EurJOC
European Journal of Organic Chemistry

Communications
doi.org/10.1002/ejoc.202001643

Chemistry Europe
European Chemical Societies Publishing

Catalytic Synthesis of Dibenzazepines and Dibenzazocines by 7-*Exo*- and 8-*Endo-Dig*-Selective Cycloisomerization

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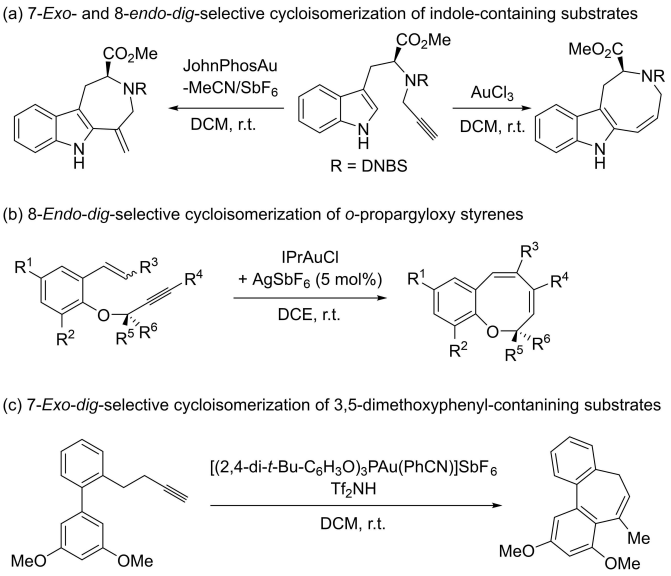
The 7-*exo*- and 8-*endo-dig*-selective gold-catalyzed cycloisomerizations of 2-propargylamino biphenyl derivatives were developed. The reaction of terminal alkynes gave dibenzo[*b*,*d*] azepines by 7-*exo-dig* cycloisomerization. In contrast, when internal alkynes were subjected to the reaction, 8-*endo-dig* cycloisomerization proceeded to provide dibenzo[*b*,*d*]azocines. The nucleophilicity at the reaction site and the electron-withdrawing effect of a tosyl group were important for the present selective transformation. This protocol could be used for ynamide substrates and a silver-catalyzed reaction gave 7-*exo-dig* products selectively.

Introduction

Gold-catalyzed cycloisomerization of 1,*n*-enynes is an atom-economical and convenient methodology for the synthesis of various cyclic compounds.[1] In particular, the use of a benzene ring as an ene moiety enabled the construction of benzo-fused bicyclic compounds. Generally, the cycloisomerization of enynes using a benzene ring as an ene moiety can be categorized by Baldwin's rule and the most well-established cycloisomerization is 6-*endo-dig* cyclization.[2,3] Despite the extensive development of gold-catalyzed cycloisomerization, there have been a few reports on the construction of a more than seven-membered ring.[4–8] Especially, the selective transformation of compounds with various cyclization patterns and/or multiple reaction sites is still a challenging topic. To control the reaction pathway, the use of a highly reactive substrate is a possible strategy (Scheme 1): Echavarren and co-workers reported the gold-catalyzed 7-*exo-dig*- or 8-*endo-dig*-selective cycloisomerization of alkynylindoles (Scheme 1a).[4] The reaction selectively proceeded at the highly nucleophilic C2 position of the indole ring, and the regioselectivity could be perfectly controlled by the choice of the gold catalyst. The 8-*endo-dig* product was considered to be delivered via a 7-*endo-dig* spirocyclic intermediate. Van der Eycken and co-workers also reported similar gold-catalyzed 8-*endo-dig*-selective cycloisomerization.[5] Waldmann and co-workers achieved the 8-*endo-dig*-selective cycloisomerization of *o*-propargyloxy styrenes to provide benzoxines (Scheme 1b).[6] The electron-donating resonance effect of oxygen atom was essential for the selective 8-*endo-dig* reaction[7] and the substituent (R^2) hampered the reaction site for 6-*endo-dig* cyclization. Notably, examples of gold-catalyzed 8-*endo-dig*-selective cycloisomerization, not via a 7-*endo-dig* intermediate, are still rare.[7] Hashmi and co-workers reported the 7-*exo-dig*-selective cycloisomerization of a biaryl possessing a homopropargyl substituent to give dibenzocycloheptatrienes (Scheme 1c).[8] The 5-*exo*- and 6-*endo-dig* cyclization was prevented by using 3,5-dimethoxyphenyl moiety as an electron-rich arene ring.



