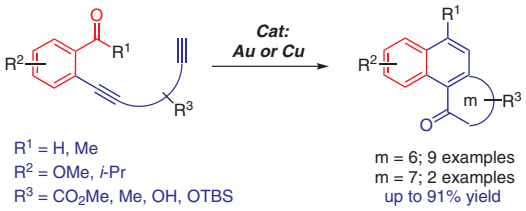
Synlett J. Kang et al. Letter

Synthesis of [6,6,m]-Tricyclic Compounds *via* [4+2] Cycloaddition with Au or Cu Catalyst

Juyeon Kang
Seunghwan Ham
Chaehyeon Seong
Chang Ho Oh*

Department of Chemistry and Research Institute of Natural Science, Hanyang University, Sungdong-Gu, Seoul 04763, Korea
changho@hanyang.ac.kr



Received: 21.03.2021
Accepted after revision: 11.04.2021
Published online: 11.04.2021
DOI: 10.1055/a-1479-6005; Art ID: st-2021-u0108-l

Abstract We synthesized [6,6,6]- and [6,6,7]-tricyclic compounds *via* intramolecular [4+2] cycloaddition by gold or copper catalysts. Substrates for cyclization were prepared by coupling reactions between eight types of diyne and four types of aromatic moieties. We have successfully synthesized eleven tricyclic compounds.

Key words catalysis, [4+2] cycloaddition, abietane, *Dendrobium*, [6,6,m]-cyclic compound, copper, gold

Ring formation is an important method to efficiently assemble compounds with complex molecular structures like natural compounds.[1] The rate enhancement of cycloaddition reaction is induced by thermal, photochemical, Lewis acid, high pressure, and ultrasonic treatments.[2] One of the rate-enhancing factors, the metal-based Lewis acid additive, acts as an electron-pair acceptor in cyclization reactions.[3] The cooperation of Lewis acid with transition metals increases the activity and selectivity as well as the reactivity of the substrate.[4] Lewis acids can selectively promote the activation of C–H bond through metal coordination.[5] In addition, C–C and C–N bonds can be formed by introducing Lewis acid additives into the transition-metal catalysts as a bond-forming catalyst. Furthermore, the Au-catalyzed and Pd-catalyzed alkyne functionalization reactions can be accelerated by the addition of Lewis acids.[6]

One of the methods to synthesize natural products is to form polycyclic compounds using transition-metal compounds.[7] Metal compounds are formed by binding of Lewis base or ligand to a metal that acts as Lewis acid.[8] The synthesis of complex natural products with unique structural motifs is difficult to obtain due to the long route, low yield, and efficiency. However, total synthesis *via* transition-metal-catalyzed reaction can shorten the reaction pathway and control the regioselectivity and stereoselectivity.

Synthesis of natural products using various transition-metal catalysts such as palladium, gold, and copper has been reported by several research groups. Shibasaki et al. reported the synthesis of an intermediate for diterpene synthesis through an asymmetric Heck reaction using a palladium catalyst.[9] Majetich et al. reported the conversion of dienones into functionalized hydrophenanthrene natural products using a $BF_3{\cdot}Et_2O$ catalyst.[10] Dyker et al. reported the synthesis of dihydrophenanthrene derivative using a gold-catalyzed domino process. Hashmi et al. reported the nucleophilic addition by gold catalyst for the synthesis of C–C multiple bonds from various substrates.[11] Yamamoto et al. investigated the Lewis acid catalyzed intramolecular [4+2] benzannulation reaction. The transition-metal-catalyzed [4+2] approach was used for the regioselective synthesis of polysubstituted benzene. Naphthyl ketone derivatives were obtained through the benzannulation of *o*-alkynyl(oxo)benzene and alkyne with gold and copper catalysts.[12] They also reported the synthesis of naphthyl ketone products from alkynyl terminus substrates using copper and gold catalysts through a bottom-up approach.[13] In this study, the benzopyrylium-type intermediate was produced by a metal-catalyzed cyclization. This structure is important as the basis for the synthesis of [6,6,6]-tricyclic compounds of abietane diterpenoids.

