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An Efficient Stereoselective Synthesis of *cis*-2,6-Disubstituted Tetrahydropyrans via Gold-Catalyzed Meyer–Schuster Rearrangement/Hydration/*oxa*-Michael Addition Sequence

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Abstract: An efficient stereoselective synthesis of *cis*-2,6-disubstituted tetrahydropyrans **14a–c** has been achieved via gold-catalyzed Meyer–Schuster rearrangement/hydration/oxa-Michael addition sequence from bis-propargylic alcohols **13a–c**. The reaction of **13a** proceeds via 2,6-disubstituted tetrahydropyran **14′a** as an intermediate.

Keywords: gold catalyst; Meyer–Schuster rearrangement; hydration; *oxa*-Michael addition; 2,6-disubstituted tetrahydropyrans

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1. Introduction

cis-2,6-Disubstituted tetrahydropyrans are important skeletons found in biologically active natural products [1,2]. For example, decytosporides A [3,4], aspergillide [5,6] and phorboxazole A [7] have important biological activities, including anti-tumor activity against the A549 tumor cell line, potent cytotoxic activity against murine platelet leukaemia cells, and NIC anti-cancer activity (Figure 1). Therefore, a great deal of effort has been devoted to the development of synthetic methods for the synthesis of 2,6-*cis*-disubstituted tetrahydropyrans [8–15], which remains an important topic in organic synthesis.

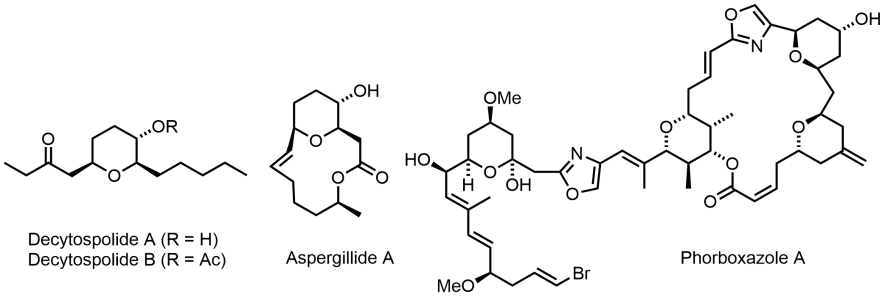
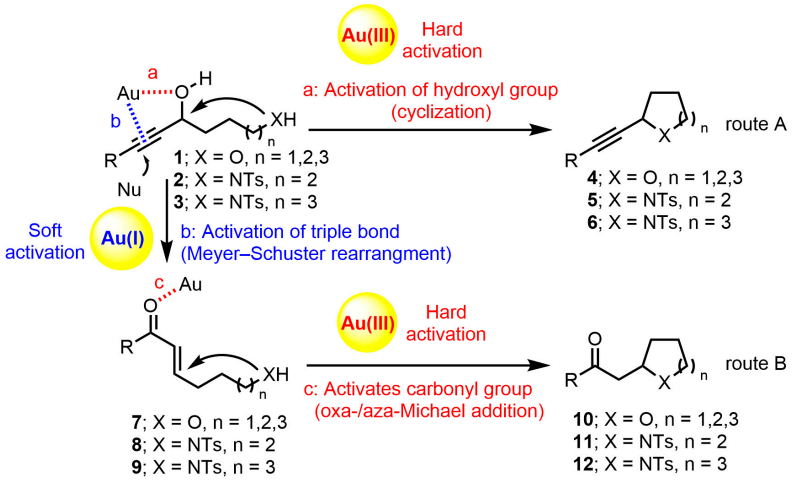


Figure 1. Natural Products bearing 2,6-*cis*-disubstituted tetrahydropyran.

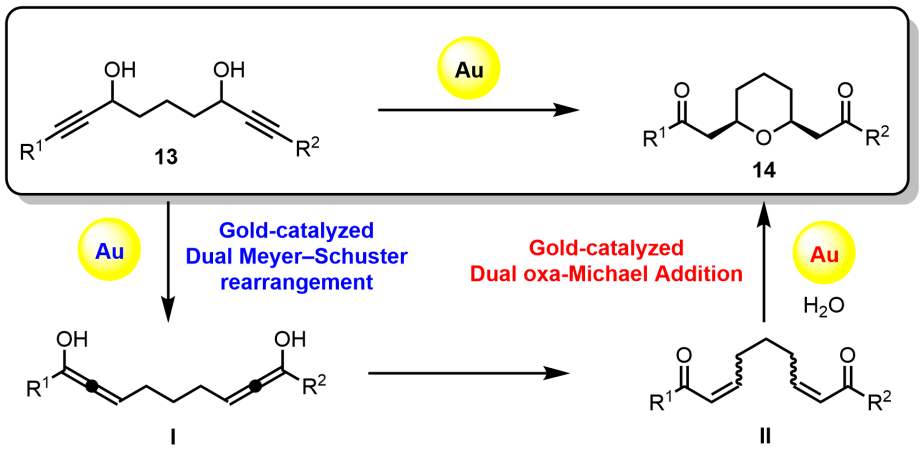
We have developed an efficient synthesis of heterocyclic compounds (cyclic ethers **4**,**10** [16]/piperidines **5**,**11** [17]/azepanes **6**,**12** [18]) from propargylic alcohols **1**–**3** by strategic use of oxophilic (hard) gold (III) and π-philic (soft) gold (I) catalysts (Scheme 1). For example, heating propargylic alcohols **1** with an oxophilic gold (III) catalyst (5 mol% $AuBr_3$) results in cyclization to afford cyclic ethers **4** bearing an acetylene moiety due to activation of the propargylic position by coordination (a) of gold (III) (Scheme 1, route A) [16]. On the other hand, in the presence of a π-philic gold (I) catalyst (2 mol% $Ph_3PAuNTf_2$), propargylic alcohols **1** undergo Meyer–Schuster rearrangement [19,20] to afford α,β-unsaturated ketones **7**, which in turn undergo gold (III)-catalyzed intramolecular oxa-Michael addition [21–24] to afford cyclic ethers **10** bearing a carbonyl group [16]. In this case, the

Meyer–Schuster rearrangement reaction involves activation of the triple bond by coordination (b) of gold (I), and the subsequent addition reaction involves activation of the carbonyl group by coordination (c) of gold (III) (Scheme 1, route B). We have also successfully developed the methods for the synthesis of 2-substituted piperidines **5**,**11** and 2-substituted azepanes **6**,**12** from propargylic alcohols **2**,**3** bearing nitrogen functionality by a similar strategy using oxophilic (hard) gold (III) and π-philic (soft) gold (I) catalysts (Scheme 1, routes A and B) [17,18].



