7. Mechanistic Explanation for the Gold-Catalyzed Oxycyclization Reaction of Dioxolane-Tethered 1,3-Enyne 2d into Tricyclic Bridged Acetal 8



water and brine, dried ($MgSO_4$), and concentrated under reduced pressure to give 258 mg (92%) of analytically pure compound (−)-[D]-**2a**.

*Deuterated alkyne (−)-[D]-**2a**:* colorless oil; $[\alpha]_D$ = −12.0 (*c* 0.8, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 8.00 (dd, 2H, *J* = 8.0, 1.8 Hz), 7.48 (d, 2H, *J* = 9.1 Hz), 7.34 (m, 3H), 6.81 (d, 2H, *J* = 9.1 Hz), 4.74 (d, 1H, *J* = 5.7 Hz), 4.51 (dd, 1H, *J* = 12.6, 6.7 Hz), 4.12 (2H, *J* = 6.7 Hz), 3.73 (s, 3H), 1.36 (s, 3H), 1.27 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 158.6, 156.6, 142.1, 133.4, 131.3, 130.0, 129.2 (2C), 128.3 (2C), 123.2, 119.7 (2C), 114.2 (2C), 109.7, 83.0, 80.0, 77.3, 67.0, 61.9, 55.5, 26.4, 25.5; IR ($CHCl_3$) ν 1733, 1602 cm^{-1}; HRMS (ES) calcd for $C_{24}H_{22}DNO_4$ $[M]^+$ 390.1690, found 390.1671.

General Procedure for the Synthesis of Bromoalkynes 3. To a solution of the corresponding enyne **2** (120 mg, 0.50 mmol) in acetone (3.4 mL) were added NBS (111 mg, 0.63 mmol) and silver acetate (25 mg, 0.15 mmol). The reaction mixture was stirred at room temperature in the dark until disappearance (TLC) of the starting material. The solids were removed by filtration through a Celite pad (washing with ethyl acetate). The combined organic filtrates were washed with water and brine, dried (Na_2SO_4), concentrated under reduced pressure, and then purified by column chromatography eluting with ethyl acetate/hexanes mixtures to give analytically pure bromoalkynes **3**.

*Bromoenyne (+)-**3a**.* From 300 mg (0.77 mmol) of the 1,3-enyne (−)-**2a** and after chromatography of the residue using hexanes/ethyl acetate (2:1) as eluent compound (+)-**3a** (325 mg, 90%) was obtained as a colorless oil: $[\alpha]_D$ = +16.7 (*c* 0.9, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.95 (dd, 2H, *J* = 8.0, 1.7 Hz), 7.49 (d, 2H, *J* = 9.2 Hz), 7.34 (m, 3H), 6.81 (d, 2H, *J* = 9.2 Hz), 4.73 (d, 1H, *J* = 5.9 Hz), 4.45 (m, 1H), 4.14 (dd, 1H, *J* = 8.6, 6.2 Hz), 4.03 (m, 1H), 3.73 (s, 3H), 1.39 (s, 3H), 1.28 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 158.8, 157.0, 142.2, 133.7, 131.7, 130.4, 129.5 (2C), 128.7 (2C), 124.2, 120.0 (2C), 114.5 (2C), 110.2, 78.2, 77.7, 67.5, 62.1, 59.4, 55.9, 26.8, 25.9; IR ($CHCl_3$) ν 1735, 1605 cm^{-1}; HRMS (ES) calcd for $C_{24}H_{22}BrNO_4$ $[M]^+$ 467.0732, found 467.0752.

*Bromoenyne (−)-**3b**.* From 110 mg (0.29 mmol) of the 1,3-enyne (−)-**2b** and after chromatography of the residue using hexanes/ethyl acetate (3:1) as eluent compound (−)-**3b** (124 mg, 94%) was obtained as a colorless oil: $[\alpha]_D$ = −7.8 (*c* 0.4, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.96 (dd, 2H, *J* = 8.2, 1.9 Hz), 7.28 (m, 8H), 4.95 (d, 1H, *J* = 14.9 Hz), 4.32 (d, 1H, *J* = 6.6 Hz), 4.27 (d, 1H, *J* = 14.9 Hz), 4.11 (dd, 1H, *J* = 8.6, 6.6 Hz), 3.96 (d, 1H, *J* = 6.5 Hz), 3.81 (dd, 1H, *J* = 8.6, 6.3 Hz), 1.37 (s, 3H), 1.30 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 161.1, 143.7, 135.9, 133.2, 129.9, 129.9 (2C), 128.8 (2C), 128.7 (2C), 128.3 (2C), 127.8, 122.8, 109.7, 81.3, 78.0, 77.3, 67.5, 60.8, 45.8, 26.5, 25.4; IR ($CHCl_3$) ν 1734, 1608 cm^{-1}; HRMS (ES) calcd for $C_{24}H_{22}BrNO_3$ $[M]^+$ 451.0783, found 451.0803.

