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Synthesis of Polysubstituted Polycyclic Aromatic Hydrocarbons by Gold-Catalyzed Cyclization-Oxidation of Alkylidenecyclopropane (ACP)-containing 1,5-Enynes

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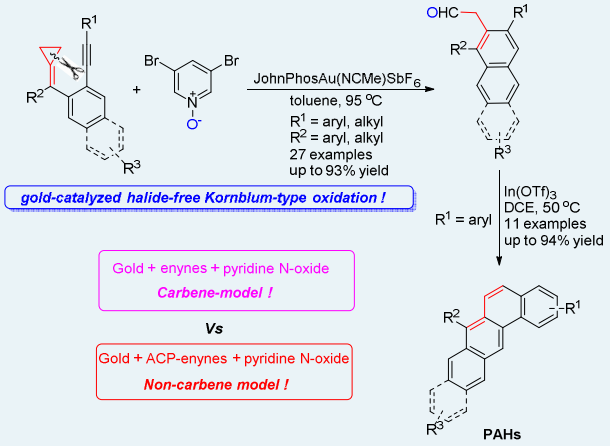
ABSTRACT: *A gold-catalyzed tandem cyclization-oxidation of alkylidenecyclopropane (ACP)-containing 1,5-enynes with 3,5-dibromo-pyridine N-oxide via non-carbene model has been developed, providing a range of synthetically valuable and useful arylacetaldehyde derivatives in moderate to good yields without oxidation of alkynes. Moreover, the corresponding aldehydes can be further transformed into polycyclic aromatic hydrocarbons (PAHs) in the presence of catalytic amount of Lewis acid In(OTf)$_3$. The reaction represents an example of gold-catalyzed halide-free Kornblum-type oxidation through the oxidation of cyclopropane moiety.*



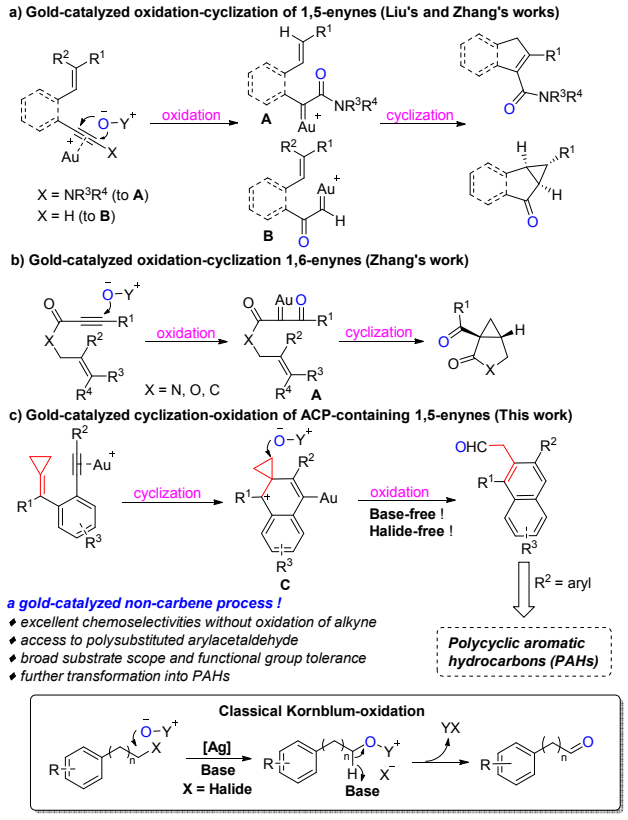
KEYWORDS: *gold catalysis, non-carbene model, alkylidenecyclopropane (ACP)-containing 1,5-enynes, 3,5-dibromo-pyridine N-oxide, polycyclic aromatic hydrocarbons (PAHs)*

INTRODUCTION

Polycyclic aromatic hydrocarbons (PAHs) with annulated aromatic ring have attracted considerable attention owing to their fascinating structural features and wide application in organic, optical, and electronic materials.[1] Additionally, they have also proven to be active semiconductor materials that have been utilized extensively in organic field-effect transistors (OFETs) and organic light-emitting diode application.[2] Strategies for the preparation of PAHs include thermolysis of prefunctional precursors, oxidative photocyclization, Diels-Alder reactions and metal-catalyzed cross-coupling and cycloaddition reactions.[3] However, most methods often suffer from poor yields, narrow substrate scope, harsh reaction conditions and multistep syntheses. Therefore, the effective and convenient approaches to highly substituted PAHs remain challenging and urgently pursued.

