

HETEROCYCLES, Vol. 95, No. 1, 2017, pp. 172-180. © 2017 The Japan Institute of Heterocyclic Chemistry  
 Received, 29th August, 2016, Accepted, 17th October, 2016, Published online, 13th December, 2016  
 DOI: 10.3987/COM-16-S(S)47

## GOLD(III)-CATALYZED SYNTHESIS OF 2,3,4-TRISUBSTITUTED DIHYDROPYRANS FROM PROPARGYLIC ALCOHOLS WITH 1,3-DICARBONYL COMPOUNDS

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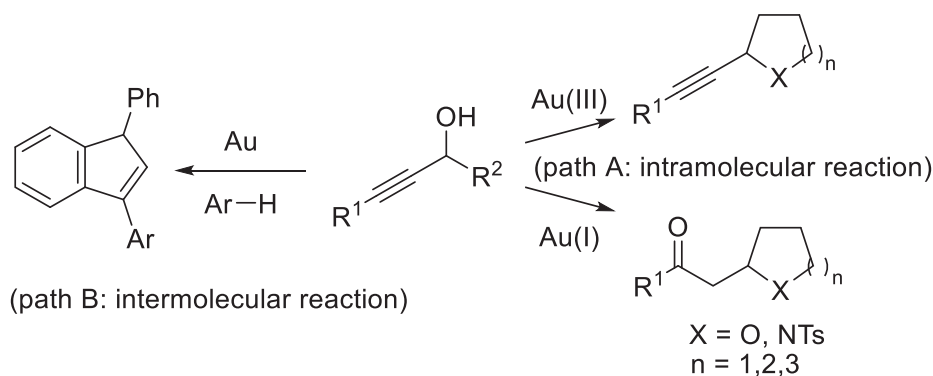
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*This paper is dedicated to Prof. Dr. Masakatsu Shibasaki, Professor Emeritus of the University of Tokyo, on the occasion of his 70th birthday.*

**Abstract** – 2,3,4-Trisubstituted dihydropyrans were efficiently synthesized by tandem reaction of propargylic alcohols with 1,3-dicarbonyl compounds in the presence of 5 mol% gold(III) catalyst (dichloro[2-pyridinecarboxylato]gold) and 10 mol% silver catalyst (AgNTf<sub>2</sub>).

Many natural products and potential pharmaceutical agents contain functionalized dihydro- and tetrahydropyran rings.<sup>1</sup> Therefore, the synthesis of these compounds has been extensively studied,<sup>1</sup> and remains an important topic in organic synthesis.

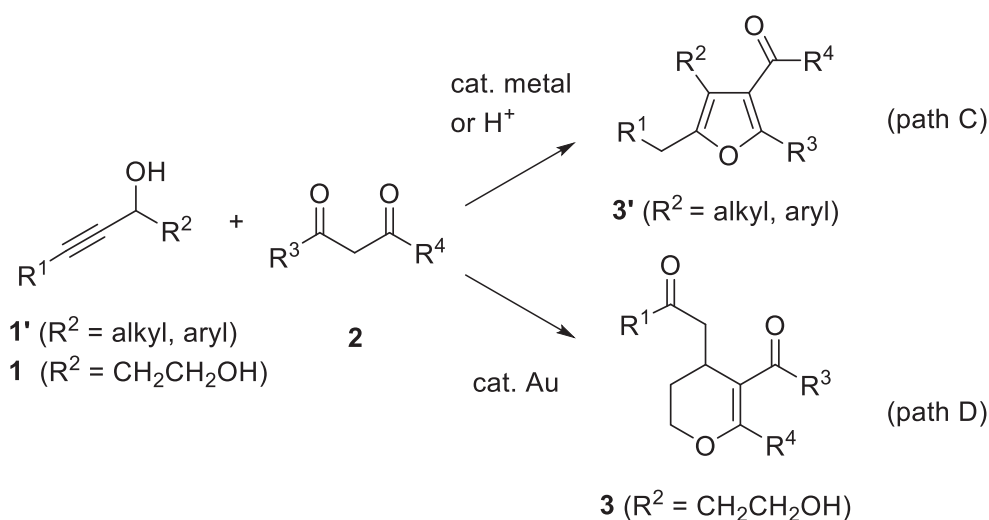
We recently reported a gold(I)/(III)-catalyzed intramolecular reaction for synthesis of cyclic ethers<sup>2</sup>/piperidines<sup>3</sup>/azepanes<sup>4</sup> from propargylic alcohols (Scheme 1, path A). Subsequently, we extended the scope of this reaction to gold-catalyzed intermolecular reaction of propargylic alcohols with



