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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†

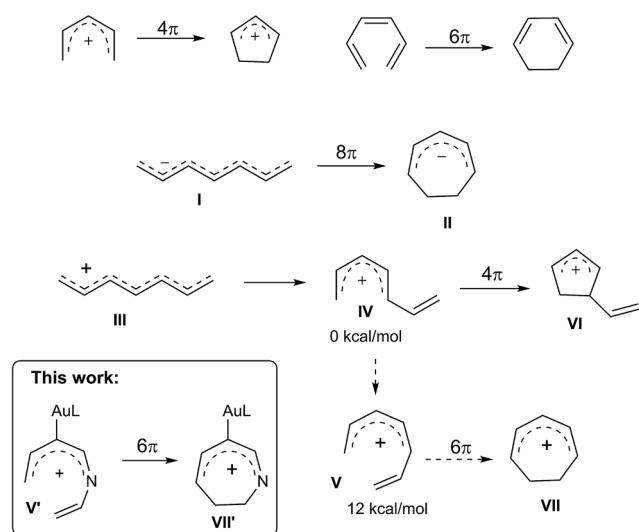
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New gold-catalyzed [4+3]-annulations of 3-en-1-ynamides with isoxazoles afford 4*H*-azepines efficiently; this process involves 6π electrocyclizations of gold-stabilized 3-azaheptatrienyl cations. In the presence of $\text{Zn}(\text{OTf})_2$, the resulting 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.

Introduction

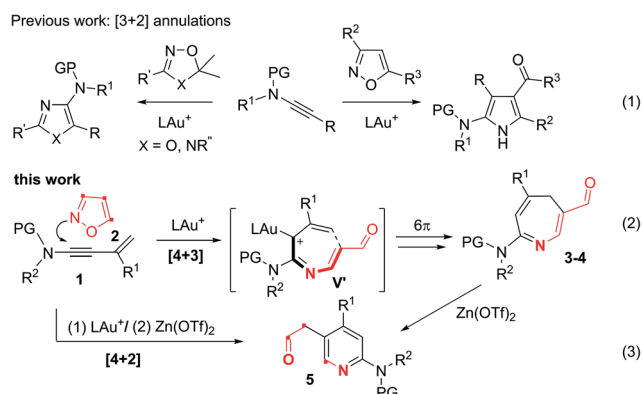
Electrocyclizations of acyclic conjugated π -motifs are powerful tools to access five-, six- and seven-membered carbocycles;¹ prominent examples include Nazarov cyclizations of pentadienyl cations² and 6π electrocyclizations of trienes,³ which have found widespread applications in organic synthesis.

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

				Yield ^b [%]		
Entry	Catalyst [mol%]	x	Time [h]	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

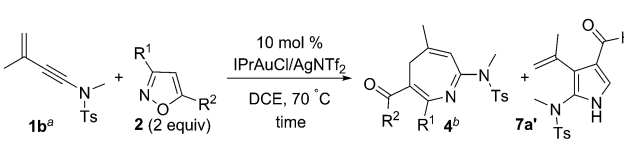
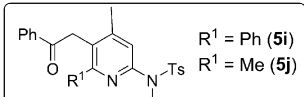
^a [1a] = 0.15 M. ^b Product yields are reported after separation from a silica column. ^c L = *p*-(*t*-Bu)₂(*o*-biphenyl). ^d IPr = 1,3-bis(diisopropylphenyl)-imidazol-2-ylidene. Ms = methanesulfonyl, DCE = 1,2-dichloroethane, and Tf = trifluoromethanesulfonyl.

