ACS Catalysis

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Gold-Catalyzed Reactivity Reversal of Indolizidinone-Tethered β-Amino Allenes Controlled by the Stereochemistry

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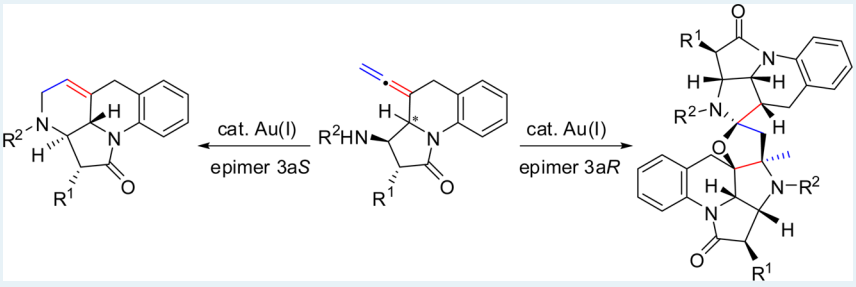
Supporting Information



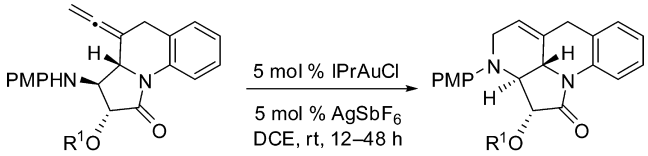
ABSTRACT: The controllable cyclization reaction of indolizidinone-tethered β-amino allenes has been achieved through gold catalysis. The expected cycloisomerization of the *syn*-isomer sharply contrasts to the unprecedented bis(azacyclization)−spirocyclization sequence of the epimeric *anti*-isomer, offering highly selective access to enantiopure fused and spiranic azapolycycles.

KEYWORDS: *allenes, density functional calculations, gold, heterocycles, selectivity*

Controlling reaction selectivity in an efficient way, in particular the switchable synthesis of different products from similar precursors using a catalytic system, is an important goal in synthetic methodology. Our combined interest in the use of β-lactams and allenes prompted us to evaluate the allenylation of enantiopure β-lactam-linked imines followed by ring expansion and metal-catalyzed cyclizations as a feasible route to enantiopure fused or spirocyclic indolizidines.

Gold-catalyzed reactions between allenes and nitrogen nucleophiles are important C−N bond-forming processes.[1] Unfortunately, effective activation protocols for the cyclization of free amines are not widespread,[2] mainly due to the high coordination ability of the basic amine moiety which may deactivate the catalyst. To explore the reactivity of aminoallene-tethered indolizidines *syn*-**1** toward hydroamination, we selected *syn*-**1a** as a model substrate.[3] Preliminary studies about the activity of gold salts were promising, because under $AuCl_3$ catalysis, tetracycle **2a** was isolated in low yield (28%) but in a totally selective fashion. Treatment of aminoallene *syn*-**1a** with $[(Ph_3P)AuNTf_2]$ in 1,2-dichloroethane gave full conversion; being isolated benzo[*b*]pyrrolo[3,2,1-ij][1,7]naphthyridin-1-one **2a** in 49% yield. Our catalyst screening led to the identification of $[IPrAuSbF_6]$ as the most suitable promoter because adduct **2a** was obtained in 82% yield after 12 h at room temperature (Scheme 1, Table S1 in the Supporting Information). Similar yields were observed for tetracyclic products **2b−f** without harming the sensitive γ-lactam ring

Scheme 1. Gold-Catalyzed Synthesis of Benzo[*b*]pyrrolo-naphthyridin-1-ones 2[a]



(+)-*syn*-1a R^1 = Me
(−)-*syn*-1b R^1 = Bn
(−)-*syn*-1c R^1 = Ph
(−)-*syn*-1d R^1 = 4-$MeOC_6H_4$
(−)-*syn*-1e R^1 = 4-BrC_6H_4
(+)-*syn*-1f R^1 = 4-ClC_6H_4

(−)-2a (82%)
(−)-2b (62%)
(−)-2c (64%)
(−)-2d (72%)
(+)-2e (88%)
(+)-2f (63%)

[a]PMP = 4-$MeOC_6H_4$. IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene.

