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Gold(I)-Catalyzed Cascade Cyclization Reactions of Allenynes for the Synthesis of Fused Cyclopropanes and Acenaphthenes

Takaya Ikeuchi, Shinsuke Inuki, Shinya Oishi, Hiroaki Ohno*

Abstract: Gold-catalyzed reaction of phenylene-tethered allenynes with a benzofuran gave 1-(naphth-1-yl)cyclopropan[b]benzofuran derivatives, whereas the reaction of 1-allenyl-2-ethynyl-3-methylbenzene derivatives in the absence of benzofurans gave acenaphthenes in good yields. These results can be rationalized by nucleophilic attack of the alkyne moiety to an activated allene to form a vinyl cation intermediate.

Gold catalysis has emerged as a powerful tool for electrophilic activation of carbon–carbon multiple bonds to promote nucleophilic reactions under mild conditions.[1] Allenes are well known as versatile building blocks for the construction of cyclic compounds by gold-catalyzed reactions.[2] Intramolecular reaction of allenynes with a heteronucleophile such as nitrogen, oxygen, or sulfur derivatives are highly useful for the synthesis of a variety of heterocyclic compounds, including dihydropyrroles, dihydrofurans, and dihydrothiophenes. Allenynes undergo various types of carbocyclizations including [2+2], [2+3], and [4+3]-type reactions,[3] proceeding through formation of allylic cation species. However, the gold-catalyzed cyclization of allenynes is relatively undeveloped. Two reaction modes are possible for gold-catalyzed intramolecular carbocyclization of allenynes: (1) the allene functions as a nucleophile to form an allylic cation species (Scheme 1A)[6] and (2) the alkyne functions as a nucleophile to form a vinyl cation species (Scheme 1B).[7] In both cases, the reactions are terminated by nucleophilic attack or deprotonation. It should be noted that a gold(I)-catalyzed cascade cyclization of allenynes by contiguous formation of carbon–carbon bonds via vinyl cation formation has not yet been achieved.[8]

Recently, we investigated gold-catalyzed cascade cyclizations of substrates bearing several alkynes.[8] As part of an ongoing program directed toward the development of efficient carbocyclization reactions, we designed a carbocyclization of allenynes that terminates with a carbon–carbon bond formation. Our approach is shown in Scheme 1C. Activation of allene 1 would generate vinyl cation intermediate A[10] via nucleophilic attack of the alkyne moiety on the activated allene. Intermediate A would then be trapped by a heteroarene such as benzofuran to give naphthalene derivative 2 or 3. During the course of this study, we found that the 3-methyl congener 1’ underwent a second intramolecular carbon–carbon bond formation to give acenaphthenes 4 without forming 2 or 3. In this paper, we report gold-catalyzed cyclizations of allenynes to form naphthalene-fused cyclopropanes 2 and acenaphthenes 4, depending on the substrate structure.

We chose allene 1a as the model substrate and investigated the reaction with benzofuran 5a as the nucleophile (Table 1). The reaction of 1a and 5a with 5 mol % JohnPhosAuCl/AgNTf2 in dichloromethane (DCM) at room temperature gave fused cyclopropane 2aa bearing a naphthyl group in 47% yield as the sole stereoisomer (entry 1). The NOE analysis of 2aa revealed that the naphthyl group is located at the convex face of the fused cyclopropane (see the Supporting information). Among the catalysts examined (entries 2–12), BrettPhosAuNTf2 provided the highest yield of 2aa (63%, entry 12). Alternative solvents, such as toluene, MeCN, THF, and iPrOH were not effective, nor was the addition of HFIP or iPrOH as a proton source (Table S1 in the Supporting information). As a result of further investigations into the substrate concentration and reaction temperature (Table S1), the reaction proceeded...
most effectively at 0.5 M and 0 °C (entry 13) to give 2aa in 78% isolated yield on a 1.0 mmol scale.

Table 1. Optimization of the reaction conditions for cyclopropanation.