Scheme 1. Strategic use of oxophilic (hard) gold (III) and π-philic (soft) gold (I) catalysts for the synthesis of heterocyclic compounds (Previous work).

To develop the synthetic procedure of *cis*-2,6-disubstituted tetrahydropyrans **14**, we expanded the substrate from propargylic alcohols **1**–**3** to bis-propargylic alcohol **13** (Scheme 2). Bis-propargylic alcohol **13** is first catalyzed with the gold (I) complex to bring about the dual Meyer–Schuster rearrangement reaction, forming bis-enone **II** via bis-enol **I** as an intermediate. Then, the addition of H_2O leads to a sequential *oxa*-Michael addition reaction to give the desired 2,6-*cis*-disubstituted tetrahydropyrans **14**. Here, we report a gold-catalyzed Meyer–Schuster rearrangement followed by a gold-catalyzed *oxa*-Michael addition of water for the stereoselective synthesis of *cis*-2,6-disubstituted tetrahydropyrans **14** from bis-propargylic alcohols **13**.

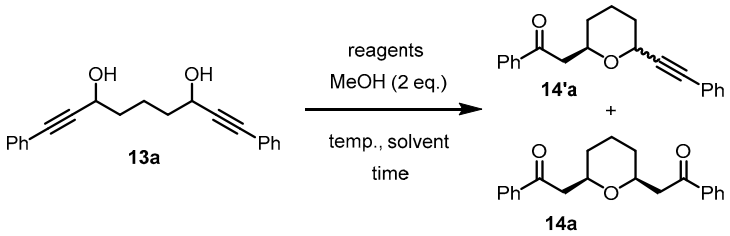


Scheme 2. Strategy for the synthesis of 2,6-*cis*-disubstituted tetrahydropyrans **14** by gold-catalyzed dual Meyer–Schuster rearrangement followed by gold-catalyzed dual *oxa*-Michael addition (This work).

2. Results and Discussion

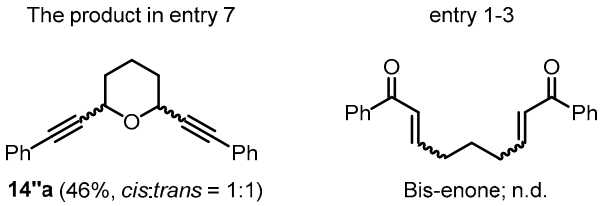
We began by investigating the gold-catalyzed sequential reaction with bis-propargylic alcohol **13a** as a model substrate in the presence of various gold (I) catalysts (Table 1).

Table 1. Optimization of reaction conditions in gold-catalyzed Meyer–Schuster rearrangement followed by gold-catalyzed oxa-Michael addition.



Entry	Reagents	Solvent	Temp.	Time	14′a Yield [a] (*cis*:*trans*) [b]	14a Yield [a,b]
1	$Ph_3PAuNTf_2$ (10 mol%)	toluene	reflux	3 h	38% (1:1)	N.D.
2	Ph_3PAuCl (10 mol%) $AgNTf_2$ (10 mol%)	toluene	reflux	3 h	74% (1:1)	N.D.
3	$(C_6F_5)_3PAuCl$ (10 mol%) $AgNTf_2$ (10 mol%)	toluene	reflux	1 h	68% (2:1)	N.D.
4	Ph_3PAuCl (10 mol%) $AgNTf_2$ (10 mol%)	$ClCH_2CH_2Cl$	50 °C	3 h	14% (3:4)	37%
5	Ph_3PAuCl (10 mol%) $AgNTf_2$ (10 mol%) H_2O (10 eq.)	$ClCH_2CH_2Cl$	50 °C	2 h	trace	56%
6	Ph_3PAuCl (10 mol%) $AgNTf_2$ (10 mol%) H_2O (10 eq.)	toluene	reflux	3 h	28% (1:1)	trace
7	$AuBr_3$ (10 mol%)	$ClCH_2CH_2Cl$	reflux	48 h	N.D.	N.D.

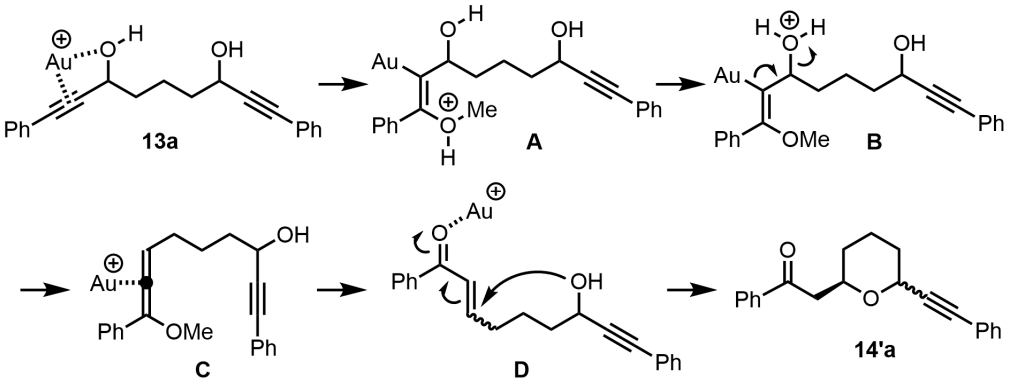
[a] Isolated yield. [b] Stereochemical assignment of tetrahydropyran **14′a** and **14a** was based on ^{1}H-NMR spectra, chemical shifts (ppm), coupling constant (*J* values) and application of NOE measurement.



