

HETEROCYCLES, Vol. 101, No. 1, 2020, pp. 195 - 208. © 2020 The Japan Institute of Heterocyclic Chemistry
Received, 7th May, 2019, Accepted, 4th June, 2019, Published online, 31st July, 2019
DOI: 10.3987/COM-19-S(F)13

GOLD(I)-CATALYZED 10-*ENDO-DIG*-SELECTIVE CYCLO-ISOMERIZATION OF *N*-(2-ANILINO BENZYL)PROPARGYLAMINES

Mamoru Ito,*¹ Daisuke Inoue,¹ Asahi Takaki,¹ Kyalo Stephen Kanyiva,² and Takanori Shibata*¹

¹ Department of Chemistry and Biochemistry, School of Advanced Science and Engineering, Waseda University, 3-4-1 Okubo, Shinjuku, Tokyo 169-8555, Japan.

² Global Center for Science and Engineering, School of Advanced Science and Engineering, Waseda University, 3-4-1 Okubo, Shinjuku, Tokyo 169-8555, Japan.

E-mail: tshibata@waseda.jp

Dedicated to Professor Kaoru Fuji on the occasion of his 80th birthday

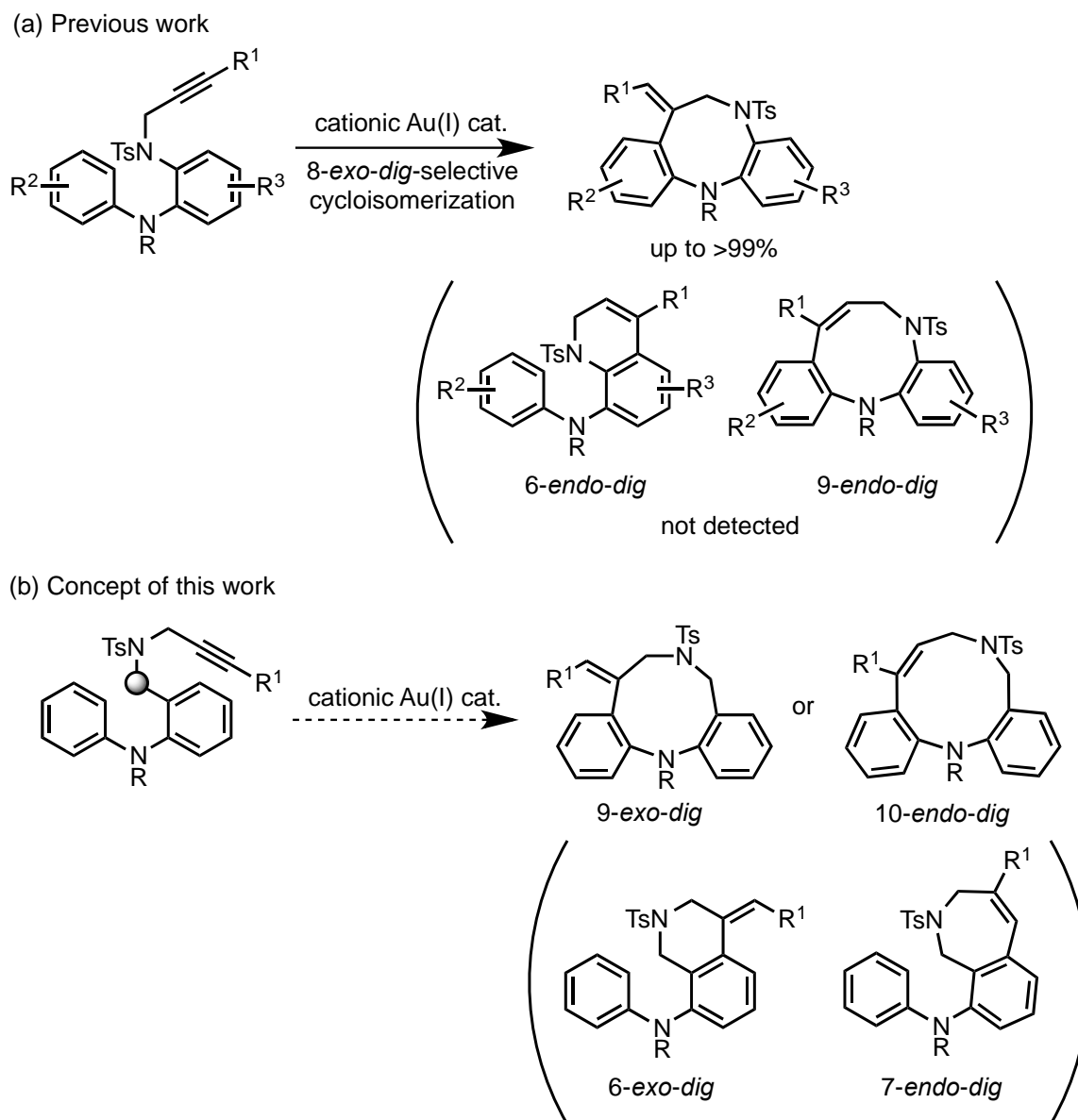
Abstract – The cationic gold(I)-catalyzed 10-*endo-dig*-selective cycloisomerization of *N*-(2-anilinobenzyl)propargylamine derivatives was developed. The reaction proceeded smoothly under mild conditions to give dibenzodiazecines. The catalytic construction of an entropically and enthalpically disfavored ten-membered ring was achieved by using a highly nucleophilic 3,5-dimethoxyanilino group as a reaction site.

INTRODUCTION

The formation of medium-sized rings is a challenging topic because of unfavorable entropic and enthalpic factors.^{1a,b} Several strategies have been developed for the construction of medium-sized rings. The most common methodologies are the ring expansion of cyclic compounds and the cyclization of acyclic compounds.^{1a,b} In particular, ring-closing metathesis of vinyl group-containing compounds is a well-developed method.^{1c-e} However, the scope of substrates is still limited and the development of a new protocol for the formation of medium-sized rings is still important.

Against this background, gold-catalyzed cyclization has been vigorously studied because of its high atom efficiency and diverse reactivity.² In 2018, we reported gold(I)-catalyzed 8-*exo-dig*-selective cycloisomerization to give dibenzodiazocines selectively (Scheme 1a).³ The two nitrogen atoms at the tether moiety and the ligand were important for the 8-*exo-dig*-selectivity by suppressing 6-*endo-dig* and 9-*endo-dig* products. We next chose *N*-(2-anilinobenzyl)propargylamine derivatives as substrates, which

are one-carbon homologues of the substrates in our previous work. We sought to obtain *9-exo-dig* and/or *10-endo-dig* cycloadducts without the formation of *6-exo-dig* or *7-endo-dig* products (Scheme 1b).