Abietane is a naturally occurring diterpenoid isolated from various terrestrial plants.[14] Aromatic abietane is a compound having an A–B–C ring skeleton of 20 carbons and exhibits different oxidation degrees at B- and C-ring carbons. It is largely divided into three types according to the number of double bonds of the C-ring and the type of carbon ring structure.[15] And most of them have a variety of biological activities.[16] Aromatic *Dendrobium* contains phenanthrene, bibenzyl, flavone, aromatic acid and ester

Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany

series.[17] Among them, the phenanthrene skeleton of *Dendrobium* is a hydroxyl and/or methoxy-substituted 9,10-dihydro or hydro derivative.[18] Dendrodevonin A, which is extracted from *Dendrobium devonianum*, is used as a Chinese herbal medicine and exhibits cytotoxicity to human colon cancer HT-29 cell (Figure 1).

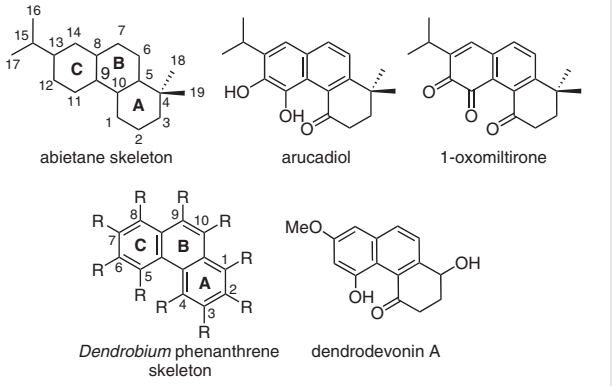


Figure 1 Abietane, *Dendrobium* phenanthrene skeleton, and structure of arucadiol, 1-oxomiltirone, and dendrodevonin A

We have investigated the synthesis of polycyclic compounds for the past 15 years by synthesizing natural products using transition-metal catalysts, such as platinum, palladium, and rhodium.[19] When cyclization reaction was carried out with *o*-alkynylbenzaldehyde using a gold catalyst, [6,7,5]-tricyclic compound was obtained as major product through Huisgen-type [3+2] cycloaddition. And [6,6,6]-tricyclic compound was obtained by [4+2] cycloaddition reaction.[20] Our group is recently interested in the synthesis of abietane diterpenoid skeleton [6,6,6]-tricyclic compound. We have studied gold- and copper-catalyzed reactions based on the research of Yamamoto group. We reported on the synthesis of 1-oxomiltirone and arucadiol, which belong to the class of abietane diterpenoids, from diyne using gold and copper catalysts.[21]

In this paper, we have described the synthesis of various [6,6,6]-tricyclic compounds that can be used as building blocks for natural product abietane diterpenoid skeleton synthesis *via* transition-metal-catalyzed cyclization reaction. In addition, we have discussed the pathway to synthesize [6,6,7]-tricyclic compounds by increasing the carbon tether of the substrate. The tricyclic compounds were synthesized by the reaction of either gold or copper catalyst. We synthesized the substrates by coupling reactions between eight types of diyne and four types of aromatic parts. The catalytic cyclization reaction was carried out using $AuBr_3$ and $Cu(OTf)_2$ as gold and copper catalysts, respectively.

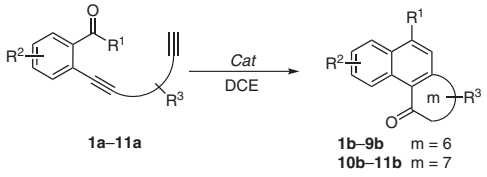
First, 1,6-diynes **1a**–**7a** were cyclized under gold catalyst (Table 1 entries 1–7). And some of the compounds (**1a**, **3a**–**5a**) were also reacted under copper catalyst. In the synthesis of **1a**, the aromatic part was 2-bromobenzaldehyde, and the diyne part was, respectively, coupled and synthesized. Diynal substrate **1a** was synthesized by palladium-catalyzed Sonogashira coupling reaction of the diyne obtained from the alkylation of dimethyl malonate and 2-bromobenzaldehyde.[22] The [6,6,6]-tricyclic compound **1b** was synthesized by an intramolecular [4+2] cycloaddition reaction using copper and gold catalysts. The product yield was high, when the process was carried out with a gold catalyst at 80 °C for 2 h or with a copper catalyst at 60 °C for 1 h (entry 1).[23] The **2a** diyne substrate was obtained through trimethylsilyl (TMS) protection at one end of the alkyne obtained by alkylation of dimethyl malonate. Compound **2a** was synthesized *via* Sonogashira coupling between 2-bromobenzaldehyde and diyne. As a result of the catalytic cyclization reaction, product **2b** was obtained in reasonable yield when using the $AuBr_3$ catalyst (entry 2), but byproduct was formed when using $Cu(OTf)_2$ catalyst.