Received: May 21, 2015
Revised: July 15, 2015
Published: July 20, 2015

DOI: 10.1021/acscatal.5b01061
ACS Catal. 2015, 5, 4842−4845

(Scheme 1). The pyrrolonaphthyridine core of tetracycles **2** is an uncommon heterocyclic nucleus which exhibited interesting properties. The structure and stereochemistry of adduct **2a** was unambiguously assigned through its X-ray structure (Figure 1).[4]

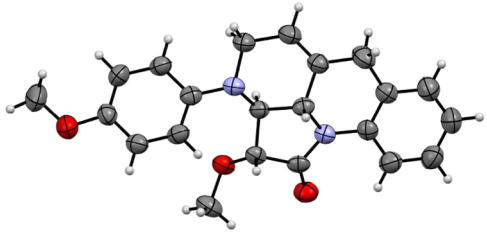
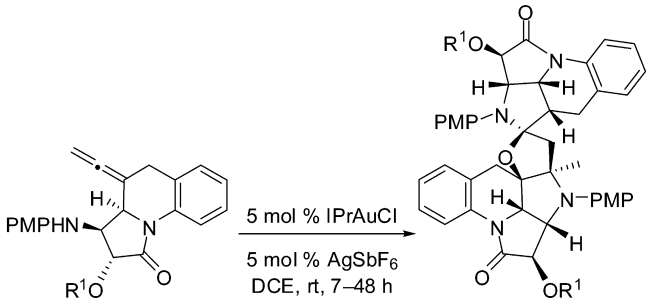


Figure 1. ORTEP drawing of fused pyrrolonaphthyridin-1-one **2a**. Thermal ellipsoids shown at 50% probability.

Indolizidinone-tethered *β*-amino allenes *anti*-**1a**−**f** were subjected to the same gold-catalyzed conditions used for *β*-amino allenes *syn*-**1a**−**f**. A remarkable effect of the stereochemistry of the starting allene on the product formation was observed (Scheme 2). Surprisingly, unlike reactions of

Scheme 2. Gold-Catalyzed Synthesis of Spirocycles 3[a]



(+)-*anti*-1a R^1 = Me
(+)-*anti*-1b R^1 = Bn
(+)-*anti*-1c R^1 = Ph
(+)-*anti*-1d R^1 = 4-$MeOC_6H_4$
(+)-*anti*-1e R^1 = 4-BrC_6H_4
(+)-*anti*-1f R^1 = 4-ClC_6H_4

(+)-3a (35%)
(+)-3b (34%)
(+)-3c (46%)
(−)-3d (45%)
(+)-3e (43%)
(+)-3f (39%)

[a]PMP = 4-$MeOC_6H_4$. IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene.

heterocycle-linked allenes *syn*-**1a**−**f** shown in Scheme 2, derivatives *anti*-**1a**−**f** (which are epimeric at the *α*-amino center) readily undergo an unprecedented and intriguing heterocyclization/spirocyclization sequence, yielding the corresponding spiranic polycycles **3a**−**f** with no evidence of formation of the corresponding cycloisomerization derivatives in the crude reaction mixtures. Complete conversion was observed by TLC and ^{1}H NMR analyses of the crude reaction mixtures of *β*-amino allenes *anti*-**1**, and no side-products were detected. Unfortunately, some decomposition was observed on sensitive spirocycles **3** during purification by flash chromatography, which may be responsible for the moderate isolated yields. This fascinating tandem process on indolizidinone-linked allenes *anti*-**1** differs from reaction of epimers *syn*-**1**, where the corresponding benzo[*b*]pyrrolo-naphthyridin-1-one derivatives **2** were obtained, and constitutes a new addition to the shortlist of gold-catalyzed allene heterocyclization/dimerization reactions.[5] Another interesting feature is that the four novel stereogenic centers in polycycles **3** were completely controlled. For conclusive assessment of the structure of compounds **3**, the X-ray crystallographic analysis of the crystals of spirocycle **3c** was undertaken (Figure 2).[6] On the basis of the structure of adducts **3**, we

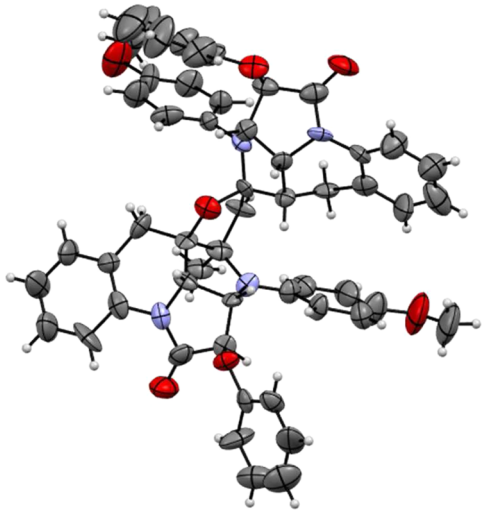


Figure 2. ORTEP drawing of spirocycle **3c**. Thermal ellipsoids shown at 50% probability.

hypothesize that adventitious water was involved in this Au(I)-catalyzed tandem reaction. Many natural products are dimers or pseudodimers, because dimerization usually increases affinity for biological targets. Compounds **3** can be considered as homodimers of polycyclic benzo-fused indolizidine-type alkaloids bearing the N,O-aminal moiety.

