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Gold-catalyzed [4+3]- and [4+2]-annulations of 3-en-1-ynamides with isoxazoles *via* novel 6π -electrocyclizations of 3-azahepta trienyl cations†

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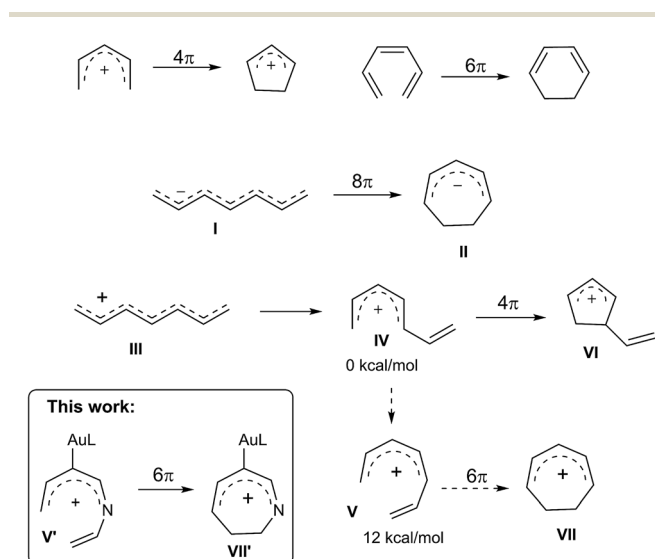
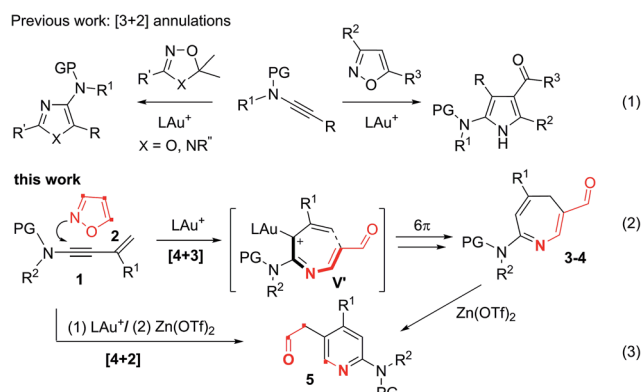
New gold-catalyzed [4+3]-annulations of 3-en-1-ynamides with isoxazoles afford 4*H*-azepines efficiently; this process involves 6π electrocyclizations of gold-stabilized 3-azaheptatrienyl cations. In the presence of $\text{Zn}(\text{OTf})_2$, the resulting 4*H*-azepines undergo skeletal rearrangement to furnish substituted pyridine derivatives. We subsequently develop new catalytic [4+2]-annulations between the same 3-en-1-ynamides and isoxazoles to deliver substituted pyridine products using $\text{Au}(\text{I})/\text{Zn}(\text{II})$ catalysts. This work reports the first success of the 6π electrocyclizations of heptatrienyl cations that are unprecedented in literature reports.

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Introduction

Electrocyclizations of acyclic conjugated π -motifs are powerful tools to access five-, six- and seven-membered carbocycles;¹ prominent examples include Nazarov cyclizations of penta-dienyl cations² and 6π electrocyclizations of trienes,³ which have found widespread applications in organic synthesis.

In the context of seven-carbon π -motifs, heptatrienyl anions **I** undergo facile 8π electrocyclizations *via* rapid interconversions among various anion configurations (Scheme 1).⁴ In contrast, heptatrienyl cations **III**⁵ exclusively undergo Nazarov reactions because of the difficulties of forming all σ -*cis* configured cations **V** that have a high energy state.^{5b} 1-Aza- and 1-oxaheptatrienyl cations⁶ were also reported to follow Nazarov cyclizations. The realization of a 6π electrocyclization of conjugated seven-membered cations is formidable but challenging. This work reveals the first success of such seven-membered cyclizations of gold-stabilized 3-azaheptatrienyl cations **V'** to form azacyclic products **3–4** *via* a new C–C bond formation.