Since Zhang and co-workers reported their pioneering work for the gold-catalyzed oxidation of alkyne with pyridine N-oxides,[4] the utilization of α-oxo gold carbenes formed from gold-catalyzed oxidation of alkynes with either pyridine N-oxides or nitrones to construct uncommon and useful carbo- and heterocyclic frameworks have been intensively investigated.[5] In most cases, the oxidation preferentially occurs by an attack of highly basic N-O oxides at gold-π-alkynes,[6] followed by X-H insertions (X = C, N, O),[7] cyclopropanations,[8] and annulation reactions.[9] However, the carbene model can be also interpreted that cyclization preferentially occurs to form cyclopropyl gold carbene, followed by O-transfer from pyridine N-oxide.[10] On the other hand, gold-catalyzed cyclization of 1,n-enynes has emerged as a powerful transformation to construct molecular complexity in an atom- and step-economic manner,[11] and gold-catalyzed oxidation of enynes also attracted much attention. In most cases, all these reactions were proposed to occur via a carbene mechanism in which the α-carbonyl-carbenoids **A** and **B** were preferentially formed. For example, Liu's group reported two oxidation-cyclizations of 1,5-enynes with 8-methylquinoline N-oxide, in which the success relies on the proposed prior oxidation of alkyne moiety (Scheme 1a).[8b] Thereafter, Zhang's group reported an enantioselective gold-catalyzed intramolecular oxidation-cyclopropanation of 1,5-enynes using a novel P,N-bidentate ligand (Scheme 1a).[8f] Moreover, Zhang's group also developed a gold-catalyzed highly diastereo- and enantioselective tandem oxidation-cyclopropanation sequence of 1,6-enynes with pyridine N-oxide or 8-methylquinoline N-oxide to provide densely functionalized bicyclo[3.1.0]hexanes (Scheme 1b).[8a,e] Herein, we wish to report a different reaction pathway via

non-carbene model using electron-rich alkylidenecyclopropane (ACP)-containing 1,5-enynes,[12] in which the cyclization preferentially occurs to form intermediate **C**, which also resonates with cyclopropyl gold carbine,[10a] and followed by a Kornblum-type oxidation, rather than oxygen transfer to cyclopropyl gold carbene using pyridine N-oxide (Scheme 1c). The entire process represents gold-catalyzed halide-free and base-free Kornblum oxidation as compared to a classical one.[13] During our preparation this manuscript, a similar oxidation has been reported using pyridine N-oxide under Brønsted acid catalysis, in which the halonium ion intermediate was attacked by pyridine N-oxide via a Kornblum-type mechanism.[14] Moreover, the obtained products can be easily transformed to polycyclic aromatic hydrocarbons (PAHs) in the presence of a Lewis acid.

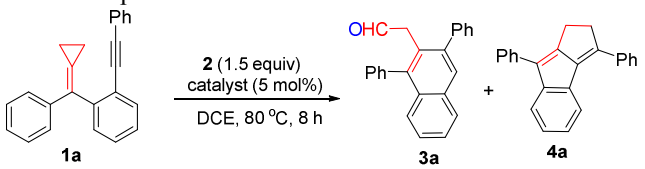


Scheme 1. Carbene *vs* non-carbene model.