Scheme 1

aromatic compounds as nucleophiles, and we applied this reaction to the synthesis of 1,3-diarylindenes (Scheme 1, path B), which are a basic skeleton of antagonists of nonpeptide endothelin receptors (ET<sub>A</sub> and ET<sub>B</sub>).<sup>5</sup>

Here, we aimed to further extend our strategy of gold-catalyzed intermolecular reaction of propargylic alcohols by examining the availability of 1,3-dicarbonyl compounds as nucleophiles. Previous studies of the reaction of propargylic alcohols **1'** having an alkyl or aryl group at the propargylic position with 1,3-dicarbonyl compounds **2** in the presence of transition metal catalysts (Ru, Cu, Ag, In) or Brønsted acids afforded poly-substituted furans **3'** (Scheme 2, path C).<sup>6,7</sup> Surprisingly, however, we found that gold(III)-catalyzed reaction of propargylic alcohols **1** bearing a hydroxyethyl group at the propargylic position with 1,3-dicarbonyl compounds **2** gave 2,3,4-trisubstituted dihydropyrans **3** without any formation of poly-substituted furans **3'** (Scheme 2, path D).<sup>8</sup> Since substituted dihydropyrans can be readily transformed into substituted tetrahydropyrans with various functional groups through hydrogenation or addition reactions at the unsaturated bond, this method opens up a new and efficient synthetic route to 2,3,4-trisubstituted tetrahydropyrans. Herein, we present the gold(III)-catalyzed tandem reaction of propargylic alcohols **1** with 1,3-dicarbonyl compounds **2** to afford 2,3,4-trisubstituted dihydropyrans **3** (Scheme 2, path D).



**Scheme 2**

Initially, we investigated the reaction of propargylic alcohol **1a** with methyl acetoacetate (**2a**) as a nucleophile in the presence of various gold catalysts (Table 1). Reaction of **1a** with **2a** in the presence of various gold(III) catalysts (5 mol%) such as AuBr<sub>3</sub>, NaAuCl<sub>4</sub>, LiAuCl<sub>4</sub> and KAuCl<sub>4</sub> together with silver co-catalyst (15 mol% of AgNTf<sub>2</sub>) furnished 2,3,4-trisubstituted dihydropyran **3aa** in low yields

(entries 1-4). The use of gold(III) complexes **A** and **B** with AgNTf<sub>2</sub> (10 mol% or 15 mol%) improved the yield of **3aa** to 59% and 50%, respectively (entries 5 and 6). In contrast, reactions with gold(I) catalyst were less effective. Thus, the use of gold(I) catalyst (5 mol% of AuCl) and AgNTf<sub>2</sub> (5 mol%) furnished **3aa** in low yield (entry 7), and the reaction with 5 mol% of Ph<sub>3</sub>PAuNTf<sub>2</sub> and 1 eq of MeOH in toluene<sup>2-4,9</sup> afforded a complex mixture (entry 8).

