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Metal-Catalyzed Cycloisomerization and Tandem Oxycyclization/Hydroxylation of Alkynols: Synthesis of Nonfused, Spiranic and Fused Oxabicyclic β-Lactams

Benito Alcaide,*[a] Pedro Almendros,*[b] Teresa Martínez del Campo,[a] and Rocío Carrascosa[a]

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2-Azetidinone-tethered alkynols, readily prepared from the corresponding aldehydes or ketones, were used as starting materials for the oxycyclization reaction catalyzed by precious metals. AgOAc exclusively affords dihydrofurans, methylenetetrahydrofurans, or methylenetetrahydro-2*H*-pyrans through specific 5-*endo*, 5-*exo*, or 6-*exo* pathways, respectively. Interestingly, in the presence of a catalytic amount of Pt^{II} or Au^{III} salts, cyclization reactions occurred preferentially through a tandem oxycyclization/hydroxylation of alkynols to afford a variety of nonfused, spiranic and fused oxabicyclic β-lactams in moderate to high yields. Besides, it has been observed that the tandem gold-catalyzed cycloetherification/hydroxylation of a methoxymethyl alkynyl ether can be accomplished.

Introduction

The structural motifs of tetrahydrofuran and pyran are present in a wide variety of natural products and biologically relevant compounds. Therefore, the development of synthetic methods for their construction has attracted much attention.[1] Among the possibilities, transition-metal-assisted intramolecular addition of oxygen nucleophiles across a carbon–carbon triple bond 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.[2] However, relatively few methods for the construction of tetrahydrofuran- or pyran-based β-lactams are available.[3] The highly selective properties of metals would seem to recommend their application to the preparation of highly functionalized β-lactams. Our combined interest in the area of β-lactams and the synthetic use of metals[4] led us to explore metal-mediated alkynol cyclization strategies for developing a novel and versatile entry to diversely functionalized nonfused, spiranic and fused oxabicyclic β-lactams as an alternative to existing methodologies.

[a] 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
Fax: +34-91-39444103
E-mail: alcaideb@quim.ucm.es
[b] Instituto de Química Orgánica General, Consejo Superior de Investigaciones Científicas, CSIC,
Juan de la Cierva 3, 28006 Madrid, Spain
Fax: +34-91-5644853
E-mail: Palmendrosb@iqog.csic.es
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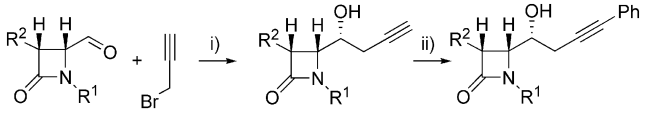
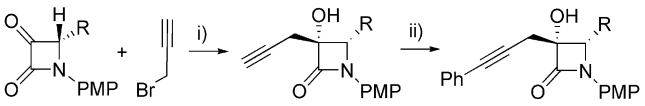
Results and Discussion

Precursors for the nonfused and spiranic oxacycles, homopropargylic alcohols **2a**–**c** and **5a**–**c**, were made starting from 4-oxoazetidine-2-carbaldehydes **1a**–**c** (Scheme 1) and azetidine-2,3-diones **4a**–**c** (Scheme 2) through regio-



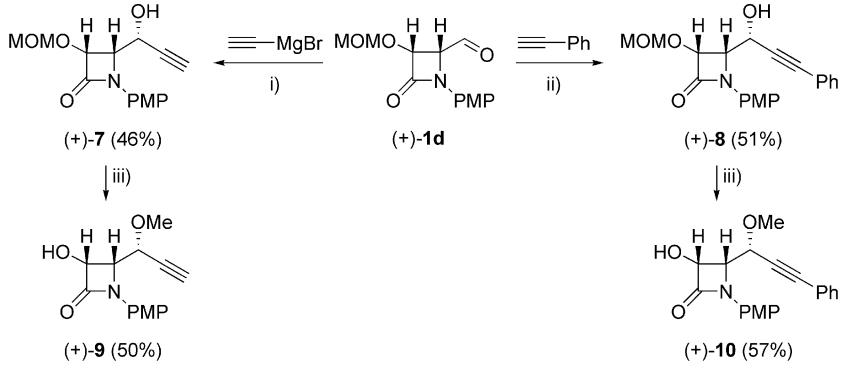
(+)-**1a** R^1 = PMP, R^2 = MeO — (+)-**2a** (65%) — (–)-**3a** (72%)
(+)-**1b** R^1 = Bn, R^2 = MeO — (+)-**2b** (61%) — (+)-**3b** (73%)
(–)-**1c** R^1 = Bn, R^2 = PMPOCO — (+)-**2c** (50%) — (+)-**3c** (41%)

Scheme 1. Zinc-mediated Barbier-type carbonyl propargylation of aldehydes **1** followed by Sonogashira functionalization. Synthesis of alkynyl-β-lactams **2** and **3**. Reagents and conditions: (i) Zn, THF, NH_4Cl (aq. sat.), room temp., **2a**: 12 h; **2b**: 9 h; **2c**: 10 h. (ii) PhI, $Pd(PPh_3)_2Cl_2$ (1 mol-%), CuI (2 mol-%), Et_3N, MeCN, room temp., **3a**: 48 h; **3b**: 22 h; **3c**: 30 h. PMP = 4-$MeOC_6H_4$.



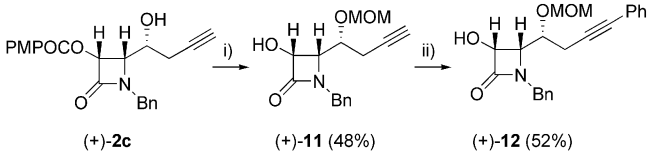
(+)-**4a** R = Diox — (+)-**5a** (70%) — (+)-**6a** (62%)
(±)-**4b** R = Tol — (±)-**5b** (60%) — (±)-**6b** (56%)
(±)-**4c** R = 3-furyl — (±)-**5c** (63%) — (±)-**6c** (60%)

Scheme 2. Zinc-mediated Barbier-type carbonyl propargylation of ketones **4** followed by Sonogashira functionalization. Synthesis of alkynyl-β-lactams **5** and **6**. Reagents and conditions: (i) Zn, THF, NH_4Cl (aq. sat.), room temp., **5a**: 12 h; **5b**: 24 h; **5c**: 20 h. (ii) PhI, $Pd(PPh_3)_2Cl_2$ (1 mol-%), CuI (2 mol-%), Et_3N, MeCN, room temp., **6a**: 19 h; **6b**: 19 h; **6c**: 23 h. PMP = 4-$MeOC_6H_4$. Diox = (*S*)-2,2-dimethyl-1,3-dioxolan-4-yl. Tol = 4-MeC_6H_4.