RESULTS AND DISCUSSION

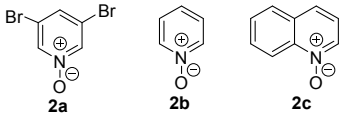
Our studies commenced with easily available 1-(cyclopropylidene(phenyl)methyl)-2-(phenylethynyl)benzene **1a** (0.15 mmol, 1.0 equiv) as the test substrate, 3,5-dibromopyridine-N-oxide (1.5 equiv) as an oxidation reagent, and PPh_3AuNTf_2 (0.05 equiv) in 1,2-dichloroethane (DCE) (1.5 mL) at 80 °C under argon atmosphere for 8 h, giving the desired 2-naphthylacetaldehyde **3a** in 70% yield without the oxidation of alkyne (Table 1, entry 1). The isolated yield of **3a** could further be improved to 76% upon changing the coordinated anion of gold complex to SbF_6 (Table 1, entry 2). Further catalyst screening revealed that both NHC carbene-ligated and electron-deficient phosphine-ligated cationic gold catalysts were detrimental to the reaction efficiency (Table 1, entries 3 and 6). An obvious change was observed when a sterically bulky phosphine ligand was used: sterically hindered (JohnPhos)Au(NCMe)SbF_6 and Me_4[t]BuXPhosAu(NCMe)SbF_6 further improved the yield to 80% and 78% yields, respectively (Table 1, entries 4 and 5). With $AgSbF_6$ as a sole catalyst, the reaction became sluggish and even prolonged reaction time did not produce significant amounts of **3a** (Table 1, entry 7). Next, we examined the reaction outcome of other pyridine N-oxide, and astonishingly, only trace amount of **3a** was detectable when commercially available **2b** and **2c** were used as the oxidants (Table 1, entries 8 and 9). Solvent effect was also investigated, and it was identified that toluene was better than other solvents such as 1, 4-dioxane, MeCN, and DCE (Table 1, entries 10-12). Raising the reaction temperature to 95 °C could improve the yield to 92%, along with the formation of thermally induced [3+2] cycloaddition product **4a** in 3% yield (Table 1, entry 13). However, further raising the reaction temperature to 110 °C, the isolated yield of **3a** was reduced to 86% along with an improved yield of **4a** (Table 1, entry 14). Moreover, thermally induced product **4a** was obtained in good yields if raising the temperature to 120 °C without pyridine N-oxide for 12 h. No reaction occurred in the absence of the gold catalyst, and only **4a** was obtained in 19% yield (Table 1, entry 15).

Table 1. Optimization of reaction conditions[a]



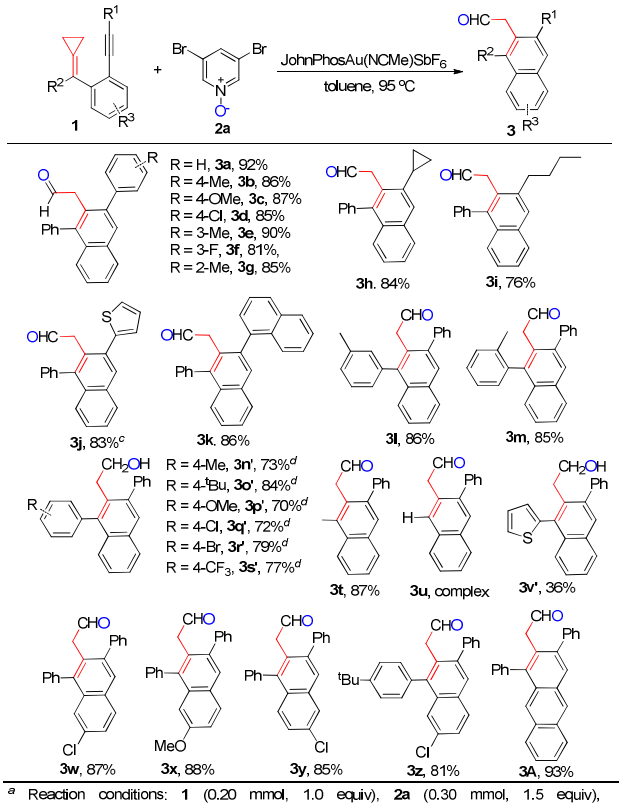
entry	catalyst	N-oxide	solvent	yield (%)[b]
1	PPh_3AuNTf_2	**2a**	DCE	70
2	PPh_3AuSbF_6	**2a**	DCE	76
3	$IPrAuSbF_6$	**2a**	DCE	54
4	(JohnPhos)Au(NCMe)SbF_6	**2a**	DCE	80
5	Me_4[t]BuXPhosAu(NCMe)SbF_6	**2a**	DCE	78
6	$(ArO)_3PAuSbF_6$	**2a**	DCE	64
7[c]	$AgSbF_6$	**2a**	DCE	trace
8	(JohnPhos)Au(NCMe)SbF_6	**2b**	DCE	trace
9	(JohnPhos)Au(NCMe)SbF_6	**2c**	DCE	trace
10	(JohnPhos)Au(NCMe)SbF_6	**2a**	1,4-dioxane	47
11	(JohnPhos)Au(NCMe)SbF_6	**2a**	toluene	84
12	(JohnPhos)Au(NCMe)SbF_6	**2a**	MeCN	50
13[d,e]	(JohnPhos)Au(NCMe)SbF_6	**2a**	toluene	92 (3)
14[f,g]	(JohnPhos)Au(NCMe)SbF_6	**2a**	toluene	86 (8)
15[d,e,h]	-	**2a**	toluene	N D