Scheme 1. Gold-catalyzed construction of seven- and eight-membered rings.

Previously, we reported the gold-catalyzed 8-*exo-dig*-selective cycloisomerization of *N*,*N*-diphenyl-2-(propargylamino) aniline derivatives to provide dibenzodiazocines (Scheme 2a).[9e] In this work, we considered that the steric repulsion between tosyl group and diphenylamino group induced the desired 8-*exo-dig* cyclization of the alkyne moiety with the arene ring (Ar^1) and that the electron-withdrawing effect of the tosyl group reduced the reactivity of the arene ring (Ar^2), which is derived into undesired 6-*endo-dig* cycloadduct. Against this background, we envisioned the gold-catalyzed 7-*exo*- and 8-*endo*-

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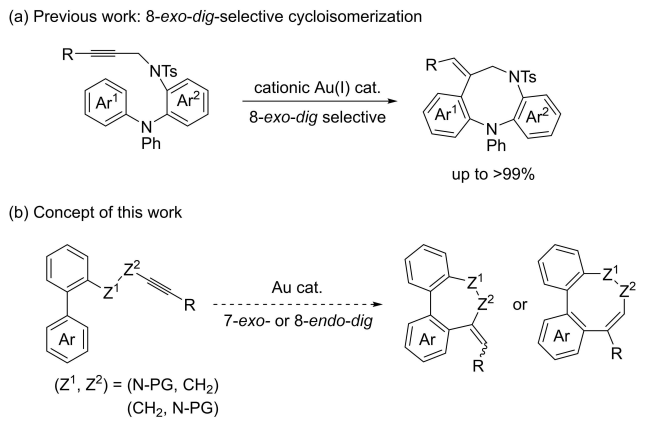
Supporting information for this article is available on the WWW under https://doi.org/10.1002/ejoc.202001643

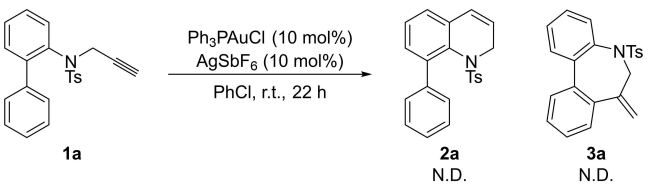


Scheme 2. Our previous work and concept of this work

dig-selective cycloisomerization of nitrogen-tethered biphenyl-containing alkynes for the synthesis of dibenzazepines and dibenzazocines (Scheme 2b). While some reports have disclosed that the regioselectivity was changed by the substituent at the alkyne termini,[4b,5] we anticipated that the reaction pathway could be controlled by the choice of internal or terminal alkyne.

Results and Discussion

First, we subjected 2-propargylamino-*N*-tosylbiphenyl (**1a**) to gold(I)-catalyzed cycloisomerization using $AgSbF_6$ as a silver salt



Scheme 3. Cationic gold-catalyzed reaction of biphenyl **1a**.

in chlorobenzene, which were the best conditions in our previous study[9e] (Scheme 3). However, the starting material remained and undesired 6-*endo-dig* product **2a** or desired 7-*exo-dig* product **3a** was not detected along with the formation of a ketone by alkyne hydration.

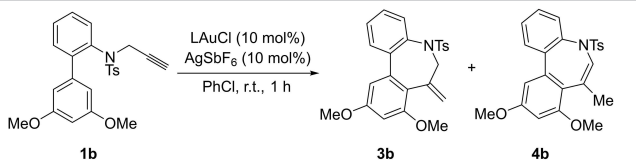
We introduced two methoxy groups to enhance the nucleophilic nature of the arene moiety (Table 1). To our delight, the gold-catalyzed reaction of **1b** proceeded at room temperature to give the desired 7-*exo-dig* product **3b** and isomerized product **4b** as a mixture in moderate yield (Entry 1). We pleased to find that NHC ligands were effective for the present cycloisomerization (Entries 2 and 3). When IPr was used, the 7-*exo-dig* product **3b** was obtained in excellent yield, which was isomerized to **4b** by acidic treatment using $HNTf_2$ (Entry 2).[10] In contrast, in the case of ICy, the formation of **3b** could not be detected and **4b** was the only product (Entry 3).[7] We chose IPrAuCl as an optimum catalyst because of its stability and readily availability.