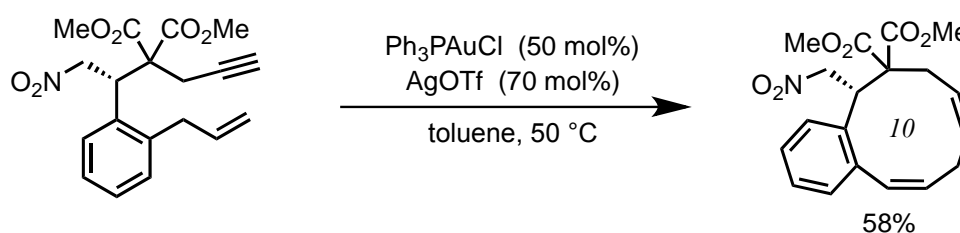


Scheme 1. Our previous work and concept of this research

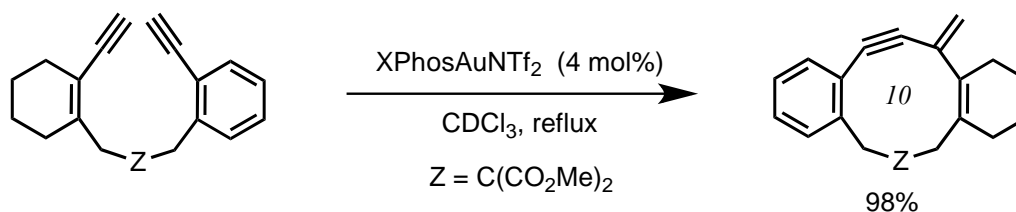
There are only a few examples of the direct construction of a nine- or ten-membered ring via gold-catalyzed enyne cycloisomerization (Scheme 2).⁴ While Porco and co-workers reported the first example of gold(I)-catalyzed *10-endo-dig*-selective cycloisomerization of 1,9-enyne, the yield was moderate even with the use of a substoichiometric amount of a cationic gold catalyst (Scheme 2a).^{4a} Gagosz and co-workers developed 9- or *10-exo-dig*-selective cycloisomerization of diynes to provide medium-sized cycloalkynes (Scheme 2b).^{4b} In this transformation, the gold catalyst is considered to play two roles: conventional electrophilic activation by its π -coordination to alkyne and nucleophilic activation

by the formation of gold acetylide prepared from a terminal alkyne moiety. [2+2] Cycloaddition of enynes has also been developed to construct medium rings including nine- and ten-membered rings. Echavarren and co-workers achieved the macrocyclization of 1,*n*-enynes by intramolecular [2+2] cycloaddition (Scheme 2c).^{4c} Snyder and a co-worker reported the gold(III)-catalyzed 9-*exo-dig*-selective hydroarylation of alkynes (Scheme 2d).^{4d} The reaction proceeded at the highly nucleophilic 3,5-dimethoxyphenyl ring.

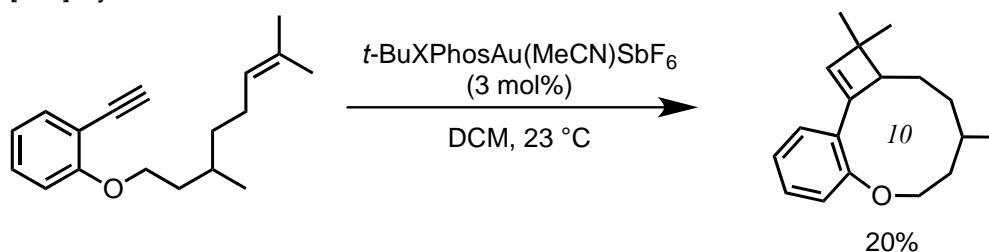
(a) 10-*endo-dig* Cycloisomerization



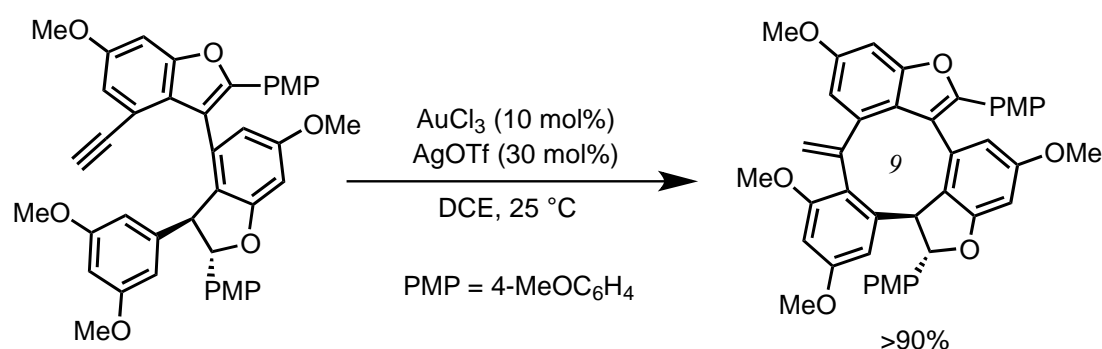
(b) 10-*exo-dig* Cycloisomerization



(c) [2+2] Cycloaddition



(d) 9-*exo-dig* Hydroarylation



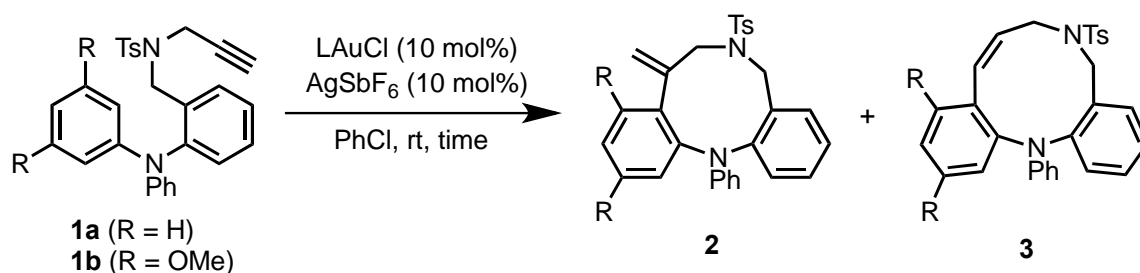
Scheme 2. Gold-catalyzed construction of nine and ten-membered rings

RESULTS AND DISCUSSION

Initially, we chose *N*-(2-(diphenylamino)benzyl)-*N*-tosylpropargylamine (**1a**) as a model substrate, based

on our previous work (Table 1).³ When the reaction of **1a** was conducted using chloro(triphenylphosphine)gold(I) and silver hexafluoroantimonate in chlorobenzene at room temperature for 24 h, most of the substrate remained unreacted and the desired cyclized product **2** or **3** was not detected (Entry 1). To increase the reactivity of the alkyne moiety, more-electrophilic gold catalysts were used, but the starting material was not consumed and no cyclized product was obtained (Entries 2 and 3). We next considered nucleophilic activation of the arene moiety by the introduction of electron-donating groups, and chose 3,5-dimethoxyphenyl group as a reaction site.⁵ Gratifyingly, the reaction of 3,5-dimethoxyphenyl group-containing substrate **1b** concluded within 1 h to give 10-*endo-dig* cycloadduct **3b** selectively in excellent yield (Entry 4). The structure of **3b** was finally confirmed by single-crystal X-ray structure analysis (Figure 1). Based on the results of ¹H NMR, a trace amount of 9-*exo-dig* product **2b** was also obtained, but the amount was too little to be fully characterized.

Table 1. Screening of reaction conditions^a



| Entry | R | Ligand (L) | Time (h) | Yield of 2 (%) | Yield of 3 (%) |
|-------|-----|--|----------|-----------------------|-----------------------|
| 1 | H | PPh ₃ | 24 | N.D. | N.D. |
| 2 | H | P(C ₆ F ₅) ₃ | 24 | N.D. | N.D. |
| 3 | H | P(4-CF ₃ C ₆ H ₄) ₃ | 24 | N.D. | N.D. |
| 4 | OMe | PPh ₃ | 1 | trace | 97 (3b) |

^a Reaction conditions: **1** (0.05 mmol), LAuCl (10 mol%), AgSbF₆ (10 mol%), PhCl (0.5 mL).