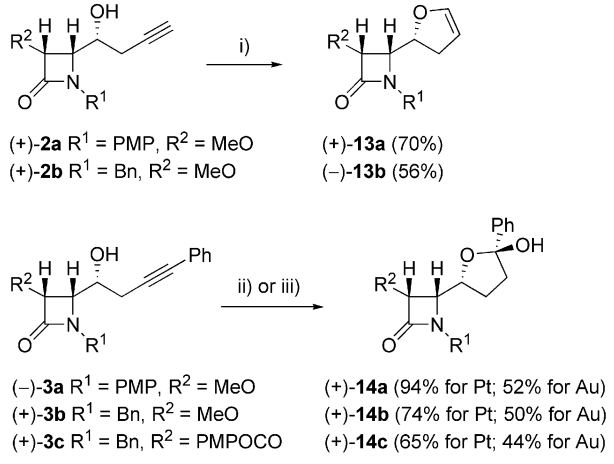
Scheme 3. Preparation of alkynols **9** and **10**. Reagents and conditions: (i) THF, –78 °C, 1.5 h. (ii) *n*BuLi, THF, –78 °C, 5 h. (iii) (a) Me_2SO_4, NaOH, TBAI, DCM/H_2O, room temp., 3 h; (b) HCl (conc.), *i*PrOH/THF (1:1), room temp., 24 h. PMP = 4-$MeOC_6H_4$. MOM = $MeOCH_2$. TBAI = tetrabutylammonium iodide.

and stereocontrolled zinc-mediated Barbier-type carbonyl–propargylation reaction in aqueous media.[5] Terminal alkynes **2** and **5** were functionalized as their corresponding phenyl alkynols **3** and **6** by treatment with iodobenzene under Sonogashira conditions (Schemes 1 and 2). Precursors for the fused oxacycles, alkynols **9** and **10**, were prepared by the diastereoselective addition of magnesium or lithium acetylides to carbaldehyde **1d**,[6] followed by protecting group manipulation (Scheme 3). Starting alkynol **11** was prepared by selective transformations of the hydroxy groups of compound **2c**, whereas phenyl alkynol **12** was available from precursor **11** and iodobenzene by using the Sonogashira protocol (Scheme 4).



Scheme 4. Preparation of alkynols **11** and **12**. Reagents and conditions: (i) (a) MOMCl, Hünig's base, CH_2Cl_2, reflux, 12 h; (b) NaOMe, MeOH, 0 °C, 5 h. (ii) PhI, $Pd(PPh_3)_2Cl_2$ (1 mol-%), CuI (2 mol-%), Et_3N, MeCN, room temp., 19 h. PMP = 4-MeO-C_6H_4. MOM = $MeOCH_2$.

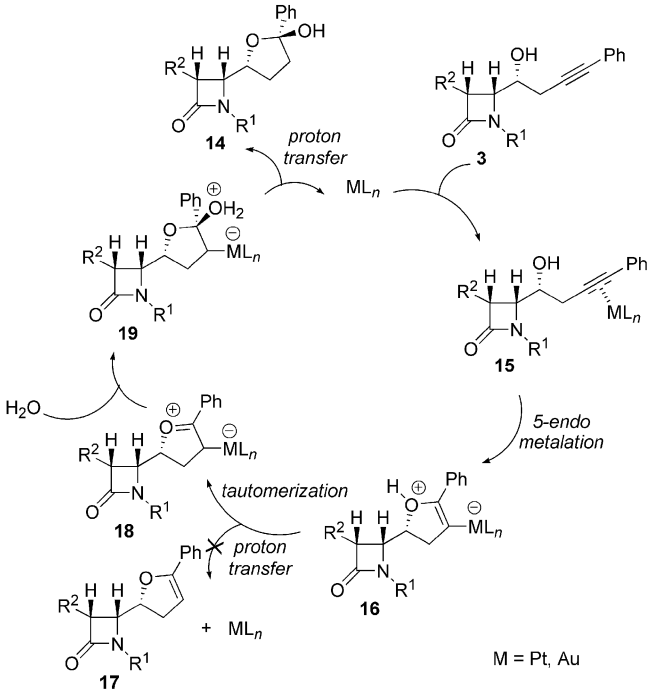
Our investigations began with alkynols **2a** and **3a** as model substrates. Attempts to cyclize **2a** by using gold or platinum catalysts failed. However, reaction of terminal alkynol **2a** with silver acetate in the presence of triethylamine afforded 2-azetidinone-tethered dihydrofuran **13a** in a reasonable 70% yield. The stage was thus set for the metal-catalyzed cycloetherification reaction of phenyl alkynol **3a**. Conversion into the corresponding dihydrofuran could not be satisfied with silver promoters. Nicely, we found that under the appropriate reactions conditions $AuCl_3$ and $[PtCl_2(CH_2{=}CH_2)]_2$ could be excellent catalyst for this purpose. Extrapolation of the cycloetherification reaction to the rest of alkynols **2** and **3** was easily achieved (Scheme 5). Examples in Scheme 5 show that tetrahydrofuryl hemiacetals **14a**–**c** are accessible as single isomers in good yields through the gold- or particularly platinum-catalyzed tandem oxycyclization/hydroxylation reaction of 2-azetidinone-tethered homopropargylic alcohols. For the conversion of alkynols **3** into tetrahydrofuryl hemiacetals **14**, water is required, and it probably comes from the trace amounts of water present in the solvent or the catalyst. Additionally, it should be noted that PTSA has water in it and the monohydrate is actually employed. Another difference between silver and gold/platinum catalysis is that the reaction conditions are basic for the silver catalysts, whereas the reaction conditions are acidic for the gold and platinum catalysts, making further hydration highly likely. Qualitative homonuclear NOE difference spectra allowed us to assign the stereochemistry at the newly formed stereocenter of tetrahydrofuryl hemiacetals **14**.



Scheme 5. Cycloetherification of 2-azetidinone-tethered homopropargylic alcohols **2** and **3**. Synthesis of nonfused tetrahydrofuryl β-lactams **13** and **14**. Reagents and conditions: (i) AgOAc, Et_3N, acetone, room temp., **13a**: 48 h; **13b**: 40 h. (ii) $AuCl_3$ (5 mol-%), PTSA (10 mol-%), CH_2Cl_2, room temp., **14a**: 6 h; **14b**: 5 h; **14c**: 6 h. (iii) $[PtCl_2(CH_2{=}CH_2)]_2$ (1 mol-%), TDMPP (2 mol-%), CH_2Cl_2, room temp., **14a**: 5 h; **14b**: 2.5 h; **14c**: 3 h. PMP = 4-MeO-C_6H_4. PTSA = *p*-toluenesulfonic acid. TDMPP = tris(2,6-dimethoxyphenyl)phosphane.