Density functional theory (DFT) calculations[7] were carried out to gain insight into the markedly different outcome of the gold-catalyzed reactions involving epimers *syn*-**1** and *anti*-**1**. To this end, we computed the corresponding reaction profiles for the initial aminoauration reaction of model reactants **1M-syn** and **1M-anti** in the presence of $[Au(NHC)]^+$ (NHC = 1,3-dimethylimidazol-2-ylidene) as catalyst. The results are shown in Figure 3, which gathers the corresponding relative free energies (ΔG_{298}, at 298 K) in DCE as solvent (PCM-B3LYP-D3/def2-TZVP//B3LYP/def2-SVP level).

From the data in Figure 3, it is clear that the aminoauration reaction involving **1M-syn** exclusively leads to the formation of the 6-*endo* adduct **INT2-syn** through the transition state **TS1-syn** ($\Delta G‡$ = 6.4 kcal/mol) in an exergonic transformation (ΔG_R = −7.8 kcal/mol). The complete regioselectivity of the process takes place under both kinetic and thermodynamic control, in view of the considerably higher activation energy ($\Delta G‡$ = 13.3 kcal/mol) and endergonicity (ΔG_R = 12.1 kcal/mol) computed for the formation of the alternative 5-*exo* adduct **INT3-syn** (from the initially formed cationic complex **INT1-syn**). Subsequent loss of proton from **INT2-syn** followed by protonolysis of the carbon−gold bond would generate the experimentally observed diazatetracycles **2** with concurrent regeneration of the gold catalyst, following a similar mechanism to that reported by us in related gold(I)-catalyzed processes.[8,9]

A completely different scenario was computed for the epimer **1M-anti**, which initially forms the cationic complex **INT1-anti** upon coordination of the gold(I)-catalyst to the distal allenic double bond. In this particular case, our calculations suggest that the 5-*exo* aminocyclization reaction via **TS2-anti** is mainly