Under the conditions for Entry 2 in Table 1, the substituents on the *ortho*-phenylene tether were investigated (Table 2). All products were isolated and characterized as *endo* olefins **4** after acidic treatment. Both electron-donating and -withdrawing substituents could be tolerated to give the corresponding cycloadducts (Entries 1–8). In particular, the reaction of sterically hindered 4-Me-substituted substrate **1j** also gave the corresponding product **4j** in high yield, which had axial chirality.[11]

Next, we examined the effect of the aromatic ring and protecting group of the nitrogen (Scheme 4). When 3-methoxyphenyl was introduced in place of a 3,5-dimethoxyphenyl group, the reaction of **1k** proceeded to give *exo* olefin **3k** as an inseparable mixture with a small amount of unknown product(s). When PPh_3 was used as a ligand, product **3k** could be isolated in moderate yield without formation of regioisomer **3k'** (eq. (1)). The reaction of NH-free substrate **1l** gave 6-*endo-dig* product **2l** along with aromatization, yet in low yield, and 7-*exo-dig* product could not be detected at all (eq. (2)). This result indicated that the electron-withdrawing effect of a tosyl group suppressed 6-*endo-dig* cyclization.

The results using internal alkynes are shown in Table 3. When the reaction of Ph-substituted alkyne **5a** was conducted under the optimal conditions, starting material **5a** was

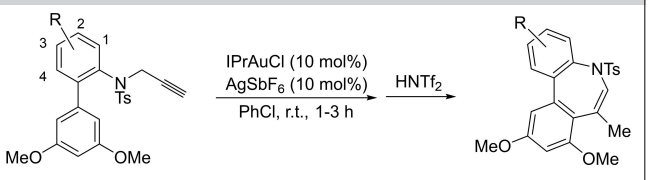
Table 1. Screening of reaction conditions.[a]



Entry	L	Yield of **3b** [%][b]	Yield of **4b** [%][b]
1	PPh_3	21[c]	21[c]
2	IPr	ca. 98 (N.D.)	trace (>99)
3	ICy	N.D.	>99

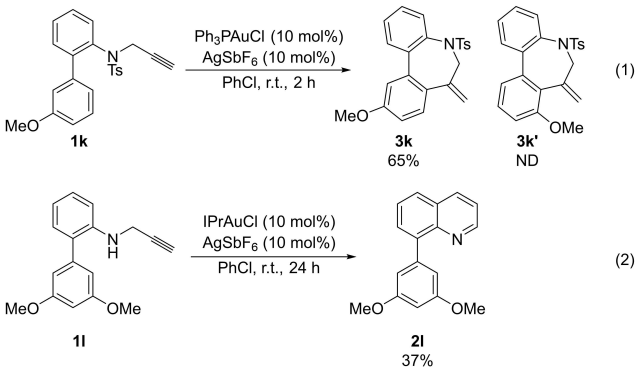
[a] Reaction conditions: **1a** (0.05 mmol), LAuCl (10 mol%), $AgSbF_6$ (10 mol%), PhCl (0.5 mL), r.t., 1 h. [b] Isolated yield. The yield after the treatment of $HNTf_2$ (10 mol%) is shown in the in parentheses. [c] The NMR yields were measured using 1,1,2,2-tetrachloroethane as an internal standard. IPr: 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene, ICy: 1,3-dicyclohexylimidazol-2-ylidene.

Table 2. Scope of substituents on phenylene-tether.[a]



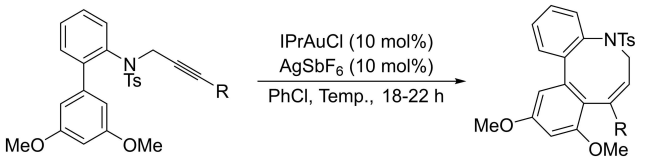
Entry	R	Yield [%][b]	Entry	R	Yield [%][b]
1	1-F (**1c**)	91 (**4c**)	5	3-Me (**1g**)	94 (**4g**)
2	2-Me (**1d**)	94 (**4d**)	6	3-CF_3 (**1h**)	95 (**4h**)
3	2-Cl (**1e**)	97 (**4e**)	7	3-*i*-Pr (**1i**)	88 (**4i**)
4	2-CF_3 (**1f**)	>99 (**4f**)	8	4-Me (**1j**)	90 (**4j**)

[a] Reaction conditions: **1** (0.05 mmol), IPrAuCl (10 mol%), $AgSbF_6$ (10 mol%), PhCl (0.5 mL), r.t., then $HNTf_2$ (ca. 5 mg). [b] Isolated yield.