**Table 1.** Optimization of reaction conditions in the gold-catalyzed tandem reaction

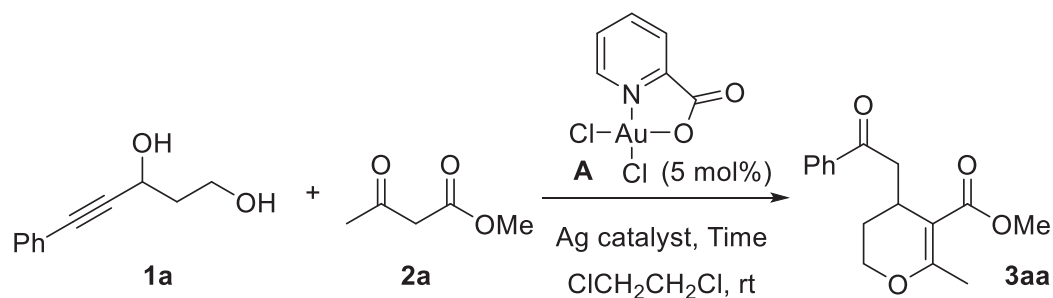
Entry	Catalyst (mol%)	Solvent	Yield
1	AuBr <sub>3</sub> (5)/AgNTf <sub>2</sub> (15)	ClCH <sub>2</sub> CH <sub>2</sub> Cl	36%
2	NaAuCl <sub>4</sub> (5)/AgNTf <sub>2</sub> (15)	ClCH <sub>2</sub> CH <sub>2</sub> Cl	28%
3	LiAuCl <sub>4</sub> (5)/AgNTf <sub>2</sub> (15)	ClCH <sub>2</sub> CH <sub>2</sub> Cl	33%
4	KAuCl <sub>4</sub> (5)/AgNTf <sub>2</sub> (15)	ClCH <sub>2</sub> CH <sub>2</sub> Cl	23%
5	cat. <b>A</b> (5)/AgNTf <sub>2</sub> (10)	ClCH <sub>2</sub> CH <sub>2</sub> Cl	59%
6	cat. <b>B</b> (5)/AgNTf <sub>2</sub> (15)	ClCH <sub>2</sub> CH <sub>2</sub> Cl	50%
7	AuCl (5)/AgNTf <sub>2</sub> (5)	ClCH <sub>2</sub> CH <sub>2</sub> Cl	37%
8	Ph <sub>3</sub> PAuNTf <sub>2</sub> (5), MeOH (1 eq.)	toluene	complex mixture

cat. **A**

cat. **B**

To examine the effect of the counter anion of the silver co-catalyst, we conducted the reaction with various types of silver catalyst (Table 2). The use of AgOTf, AgPF<sub>6</sub> and AgBF<sub>4</sub> in place of AgNTf<sub>2</sub> lowered the yield of **3aa** (entries 2-4).

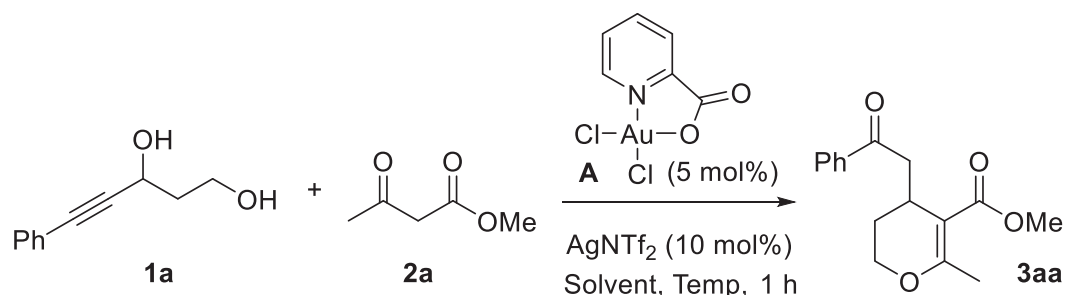
**Table 2.** Effect of the counter anion of silver catalyst in the gold(III)-catalyzed tandem reaction