DOI: 10.1021/acscatal.5b01061
ACS Catal. 2015, 5, 4842−4845

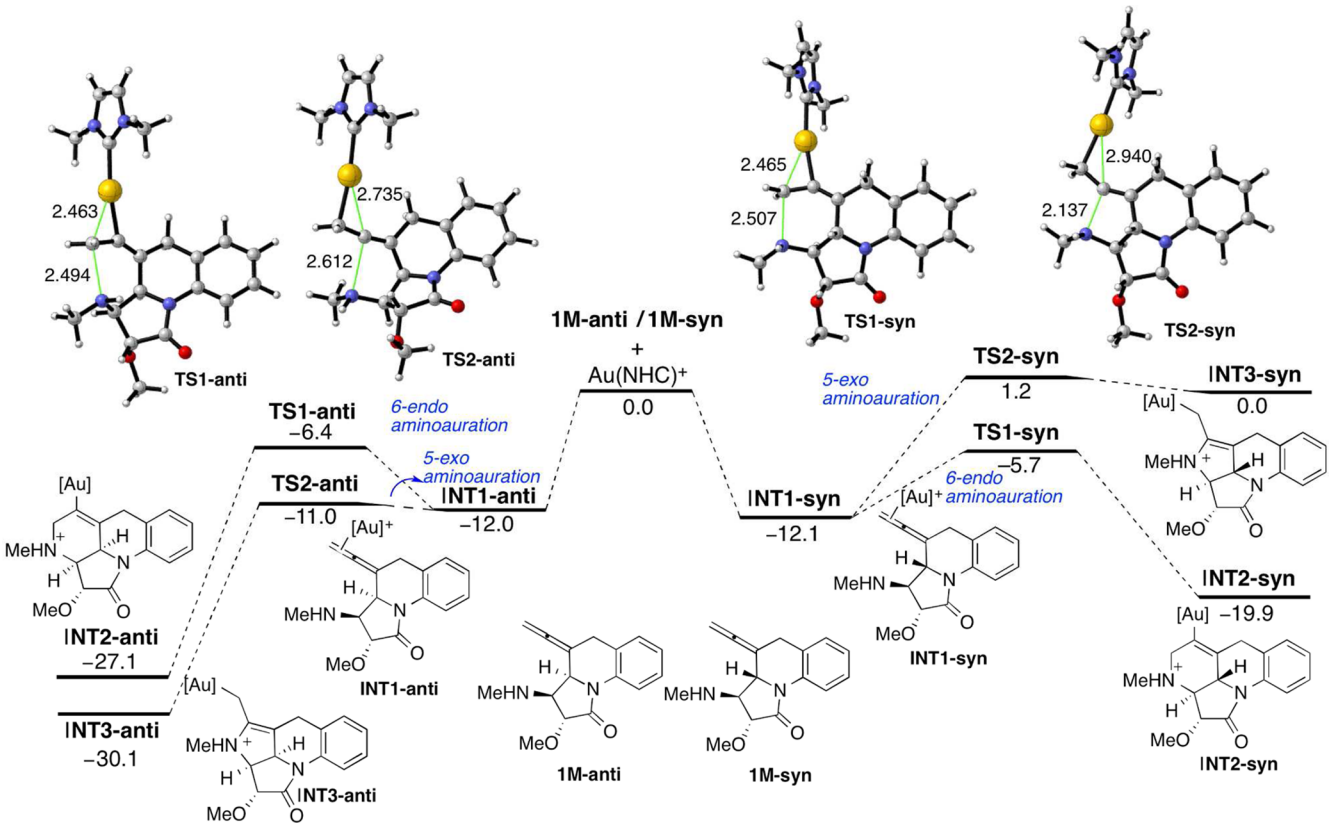


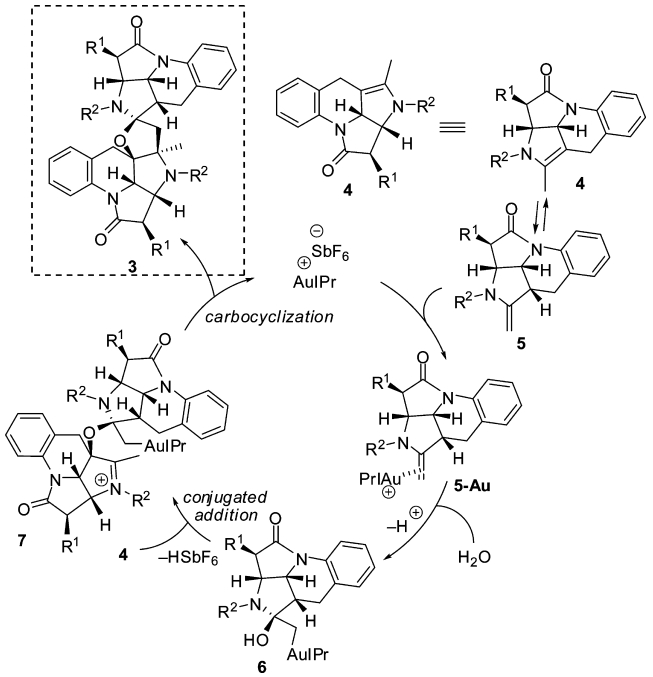
Figure 3. Computed reaction profiles for the reaction of **1M-syn** and **1M-anti** in the presence of model catalyst [Au(NHC)]$^+$ (NHC = 1,3-dimethylimidazol-2-ylidene). Relative free energies (ΔG_{298}, at 298 K) and bond distances are given in kcal/mol and angstroms, respectively. All data have computed at the PCM(DCE)-B3LYP-D3/def2-TZVP//B3LYP/def2-SVP level.

kinetically ($\Delta\Delta G‡$ = 4.6 kcal/mol) but also thermodynamically ($\Delta\Delta G_R$ = 3.0 kcal/mol) preferred over the alternative 6-*endo* cyclization (through **TS1-anti**, see Figure 3).[10] This leads to the exclusive formation of the cationic intermediate **INT3-anti**, which upon protonolysis of the corresponding C−Au gold should produce the corresponding tetracyclic species **4** (Scheme 3).[9] Therefore, it becomes clear that the different outcome of the processes involving epimers *syn*-**1** and *anti*-**1** is strongly related to the initial aminoauration reaction leading exclusively to the 6-*endo* or 5-*exo* adducts, respectively.

Despite that and according to the experimental results described above, the putative tetracyclic intermediates **4** are not observed but are readily transformed into spirocycles **3**. A conceivable mechanistic rationale for this transformation is sketched in Scheme 3. Species **4** may evolve to methylenic azacycles **5** which produce the cationic complexes **5-Au** through coordination of the gold salt. This coordination would facilitate the nucleophilic addition of water[11] which is then followed by loss of a proton resulting in aminal **6**. Subsequent intermolecular nucleophilic attack of the hydroxy moiety to the endocyclic enamine **4** would generate cyclic iminium **7**. This step is associated with a proton abstraction in **6** by the SbF_6^- anion. Finally, intramolecular nucleophilic attack of the organo-gold moiety to the iminium cation in intermediates **7** would form neutral spirocycles **3** with concomitant regeneration of the Au(I) catalyst, therefore closing a second catalytic cycle (Scheme 3).