[a] All the reactions were carried out on a 0.15 mmol scale in solvent (0.15 mL) at 80 °C for 8 h unless otherwise specified. [b] Isolated yield of **3a** and **4a** (in parentheses). [c] The reaction was carried out for 48 h. [d] At 95 °C. [e] For 4 h. [f] At 110 °C. [g] For 2 h. [h] **4a** was isolated in 19% yield. Ar = 2,4-di-tert-butylphenyl. DCE = 1,2-dichloroethane.



Having established the optimal reaction conditions, we began to investigate the substrate scope of *ortho*-alkynylaryl-substituted alkylidenecyclopropanes (ACPs) carefully and the results are shown in Table 2. When R^1 is an aryl group, a variety of arylalkynes were compatible and the reactions proceeded smoothly to furnish the corresponding naphthylacetaldehydes **3a-3g** in good yields ranging from 81% to 92% yield, accompanied by the formation of thermally induced [3+2] cycloaddition products in less than 3% yield. Cyclopropyl and ^{n}butyl alkynes were also compatible under the optimum conditions, thus delivering **3h** and **3i** in 84% and 76% yields, respectively. Moreover, thienyl alkyne **1j** and naphthyl alkyne **1k** were also tolerable, thereby giving products **3j** and **3k** in 83% and 86% yields, respectively. Then, we examined the electronic effect and steric hindrance of R^2, when it was an aryl group: *meta*-methyl-substituted and *ortho*-methyl-substituted substrates **1l** and **1m** performed very well, affording **3k** and **3m** in good yields. However, the *para*-substituted naphthylacetaldehydes were not stable when they were purified by silica gel flash chromatography. Thus the corresponding alcohols were synthesized after one-pot treatment of the formed aldehydes with 2.0 equivalents of $NaBH_4$. All the reactions proceeded smoothly to furnish the desired alcohols **3n'-3s'** in 70-84% yields regardless of whether they have electron-rich or electron-deficient aromatic ring. Substrate **1t**, replacing aryl group with a methyl group, could also afford the corresponding aldehyde **3t** in 87% yield. As for thienyl group-substituted substrate **1v**, the corresponding product **3v'** was also formed, albeit in 36% yield. However, when R^2 was non-substituted, the reaction system became complex, probably because of the lower stability of carbocationic intermediate. Changing R^3 to OMe group or Cl atom, the reactions still worked efficiently and the products **3w-3y** were isolated in good yields as well. Both phenyl rings substituted substrate **1z** was also tolerable, affording **3z** in 81% yield. Finally, the three annelated aldehyde **3A** was also obtained in 93% yield using naphthalene-linked substrate **1A**. The structure of **3w** was confirmed by single crystal X-ray analysis.[15]