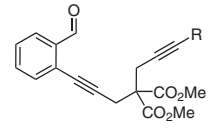
In the synthesis of substrate diynal **3a**, the alkyne was synthesized from ethyl isobutyrate through alkylation and reduction. It was combined with 2-bromobenzaldehyde through Sonogashira coupling reaction. After protecting the aldehyde with an acetal protecting group, **3a** was obtained through Swern oxidation, ethynylation, and acetal deprotection. In synthesizing **3b**, the reaction proceeded efficiently at 55 °C for 2 h using the gold catalyst (entry 3). The diyne for **4a** was synthesized from ethyl isobutyrate in five steps: alkylation, reduction, TMS protection, Swern oxidation, and ethynylation. The substrate **4a** was obtained through Sonogashira coupling between the diyne and 2-bromobenzaldehyde. It was confirmed that the gold-catalyzed reaction proceeded efficiently at 60 °C for 1 h to obtain **4b** (entry 4). We synthesized acetophenone substrates after diynal substrate studies.

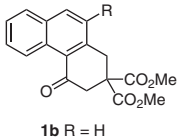
Substrate **5a** was easily synthesized by the Sonogashira coupling of 2′-bromoacetophenone and diyne. For **5a**, the reaction proceeded at 60 °C for 1 h with gold catalyst (entry 5). The diyne of substrate **6a** was synthesized from ethyl formate by Grignard reaction with propargyl bromide. Substrate **6a** was synthesized by TBS protection with aromatic, diyne moiety combined by Sonogashira reaction. Compound **6b** was synthesized at 60 °C and 1 h under gold catalyst (entry 6). The aromatic part of substrate **7a** was synthesized from methyl 3,5-dihydroxybenzoate through four steps: methylation, reduction, bromination, and oxidation. We combined the aromatic part and 4-pentyn-1-ol through the Sonogashira reaction, and then proceeded oxidation. Dialdehyde in aromatic and aliphatic moiety was reacted with ethynylmagnesium bromide solution, and only aliphatic aldehyde was reacted. And **7a** was synthesized through TBS protection. Product **7b** was mildly synthesized under gold catalyst at room temperature within 1 h (entry 7).

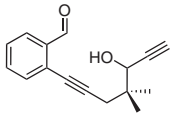
Additionally, tricyclic compound **6c** was synthesized through TBS deprotection from **6b**. And we got **7c** with demethylation followed by TBS deprotection from **7b** (Scheme 1). Product **7c** plays an important role as an intermediate in the synthesis of dendrodevonin A. Demethylation from **7b**

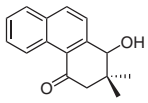
Table 1 Synthesis of **1b–11b** with Au- or Cu-Catalyzed Cyclization[a]