Entry	Ag catalyst (mol%)	Time	Yield
1	AgNTf <sub>2</sub> (10)	1 h	59%
2	AgOTf (10)	1 h	8%
3	AgPF <sub>6</sub> (10)	24 h	trace
4	AgBF <sub>4</sub> (10)	24 h	trace

Next, we examined the effect of solvent (Table 3). The use of higher temperature in dichloroethane tended to decrease the yield of the product **3aa**, probably due to instability at high temperature (entries 1-3). The reaction in CH<sub>2</sub>Cl<sub>2</sub>, MeOH, toluene, MeNO<sub>2</sub> or CF<sub>3</sub>CH<sub>2</sub>OH gave only a low yield of the product **3aa** or a complex mixture (entries 4-8). Finally, the catalyst system of gold(III) complex **A** (5 mol%) with AgNTf<sub>2</sub> (10 mol%) was identified as optimal for formation of **3aa**.

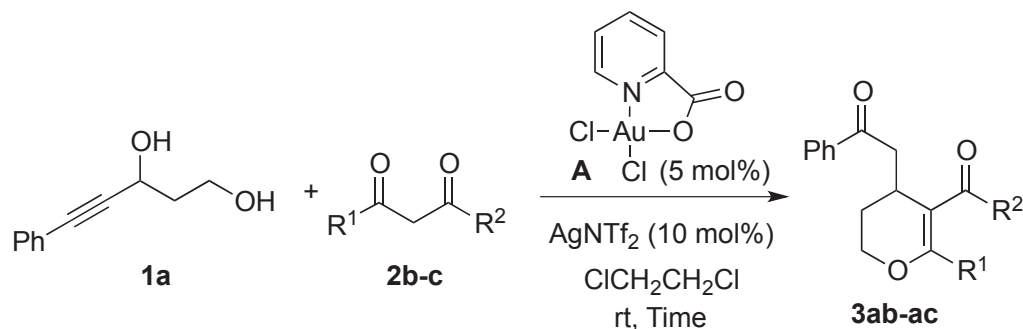
**Table 3.** Effect of solvent in the gold(III)-catalyzed tandem reaction



Entry	Solvent	Temp	Yield
1	ClCH <sub>2</sub> CH <sub>2</sub> Cl	rt	59%
2	ClCH <sub>2</sub> CH <sub>2</sub> Cl	60 °C	complex mixture
3	ClCH <sub>2</sub> CH <sub>2</sub> Cl	reflux	complex mixture
4	CH <sub>2</sub> Cl <sub>2</sub>	rt	36%
5	MeOH	rt	trace
6	toluene	rt	21%
7	MeNO <sub>2</sub>	rt	19%
8	CF <sub>3</sub> CH <sub>2</sub> OH	rt	complex mixture

The scope and limitations of the gold-catalyzed reaction for the synthesis of 2,3,4-trisubstituted dihydropyrans **3** were next examined (Table 4). Reaction of propargylic alcohol **1a** with acetylacetone (**2b**) in the presence of gold(III) catalyst **A** (5 mol%) and AgNTf<sub>2</sub> (10 mol%) afforded the corresponding dihydropyran **3ab** in 33% yield, whereas the reaction with ethyl benzoylacetate (**2c**) failed to give the desired product **3ac**.

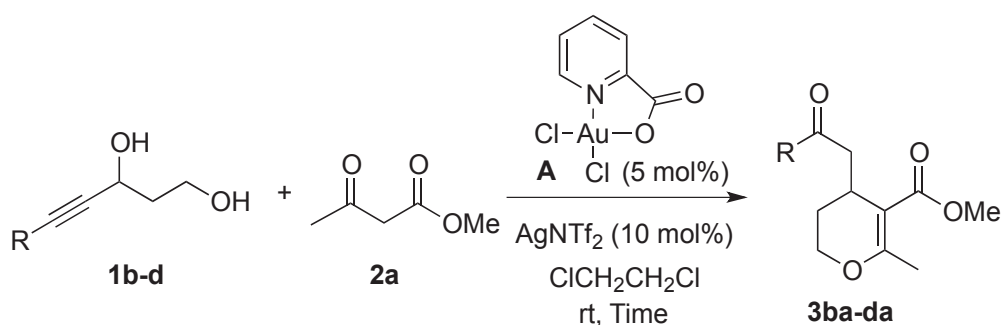
**Table 4.** Scope and limitations of the gold(III)-catalyzed tandem reaction with various dicarbonyl compounds