Treatment of bis-propargyl alcohol **13a** with MeOH (2 eq.) in the presence of $Ph_3PAuNTf_2$ (10 mol%) in toluene at reflux afforded a moderate yield of the product **14′a** (*cis*:*trans* = 1:1) without the formation of the desired 2,6-*cis*-disubstituted tetrahydropyran **14a** (entry 1). The reaction with the activated gold (I) species generated from Ph_3PAuCl (10 mol%) or $(C_6F_5)_3PAuCl$ (10 mol%) by the silver catalyst $AgNTf_2$ (10 mol%) furnished the product **14′a** in 74% yield (*cis*:*trans* = 1:1) and 68% yield (*cis*:*trans* = 2:1), respectively, without the desired product **14a** (entries 2 and 3). The reaction with Ph_3PAuCl (10 mol%) and $AgNTf_2$ (10 mol%) in $ClCH_2CH_2Cl$ as solvent instead of toluene furnished the desired product **14a** in 37% yield, along with 14% yield of the product **14′a** (entry 4). The reaction in $ClCH_2CH_2Cl$ with H_2O (10 eq.) to accelerate the oxa-Michael addition reaction afforded the desired *cis*-2,6-disubstituted tetrahydropyran **14a** in 56% yield (entry 5), while the reaction with H_2O (10 eq.) in toluene furnished 28% yield of the tetrahydropyran **14′a** without the desired *cis*-2,6-disubtituted tetrahydropyran **14a** (entry 6). Changing the reaction solvent from toluene to 1,2-dichloroethane gave the desired *cis*-2,6-disubstituted tetrahydropyran **14a**, probably

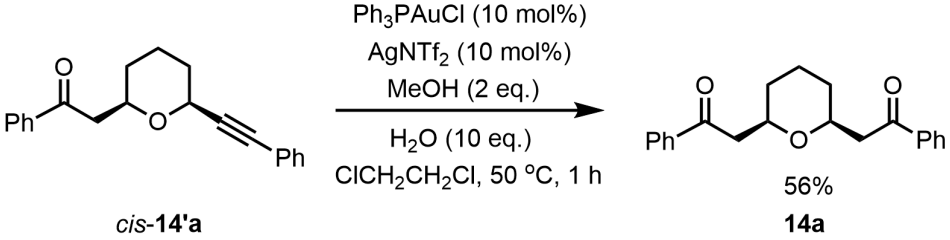
due to the difference in water solubility of the solvents. Thus, the solubility of water (8.60 g/L, 25 °C) [25] in 1,2-dichloroethane is higher than that of toluene (515 mg/L, 20 °C) [26], which suggests that water is involved in the reaction in the dichloroethane to obtain the desired product. On the other hand, the reaction with $AuBr_3$ (10 mol%) in 1,2-dichloroethane at reflux for 48 h gave 2,6-disubstituted tetrahydropyran **14′′a** in 46% yield (*cis*:*trans* = 1:1) (entry 7). Finally, the optimal reaction conditions for preparation of the desired product **14a** from bis-propargylic alcohol **13a** were found to be Ph_3PAuCl (10 mol%) and $AgNTf_2$ (10 mol%) in the presence of MeOH (2 eq.) and H_2O (10 eq.) in $ClCH_2CH_2Cl$ stirred at 50 °C.

From this result, the plausible reaction mechanism for the preparation of 2,6-disubstituted tetrahydropyran **14′a** was shown in Scheme 3. It is assumed that the tetrahydropyran **14′a** is formed by the Meyer–Schuster rearrangement reaction followed by the intramolecular oxa-Michael addition reaction. First, the gold (I) catalyst is coordinated to the triple bond and hydroxyl group on one side of bis-propargylic alcohol **13a**, resulting in the addition of methanol to the activated triple bond by gold (I) to afford the allenyl ether **C** (**13a**→**A**→**B**→**C**). Then, hydrolysis of the allenyl ether **C** gives α,β-unsaturated ketone **D**, which undergoes oxa-Michael addition to furnish the tetrahydropyran **14′a** (**C**→**D**→**14′a**). However, it was not clear whether the mechanism of formation for the desired *cis*-2,6-disubstituted tetrahydropyran **14a** was from the tetrahydropyran **14′a** or some other mechanism.

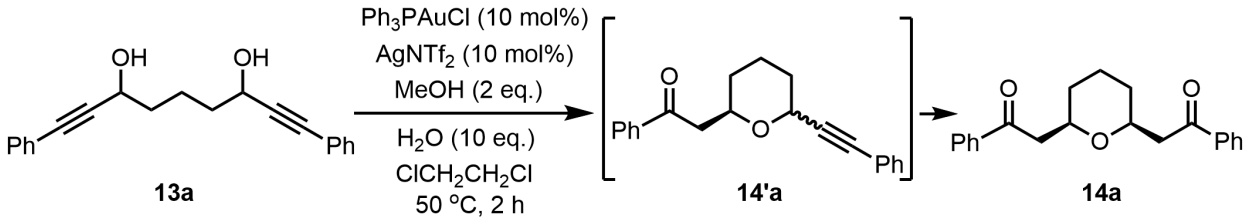


Scheme 3. Plausible reaction mechanism for the preparation of 2,6-disubstituted tetrahydropyran **14′a**.

Next, to elucidate the mechanism of formation of the desired *cis*-2,6-disubstituted tetrahydropyran **14a**, the reaction of *cis*-disubstituted tetrahydropyran **14′a** was performed under optimal reaction conditions (Scheme 4). Treatment of tetrahydropyran **14′a** with Ph_3PAuCl (10 mol%) and $AgNTf_2$ (10 mol%) in the presence of MeOH (2 eq.) and H_2O (10 eq.) in $ClCH_2CH_2Cl$ at 50 °C for 1 h furnished the desired *cis*-2,6-disubstituted tetrahydropyran **14a** in 56% yield. The yield of *cis*-2,6-disubstituted tetrahydropyran **14a** in this reaction was exactly the same as the yield from bis-propargyl alcohol **13a** (Table 1, entry 5). This result most likely indicates that the reaction proceeded from bis-propargylic alcohol **13a** through the tetrahydropyran **14′a** as the intermediate to *cis*-2,6-disubstituted tetrahydropyran **14a**. (Scheme 5).



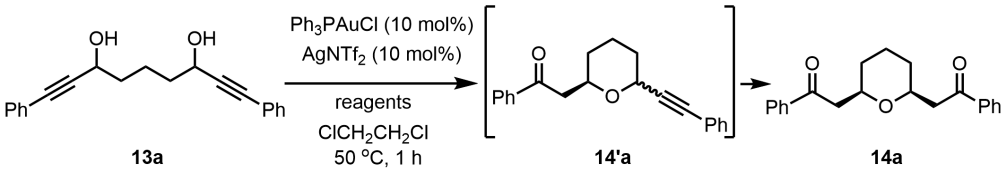
Scheme 4. The gold-catalyzed reaction of *cis*-2,6-disubtituted tetrahydropyran **14′a** to *cis*-2,6-disubstituted tetrahydropyran **14a**.



Scheme 5. The gold-catalyzed reaction of bis-propargyl alcohol **13a** to *cis*-2,6-disubstituted tetrahydropyran **14a**.