Scheme 4. Effect of aromatic ring and protecting group of nitrogen.

Table 3. Scope of internal alkynes.[a]



Entry	R	Temp. [°C]	Yield [%][b]
1	Ph (**5a**)	20	67
2	4-FC_6H_4 (**5b**)	r.t.	>99
3	4-ClC_6H_4 (**5c**)	r.t.	85
4[c]	4-$CF_3C_6H_4$ (**5d**)	r.t.	67
5[c]	4-MeC_6H_4 (**5e**)	10	58
6[c]	4-$MeOC_6H_4$ (**5f**)	10	41
7	Me (**5g**)	r.t.	N.D.

[a] Reaction conditions: **5** (0.05 mmol), IPrAuCl (10 mol%), and $AgSbF_6$ (10 mol%), PhCl (0.5 mL). [b] Isolated yield. [c] IPrAuCl (20 mol%), $AgSbF_6$ (20 mol%) were used.

completely consumed at room temperature (25 °C). Surprisingly, 8-*endo-dig* cyclization proceeded to give dibenzazocine **6a** as an inseparable mixture with a small amount of unknown product(s). The present reaction was susceptible to the reaction temperature and product **6a** was isolated in moderate yield at 20 °C (Entry 1) and its structure was finally confirmed by single-crystal X-ray analysis (Figure 1). Electron-withdrawing group-substituted alkynes **5b**–**5d** gave the desired products **6b**–**6d** in good to excellent yield at room temperature. In contrast, the reaction of electron-donating group-substituted alkynes **5e** and **5f** should be conducted at 10 °C, and the corresponding cycloadducts **6e** and **6f** were isolated in moderate yields. When the reaction of Me-substituted alkyne **5g** was conducted, the substrate was completely consumed, but the cyclized products could not be obtained. In all entries, the formation of 7-*exo-dig* products could not be ascertained.

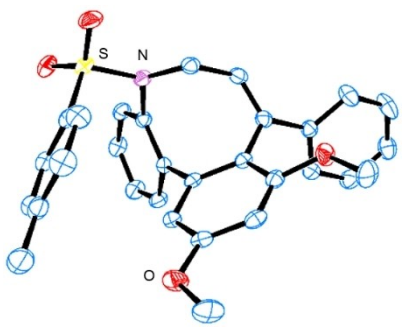
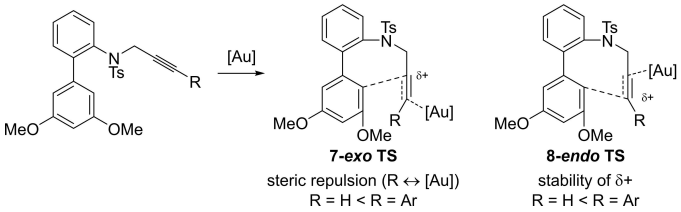


Figure 1. ORTEP diagram of **6a**. Ellipsoids are set at 50% probability.

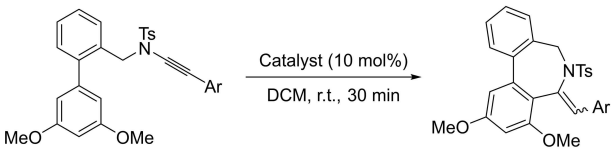
We can explain the perfect regioselectivity dependent on the substituent on the alkyne terminus in terms of steric repulsion and cation stability (Scheme 5). In the case of a terminal alkyne (R = H), the gold catalyst attaches to the less bulky terminal position of the alkyne, which is derived into the 7-*exo-dig* cyclization. In contrast, in the reaction of aryl-substituted alkyne (R = Ar), the gold catalyst reacts with the relatively less bulky internal position of the alkyne, which induces the cation at the benzylic position.

As an extension of the substrate scope, we next examined ynamide **7a**, in which nitrogen is moved to the homo-benzylic position (Table 4). With the combination of Ph_3PAuCl and $AgSbF_6$, the reaction gave 7-*exo-dig* product **8a** as an *E*/*Z* mixture in high total yield (Entry 1). The choice of silver salt affected the *E*/*Z* ratio, and (*Z*)–**8a** was the only product with the use of $AgNTf_2$ and AgOTf (Entries 2 and 3). Actually, the present transformation could be achieved using only the silver salt without the gold complex (Entries 4 and 5). Interestingly, even a substoichiometric amount of Brønsted acid could facilitate this reaction and (*E*)–**8a** was the only product (Entry 6). We



Scheme 5. Explanation for regioselectivity.