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

(1) R ⁴ , EWG = CH ₃ , Ts (3b , 3 h, 84%, x-ray)	(5) (3f, 22 h, 64%)	(6) R ¹ = <i>i</i> -Pr (3g , 4 h, 74%)	(9) R ⁴ , EWG = <i>n</i> -Bu, Ms (3j , 5 h, 55%, 3j/3j' = 5:1)
(2) R ⁴ , EWG = <i>c</i> -Pr, Ts (3c , 7 h, 86%)		(7) R ¹ = <i>c</i> -Pr (3h , 2 h, 79%)	(10) R ⁴ , EWG = CH ₃ , Ts (3k , 4 h, 68%, 3k/3k' = 11.1:1)
(3) R ⁴ , EWG = Bn, Ts (3d , 4.5 h, 87%)		(8) R ¹ = Ph (3i , 2.5 h, 58%)	
(4) R ⁴ , EWG = <i>n</i> -Bu, <i>n</i> -BuSO ₂ (3e , 6 h, 90%)			
(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 [%]	4
(1)	H, H	2b	4	84	4a (X-ray)
(2)	H, Me	2d	3	8	7a'
(3)	Me, H	2c	3	75	4b
(4)	Et, Et	2e	6	87	4c
(5)	Et, Et	2e	6	85	4d
(6)	<i>n</i> -Bu, <i>n</i> -Bu	2f	7	81	4e
(7)	Me, <i>n</i> -Bu	2g	3	82	4f
(8)	<i>n</i> -Bu, <i>c</i> -Pr	2h	2	77	4g
(9)	Ph, <i>n</i> -Bu	2i	4	69	4h
(10)	Ph, Ph	2j	6.5	61	4i
				30	5i (X-ray)
(10)	Me, Ph	2k	4	71	4j
					
				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).

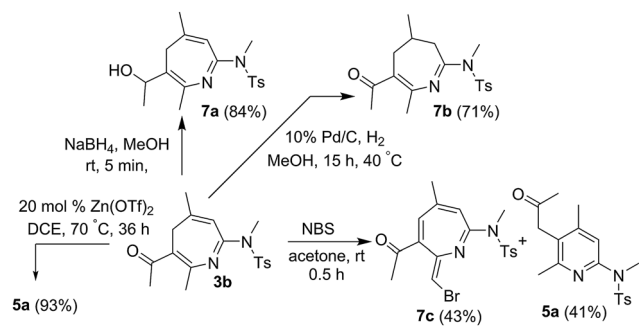
We altered the C(3)-substituents as in substrates **1g–1i**; their resulting products **3g–3h** (R¹ = isopropyl and cyclopropyl) were obtained in 74–79%, and **3i** (R¹ = Ph) with only 58% yield (entries 6–8). Notably, when a long *n*-butyl group was present as in species **1j** and **1k**, their corresponding 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



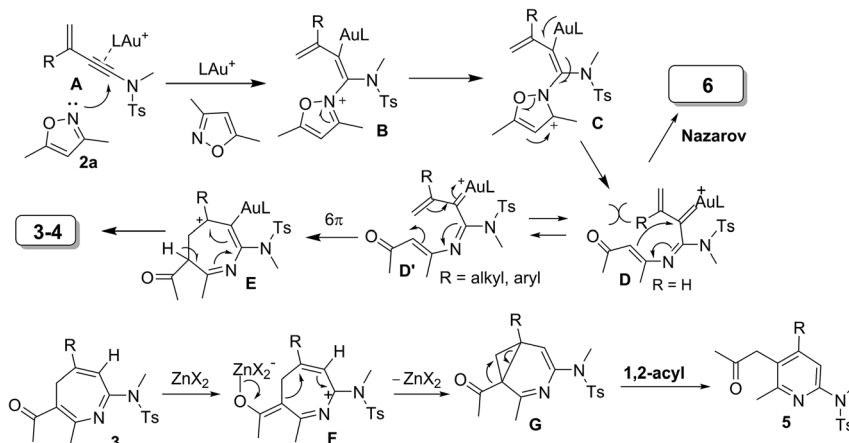
Scheme 2 New functionalization of 4*H*-azepines.

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

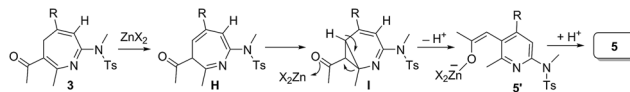
The authors thank the Ministry of Science and Technology and the Ministry of Education, Taiwan, for supporting this work.

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- 11 Crystallographic data of compounds **3b**, **3l**, **4a**, **5a**, **5i**, and **6m** were deposited in Cambridge Crystallographic Data Center: **3b**: CCDC 1589549, **3l**: CCDC 1589562, **4a**: CCDC 1589561, **5a**: CCDC 1589558, **5i**: CCDC 1589559 and **6m**: CCDC 1589560.†
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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.