In the study, as shown in Table 1, we confirmed the termination of the reaction by the disappearance of bis-propargylic alcohol **13a**. However, from the studies in the previous section (Schemes 4 and 5), it was estimated that tetrahydropyran **14′a** was likely to be an intermediate in this reaction. Therefore, it was decided to change the confirmation of the end of the reaction by the disappearance of tetrahydropyran **14′a** and to examine the reaction again (Table 2).

Table 2. Re-optimization of reaction conditions in gold-catalyzed reaction for the preparation of *cis*-2,6-disubstituted tetrahydropyran **14a** from bis-propargylic alcohol **13a**.



Entry	Reagents	Time	14a Yield
1	MeOH (2 eq.)	3 h	37%
2	MeOH (2 eq.), H_2O (10 eq.)	2 h	56%
3	MeOH (2 eq.), H_2O (10 eq.)	5 h	61%
4 *	MeOH (2 eq.), H_2O (10 eq.)	24 h	48%
5	MeOH (2 eq.), H_2O (1 eq.)	24 h	41%
6	H_2O (10 eq.)	24 h	25%

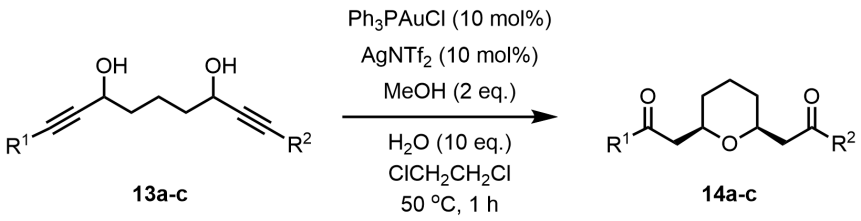
* The reaction was conducted with Ph_3PAuCl (5 mol%) and $AgNTf_2$ (5 mol%).

Entries 1 and 2 in Table 2 are the results shown in Table 1, entries 4 and 5. The reaction of entry 2 (reaction time: 2 h) was extended until the disappearance of intermediate **14′a** was confirmed, resulting in an extension of the reaction time to 5 h and a slightly higher yield of 61%. (entry 3). When the reaction was carried out with the reduction of the catalytic amount to 5 mol% Ph_3PAuCl and 5 mol% $AgNTf_2$, the yield of the product **14a** was slightly lower, 48% (entry 4). Furthermore, when the reaction with 10 mol% Ph_3PAuCl and 10 mol% $AgNTf_2$ was conducted with reducing the amount of water to 1 eq., the tetrahydropyran **13a** did not disappear even after 24 h, and the yield of the desired *cis*-2,6-disubstituted tetrahydropyran **14a** was obtained in 41% yield (entry 5). This result indicates that additional water is essential for the reaction to proceed efficiently. On the other hand, the reaction was conducted only with the addition of water (10 eq.) without methanol, resulting in a low yield of the desired *cis*-2,6-disubstituted tetrahydropyran **14a** (entry 6). Finally, the optimal reaction conditions for preparation of the desired *cis*-2,6-disubstituted tetrahydropyran **14a** from bis-propargylic alcohol **13a** were found to be Ph_3PAuCl (10 mol%) and $AgNTf_2$ (10 mol%) in the presence of MeOH (2 eq.) and H_2O (10 eq.) in $ClCH_2CH_2Cl$ stirred at 50 °C for 5 h.

Next, we examined the scope of the reaction with bis-propargylic alcohols **13** bearing other substituents of the alkyne moiety (Table 3). Treatment of bis-propargylic alcohols **13b** bearing a hexyl group at the alkyne terminus with Ph_3PAuCl (10 mol%) and $AgNTf_2$

(10 mol%) in the presence of MeOH (2 eq.) and H_2O (10 eq.) at 50 °C in 1,2-dichloroethane for 3.5 h afforded the corresponding *cis*-2,6-disubstituted tetrahydropyran **14b** in 59% (entry 2). The reaction with bis-propargylic alcohol **13c** having *n*-Hex and Ph groups as substituents at the alkyne terminus also furnished the corresponding *cis*-2,6-disubstituted tetrahydropyran **14c** in 61% yield (entry 3).

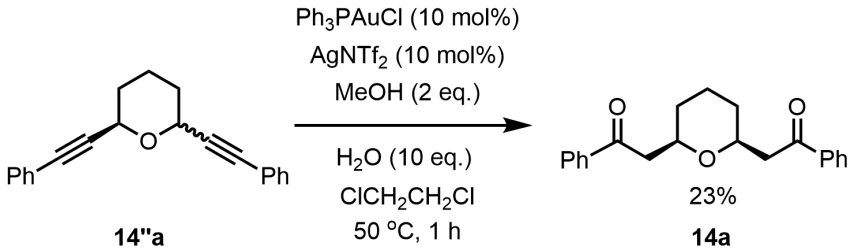
Table 3. The scope of the gold-catalyzed reaction for preparation of *cis*-2,6-disubstituted tetrahydropyrans **14a–c** bearing dicarbonylmethyl group from propargylic alcohols **13a–c**.



13a-c **14a-c**

Entry	Reactant	R^1	R^2	Time	14 Yield
1	**13a**	Ph	Ph	5 h	**14a**: 61%
2	**13b**	*n*-Hex	*n*-Hex	3.5 h	**14b**: 59%
3	**13c**	*n*-Hex	Ph	3.5 h	**14c**: 61%

Next, the transformation of the triple bond in tetrahydropyran **14** to the carbonylmethyl group via hydration reaction was investigated. Treatment of tetrahydropyran **14′′a** with Ph_3PAuCl (10 mol%) and $AgNTf_2$ (10 mol%) in the presence of MeOH (2 eq.) and H_2O (10 eq.) at 50 °C in 1,2-dichloroethane for 1 h afforded *cis*-2,6-disubstitued tetrahydropyran **14a** in a 23% yield (Scheme 6).

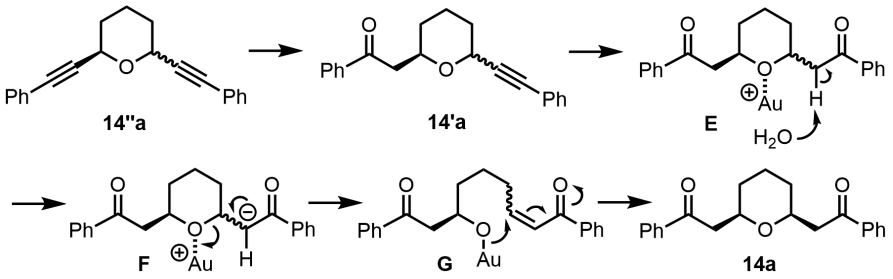


14"a **14a**

Scheme 6. Gold-catalyzed reaction of 2,6-disubtituted tetrahydropyran **14′′a** to *cis*-2,6-disubstituted terahydropyran **14a**.