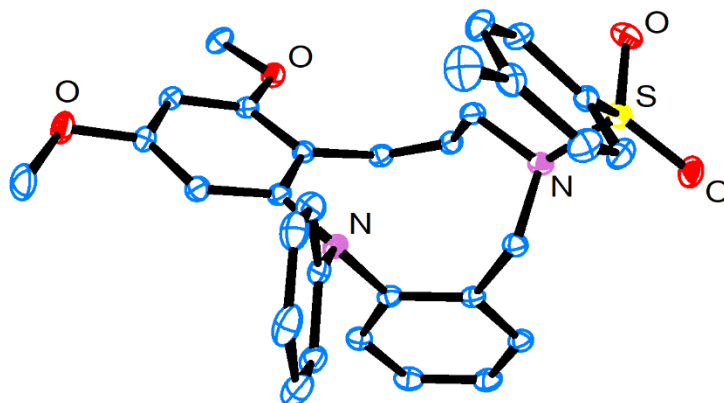
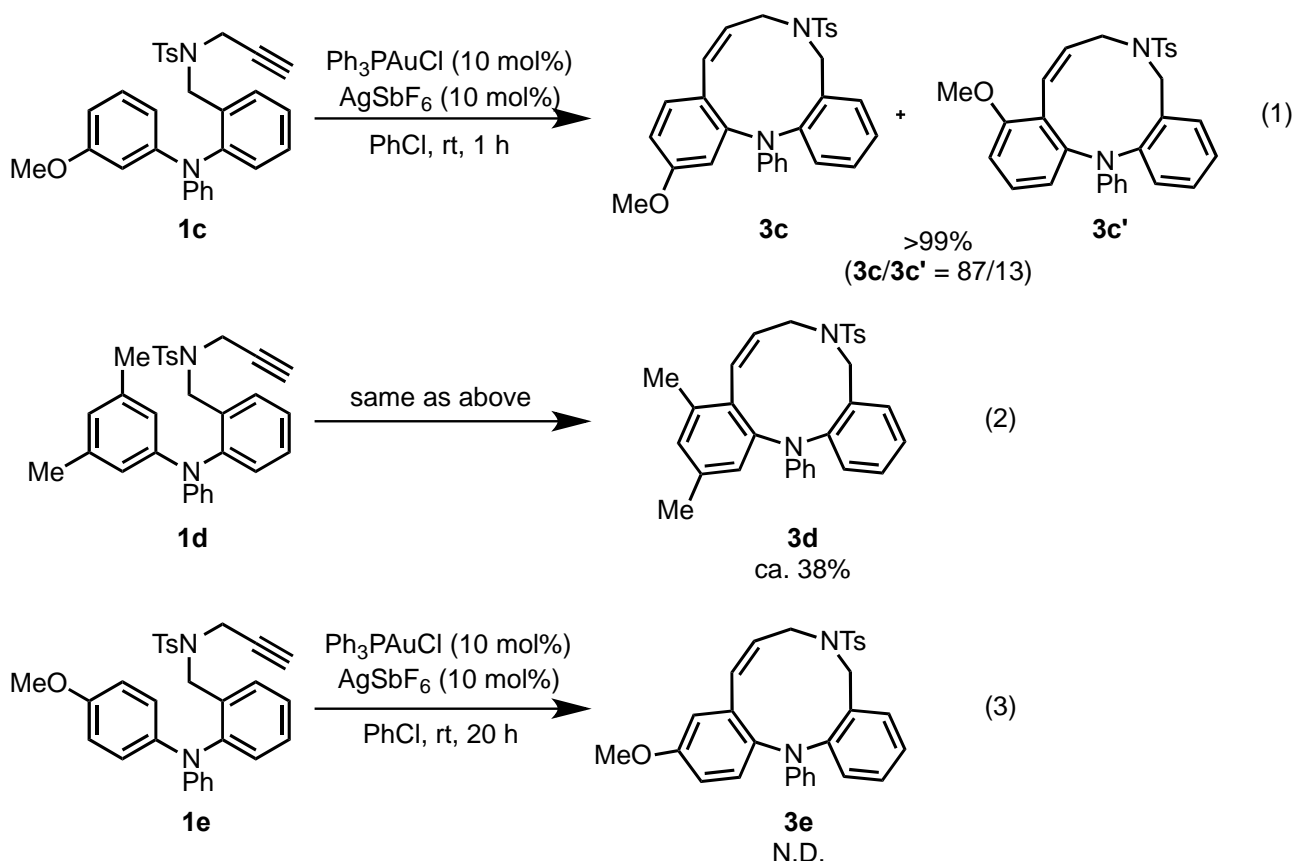


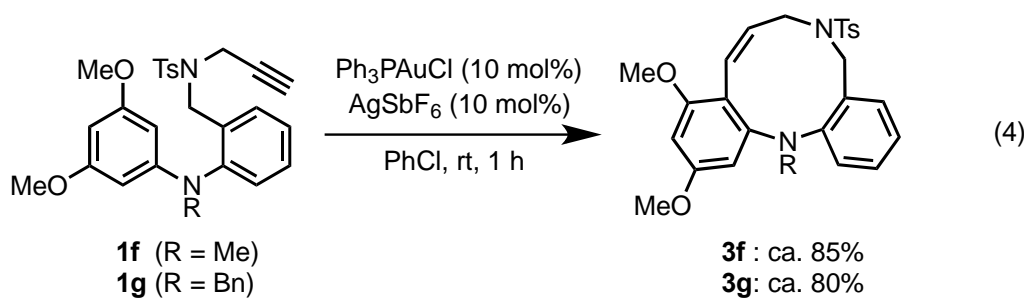
Figure 1. ORTEP diagram of compound **3b** (thermal ellipsoids shown at 50% probability)

Under the optimized conditions of Entry 4 in Table 1, we examined the effect of electron-donating group(s) on the arene moiety (Scheme 3). The reaction of *m*-methoxyphenyl group-containing substrate **1c** gave the 10-*endo-dig* products selectively as a mixture of regioisomers **3c** and **3c'** in excellent total yield [Scheme 3, Equation (1)]. The reaction proceeded at a less-hindered site to provide **3c** as a major isomer, as expected. When 3,5-dimethylphenyl group-containing substrate **1d** was examined, it was consumed, but the reaction was messy. The desired product **3d** was obtained along with a small amount of inseparable by-product, which might be the 9-*exo-dig* product based on the results of ¹H NMR [Scheme 3, Equation (2)]. While *p*-methoxyphenyl group-containing substrate **1e** was completely consumed in 20 h, cycloadducts including the desired product **3e** were not detected among many products [Scheme 3, Equation (3)]. These results indicate that the strong electron-donating resonance effect of a methoxy group is needed for selective 10-*endo-dig* cycloisomerization.