Table 4. Screening of reaction conditions of ynamide **7a**.[a]

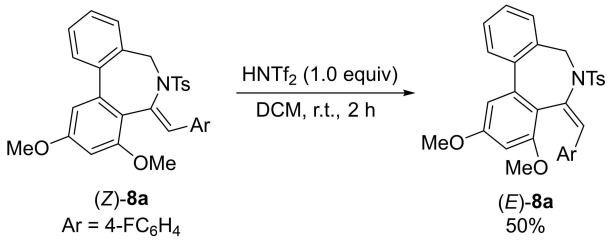


Entry	Catalyst	Yield of (*Z*)–**8a** [%][b]	Yield of (*E*)–**8a** [%][b]
1	$Ph_3PAuCl + AgSbF_6$	24	66
2	$Ph_3PAuCl + AgNTf_2$	94	N.D.
3	$Ph_3PAuCl + AgOTf$	82	N.D.
4	$AgNTf_2$	93 (92)[c]	N.D.
5	AgOTf	84	N.D.
6	TfOH (30 mol%)	N.D.	87

[a] Reaction conditions: **7a** (0.05 mmol), catalyst (10 mol%), DCM (0.5 mL), r.t., 30 min. [b] Isolated yield. [c] The yield of 0.25 mmol scale is shown in the parentheses.

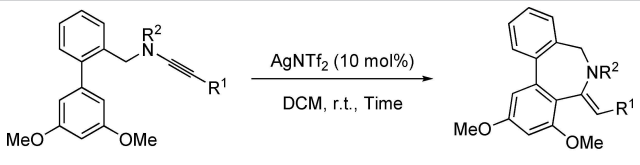
ascertained that (*E*)-**8a** is the secondary product by the double-bond isomerization of (*Z*)–**8a** in acidic conditions (Scheme 6).

Table 5 shows the scope of the aryl group at the alkyne terminus in the silver-catalyzed 7-*exo-dig* cyclization. Electron-withdrawing groups at the *para*, *meta*, and *ortho* positions were tolerable and the corresponding dibenzo[*c*,*e*]azepane derivatives **8b**–**8g** were obtained in good to excellent yields (Entries 1–6). The parent Ph-substituted ynamide **7h** also gave the desired product **8h** in good yield under the same reaction conditions (Entry 7). In the case of electron-donating methyl-substituted substrate **7i**, the reaction proceeded smoothly, however, the 7-*exo-dig* product **8i** was obtained as an *E*-isomer (Entry 8). We hypothesized that a resonance effect of the nitrogen atom induced the double-bond isomerization. In fact, more electron-deficient nosyl-substituted nitrogen substrate **7i'** selectively provided **8i'** in the *Z*-form at an elevated reaction temperature (Entry 9). Ns protection could also be used for electron-deficient aryl-substituted ynamide **7a'**, and the desired compound **8a'** was obtained in high yield (Entry 10). Alkyl-substituted alkyne was also available and compound **7j** could be transformed into cycloadduct (*Z*)–**8j** stereoselectively (Entry 11).



Scheme 6. Double bond isomerization under the acidic conditions.

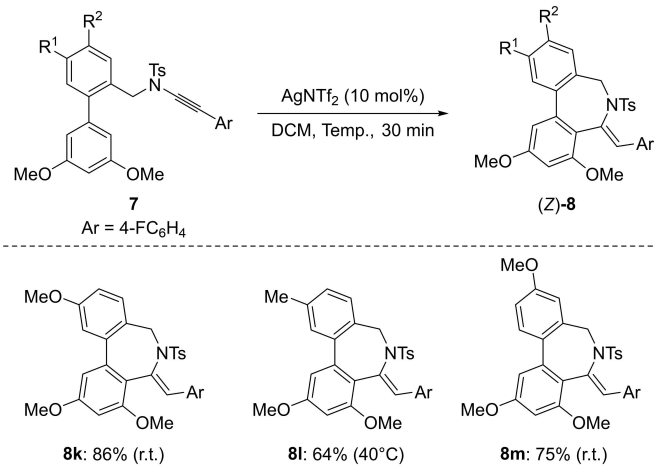
Table 5. Scope of substituents on ynamide.[a]