Scheme 1 Electrocyclizations of conjugated π -motifs.

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The advent of gold catalysis has inspired new annulations between alkynes and poor nucleophiles.⁷ N–O containing nucleophiles serve as useful building blocks to construct valuable azacyclic frameworks.⁷ Ye and Hashmi reported interesting [3+2]-annulations of isoxazoles or benzisoxazoles with electron-

rich ynamides, yielding substituted pyrrole derivatives through aza-Nazarov cyclizations of the key intermediate [eqn (1)].^{7,8} These [3+2]-annulations were extensively expanded to other N–O heterocycles including benzisoxazoles, 1,2,4-oxadiazoles, 1,4,2-dioxazoles and 4,5-dihydro-1,2,4-oxadiazoles, yielding additional five-membered azacycles as depicted in [eqn (1)].⁹ Here, we report two distinct [4+3]- and [4+2]-annulations between 3-en-1-ynamides and isoxazoles using varied catalysts. An Au(I) catalyst alone delivers 4*H*-azepines **3–4** through 6 π electrocyclizations of intermediates **V'** [eqn (2)] whereas a combined action of Au(I)/Zn(II) on the same reactants furnishes highly functionalized pyridines **5** [eqn (3)]. With our convenient synthesis, the synthetic utility of new 4*H*-azepines **3–4** is also reported.¹⁰

Results and discussion

We examined the reactions of 3-methyl-3-en-1-ynamide **1a** with 3,5-dimethylisoxazole **2a** using various gold catalysts. Heating this mixture (**1a/2a** = 1 : 2 ratio) in hot DCE with 5 mol% LAuCl/AgNTf₂ [L = *p*-(*t*-Bu)₂(*o*-biphenyl)] and IPr afforded a [4+3]-annulation product, 4*H*-azepine **3a**, in 64% and 75% yields respectively (Table 1, entries 1–2). Under these conditions, a low loading (1.2 equiv.) of 3,5-dimethylisoxazole **2a** gave **3a** in a decreased yield, *ca.* 62% (entry 3). With a 10 mol% catalyst, IPrAuCl/AgNTf₂ gave a clean reaction, yielding desired **3a** up to 91% (entry 4). We tested other phosphine ligands such as PPh₃ and P(OPh)₃, yielding desired **3a** in satisfactory yields (78–81%, entries 5–6). Other counter anions such as OTf[−] and SbF₆[−] were also effective in producing **3a** in 85–88% yields (entries 7–8). AgNTf₂ alone was not active at all (entry 9).

Table 1 [4+3]-Annulations over various gold catalysts

| Entry | Catalyst [mol%] | x | Time [h] | Yield ^b [%] | | |
|----------------|--|-----|----------|------------------------|----|--------------|
| | | | | 1a | 3a | 1a-H'/1a-H'' |
| 1 ^c | LAuCl/AgNTf ₂ [5] | 2 | 3 | 20 | 64 | — |
| 2 ^d | IPrAuCl/AgNTf ₂ [5] | 2 | 7 | 12 | 75 | 7 [2.5 : 1] |
| 3 | IPrAuCl/AgNTf ₂ [5] | 1.2 | 7 | 23 | 62 | 5 [1 : 1] |
| 4 | IPrAuCl/AgNTf ₂ [10] | 2 | 3 | — | 91 | Trace |
| 5 | PPh ₃ AuCl/AgNTf ₂ [10] | 2 | 3.5 | — | 81 | 5 [1.25 : 1] |
| 6 | [PhO] ₃ PAuCl/AgNTf ₂ [10] | 2 | 3.5 | — | 78 | 13 [1.1 : 1] |
| 7 | IPrAuCl/AgSbF ₆ [10] | 2 | 2.5 | — | 85 | 6 [1.4 : 1] |
| 8 | IPrAuCl/AgOTf [10] | 2 | 2 | — | 88 | Trace |
| 9 | AgNTf ₂ [10] | 2 | 15 | 33 | — | 11 |

^a [1a] = 0.15 M. ^b Product yields are reported after separation from a silica column. ^c L = *p*-(*t*-Bu)₂(*o*-biphenyl). ^d IPr = 1,3-bis(diisopropylphenyl)-imidazol-2-ylidene. Ms = methanesulfonyl, DCE = 1,2-dichloroethane, and Tf = trifluoromethanesulfonyl.