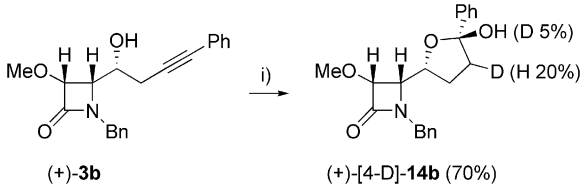
A possible pathway for the gold- or platinum-catalyzed achievement of 2-azetidinone-tethered tetrahydrofuryl hemiacetals **14** may initially involve the formation of π complex **15** through coordination of the gold or platinum chlorides to the triple bond of phenyl alkynols **3**. Next, 5-*endo* oxymetalation forms intermediates **16**. Enol vinylmetal species

16 did not evolve through demetalation and proton transfer, generating dihydrofuran **17** and releasing the metal catalyst. By contrast, rearrangement (phosphane-catalyzed for Pt and Brønsted acid catalyzed for Au) of species **16** generate isomeric metalaoxocarbeniums **18**, enhancing the electrophilicity of the alkene moiety. Subsequent nucleophilic attack of water to the benzylic position from the less hindered face would form ate complex **19**. Demetalation linked to proton transfer liberate adduct **14** with concomitant regeneration of the Pt^{II} or Au^{III} species (Scheme 6).



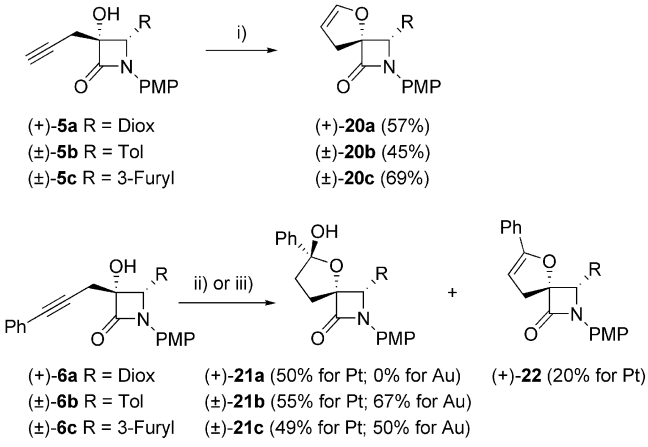
Scheme 6. Mechanistic explanation for the metal-catalyzed tandem oxycyclization/hydroxylation of homopropargylic alcohols **3**.

With the aim of trapping the organometal intermediate to confirm the mechanism of this reaction, we performed deuterium labeling studies with deuterium oxide. When the platinum-catalyzed tandem oxycyclization/hydroxylation of homopropargylic alcohol **3b** was carried out in the presence of two equivalents of D_2O, adduct **14b** with additional deuterium incorporation at the C4 tetrahydrofuran carbon (80% D) was achieved (Scheme 7). The fact that the platinum-catalyzed conversion of alkynol **3b** into tetrahydrofuryl hemiacetal **14b** in the presence of two equivalents of D_2O afforded [4-D]-**14b**, as judged by the decrease of the peak at δ = 3.14 ppm in the ^1H NMR spectrum, which is the signal of the H4 proton of the five-membered ring on the 4-(5-hydroxy-5-phenyltetrahydrofuran-2-yl)-3-methoxyazetidin-2-one (**14b**), suggests that deuteriolysis of the carbon–platinum bond in species **19** had occurred. Along with the clarification of the reaction mechanism, we should point out at the same time that, although metal-catalyzed cycloisomerization reactions of alkynes are well known in alkynols, tandem oxycyclization/hydroxylation is not an easy task and still remains a real challenge.



Scheme 7. Pt^{II}-catalyzed tandem oxycyclization/hydroxylation reaction of alkynol **3b**. Reagents and conditions: (i) $[PtCl_2(CH_2=CH_2)]_2$ (1 mol-%), TDMPP (2 mol-%), D_2O (2 equiv.), CH_2Cl_2, room temp., 2.5 h. TDMPP = tris(2,6-dimethoxyphenyl)phosphane.

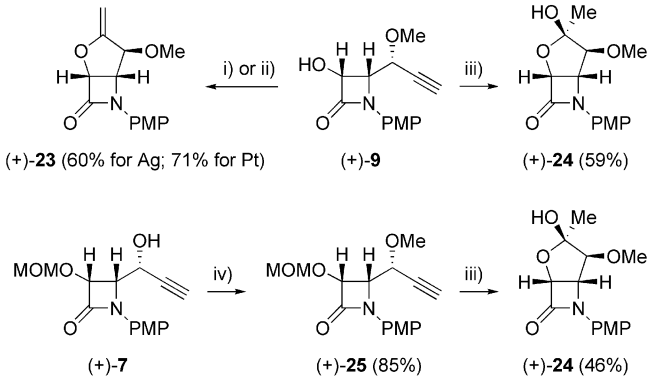
To determine whether the conclusions with homopropargylic alcohols **2** and **3** could be extrapolated to other alkynols, we examined the series of tertiary carbinols **5a**–**c** and **6a**–**c**. Under similar conditions, except the use of heat for Pt, spiranic β-lactams **20a**–**c** and **21a**–**c** were obtained as single isomers in good yields (Scheme 8). One problem of electrophilic metal catalysis is functional group compatibility in the presence of acid-sensitive protecting groups. The gold-catalyzed hydroalkoxylation reaction of alkynol **6a** was troublesome because of the acid lability of the acetonide moiety, indicating a better functional group compatibility of Pt^{II}-based catalyst as compared to the Au^{III} catalyst.



Scheme 8. Cycloetherification of 2-azetidinone-tethered homopropargylic alcohols **5** and **6**. Synthesis of spiranic tetrahydrofuryl β-lactams **20**–**22**. Reagents and conditions: (i) AgOAc, Et_3N, acetone, room temp., **20a**: 48 h; **20b**: 72 h; **20c**: 72 h. (ii) $AuCl_3$ (5 mol-%), PTSA (10 mol-%), CH_2Cl_2, room temp., **21a**: 48 h; **21b**: 72 h; **21c**: 48 h. (iii) $[PtCl_2(CH_2=CH_2)]_2$ (1 mol-%), TDMPP (2 mol-%), CH_2Cl_2, sealed tube, **21a**: 27 h, 50 °C; **21b**: 48 h, 95 °C; **21c**: 48 h, 95 °C. PMP = 4-$MeOC_6H_4$. Diox = (*S*)-2,2-dimethyl-1,3-dioxolan-4-yl. Tol = 4-MeC_6H_4. PTSA = *p*-toluenesulfonic acid. TDMPP = tris(2,6-dimethoxyphenyl)phosphane.

To further probe the scope of these transformations, we tested the tolerance of the noble metal-catalyzed heterocyclization reactions of alkynols to the fused bicyclic version. Gratifyingly, treatment of 2-azetidinone-tethered bishomopropargylic alcohol **9** with silver acetate provided tetrahydrofuran **23** (Scheme 9); nucleophilic attack took place at the internal alkyne carbon through a 5-*exo*-*dig* hydroalkoxylation. Similarly, under Pt^{II} catalysis, **9** afforded bicycle **23**.

