

# Gold-Catalyzed Tandem 1,3-Migration/[2 + 2] Cycloaddition of 1,7-Enyne Benzoates to Azabicyclo[4.2.0]oct-5-enes

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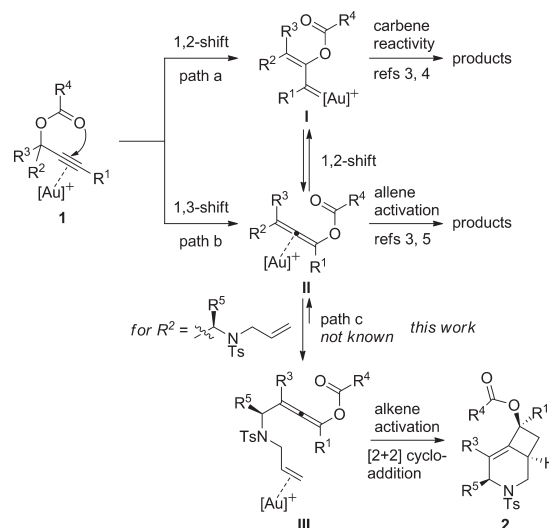
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Supporting Information

**ABSTRACT:** A synthetic method that relies on gold(I)-catalyzed tandem 1,3-migration/[2 + 2] cycloaddition of 1,7-enyne benzoates to prepare azabicyclo[4.2.0]oct-5-enes is described.

Gold-catalyzed 1,*n*-enyne cycloisomerizations offer a highly efficient and atom-economical synthetic strategy for increasing molecular complexity and diversity in a single step.<sup>1–5</sup> The field has seen rapid growth in recent years, with a number of impressive methods for the conversion of 1,*n*-enyne derivatives to various synthetically valuable products being developed. This has hitherto included approaches that make use of easily accessible 1,*n*-enyne derivatives bearing a carboxylic ester at the propargylic position.<sup>3–5</sup> As shown in Scheme 1, the reaction relies on the propensity of the acyloxy moiety to undergo 1,2- or 1,3-migration to give the corresponding gold carbene and allene intermediates I and II that are poised for further functionalization by a remaining pendant group. In the case of 3,3-rearrangements, which DFT calculations have recently shown could also possibly occur via two sequential 1,2-migrations,<sup>5d</sup> allene activation is typically required before further functional group transformations can take place. On the other hand, a tandem process involving 1,3-*O*-ester migration followed by selective coordination of the gold catalyst to an appropriately placed unactivated alkene rather than the allenic moiety is not known (paths b and c in Scheme 1).<sup>6</sup> We anticipated that the gold(I)-coordinated species III generated from this change in selectivity by the metal catalyst might then be more prone to undergo a stepwise [2 + 2] process and provide synthetically useful bicyclic derivatives fused with a cyclobutane ring. To our knowledge, this mode of reactivity is not observed in 1,*n*-enyne cycloisomerizations because other more generally favored skeletal rearrangements occur.<sup>1–5</sup> Added to this is a recent report showing acyloxy-substituted 1,6-enynes derived from dipropargylic amides to be resistant to the gold-catalyzed cycloisomerization process.<sup>7</sup> As part of an ongoing program exploring the scope of gold catalysis in heterocyclic synthesis,<sup>8</sup> we disclose herein the details of this chemistry involving Au(I)-mediated tandem 1,3-migration/[2 + 2] cycloaddition of 1,7-enyne benzoates (Scheme 1). This process delivers a regioselective and stereoconvergent route to azabicyclo[4.2.0]oct-5-enes, a key class of compounds in synthetic and natural product chemistry,<sup>9</sup> that gives the products in good to excellent yields as single regio- and diastereomers. The bicyclic ring adducts could also be obtained as single enantiomers with up to four stereogenic