Table 2 [4+3]-Annulations with various 3-en-1-ynamides

| Entry | (R ¹ , R ²) | Time [h] |
|-------|--|---|
| (1) | R ¹ , EWG = CH ₃ , Ts (3b) | 3 h, 84%, x-ray |
| (2) | R ¹ , EWG = <i>c</i> -Pr, Ts (3c) | 7 h, 86% |
| (3) | R ¹ , EWG = Bn, Ts (3d) | 4.5 h, 87% |
| (4) | R ¹ , EWG = <i>n</i> -Bu, <i>n</i> -BuSO ₂ (3e) | 6 h, 90% |
| (5) | R ¹ , EWG = CH ₃ , Ts (3f) | 22 h, 64% |
| (6) | R ¹ = <i>i</i> -Pr (3g) | 4 h, 74% |
| (7) | R ¹ = <i>c</i> -Pr (3h) | 2 h, 79% |
| (8) | R ¹ = Ph (3i) | 2.5 h, 58% |
| (9) | R ¹ , EWG = <i>n</i> -Bu, Ms (3j) | 5 h, 55%, 3j/3j' = 5:1 |
| (10) | R ¹ , EWG = CH ₃ , Ts (3k) | 4 h, 68%, 3k/3k' = 11.1:1 |
| (11) | (3l) | 2.5 h, 48%, x-ray (6l , 43%, <i>E/Z</i> = 3.3:1) |
| (12) | (3m) | 14 h, 16% (6m , 73%, x-ray) |

^a [1] = 0.15 M. ^b Product yields are reported after separation from a silica column. EWG = electron withdrawing group.

Table 3 [4+3]-Annulations with various isoxazoles

| Entry | (R ¹ , R ²) | 2 | Time [h] | Yield [%] |
|-------|------------------------------------|-----------|----------|-----------|
| (1) | H, H | 2b | 4 | 84 |
| (2) | H, Me | 2d | 3 | 75 |
| (3) | Me, H | 2c | 3 | 87 |
| (4) | Et, Et | 2e | 6 | 85 |
| (5) | <i>n</i> -Bu, <i>n</i> -Bu | 2f | 7 | 81 |
| (6) | Me, <i>n</i> -Bu | 2g | 3 | 82 |
| (7) | <i>n</i> -Bu, <i>c</i> -Pr | 2h | 2 | 77 |
| (8) | Ph, <i>n</i> -Bu | 2i | 4 | 69 |
| (9) | Ph, Ph | 2j | 6.5 | 61 |
| (10) | Me, Ph | 2k | 4 | 71 |
| | | | | 15 |
| | | | | 5j |

^a [1b] = 0.15 M. ^b Product yields are reported after separation from a silica column.

Suitable substituents of 3-en-1-ynamides **1** are crucial to achieve 6π cyclizations of 3-azaheptatrienyl cations **V'** [eqn (2)]. We tested the reactions on 3-en-1-ynes **1b–1m** bearing a C(3)-substituent to circumvent aza-Nazarov cyclizations as reported in Ye's work.⁷ Herein, only entries 9 and 10 showed the presence of 3-azanorcaradienes **3'**. We examined these [4+3]-annulations on 3-methyl-3-en-1-ynamides **1b–1e** bearing various sulfonamides NTsR⁴ (R⁴ = Me, cyclopropyl, benzyl and N(*n*-C₄H₉) (–SO₂Bu)), affording the desired 4*H*-azepines **3b–3e** in high yields (84–90%, Table 2, entries 1–4). Nevertheless, this new annulation becomes less efficient for 3-en-1-ynamide **1f** bearing an oxazolidin-2-one to yield product **3f** in 64% yield (entry 5).