Palladium-Catalyzed Reaction between 1-Iodo-4-methoxybenzene and Terminal Enyne (−)-2a. Procedure for the Synthesis of Aryl-Substituted Enyne (+)-4. $PdCl_2(PPh_3)_2$ (7 mg, 0.01 mmol), CuI (3.8 mg, 0.02 mmol), and triethylamine (60.6 mg, 0.6 mmol) were sequentially added to a solution of the enyne (−)-**2a** (400 mg, 1.0 mmol) and the iodoarene (1.0 mmol) in acetonitrile (0.8 mL) under argon atmosphere. The reaction mixture was stirred at room temperature. After completion of the reaction as indicated by TLC, the mixture was poured into water (5 mL) and extracted with ethyl acetate (3 × 5 mL). The organic layer was washed with water (2 × 10 mL) and brine (2 × 10 mL), dried over $MgSO_4$, and concentrated under reduced pressure. Chromatography of the residue eluting with hexanes/ethyl acetate (2:1) gave 324 mg (64%) of analytically pure compound (+)-**4**.

*Aryl-substituted enyne (+)-**4**:* colorless oil; $[\alpha]_D$ = +10.0 (*c* 0.2, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 8.10 (dd, 2H, *J* = 8.1, 1.6 Hz), 7.62 (d, 2H, *J* = 9.0 Hz), 7.53 (d, 2H, *J* = 8.8 Hz), 7.44 (m, 3H), 6.94 (d, 2H, *J* = 8.8 Hz), 6.90 (d, 2H, *J* = 9.1 Hz), 4.86 (d, 1H, *J* = 6.3 Hz), 4.58 (dd, 1H, *J* = 13.3, 6.5 Hz), 4.30 (m, 2H), 3.87 (s, 3H), 3.82 (s, 3H), 1.47 (s, 3H), 1.36 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 160.6, 159.1, 156.4, 139.1, 134.1, 133.5 (2C), 131.6, 131.4, 130.0, 129.8. 129.3 (2C), 128.2 (2C), 125.0, 119.5 (2C), 114.4 (2C), 114.1 (2C), 109.7, 98.3, 86.1, 78.1, 67.2, 62.2, 55.5, 26.5, 25.5; IR ($CHCl_3$) ν 1735, 1603 cm^{-1}; HRMS (ES) calcd for $C_{31}H_{29}NO_5$ $[M]^+$ 495.2046, found 495.2038.

Copper(I) Chloride Promoted Heterocoupling Reaction between Bromoenyne (+)-3a and Phenylacetylene. Procedure for the Synthesis of Phenylbuta-1,3-diynylalkene (−)-5. A few crystals of hydroxylamine hydrochloride, a 70% $EtNH_2$ (0.25 mL) aqueous solution, and CuCl (0.0072 mmol, 0.002 equiv) were

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sequentially added at room temperature to a solution of the bromoenyne (+)-**3a** (175 mg, 0.36 mmol) in methanol (1.8 mL). Then phenylacetylene (0.36 mmol) in CH_2Cl_2 (5 mL) was added to the above acetylide suspension cooled at 0 °C. More crystals of hydroxylamine hydrochloride were added throughout the reaction as necessary to prevent the solution from turning blue or green. The reaction mixture was stirred until disappearance (TLC) of the starting materials. The products were extracted with ethyl acetate (3 × 5 mL), dried over $MgSO_4$, and concentrated under reduced pressure. Purification by column chromatography eluting with hexanes/ethyl acetate (4:1) gave 154 mg (85%) of analytically pure phenylbuta-1,3-diynyl alkene (−)-**5**.