**Scheme 1. Gold-Catalyzed Reactivities of 1,*n*-Enyne Carboxylates**

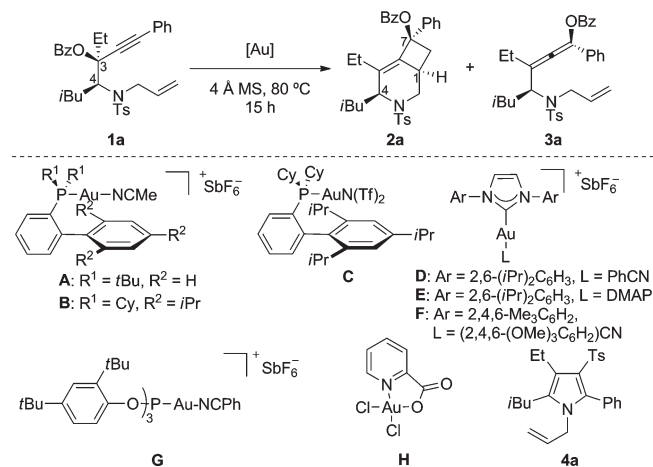


centers, demonstrating the reaction to proceed with efficient transfer of chirality from the enantiopure substrate to the product.

To test the feasibility of our hypothesis, the enantiopure *syn*-1,7-enyne benzoate **1a**, prepared from *L*-leucine following literature procedures,<sup>10</sup> was chosen as the model substrate to establish the reaction conditions (Table 1). The (3*S*,4*S*) absolute configuration of the starting ester was determined by X-ray crystal structure analysis of a precursor of the substrate.<sup>11</sup> This study revealed that treating **1a** with 5 mol % Au(I) catalyst **A** and 4 Å molecular sieves (MS) in (CH<sub>2</sub>Cl)<sub>2</sub> at 80 °C for 15 h gave the best result, furnishing **2a** in 82% yield as a single regio-, diastereo-, and enantiomer (entry 1). The (1*R*,4*S*,7*R*) absolute configuration of the cyclobutane-fused piperidine product was determined by X-ray crystallography.<sup>11</sup> Lower product yields were obtained when the reaction was repeated at room temperature, with the more sterically crowded Au(I) complex **B** or **C** in place of **A** as the catalyst, or in the absence of 4 Å MS (entries 2, 3, 8, and 9).<sup>10</sup> The reaction at room temperature also afforded allenene **3a** in 48% yield (entry 3).<sup>12</sup> In marked contrast, only the allenene was obtained in 77–95% yield when the solvent was changed from (CH<sub>2</sub>Cl)<sub>2</sub> to either MeCN, MeNO<sub>2</sub>, 1,4-dioxane, or toluene (entries 4–7). A survey of other Au(I) and Au(III) complexes as

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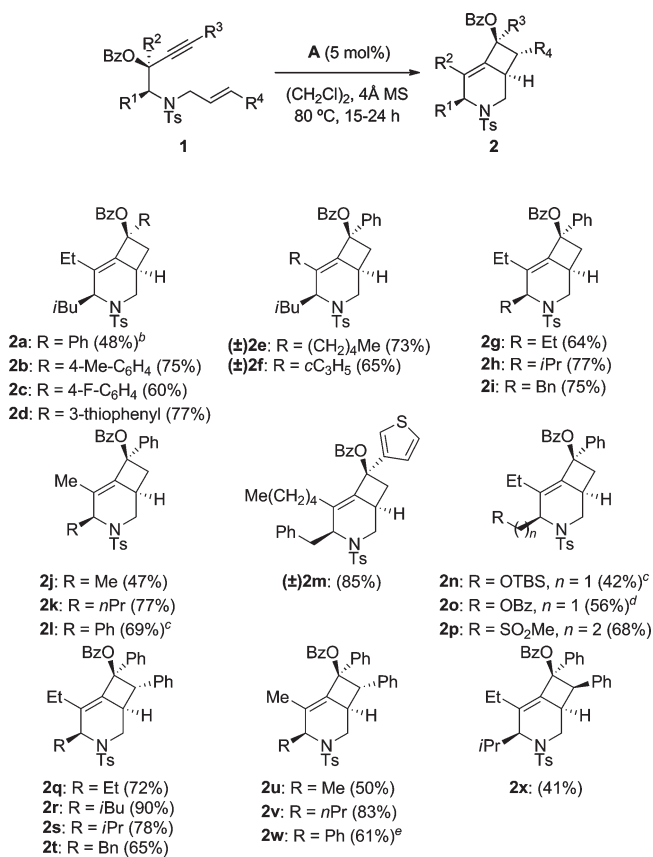
Table 1. Optimization of the Reaction Conditions<sup>a</sup>