Entry	<b>2</b>	R <sup>1</sup>	R <sup>2</sup>	Time	Yield
1	<b>2b</b>	Me	Me	3 h	<b>3ab</b> 33%
2	<b>2c</b>	Ph	OEt	24 h	<b>3ac</b> no reaction

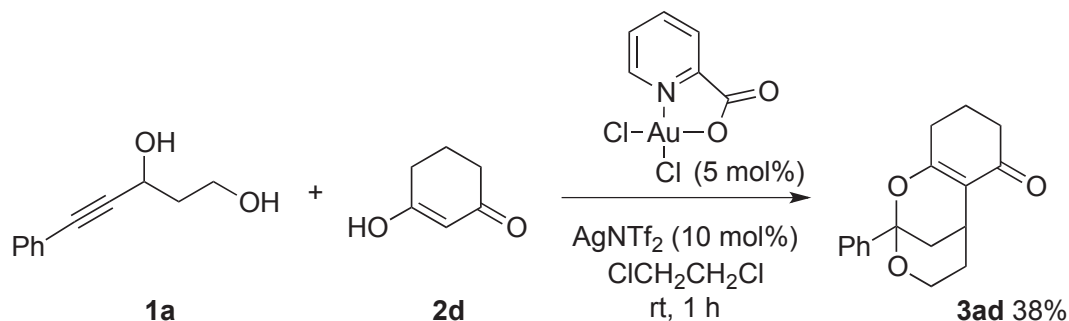
Next, we investigated the scope and limitations of the reaction with propargylic alcohols bearing various substituents at the terminal position of alkyne (Table 5). Although the reaction of propargylic alcohol **1a** having a phenyl group afforded the product in good yield (entry 1, Table 3), the reaction of propargylic alcohols bearing aliphatic substituents (**1b**: *n*-Hex, **1c**: *c*-Hex, **1d**: *t*-Bu) gave only low yields (entries 1-3, Table 5).<sup>10</sup>