*Phenylbuta-1,3-diynylalkene (−)-**5**:* colorless oil; $[\alpha]_D$ = −32.5 (*c* 0.6, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.98 (dd, 2H, *J* = 8.0, 1.7 Hz), 7.48 (m, 4H), 7.32 (m, 6H), 6.80 (dd, 2H, *J* = 7.0, 2.0 Hz), 4.77 (d, 1H, *J* = 5.6 Hz), 4.51 (m, 1H), 4.17 (dd, 1H, *J* = 8.6, 6.3 Hz), 4.09 (m, 1H), 3.71 (s, 3H), 1.38 (s, 3H), 1.28 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 158.3, 156.7, 142.9, 133.3, 132.8 (2C), 131.3, 130.1, 129.9, 129.2 (2C), 128.6 (2C), 128.4 (2C), 123.4, 121.1, 119.6 (2C), 114.2 (2C), 109.8, 85.1, 81.9, 78.4, 77.1, 73.4, 67.0, 61.7, 55.5, 26.4, 25.5; IR ($CHCl_3$) ν 1737, 1605 cm^{-1}; HRMS (ES) calcd for $C_{32}H_{27}NO_4$ $[M]^+$ 489.1940, found 489.1965.

General Procedure for the Gold-Catalyzed Reactions of Enynyldioxolanes 2−5. [AuClPPh$_3$] (0.0093 mmol), AgOTf (0.0093 mmol), *p*-toluenesulfonic acid (0.037 mmol), and water (0.37 mmol) were sequentially added to a solution of the corresponding enynyldioxolane **2**−**5** (0.37 mmol) in dichloromethane (0.37 mL). The resulting mixture was heated in a sealed tube at 80 °C until disappearance of the starting material (TLC). The reaction was allowed to cool to room temperature and filtered through a pack of Celite. The filtrate 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 eluting with ethyl acetate/hexanes mixtures gave analytically pure adducts **6** and **8**−**12**.

*Tetrahydrofuran-Fused β-Lactam (+)-**6a**.* From 30 mg (0.08 mmol) of the enynyldioxolane (−)-**2a** and after chromatography of the residue using hexanes/ethyl acetate (2:1) as eluent compound (+)-**6a** (19 mg, 67%) was obtained as a colorless oil: $[\alpha]_D$ = +51.0 (*c* 0.7, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.23 (m, 5H), 7.10 (d, 2H, *J* = 9.1 Hz), 6.69 (d, 2H, *J* = 8.9 Hz), 4.76 (br s, 1H), 4.60 (s, 1H), 4.45 (s, 1H), 4.32 (br s, 1H), 4.17 (d, 1H, *J* = 10.7 Hz), 3.92 (dd, 1H, *J* = 10.7, 3.0 Hz), 3.65 (s, 3H), 2.14 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 208.4, 162.5, 156.7, 134.2, 131.0, 129.5 (2C), 129.2 (2C), 129.0, 118.3 (2C), 114.5 (2C), 96.8, 76.1, 70.5, 65.0, 56.7, 55.5, 30.8; IR ($CHCl_3$) ν 3056, 1746, 1702 cm^{-1}; HRMS (ES) calcd for $C_{21}H_{21}NO_5$ $[M]^+$ 367.1420, found 367.1402.

*Tetrahydrofuran-Fused β-Lactam (+)-**6b**.* From 86 mg (0.23 mmol) of the enynyldioxolane (−)-**2b** and after chromatography of the residue using hexanes/ethyl acetate (3:2) as eluent compound (+)-**6b** (49 mg, 61%) was obtained as a colorless solid: mp 163−164 °C; $[\alpha]_D$ = +312.6 (*c* 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.33 (m, 3H), 7.22 (m, 2H), 7.07 (m, 3H), 6.42 (d, 2H, *J* = 7.0 Hz), 4.61 (d, 1H, *J* = 11.7 Hz), 4.56 (s, 1H), 4.37 (d, 1H, *J* = 15.3 Hz), 4.14 (dd, 1H, *J* = 10.4, 1.2 Hz), 3.95 (m, 2H), 3.72 (d, 1H, *J* = 15.3 Hz), 2.11 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 208.4, 165.7, 134.3, 131.2, 129.6 (2C), 129.5 (2C), 128.8, 128.8 (2C), 127.7, 127.5 (2C), 97.9, 76.3, 70.3, 64.6, 56.4, 43.7, 30.9; IR ($CHCl_3$) ν 3052, 1745, 1704 cm^{-1}; HRMS (ES) calcd for $C_{21}H_{21}NO_4$ $[M]^+$ 351.1471, found 351.1482.