entry	catalyst	solvent	yield (%) <sup>b</sup>	
			2a	3a
1	A	(CH <sub>2</sub> Cl) <sub>2</sub>	82	—
2 <sup>c</sup>	A	(CH <sub>2</sub> Cl) <sub>2</sub>	53	—
3 <sup>d</sup>	A	(CH <sub>2</sub> Cl) <sub>2</sub>	44	48
4	A	MeCN	—	95
5	A	1,4-dioxane	—	88
6	A	MeNO <sub>2</sub>	—	80
7	A	PhMe	—	77
8	B	(CH <sub>2</sub> Cl) <sub>2</sub>	69	—
9	C	(CH <sub>2</sub> Cl) <sub>2</sub>	68	—
10	D	(CH <sub>2</sub> Cl) <sub>2</sub>	—	29 <sup>e</sup>
11	E	(CH <sub>2</sub> Cl) <sub>2</sub>	—	93
12	F	(CH <sub>2</sub> Cl) <sub>2</sub>	—	86
13	G	(CH <sub>2</sub> Cl) <sub>2</sub>	—	83
14	Ph <sub>3</sub> PAuNTf <sub>2</sub>	(CH <sub>2</sub> Cl) <sub>2</sub>	—	88
15	H	(CH <sub>2</sub> Cl) <sub>2</sub>	—	95
16	AuBr <sub>3</sub>	(CH <sub>2</sub> Cl) <sub>2</sub>	—	63
17	PtCl <sub>2</sub>	(CH <sub>2</sub> Cl) <sub>2</sub>	—	96

<sup>a</sup> All reactions were performed on a 0.15 mmol scale with a catalyst:**1a** ratio of 1:20 and 4 Å MS (150 mg) at 80 °C for 15 h. <sup>b</sup> Isolated yields. <sup>c</sup> The reaction was carried out in the absence of 4 Å MS. <sup>d</sup> The reaction was carried out at room temperature for 30 h. <sup>e</sup> Pyrrole **4a** was obtained in 20% yield.

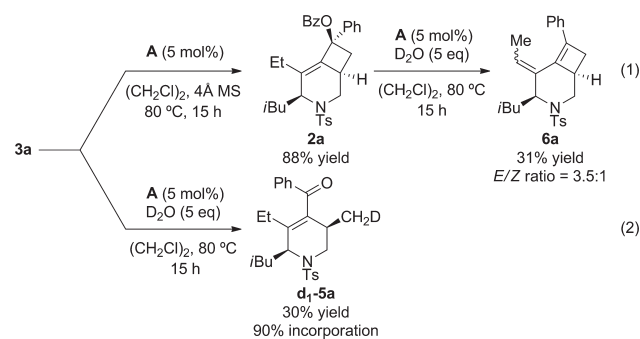
well as PtCl<sub>2</sub> as the catalyst gave similar outcomes (entries 10–17). In all but one of these latter experiments, the allenene adduct was again obtained in 63–96% yield. In our hands, the analogous reaction of **1a** with gold(I) carbene complex **D** as the catalyst was the only instance that afforded the pyrrole byproduct **4a** along with **3a**, in 20 and 29% yield, respectively (entry 10).<sup>10</sup> The structure of the aromatic N-heterocycle was structurally confirmed by X-ray crystallographic analysis.<sup>11</sup>