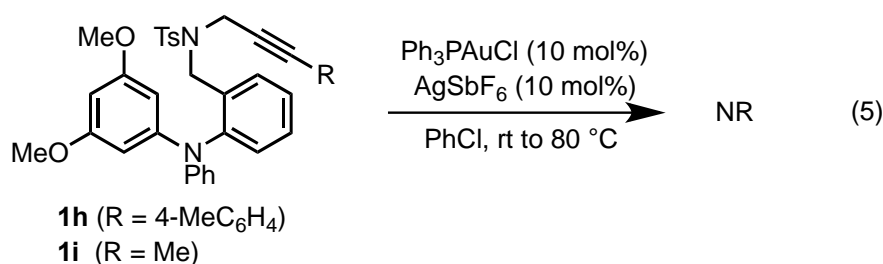
Scheme 3. Effect of electron-donating group(s) on the arene moiety

To expand the scope of this transformation, the substituent on the nitrogen atom was explored (Scheme 4). In the case of methyl-substituted substrate, the reaction proceeded smoothly to provide **3f** in high yield. When readily deprotectable benzyl-substituted substrate **1g** was subjected to the reaction, the desired product **3g** was obtained in high yield. In both reactions, by-products, which might be 9-*exo-dig* products judging from ¹H NMR, were also obtained in ca. 10% yield, but could not be excluded from **3f** or **3g**.



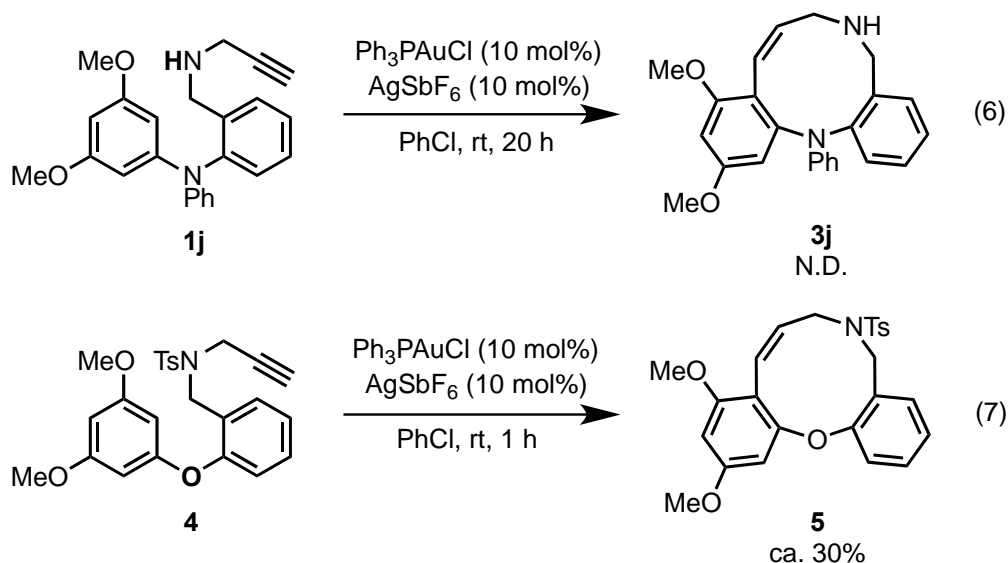
Scheme 4. Reaction of *N*-alkyl substrates

Next, internal alkynes **1h** and **1i** were subjected to the optimized conditions, but, in each case, no reaction proceeded even at high temperature in each case (Scheme 5). We considered that the steric repulsion between substituent (R) and methoxy group interfered with the approach of an alkyne moiety to the reaction site.



Scheme 5. Reaction of internal alkynes

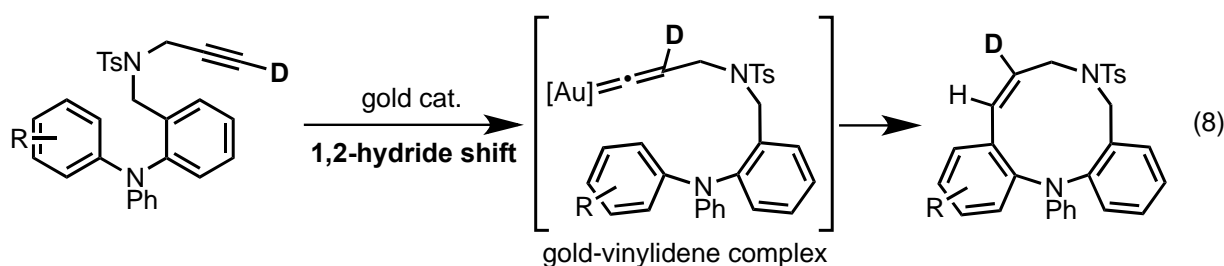
During substrate screening, we found that the tosyl group played an important role [Scheme 6, Equation (6)]. The reaction of *N*-H-free substrate **1j** did not give any cyclized product, and the substrate was recovered. To examine the effect of the tether moiety, the reaction of aryl ether **4**, an oxygen analogue of **1b**, was examined under the optimal reaction conditions [Scheme 6, Equation (7)]. The desired cycloadduct **5** (ca. 30%) was obtained together with the unreacted substrate **4** (ca. 70%), as ascertained by ¹H NMR.⁶ We speculated that the flexible aryloxy group decreased the probability of its access to the alkyne moiety compared with a diarylamino group.



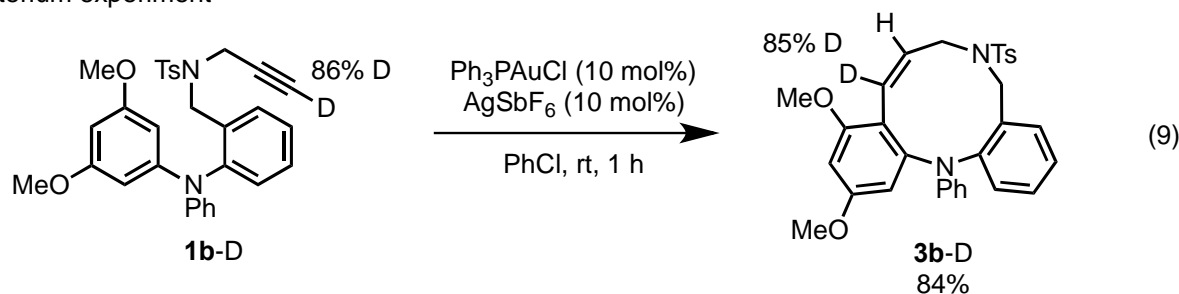
Scheme 6. Effect of the tether moiety on the cycloisomerization

N-Benzylpropargylamine derivatives were reported to be less reactive for 6-*exo*- or 7-*endo-dig* transformation under gold-catalyzed conditions.⁷ To gain further insight into 10-*endo-dig* selectivity, a deuterium experiment was conducted (Scheme 7). When the reaction proceeded via a gold-vinylidene complex generated by a 1,2-hydride shift, the migration of deuterium would be observed [Scheme 7, Equation (8)].⁸ When the reaction of **1b-D** was examined, no deuterium-migration was detected. This result indicated that the gold-catalyzed reaction proceeded by π -activation of the terminal alkyne. We considered that the steric factor would give 10-*endo-dig* cycloisomerization an advantage over 9-*endo-dig* cycloisomerization, because no reaction proceeded for the internal alkynes (Scheme 5).

Speculated mechanism of 10-*endo-dig* selectivity



Deuterium experiment



Scheme 7. Deuterium experiments as a mechanistic study

In conclusion, we achieved 10-*endo-dig*-selective cycloisomerization by using a 3,5-dimethoxyphenyl group as a nucleophile. The structure was confirmed by single-crystal X-ray analysis. The strong electron-donating effect of a methoxy group was crucial for high reactivity and a terminal alkyne could be used for this reaction. The reactions of other tether-containing substrates revealed that the substituents on nitrogen atoms were important for the high reactivity. A deuterium experiment indicated that the reaction proceeded via π -activation of the terminal alkyne.

