Synthetic Methods

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Metal-Catalyzed Regiodivergent Cyclization of γ-Allenols: Tetrahydrofurans versus Oxepanes**

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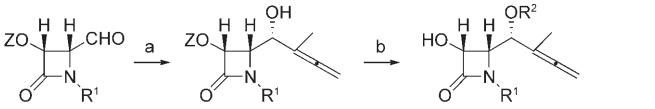
Dedicated to Professor Vicente Gotor on the occasion of his 60th birthday

Tetrahydrofuran and oxepane ether rings are ubiquitous structural units that are extensively encountered in a number of biologically active natural products and functional molecules. Therefore, the development of synthetic methods for their construction has attracted much attention.[1] On the other hand, the allene moiety has developed from almost a rarity to an established member of the weaponry used in modern organic synthetic chemistry.[2] In particular, transition-metal-catalyzed cyclization of functionalized allenes bearing a nucleophilic center has attracted much attention.[3] However, regioselectivity problems are significant (*endo-trig* versus *exo-dig* versus *exo-trig* cyclization). In continuation of our interest in heterocyclic and allene chemistry,[4] we have now discovered examples in which, by either changing the metal or using a protecting group, the 5-*exo-trig* cyclization pathway of γ-allenols can be completely reversed and 7-*endo-trig* alkoxycyclization dominates instead.

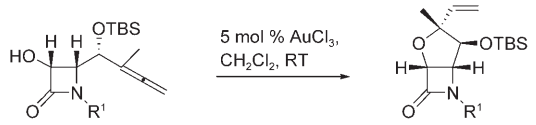
Precursors for the formation of tetrahydrofuran and tetrahydrooxepine, enantiopure γ-allenols **3a–d**, were readily prepared in good overall yield beginning from the appropriate carbaldehydes **1a–d** by a regiocontrolled, indium-mediated, Barbier-type carbonyl–allenylation reaction in aqueous media to give α-allenols **2a–d** (see Supporting Information, Table 1),[5] followed by protecting-group manipulation (Scheme 1).



(–)-**1a** R^1 = Bn (+)-**2a** R^1 = Bn (68%) (–)-**3a** R^1 = Bn, R^2 = TBS (70%)
(–)-**1b** R^1 = allyl (–)-**2b** R^1 = allyl (61%) (+)-**3b** R^1 = allyl, R^2 = TBS (71%)
(–)-**1a** R^1 = Bn (+)-**2a** R^1 = Bn (68%) (–)-**3c** R^1 = Bn, R^2 = MOM (79%)
(+)-**1c** R^1 = CH_2E (+)-**2c** R^1 = CH_2E (65%) (–)-**3d** R^1 = CH_2E, R^2 = MOM (61%)

Scheme 1. Synthesis of enantiopure monocyclic γ-allenols **3a–d**. Reagents and conditions: a) In, 1-bromobut-2-yne, THF/NH_4Cl (aq. sat.), RT, 5 h. b) 1. TBSOTf, CH_2Cl_2, RT, 14 h; or MOMCl, Hünig's base, CH_2Cl_2, reflux, 2 h; 2. NaOMe, MeOH, RT, 0 °C, 3 h. Z = 4-$MeOC_6H_4CO$, Bn = benzyl, E = CO_2Me, MOM = $MeOCH_2$, TBS = *tert*-butyldimethylsilyl, Tf = trifluoromethanesulfonyl.

We decided to use γ-allenol **3a** as initial substrate in a screen to identify regioselective hydroalkoxylation catalysts. Thus, $[PtCl_2(CH_2{=}CH_2)]_2$ and $AgNO_3$ afforded a rather low yield or a disappointing diastereomeric mixture of bicyclic compound **4a**.[6,7] Although $AgNO_3$ was less diastereoselective than $[PtCl_2(CH_2{=}CH_2)]_2$ (60:40 vs. 100:0), it was a more efficient catalyst that afforded adduct **4a** in reasonable yield (54% vs. 12%). Gratifyingly, we found that Au^I or Au^{III} salts were effective as 5-*exo*-selective hydroalkoxylation catalysts.[8] $AuCl_3$ was selected as catalyst of choice because of its superior performance. No diastereo- or regioisomeric products were detected, thus giving exclusively the fused five-membered oxacycles **4** (Scheme 2). Compounds **4** are remarkable as they bear a quaternary stereocenter.[9] Qualitative homonuclear NOE difference spectra allowed us to assign the stereochemistry at the newly formed stereocenter of tetrahydrofurans **4**.



