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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†

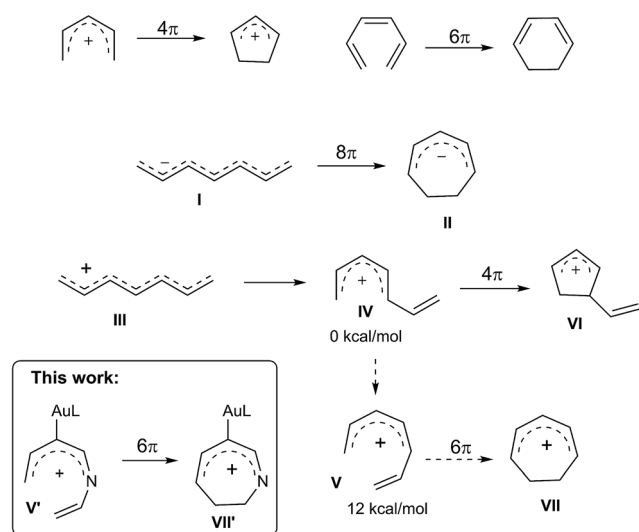
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New gold-catalyzed [4+3]-annulations of 3-en-1-ynamides with isoxazoles afford 4*H*-azepines efficiently; this process involves  $6\pi$  electrocyclizations of gold-stabilized 3-azaheptatrienyl cations. In the presence of  $\text{Zn}(\text{OTf})_2$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

## Introduction

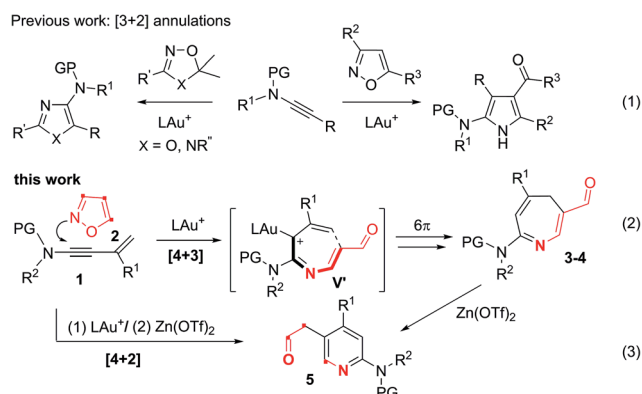
Electrocyclizations of acyclic conjugated  $\pi$ -motifs are powerful tools to access five-, six- and seven-membered carbocycles;<sup>1</sup> prominent examples include Nazarov cyclizations of penta-dienyl cations<sup>2</sup> and  $6\pi$  electrocyclizations of trienes,<sup>3</sup> which have found widespread applications in organic synthesis.

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.

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

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The advent of gold catalysis has inspired new annulations between alkynes and poor nucleophiles.<sup>7</sup> N–O containing nucleophiles serve as useful building blocks to construct valuable azacyclic frameworks.<sup>7</sup> 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)].<sup>7,8</sup> 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)].<sup>9</sup> 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 $\pi$  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.<sup>10</sup>

## 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/AgNTf<sub>2</sub> [L = *p*-(*t*-Bu)<sub>2</sub>(*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/AgNTf<sub>2</sub> gave a clean reaction, yielding desired **3a** up to 91% (entry 4). We tested other phosphine ligands such as PPh<sub>3</sub> and P(OPh)<sub>3</sub>, yielding desired **3a** in satisfactory yields (78–81%, entries 5–6). Other counter anions such as OTf<sup>−</sup> and SbF<sub>6</sub><sup>−</sup> were also effective in producing **3a** in 85–88% yields (entries 7–8). AgNTf<sub>2</sub> alone was not active at all (entry 9).

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

| Entry          | Catalyst [mol%]                                  | x   | Time [h] | Yield <sup>b</sup> [%] |    |              |
|----------------|--------------------------------------------------|-----|----------|------------------------|----|--------------|
|                |                                                  |     |          | 1a                     | 3a | 1a-H'/1a-H'' |
| 1 <sup>c</sup> | LAuCl/AgNTf <sub>2</sub> [5]                     | 2   | 3        | 20                     | 64 | —            |
| 2 <sup>d</sup> | 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           |

