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Citation	Angewandte Chemie - International Edition (2019), 58(23): 7792-7796
Issue Date	2019-6-3
URL	http://hdl.handle.net/2433/241629
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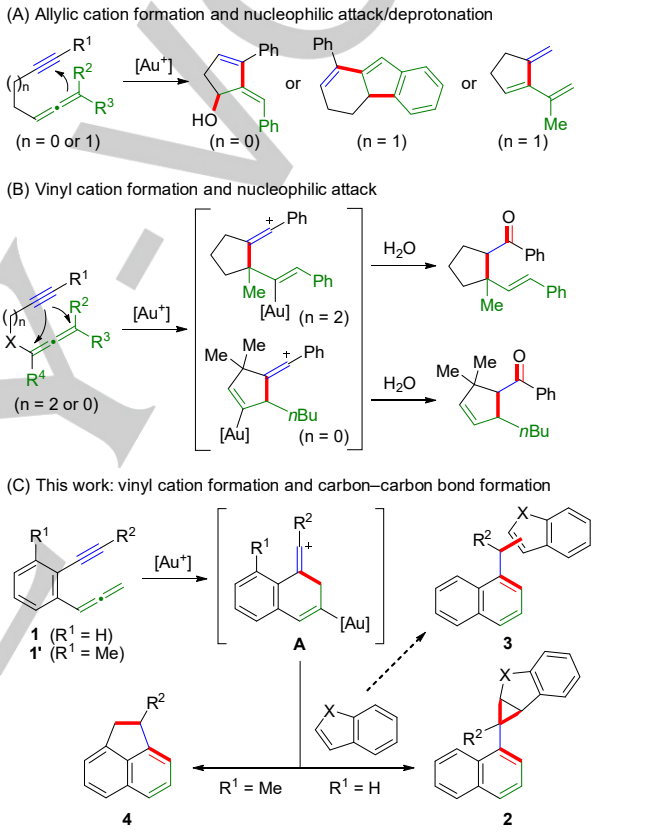
Gold(I)-Catalyzed Cascade Cyclization Reactions of Allenynes for the Synthesis of Fused Cyclopropanes and Acenaphthenes

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

Abstract: Gold-catalyzed reaction of phenylene-tethered allenynes with a benzofuran gave 1-(naphth-1-yl)cyclopropa[*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 allenes 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. Allenenes undergo various types of carbocyclizations including [2+2]-,[3] [2+3]-,[4] and [4+3]-type reactions,[5] proceeding through formation of alkyl 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.[9] As a 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 allenyne **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.



Scheme 1. Related research and this work.

We chose allenyne **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/$AgNTf_2$ 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), BrettPhosAuNTf$_2$ provided the highest yield of **2aa** (63%, entry 12). Alternative solvents, such as toluene, MeCN, THF, and *i*PrOH were not effective, nor was the addition of HFIP or *i*PrOH 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

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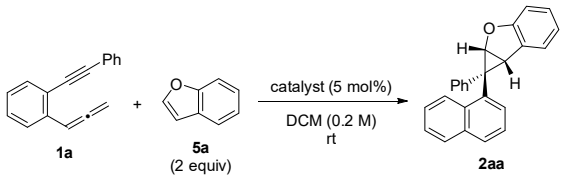
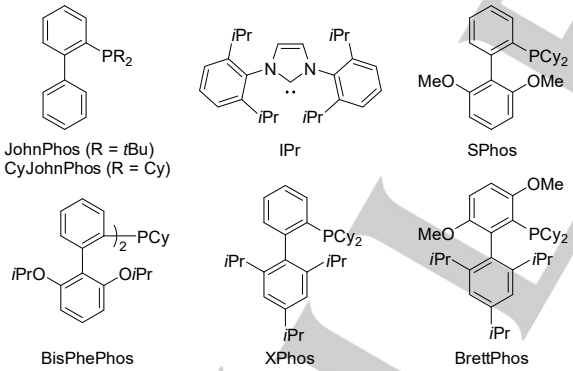
Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under: https://doi.org/10.1002/anie.201903384.

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.