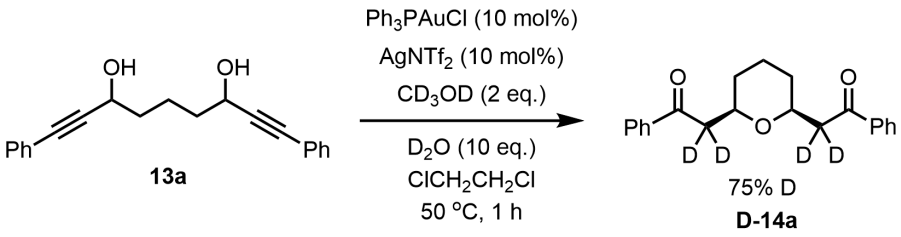
If the hydration reaction occurred without the ring-opening reaction of the tetrahydropyran ring, the product, tetrahydropyran **14a**, should be a mixture of *cis*- and *trans*-forms. In practice, however, only *cis*-2,6-disubstituted tetrahydropyran **14a** was obtained as a product in the reaction, so it is assumed that the ring-opening reaction occurred during the hydration reaction.

The plausible reaction mechanism for the preparation of the *cis*-2,6-disubstituted tetrahydropyran **14a** from tetrahydropyran **14′′a** is shown in Scheme 7. First, the first hydration reaction occurs at one triple bond in tetrahydropyran **14′′a**, forming the mixture of *cis*- and *trans*-2,6-disubstituted tetrahydropyran **14′a** bearing a carbonylmethyl group (**14′′a**→**14′a**). Next, the second hydration reaction occurs at the other triple bond in tetrahydropyran **14′a** to form the mixture of *cis*- and *trans*-2,6-disubstituted tetrahydropyran **14a**. Then, the coordination of the gold catalyst with the oxygen atom of tetrahydropyran **14a** (**E**) and the water-induced elimination of α-hydrogen result in a ring-opening reaction by reverse oxa-Michael addition (**F**→**G**) and a ring-closing reaction by oxa-Michael addition (**G**→**14a**), ultimately yielding stable *cis*-2,6-disubstituted tetrahydropyran **14a**.



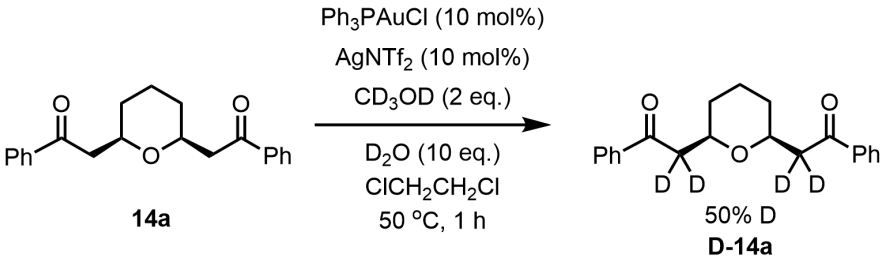
Scheme 7. Plausible reaction mechanism for the preparation of *cis*-2,6-disubstituted tetrahydropyran **14a** from 2,6-disubstituted tetrahydropyran **14″a**.

Deuteration experiments were conducted to understand the reaction mechanism. Treatment of bis-propargylic alcohol **13a** with Ph_3PAuCl (10 mol%) and $AgNTf_2$ (10 mol%) in the presence of CD_3OD (2 eq.) and D_2O (10 eq.) at 50 °C in 1,2-dichloroethane for 1 h afforded the desired 2,6-*cis*-disubstituted tetrahydropyran **D-14a**, showing that the methylene groups at 2,6-positions were both 75% deuterated in the ^1H NMR spectrum (Scheme 8).



Scheme 8. Deuteration experiments of bis-propargylic alcohol **13a**.

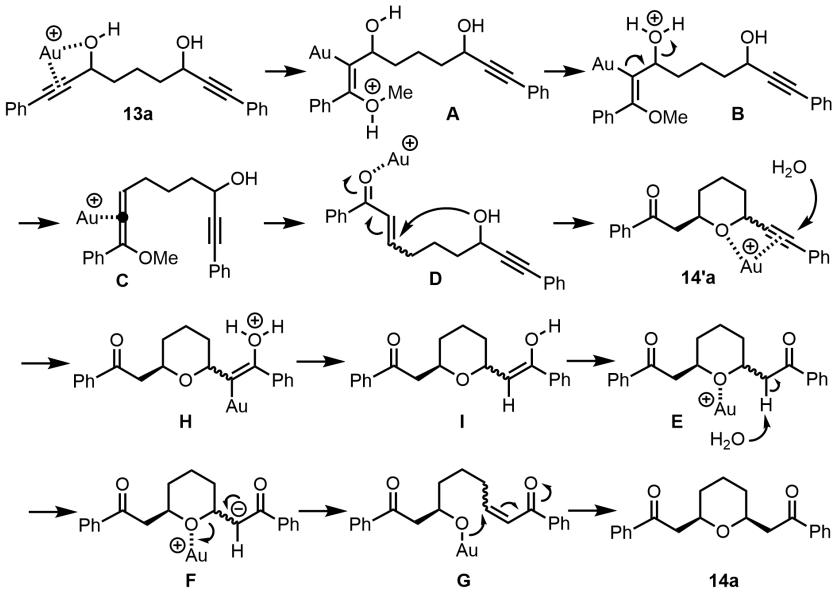
Next, deuteration experiments were performed on *cis*-2,6-disubstituted tetrahydropyran **14a**. Treatment of the tetrahydropyran **14a** with Ph_3PAuCl (10 mol%) and $AgNTf_2$ (10 mol%) in the presence of CD_3OD (2 eq.) and D_2O (10 eq.) at 50 °C for 1 h in 1,2-dichloroethane afforded the tetrahydropyran **D-14a**, showing that the methylene groups at 2,6-positions were both 50% deuterated in the ^1H NMR spectrum (Scheme 9). Although the result of this deuteration experiment indicates that deuteration also occurs after the formation of tetrahydropyran **14a**, the deuteration rate is higher in the reaction from bis-propargyl alcohol **13a** (Scheme 8) than in the reaction from tetrahydropyran **14a** (Scheme 9), which suggests that MeOH and H_2O are involved in the formation of tetrahydropyran **14a** from bis-propargyl alcohol **13a**.