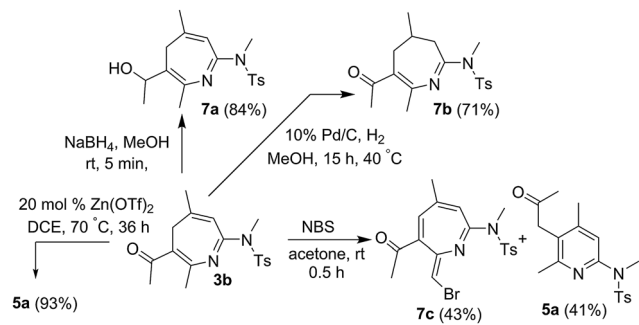
We altered the C(3)-substituents as in substrates **1g–1i**; their resulting products **3g–3h** (R¹ = isopropyl and cyclopropyl) were obtained in 74–79%, and **3i** (R¹ = Ph) with only 58% yield (entries 6–8). Notably, when a long *n*-butyl group was present as in species **1j** and **1k**, their corresponding reactions afforded compounds **3j/3j'** = 5/1 and **3k/3k'** = 11.1 : 1, respectively, in 55% and 68% yields (entries 9–10). For *E*-configured trisubstituted 3-en-1-yne **1l** (R¹ = Me, R² = Ph and R³ = H), 4*H*-azepine **3l**

and pyrrole **6l** were obtained in equal proportions (entry 11). When a cyclohexenyl group was present for alkene as in species **1m**, pyrrole product **6m** was dominant over azepine **3m** (entry 12). Accordingly, preferable 3-en-1-ynes comprise a small R² or R³ substituent whereas R¹ must be substituted. Herein, the structures of 4*H*-azepines **3b** and **3l**, and pyrrole species **6m** were confirmed with X-ray diffraction.¹¹

Isoxazoles of a wide scope are compatible with these [4+3]-annulations, as depicted in Table 3. The reaction of unsubstituted isoxazole **2b** with model 3-en-1-ynamide **1b** afforded the desired 4*H*-azepine **4a** in 84% yield, together with pyrrole **7a'** in only 8% yield (entry 1). Mono-substituted 3-methyl or 5-methyl isoxazoles **2c** and **2d** are also suitable for these annulations to afford compounds **4b** and **4c** in 75% and 87% yields, respectively (entries 2–3). We prepared additional 3,5-disubstituted isoxazoles **2e–2i** with R¹ = alkyl and phenyl, and R² = alkyl; their annulations proceed smoothly to produce desired **4d–4h** in 69–85% yields (entries 4–8). For di-substituted isoxazoles **2j** and **2k** bearing R² = Ph, 4*H*-azepines **4i** and **4j** were obtained in 61% and 71% yields respectively, together with their rearrangement products **5i** and **5j** in 15–30% yields (entries 9–10). Compounds **4a** and **5i** were characterized by X-ray diffraction.¹¹

Our convenient synthesis of 4*H*-azepines provides new synthetic utilities; several new functionalizations are depicted in Scheme 2. NaBH₄-reduction of species **3b** delivered an alcohol derivative **7a** in 84% yield. Selective hydrogenation of the same species afforded 2-aza-1,3-dien-5-one **7b** in 71% yield. A final treatment of 4*H*-azepine **3b** with NBS in acetone afforded compound **7c**, of which the molecular structure was determined by ¹H NOE spectra.