With the optimal conditions in hand, we next sought to evaluate their generality for a series of 1,7-enyne benzoates prepared from the corresponding *L*-α-amino acids, and the results are summarized in Table 2. These experiments showed that with the Au(I) complex **A** as the catalyst, the conditions proved to be broad, and a variety of highly substituted azabicyclo[4.2.0]oct-5-enes could be obtained in 41–90% yield from the corresponding substrates **1b–x**. This hitherto included starting 1,7-enynes containing a thiophene, cyclopropane, OTBS, or MeSO<sub>2</sub> moiety (**1d** and **1m**, **1f**, **1n**, and

Table 2. Tandem 1,3-Migration/[2 + 2] Cycloaddition of 1,7-Enyne Benzoates **1b–x** Catalyzed by **A**<sup>a</sup>

<sup>a</sup> All reactions were performed on a 0.15 mmol scale with an **A**:**1** ratio of 1:20 and 4 Å MS (150 mg) at 80 °C for 15–24 h. Values in parentheses denote isolated product yields. <sup>b</sup> The reaction was conducted with (3*R*,4*S*)-**1a** and 10 mol % **A**. <sup>c</sup> The reaction was conducted with an inseparable 1:1 mixture of diastereomers of the substrate. <sup>d</sup> The reaction was conducted with an inseparable 4:1 mixture of diastereomers of the substrate. <sup>e</sup> The reaction was conducted with an inseparable 3.3:1 mixture of diastereomers of the substrate.

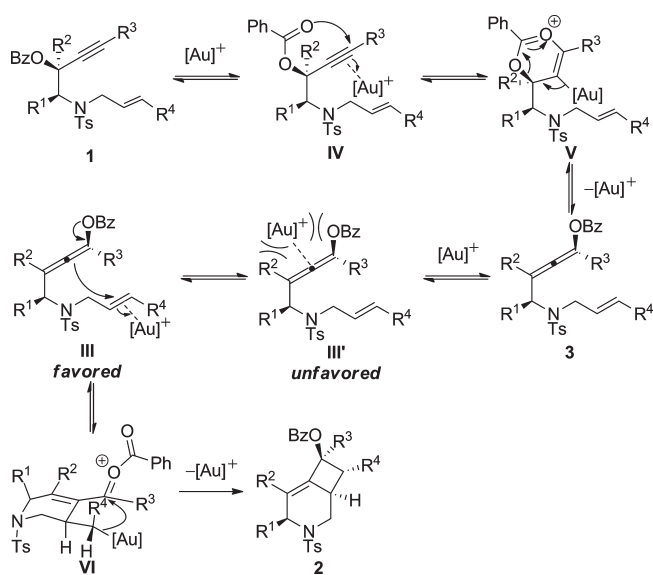
**1p**, respectively), showing that such functional groups were well-tolerated under the reaction conditions. Similarly, reactions of substrates containing an activated alkene moiety (**1q–x**) were found to proceed well and provide the corresponding bicyclic adducts in excellent yields. More notably, these intramolecular cyclizations also demonstrated that the ring-forming process occurs in a highly selective manner. We found the [2 + 2] cycloaddition step to occur regioselectively at the distal 2π component of the in situ-formed allene moiety, affording the cyclobutane-fused piperidine as the sole product in all of the reactions shown in Table 2. The pyrrolidine regioisomer resulting from [2 + 2] cycloaddition at the proximal 2π component of the in situ-formed allene moiety was not observed using NMR analysis of the crude reaction mixtures.<sup>13</sup> The reaction was additionally shown to give the corresponding products as single diastereomers irrespective of whether it started from a single isomer or a diastereomeric mixture of the substrate. In the case of reactions with **1b–d**, **1g–k**, and **1p–x**, the corresponding adducts were also furnished as single enantiomers with up to four stereogenic centers, illustrating efficient transfer of chirality from the enantiopure substrate to the bicyclic product. Moreover, the formation of cyclobutane-fused piperidines as single diastereomers from