EXPERIMENTAL

General: ^1H NMR spectra were recorded on JEOL ECX-500 (500 MHz) spectrometers. The chemical shifts were reported in parts per million (δ) relative to internal standard TMS (0 ppm) for CDCl_3 . The coupling constants, J , are reported in Hertz (Hz). The peak patterns are indicated as follows: s, singlet; d, doublet; dd, doublet of doublet; t, triplet; dt, doublet of triplet; m, multiplet; q, quartet; brs, broad singlet. ^{13}C NMR spectra were obtained by JEOL ECX-500 (125 MHz) spectrometers and referenced to the internal solvent signals (central peak is 77.16 ppm in CDCl_3). CDCl_3 was used as a NMR solvent. High-resolution mass spectra (HRMS) were measured on a JMS-T100CS with ESI (Electro Spray Ionization) method. Preparative thin-layer chromatography (PTLC) was performed with silica gel-precoated glass plates (Wakogel B-5F) prepared in our laboratory, and flash silica gel column chromatography was performed over silica gel 200-300. All reagents except gold(I) complex and silver salt were weighed and handled in air and backfilled under argon at room temperature. Gold(I) complex and silver salt were weighed under argon in globe box at room temperature. All reactions were performed under an argon atmosphere. 3,5-Dimethoxy-*N*-phenylbenzenamine⁹ and 3,5-dimethoxyphenol¹⁰ were known compounds. All reagents were purchased from Wako, Kanto, Aldrich, TCI, and Strem and used without further purification.

General Procedures for the Au(I)-Catalyzed Cycloisomerization

Benzylpropargyltosylaminodiphenylaniline derivative **1** (0.050 mmol) was placed in a Schlenk tube in air. This reaction vessel was evacuated and backfilled with argon ($\times 3$), and then gold(I) complex (10 mol%) and silver salt (10 mol%) were placed to the reaction vessel in globe box. After solvent (0.5 mL) was added, the solution was stirred at room temperature for 1 h. After removal of solvent, the crude products were filtered through a pad of silica, and purified by PTLC (hexane/ CH_2Cl_2 = 1:2) to give desired cyclized product **3**.

Physical properties of new compounds

***N*-(2-(Diphenylamino)benzyl)-4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide (1a):** it was isolated by flash silica gel column chromatography (hexane/EtOAc = 5/1). The title compound was obtained as a white solid (441.0 mg). mp 121-123 °C; ^1H NMR: δ = 7.58-7.64 (m, 1H), 7.64 (d, J = 8.2 Hz, 2H),

7.23-7.29 (m, 2H), 7.14-7.23 (m, 6H), 7.07-7.12 (m, 1H), 6.95 (t, $J = 7.1$ Hz, 2H), 6.92 (d, $J = 7.4$ Hz, 4H), 4.07 (s, 2H), 4.05 (d, $J = 2.4$ Hz, 2H), 2.38 (s, 3H), 1.79 (t, $J = 2.4$ Hz, 1H) ppm. ^{13}C NMR: $\delta = 147.8, 145.4, 143.5, 135.4, 132.4, 129.4, 129.3, 129.3, 129.0, 128.9, 127.9, 126.2, 122.3, 122.1, 75.9, 74.5, 46.6, 36.8, 21.7$ ppm. HRMS (ESI, positive): m/z calcd. For $\text{C}_{29}\text{H}_{27}\text{N}_2\text{O}_2\text{S}$ ($[\text{M} + \text{H}]^+$) 467.1788, found 467.1783.

***N*-(2-((3,5-Dimethoxyphenyl)(phenyl)amino)benzyl)-4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide (1b)**: it was isolated by flash silica gel column chromatography (hexane/EtOAc = 5/1). The title compound was obtained as a white solid (377.3 mg). mp 144-145 °C; ^1H NMR: $\delta = 7.56-7.62$ (m, 1H), 7.50 (d, $J = 8.4$ Hz, 2H), 7.15-7.30 (m, 6H), 7.08-7.14 (m, 1H), 6.91-7.00 (m, 3H), 6.10 (t, $J = 2.2$ Hz, 1H), 6.06 (d, $J = 2.2$ Hz, 2H), 4.10 (s, 2H), 4.05 (d, $J = 2.4$ Hz, 2H), 3.66 (s, 6H), 2.40 (s, 3H), 1.81 (t, $J = 2.4$ Hz, 1H) ppm. ^{13}C NMR: $\delta = 161.4, 149.6, 147.4, 145.2, 143.5, 135.4, 132.7, 129.4, 129.3, 129.2, 128.9, 128.9, 128.0, 126.4, 122.9, 122.4, 100.7, 94.3, 75.0, 74.5, 54.3, 46.5, 36.9, 21.6$ ppm. HRMS (ESI, positive): m/z calcd. For $\text{C}_{31}\text{H}_{31}\text{N}_2\text{O}_4\text{S}$ ($[\text{M} + \text{H}]^+$) 527.1999, found 527.1999.

***N*-(2-((3-Methoxyphenyl)(phenyl)amino)benzyl)-4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide (1c)**: it was isolated by flash silica gel column chromatography (hexane/EtOAc = 3/1). The title compound was obtained as a white solid (88.5 mg). mp 116-117 °C; ^1H NMR: $\delta = 7.55-7.65$ (m, 1H), 7.47 (d, $J = 8.1$ Hz, 2H), 7.05-7.29 (m, 8H), 6.88-6.98 (m, 3H), 6.44-6.54 (m, 3H), 4.09 (s, 2H), 4.04 (d, $J = 2.2$ Hz, 2H), 3.67 (s, 3H), 2.38 (s, 3H), 1.80 (t, $J = 2.2$ Hz, 1H) ppm. ^{13}C NMR: $\delta = 160.6, 149.1, 147.6, 145.3, 143.5, 135.4, 132.6, 129.9, 129.5, 129.4, 129.3, 129.0, 128.9, 128.0, 126.3, 122.7, 122.3, 114.8, 108.2, 107.5, 76.0, 74.5, 55.3, 46.6, 36.8, 21.7$ ppm. HRMS (ESI, positive): m/z calcd. For $\text{C}_{30}\text{H}_{29}\text{N}_2\text{O}_3\text{S}$ ($[\text{M} + \text{H}]^+$) 497.1893, found 497.1891.

***N*-(2-((3,5-Dimethylphenyl)(phenyl)amino)benzyl)-4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide (1d)**: it was isolated by flash silica gel column chromatography (hexane/EtOAc = 5/1). The title compound was obtained as a white solid (93.7 mg). mp 105-106 °C; ^1H NMR: $\delta = 7.58-7.62$ (m, 1H), 7.48 (d, 2H), 7.23-7.28 (m, 2H), 7.16-7.21 (m, 4H), 7.08-7.12 (m, 1H), 6.94 (t, $J = 7.3$ Hz, 1H), 6.87 (d, $J = 7.8$ Hz, 2H), 6.62 (s, 1H), 6.55 (s, 2H), 4.08 (s, 2H), 4.05 (d, $J = 2.3$ Hz, 2H), 2.39 (s, 3H), 2.19 (s, 6H), 1.79 (t, $J = 2.3$ Hz, 1H) ppm. ^{13}C NMR: $\delta = 148.0, 147.6, 145.5, 143.5, 138.9, 135.5, 132.5, 129.4, 129.3, 129.2, 128.9, 128.7, 128.0, 126.1, 124.2, 122.1, 121.7, 120.5, 76.0, 74.4, 46.6, 36.8, 21.7, 21.5$ ppm. HRMS (ESI, positive): m/z calcd. For $\text{C}_{31}\text{H}_{31}\text{N}_2\text{O}_2\text{S}$ ($[\text{M} + \text{H}]^+$) 495.2101, found 495.2095.