(–)-**3a** R^1 = Bn (+)-**4a** R^1 = Bn (57%)
(+)-**3b** R^1 = allyl (+)-**4b** R^1 = allyl (58%)

Scheme 2. Gold-catalyzed heterocyclization reaction of γ-allenol derivatives **3a** and **3b**. Reaction time: 48 h.

One of the challenges of modern synthesis is to create distinct types of complex molecules from identical starting materials based solely on catalyst selection. Thus, having found a solution for the 5-*exo*-selective hydroalkoxylation, we next examined the more intricate heterocyclization problem associated with tuning the regioselectivity of γ-allenols. Notably, the Pd^{II}-catalyzed cyclizative coupling reaction of γ-allenols **3a** and **3b** with allyl halides gave impressive yields

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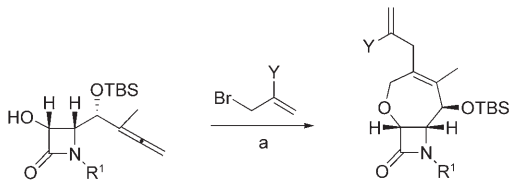
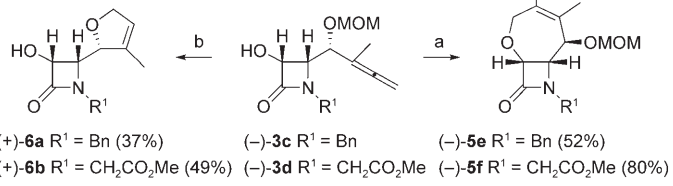
(up to 94%) of the desired seven-membered adducts **5a–d** (Scheme 3), which resulted from a 7-*endo* oxycyclization.[10]

Having demonstrated the stability of the TBS protecting group to the Au^{III} or Pd^{II} catalysis conditions, we decided to see if (methoxymethyl)oxy substitution has a beneficial impact on the cyclization reactions. In the event, MOM cleavage was observed to a small extent during the reaction of γ-allenols **3c** and **3d** with allyl bromide in the presence of $PdCl_2$ (Scheme 4). Surprisingly, when γ-allenols **3c** and **3d** were treated with $AuCl_3$, the 2,5-dihydrofurans **6a** and **6b** were the sole products (Scheme 4). This transformation may involve a chemoselective (5-*endo-trig* versus 7-*endo-trig*) allenol oxycyclization with concomitant MOM ether deprotection.[11]



Scheme 3. Palladium-promoted preparation of seven-membered oxacycles **5a–d**. Reagents and conditions: a) $PdCl_2$ (5 mol%), DMF, RT. Reaction times: 16, 24, 21, and 24 h for **5a–d**, respectively. DMF = *N*,*N*-dimethylformamide.

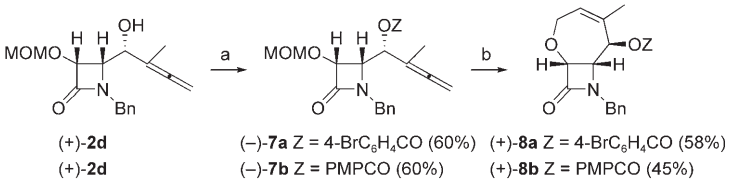


Scheme 4. Metal-catalyzed heterocyclization reactions of γ-allenol derivatives **3c** and **3d**. Reagents and conditions: a) 1. $PdCl_2$ (5 mol%), allyl bromide, DMF, RT, **5e**: 5 h; **5f**: 6 h; 2. MOMCl, Hünig's base, CH_2Cl_2, reflux, 2 h. b) $AuCl_3$ (5 mol%), CH_2Cl_2, RT, **6a**: 22 h; **6b**: 16 h.

