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

Sovan Sundar Giri and Rai-Shung Liu \*\*

New gold-catalyzed [4+3]-annulations of 3-en-1-ynamides with isoxazoles afford 4H-azepines efficiently; this process involves  $6\pi$  electrocyclizations of gold-stabilized 3-azaheptatrienyl cations. In the presence of Zn(OTf)<sub>2</sub>, the resulting 4H-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 Au(i)/Zn(ii) catalysts. This work reports the first success of the  $6\pi$  electrocyclizations of heptatrienyl cations that are unprecedented in literature reports.

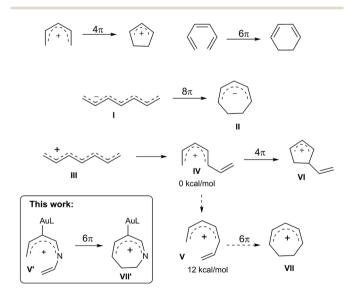
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#### Introduction

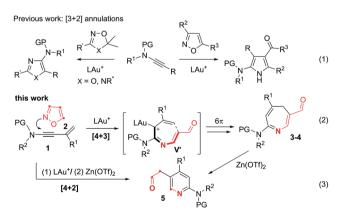
Electrocyclizations of acyclic conjugated  $\pi$ -motifs are powerful tools to access five-, six- and seven-membered carbocycles; prominent examples include Nazarov cyclizations of pentadienyl cations and  $6\pi$  electrocyclizations of trienes, which have found widespread applications in organic synthesis.



**Scheme 1** Electrocyclizations of conjugated  $\pi$ -motifs.

Department of Chemistry, National Tsing-Hua University, Hsinchu, Taiwan, Republic of China. E-mail: rsliu@mx.nthu.edu.tw

In the context of seven-carbon  $\pi$ -motifs, heptatrienyl anions I undergo facile  $8\pi$  electrocyclizations via rapid interconversions among various anion configurations (Scheme 1).<sup>4</sup> In contrast, heptatrienyl cations III<sup>5</sup> exclusively undergo Nazarov reactions because of the difficulties of forming all  $\sigma$ -cis configured cations V that have a high energy state.<sup>5b</sup> 1-Aza- and 1-oxaheptatrienyl cations<sup>6</sup> were also reported to follow Nazarov cyclizations. The realization of a  $6\pi$  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.



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

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rich ynamides, yielding substituted pyrrole derivatives through aza-Nazarov cyclizations of the key intermediate [eqn (1)]. 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)]. Here, we report two distinct [4+3]- and [4+2]-annulations between 3-en-1-ynamides and isoxazoles using varied catalysts. An Au(ı) catalyst alone delivers 4*H*-azepines 3–4 through 6 $\pi$  electrocyclizations of intermediates V' [eqn (2)] whereas a combined action of Au(ı)/Zn(ıı) 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. O

#### Results and discussion

We examined the reactions of 3-methyl-3-en-1-ynamide  ${\bf 1a}$  with 3,5-dimethylisoxazole  ${\bf 2a}$  using various gold catalysts. Heating this mixture  $({\bf 1a}/{\bf 2a}=1:2 \text{ ratio})$  in hot DCE with 5 mol% LAuCl/AgNTf2 [L =  $p(t\text{-Bu})_2(o\text{-biphenyl})$  and IPr] afforded a [4+3]-annulation product, 4H-azepine  ${\bf 3a}$ , in 64% and 75% yields respectively (Table 1, entries 1–2). Under these conditions, a low loading (1.2 equiv.) of 3,5-dimethylisoxazole  ${\bf 2a}$  gave  ${\bf 3a}$  in a decreased yield,  ${\bf ca}$ . 62% (entry 3). With a 10 mol% catalyst, IPrAuCl/AgNTf2 gave a clean reaction, yielding desired  ${\bf 3a}$  up to 91% (entry 4). We tested other phosphine ligands such as PPh3 and P(OPh)3, yielding desired  ${\bf 3a}$  in satisfactory yields (78–81%, entries 5–6). Other counter anions such as OTf $^-$  and SbF $_6$  $^-$  were also effective in producing  ${\bf 3a}$  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

			<b>m</b> :	Yiel	$d^b$ [%	$\mathbf{d}^b \left[\% ight]$		
Entry	Catalyst [mol%]	x	Time [h]	1a	3a	1a-H'/1a-H"		
1 <sup>c</sup>	LAuCl/AgNTf <sub>2</sub> [5]	2	3	20	64	_		
$2^d$	IPrAuCl/AgNTf <sub>2</sub> [5]	2	7	12	75	7 [2.5:1]		
3	IPrAuCl/AgNTf <sub>2</sub> [5]	1.2	7	23	62	5 [1:1]		
4	IPrAuCl/AgNTf <sub>2</sub> [10]	2	3	_	91	Trace		
5	PPh <sub>3</sub> AuCl/AgNTf <sub>2</sub> [10]	2	3.5	_	81	5 [1.25:1]		
6	[PhO] <sub>3</sub> PAuCl/AgNTf <sub>2</sub> [10]	2	3.5	_	78	13[1.1:1]		
7	IPrAuCl/AgSbF <sub>6</sub> [10]	2	2.5	_	85	6 [1.4:1]		
8	IPrAuCl/AgOTf [10]	2	2	_	88	Trace		
9	AgNTf <sub>2</sub> [10]	2	15	33	_	11		