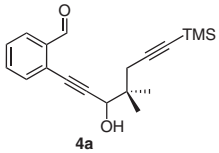


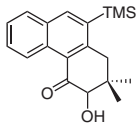

1a R = H
2a R = TMS

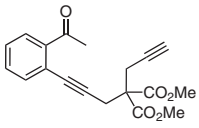

1b R = H
2b R = TMS

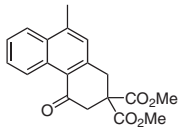

3a

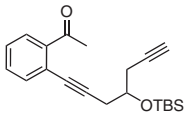

3b

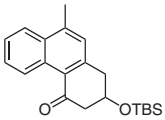

4a

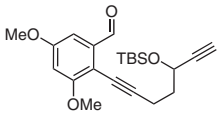

4b

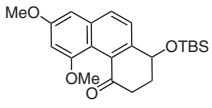

5a

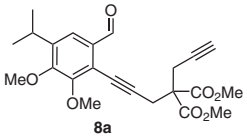

5b

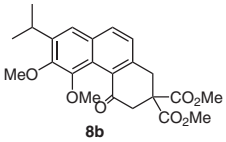

6a

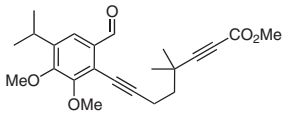

6b

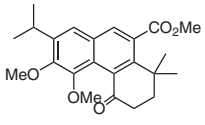

7a

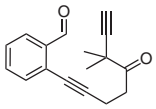

7b

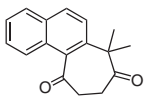

8a

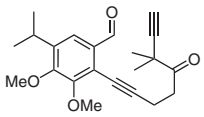

8b

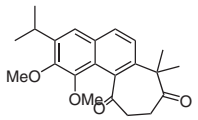

9a


9b


10a

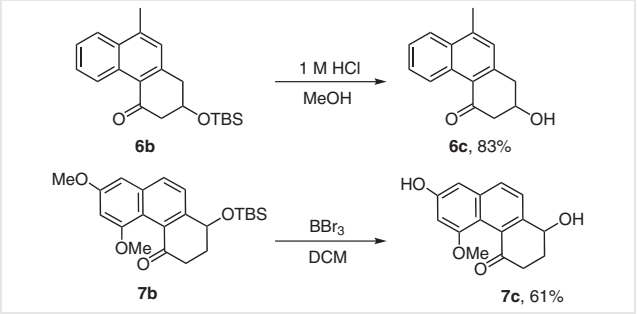

10b


11a

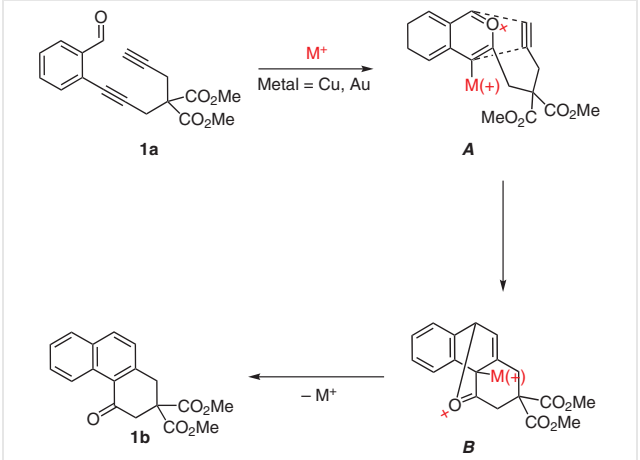

11b

Entry	Reactant	Catalyst	Temp (°C)	Time (h)	Product	Yield (%)
1	**1a**	$AuBr_3$	80	2	**1b**	82
2	**2a**	$AuBr_3$	50	1.5	**2b**	88
3	**3a**	$AuBr_3$	55	2	**3b**	91
4	**4a**	$AuBr_3$	60	1	**4b**	73
5	**5a**	$AuBr_3$	60	1	**5b**	85
6	**6a**	$AuBr_3$	60	1	**6b**	72
7	**7a**	$AuBr_3$	rt	1	**7b**	67
8[b]	**8a**	$Cu(OTf)_2$	120	0.5	**8b**	79
9[b]	**9a**	$Cu(OTf)_2$	120	1	**9b**	76
10	**10a**	$AuBr_3$	60	1	**10b**	91
11	**11a**	$AuBr_3$	60	2	**11b**	76

[a] Reaction conditions: $AuBr_3$ (2–20 mol%), 1,2-dichloroethane (DCE) under argon atmosphere.
[b] Reaction conditions: $Cu(OTf)_2$ (5–10 mol%), 1,2-dichloroethane (DCE) under argon atmosphere.