*Tetrahydrofuran-Fused β-Lactam (+)-**6c**.* From 63 mg (0.13 mmol) of the enynyldioxolane (−)-**2c** and after chromatography of the residue using hexanes/ethyl acetate (2:1) as eluent compound (+)-**6c** (37 mg, 63%; 60:40 mixture of epimers) was obtained as a colorless oil: $[\alpha]_D$ = +104.0 (*c* 0.8, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.47 (d, 0.8H, *J* = 8.5 Hz), 7.40 (d, 1.2H, *J* = 8.5 Hz), 7.31 (d, 0.8H, *J* = 9.1 Hz), 7.17 (m, 3.2H), 6.81 (d, 0.8H, *J* = 9.1 Hz), 6.72 (d, 1.2H, *J* = 9.1 Hz), 4.59 (m, 1.2H), 4.36 (m, 1.8H), 4.17 (m, 1.2H), 3.92 (m, 1.8H), 3.72 (s, 1.2H), 3.67 (s, 1.8H), 2.15 (s, 1.8H), 2.04 (s, 1.2H); ^{13}C NMR ($CDCl_3$) δ 208.0 (M), 207.0 (m), 162.7 (m), 162.3 (M), 156.8, 132.8 (2C), 132.2 (M), 131.8 (m), 130.8 (2C), 130.0 (M), 129.9 (m), 123.4 (M), 123.0 (m), 118.3 (2C), 114.7 (2C), 96.5 (M), 94.2 (m), 76.1 (M), 75.7 (m), 70.6, 67.3 (m), 65.0 (M), 57.8 (m), 56.0 (M), 55.5, 30.9 (M), 29.6 (m); IR ($CHCl_3$) ν 3055, 1746, 1703 cm^{-1}; HRMS (ES) calcd for $C_{21}H_{20}BrNO_5$ $[M]^+$ 445.0525, found 445.0531.

*Reaction of Enynyldioxolane (+)-**3a**.* From 100 mg (0.21 mmol) of enynyldioxolane (+)-**3a**, and after chromatography of the residue using hexanes/ethyl acetate (3:1) as eluent, 27 mg (29%) of compound (+)-**6e**, 25 mg (27%) of compound (+)-**9a**, and 16 mg (18%) of compound (+)-**10** were obtained.

*Tetrahydrofuran-fused β-lactam (+)-**6e**:* colorless oil; $[\alpha]_D$ = +110.0 (*c* 0.7, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.36 (m, 5H), 7.21 (d, 2H), 6.80 (d, 2H), 5.04 (s, 1H), 4.54 (s, 1H), 4.43 (dd, 1H, *J* = 12.3, 2.5 Hz), 4.29 (td, 2H, *J* = 12.3, 1.3 Hz), 4.06 (d, 1H, *J* = 13.6 Hz), 4.05 (dd, 1H, *J* = 11.1, 3.1 Hz), 3.97 (d, 1H, *J* = 13.9 Hz), 3.76 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 201.4, 162.0, 156.7, 130.1, 129.7 (2C), 129.4, 129.2, 129.1 (2C), 118.4 (2C), 114.5 (2C), 96.7, 76.2, 70.4, 65.1, 55.5, 53.7, 34.3; IR ($CHCl_3$) ν 3477, 1749, 1706 cm^{-1}; HRMS (ES) calcd for $C_{21}H_{20}BrNO_5$ $[M]^+$ 445.0525, found 445.0547.

*Tricyclic Bridged Acetal (+)-**9a**:* colorless oil; $[\alpha]_D$ = +122.0 (*c* 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.42 (m, 5H), 7.15 (d, 2H, *J* = 8.9 Hz), 6.80 (d, 2H, *J* = 9.1 Hz), 5.14 (m, 1H), 4.90 (d, 1H, *J* = 3.5 Hz), 4.04 (dd, 1H, *J* = 8.3, 7.3 Hz), 3.77 (m, 3H), 3.71 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 156.4, 134.3 (2C), 134.1 (2C), 132.0, 131.9, 29.4 (2C), 129.2 (2C), 128.6, 128.5, 117.2, 114.8, 105.3, 75.3, 63.2, 56.0, 55.5, 29.3; IR ($CHCl_3$) ν 1746, 1583 cm^{-1}; HRMS (ES) calcd for $C_{21}H_{18}BrNO_4$ $[M]^+$ 427.0419, found 427.0433.