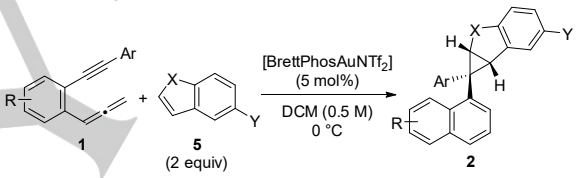
Entry	Catalyst[a]	Time [h]	Yield [%][b]	Recov. [%][b]
1	JohnPhosAuCl/AgNTf$_2$	2	47	–
2	CyJohnPhosAuCl/AgNTf$_2$	3	42	–
3	IPrAuCl/AgNTf$_2$	2	37	–
4	SPhosAuCl/AgNTf$_2$	24	29	19
5	PPh$_3$AuCl/AgNTf$_2$	24	6	74
6	BisPhePhosAuCl/AgNTf$_2$	1	42	–
7	XPhosAuCl/AgNTf$_2$	2	56	–
8	BrettPhosAuCl/AgNTf$_2$	1	60	–
9	BrettPhosAuCl/AgSbF$_6$	1	61	–
10	BrettPhosAuCl/AgOTf	24	13	27
11	BrettPhosAu(MeCN)SbF$_6$	2	60	–
12	BrettPhosAuNTf$_2$	1	63	–
13[c]	BrettPhosAuNTf$_2$	9	74 (78)	–

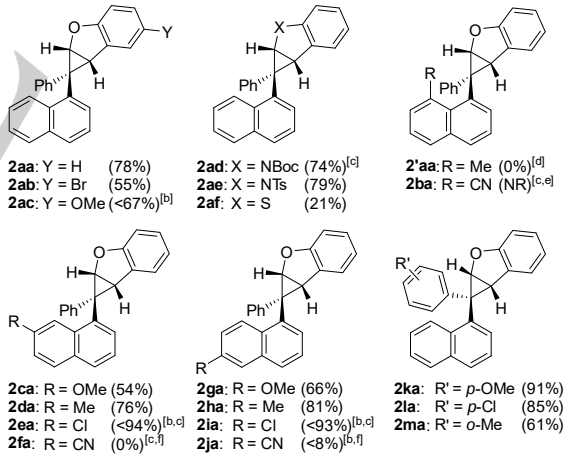


[a] The ligand structures are shown above. [b] Determined by ^{1}H NMR analysis. Yield in parenthesis is the isolated yield on a 1.0 mmol scale. [c] Reaction was conducted at 0.5 M concentration at 0 °C. Recov. = recovery of starting material.

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 **2ad** (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 alkyne 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 alkyne terminus, the desired products (**2ka**–**2ma**) were obtained in good yields. When a methyl group was present at the *ortho* position of the alkyne, change of reaction mode was observed (no formation of cyclopropane **2'aa** but of acenaphthene, *vide infra*).

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

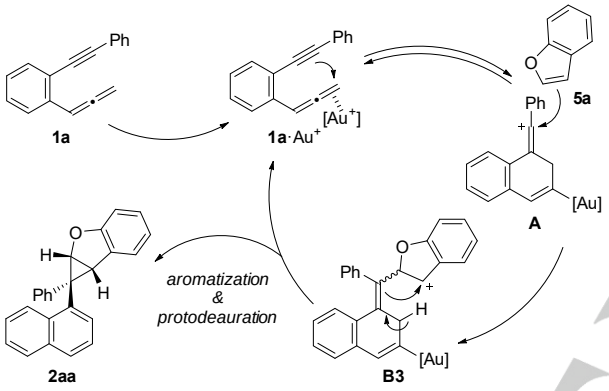




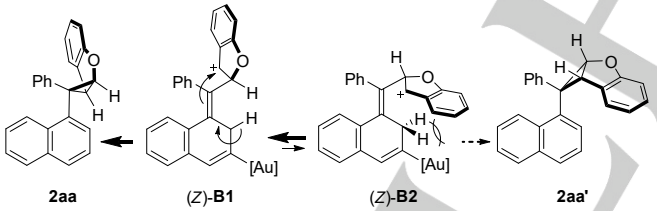
[a] Isolated yields. [b] Containing small amounts of impurities. [c] The reaction was conducted at room temperature. [d] Acenaphthene **4a** was produced in 85% yield (*vide infra*). [e] No reaction. [f] A complex mixture of unidentified products was observed.

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 alkyne 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 benzofuran and the hydrogens of the dihydronaphthalene. Therefore, the cyclopropanation selectively proceeds through the favorable conformation (*Z*)-**B1** resulting in exclusive formation of **2aa**. Similarly, the *E* isomer of the intermediate **B** would stereoselectively provide the same isomer **2aa** for steric reasons (see Scheme S1 in the Supporting information).