In conclusion, the present study has established the influence of the stereochemistry on the allene precursor on the outcome of the gold-catalyzed heterocyclization reaction of indolizidinone-tethered β-amino allenes. Thus, whereas the *syn*-epimers exclusively lead to 6-*endo* adducts, the *anti*-counterparts produce 5-*exo* reaction products, which are readily transformed

Scheme 3. Explanation for the Dimerization/Spirocyclization Reaction of Tetracyclic Species 4 Formed from Indolizidinone-Tethered Allenes *anti*-1



DOI: 10.1021/acscatal.5b01061
ACS Catal. 2015, 5, 4842−4845

into spirocycles **3** through an unprecedented gold-catalyzed dimerization/spirocyclization reaction.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.5b01061.

Experimental procedures, characterization data of new compounds, copies of NMR spectra, and computational details (PDF)

Crystallographic data (CIF)

Crystallographic data (CIF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support from the MINECO and FEDER (Projects CTQ2012-33664-C02-01, CTQ2012-33664-C02-02, and CTQ2013-44303-P) and UCM-BANCO SANTANDER (Project GR3/14) is gratefully acknowledged. F. M.-P. thanks Comunidad Autónoma de Madrid and Fondo Social Europeo for a predoctoral contract. Dr. J. M. Alonso is acknowledged for helpful discussion.

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(3) See the Supporting Information for the preparation of starting materials.

(4) CCDC 923446 contains the supplementary crystallographic data for compound **2a** in this paper.

(5) For the gold-catalyzed homodimerization of α-allenones, see: (a) Hashmi, A. S. K. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1581−1583. For gold-catalyzed dimerizations from intermediate enamines, see: (b) Qian, J.; Liu, Y.; Cui, J.; Xu, Z. *J. Org. Chem.* **2012**, *77*, 4484−4490. (c) Miró, J.; Sánchez-Roselló, M.; González, J.; del Pozo, C.; Fustero, S. *Chem. - Eur. J.* **2015**, *21*, 5459−5466.

(6) CCDC 1006864 contains the supplementary crystallographic data for compound **3c** in this paper.

(7) See Computational Details in the Supporting Information.

(8) See, for instance: (a) Alcaide, B.; Almendros, P.; Alonso, J. M.; Fernández, I.; Gómez-Campillos, G.; Torres, M. R. *Chem. Commun.* **2014**, *50*, 4567−4570. See also: (b) Soriano, E.; Fernández, I. *Chem. Soc. Rev.* **2014**, *43*, 3041−3105.

(9) The proton transfer reaction does not proceed via a direct proton transfer, but it is a two-step acid/base process mediated by the counteranion (in this particular case, SbF_6^- rather than Cl^-). Therefore, this anion first deprotonates the NH moiety, and then the readily formed SbF_6−H acid promotes the C−Au protoaurolysis reaction. In addition, these acid/base processes typically occur with very low activation barriers (less than 5 kcal/mol, see for instance: Alcaide, B.; Almendros, P.; Cembellín, S.; Martínez del Campo, T.; Fernández, I. *Chem. Commun.* **2013**, *49*, 1282) therefore indicating that the nucloephilic attack is indeed the rate-determining step of the reaction. .

(10) As experimental results reveal, dimerization via 5-*exo* aminocyclization falters in indolizidinone-tethered β-amino allenes *syn*-**1**. Probably, the 5-*exo* aminoauration in *syn*-**1** is restricted by the *trans* fusion of the pyrrolo[4,3,2-*hi*]indolizin-7-one moiety in a hypothetical intermediate of type **INT3-anti**.

(11) In order to interpret the bis(azacyclization)−spirocyclization reaction outcome in a more useful manner, an ^{18}O-labeling experiment was planned. We performed the gold-catalyzed reaction of β-amino allene *anti*-**1c** in presence of 2 equivalents of $H_2{}^{18}O$ (97% of ^{18}O), and product ^{18}O-**3c** with 20% ^{18}O content was formed. In addition, the gold-catalyzed reaction of β-amino allene *anti*-**1c** in an oxygen atmosphere did not get the final product **3c**. Taking into account the above experiments (Scheme S3 and mass spectra in the Supporting Information), we are confident that the extra oxygen atom in products **3** was not coming from O_2, and rather arises from the presence of H_2O.

DOI: 10.1021/acscatal.5b01061
ACS Catal. 2015, 5, 4842−4845