**Table 5.** Scope and limitations of the gold(III)-catalyzed tandem reaction with various propargylic alcohols



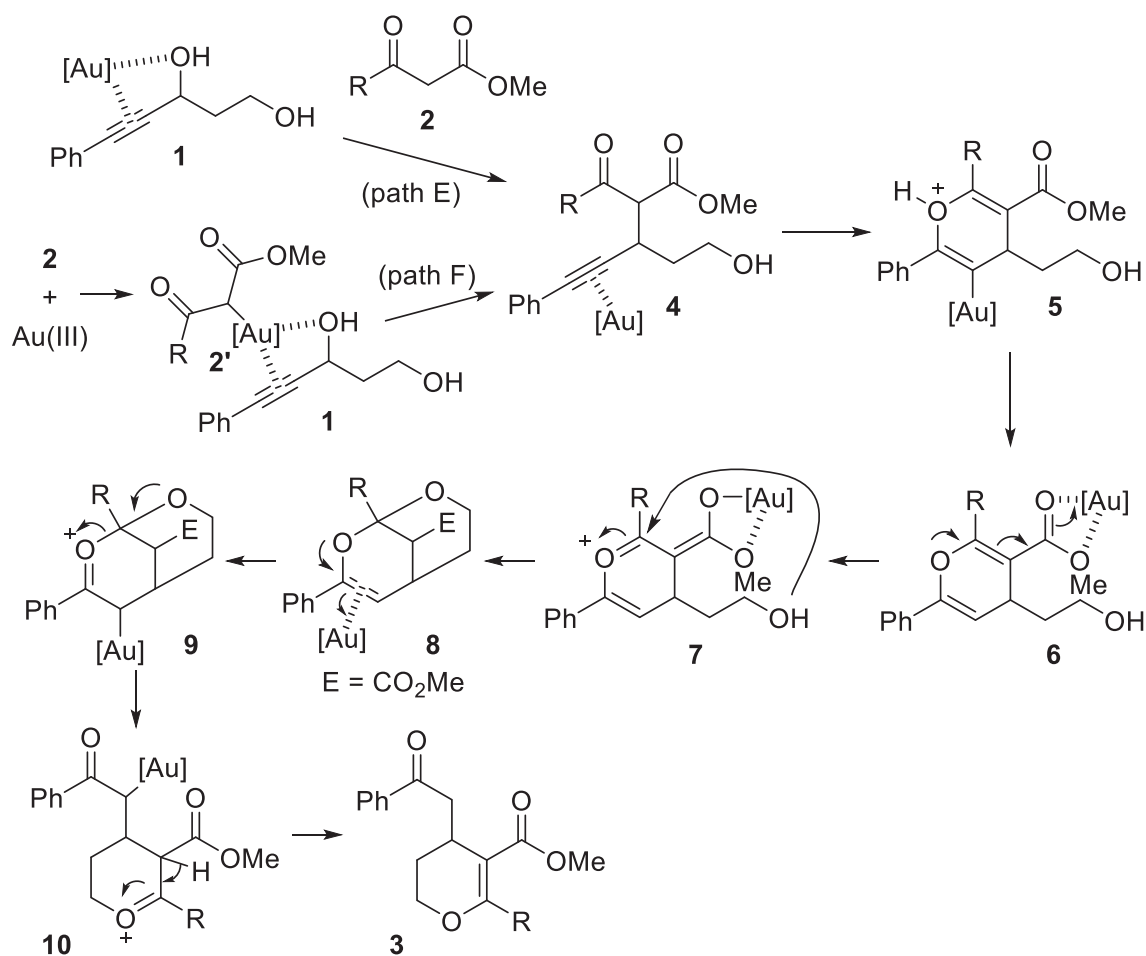
Entry	<b>1</b>	R	Time	Yield
1	<b>1b</b>	<i>n</i> -Hex	2 h	<b>3ba</b> 17%
2	<b>1c</b>	<i>c</i> -Hex	3 h	<b>3ca</b> 17%
3	<b>1d</b>	<i>t</i> -Bu	3 h	<b>3da</b> 19%

In addition, the reaction with 1,3-cyclohexanedione (**2d**) smoothly proceeded to afford the corresponding bicyclo[3.3.1]ketal **3ad** which is constituted in natural products having very important biological activities<sup>11</sup> (Scheme 3).



Scheme 3

A plausible mechanism for the gold-catalyzed formation of 2,3,4-trisubstituted dihydropyrans **3** from propargylic alcohols **1** and 1,3-dicarbonyl compounds **2** is shown in Scheme 4.



Scheme 4

There are two possible mechanisms for gold-catalyzed propargylic substitution<sup>12</sup> of 1,3-dicarbonyl compounds **2**. In the first mechanism, gold(III) catalyst **A** would coordinate to the triple bond and the oxygen atom of the hydroxyl group in **1**<sup>2-5,12</sup> to promote propargylic substitution of 1,3-dicarbonyl compounds **2** (Scheme 4, path E). Alternatively, carbon-gold(III) species **2'**<sup>13</sup> would be formed in the first step of the reaction at gold(III) catalyst **A** with 1,3-dicarbonyl compounds **2**, and propargylic substitution would occur with coordination of the gold(III) center in **2'** to the triple bond and oxygen atom in **1**<sup>2-5,12</sup> (Scheme 4, path F). At present, it remains unclear whether gold(III)-enolate species **2'** is actually generated in this gold(III)-catalyzed propargylic substitution. Propargylic substitution product **4** would be transformed into **6** via cyclization by addition of carbonyl oxygen to the gold(III)-activated triple bond. Next, oxonium intermediate **7** would be generated by coordination of gold(III) catalyst to the two oxygen atoms of ester group in **6**. The terminal hydroxyl group attacks the oxonium ion in **7**, affording bicycle[3.3.1]ketal intermediate **8**. Then, generation of oxonium intermediate **9** leads to **10** via ring-opening of bicycle[3.3.1]ketal intermediate **9**, furnishing 2,3,4-trisubstituted dihydropyran **3**.