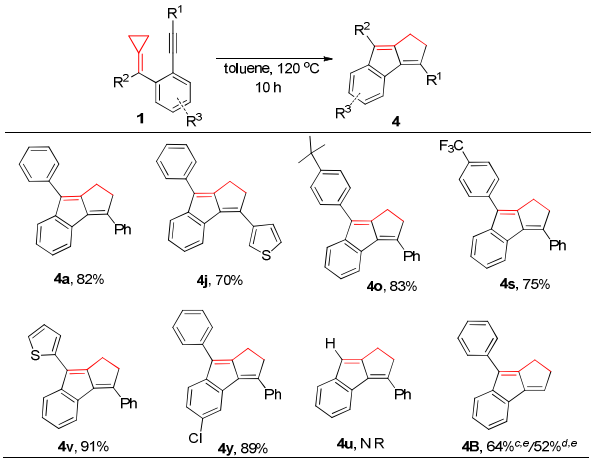
Table 2. Substrate scope for gold-catalyzed cyclization-oxidation of ACP-containing enynes[a,b]



[a] Reaction conditions: **1** (0.20 mmol, 1.0 equiv), **2a** (0.30 mmol, 1.5 equiv), JohnPhosAu(MeCN)SbF_6 (0.015 mmol, 5 mol%), toluene (2.0 mL), 95 °C, argon atmosphere for 4 h. In every reaction, [3+2] cycloaddition product was obtained in less than 3% yield. [b] Isolated yield. [c] At 90 °C. [d] One-pot synthesis of naphthyl ethanol.

Next, we further investigated the substrate scope of this thermally induced [3+2] cycloaddition reaction using a series of *ortho*-alkynylaryl-substituted alkylidenecyclopropanes in toluene at 120 °C, and the results are shown in Table 3. To our delight, the electronic effect had no obvious effect on the reaction outcome and the corresponding products **4a** to **4B** were obtained in 70-91% yields. To be noted, the thienyl group substituted substrates **1j** and **1v** were also tolerable without erosion of heterocyclic subunit, delivering the corresponding products **4j** and **4v** in 70% and 91% yields, respectively. However, when R^2 was non-substituted, the reaction became sluggish. Moreover, trimethylsilyl group protected substrate and terminal alkyne substituted substrate gave the same product **4B** in 64% and 52% yields in the presence of gold catalyst, respectively. The structure of **4v** has been also confirmed by single crystal X-ray analysis.[16]

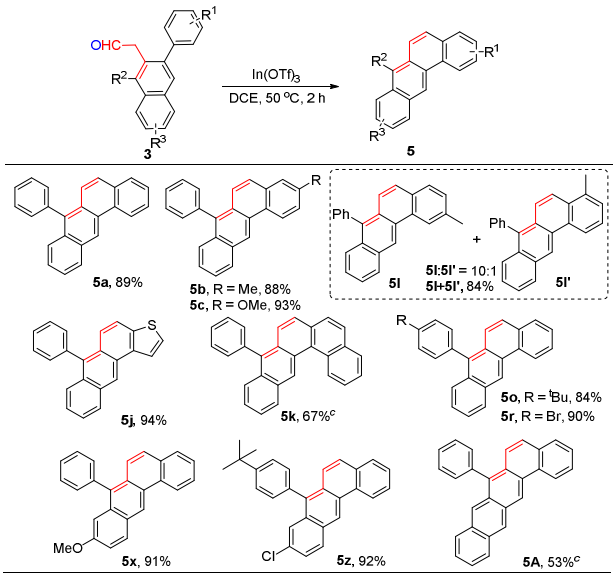
Table 3. Substrate scope for thermally induced [3+2] cycloaddition of **1**[a,b]