We also examined the catalytic activity of $AuCl_3$ for the reaction of **9**. Alkynol **9** was exposed to our initially disclosed conditions for substrates **3** and **6**. Nicely, desired cycloetherification/hydroxylation product **24** was obtained in good yield. Interestingly, the gold-catalyzed reaction of **25** possessing a (methoxymethyl)oxy moiety instead of the free hydroxy group also proceeded smoothly to give cyclization product **24**, albeit in lower yield (Scheme 9). Notably, the observed regioselectivity (5-*exo* cyclization) was not affected by the nature of the metal or the presence of a protective group at the hydroxy moiety. Phenyl alkynol **10** does not react efficiently under these conditions.

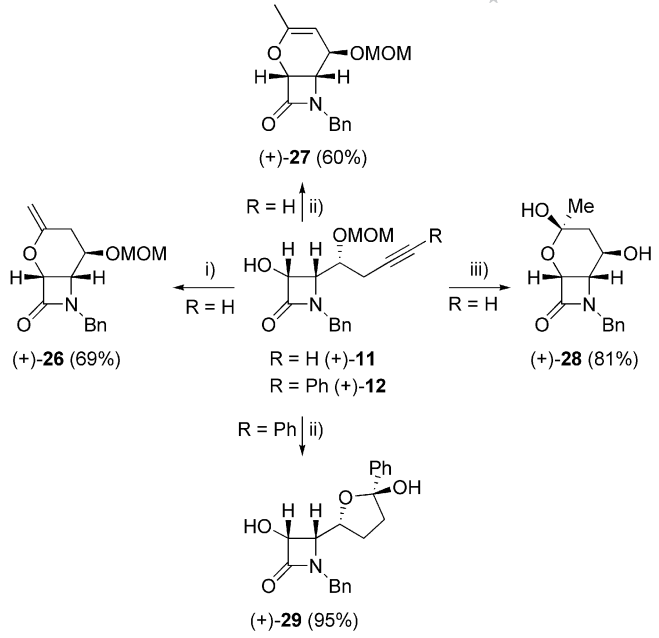


Scheme 9. Cycloetherification of 2-azetidinone-tethered bishomopropargylic alcohol **9** and bishomopropargylic ether **25**. Synthesis of fused tetrahydrofuryl β-lactams **23** and **24**. Reagents and conditions: (i) AgOAc, Et_3N, acetone, room temp., 2 h. (ii) $[PtCl_2(CH_2{=}CH_2)]_2$ (1 mol-%), TDMPP (2 mol-%), CH_2Cl_2, room temp., 3.5 h. (iii) $AuCl_3$ (5 mol-%), PTSA (10 mol-%), CH_2Cl_2, room temp., from **9**: 5.5 h; from **25**: 12 h. (iv) Me_2SO_4, NaOH, TBAI, DCM/H_2O, room temp., 3 h. PMP = 4-$MeOC_6H_4$. PTSA = *p*-toluenesulfonic acid. TDMPP = tris(2,6-dimethoxyphenyl)phosphane. MOM = $MeOCH_2$.

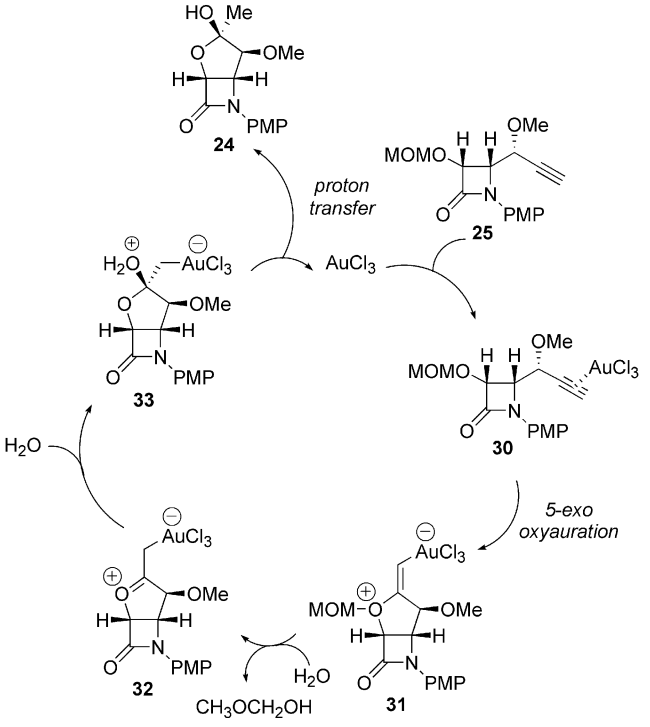
These metal-catalyzed oxycyclizations were successfully extended to trishomopropargylic alcohol **11**. The results of these studies are shown in Scheme 10. The nature of the catalyst system greatly influences the reactivity, but the same regioselectivity was still exhibited. Whereas Ag^I gave 6-*exo*-*dig* cyclization product **26**, Pt^{II} afforded isomeric bicycle **27**, and Au^{III} yielded oxycyclization/hydroxylation adduct **28** with concomitant MOM cleavage. By contrast, the presence of a phenyl substituent at the terminal alkyne carbon showed a substantial effect on the reactivity. Thus, phenyl alkynol **12** favors the formation of nonfused tetrahydrofuran **29** through a 5-*endo*-*dig* oxycyclization/hydroxylation sequence under platinum catalysis, whereas $AuCl_3$ afforded a complex mixture.

The stereochemistry of the hemiacetal stereocenters in fused bicycles **24** and **28** was determined by qualitative homonuclear NOE difference spectra. The total diastereoselectivity for tetrahydrofuran **24** and tetrahydropyran **28** could be explained by attack of water to the alkenemetal complex from the less hindered face (opposite to the β-lactam ring).

A conceivable mechanism for the achievement of bicyclic tetrahydrofuran **24** from methoxymethyl ether **25** may initially involve the formation of π complex **30** through coordination of the gold trichloride to the alkyne moiety (Scheme 11). Next, it could be presumed that initially



Scheme 10. Cycloetherification of 2-azetidinone-tethered trishomopropargylic alcohols **11** and **12**. Synthesis of fused pyranyl β-lactams **26**–**28** and nonfused tetrahydrofuryl β-lactam **29**. Reagents and conditions: (i) AgOAc, Et_3N, acetone, room temp., 96 h. (ii) $[PtCl_2(CH_2{=}CH_2)]_2$ (1 mol-%), TDMPP (2 mol-%), CH_2Cl_2, room temp., **27**: 4 h; **29**: 7 h. (iii) $AuCl_3$ (5 mol-%), PTSA (10 mol-%), CH_2Cl_2, room temp., 6 h. MOM = $MeOCH_2$. PTSA = *p*-toluenesulfonic acid. TDMPP = tris(2,6-dimethoxyphenyl)phosphane.