Scheme 9. Deuteration experiments of *cis*-2,6-disubstituted tetrahydropyran **14a**.

The plausible reaction mechanism for the preparation of *cis*-2,6-disubstituted tetrahydropyran **14a** from bis-propargyl alcohol **13a** is shown in Scheme 10. First, the coordination of the gold (I) catalyst to the triple bond and hydroxyl group of bis-propargylic alcohol **13a** results in a nucleophilic attack by MeOH on the activated triple bond to form vinyl gold species **A** (**13a**→**A**). Next, the carbon-gold bond in vinyl gold species **A** is cleaved with the elimination of water, forming the allene intermediate **C** (**A**→**B**→**C**). Subsequently,

the addition of water transforms the allene intermediate **C** to α,β-enone **D**, completing the Meyer–Schuster rearrangement reaction (**C**→**D**). Furthermore, the gold catalyst coordinates with the carbonyl oxygen to enhance the reactivity of α,β-enone, resulting in the intramolecular oxa-Michael addition reaction to afford intermediate **14′a** (**D**→**14′a**). Then, the gold (I) catalyst coordinates with the other triple bond and the oxygen atom of tetrahydropyran **14′a** to bring about the hydration reaction, giving the mixture of *cis*- and *trans*-2,6-disubstituted tetrahydropyran **14a** (**H**→**I**→**E**). The reaction mechanism for the formation of *cis*-2,6-disubstituted tetrahydropyran **14a** from the mixture of *cis*- and *trans*-2,6-disubstituted tetrahydropyran is described in Scheme 7.



Scheme 10. Plausible reaction mechanism for the preparation of *cis*-2,6-disubstituted tetrahydropyran **14a** from bis-propargylic alcohol **13a**.

The stereochemistry of *cis*-2,6-disubstituted tetrahydropyran **14c** was confirmed by NOE measurements (Figure 2). The stereochemical outcome of the reaction can be explained based on transition-state structures **G-I** and **G-II** (Figure 2). During the equilibration between the reverse oxa-Michael addition and oxa-Michael addition (Scheme 10), the bulky substituent (α,β-enone) occupies a pseudo-equatorial position to avoid 1,3-diaxial interactions (**G-II**). As the α,β-enone group is bulkier than hydrogen, it tends to take a pseudo-equatorial position (**G-I**) rather than a pseudoaxial position (**G-II**) to avoid 1,3-diaxial interaction, resulting in stereoselective synthesis of *cis*-2,6-disubstituted tetrahydropyran **14** [13,27].

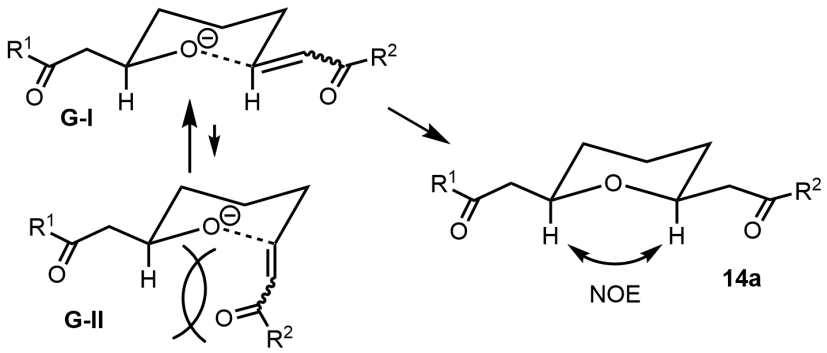


Figure 2. Description of the stereochemical results in the gold-catalyzed stereoselective synthesis of cis-2,6-disubstituted tetrahydropyrans **14** from bis-propargylic alcohols **13**.

3. Materials and Methods

3.1. General Information

^{1}H and ^{13}C NMR spectra were recorded with a JEOL JNM-AL300 (Japan Electron Optics Laboratory Co., Ltd., Tokyo, Japan) or BRUKER AV-300 spectrometer (Bruker, Billerica, MA, USA) at room temperature, with tetramethylsilane as an internal standard ($CDCl_3$ solution). Chemical shifts were recorded in ppm and coupling constants (*J*) in Hz. Infrared (IR) spectra were recorded with a Shimadzu FTIR-8200A spectrometer (Shimadzu Corporation, Kyoto, Japan). Mass spectra were recorded on JEOL JMS-700 spectrometers (Japan Electron Optics Laboratory Co., Ltd., Tokyo, Japan). Merck silica gel 60 (1.09385) (Merck, Darmstadt, Germany) and Merck silica gel 60 F254 (Merck, Darmstadt, Germany) were used for column chromatography and thin-layer chromatography (TLC), respectively.

1,9-Diphenylnona-1,8-diyne-3,7-diol (**13a**): Colorless oil, IR (KBr) 3319, 3055, 2947, 2864, 2228, 1599, 1489, 1443, 1026, 756, 691 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.42–7.40 (4H, m), 7.31–7.26 (6H m), 4.65 (2H, t, *J* = 6.0 Hz), 2.07 (2H, br s), 1.90–1.79 (6H, m); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 131.7, 128.4, 128.3, 122.5, 89.8, 85.1, 62.8, 37.3, 21.0; HRMS (EI) *m*/*z* calcd for $C_{21}H_{20}O_2$ $[M]^+$ 304.1463, found 304.1452.

Henicosa-7,14-diyne-9,13-diol (**13b**): Colorless oil, IR (KBr) 3362, 2928, 2856, 2233, 1464, 1082, 1022 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 4.37 (4H, br s), 2.20 (2H, td, *J* = 7.1, 1.8 Hz), 1.74–1.68 (3H, m), 1.65–1.59 (5H, m), 1.53–1.48 (3H, m), 1.40–1.27 (13H, m), 0.89 (6H, t, *J* = 6.6 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 85.6, 81.1, 62.4, 37.7, 31.3, 28.6, 28.5, 22.5, 21.0, 18.6, 14.0; HRMS (FAB) *m*/*z* calcd for $C_{21}H_{37}O_2$ $[M + H]^+$ 321.2794, found 321.2740.