*Fused 3,6-dihydro-2H-pyran (+)-**10**:* colorless oil; $[\alpha]_D$ = +56.0 (*c* 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.53 (d, 2H, *J* = 9.1 Hz), 7.41 (m, 2H), 7.35 (m, 3H), 6.82 (d, 2H, *J* = 9.0 Hz), 5.62 (s, 1H), 4.74 (d, 1H, *J* = 4.7 Hz), 4.31 (m, 2H), 4.16 (m, 1H), 3.71 (s, 3H), 2.63 (d, 1H, *J* = 7.7 Hz); ^{13}C NMR ($CDCl_3$) δ 157.9, 157.3, 156.4, 134.5, 133.2, 132.7, 131.6, 129.9 (2C), 129.8, 128.8 (2C), 118.3 (2C), 114.6 (2C), 99.5, 76.8, 73.2, 65.6, 55.5; IR ($CHCl_3$) ν 3439, 1729, 1511 cm^{-1}; HRMS (ES) calcd for $C_{21}H_{18}BrNO_4$ $[M]^+$ 427.0419, found 427.0414.

*Tetrahydrofuran-Fused β-Lactam (+)-**6f**.* From 120 mg (0.27 mmol) of the enynyldioxolane (−)-**3b** and after chromatography of the residue using hexanes/ethyl acetate (3:2) as eluent compound (+)-**6f** (71 mg, 61%) was obtained as a colorless oil: $[\alpha]_D$ = +160.1 (*c* 0.9, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.34 (m, 3H), 7.20 (m, 2H), 7.07 (m, 3H), 6.43 (d, 2H, *J* = 7.2 Hz), 4.90 (s, 1H), 4.37 (d, 1H, *J* = 15.2 Hz), 4.16 (dd, 1H, *J* = 10.4, 0.9 Hz), 3.87 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 201.3, 165.2, 134.2, 130.3, 129.8 (2C), 129.5 (2C), 129.2, 128.8 (2C), 127.8, 127.5 (2C), 97.9, 76.5, 70.3, 64.7, 53.5, 43.8, 34.4; IR ($CHCl_3$) ν 3479, 1756, 1710 cm^{-1}; HRMS (ES) calcd for $C_{21}H_{20}BrNO_4$ $[M]^+$ 429.0576, found 429.0585.

*Tricyclic Bridged Acetal (+)-**8**.* From 20 mg (0.04 mmol) of the enynyldioxolane (−)-**2d** and after chromatography of the residue using hexanes/ethyl acetate (3:1) as eluent compound (+)-**8** (17 mg, 92%) was obtained as a colorless oil: $[\alpha]_D$ = +36.3 (*c* 0.8, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.56 (m, 2H), 7.23 (m, 13H), 4.51 (d, 1H, *J* = 7.5 Hz), 4.40 (d, 1H, *J* = 12.0 Hz), 4.33 (t, 1H, *J* = 7.2 Hz), 4.11 (m, 4H), 3.60 (dd, 1H, *J* = 8.5, 6.3 Hz), 3.40 (d, 1H, *J* = 7.5 Hz), 1.97 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 160.9, 136.6, 136.1, 135.5, 133.4, 133.1, 132.2, 128.0 (2C), 127.9, 127.7 (2C), 127.6 (2C), 127.4 (2C), 127.1, 127.0 (3C), 126.6, 110.0, 86.2, 77.5, 70.7, 67.3, 59.9, 44.9, 21.9; IR ($CHCl_3$) ν 1742 cm^{-1}; HRMS (ES) calcd for $C_{29}H_{27}NO_4$ $[M]^+$ 453.1940, found 453.1942.

*Diarylenyne **11**.* From 60 mg (0.12 mmol) of the enynyldioxolane (+)-**4** and after chromatography of the residue using hexanes/ethyl acetate (2:1) as eluent compound **11** (25 mg, 86%) was obtained as a colorless oil: ^1H NMR ($CDCl_3$) δ 7.79 (d, 2H, *J* = 8.9 Hz), 7.58 (m, 2H), 7.44 (m, 3H), 6.92 (d, 2H, *J* = 9.1 Hz), 6.79 (d, 1H, *J* = 1.5 Hz), 6.34 (d, 1H, *J* = 1.4 Hz), 3.81 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 163.0, 161.9, 160.6, 156.0, 136.3, 130.6, 129.2, 127.5 (2C), 126.8 (2C), 124.1, 114.4 (2C), 108.1, 100.0, 55.5; IR ($CHCl_3$) ν 3061 cm^{-1}; HRMS (ES) calcd for $C_{17}H_{14}O$ $[M]^+$ 234.1045, found 234.1037.