The Lewis-catalyzed rearrangement of 4*H*-azepines **3–4** to substituted pyridines **5** [eqn (3)] is unprecedented in 4*H*-azepine chemistry.¹⁰ We undertook such novel [4+2]-annulations

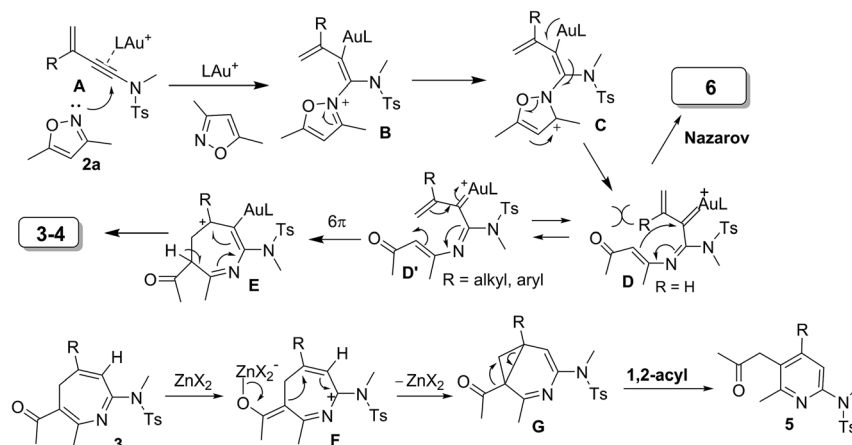


Scheme 2 New functionalization of 4*H*-azepines.

Table 4 [4+2]-Annulations between 3-en-1-ynamides and isoxazoles

| Entry | (R ¹ , R ² , EWG) | 1 | (R ³ , R ⁴) | 2 | Time [h] | Yield [%] | 5 |
|-------|---|-----------|------------------------------------|-----------|----------|----------------------|-------------------|
| (1) | Me, Me, Ts | 1b | Me, Me | 2a | 19 | 73 (35) ^c | 5a (X-ray) |
| (2) | <i>n</i> -Bu, Me, Ts | 1k | Me, Me | 2a | 33 | 64 | 5b |
| (3) | <i>c</i> -Pr, Me, Ts | 1h | Me, Me | 2a | 20 | 56 | 5c |
| (4) | <i>i</i> -Pr, Me, Ts | 1g | Me, Me | 2a | 15 | 51 | 5d |
| (5) | Me, <i>n</i> -Bu, Ms | 1a | Me, Me | 2a | 28 | 63 | 5e |
| (6) | Me, Me, Ts | 1b | <i>n</i> -Bu, <i>n</i> -Bu | 2f | 19 | 78 | 5f |
| (7) | Me, Me, Ts | 1b | Et, Et | 2e | 16 | 69 | 5g |
| (8) | Me, Me, Ts | 1b | <i>n</i> Bu, <i>c</i> -Pr | 2h | 20 | 75 | 5h |
| (9) | Me, Me, Ts | 1b | Ph, Ph | 2j | 24 | 80 | 5i (X-ray) |
| (10) | Me, Me, Ts | 1b | Me, Ph | 2k | 30 | 75 | 5j |

^a [1] = 0.15 M. ^b Product yields are reported after separation from a silica column. ^c The value in parentheses is reported using a mixture of IPrAuCl/AgNTf₂ (10 mol%) and Zn(OTf)₂ (20 mol%) in hot DCE (70 °C, 48 h); **3b** was also isolated in 28% yield.



Scheme 3 A plausible reaction mechanism.

between 3-en-1-ynamides **1** and isoxazoles **2** using Au(I)/Zn(II) in a relay series, as depicted in Table 4. In the reactions of various 3-substituted 3-en-1-ynamides **1** (R^1 = methyl, *n*-butyl, cyclopropyl and isopropyl) with 3,5-dimethylisoxazole **2a**, substituted pyridines **5a–5d** were obtained in satisfactory yields (51–73%, entries 1–4). In entry 1, if the reaction was performed with combined Au(I)/Zn(II) catalysts in a non-relay operation, compounds **5a** and **3b** were isolated in 35% and 28% yields respectively. For 3-en-1-ynamide **1a** bearing a NMs(*n*-butyl), the corresponding product **5e** was obtained in 63% yield (entry 5). We tested the reactions on 3,5-disubstituted isoxazoles **2e–2f** & **2h** bearing all alkyl substituents, producing desired **5f–5h** in good yields (69–78%, entries 6–8). For such disubstituted isoxazoles bearing R^4 = Ph, the reactions afforded the desired pyridine derivatives **5i** and **5j** in 75–80% yields (entries 9–10). The molecular structures of compounds **5a** and **5i** were characterized by X-ray diffraction.¹¹