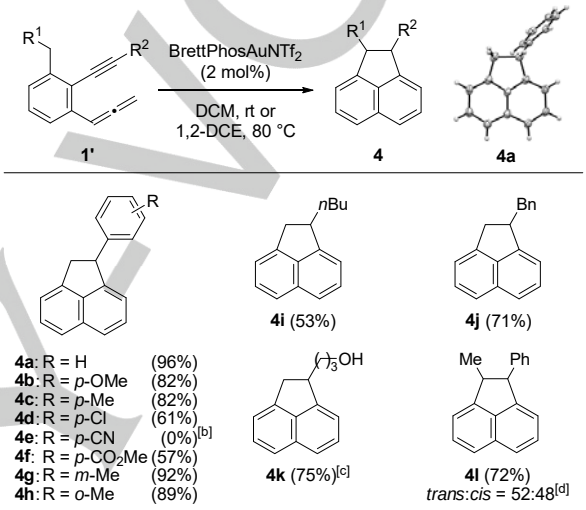
Scheme 2. Proposed reaction mechanism for the cyclopropanation reaction.



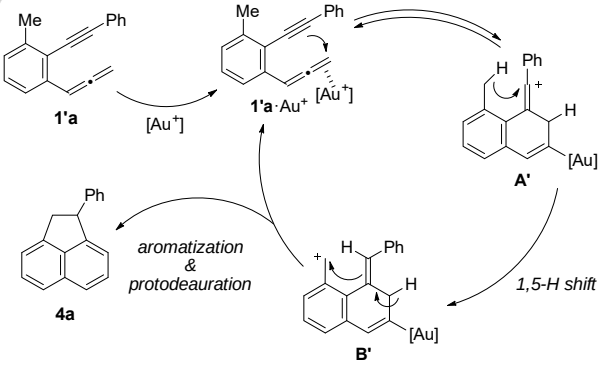
Scheme 3. Rationalization of the observed stereoselectivity.

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(sp^3)–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 BrettPhosAuNTf$_2$ 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 allenyne **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 R^2) were well tolerated to produce acenaphthenes **4i**–**4k**. When using ethyl-substituted allenyne **1'l**, the reaction proceeded without stereoselectivity to give **4l** as a mixture of diastereomers (*trans*:*cis* = 52:48).

Table 3. Scope of the acenaphthene formation.[a]



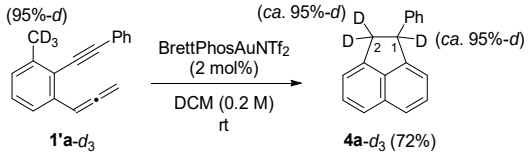
[a] Isolated yields. [b] A complex mixture of unidentified products was obtained. [c] Using silylated substrate and TBAF treatment after completion. [d] Determined by ^{1}H NMR analysis.



Scheme 4. Proposed reaction mechanism for the acenaphthene formation.

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 alkyne 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

protodeauration results in the formation of **4a**. This proposal is supported by a deuterium labelling experiment (Scheme 5). Reaction of the deuterated substrate **1'a**-d_3 (95%-*d*) under the standard conditions gave the corresponding acenaphthene **4a**-d_3 bearing deuterium atoms at the 1-and 2-positions without a loss of deuterium content.



Scheme 5. Isotopic labeling experiment.

In conclusion, we have developed a gold(I)-catalyzed cyclization of allenynes 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 alkyne 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.

Acknowledgements

This work was supported by the JSPS KAKENHI (Grant Numbers JP15KT0061, JP17H03971, and JP18H04408), Basis for Supporting Innovative Drug Discovery and Life Science Research (BINDS, JP18am0101092j0001) from AMED, Japan, and the Hoansha Foundation.

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

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[11] CCDC 1900611 (**2ab**) and 1900610 (**4a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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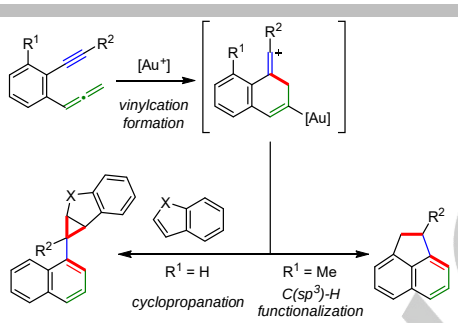
[15] C-H insertion mechanism would be another possible reaction pathway, see ref. 14d.

Entry for the Table of Contents

COMMUNICATION

One golden stone, two birds: Reaction of phenylene-tethered allenynes with a benzofuran gave 1-(naphth-1-yl)cyclopropa[*b*]benzo-furan derivatives, whereas the reaction of 1-allenyl-2-ethynyl-3-methybenzene derivative in the absence of benzofuran gave acenaphthenes, both via vinylcation intermediates.



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