7
R^2 = Ts: **7b**-**7j**
R^2 = Ns: **7a'**, **7i'**

Entry	R^1	Time [h]	Yield of **8** [%][b]
1	4-$CF_3C_6H_4$ (**7b**)	1	91 (**8b**)
2	3-FC_6H_4 (**7c**)	1	88 (**8c**)
3	3-ClC_6H_4 (**7d**)	1.5	79 (**8d**)
4	3-$NO_2C_6H_4$ (**7e**)	4.5	61 (**8e**)
5	2-FC_6H_4 (**7f**)	1	88 (**8f**)
6	2-ClC_6H_4 (**7g**)	1	93 (**8g**)
7	Ph (**7h**)	1.5	76 (**8h**)
8	4-MeC_6H_4 (**7i**)	6	73 (**8i**)[c]
9[d]	4-MeC_6H_4 (**7i'**)	0.5	73 (**8i'**)
10[d]	4-FC_6H_4 (**7a'**)	0.5	90 (**8a'**)
11	*n*-C_6H_{13} (**7j**)	2	75 (**8j**)

[a] Reaction conditions: **7a** (0.05 mmol), catalysts (10 mol%), DCM (0.5 mL), r.t. [b] Isolated yield. [c] The *E* isomer was obtained. [d] 40 °C.



Scheme 7. Scope of *ortho*-phenylene-tether.

The substituent on the *ortho*-phenylene tether was investigated (Scheme 7). Methyl- and methoxy-substituted substrates could be transformed into multi-substituted dibenzo[*c*,*e*]azepanes **8k**–**8m**.

Conclusions

We achieved the selective construction of dibenzo[*b*,*d*]azepine and dibenzo[*b*,*d*]azocine skeletons by the gold(I)-catalyzed cycloisomerization of (2-propargylamino)biphenyl: while the reaction of terminal alkynes proceeded in a 7-*exo-dig* manner, aryl-substituted alkynes underwent 8-*endo-dig*-selective cyclization. The selective formation of dibenzo[*c*,*e*]azepanes was attained by the silver-catalyzed 7-*exo-dig* cyclization of ynamides. The hydroarylation proceeded in *Z* selectivity with the use of silver catalysts and in *E* selectivity with the use of Brønsted acid.

Experimental Section

General procedures for the cycloisomerization in Table 2: 2-propargyltosylaminodiphenylaniline derivative **1** (0.050 mmol) was placed in a Schlenk tube in air. This reaction vessel was evacuated and backfilled with argon (×3), and then IPrAuCl (10 mol%) and $AgSbF_6$ (10 mol%) were added to the reaction vessel in a globe box. After the addition of solvent (0.5 mL), the reaction mixture was stirred at room temperature for 1–3 h. Then, $HNTf_2$ (ca. 5 mg) was added to the reaction mixture and the resulting solution was stirred for 5 min. After removal of solvent, the crude products were filtered through a pad of silica gel, and purified by PTLC to give desired cyclized product **4**.

General procedures for the cycloisomerization in Table 3: internal alkyne **5** (0.050 mmol) was placed in a Schlenk tube in air. This reaction vessel was evacuated and backfilled with argon (×3), and then IPrAuCl (10 mol%) and $AgSbF_6$ (10 mol%) were added to the reaction vessel in a globe box. After the addition of PhCl (0.5 mL), the reaction mixture was stirred at corresponding temperature for 18–22 h. After removal of solvent, the crude products were filtered

through a pad of silica gel, and purified by PTLC to give desired cyclized product **6**.

General cycloisomerization in Table 5: in a dried Schlenk tube, $AgNTf_2$ (10 mol%) was placed in a glove box. Then, ynamide derivatives **7** (0.050 mmol) dissolved in DCM (0.5 mL) was added to the reaction vessel and stirred at room temperature for 0.5–6 h. After removing solvent under reduced pressure, the crude products were purified by preparative TLC to give desired product (*Z*)–**8**.

Deposition Numbers 2045661 (for **6a**), 2049210 (for (*E*)–**8a**), and 2046078 (for (*Z*)–**8a**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service www.ccdc.cam.ac.uk/structures.

Acknowledgements

This work was supported by Waseda University Grant for Special Research Projects (2019C-565).

Conflict of Interest

The authors declare no conflict of interest.

Keywords: Cycloisomerization · Gold catalysis · 7-*Exo-dig* · 8-*Endo-dig* · NHC ligands

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Manuscript received: December 19, 2020
Revised manuscript received: February 1, 2021
Accepted manuscript online: February 10, 2021