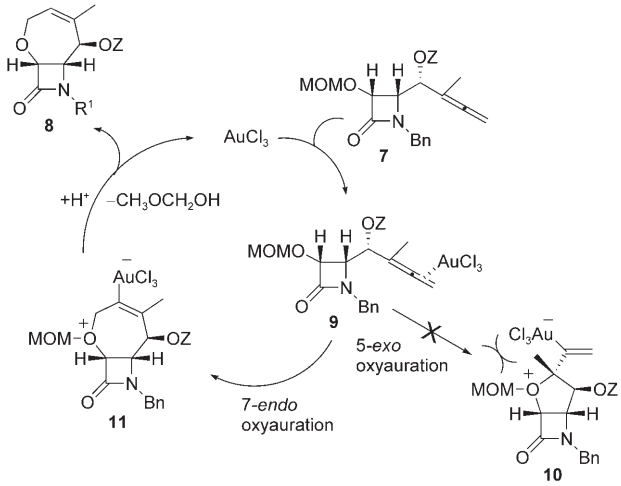
After taking into account the above results, we decide to test if the Au^{III}-catalyzed preparation of bicyclic compounds **4** can be directly accomplished from MOM-protected γ-allenol derivatives **7a** and **7b**. Much to our delight, the 5-*exo* mode completely reverted to a 7-*endo* cyclization to afford bicyclic compounds **8** in fair yields (Scheme 5). To the best of our knowledge, this observation is unprecedented. It seems that the reactivity in this type of Au^{III}-catalyzed reaction is determined by the presence or absence of a MOM protecting group at the γ-allenol oxygen atom, as the free γ-allenols **3a** and **3b** gave 5-*exo* hydroalkoxylation, whereas MOM-protected γ-allenol derivatives **7a** and **7b** exclusively underwent a 7-*endo* oxycyclization. No other isomers or side products were detected. Although complete conversion of the crude reaction mixtures was observed by TLC and ^{1}H NMR analysis, some decomposition of sensitive adducts **4**, **6**, and **8** was detected during purification by flash chromatography, which may be responsible for the moderate yields of isolated products obtained in some cases.

The pathway proposed in Scheme 6 looks valid for the formation of products **8**. It can be presumed that the initially formed allene–gold complex **9** undergoes an intramolecular attack (7-*endo* versus 5-*exo* oxyauration) by the (methoxymethyl)oxy group, which gives rise not to species **10** but to the tetrahydrooxepine intermediate **11**. Protonolysis of the carbon–gold bond linked to an elimination of methoxymethanol would then liberate the bicyclic compound **8** with concomitant regeneration of the Au^{III} species. Probably, the proton in the last step of the catalytic cycle comes from the trace amount of water present in the solvent or the catalyst.

To confirm the mechanistic proposal of Scheme 6, we performed labeling studies with deuterium oxide. Thus, the



Scheme 5. Au^{III}-catalyzed heterocyclization reaction of MOM-protected γ-allenol derivatives **7a** and **7b**. Reagents and conditions: a) 4-BrC_6H_4COCl or PMPCOCl, Et_3N, DMAP, CH_2Cl_2, reflux, **7a**: 6 h; **7b**: 8 h. b) $AuCl_3$ (5 mol%), CH_2Cl_2, RT, **8a**: 72 h; **8b**: 72 h. DMAP = 4-(dimethylamino)pyridine, PMP = 4-$MeOC_6H_4$.