Scheme 1 Synthesis of **6c** and **7c** with deprotection



Scheme 2 Proposed mechanism of the metal-catalyzed reaction of **1a**

to **7c** was deprotected only at one position due to the influence of ketone and OMe groups closely attached to the A- and C-rings. By controlling the protecting group of the aromatic moiety, we plan to synthesize the dendrodevonin series through further study.Second, 1,6-diynes **8a** and **9a** were cyclized with copper catalyst (Table 1 entries 8 and 9). The aromatic parts of substrate **8a** and **9a** were obtained from 1,2-dimethoxybenzene in four steps.[21] Diynal substrate **8a** can be synthesized through Sonogashira coupling between the aromatic and diyne parts. Product **8b** was synthesized in good yield by cyclization using a copper catalyst at 120 °C for 0.5 h (entry 8). The reaction did not proceed with gold catalyst. The diyne of **9a** was synthesized from ethyl isobutyrate in six steps. First, an aldehyde was obtained through alkylation, reduction, and oxidation. And aldehyde was converted into an alkyne *via* Corey–Fuchs reaction and elimination. After the introduction of the CO_2Me group, diyne was synthesized with a functional group attached only at one side after TMS deprotection. Substrate **9a** was synthesized through a Sonogashira coupling reaction between the aromatic and diyne moiety. Finally, **9b** was synthesized using the copper catalyst at 120 °C for 1 h (entry 9). The reaction did not proceed with the gold catalyst.

After synthesizing various [6,6,6]-tricyclic compounds, we experimented to expand [6,6,7] ring compounds. Ring expansion can proceed by introducing additional carbons or heteroatoms into the ring.[24] However, we increased the number of carbon chains by changing the substrate from 1,6-diyne to 1,7-diyne. According to the mechanistic study of Scheme 2, the number of rings can be adjusted by increasing the carbon chain of the diyne unit.

Third, 1,7-diynes **10a** and **11a** were cyclized with gold catalyst (Table 1, entries 10 and 11). Two types of substrates **10a** and **11a** were synthesized according to the functional group attached to the aromatic part. Substrate **10a** (R^1, R^2, R^3 = H) was synthesized through the reactions mentioned below. After combining 2-bromobenzaldehyde and 4-pentyn-1-ol through Sonogashira coupling, aliphatic aldehyde was introduced through acetal protection and Swern oxidation. The synthesis of aldehyde to propargylic alcohol has been reported in the literature. They reported a selective synthesis of allenic and propargylic alcohols by treating aldehyde and propargyl halide with zinc in THF/aq. NH_4Cl solution.[25] Based on this, the aldehyde was treated with allenyl bromide and zinc dust in solvent mixture to obtain propargylic alcohol by Barbier reaction. Then, **10a** was synthesized through oxidation and acetal deprotection. Substrate **11a** was synthesized from the aromatic part obtained from 1,2-dimethoxybenzene, and the synthetic method was the same as for substrate **10a**.[21] As a result of the gold-catalyzed reaction of two substrates, the desired [6,6,7]-tricyclic compounds **10b** and **11b** were obtained at 60 °C within 1–2 h (entries 10 and 11). However, in the case of the copper catalyst, the desired product could not be obtained due to the byproduct.

We attached various functional groups while synthesizing diynal substrates and observed the tolerance of the catalytic cyclization reaction for those functional groups. The catalytic reaction of diynal obtained from 1,6-diyne proceeded differently depending on the aromatic type. Substrates **1a**–**4a** from 2-bromobenzaldehyde proceeded better under gold catalyst. Substrates **5a** and **6a** from 2′-bromoacetophenone performed better under gold catalyst. Substrate **7a** has attached a substituent at the *meta* position of the aromatic part from methyl 3,5-dihydroxybenzoate, and the gold-catalyzed reaction proceeded as a major. However, when OMe groups were attached as substituent (**8a**, **9a**) at the *ortho* position of the aromatic part, the reaction proceeded only with copper catalyst. In the case of diynal (**10a**, **11a**) obtained with 1,7-diyne, the reaction proceeded better under gold catalyst. The methoxy group at the *ortho* position of the aromatic moiety creates a ring closure of intermediate ***A***. So, it forms another intermediate to proceed to the [6,6,5]-tricyclic compound.[21] This is because the Lewis acidity of $AuBr_3$ is stronger than that of $Cu(OTf)_2$. Therefore, in this case (**8a**, **9a**) it was confirmed that the copper catalyst reacted better than the gold catalyst.