*Diol (+)-**12a**.* From 55 mg (0.11 mmol) of the enynyldioxolane (−)-**5** and after chromatography of the residue using hexanes/ethyl acetate (2:1) as eluent compound (+)-**12a** (37 mg, 75%) was obtained as a colorless oil: $[\alpha]_D$ = +17.5 (*c* 0.4, $CHCl_3$); ^1H NMR ($CDCl_3$) δ

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8.02 (dd, 2H, J = 8.2, 2.0 Hz), 7.50 (dd, 2H, J = 8.0, 1.6 Hz), 7.30 (m, 8H), 6.84 (d, 2H, J = 8.9 Hz), 4.87 (d, 1H, J = 2.9 Hz), 4.42 (br s, 1H), 3.75 (m, 2H), 3.73 (s, 3H), 2.41 (s, 1H), 1.93 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 158.5, 156.9, 143.4, 133.1, 132.8 (2C), 130.9, 130.1, 129.9, 129.1 (2C), 128.6 (2C), 128.4 (2C), 123.3, 121.0, 119.7 (2C), 114.6 (2C), 81.8, 78.2, 77.2, 73.2, 71.7, 64.2, 61.5, 55.6; IR ($CHCl_3$) ν 3448, 1727 cm^{-1}; HRMS (ES) calcd for $C_{29}H_{23}NO_4$ $[M]^+$ 449.1627, found 449.1633.

Reaction of Deuterated Alkyne (−)-[D]-2a. From 250 mg (0.64 mmol) of enynyldioxolane (−)-[D]-**2a**, and after chromatography of the residue using hexanes/ethyl acetate (2:1) as eluent, 60 mg (27%) of the less polar compound (+)-**9b** and 96 mg (41%) of the more polar compound (+)-**6a** were obtained.

*Tricyclic bridged acetal (+)-**9b**:* colorless oil; $[\alpha]_D$ = +252.1 (c 0.7, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.50 (m, 2H), 7.33 (m, 3H), 7.15 (d, 2H, J = 8.9 Hz), 6.79 (d, 2H, J = 8.9 Hz), 5.03 (m, 1H), 4.81 (d, 1H, J = 3.7 Hz), 3.90 (dd, 1H, J = 8.3, 6.7 Hz), 3.69 (s, 3H), 3.59 (dd, 1H, J = 8.6, 2.8 Hz), 1.69 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 158.9, 156.3, 141.2, 132.7, 132.0, 130.4, 129.5, 129.0 (2C), 128.3 (2C), 117.2 (2C), 114.8 (2C), 105.6, 74.9, 62.1, 56.2, 55.6, 19.2; IR ($CHCl_3$) ν 1747, 1585 cm^{-1}; HRMS (ES) calcd for $C_{21}H_{19}NO_4$ $[M]^+$ 349.1314, found 349.1301.

General Procedure for the Gold-Catalyzed Reaction of Enynyldioxolanes 2 in the Presence of $H_2{}^{18}O$. Preparation of ^{18}O-Labeled Tetrahydrofuran-Fused β-Lactams 6. $[AuClPPh_3]$ (0.0093 mmol), AgOTf (0.0093 mmol), p-toluenesulfonic acid (0.037 mmol), and $H_2{}^{18}O$ (0.37 mmol) were sequentially added to a solution of the corresponding enynyldioxolane **2** (0.37 mmol) in dichloromethane (0.37 mL). The resulting mixture was heated in a sealed tube at 80 °C until disappearance of the starting material (TLC). The reaction was allowed to cool to room temperature and filtered through a pack of Celite. The filtrate 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 eluting with ethyl acetate/hexanes mixtures gave analytically pure ^{18}O-labeled compounds **6**.