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<tbody>
<tr>
<td>1</td>
<td>JohnPhosAuCl/AgNTf₂</td>
<td>2</td>
<td>47</td>
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<tr>
<td>2</td>
<td>CyJohnPhosAuCl/AgNTf₂</td>
<td>3</td>
<td>42</td>
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<tr>
<td>3</td>
<td>iPrAuCl/AgNTf₂</td>
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<tr>
<td>4</td>
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<tr>
<td>5</td>
<td>PPh₃AuCl/AgNTf₂</td>
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<td>6</td>
<td>74</td>
</tr>
<tr>
<td>6</td>
<td>BisPhePhosAuCl/AgNTf₂</td>
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<td>42</td>
<td>–</td>
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<tr>
<td>7</td>
<td>XPhosAuCl/AgNTf₂</td>
<td>2</td>
<td>56</td>
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<tr>
<td>8</td>
<td>BrettPhosAuCl/AgNTf₂</td>
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<td>60</td>
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<tr>
<td>9</td>
<td>BrettPhosAuCl/AgSbF₆</td>
<td>1</td>
<td>61</td>
<td>–</td>
</tr>
<tr>
<td>10</td>
<td>BrettPhosAuCl/AgOTf</td>
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<td>13</td>
<td>27</td>
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<td>11</td>
<td>BrettPhosAu(NeCN)SbF₆</td>
<td>2</td>
<td>60</td>
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</tr>
<tr>
<td>12</td>
<td>BrettPhosAuNTf₂</td>
<td>1</td>
<td>63</td>
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</tr>
<tr>
<td>13[b]</td>
<td>BrettPhosAuNTf₂</td>
<td>9</td>
<td>74 (78)</td>
<td>–</td>
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</table>

[a] The ligand structures are shown above. [b] Determined by ¹H NMR analysis. Yield in parenthesis is the isolated yield on a 1.0 mmol scale. [c] Reaction was conducted at 0.5 M concentration at 0 °C. Recov. = recovery of starting material.

With the optimized conditions in hand (Table 1, entry 13), we investigated the scope of the cyclopropanation reaction (Table 2). The use of benzofuran with an electron-withdrawing (Br) or donating group (OMe) at the 5-position resulted in formation of the desired products 2ab and 2ac in moderate yields (55% and 67%, respectively). The structure of 2ab was confirmed by X-ray crystallography (see the Supporting information).[11] Indoles protected by a Boc or Ts group also worked well as the nucleophile to provide the corresponding cyclopropane-fused indoles 2af (74%) and 2ae (79%), respectively. Unfortunately, the use of benzothiophene in the reaction gave 2af in poor yield (21%).[12] Next, the scope of the allenynes 1 was examined. Substrates bearing a cyano group on the phenylene tether only produced, if any, a small amount of the desired products (2ba, 2fa, and 2ja)[13] while allenynes substituted with an electron-withdrawing chloro substituent were smoothly transformed to the fused cyclopropanes 2ea and 2ia in high yields (93–94%). Electron-donating substituents on the phenylene tether (Me and OMe) at the meta or para position to the alkyn were tolerated in the reaction, although a small decrease in yields was observed in some cases (2ca, 2da, 2ga and 2ha; 54–81%). Additionally, when using allenynes bearing a substituent (p-OMe, p-Cl, or o-Me) on the phenyl group at the alkyn terminus, the desired products (2ka–2ma) were obtained in good yields. When a methyl group was present at the ortho position of the alkyn, change of reaction mode was observed (no formation of cyclopropane 2aa but of acenaphthene, vide infra).

Table 2. Scope of the cyclopropanation reaction.[a]

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<tr>
<td>1</td>
<td>1a</td>
<td>2</td>
<td>78</td>
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<tr>
<td>2</td>
<td>1b</td>
<td>2</td>
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<td>3</td>
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<td>7</td>
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<td>8</td>
<td>1h</td>
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<td>2</td>
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<td>10</td>
<td>1j</td>
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<td>11</td>
<td>1k</td>
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<td>79</td>
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<tr>
<td>12</td>
<td>1l</td>
<td>2</td>
<td>78</td>
<td>–</td>
</tr>
<tr>
<td>13</td>
<td>1m</td>
<td>2</td>
<td>79</td>
<td>–</td>
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</tbody>
</table>

[a] Isolated yields. [b] Containing small amounts of impurities. [c] The reaction was conducted at room temperature. [d] Acenaphthene 4a was produced in 85% yield (vide infra). [e] No reaction. [f] A complex mixture of unidentified products was observed.