Scheme 11. Mechanistic explanation for the gold-catalyzed tandem oxycyclization/hydroxylation of bishomopropargylic methoxymethyl ether **25**.

formed alkynegold complex **30** undergoes regioselective intramolecular attack (5-*exo* vs. 6-*endo* oxyauration) by the (methoxymethyl)oxy group, giving rise to vinylgold intermediate **31**, which after elimination of methoxymethanol would then isomerize to metalaoxocarbenium species **32**. Probably, the water molecule in the third step of the catalytic cycle comes from the trace amounts of water present in the solvent or the catalyst. Subsequent nucleophilic attack of water from the less hindered face of intermediate **32** would form ate complex **33**. Deauration and proton transfer liberate adduct **24** with concomitant regeneration of the Au^{III} species. In an independent experiment, we did not obtain hydroxytetrahydrofuran **24** through the $AuCl_3$-catalyzed reaction of methylenetetrahydrofuran **23** (obtained from alkynol **9** by using silver acetate), which should follow Markovnikov-type water addition, which strongly discards its role as an intermediate in the gold-catalyzed oxycyclization/hydroxylation sequence.

Conclusions

In conclusion, we have developed efficient catalyst systems based on precious metal salts for the asymmetric synthesis of a variety of nonfused, spiranic and fused oxabicyclic β-lactams.[7] Silver exclusively affords cycloisomerization products, whereas the presence of a catalytic amount of platinum or gold salts favors the formation of tandem oxycyclization/hydroxylation adducts. At the present time, the application of these protocols to the preparation of other types of heterocyclic compounds is ongoing in our group.

Experimental Section

General Methods: ^1H and ^{13}C NMR spectra were recorded with a Bruker AMX-500, Bruker Avance-300, Varian VRX-300S, or Bruker AC-200 instrument. NMR spectra were recorded in $CDCl_3$ solutions, except otherwise stated. Chemical shifts are given in ppm relative to TMS (^1H, 0.0 ppm) or $CDCl_3$ (^{13}C, 76.9 ppm). Low- and high-resolution mass spectra were taken with an Agilent 6520 Accurate-Mass QTOF LC–MS spectrometer by using the electronic impact (EI) or electrospray modes (ESI) unless otherwise stated. IR spectra were recorded with a Bruker Tensor 27 spectrometer. All commercially available compounds were used without further purification.

General Procedure for the Silver-Promoted Cyclization of α-, β-, or γ-Alkynol 2, 5, or 11: Silver acetate (0.29 mmol) and triethylamine (0.23 mmol) were sequentially added to a stirred solution of alkynol **2**, **5**, or **11** (0.23 mmol) in acetone (1.5 mL). The reaction mixture was stirred at room temperature protected from sunlight until disappearance of the starting material (TLC). The mixture was filtered through a pad of Celite before the filtrate was extracted with ethyl acetate (4 × 5 mL). The organic extract was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue (hexanes/ethyl acetate) gave analytically pure **13**, **20**, or **26**.

Nonfused Dihydrofuran (+)-13a: From alkynol (+)-**2a** (50 mg, 0.18 mmol). Chromatography of the residue (hexanes/ethyl acetate, 4:1) gave (+)-**13a** (35 mg, 70%) as a colorless oil. $[\alpha]_D^{20}$ = +68.7 (*c* = 2.8, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.56 and 6.87 (d, *J* = 9.0 Hz, each 2 H, Ar*H*), 6.33 (dd, *J* = 4.4, 2.5 Hz, 1 H, =C*H*), 4.98 (dd, *J* = 5.1, 2.4 Hz, 1 H, =C*H*), 4.81 (dd, *J* = 18.5, 8.5 Hz, 1 H, OC*H*), 4.61 (d, *J* = 5.4 Hz, 1 H, H3), 4.34 (dd, *J* = 9.0, 5.4 Hz, 1 H, H4), 3.79 (s, 3 H, OMe), 3.63 (s, 3 H, OMe), 2.88 (ddt, *J* = 15.6, 10.1, 2.4 Hz, 1 H, CH*H*), 2.40 (ddt, *J* = 15.8, 8.2, 2.4 Hz, 1 H, C*H*H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 165.2, 156.5, 144.7, 131.1, 119.7, 114.0, 99.8, 82.3, 82.1, 61.2, 59.5, 55.4, 32.9 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 1745 cm^{-1}. HRMS (ESI): calcd. for $C_{15}H_{17}NO_4$ $[M]^+$ 275.1158; found 275.1154.

Nonfused Dihydrofuran (–)-13b: From alkynol (+)-**2b** (55 mg, 0.22 mmol). Chromatography of the residue (hexanes/ethyl acetate, 3:1) gave (–)-**13b** (32 mg, 56%) as a colorless oil. $[\alpha]_D^{20}$ = –8.3 (*c* = 0.3, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.30 (m, 5 H, Ar*H*), 6.27 (q, *J* = 2.4 Hz, 1 H, =C*H*), 4.89 (dd, *J* = 5.1, 2.4 Hz, 1 H, =C*H*), 4.83 and 4.21 (d, *J* = 14.9 Hz, each 1 H, NC*HH*), 4.74 (m, 1 H, OC*H*), 4.45 (d, *J* = 4.9 Hz, 1 H, H3), 3.62 (dd, *J* = 9.0, 4.9 Hz, 1 H, H4), 3.56 (s, 3 H, OMe), 2.78 (ddt, *J* = 15.9, 10.3, 2.2 Hz, 1 H, CH*H*), 2.20 (ddt, *J* = 15.6, 7.1, 2.4 Hz, 1 H, C*H*H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 167.5, 144.7, 139.8, 128.7, 128.6, 128.4, 127.6, 99.4, 83.1, 81.9, 59.3, 45.1, 32.6 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 1743 cm^{-1}. MS (ESI): *m*/*z* (%) = 260 (100) $[M + H]^+$, 259 (23) $[M]^+$.

Spirocyclic Dihydrofuran (+)-20a: From alkynol (+)-**5a** (44 mg, 0.13 mmol). Chromatography of the residue (hexanes/ethyl acetate, 2:1) gave (+)-**20a** (25 mg, 57%) as a pale-yellow solid. M.p. 155–156 °C. $[\alpha]_D^{20}$ = +9.1 (*c* = 0.4, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.71 and 6.89 (d, *J* = 9.2 Hz, each 2 H, Ar*H*), 6.32 and 5.10 (q, *J* = 2.7 Hz, each 1 H, C*H*=C*H*), 4.42 (m, 1 H, C*H*O), 4.22 (dd, *J* = 9.0, 7.0 Hz, 1 H, C*H*HO), 4.03 (d, *J* = 8.5 Hz, 1 H, H4), 3.81 (s, 3 H, OMe), 3.66 (dd, *J* = 9.0, 6.0 Hz, 1 H, CH*H*O), 3.25 and 2.91 (dt, *J* = 16.6, 2.2 Hz, each 1 H, =CHC*HH*), 1.55 and 1.35 (s, each 3 H, Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 165.0, 156.6, 131.1, 119.8, 114.4, 114.0, 110.0, 100.1, 91.1, 76.8, 72.3, 68.0, 55.5, 26.7, 25.6, 24.7 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 1746 cm^{-1}. MS (EI): *m*/*z* (%) = 331 (61) $[M]^+$, 149 (100) $[M – 182]^+$. $C_{18}H_{21}NO_5$ (331.4): calcd. C 65.24, H 6.39, N 4.23; found C 65.37, H 6.34, N 4.20.