*β-Alkoxy Ketone [^{18}O]-**6a**.* From 65 mg (0.17 mmol) of the enynyldioxolane (−)-**2a** and after chromatography of the residue using hexanes/ethyl acetate (2:1) as eluent 31 mg (52%) of compound (+)-[^{18}O]-**6a** (^{16}O 30%) was obtained as a colorless oil: $[\alpha]_D$ = +77.2 (c 0.9, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.26 (m, 5H), 7.11 (d, 2H, J = 9.1 Hz), 6.70 (d, 2H, J = 9.0 Hz), 4.60 (broad s, 1H), 4.44 (broad s, 1H), 4.32 (broad s, 1H), 4.18 (dd, 1H, J = 10.7, 1.2 Hz), 3.93 (dd, 1H, J = 10.7, 2.9 Hz), 3.66 (s, 3H), 2.15 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 208.3 [δC(^{18}O) = −7 ppb, C═O], 162.5, 156.7, 131.0, 129.5 (2C), 129.4 (2C), 129.2, 129.0, 118.3 (2C), 114.5 (2C), 96.7, 76.1, 70.5, 65.0, 56.6, 55.5, 30.8; IR ($CHCl_3$) ν 3055, 1745, 1704 cm^{-1}; HRMS (ES) calcd for $C_{21}H_{20}N^{16}O_4{}^{18}O$ $[M]^+$ 369.1462, found 369.1455.

*β-Alkoxy Ketone [^{18}O]-**6b**.* From 75 mg (0.20 mmol) of the enynyldioxolane (−)-**2b** and after chromatography of the residue using hexanes/ethyl acetate (1:1) as eluent 44 mg (62%) of compound (+)-[^{18}O]-**6b** was obtained as a colorless oil: $[\alpha]_D$ = +205.3 (c 0.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.43 (m, 3H), 7.32 (m, 2H), 7.17 (m, 3H), 6.53 (d, 2H, J = 7.1 Hz), 4.66 (s, 1H), 4.47 (d, 1H, J = 15.3 Hz), 4.24 (dd, 1H, J = 10.5, 1.2 Hz), 4.11 (m, 1H), 4.05 (m, 2H), 3.82 (d, 1H, J = 15.2 Hz), 2.21 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 208.3 [δC(^{18}O) = −73 ppb, C═O], 165.7, 134.3, 131.2, 129.6 (2C), 129.5 (2C), 128.8, 128.7 (2C), 127.7, 127.5 (2C), 97.9, 76.3, 70.3, 64.6, 56.4, 43.7, 30.8; IR ($CHCl_3$) ν 3056, 1747, 1705 cm^{-1}; HRMS (ES) calcd for $C_{21}H_{21}N^{16}O_3{}^{18}O$ $[M]^+$ 353.1573, found 353.1549.

Procedure for the Platinum-Catalyzed Reaction of Enynyldioxolane (−)-2a. $[PtCl_2]$ (0.0058 mmol), AgOTf (0.0058 mmol), p-toluenesulfonic acid (0.023 mmol), and water (0.23 mmol) were sequentially added to a solution of the enynyldioxolane (−)-**2a** (90 mg, 0.23 mmol) in dichloromethane (0.23 mL). The resulting mixture was heated in a sealed tube at 80 °C until disappearance of the starting material (TLC). The reaction was allowed to cool to room temperature and filtered through a pack of Celite. The filtrate 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 using hexanes/ethyl acetate (3:2) as eluent gave 19 mg (23%) of the less polar compound (+)-**6a** and 8 mg (9%) of the more polar compound (−)-**7a**.

*Tetrahydrofuran-fused β-lactam (−)-**7a**:* colorless oil; $[\alpha]_D$ = −80.2 (c 0.7, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.33 (m, 7H), 6.81 (d, 2H, J = 9.1 Hz), 4.40 (d, 1H, J = 0.9 Hz), 4.29 (s, 1H), 4.11 (dd, 1H, J = 10.8, 1.2 Hz), 3.89 (dd, 1H, J = 10.8, 3.1 Hz), 3.72 (s, 3H), 3.44 (d, 1H, J = 11.7 Hz), 2.05 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 207.3, 163.0, 156.7, 133.4, 130.1 (2C), 129.1 (2C), 128.6, 118.2 (2C), 114.7 (2C), 94.6, 76.1, 75.4, 70.6, 67.0, 58.4, 55.6, 29.6; IR ($CHCl_3$) ν 3054, 1745, 1703 cm^{-1}; HRMS (ES) calcd for $C_{21}H_{21}NO_5$ $[M]^+$ 367.1420, found 367.1430.

Procedure for the Gold-Catalyzed Reaction of Enynyldioxolane (+)-3a in the Absence of Water. $[AuClPPh_3]$ (0.0080 mmol), AgOTf (0.0080 mmol), and p-toluenesulfonic acid (0.032 mmol) were sequentially added to a solution of the enynyldioxolane (+)-**3a** (150 mg, 0.32 mmol) in dichloromethane (0.32 mL). The resulting mixture was heated in a sealed tube at 80 °C until disappearance of the starting material (TLC). The reaction was allowed to cool to room temperature and filtered through a pack of Celite. The filtrate 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 using hexanes/ethyl acetate (3:2) as eluent gave 64 mg (58%) of compound (+)-**9a** as a colorless oil.