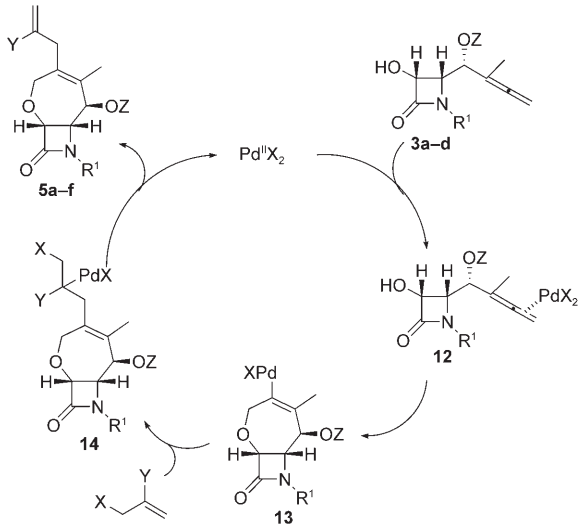


Scheme 6. Mechanistic explanation for the Au^{III}-catalyzed heterocyclization reaction of MOM-protected γ-allenol derivatives **7a** and **7b**.

addition of two equivalents of D_2O to the solution of MOM-protected γ-allenol **7b** and $AuCl_3$ in dichloromethane caused the disappearance of the peak at 6.35 ppm, which is the signal of the proton H4 on 2-oxa-8-azabicyclo[5.2.0]non-4-en-9-one (**8b**). The fact that the $AuCl_3$-catalyzed conversion of allenol **7b** into bicyclic compound **8b** in the presence of two

equivalents of D_2O afforded [4-D]-**8b**, as judged by ^1H NMR spectroscopy (see Supporting Information), suggests that deuterolysis of the carbon–gold bond in species **11** has occurred. It may be inferred that different steric effects in the organometallic species **10** and **11** may be responsible for the different reactivity preference, by stabilizing one of the intermediates rather than the other. In the presence of a MOM group, 5-*exo* cyclization falters. Probably, 5-*exo* oxyauration via **10** is restricted by the steric hindrance between the (methoxymethyl)oxy group and the substituents at the quaternary stereocenter.

Scheme 7 outlines a mechanistic hypothesis for the achievement of compounds **5**. Initial Pd^{II} coordination gave an allene–palladium complex **12**. Species **12** underwent an



Scheme 7. Mechanistic explanation for the Pd^{II}-catalyzed heterocyclization reaction of γ-allenols **3a–d**.

intramolecular cycloetherification reaction to give the palladatetrahydrooxepine **13**. Intermediate **13** reacted with the appropriate allyl halide to form intermediate **14**, which after dehalopalladation generated tetrahydrooxepine-β-lactams **5** with concomitant regeneration of the Pd^{II} species.

In conclusion, an efficient metal-controlled regiodivergent preparation of tetrahydrofurans and tetrahydrooxepines starting from enantiopure γ-allenols has been developed.[12] In addition, it has been observed that a (methoxymethyl)oxy protecting group not only masks a hydroxyl functionality, but also exerts directing effects as a controlling unit in regioselectivity reversal.

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[6] The only available Pt-mediated oxycyclization of a γ-allenol is the 6-*exo* cyclization of 2,2-diphenylhexa-4,5-dien-1-ol, which leads to 6-methyl-3,3-diphenyl-3,4-dihydro-2*H*-pyran. See: Z. Zhang, C. Liu, R. E. Kinder, X. Han, H. Qian, R. A. Widenhoefer, *J. Am. Chem. Soc.* **2006**, *128*, 9066.

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Wiley-VCH, Weinheim, **2005**; b) B. M. Trost, C. H. Jiang, *Synthesis* **2006**, 369.

[10] As far as we know, the Pd-catalyzed cyclizative coupling reaction of γ-allenols with allyl halides has not yet been reported. For its pioneering use in α-allenols, see: S. Ma, W. Gao, *J. Org. Chem.* **2002**, *67*, 6104.

[11] To the best of our knowledge, no truly catalytic deprotection of MOM ethers has previously been reported. For comprehensive reviews, see: a) P. G. M. Wutz, T. W. Greene, *Protective Groups in Organic Synthesis*, 4th ed., Wiley, New York, **2006**; b) P. J. Kocienski, *Protecting Groups*, 3rd ed., Thieme, Stuttgart, **2003**.

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