 $^a$  [1a] = 0.15 M.  $^b$  Product yields are reported after separation from a silica column.  $^c$  L =  $p(t\text{-Bu})_2(o\text{-biphenyl})$ .  $^d$  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

 $^a$  [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

		•			15
Entry	$(R^1, R^2)$	2	Time [h]	Yield [%]	4
(1)	Н, Н	2b	4	84	4a (X-ray)
. ,				8	7a'
(2)	H, Me	2d	3	75	4b
(3)	Me, H	2c	3	87	4c
(4)	Et, Et	2e	6	85	4d
(5)	n-Bu, n-Bu	2f	7	81	4e
(6)	Me, <i>n</i> -Bu	2g	3	82	<b>4f</b>
(7)	<i>n</i> -Bu, <i>c</i> -Pr	2h	2	77	4g
(8)	Ph, <i>n</i> -Bu	2i	4	69	4h
(9)	Ph, Ph	2j	6.5	61	4i
				30	5i (X-ray)
(10)	Me, Ph	2k	4	71	4j
	Ph N	N_Ts	R <sup>1</sup> = Ph (5i) R <sup>1</sup> = Me (5j)	15	5j

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

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Suitable substituents of 3-en-1-ynamides 1 are crucial to achieve  $6\pi$  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. 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 NTsR<sup>4</sup> (R<sup>4</sup> = Me, cyclopropyl, benzyl and N(n-C<sub>4</sub>H<sub>9</sub>) (-SO<sub>2</sub>Bu)), affording the desired 4H-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 ( $R^1 = isopropyl$  and cyclopropyl) were obtained in 74-79%, and 3i ( $R^1 = Ph$ ) 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  $3\mathbf{j}/3\mathbf{j}' = 5/1$  and  $3\mathbf{k}/3\mathbf{k}' = 11.1:1$ , respectively, in 55% and 68% yields (entries 9-10). For E-configured trisubstituted 3-en-1-yne 11 ( $R^1 = Me$ ,  $R^2 = Ph$  and  $R^3 = H$ ), 4*H*-azepine 31

Scheme 2 New functionalization of 4H-azepines.

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 R<sup>2</sup> or R<sup>3</sup> substituent whereas R<sup>1</sup> must be substituted. Herein, the structures of 4H-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 4H-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  $R^1 = alkyl$  and phenyl, and  $R^2 = alkyl$ ; their annulations proceed smoothly to produce desired 4d-4h in 69-85% yields (entries 4-8). For di-substituted isoxazoles 2j and 2k bearing  $R^2 = Ph$ , 4*H*-azepines 4**i** and 4**j** 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 4H-azepines provides new synthetic utilities; several new functionalizations are depicted in Scheme 2. NaBH<sub>4</sub>-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 4H-azepine 3b with NBS in acetone afforded compound 7c, of which the molecular structure was determined by <sup>1</sup>H NOE spectra.

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

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

<sup>&</sup>lt;sup>a</sup> [1] = 0.15 M. <sup>b</sup> Product yields are reported after separation from a silica column. <sup>c</sup> The value in parentheses is reported using a mixture of IPrAuCl/ AgNTf<sub>2</sub> (10 mol%) and Zn(OTf)<sub>2</sub> (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(1)/Zn(11) 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 3en-1-ynamides in the chemoselectivity that relies on two conformational structures **D** versus **D**'. The N-attack of isoxazole at gold- $\pi$ -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  $\sigma$ -cis configured species  $\mathbf{D}'$  are the preferable geometry to induce novel  $6\pi$  electrocyclizations. This ring closure is expected to proceed through an attack of enamide at the alkenylgold moiety that is also visualized as a goldstabilized 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. 4H-Azepines 3-4 bear an enone conjugated with a triene; this extensive conjugation is very stable to impede a  $6\pi$  electrocyclization of their triene moieties unless a Lewis acid is present. Zn(OTf)<sub>2</sub> likely coordinates with the carbonyl of 4H-azepine 3 to generate a 2azapentadienyl 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] annulations of 3-substituted 3-en-1-ynamides with isoxazoles to form 4*H*-azepines. A relay catalysis is also developed with Au(1)/Zn(11) catalysts to achieve [4+2] annulations from the same reactants. The mechanisms of gold-catalyzed [4+3] annulations involve unprecedented  $6\pi$  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)<sub>2</sub> to undergo new rearrangement reactions to form substituted pyridine derivatives.

#### Conflicts of interest

The authors declare no conflict of interest.

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$$0 \xrightarrow[]{R} \xrightarrow[T_S]{H} \times \underbrace{\sum_{Z_1Z_2} \sum_{Z_1Z_1} \sum_{Z_2Z_1} \sum_{X_2Z_1} \sum_{X_2Z_2} \sum_{X_2Z_1} \sum_{X_2Z_2} \sum_{X_2Z_1} \sum_{X_2Z_2} \sum_{X_2} \sum_{X_2Z_2} \sum_{X_2} \sum_{X_2} \sum_{X_2} \sum_{X_2} \sum_{X_2} \sum_{X$$

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