1-Phenylpentadeca-1,8-diyne-3,7-diol (**13c**): Colorless oil, IR (KBr) 3354, 3082, 2932, 2860, 2233, 1599, 1490, 1026 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.45–7.41 (2H, m), 7.32–7.26 (3H, m), 4.62 (1H, t, *J* = 6.0 Hz), 4.40–4.38 (1H, m), 2.19 (2H, td, *J* = 7.0, 0.9 Hz), 2.07 (1H, br s), 1.88–1.82 (3H, m), 1.79–1.69 (4H, m), 1.53–1.44 (2H, m), 1.38–1.27 (6H, m), 0.88 (3H, t, *J* = 7.5 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 131.6, 128.23, 128.16, 122.6, 90.0, 85.6, 84.8, 81.0, 62.6, 62.4, 37.5, 37.3, 31.2, 28.6, 28.5, 22.4, 20.9, 18.6, 14.0; HRMS (EI) *m*/*z* calcd for $C_{21}H_{28}O_2$ $[M]^+$ 312.2089, found 312.2076.

3.2. Synthetic Procedure of 2,6-Disubstituted Tetrahydropyran **14′a** *from Bis-Propargylic Alcohol* **13a**

MeOH (13 μL, 0.33 mmol, 2 eq.), Ph_3PAuCl (8.1 mg, 0.016 mmol, 10 mol%) and $AgNTf_2$ (6.4 mg, 0.016 mmol, 10 mol%) were added to a solution of bis-propargylic alcohol **13a** (50 mg, 0.16 mmol) in toluene (5 mL) at room temperature, and the mixture was stirred at reflux for 3.5 h. The solvent was removed in vacuo and the crude product was subjected to SiO_2 column chromatography (hexane:CH_2Cl_2 = 2:1) to give the mixture of 2,6-disubstituted tetrahydropyran *cis*-**14′a** (17 mg, 34%) and *trans*-**14a′** (20 mg, 40%).

Phenyl-2-[(2R,6S*)-6-(phenylethynyl)tetrahydro-2H-pyran-2-yl]ethan-1-one* (*cis*-**14′a**). Colorless oil (hexane:CH_2Cl_2 = 2:1), IR (KBr) 3059, 2926, 2855, 2230, 1684, 1597, 1491, 1448, 1047 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.97 (2H, d, *J* = 7.2 Hz), 7.57 (1H, t, *J* = 7.4 Hz), 7.49–7.42 (4H, m), 7.30–7.27 (3H, m), 4.43 (1H, dd, *J* = 11.0, 2.1 Hz), 4.13–4.06 (1H, m), 3.45 (1H, dd, *J* = 16.8, 5.1 Hz), 3.07 (1H, dd, *J* = 16.8, 7.2 Hz), 1.96–1.75 (4H, m), 1.42–1.29 (2H, m); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 137.1, 133.2, 131.9, 128.6, 128.3, 128.2, 128.1, 122.6, 88.4, 84.4, 74.6, 68.9, 45.3, 32.5, 30.9, 23.2; HRMS (FAB) *m*/*z* calcd for $C_{21}H_{21}O_2$ $[M + H]^+$ 305.1542, found 305.1538.

1-Phenyl-2-[(2R,6R*)-6-(phenylethynyl)tetrahydro-2H-pyran-2-yl]ethan-1-one* (*trans*-**14′a**). Colorless oil (hexane:CH_2Cl_2 = 2:1), IR (KBr) 3061, 2926, 2853, 1686, 1597, 1489, 1448, 1038 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.97 (2H, d, *J* = 7.5 Hz), 7.56 (1H, t, *J* = 7.5 Hz), 7.48–7.41 (4H, m), 7.31–7.29 (3H, m), 4.96 (1H, d, *J* = 4.2 Hz), 4.67–4.59 (1H, m), 3.28 (1H, dd, *J* = 15.6, 6.0 Hz), 3.03 (1H, dd, *J* = 15.6, 6.6 Hz), 2.02 (1H, tt, *J* = 12.4, 3.6 Hz), 1.88–1.75 (4H, m), 1.43–1.30 (2H, m); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 198.1, 137.2, 133.0, 131.8, 128.5, 128.2, 122.8, 87.4, 86.8, 68.8, 65.9, 45,4, 31.6, 30.4, 29.7, 19.4; HRMS (FAB) *m*/*z* calcd for $C_{21}H_{21}O_2$ $[M + H]^+$ 305.1542, found 305.1536.

3.3. General Procedure for Gold-Catalyzed Synthesis of 2,6-Disubstituted Tetrahydropyrans **14a** *from Bis-Propargylic Alcohols* **13**

Ph_3PAuCl (10 mol%) and $AgNTf_2$ (10 mol%) were added to a solution of bis-propargylic alcohol **13**, MeOH (2 eq.) and H_2O (10 eq.) in $ClCH_2CH_2Cl$ at room temperature, and the mixture was stirred at 50 °C. After complete consumption of 2,6-disubstituted tetrahydropyran **14′** (the reaction was monitored by thin layer chromatography; usually within 5 h), the solvent was removed in vacuo and the crude product was subjected to SiO_2 column chromatography (eluents = hexane:CH_2Cl_2) to give *cis*-2,6-disubstituted tetrahydropyran **14**.

2,2′-[(2R,6S*)-Tetrahydro-2H-pyran-2,6-diyl]bis(1-phenylethan-1-one)* (*cis*-**14a**). Bis-propargylic alcohol **13a** (30 mg, 0.099 mmol), MeOH (8.0 µL, 0.20 mmol, 2 eq.), H_2O (18 µL, 0.99 mmol, 10 eq.), Ph_3PAuCl (4.9 mg, 0.0099 mmol, 10 mol%) and $AgNTf_2$ (3.9 mg, 0.0099 mmol, 10 mol%) in $ClCH_2CH_2Cl$ (5 mL) furnished *cis*-**14a** (20 mg, 61%) as a colorless oil (hexane:CH_2Cl_2 = 6:1).

IR (KBr) 3063, 2926, 2855, 1684, 1597, 1510, 1448, 1063 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.92–7.89 (4H, m), 7.53 (2H, tt, *J* = 7.2, 1.5 Hz), 7.45–7.39 (4H, m), 4.05–3.97 (2H, m), 3.24 (2H, dd, *J* = 15.9, 6.3 Hz), 2.94 (2H, dd, *J* = 15.9, 6.6 Hz), 1.86–1.74 (2H, m), 1.68–1.57 (2H, m), 1.35–1.27 (2H, m); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 198.3, 137.3, 133.0, 128.5, 128.2, 74.7, 45.4, 31.4, 23.3; HRMS (EI) *m*/*z* calcd for $C_{21}H_{22}O_3$ $[M]^+$ 304.1569, found 322.1570.