Scheme 3 rationalizes the crucial roles of substituents of 3-en-1-ynamides in the chemoselectivity that relies on two conformational structures **D** versus **D'**. The N-attack of isoxazole at gold- π -ynamide **A** is expected to form a gold-carbene **D'**, which can be visualized as a gold-stabilized cycloheptatrienyl cation. Conformation **D** is favorable with R = H, which prefers aza-Nazarov reactions.¹² When a C(3)-substituent is present (R = alkyl and aryl), all σ -*cis* configured species **D'** are the preferable geometry to induce novel 6π electrocyclizations. This ring closure is expected to proceed through an attack of enamide at the alkenylgold moiety that is also visualized as a gold-stabilized cation. Additional C(4)-substituents render the formation of cations **D'** difficult, thus yielding pyrrole **6** as byproducts. A loss of an acidic proton from seven-membered cations **E** is expected to yield azepines **3–4**. 4*H*-Azepines **3–4** bear an enone conjugated with a triene; this extensive conjugation is very stable to impede a 6π electrocycloheptatrienyl cation of their triene moieties unless a Lewis acid is present. Zn(OTf)₂ likely coordinates with the carbonyl of 4*H*-azepine **3** to generate a 2-azapentadienyl cation **F** bearing a zinc enolate, further enabling an intramolecular cyclization to generate species **G**. A 1,2-acyl shift¹⁴ of species **G** delivers the observed product **5**.¹³

Conclusions

In summary, this work describes new gold-catalyzed [4+3] annulations¹⁵ of 3-substituted 3-en-1-ynamides with isoxazoles to form 4*H*-azepines. A relay catalysis is also developed with Au(I)/Zn(II) catalysts to achieve [4+2] annulations from the same reactants. The mechanisms of gold-catalyzed [4+3] annulations involve unprecedented 6π electrocyclizations of 3-azacycloheptatrienyl cations to form 4*H*-azepines **3–4** efficiently. Control experiments confirm that 4*H*-azepines **3–4** are catalyzed by Zn(OTf)₂ to undergo new rearrangement reactions to form substituted pyridine derivatives.

Conflicts of interest

The authors declare no conflict of interest.

Acknowledgements

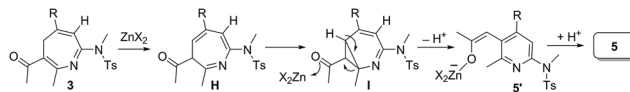
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- 13 As suggested by one reviewer, an alternative mechanism is also possible for the Zn(II)-catalyzed rearrangement; this process involves an isomerization of initial species **3** to an unconjugated iminoyl ketone **H**, followed by a 6π -cyclization to generate species **I**. A subsequent Zn(II)-catalyzed aromatization of species **I** is expected to yield the final product **5**. In this process, species **H** is relatively higher than **3** in energy, but its feasibility is not excluded.



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- 15 For reviews of gold-catalyzed cycloaddition or annulation reactions of alkynes, see (a) D. J. Gorin, B. D. Sherry and F. D. Toste, *Chem. Rev.*, 2008, **108**, 3351; (b) A. S. K. Hashmi, *Chem. Rev.*, 2007, **107**, 3180; (c) F. López and J. L. Mascareñas, *Beilstein J. Org. Chem.*, 2011, **7**, 1075; (d) C. Aubert, L. Fensterbank, P. Garcia, M. Malacria and A. Simonneau, *Chem. Rev.*, 2011, **111**, 1954; (e) D. Garayalde and C. Nevado, *ACS Catal.*, 2012, **2**, 1462; (f) M. E. Muratore, A. Homes, C. Obradors and A. M. Echavarren, *Chem.-Asian J.*, 2014, **9**, 3066.