The proposed mechanism shows a metal-catalyzed reaction from diynal to a [6,6,6]-tricyclic compound. Here, the metal catalyst can be gold, copper, or platinum. When the metal catalyst is mediated with substrate **1a**, it undergoes a benzannulation process. Through this process, it is activated by M^+ and forms the benzopyrylium intermediate ***A***.[26] Then, the bridged intermediate ***B*** is formed by the intramolecular [4+2] cycloaddition reaction. Finally, M^+ is continuously removed to synthesize a cyclic compound **1b** (Scheme 2).

In conclusion, transition-metal-catalyzed cyclization reactions were carried out with substrates obtained from the Sonogashira coupling with seven types of 1,6-diynes and four types of aromatic moieties. When the aromatic parts were 2-bromobenzaldehyde and 2′-bromoacetophenone, gold- or copper-catalyzed reactions were carried out with six substrates resulting in the formation of [6,6,6]-tricyclic compounds. The reaction using the gold catalyst proceeded well compared to that with the copper catalyst. When methoxy groups are attached to the aromatic parts, the reactivity varies depending on where they are attached. When the methoxy groups were in the *meta* position, the reaction proceeded well with the gold catalyst. However, when the methoxy groups were in the *ortho* position, the reaction proceeded well with the copper catalyst. This was because of the stronger Lewis acidity of the gold catalyst than that of the copper catalyst. In addition, we obtained [6,6,7]-tricyclic compounds in high yields through a gold-catalyzed cyclization reaction with diynal obtained from 1,7-diyne.

Conflict of Interest

The authors declare no conflict of interest.

Funding Information

This work was supported by a grant from the National Research Foundation of Korea (NRF), funded by the Korean Government, through the Center for New Directions in Organic Synthesis (NRF-2021R1A5A6002803).

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/a-1479-6005.