The ^{1}H-NMR and ^{13}C-NMR data are identical with reported values [13].

1,1′-[(2R,6S*)-Tetrahydro-2H-pyran-2,6-diyl]bis(octan-2-one)* (*cis*-**14b**). Bis-propargylic alcohol **13b** (30 mg, 0.094 mmol), MeOH (7.6 µL, 0.19 mmol, 2 eq.), H_2O (17 µL, 0.94 mmol, 10 eq.), Ph_3PAuCl (4.6 mg, 0.0094 mmol, 10 mol%) and $AgNTf_2$ (3.6 mg, 0.0094 mmol, 10 mol%) in $ClCH_2CH_2Cl$ (5 mL) furnished *cis*-**14b** (19 mg, 59%) as a colorless oil (hexane:CH_2Cl_2 = 3:1) as a colorless oil.

IR (KBr) 2930, 2858, 1715, 1373, 1080 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 3.84–3.76 (2H, m), 2.59 (2H, dd, *J* = 15.2, 8.1 Hz), 2.43–2.33 (6H, m), 1.84–1.79 (1H, m), 1.68–1.50 (8H, m), 1.27–1.15 (13H, m), 0.88 (6H, t, *J* = 6.6 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 209.5, 74.4, 49.4, 43.6, 31.6, 31.1, 28.8, 23.5, 23.2, 22.5, 14.0; HRMS (EI) *m*/*z* calcd for $C_{21}H_{38}O_3$ $[M]^+$ 338.2821, found 338.2812.

1-[(2R,6S*)-6-(2-Oxo-2-phenylethyl)tetrahydro-2H-pyran-2-yl]octan-2-one* (*cis*-**14c**). Bis-propargylic alcohol **13c** (30 mg, 0.096 mmol), MeOH (7.8 µL, 0.19 mmol, 2 eq.), H_2O (18 µL, 0.94 mmol, 10 eq.), Ph_3PAuCl (4.8 mg, 0.0096 mmol, 10 mol%) and $AgNTf_2$ (3.8 mg, 0.0096 mmol, 10 mol%) in $ClCH_2CH_2Cl$ (5 mL) furnished *cis*-**14c** (19 mg, 59%) as a colorless oil (hexane:CH_2Cl_2 = 2:1) as a colorless oil.

IR (KBr) 3069, 2932, 2860, 1713, 1686, 1597, 1491, 1448 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.97–7.92 (2H, m), 7.56 (1H, tt, *J* = 7.5, 1.5 Hz), 7.49–7.42 (2H, m), 4.04–3.94 (1H, m), 3.86–3.77 (1H, m), 3.26 (1H, dd, *J* = 15.6, 6.6 Hz), 2.89 (1H, dd, *J* = 15.6, 6.0 Hz), 2.58 (1H, dd, *J* = 15.3, 7.8 Hz), 2.40–2.30 (3H, m), 1.89–1.60 (4H, m), 1,51–1.40 (2H, m), 1.29–1.18 (8H, m), 0.86 (3H, t, *J* = 6.6 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 209.7, 198.4, 137.3, 133.0, 128.5, 128.2, 74.7, 74.6, 49.5, 45.2, 43.5, 31.6, 31.2, 28.8, 23.4, 23.2, 22.5, 14.0; HRMS (EI) *m*/*z* calcd for $C_{21}H_{30}O_3$ $[M]^+$ 330.2195, found 330.2202.

3.4. Synthetic Procedure of 2,6-Disubstituted Tetrahydropyran **14″a** *from Bis-Propargylic Alcohols* **13a**

$AuBr_3$ (4.3 mg, 0.00099 mmol, 10 mol%) were added to a solution of bis-propargylic alcohol **13a** (30 mg, 0.099 mmol) in $ClCH_2CH_2Cl$ (5 mL) at room temperature, and the mixture was stirred at reflux for 48 h. The solvent was removed in vacuo and the crude product was subjected to SiO_2 column chromatography (hexane:CH_2Cl_2) to give the mixture of 2,6-disubstituted tetrahydropyran *cis*-**14″a** (7.4 mg, 26% yield) and *trans*-**14″a** (5.6 mg, 20% yield).

(2R,6S*)-2,6-Bis(phenylethynyl)tetrahydro-2H-pyran* (*cis*-**14″a**). Colorless oil (hexane:CH_2Cl_2 = 5:2), IR (KBr) 3080, 2947, 2922, 2850, 2360, 1599, 1491, 1379, 1072 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.46–7.42 (4H, m), 7.32–7.28 (6H, m), 4.43 (2H, dd, *J* = 10.8, 2.4 Hz), 2.00–1.91 (3H, m), 1.87–1.78

(2H, m), 1.72–1.61 (1H, m); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 131.8, 128.4, 128.2, 122.6, 87.8, 84.9, 68.9, 32.0, 29.7, 23.3; HRMS (EI) *m*/*z* calcd for $C_{21}H_{18}O$ $[M]^+$ 286.1358, found 286.1361.

(2R,6R*)-2,6-Bis(phenylethynyl)tetrahydro-2H-pyran* (*trans*-**14′a**). Colorless oil (hexane: CH_2Cl_2 = 2:1), IR (NaCl) 3055, 2924, 2851, 2359, 2235, 1599, 1491, 1194, 1026 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.49–7.45 (4H, m), 7.33–7.30 (6H, m), 5.05–5.01 (2H, m), 2.00–1.90 (4H, m), 1.84–1.77 (2H, m); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 131.8, 128.4, 128.2, 122.6, 87.5, 86.0, 64.6, 31.2, 29.7, 19.3; HRMS (EI) *m*/*z* calcd for $C_{21}H_{18}O$ $[M]^+$ 286.1358, found 286.1360.Meyer–Schuster rearrangement/hydration/*oxa*-Michael

4. Conclusions

In conclusion, we present a gold-catalyzed addition for the synthesis of emphcis-2,6-disubstituted tetrahydropyrans **14** from bis-propargylic alcohols **13**. We are currently applying this method to the synthesis of biologically active tetrahydropyran derivatives. Experimental and theoretical investigations on the reaction mechanism are also in progress.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/catal14040228/s1, ^{1}H, ^{13}C-NMR spectrum.

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