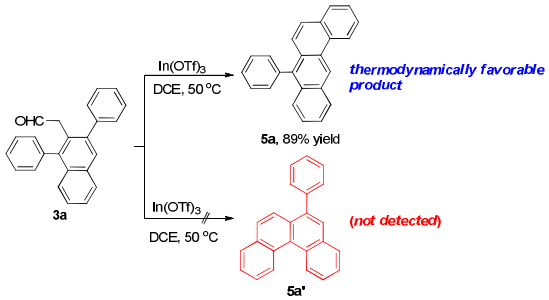
[a] Reaction conditions: **1** (0.20 mmol, 1.0 equiv), toluene (2.0 mL), 120 °C, argon atmosphere for 10 h. [b] Isolated yield. [c] Trimethylsilyl group protected alkyne was used as substrate. [d] Terminal alkyne was used as substrate. [e] 5 mol% JohnPhosAu(NCMe)SbF$_6$ was added.

With a diverse range of functionalized naphthylacetaldehydes in hand, we then embarked on their transformation into polycyclic aromatic hydrocarbons and the results are shown in Table 4. Gratifyingly, a series of tetraphenes **5** containing four-fused aromatic rings were readily prepared in the presence of catalytic amount of Lewis acid In(OTf)$_3$ (5 mol%) at 50 °C in DCE from naphthylacetaldehydes **3**. Both electron-rich and electron-deficient substrates were compatible, thus affording the corresponding annulated PAHs **5a-5A** in 84%-94% yields. Notably, as for the *meta*-methyl-substituted substrate **3l**, a couple of regioisomers were formed in 10:1 ratio, in which the cyclization preferentially occurred at less hindered position in 84% total yield, and heteroacene **5j** and disubstituted acene **5z** were also obtained in 94% and 92% yields, respectively. Moreover, the five annelated PAHs benzo[a]tetraphene **5k** and benzo[a]tetracene **5A** were also obtained at 80 °C in 67% and 53% yields, respectively. The structures of **5a** and **5b** were confirmed by single crystal X-ray analysis.[17] It should be stressed here that product **5a** was exclusively obtained and another possible annulated product **5a'** was not detected (Scheme 2).

Table 4. Substrate scope for In(OTf)$_3$-catalyzed synthesis of PAHs from **3**[a,b]



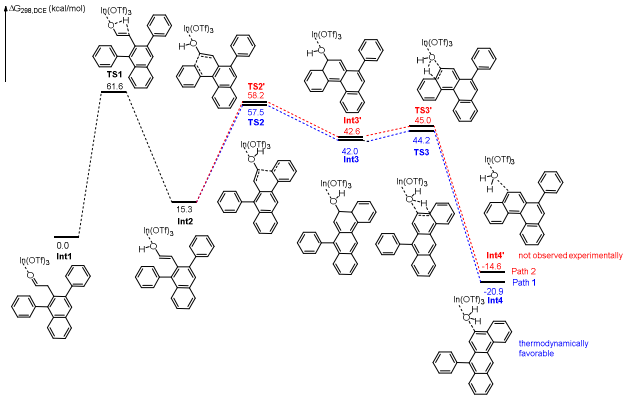
[a] Reaction conditions: **3** (0.20 mmol, 1.0 equiv), In(OTf)$_3$ (0.01 mmol, 0.05 equiv), DCE (2.0 mL), 50 °C, argon atmosphere for 2 h. [b] Isolated yield. [c] At 80 °C.