Procedure for the Metal-Free PTSA-Catalyzed Reaction of Enynyldioxolane (−)-2b. p-Toluenesulfonic acid (0.032 mmol) was added to a solution of the enynyldioxolane (−)-**2b** (120 mg, 0.32 mmol) in dichloromethane (0.32 mL). The resulting mixture was heated in a sealed tube at 80 °C until disappearance of the starting material (TLC). The reaction was allowed to cool to room temperature and filtered through a pack of Celite. The filtrate 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 using hexanes/ethyl acetate (2:1) as eluent gave 12 mg (12%) of the less polar compound **13**, 26 mg (23%) of compound (+)-**6b**, and 19 mg (17%) of the more polar compound (−)-**7b**.

*Tetrahydrofuran-fused β-lactam (−)-**7b**:* pale yellow oil; $[\alpha]_D$ = −45.8 (c 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.35 (m, 10H), 4.42 (dd, 2H, J = 30.3, 14.9 Hz), 4.30 (s, 1H), 4.01 (d, 1H, J = 11.1 Hz), 4.00 (s, 1H), 3.87 (dd, 1H, J = 10.6, 2.9 Hz), 3.80 (d, 1H, J = 6.7 Hz), 2.75 (br s, 1H), 2.14 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 206.9, 166.1, 135.5, 133.5, 129.9 (2C), 129.0 (3C), 128.6 (2C), 128.5, 128.2 (2C), 96.0, 75.1, 70.6, 67.4, 58.3, 45.1, 29.7; IR ($CHCl_3$) ν 3049, 1744, 1705 cm^{-1}; HRMS (ES) calcd for $C_{21}H_{21}NO_4$ $[M]^+$ 351.1471, found 351.1472.

*Bicycle **13**:* pale yellow oil; ^{1}H NMR ($CDCl_3$) δ 7.29 (m, 9H), 6.94 (d, 2H, J = 6.6 Hz), 6.34 (d, 1H, J = 5.7 Hz), 5.17 (s, 2H), 2.18 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 159.5, 145.5, 138.3, 136.0, 133.1, 131.1, 130.6 (2C), 129.2 (2C), 128.1, 127.8 (2C), 126.8, 125.9 (2C), 121.2, 106.7, 96.5, 47.7, 10.7; IR ($CHCl_3$) ν 1730 cm^{-1}; HRMS (ES) calcd for $C_{21}H_{17}NO_2$ $[M]^+$ 315.1259, found 315.1259.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

ORTEP drawing of compound **6b** as well as copies of the ^{1}H NMR and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(12) X-ray data of **6b**: crystallized from ethyl acetate/*n*-hexane at 20 °C; $C_{21}H_{21}NO_4$ (M_r = 351.39); orthorhombic; space group = *P*2(1) 2(1)2(1); *a* = 6.4739(6) Å, *b* = 15.5769(15) Å; *c* = 18.5242(17) Å; α = 90°; β = 90°; γ = 90°; V = 1868.0(3) Å3; *Z* = 4; *cd* = 1.249 mg m^{-3}; μ = 0.087 mm^{-1}; *F*(000) = 744. A transparent crystal of 0.19 × 0.13 × 0.06 mm^3 was used. 4058 [*R*(int) = 0.0803] independent reflections were collected on a difractomer using graphite-monochromated Mo Kα radiation (λ = 0.71073 Å) operating at 50 Kv and 35 mA. Data were collected over a hemisphere of the reciprocal space by combination of three exposure sets. Each exposure of 20s covered 0.3 in ω. The cell parameters were determined and refined by a least-squares fit of all reflections. The first 100 frames were recollected at the end of the data collection to monitor crystal decay, and no appreciable decay was observed. The structure was solved by direct methods and Fourier synthesis. It was refined by full-matrix least-squares procedures on F^2 (SHELXL-97). All non-hydrogen atoms were refined anisotropically. All hydrogen atoms were included in the calculated positions and refined riding on the respective carbon atoms. Final *R*(Rw) values were R1 = 0.0393, wR2 = 0.0798. CCDC-881465 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via the www.ccdc.can.ac.uk/deposit, (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB21EZ, UK; Fax (+44)1223-336033; or deposit@cccdc.cam.ac.uk).

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