***N*-(2-((4-Methoxyphenyl)(phenyl)amino)benzyl)-4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide (1e)**: it was isolated by flash silica gel column chromatography (hexane/EtOAc = 5/1). The title compound was obtained as yellow oil (70.3 mg) ^1H NMR: $\delta = 7.59$ (dd, $J = 2.1, 7.1$ Hz, 1H), 7.47 (d, $J = 8.3$ Hz, 2H), 7.24 (dt, $J_d = 2.1$ Hz, $J_t = 7.6$ Hz, 2H), 7.15-7.22 (m, 4H), 7.07 (dd, $J = 2.0, 7.7$ Hz, 1H), 6.87-6.94 (m, 3H), 6.76-6.82 (m, 4H), 4.08 (s, 2H), 4.05 (d, $J = 2.5$ Hz, 2H), 3.79 (s, 3H), 2.40 (s, 3H),

1.81 (t, $J = 2.5$ Hz, 1H) ppm. ^{13}C NMR: $\delta = 155.6, 148.6, 145.8, 143.5, 141.0, 135.5, 132.0, 129.4, 129.2, 128.9, 128.9, 128.9, 128.0, 125.8, 125.3, 121.1, 120.8, 114.7, 76.0, 74.5, 55.6, 46.6, 36.8, 21.7$ ppm. HRMS (ESI, positive): m/z calcd. For $\text{C}_{30}\text{H}_{29}\text{N}_2\text{O}_3\text{S}$ ($[\text{M} + \text{H}]^+$) 497.1893, found 497.1886.

***N*-(2-((3,5-Dimethoxyphenyl)(methyl)amino)benzyl)-4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide (1f)**: it was isolated by flash silica gel column chromatography (hexane/EtOAc = 5/1). The title compound was obtained as a white solid (213.2 mg). mp 149-150 °C; ^1H NMR: $\delta = 7.68$ (d, $J = 8.2$ Hz, 2H), 7.64 (dd, $J = 1.4, 7.5$ Hz, 1H), 7.28-7.38 (m, 2H), 7.25 (d, $J = 7.8$ Hz, 2H), 7.15 (dd, $J = 1.4, 7.6$ Hz, 1H), 5.92 (t, $J = 2.1$ Hz, 1H), 5.67 (d, $J = 2.0$ Hz, 2H), 4.30 (s, 2H), 4.00 (d, $J = 2.3$ Hz, 2H), 3.70 (s, 6H), 3.17 (s, 3H), 2.41 (s, 3H), 1.90 (t, $J = 2.3$ Hz, 1H) ppm. ^{13}C NMR: $\delta = 161.8, 151.7, 147.1, 143.9, 136.3, 134.4, 130.0, 129.9, 129.9, 128.9, 128.2, 127.6, 93.0, 89.9, 76.7, 74.4, 55.5, 46.0, 40.3, 36.9, 21.9$ ppm. HRMS (ESI, positive): m/z calcd. For $\text{C}_{26}\text{H}_{29}\text{N}_2\text{O}_4\text{S}$ ($[\text{M} + \text{H}]^+$) 465.1843, found 465.1837.

***N*-(2-(Benzyl(3,5-dimethoxyphenyl)amino)benzyl)-4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide (1g)**: it was isolated by flash silica gel column chromatography (hexane/EtOAc = 5/1). The title compound was obtained as a white solid (216.3 mg). mp 170 °C (decomp.); ^1H NMR: $\delta = 7.61$ -7.65 (m, 3H), 7.20-7.33 (m, 10H), 5.93 (t, $J = 2.0$ Hz, 1H), 5.73 (d, $J = 2.3$ Hz, 2H), 4.78 (s, 2H), 4.26 (s, 2H), 3.99 (d, $J = 2.4$ Hz, 2H), 3.63 (s, 6H), 2.43 (s, 3H), 1.85 (t, $J = 2.4$ Hz, 1H) ppm. ^{13}C NMR: $\delta = 161.6, 150.6, 145.7, 143.6, 138.6, 135.8, 134.1, 129.6, 129.4, 129.3, 129.3, 128.6, 127.9, 127.3, 127.3, 127.0, 93.8, 90.2, 76.4, 74.2, 56.6, 55.2, 46.3, 36.8, 21.7$ ppm. HRMS (ESI, positive): m/z calcd. For $\text{C}_{32}\text{H}_{33}\text{N}_2\text{O}_4\text{S}$ ($[\text{M} + \text{H}]^+$) 541.2156, found 541.2149.

***N*-(2-((3,5-Dimethoxyphenyl)(phenyl)amino)benzyl)-4-methyl-*N*-(3-(*p*-tolyl)prop-2-yn-1-yl)benzenesulfonamide (1h)**: it was isolated by flash silica gel column chromatography (hexane/EtOAc = 5/1). The title compound was obtained as brown oil (89.1 mg) ^1H NMR: $\delta = 7.68$ (dd, $J = 3.7, 5.6$ Hz, 1H), 7.52 (d, $J = 8.2$ Hz, 2H), 7.24-7.29 (m, 2H), 7.11-7.18 (m, 5H), 6.93 (d, $J = 7.6$ Hz, 3H), 6.89 (d, $J = 8.0$ Hz, 2H), 6.60 (d, $J = 8.0$ Hz, 2H), 6.04 (t, $J = 2.0$ Hz, 1H), 6.00 (d, $J = 2.2$ Hz, 2H), 4.21 (s, 2H), 4.14 (s, 2H), 3.50 (s, 6H), 2.27 (s, 3H), 2.26 (s, 3H) ppm. ^{13}C NMR: $\delta = 161.4, 149.7, 147.6, 145.3, 143.4, 138.4, 135.5, 132.8, 131.6, 129.5, 129.3, 129.2, 129.0, 128.7, 128.0, 126.4, 122.9, 122.3, 119.2, 100.6, 94.4, 86.5, 80.6, 55.2, 46.5, 37.8, 21.5$ (a pair of aromatic peaks and a pair of aliphatic peaks were overlapped) ppm. HRMS (ESI, positive): m/z calcd. For $\text{C}_{38}\text{H}_{37}\text{N}_2\text{O}_4\text{S}$ ($[\text{M} + \text{H}]^+$) 617.2469, found 617.2461.