Scheme 2. Rationalization of product selectivity

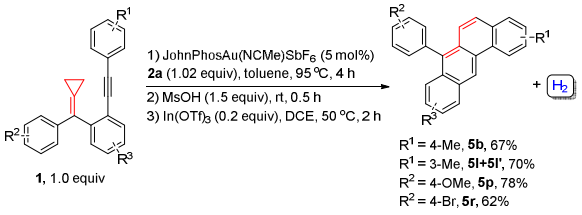
In order to account for why only product **5** was exclusively obtained, we have done DFT calculations to investigate the formation of product **5a** and another possible product **5a'**. All DFT calculations were performed with Gaussian 09 program.[18] The reaction energy profiles are depicted in Scheme 3. To be noted, all the intermediates are hexa-coordinated. Initially, coordination of In(OTf)$_3$ catalyst to the substrate **3a** generates complex **Int1**. The complex **Int1** undergoes a keto-enol tautomerization to give an enol intermediate **Int2** via transition state **TS1**. Subsequently, the intermediate **Int2** can undergo two possible reaction pathways to obtain products **5a** or **5a'**. In Path 1, passing through **TS2** with an energy barrier of 57.5 kcal/mol, the annulated intermediate **Int3** is located, which undergoes the H-shift, leading to the product complex **Int4**. In Path 2, passing through **TS2'** with an energy barrier of 58.2 kcal/mol, the annulated intermediate **Int3'** is located, which undergoes the H-shift, leading to the product complex **Int4'**. The product complex **Int4** is more stable than the **Int4'** by 6.3 kcal/mol. Kinetically, the Path 1 is slightly favorable than the Path 2. The calculation results indicate that the product **5a** is thermodynamically favorable

product, which may account for why it is obtained exclusively in experiments (For details, see Scheme S1 in the Supporting Information).



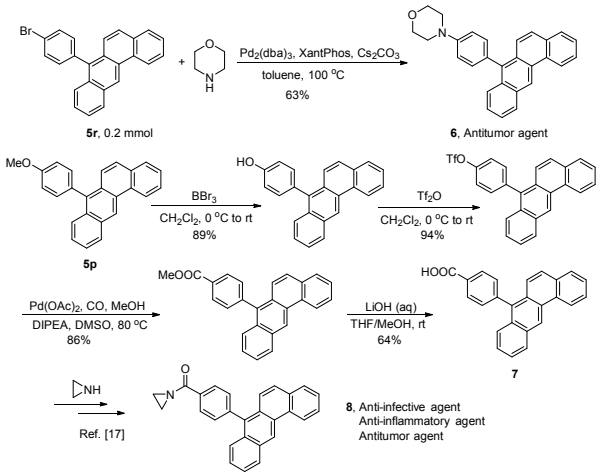
Scheme 3. DFT studies on the formation **5a**

Furthermore, we also investigated one-pot synthesis of PAHs from the ACP-containing 1,5-enynes with 3,5-dibromo-pyridine N-oxide. However, initial attempt was not successful when Lewis acid catalyst $In(OTf)_3$ was added directly or used stepwise. We wondered the Lewis acid was poisoned by coordinating with the formed 3,5-dibromo-pyridine.[4,8d] Indeed, when the reaction mixture was treated with methanesulfonic acid (1.5 equiv),[4] one-pot synthesis of PAHs **5** was realized (for details, see Scheme S2 in the Supporting Information). Several PAHs were also synthesized in a one-pot manner in 62%-78% yields (Scheme 4). The whole process represents gold-catalyzed oxidative dehydrogenation reaction of ACP-containing 1,5-enynes with 3,5-dibromo-pyridine N-oxide for synthesis of PAHs.



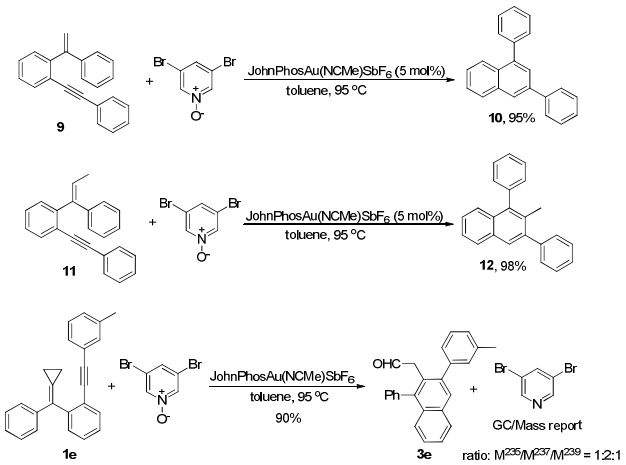
Scheme 4. One-pot synthesis of PAHs **5**