Scheme 2. Control Experiments with **2a** and **3a** Catalyzed by **A**

stereoisomeric starting 1,7-enynes that presumably were epimeric at C3 (**1l**, **1n**, **1o**, and **1w**) showed that the transformation is stereoconvergent. This was further exemplified by the Au(I)-catalyzed reaction of (3*R*,4*S*)-**1a**, which also provided (1*R*,4*S*,7*R*)-**2a** in 48% yield. On the other hand, the stereochemistry of the alkene moiety was found to be retained in the product. Substrates containing a *trans*-alkene group (**1q–w**) were found to give the corresponding bicyclo[4.2.0] adducts having the bridgehead proton and R<sup>4</sup> group *syn* with respect to each other. In contrast, the reaction of **1x** with a pendant *cis*-alkene moiety gave **2x**, in which the stereochemical relationship between these groups in the product was *anti* and epimeric at C8. The absolute configurations (1*R*,4*S*,7*R*) for **2b** and **2i**, (1*R*,4*S*,7*R*,8*S*) for **2r**, and (1*R*,4*R*,7*R*,8*R*) for **2x** were determined on the basis of X-ray crystal structure measurements.<sup>11</sup> Similarly, the relative *syn* diastereochemistry of **2m** was determined by X-ray crystallography.<sup>11</sup>

The mechanistic premise presented in Scheme 1 predicts that the Au(I)-catalyzed cycloisomerization proceeds through a tandem 3,3-rearrangement/[2 + 2] cycloaddition pathway involving an allenene intermediate. While the isolation of allenene **3a** produced by reactions of **1a** under various conditions as described in entries 3–7 and 10–17 in Table 1 was fortuitous, the result argues in favor of this being the actual intermediate in the Au(I)-catalyzed transformation. This argument is further corroborated by the fact that **2a** was furnished in 88% yield when a (CH<sub>2</sub>Cl)<sub>2</sub> solution containing **3a** was treated with 5 mol % Au(I) complex **A** under the conditions depicted in eq 1 in Scheme 2. The role of the gold(I) catalyst in triggering the stepwise [2 + 2] cycloaddition by preferentially coordinating to the unactivated alkene moiety was also shown by first repeating the reaction in the absence of the metal catalyst. This test led to recovery of only the starting allenene in nearly quantitative yield, mirroring the lack of reactivity observed in thermal [2 + 2] cycloadditions of allenenes containing an unactivated alkene moiety.<sup>14</sup> Moreover, conducting the reaction again for a second time with the gold(I) catalyst in the presence of D<sub>2</sub>O provided *cis*-piperidine **d**<sub>1</sub>-**5a** in 30% yield with 90% deuterium incorporation (eq 2 in Scheme 2). On the other hand, resubjecting **2a** to these latter conditions with the gold(I) catalyst and D<sub>2</sub>O was found to give the debenzoylated product **6a** in 31% yield (eq 1 in Scheme 2).

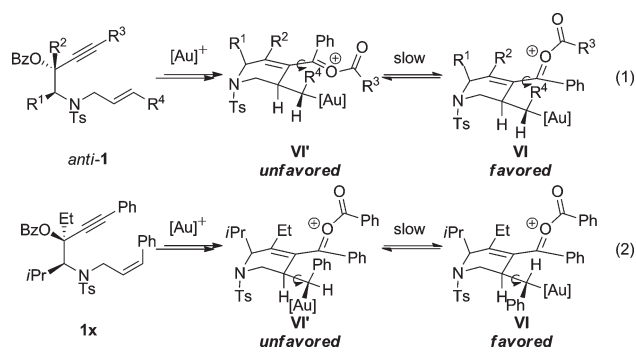
A tentative mechanism for the present Au(I)-catalyzed reaction to form cyclobutane-fused piperidines is outlined in Scheme 3. This could involve activation of the alkyne moiety of the 1,7-enyne substrate by the gold(I) catalyst, resulting in *syn* 1,3-migration of the carboxylic ester group and formation of allenene **3** via **IV** and **V**. To avoid unfavorable steric interactions between the gold complex and the substituents on the allene moiety, it is possible that the catalyst then selectively coordinates to the alkene bond of this newly formed