Spirocyclic Dihydrofuran (±)-20b: From alkynol (±)-**5b** (70 mg, 0.21 mmol). Chromatography of the residue (hexanes/ethyl acetate, 2:1) gave (±)-**20b** (31 mg, 45%) as a yellow solid. M.p. 143–144 °C. ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.31 and 6.81 (d, *J* = 9.2 Hz, each 2 H, Ar*H*), 7.19 (s, 4 H, Ar*H*), 6.11 and 5.02 (q, *J* = 2.4 Hz, each 1 H, C*H*=C*H*), 4.97 (s, 1 H, H4), 3.76 (s, 3 H, OMe), 3.33 and 3.04 (dt, *J* = 16.1, 2.4 Hz, each 1 H, =CHC*HH*), 2.36 (s, 3 H, Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 165.5, 156.4, 144.9, 138.3, 130.7, 129.3, 127.4, 119.0, 114.3, 99.3, 93.3, 77.2, 72.0, 55.4, 35.5, 21.3 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 1747 cm^{-1}. MS (EI): *m*/*z* (%) = 321 (34) $[M]^+$, 172 (100) $[M – 149]^+$. $C_{20}H_{19}NO_3$ (321.4): calcd. C 74.75, H 5.96, N 4.36; found C 74.61, H 6.01, N 4.40.

Spirocyclic Dihydrofuran (±)-20c: From alkynol (±)-**5c** (69 mg, 0.22 mmol), Chromatography of the residue (hexanes/ethyl acetate, 2:1) gave (±)-**20c** (45 mg, 69%) as a yellow solid. M.p. 172–173 °C. ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.51 (m, 1 H, Het*H*), 7.42 (m, 1 H, Het*H*), 7.36 and 6.83 (d, *J* = 9.2 Hz, each 2 H, Ar*H*), 6.43 (m, 1 H, Het*H*), 6.23 and 5.03 (q, *J* = 2.4 Hz, each 1 H, C*H*=C*H*), 4.95 (s, 1 H, H4), 3.77 (s, 3 H, OMe), 3.31 and 2.98 (dt, *J* = 16.3, 2.4 Hz, each 1 H, =CHC*HH*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 164.8, 156.5, 144.9, 143.5, 141.5, 130.6, 119.6, 118.9, 114.3, 109.9, 99.4, 93.1, 64.5, 55.4, 35.1 ppm. IR ($CHCl_3$): $\tilde{\nu}$

= 1745 cm^{-1}. MS (EI): *m*/*z* (%) = 297 (51) [M]$^+$, 148 (100) [M – 149]$^+$. $C_{17}H_{15}NO_4$ (297.3): calcd. C 68.68, H 5.09, N 4.71; found C 68.55, H 5.03, N 4.74.

Fused Methylenetetrahydropyran (+)-26: From alkynol (+)-**11** (50 mg, 0.15 mmol). Chromatography of the residue (hexanes/ethyl acetate, 3:1) gave (+)-**26** (30 mg, 69%) as a colorless oil. $[\alpha]_D^{20}$ = +8.0 (*c* = 0.6, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.34 (m, 5 H, Ar*H*), 5.05 (d, *J* = 5.1 Hz, 1 H, H3), 4.59 (dd, *J* = 15.9, 6.9 Hz, 1 H, OC*HH*), 4.49 and 4.31 (d, *J* = 14.9 Hz, each 1 H, NC*HH*), 4.43 (m, 1 H, OC*H*), 3.99 (br. s, 1 H, H4), 3.81 (m, 2 H, =C*HH*), 3.33 (s, 3 H, OMe), 2.51 (m, 2 H, C*HH*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 167.4, 153.3, 134.8, 129.1, 128.5, 128.3, 95.6, 90.6, 78.0, 69.4, 55.7, 54.7, 45.0, 28.2 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 1744 cm^{-1}. HRMS (ESI): calcd. for $C_{16}H_{19}NO_4$ [M]$^+$ 289.1314; found 289.1310.

General Procedure for the Platinum-Catalyzed Cyclization of α-, β-, or γ-Alkynol 3, 6, 9, or 11: $[PtCl_2(CH_2{=}CH_2)]_2$ (0.01 mmol) and tris(2,6-dimethoxyphenyl)phosphane (0.02 mmol) were sequentially added to a stirred solution of alkynol **3**, **6**, **9**, or **11** (1.0 mmol) in dichloromethane (1.0 mL) under an atmosphere of argon. 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 extract was washed with brine (2×). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (ethyl acetate/hexanes) gave analytically pure adduct **14**, **21**–**23**, or **27**.

Nonfused Hemiacetal (+)-14a: From alkynol (–)-**3a** (40 mg, 0.11 mmol). Chromatography of the residue (hexanes/ethyl acetate, 2:1) gave (+)-**14a** (39 mg, 94%) as a colorless oil. $[\alpha]_D^{20}$ = +16.2 (*c* = 0.6, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.95 (dd, *J* = 8.0, 1.5 Hz, 2 H, Ar*H*), 7.49 (m, 3 H, Ar*H*), 7.42 and 6.88 (d, *J* = 9.3 Hz, each 2 H, Ar*H*), 4.65 (d, *J* = 5.4 Hz, 1 H, H3), 4.36 (dd, *J* = 5.4, 3.7 Hz, 1 H, H4), 4.11 (m, 1 H, OC*H*), 3.79 (s, 3 H, 3H), 3.67 (s, 3 H, 3H), 3.18 (t, *J* = 6.7 Hz, 2 H, C*HH*), 2.84 (dd, *J* = 4.1, 1.3 Hz, 1 H, O*H*), 2.01 (m, 2 H, C*HH*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 200.2, 165.1, 156.8, 133.1, 130.7, 128.6, 128.0, 120.4, 119.7, 114.3, 82.9, 70.3, 61.0, 59.8, 55.5, 35.0, 28.3 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3347, 1744 cm^{-1}. HRMS (ESI): calcd. for $C_{21}H_{23}NO_5$ [M]$^+$ 369.1576; found 369.1580.