In conclusion, we present a gold(III)-catalyzed tandem reaction for synthesis of 2,3,4-trisubstituted dihydropyrans **3** from propargylic alcohols **1** with 1,3-dicarbonyl compounds **2**. We are currently applying this method to the synthesis of biologically active cyclic ether derivatives. Experimental and theoretical investigations on the reaction mechanism are also in progress.

## ACKNOWLEDGEMENTS

This research was supported by grants from the Platform Project for Supporting Drug Discovery and Life Science Research (Platform for Drug Discovery, Informatics, and Structural Life Science) from the Ministry of Education, Culture, Sports, Science (MEXT), and the Japan Agency for Medical Research and Development (AMED).

## REFERENCES AND NOTES

1. For synthesis of natural dihydropyrans and tetrahydropyrans, see: (a) T. Martín, J. I. Padrón, and V. S. Martín, *Synlett*, 2014, **25**, 12; (b) N. M. Nasir, K. Ermanis, and P. A. Clarke, *Org. Biomol. Chem.*, 2014, **12**, 3323; (c) C. Olier, M. Kaafarani, S. Gastaldi, and M. P. Bertrand, *Tetrahedron*, 2010, **66**, 413; (d) A. B. Smith III, R. J. Fox, and T. M. Razler, *Acc. Chem. Res.*, 2008, **41**, 675; (e) K.-S. Yeung, and I. Paterson, *Chem. Rev.*, 2005, **105**, 4237; (f) I. Kadota and Y. Yamamoto, *Acc. Chem. Res.*, 2005, **38**, 423; (g) T. Yasumoto and M. Murata, *Chem. Rev.*, 1993, **93**, 1897.
2. N. Morita, A. Yasuda, M. Shibata, S. Ban, Y. Hashimoto, I. Okamoto, and O. Tamura, *Org. Lett.*, 2015, **17**, 2688.