Scheme 3. Tentative Mechanism for Tandem 1,3-Migration/[2 + 2] Cycloaddition of **1** Catalyzed by **A**

allenene intermediate to give gold-activated adduct **III**. This is the active species that undergoes the stepwise [2 + 2] cycloaddition process involving *anti* addition of the allenic group to the gold-coordinated alkene moiety to give piperidine adduct **VI**.<sup>15</sup> Subsequent nucleophilic addition of the Au–C(sp<sup>3</sup>) bond to the carbonyl carbon center of the benzoyl cationic moiety generated from this initial intramolecular cyclization step would then deliver **2** with release of the gold(I) catalyst.<sup>16</sup> The pyrrole byproduct **4a** could originate from coordination of the gold catalyst to the alkyne unit in **1** or the allene moiety in **3** followed by nucleophilic attack of the tethered sulfonamide moiety and a deauration step involving 1,3-migration of the Ts group.<sup>17</sup> We surmise that the obtained product regioselectivities result from the greater electron-donating ability of the OBz moiety relative to that of the R<sup>2</sup> group in **3**. This would consequently make the distal 2*π* component of the allene side chain more nucleophilic in character and therefore more likely to take part in the first step of the [2 + 2] cycloaddition. The observed stereoconvergence leading to a single diastereomer regardless of the stereochemistry at C3 in the substrate could be due to the oxonium species adopting the conformation shown in Scheme 3. This would provide optimal orbital alignment and thus overlap between the HOMO of the Au–C(sp<sup>3</sup>) bond and the LUMO of the carbonyl carbon center, enabling the second C–C bond-forming step of the [2 + 2] cycloaddition to proceed efficiently. It would also explain the lower reactivities observed in reactions with the *anti* isomer of **1a** and substrates containing this diastereomer (**1l**, **1n**, **1o**, and **1w**), since the close proximity of the bulky alkyl gold side chain could significantly restrict the rotational freedom of the benzoyl C–C bond (eq 1 in Scheme 4). A similar rationale could be applied to account for the preferential nucleophilic attack of the Au–C(sp<sup>3</sup>) bond from below the plane of the benzoyl moiety and the moderate product yield obtained for the reaction of **1x** containing a *cis*-alkene unit (eq 2 in Scheme 4). The formation of the product as a single enantiomer from an enantiopure substrate additionally suggests that neither the starting material nor any of the putative intermediates are prone to racemization. This consequently allows efficient transfer of the retained chirality at the  $\alpha$ -carbon center to the amino group, giving the enantioselectivities observed at the newly formed stereogenic centers.



**Scheme 4. Possible Conformational States for Tandem 1,3-Migration/[2 + 2] Cycloaddition of 1 Catalyzed by A**



In summary, we have demonstrated gold(I)-catalyzed tandem 1,3-migration/[2 + 2] cycloaddition of 1,7-enyne benzoates to be a regioselective and stereoconvergent strategy for the construction of highly functionalized azabicyclo[4.2.0]oct-5-enes. The reaction has been shown to tolerate a diverse set of 1,7-enyne substrates and furnish stereochemically well-defined cyclobutane-fused piperidines for applications in natural product synthesis and as versatile privileged scaffolds in medicinal chemistry. Our studies suggest that when allene activation is not possible in 1,*n*-enyne cycloisomerizations involving a 1,3-migration step, the gold catalyst preferentially coordinates to the alkene moiety. This results in bicyclic ring formation via a [2 + 2] cycloaddition pathway, which is not typically favored in 1,*n*-enyne cycloisomerizations. Efforts to study this mechanistic dichotomy further and explore the scope and synthetic applications of the present reaction are in progress and will be reported in due course.

## ■ ASSOCIATED CONTENT

**Supporting Information.** Experimental procedures, characterization data, crystal structure data (CIF), and complete ref S5 and 9a. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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## ■ ACKNOWLEDGMENT

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