<sup>a</sup> [1a] = 0.15 M. <sup>b</sup> Product yields are reported after separation from a silica column. <sup>c</sup> L = *p*-(*t*-Bu)<sub>2</sub>(*o*-biphenyl). <sup>d</sup> 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 <sup>1</sup> , R <sup>2</sup> )                                             | Time [h]                                                        |
|-------|--------------------------------------------------------------------------------|-----------------------------------------------------------------|
| (1)   | R <sup>1</sup> , EWG = CH <sub>3</sub> , Ts ( <b>3b</b> )                      | 3 h, 84%, <b>x-ray</b>                                          |
| (2)   | R <sup>1</sup> , EWG = <i>c</i> -Pr, Ts ( <b>3c</b> )                          | 7 h, 86%                                                        |
| (3)   | R <sup>1</sup> , EWG = Bn, Ts ( <b>3d</b> )                                    | 4.5 h, 87%                                                      |
| (4)   | R <sup>1</sup> , EWG = <i>n</i> -Bu, <i>n</i> -BuSO <sub>2</sub> ( <b>3e</b> ) | 6 h, 90%                                                        |
| (5)   | R <sup>1</sup> , EWG = CH <sub>3</sub> , Ts ( <b>3f</b> )                      | 22 h, 64%                                                       |
| (6)   | R <sup>1</sup> = <i>i</i> -Pr ( <b>3g</b> )                                    | 4 h, 74%                                                        |
| (7)   | R <sup>1</sup> = <i>c</i> -Pr ( <b>3h</b> )                                    | 2 h, 79%                                                        |
| (8)   | R <sup>1</sup> = Ph ( <b>3i</b> )                                              | 2.5 h, 58%                                                      |
| (9)   | R <sup>1</sup> , EWG = <i>n</i> -Bu, Ms ( <b>3j</b> )                          | 5 h, 55%, <b>3j/3j'</b> = 5:1                                   |
| (10)  | R <sup>1</sup> , EWG = CH <sub>3</sub> , Ts ( <b>3k</b> )                      | 4 h, 68%, <b>3k/3k'</b> = 11.1:1                                |
| (11)  | R <sup>1</sup> , EWG = CH <sub>3</sub> , Ts ( <b>3l</b> )                      | 2.5 h, 48%, <b>x-ray</b> ( <b>6l</b> , 43%, <i>E/Z</i> = 3.3:1) |
| (12)  | R <sup>1</sup> , EWG = CH <sub>3</sub> , Ts ( <b>3m</b> )                      | 14 h, 16% ( <b>6m</b> , 73%, <b>x-ray</b> )                     |

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

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

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

<sup>a</sup> [1b] = 0.15 M. <sup>b</sup> Product yields are reported after separation from a silica column.

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.<sup>7</sup> 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 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).

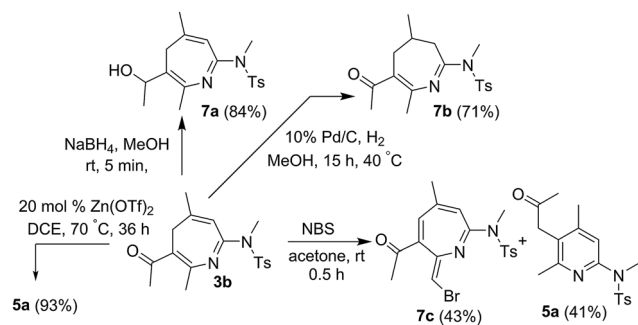
We altered the C(3)-substituents as in substrates **1g–1i**; their resulting products **3g–3h** (R<sup>1</sup> = isopropyl and cyclopropyl) were obtained in 74–79%, and **3i** (R<sup>1</sup> = Ph) with only 58% yield (entries 6–8). Notably, when a long *n*-butyl group was present as in species **1j** 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** (R<sup>1</sup> = Me, R<sup>2</sup> = Ph and R<sup>3</sup> = 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 R<sup>2</sup> or R<sup>3</sup> substituent whereas R<sup>1</sup> must be substituted. Herein, the structures of 4*H*-azepines **3b** and **3l**, and pyrrole species **6m** were confirmed with X-ray diffraction.<sup>11</sup>

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 R<sup>1</sup> = alkyl and phenyl, and R<sup>2</sup> = 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<sup>2</sup> = 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.<sup>11</sup>

Our convenient synthesis of 4*H*-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 4*H*-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 4*H*-azepines **3–4** to substituted pyridines **5** [eqn (3)] is unprecedented in 4*H*-azepine chemistry.<sup>10</sup> We undertook such novel [4+2]-annulations



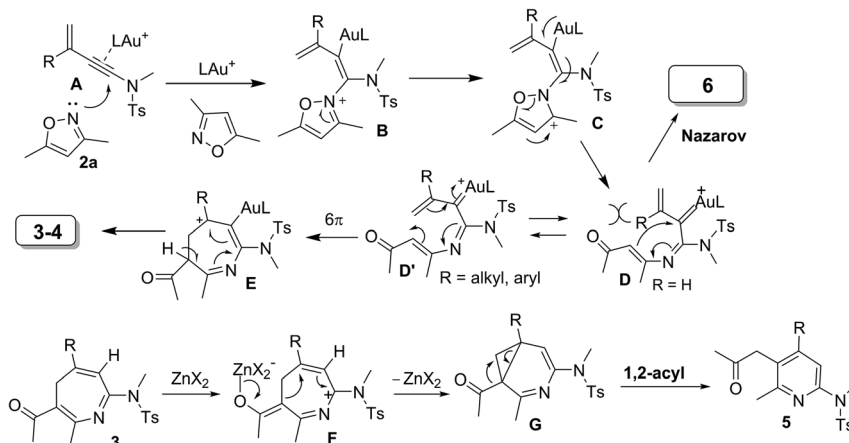
Scheme 2 New functionalization of 4*H*-azepines.

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

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

<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(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.<sup>11</sup>

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- $\pi$ -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.<sup>12</sup> When a C(3)-substituent is present ( $R$  = alkyl and aryl), all  $\sigma$ -*cis* configured species **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 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  $6\pi$  electrocycloization of their triene moieties unless a Lewis acid is present. Zn(OTf)<sub>2</sub> 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 shift<sup>14</sup> of species **G** delivers the observed product **5**.<sup>13</sup>

## Conclusions

In summary, this work describes new gold-catalyzed [4+3] annulations<sup>15</sup> 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  $6\pi$  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.

## Acknowledgements

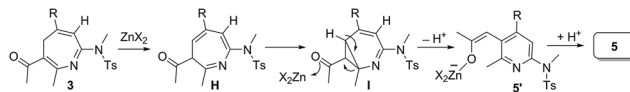
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