***N*-(But-2-yn-1-yl)-*N*-(2-((3,5-dimethoxyphenyl)(phenyl)amino)benzyl)-4-methylbenzenesulfonamide (1i)**: it was isolated by flash silica gel column chromatography (hexane/EtOAc = 5/1). The title compound was obtained as a white yellow solid (91.7 mg). mp 113-114 °C; ^1H NMR: $\delta = 7.58$ -7.63 (m, 1H), 7.49 (d, $J = 8.1$ Hz, 2H), 7.15-7.27 (m, 6H), 7.08-7.13 (m, 1H), 6.91-6.98 (m, 3H), 6.10 (t, $J = 2.2$ Hz, 1H), 6.05 (d, $J = 2.2$ Hz, 2H), 4.05 (s, 2H), 3.96 (d, $J = 2.3$ Hz, 2H), 3.65 (s, 6H), 2.38 (s, 3H), 1.25 (t, $J = 2.3$ Hz, 3H) ppm. ^{13}C NMR: $\delta = 161.4, 149.7, 147.5, 145.1, 143.2, 135.5, 132.9, 129.3, 129.2, 129.1,$

128.8, 128.1, 126.4, 122.9, 122.3, 100.7, 94.1, 82.6, 71.1, 55.3, 46.4, 37.3, 21.6, 3.1 (a pair of aromatic peaks was overlapped) ppm. HRMS (ESI, positive): m/z calcd. For $C_{32}H_{33}N_2O_4S$ ($[M + H]^+$) 541.2156, found 541.2148.

3,5-Dimethoxy-*N*-phenyl-*N*-(2-((prop-2-yn-1-ylamino)methyl)phenyl)aniline (1j): it was isolated by flash silica gel column chromatography (hexane/EtOAc = 5/1). The title compound was obtained as colorless oil (35.0 mg). 1H NMR: δ = 7.47 (dd, J = 1.7, 7.4 Hz, 1H), 7.18-7.29 (m, 4H), 7.14 (dd, J = 1.6, 7.6 Hz, 1H), 6.99-7.04 (m, 2H), 6.92-6.97 (m, 1H), 6.11 (d, J = 2.2 Hz, 2H), 6.08 (t, J = 2.1 Hz, 1H), 3.67 (s, 6H), 3.64 (s, 2H), 3.28 (d, J = 2.4 Hz, 2H), 2.12 (t, J = 2.4 Hz, 1H), 1.55 (s, 1H) ppm. ^{13}C NMR: δ = 161.4, 149.7, 147.5, 145.3, 137.5, 130.8, 130.0, 129.2, 128.8, 126.5, 122.7, 122.3, 100.3, 93.8, 82.0, 71.6, 55.4, 48.9, 37.9 ppm. HRMS (ESI, positive): m/z calcd. For $C_{24}H_{25}N_2O_2$ ($[M + H]^+$) 373.1911, found 373.1905.

(*Z*)-10,12-Dimethoxy-14-phenyl-6-tosyl-5,6,7,14-tetrahydrodibenzo[*b,i*][1,5]diazecine (3b): it was isolated by PTLC (hexane/ CH_2Cl_2 = 1/2). The title compound was obtained as yellow solid (25.6 mg). mp 180 °C (decomp.); 1H NMR: δ = 7.51 (d, J = 8.0 Hz, 2H), 7.41 (dd, J = 1.5, 7.6 Hz, 1H), 7.24 (dd, J = 1.7, 7.9 Hz, 1H), 7.21 (d, J = 8.1 Hz, 3H), 7.13 (dt, J_d = 1.2 Hz, J_t = 7.7 Hz, 1H), 7.00-7.08 (m, 2H), 6.91 (t, J = 7.3 Hz, 1H), 6.64-6.78 (m, 2H), 6.27 (d, J = 2.3 Hz, 1H), 6.18 (d, J = 2.3 Hz, 1H), 5.70 (d, J = 11.6 Hz, 1H), 5.19 (dt, J_t = 7.7 Hz, J_d = 11.9 Hz, 1H), 3.37-3.95 (m, 2H), 3.75 (s, 3H), 3.73 (s, 1H), 3.67 (s, 1H), 3.63 (s, 3H), 2.45 (s, 3H) ppm. ^{13}C NMR: δ = 160.4, 159.8, 147.8, 147.0, 146.9, 143.0, 135.3, 134.0, 133.3, 130.2, 129.7, 129.3, 127.4, 127.3, 127.0, 126.7, 126.2, 123.1, 122.5, 122.1, 101.2, 93.2, 55.8, 55.3, 48.7, 47.6, 21.6 ppm. HRMS (ESI, positive): m/z calcd. For $C_{31}H_{31}N_2O_4S$ ($[M + H]^+$) 527.1999, found 527.2000. Crystal data of **3b**; $C_{31}H_{30}N_2O_4S$, M = 526.65, monoclinic, Space Group $P2_1/c$ (#14), a = 9.50964(17) Å, b = 21.1357(4) Å, c = 26.8785(5) Å, β = 90.958(6)°, V = 5401.65(17) Å³, T = 173.0 K, Z = 8, μ (CuK α) = 13.837 cm⁻¹, Number of Reflections Measures: Total 61400, Unique: 9758 (R_{int} = 0.0484), RI = 0.0484, $wR2$ = 0.1257. CCDC 1907588.

(*Z*)-12-Methoxy-14-phenyl-6-tosyl-5,6,7,14-tetrahydrodibenzo[*b,i*][1,5]diazecine (3c): it was isolated by PTLC (hexane/ CH_2Cl_2 = 1/2). The title compound was obtained as colorless oil (22.3 mg). 1H NMR: δ = 7.51 (d, J = 8.3 Hz, 2H), 7.41 (dd, J = 1.6, 7.8 Hz, 1H), 7.19-7.25 (m, 3H), 7.13 (dd, J = 1.2, 7.6, 7.6 Hz, 1H), 7.03-7.10 (m, 2H), 6.88-6.95 (m, 2H), 6.74 (d, J = 7.8 Hz, 1H), 6.65-6.72 (m, 3H), 6.75 (dd, J = 2.6, 8.5 Hz, 1H), 5.72 (d, J = 12.0 Hz, 1H), 5.19 (dt, J_t = 7.9 Hz, J_d = 11.6 Hz, 1H), 3.68-4.00 (m, 4H), 3.66 (s, 3H), 2.44 (s, 3H) ppm. ^{13}C NMR: δ = 159.2, 147.6, 146.8, 146.7, 143.1, 135.4, 134.0, 133.7, 133.4, 130.2, 129.8, 129.5, 127.6, 127.4, 126.9, 126.5, 126.3, 123.0, 122.6, 109.5, 108.7, 55.4, 48.8, 47.4, 21.7 (a pair of aromatic peaks was overlapped) ppm. HRMS (ESI, positive): m/z calcd. For $C_{30}H_{29}N_2O_3S$ ($[M + H]^+$) 497.1893, found 497.1893.

(*Z*)-10-Methoxy-14-phenyl-6-tosyl-5,6,7,14-tetrahydrodibenzo[*b,i*][1,5]diazecine (3c'): it was isolated

by PTLC (hexane/CH₂Cl₂ = 1/2). The title compound was obtained as colorless oil (3.1 mg). ¹H NMR: δ = 7.51 (d, J = 8.2 Hz, 2H), 7.42 (dd, J = 1.2, 7.4 Hz, 1H), 7.18-7.25 (m, 4H), 7.14 (dt, J_d = 1.0 Hz, J_t = 7.4 Hz, 1H), 7.06 (t, J = 8.1 Hz, 2H), 6.90 (t, J = 7.3 Hz, 1H), 6.76 (d, J = 8.3 Hz, 2H), 6.65 (d, J = 8.1 Hz, 2H), 6.56 (d, J = 8.1 Hz, 1H), 5.78 (d, J = 11.8 Hz, 1H), 5.26 (dt, J_t = 7.6 Hz, J_d = 11.8 Hz, 1H), 3.60-4.09 (brs, 4H), 3.77 (s, 3H), 2.44 (s, 3H) ppm. ¹³C NMR analysis could not be conducted because of its low yield HRMS (ESI, positive): m/z calcd. For C₃₀H₂₉N₂O₃S ([M + H]⁺) 497.1893, found 497.1894.