To further illustrate the synthetic value of this method, two bioactive polycyclic molecules were prepared using one-pot prepared tetraphenes (Scheme 5). Antitumor **6**[19] was obtained in 63% yield utilizing Buchwald-Hartwig amination conditions. Compound **8**, which exhibited anti-infective, anti-inflammatory, and antitumor activities,[20] could also be obtained using linear multistep synthesis after condensation of the corresponding carboxylic acid **7** (for details, see Scheme S3 in the Supporting Information).[21]



Scheme 5. Further transformation to bioactive molecules

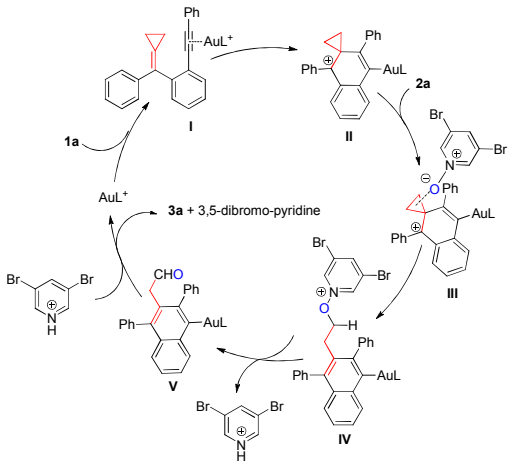
To demonstrate the necessity of the strained small ring, two control experiments using 1,5-enynes **9** and **11** having no cyclopropane moiety were conducted under the optimum reaction conditions, the desired aldehydes were not formed. Instead, polysubstituted naphthalenes **10**[22] and **12** were furnished in excellent yields without the involvement of 3, 5-dibromo-pyridine N-oxide, revealing that cyclopropane was essential for this cyclization-oxidation sequence (Scheme 6). Furthermore, the corresponding byproduct 3,5-dibromo-pyridine was also detected and characterized by GC/MS analysis (for the details, see Scheme S3 in the Supporting Information).



Scheme 6. Control experiments

On the basis of the previous reports on gold-catalyzed enynes cyclization[5,11] and the mechanism of Kornblum oxidation,[13] a plausible mechanism is outlined in Scheme 7. Initially, coordination of cationic Au^I complex to the alkyne moiety of **1a** forms intermediate **I**, followed by a 6-endo-dig cyclization to give intermediate **II**, because benzene ring and electron-rich cyclopropane can stabilize the formed carbon cation.[12,23] Then intermediate **II** is combined with external 3,5-dibromo-pyridine N-oxide to

form a reactant complex **III**, which leads to ring-opening of ACP to form intermediate **IV** (electrophilically assisted nucleophilic ring opening).[24] Finally, deprotonation utilizing the released 3,5-dibromo-pyridine and protodeauration sequence occur, thus furnishing the desired naphthylacetaldehyde **3a**.



Scheme 7. A plausible mechanism for gold-catalyzed cyclization-oxidation of ACP-containing 1,5-enynes

CONCLUSION

In summary, we have disclosed a gold-catalyzed cycloisomerization and halide-free Kornblum oxidation of ACP-containing 1,5-enynes with 3,5-dibromo-pyridine N-oxide, providing a convenient access to functionalized 2-naphthylacetaldehydes, which are further transformed into four/five annelated PAHs in the presence of Lewis acid $In(OTf)_3$. The present work exhibits selective oxidation of $C(sp^3)$-H bond of cyclopropane moiety of 1,5-enynes in the presence of gold catalyst and pyridine N-oxide without oxidation of alkyne. Moreover, the one-pot synthesis of PAHs was also realized when the reaction mixture was neutralized by MsOH. Two relevant bioactive molecules were also available utilizing this newly developed oxidative protocol. Further investigations on expanding the scope and applications of this method are undergoing in our laboratory.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.

Experimental procedures, characterization data, and ^1H and ^{13}C NMR spectra for new compounds (PDF).

X-ray data (CIF)

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Notes

The authors declare no competing financial interest.

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