References and Notes

(1) Bertz, S. H. *J. Am. Chem. Soc.* **1981**, *103*, 3599.
(2) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49.
(3) Denmark, S. E.; Beutner, G. L. *Angew. Chem. Int. Ed.* **2008**, *47*, 1560.
(4) Wang, C.; Xi, Z. *Chem. Soc. Rev.* **2007**, *36*, 1395.
(5) Sasmal, S.; Dutta, U.; Lahiri, G. K.; Maiti, D. *Chem. Lett.* **2020**, *49*, 1406.
(6) Becica, J.; Dobereiner, G. E. *Org. Biomol. Chem.* **2019**, *17*, 2055.
(7) (a) Chen, D. Y.-K.; Ma, D. *Beilstein J. Org. Chem.* **2013**, *9*, 1192. (b) Yuan, C.; Liu, B. *Org. Chem. Front.* **2018**, *5*, 106.
(8) Elsby, M. R.; Baker, R. T. *Chem. Soc. Rev.* **2020**, *49*, 8933.
(9) Kondo, K.; Sodeoka, M.; Shibasaki, M. *J. Org. Chem.* **1995**, *60*, 4322.
(10) Majetich, G.; Liu, S.; Fang, J.; Siesel, D.; Zhang, Y. *J. Org. Chem.* **1997**, *62*, 6928.
(11) (a) Dyker, G.; Hildebrandt, D. *J. Org. Chem.* **2005**, *70*, 6093. (b) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180.
(12) (a) Saito, S.; Yamamoto, Y. *Chem. Rev.* **2000**, *100*, 2901. (b) Asao, N.; Nogami, T.; Lee, S.; Yamamoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 10921.
(13) Asao, N.; Sato, K.; Menggenbateer; Yamamoto, Y. *J. Org. Chem.* **2005**, *70*, 3682.
(14) Sadowska, B.; Kuźma, Ł.; Micota, B.; Budzyńska, A.; Wysokińska, H.; Kłys, A.; Więckowska-Szakiel, M.; Różalska, B. *Microb. Pathog.* **2016**, *98*, 132.
(15) González, M. A. *Nat. Prod. Rep.* **2015**, *32*, 684.
(16) González, M. A. *Eur. J. Med. Chem.* **2014**, *87*, 834.
(17) Wu, L.; Lu, Y.; Ding, Y.; Zhao, J.; Xu, H.; Chou, G. *Nat. Prod. Res.* **2019**, *33*, 2160.
(18) Xu, J.; Han, Q.-B.; Li, S.-L.; Chen, X.-J.; Wang, X.-N.; Zhao, Z.-Z.; Chen, H.-B. *Phytochem. Rev.* **2013**, *12*, 341.
(19) (a) Oh, C. H.; Piao, L.; Jung, J.; Kim, J. *Asian J. Org. Chem.* **2016**, *5*, 1237. (b) Park, M. S.; Kim, G.; Won, H.; Han, J. W.; Oh, C. H. *Bull. Korean Chem. Soc.* **2020**, *41*, 88. (c) Le, T. Q.; Karmakar, S.; Lee, S.; Chai, U.; Le, M. H.; Oh, C. H. *ChemistrySelect* **2019**, *4*, 11926. (d) Shin, S.; Gupta, A. K.; Rhim, C. Y.; Oh, C. H. *Chem. Commun.* **2005**, 4429.
(20) Kim, N.; Kim, Y.; Park, W.; Sung, D.; Gupta, A. K.; Oh, C. H. *Org. Lett.* **2005**, *7*, 5289.
(21) Seong, C.; Kang, J.; Chai, U.; Mac, D. H.; Oh, C. H. *Synlett* **2020**, *31*, 1953.
(22) Kanwal, I.; Mujahid, A.; Rasool, N.; Rizwan, K.; Malik, A.; Ahmad, G.; Shah, S. A. A.; Rashid, U.; Nasir, N. M. *Catalysts* **2020**, *10*, 443.
(23) **Procedure for the $AuBr_3$-Catalyzed Cyclization**
In a sealed tube was added **1a** (1.0 equiv, 30.9 mg, 0.10 mmol), $AuBr_3$ (1.3 mg, 3 mol%), and dry 1,2-dichloroethane (0.4 mL) under argon atmosphere. The mixture was then stirred at 80 °C for 2 h. The solvent was removed under reduced pressure to give crude products, which were purified by flash silica gel chromatography using a mixture of ethyl acetate/hexane (1:30) to furnish **1b** (24.9 mg, 82% yield, yellow liquid).
Procedure for the $Cu(OTf)_2$-Catalyzed Cyclization
In a sealed tube was added **1a** (1.0 equiv, 34.1 mg, 0.11 mmol), $Cu(OTf)_2$ (2.4 mg, 6 mol%), and dry 1,2-dichloroethane (0.4 mL) under argon atmosphere. The mixture was then stirred at 60 °C for 1 h. The solvent was removed under reduced pressure to give crude products, which were purified by flash silica gel chromatography using a mixture of ethyl acetate/hexane (1:30) to furnish **1b** (26.8 mg, 78% yield, yellow liquid). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.44 (dt, *J* = 8.8, 0.9 Hz, 1 H), 7.96 (dd, *J* = 8.3, 2.4 Hz, 1 H), 7.81 (dd, *J* = 8.1, 1.6 Hz, 1 H), 7.64 (ddt, *J* = 8.7, 6.9, 1.7 Hz, 1 H), 7.51 (ddt, *J* = 8.0, 6.8, 1.2 Hz, 1 H), 7.34 (dd, *J* = 8.5, 2.4 Hz, 1 H), 3.72–3.65 (m, 8 H), 3.27 (t, *J* = 1.3 Hz, 2 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 195.35, 170.30, 142.05, 135.47, 133.24, 131.17, 129.42, 128.47, 126.81, 126.43, 126.08, 55.00, 53.32, 45.26, 36.78.
(24) Saito, H.; Yorimitsu, H. *Chem. Lett.* **2019**, *48*, 1019.
(25) Jõgi, A.; Mäeorg, U. *Molecules* **2001**, *6*, 964.
(26) Sato, K.; Asao, N.; Yamamoto, Y. *J. Org. Chem.* **2005**, *70*, 8977.