(Z)-10,12-Dimethyl-14-phenyl-6-tosyl-5,6,7,14-tetrahydrodibenzo[*b,i*][1,5]diazecine (3d): it was obtained as an inseparable mixture with a by-product (probably 9-*exo-dig* product) (9.5 mg). ¹H NMR: δ = 7.52 (d, J = 8.2 Hz, 2H), 7.44 (d, J = 7.2 Hz, 1H), 7.29-7.23 (m, 1H), 7.21 (d, J = 8.2 Hz, 2H), 7.15 (t, J = 7.3 Hz, 1H), 7.07-7.01 (m, 2H), 6.90-6.80 (m, 3H), 6.73 (s, 1H), 6.59 (d, J = 7.4 Hz, 2H), 5.68 (d, J = 11.2 Hz, 1H), 5.24 (dt, J_t = 7.4 Hz, J_d = 11.2 Hz, 1H), 3.80 (brs, 4H), 2.44 (s, 3H), 2.17 (s, 3H), 2.09 (s, 3H).

(Z)-10,12-Dimethoxy-14-methyl-6-tosyl-5,6,7,14-tetrahydrodibenzo[*b,i*][1,5]diazecine (3f): it was purified by PTLC (hexane/CH₂Cl₂ = 1/3) and obtained as an inseparable mixture with a small amount of by-product (probably 9-*exo-dig* product). The title compound was obtained as colorless oil (22.9 mg). ¹H NMR: δ = 7.69 (d, J = 8.3 Hz, 2H), 7.46-7.50 (m, 1H), 7.29 (d, J = 8.2 Hz, 2H), 7.11-7.18 (m, 2H), 6.54-6.58 (m, 1H), 6.30 (d, J = 2.2 Hz, 1H), 6.10 (d, J = 2.2 Hz, 1H), 5.61 (d, J = 11.6 Hz, 1H), 4.99 (dt, J_t = 7.6 Hz, J_d = 11.6 Hz, 1H), 3.20-4.81 (brs, 4H), 3.84 (s, 3H), 3.72 (s, 3H), 3.05 (s, 3H), 2.42 (s, 3H) ppm. ¹³C NMR: δ = 160.1, 160.1, 151.4, 148.2, 143.2, 133.1, 133.0, 130.1, 129.8, 129.7, 127.3, 126.5, 126.0, 124.6, 123.1, 106.5, 94.9, 89.8, 55.8, 55.3, 48.5, 48.0, 43.4, 21.6 ppm. HRMS (ESI, positive): m/z calcd. For C₂₆H₂₉N₂O₄S ([M + H]⁺) 465.1843, found 465.1840.

(Z)-14-Benzyl-10,12-dimethoxy-6-tosyl-5,6,7,14-tetrahydrodibenzo[*b,i*][1,5]diazecine (3g): it was purified by PTLC (hexane/CH₂Cl₂ = 1/3) and obtained as an inseparable mixture with a small amount of by-product (probably 9-*exo-dig* product). The title compound was obtained as colorless oil (24.3 mg). ¹H NMR: δ = 7.64 (d, J = 8.2 Hz, 2H), 7.51 (dd, J = 2.1, 7.0 Hz, 1H), 7.00-7.28 (m, 10H), 6.67 (dd, J = 1.6, 7.2 Hz, 1H), 6.04 (d, J = 5.6 Hz, 2H), 5.64 (d, J = 11.6 Hz, 1H), 5.00-5.08 (m, 1H), 4.72 (d, J = 16.9 Hz, 1H), 4.00-4.63 (m, 2H), 4.06-4.16 (m, 1H), 3.61-3.68 (m, 1H), 3.70 (s, 3H), 3.50 (s, 3H), 2.44 (s, 3H) ppm. ¹³C NMR: δ = 160.0, 159.6, 151.9, 146.7, 143.2, 138.0, 135.9, 133.2, 133.1, 130.0, 129.9, 128.7, 127.3, 126.6, 126.6, 126.3, 125.7, 125.5, 123.3, 107.2, 97.2, 90.7, 60.4, 55.7, 55.1, 48.4, 48.1, 21.7 ppm. HRMS (ESI, positive): m/z calcd. For C₃₂H₃₃N₂O₄S ([M + H]⁺) 541.2156, found 541.2155.

***N*-(2-(3,5-Dimethoxyphenoxy)benzyl)-4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide (4):** it was isolated by flash silica gel column chromatography (hexane/EtOAc = 5/1). The title compound was obtained as colorless oil (44.7 mg). ¹H NMR: δ = 7.75 (d, J = 8.4 Hz, 2H), 7.56 (dd, J = 1.6, 7.3 Hz, 1H), 7.21-7.30 (m, 3H), 7.15 (dt, J_d = 1.0 Hz, J_t = 7.6 Hz, 1H), 6.92 (dd, J = 0.8, 8.1 Hz, 1H), 6.20 (t, J = 2.2

Hz, 1H), 6.08 (d, $J = 2.2$ Hz, 2H), 4.46 (s, 2H), 4.06 (d, $J = 2.4$ Hz, 2H), 3.72 (s, 6H), 2.41 (s, 3H), 1.96 (t, $J = 2.4$ Hz, 1H); ^{13}C NMR: $\delta = 161.7, 159.3, 154.7, 143.7, 136.2, 130.5, 129.6, 129.4, 128.0, 126.8, 124.4, 119.5, 97.0, 95.4, 73.9, 55.6, 44.5, 36.6, 21.7$ (a pair of aromatic peaks was overlapped) ppm. HRMS (ESI, positive): m/z calcd. For $\text{C}_{25}\text{H}_{25}\text{NNaO}_5\text{S}$ ($[\text{M} + \text{Na}]^+$) 474.1351, found 474.1342.

(Z)-10,12-Dimethoxy-6-tosyl-5,6,7,14-tetrahydrodibenzo[*b,i*][1,5]oxazecine (5): it was obtained as an inseparable mixture with substrate **4**: ^1H NMR: $\delta = 7.71$ (d, $J = 8.2$ Hz, 2H), 7.39 (dd, $J = 1.8, 7.6$ Hz, 1H), 7.33-7.24 (m, 4H), 7.18-7.09 (m, 2H), 6.99 (dt, $J_d = 1.0$ Hz, $J_t = 7.4$ Hz, 1H), 6.40 (d, $J = 2.2$ Hz, 1H), 6.29 (d, $J = 2.2$ Hz, 1H), 5.75 (d, $J = 11.7$ Hz, 1H), 5.33 (dt, $J_t = 7.7$ Hz, $J_d = 11.7$ Hz, 1H), 4.44 (s, 2H), 3.88 (d, $J = 7.7$ Hz, 2H), 3.82 (s, 3H), 3.76 (s, 3H), 2.42 (s, 3H).

ACKNOWLEDGEMENTS

This work was supported by Mitsubishi Materials Corporation and Waseda University Joint Cooperation Grant.

SUPPORTING INFORMATION

The synthetic procedures of starting materials were listed in supporting information.

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