Nonfused Hemiacetal (+)-14b: From alkynol (+)-**3b** (50 mg, 0.16 mmol). Chromatography of the residue (hexanes/ethyl acetate, 2:1) gave (+)-**14b** (42 mg, 74%) as a colorless oil. $[\alpha]_D^{20}$ = +37.0 (*c* = 1.8, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.96 (dd, *J* = 8.1, 1.5 Hz, 2 H, Ar*H*), 7.44 (m, 8 H, Ar*H*), 4.84 and 4.27 (d, *J* = 15.1 Hz, each 1 H, NC*HH*), 4.49 (d, *J* = 5.1 Hz, 1 H, H3), 3.88 (m, 1 H, OC*H*), 3.61 (m, 4 H, OMe + H4), 3.14 (dt, *J* = 6.8, 2.9 Hz, 2 H, C*HH*), 2.74 (d, *J* = 3.7 Hz, 1 H, O*H*), 1.90 (m, 2 H, C*HH*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 200.2, 167.8, 136.8, 135.6, 133.2, 128.9, 128.6, 128.3, 128.0, 127.8, 83.5, 70.2, 60.6, 59.5, 45.6, 35.1, 28.4 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3350, 1745 cm^{-1}. MS (ESI): *m*/*z* (%) = 354 (100) [M + H]$^+$, 353 (11) [M]$^+$.

Nonfused Hemiacetal (+)-14c: From alkynol (+)-**3c** (26 mg, 0.06 mmol). Chromatography of the residue (hexanes/ethyl acetate, 3:1) gave (+)-**14c** (18 mg, 65%) as a colorless oil. $[\alpha]_D^{20}$ = +17.8 (*c* = 0.4, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 8.02 and 6.92 (d, *J* = 9.0 Hz, each 2 H, Ar*H*), 7.84 (dd, *J* = 8.3, 1.4 Hz, 2 H, Ar*H*), 7.45 (m, 8 H, Ar*H*), 6.10 (d, *J* = 4.9 Hz, 1 H, H3), 4.85 and 4.47 (d, *J* = 14.9 Hz, each 1 H, NC*HH*), 3.95 (m, 1 H, OC*H*), 3.88 (s, 3 H, OMe), 3.76 (dd, *J* = 6.8, 5.0 Hz, 1 H, H4), 3.04 (td, *J* = 6.3, 1.7 Hz, 2 H, C*HH*), 2.83 (d, *J* = 4.4 Hz, 1 H, O*H*), 1.80 (dd, *J* = 12.2, 6.0 Hz, 2 H, C*HH*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 200.6, 165.3, 164.7, 164.1, 135.6, 133.4, 132.2, 128.9, 128.6, 128.5, 128.1, 127.9, 124.0, 113.9, 74.2, 71.4, 61.2, 55.5, 46.0, 35.0, 25.7 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3352, 1744, 1722 cm^{-1}. MS (ESI): *m*/*z* (%) = 474 (100) [M + H]$^+$, 473 (17) [M]$^+$.

Preparation of Spirocycles (+)-21a and (+)-22: From alkynol (+)-**6a** (34 mg, 0.084 mmol). Chromatography of the residue (hexanes/ethyl acetate, 3:1) afforded less-polar (+)-**22** (7 mg, 20%) and more-polar (+)-**21a** (18 mg, 50%).

Spirocyclic Hemiacetal (+)-21a: Colorless oil. $[\alpha]_D^{20}$ = +7.3 (*c* = 0.4, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 8.00 (m, 2 H, Ar*H*), 7.58 and 6.87 (d, *J* = 9.2 Hz, each 2 H, Ar*H*), 7.52 (m, 3 H, Ar*H*), 5.03 (br. s, 1 H, OH), 4.46 (dd, *J* = 13.2, 6.6 Hz, 1 H, OC*H*), 4.32 (dd, *J* = 8.7, 6.7 Hz, 1 H, OC*H*H), 4.07 (d, *J* = 6.6 Hz, 1 H, H4), 3.85 (m, 1 H, OCH*H*), 3.80 (s, 3 H, OMe), 3.46 (m, 2 H, C*HH*COH), 2.36 (m, 2 H, C*HH*CH_2O), 1.47 and 1.35 (s, each 3 H, Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 201.4, 168.4, 156.6, 133.7, 131.1, 128.7, 128.3, 119.9, 114.1, 109.8, 83.8, 76.6, 67.6, 66.8, 55.5, 33.4, 30.2, 26.5, 25.1 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3352, 1747 cm^{-1}. HRMS (ESI): calcd. for $C_{24}H_{27}NO_6$ [M]$^+$ 425.1838; found 425.1834.

Spirocyclic Dihydrofuran (+)-22: Colorless oil. $[\alpha]_D^{20}$ = +8.0 (*c* = 0.4, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.74 and 6.90 (d, *J* = 9.2 Hz, each 2 H, Ar*H*), 7.54 (m, 2 H, Ar*H*), 7.36 (m, 3 H, Ar*H*), 5.46 (t, *J* = 2.8 Hz, 1 H, =C*H*), 4.54 (m, 1 H, OC*H*), 4.14 (dd, *J* = 9.0, 6.8 Hz, 1 H, OCH*H*), 4.10 (d, *J* = 8.8 Hz, 1 H, H4), 4.08 (s, 3 H, OMe), 3.67 (dd, *J* = 9.0, 6.1 Hz, 1 H, OC*H*H), 3.48 and 3.10 (dd, *J* = 17.1, 2.7 Hz, each 1 H, =CHC*HH*), 1.54 and 1.34 (s, each 3 H, Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 165.1, 154.9, 133.8, 131.1, 128.7, 128.4, 128.3, 125.1, 119.8, 114.0, 110.2, 94.3, 91.3, 83.8, 77.1, 72.6, 66.6, 55.5, 36.9, 26.7, 24.8 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 1744 cm^{-1}. HRMS (ESI): calcd. for $C_{24}H_{25}NO_5$ [M]$^+$ 407.1733; found 407.1730.

Fused Methylenetetrahydrofuran (+)-23: From alkynol (+)-**9** (24 mg, 0.09 mmol). Chromatography of the residue (hexanes/ethyl acetate, 3:1) gave (+)-**23** (17 mg, 71%) as a colorless oil. $[\alpha]_D^{20}$ = +71.8 (*c* = 0.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.38 and 6.91 (d, *J* = 9.0 Hz, each 2 H, Ar*H*), 5.40 (dd, *J* = 4.1, 0.5 Hz, 1 H, H3), 4.94 and 4.42 (d, *J* = 2.2 Hz, each 1 H, =C*HH*), 4.49 (d, *J* = 3.7 Hz, 1 H, H4), 4.24 (s, 1 H, OC*H*), 3.81 (s, 3 H, OMe), 3.43 (s, 3 H, OMe) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 161.6, 158.3, 156.8, 130.0, 118.2, 114.7, 94.5, 86.4, 77.8, 60.1, 56.3, 55.5 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 1743 cm^{-1}. HRMS (ESI): calcd. for $C_{14}H_{15}NO_4$ [M]$^+$ 261.1001; found 261.1003.