Our mechanistic proposal for the cyclopropane formation is shown in Scheme 2. The allene moiety of 1a is activated by a cationic gold catalyst to give gold complex 1a-Au⁺, followed by intramolecular nucleophilic attack by the alkyn to form a vinyl cation intermediate A.[10] Nucleophilic attack of benzofuran 5a on the cationic carbon then leads to the formation of adduct B, if the C2 attack of benzofuran is favored over C3. Finally,
cyclopropane formation accompanying aromatization and protodeauration results in the formation of the fused cyclopropane 2aa. Exclusive production of the stereoisomer where the naphthalene ring is present at the convex face of the fused ring can be rationalized as shown in Scheme 3. The Z isomer of the intermediate B has two possible conformations for cyclopropanation, (Z)-B1 and (Z)-B2. Conformation (Z)-B2 would lead to 2aa', which was not observed in any of the reactions, presumably owing to steric repulsion between the benzene ring of the benzo[1,2-]

As described above, we found that the allenyne 1'a bearing a methyl group at the ortho position to the alkynyl group gave acenaphthene 4a without forming a fused cyclopropane. The structure of 4a was confirmed by X-ray crystallography (Table 3).[11] Considering this interesting reaction which involved C(sp²)-H bond functionalization of a benzylic methyl group to form a carbon–carbon bond, we next focused our attention to the acenaphthene formation. Screening of gold catalysts in DCM at room temperature revealed that BrettPhosAuNTf₂ also exhibited the highest activity for this reaction (Table S2 in the Supporting Information). Using the optimized conditions, the reaction scope was briefly investigated (Table 3). Allenynes 1' bearing an electron-donating group (OMe, Me), halogen, or ester group at the para position of the terminal benzene ring reacted smoothly to afford the corresponding acenaphthenes 4b–4d, and 4f. Similar to the cyclopropanation reaction, no acenaphthene was produced using the cyano-substituted allene 1'e.[13] The position of the methyl group on the terminal benzene ring did not affect the reaction significantly, and produced the desired products 4c, 4g and 4h in good yields (82–92%). Alkyl groups at the alkyne terminus (substituent R₂) were well tolerated to produce acenaphthenes 4i–4k. When using ethyl-substituted allene 1f, the reaction proceeded without stereoselectivity to give 4l as a mixture of diastereomers (trans: cis = 52:48).

<table>
<thead>
<tr>
<th>Table 3. Scope of the acenaphthene formation</th>
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<tr>
<td>R¹</td>
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<tr>
<td>-----</td>
</tr>
<tr>
<td>nBu</td>
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<tr>
<td>Bn</td>
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<td>Me</td>
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<td>Me</td>
</tr>
<tr>
<td>Me</td>
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</tbody>
</table>

[a] Isolated yields. [b] A complex mixture of unidentified products was obtained. [c] Using silylated substrate and TBAF treatment after completion. [d] Determined by 'H NMR analysis.

A plausible reaction mechanism is shown in Scheme 4. Coordination of a cationic gold complex to the allene moiety of 1'a gives complex 1'a·Au+. Nucleophilic cyclization from the alkynyl forms vinyl cation intermediate A', similar to the cyclopropanation reaction.[10] The neighboring methyl group at the o-position facilitates the subsequent 1,5–H shift to produce a benzyl cation intermediate B'.[14,15] Finally, aromatization and
Functionalization • cascade reaction currently underway in our laboratory.

Standard conditions gave the corresponding acenaphthene of deuterium content.

Acknowledgements

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Keywords: gold catalysis • allene • cyclopropanation • C-H functionalization • cascade reaction


Scheme 5. Isotopic labeling experiment.

In conclusion, we have developed a gold(I)-catalyzed cyclization of allenes that terminates with a carbon–carbon bond formation for the construction of naphthalene-substituted fused cyclopropanes and acenaphthenes. These results can be explained by the formation of a vinyl cation intermediate via intramolecular nucleophilic attack of an alkene on the activated allene, followed by cyclopropanation or 1,5-H shift. Studies directed towards further determination of the reaction mechanism as well as application to π-conjugated molecules are currently underway in our laboratory.


[15] C-H insertion mechanism would be another possible reaction pathway, see ref. 14d.
One golden stone, two birds:
Reaction of phenylene-tethered allenynes with a benzofuran gave 1-(naphth-1-yl)cyclopropa[b]benzofuran derivatives, whereas the reaction of 1-allenyl-2-ethynyl-3-methybenzene derivative in the absence of benzofuran gave acenaphthenes, both via vinylcation intermediates.