3. N. Morita, T. Tsunokake, Y. Narikiyo, M. Harada, T. Tachibana, Y. Saito, S. Ban, Y. Hashimoto, I. Okamoto, and O. Tamura, *Tetrahedron Lett.*, 2015, **56**, 6269.
4. N. Morita, Y. Saito, A. Muraji, S. Ban, Y. Hashimoto, I. Okamoto, and O. Tamura, *Synlett*, 2016, **27**, 1936.
5. N. Morita, M. Miyamoto, A. Yoda, M. Yamamoto, S. Ban, Y. Hashimoto, and O. Tamura, *Tetrahedron Lett.*, 2016, **47**, 4460.
6. For synthesis of poly-substituted furan derivatives via tandem reaction from propargylic alcohols with 1,3-dicarbonyl compounds, see: (a) S. Gujarathi and G. Zheng, *Tetrahedron*, 2015, **71**, 6183; (b) S. R. Mothe, S. J. L. Lauw, P. Kothandaraman, and P. W. H. Chan, *J. Org. Chem.*, 2012, **77**, 6937; (c) P. N. Chatterjee and S. Roy, *Tetrahedron*, 2011, **67**, 4569; (d) C. R. Reddy, J. Vijaykumar, and R. Grée, *Synthesis*, 2010, 3715; (e) Y.-m. Pan, S.-y. Zhao, W.-h. Ji, and Z.-p. Zhan, *J. Comb. Chem.*, 2009, **11**, 103; (f) X. Feng, Z. Tan, D. Chen, Y. Shen, C.-C. Guo, J. Xiang, and C. Zhu, *Tetrahedron Lett.*, 2008, **49**, 4110; (g) V. Cadierno, J. Gimeno, and N. Nebra, *Adv. Synth. Catal.*, 2007, **349**, 382; (h) R. Sanz, D. Miguel, A. Martínez, J. M. Álvarez-Gutiérrez, and F. Rodríguez, *Org. Lett.*, 2007, **9**, 727.
7. To our knowledge, only one example of gold(III)-catalyzed tandem reaction of propargylic alcohol with acetylacetone leading to the corresponding furan derivative has been reported. However, the yield was very low (26%). The scope of that reaction is unknown. See: M. Georgy, V. Boucard, O. Debleds, C. D. Zotto, and J.-M. Campagne, *Tetrahedron*, 2009, **65**, 1758.
8. For similar research of the reaction of propargylic alcohol with 1,3-dicarbonyl compounds in the presence of ruthenium catalyst (furan versus pyran ring formation), see: V. Cadierno, J. Díez, J. Gimeno, and N. Nebra, *J. Org. Chem.*, 2008, **73**, 5852.
9. (a) M. N. Pennell, P. G. Turner, and T. D. Sheppard, *Chem. Eur. J.*, 2012, **18**, 4748; (b) M. N. Pennell, M. G. Unthank, P. Turner, and T. D. Sheppard, *J. Org. Chem.*, 2011, **76**, 1479.
10. This reaction would proceed via propargylic substitution reaction as shown in Scheme 4. In our recent results, we found that the propargylic substitution reaction of propargylic alcohol bearing phenyl group at the alkyne-terminus smoothly proceeded to afford the corresponding product whereas the reaction of propargylic alcohols having alkyl group (*n*-Hex, *c*-Hex, *t*-Bu) resulted in the low yields of the products or complex mixture (see: Ref. 2 and 3). Due to the low reactivity of propargylic alcohols **1b-d** to propargylic substitution reaction, the reactions gave low yields as shown in Table 5.
11. (a) T.-H. Chou, J.-J. Chen, C.-F. Peng, M.-J. Cheng, and I.-S. Chen, *Chem. Biodiversity*, 2011, **8**, 2015; (b) V. Dumontet, N. V. Hung, M.-T. Adeline, C. Riche, A. Chiaroni, T. Sévenet, and F. Guéritte, *J. Nat. Prod.*, 2004, **67**, 858; (c) A. Arnone, G. Nasini, and O. V. de Para, *J. Nat. Prod.*,



- 1997, **60**, 971; (d) A. Ogundaini, M. Farah, P. Perera, G. Samuelsson, and L. Bohlin, *J. Nat. Prod.*, 1996, **59**, 587.
12. Gold(III)-catalyzed propargylic substitution, see: (a) E. Gayon, H. Gerard, E. Vrancken, and J.-M. Campagne, *Synlett*, 2015, **26**, 2336; (b) O. Debleds, E. Gayon, E. Vrancken, and J.-M. Campagne, *Beilstein J. Org. Chem.*, 2011, **7**, 866; (c) M. Georgy, V. Boucard, and J.-M. Campagne, *J. Am. Chem. Soc.*, 2005, **127**, 14180.
13. For gold-enolate species generated from gold catalyst with 1,3-dicarbonyl compound, see: (a) J.-M. Tang, T.-A. Liu, and R.-S. Liu, *J. Org. Chem.*, 2008, **73**, 8479; (b) S. Komiya, T. Sone, Y. Usui, M. Hirano, and A. Fukuoka, *Gold Bull.*, 1996, **29**, 131; (c) M. Murakami, M. Inouye, M. Suginome, and Y. Ito, *Bull. Chem. Soc. Jpn.*, 1988, **61**, 3649.