Fused Dihydropyran (+)-27: From alkynol (+)-**11** (53 mg, 0.16 mmol). Chromatography of the residue (hexanes/ethyl acetate, 2:1) gave (+)-**27** (28 mg, 60%) as a colorless oil. $[\alpha]_D^{20}$ = +32.0 (*c* = 0.3, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.31 (m, 5 H, Ar*H*), 5.11 (d, *J* = 4.9 Hz, 1 H, H3), 4.87 (dt, *J* = 6.1, 1.2 Hz, 1 H, =C*H*), 4.60 and 4.47 (d, *J* = 7.0 Hz, each 1 H, OC*HH*), 4.59 and 4.25 (d, *J* = 14.8 Hz, each 1 H, NC*HH*), 4.03 (d, *J* = 6.1 Hz, 1 H, OC*H*), 3.92 (dt, *J* = 4.9, 1.5 Hz, 1 H, H4), 3.27 (s, 3 H, Me), 1.86 (d, *J* = 0.7 Hz, 3 H, Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 164.8, 154.8, 134.9, 128.8, 128.4, 128.2, 120.9, 94.5, 78.4, 64.7, 57.2, 55.4, 44.4, 20.2 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 1745 cm^{-1}. HRMS (ESI): calcd. for $C_{16}H_{19}NO_4$ [M]$^+$ 289.1314; found 289.1318.

General Procedure for the Gold-Catalyzed Cyclization of α-, β-, or γ-Alkynol 3, 6, 9, or 11: $AuCl_3$ (0.05 mmol) and *p*-toluenesulfonic acid (0.10 mmol) were sequentially added to a stirred solution of alkynol **3**, **6**, **9**, or **11** (1.0 mmol) in dichloromethane (1.0 mL) under an atmosphere of argon. 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 with brine (2×). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (ethyl acetate/hexanes) gave analytically pure adduct **21**, **24**, or **28**.

Spirocyclic Hemiacetal (±)-21b: From alkynol (±)-**6b** (29 mg, 0.07 mmol). Chromatography of the residue (hexanes/ethyl acetate, 3:1) gave (±)-**21b** (20 mg, 67%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 8.00 (m, 2 H, Ar*H*), 7.52 (m, 3 H, Ar*H*), 7.29 and 6.81 (d, J = 9.0 Hz, each 2 H, Ar*H*), 7.20 (m, 5 H, Ar*H*), 5.07 (s, 1 H, H4), 3.76 (s, 3 H, OMe), 3.46 (td, J = 7.1, 1.7 Hz, 2 H, C*HH*COH), 3.08 (br. s, 1 H, OH), 2.52 (m, 2 H, C*HH*CH_2CO), 2.36 (s, 3 H, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 200.2, 167.4, 156.3, 138.8, 136.6, 133.3, 130.7, 129.9, 128.6, 128.2, 127.1, 118.9, 114.4, 85.3, 68.1, 55.4, 33.1, 30.0, 21.2 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3351, 1746 cm^{-1}. MS (ESI): *m*/*z* (%) = 416 (100) $[M + H]^+$, 415 (9) $[M]^+$.

Spirocyclic Hemiacetal (±)-21c: From alkynol (±)-**6c** (39 mg, 0.10 mmol). Chromatography of the residue (hexanes/ethyl acetate, 2:1) gave (±)-**21c** (20 mg, 50%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 8.01 (m, 2 H, Ar*H*), 7.60 (m, 1 H, Het*H*), 7.56 (t, J = 1.4 Hz, 1 H, Het*H*), 7.47 (m, 3 H, Ar*H*), 7.34 and 6.83 (d, J = 9.0 Hz, each 2 H, Ar*H*), 6.41 (m, 1 H, Het*H*), 5.07 (s, 1 H, H4), 3.78 (s, 3 H, OMe), 3.45 (m, 2 H, C*HH*COH), 2.49 (m, 2 H, C*HH*CH_2CO) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 200.4, 167.2, 156.4, 144.2, 141.5, 136.5, 133.4, 130.6, 128.7, 128.2, 118.8, 114.4, 109.6, 85.0, 61.2, 55.4, 33.1, 29.6 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3354, 1747 cm^{-1}. MS (ESI): *m*/*z* (%) = 392 (100) $[M + H]^+$, 391 (5) $[M]^+$.

Fused Hemiacetal (+)-24: From alkynol (+)-**9** (24 mg, 0.09 mmol). Chromatography of the residue (hexanes/ethyl acetate, 2:1) gave (+)-**24** (15 mg, 59%) as a colorless oil. $[\alpha]_D^{20}$ = +19.8 (c = 0.8, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.35 and 6.90 (d, J = 9.0 Hz, each 2 H, Ar*H*), 5.27 (d, J = 4.0 Hz, 1 H, H3), 4.43 (d, J = 4.0 Hz, 1 H, H4), 3.80 (s, 3 H, OMe), 3.71 (s, 1 H, OC*H*), 3.55 (s, 3 H, OMe), 1.58 (s, 3 H, Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 206.9, 164.8, 156.4, 131.0, 118.0, 114.6, 85.1, 82.7, 60.3, 58.4, 55.5, 16.3 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3350, 1748 cm^{-1}. HRMS (ESI): calcd. for $C_{14}H_{17}NO_5$ $[M]^+$ 279.1107; found 279.1111.

Fused Hemiacetal (+)-28: From alkynol (+)-**11** (26 mg, 0.08 mmol).Chromatography of the residue (hexanes/ethyl acetate, 2:1) gave (+)-**28** (19 mg, 81%) as a colorless oil. $[\alpha]_D^{20}$ = +9.8 (c = 0.3, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.30 (m, 5 H, Ar*H*), 5.11 (d, J = 5.1 Hz, 1 H, H3), 5.09 (d, J = 6.6 Hz, 1 H, O*H*), 4.79 (d, J = 6.8 Hz, 1 H, O*H*), 4.46 and 4.31 (d, J = 14.9 Hz, each 1 H, NC*HH*), 4.07 (m, 1 H, OHC*H*), 3.93 (dt, J = 5.1, 1.3 Hz, 1 H, H4), 2.03 (ddd, J = 14.0, 4.2, 1.5 Hz, 1 H, CH*H*), 1.84 (ddd, J = 14.0, 1.9, 1.0 Hz, 1 H, C*H*H), 1.43 (s, 3 H, Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 206.5, 166.7, 129.1, 128.5, 128.4, 128.2, 84.1, 65.2, 55.1, 44.6, 28.0, 9.5 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3347, 1745 cm^{-1}. MS (ESI): *m*/*z* (%) = 264 (100) $[M + H]^+$, 263 (5) $[M]^+$.

Supporting Information (see footnote on the first page of this article): Compound characterization data and experimental procedures for compounds **2a**–**c**, **3a**–**c**, **5a**–**c**, **6a**–**c**, **7**–**12**, and **25** in addition to copies of the NMR spectra for all new compounds.

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