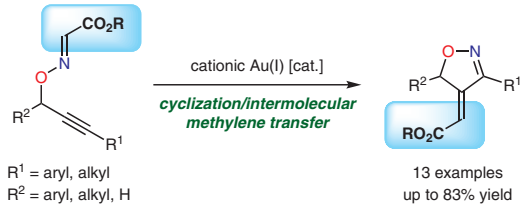
Synlett S. Gima et al. THIEME OPEN ACCESS Letter

Gold-Catalyzed Cyclization/Intermolecular Methylene Transfer Sequence of *O*-Propargylic Oximes Derived from Glyoxylates

Shinya Gima[a]
Keigo Shiga[a]
Masahiro Terada[a]
Itaru Nakamura*[b]

[a] Department of Chemistry, Graduate School of Science, Tohoku University, 6-3 Aramaki Aza Aoba, Aoba-ku Sendai, 980-8578, Japan
[b] Research and Analytical Center for Giant Molecules, Graduate School of Science, Tohoku University, 6-3 Aramaki Aza Aoba, Aoba-ku Sendai, 980-8578, Japan
itaru-n@tohoku.ac.jp

Published as part of the *30 Years SYNLETT – Pearl Anniversary Issue*



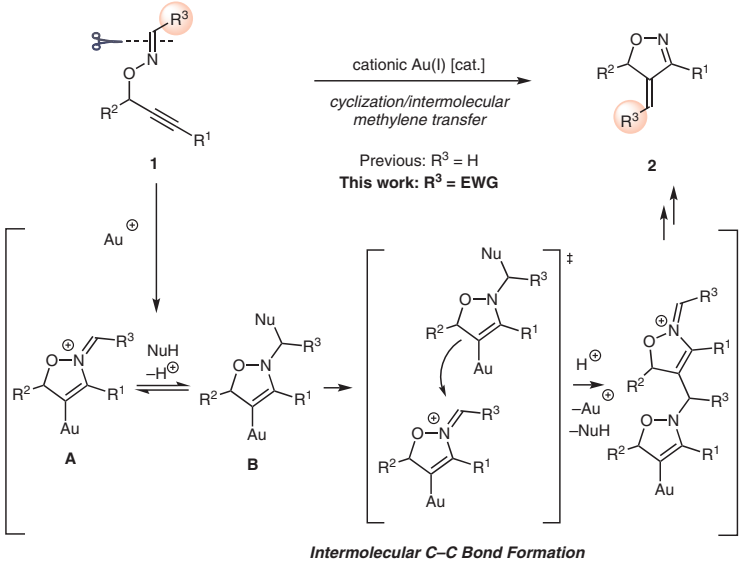
Received: 25.09.2018
Accepted after revision: 18.11.2018
Published online: 06.12.2018
DOI: 10.1055/s-0037-1611640; Art ID: st-2018-b0613-l

Abstract We successfully extended our gold-catalyzed skeletal rearrangement reaction of *O*-propargylic oximes through C=N bond cleavage to include substrates having an ester group on the oxime moiety, affording the corresponding 2-isoxazolines having an alkoxycarbonylmethylene group at the 4-position in good to high yields. Our mechanistic studies indicated that the transfer of the alkoxycarbonylmethylene group proceeded in an intermolecular manner, confirming that the reaction proceeds through cyclization followed by intermolecular transfer of the alkoxycarbonylmethylene group.

Key words gold catalysis, rearrangement, heterocycles, cyclization, progargylic oximes, isoxazolines

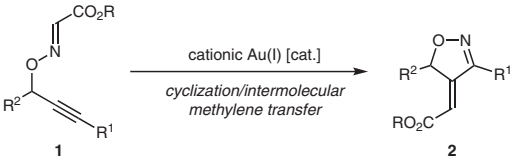
Gold-catalyzed skeletal-rearrangement reactions are powerful methods for synthesizing highly functionalized carbo- or heterocyclic compounds from readily available starting materials in a single operation under mild conditions with high functional-group compatibility.[1] Earlier studies focused mainly on the use of 1,*n*-enynes[2] or propargylic esters[3] as starting materials. We recently reported that the gold-catalyzed skeletal rearrangement reactions of *O*-propargylic formaldoximes **1** (R^3 = H) proceed through C=N bond cleavage, affording the corresponding 4-methylenated 2-isoxazolines **2** in good to excellent yields (Scheme 1).[4]

Our mechanistic studies indicated that the methylene group was transferred intermolecularly. We proposed that the reaction proceeds through π-acidic Au-promoted cyclization, followed by intermolecular C–C bond formation between the iminium moiety of the cyclized vinylgold spe-



Scheme 1 Au-catalyzed skeletal rearrangement of *O*-propargylic oximes

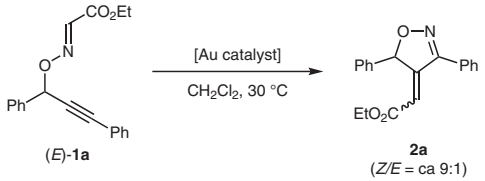
cies **A** and the enamine form **B**, generated in situ by attack of a nucleophilic species (NuH), such as trace water, on another vinylgold intermediate **A**. This intriguing rearrangement reactions was, however, restricted to the use of substrates derived from formaldoxime (R^3 = H); substrates that possessed a substituent such as an alkyl and aryl group on the oxime moiety (R^3) did not undergo the transformation. This drawback is presumably because these functional groups interrupt the intermolecular C–C bond-forming process, not only by steric repulsion, but also through low electrophilicity. Accordingly, we envisioned that less-bulky and more-electron-withdrawing functional groups might be compatible as substituents on the oxime moiety, improving the synthetic utility of the present cascade reactions. Here, we report that Au-catalyzed skeletal rearrangement reactions of *O*-propargylic oximes derived from glyoxylates **1** (R^3 = CO_2R) afford the corresponding isoxazolines **2** in good to high yields (Scheme 2).



Scheme 2 Au-catalyzed cyclization/intermolecular methylene transfer sequence of *O*-propargylic oximes **1** derived from glyoxylates

Initially, the reaction of the (*E*)-oxime (*E*)-**1a** having an ethoxycarbonyl group on the oxime moiety afforded the desired product **2a** in a moderate chemical yield (46%) under our previous reaction conditions by using 5 mol% of $Ph_3PAuNTf_2$ in CH_2Cl_2 at 30 °C (Table 1, entry 1). In contrast, the reaction of the (*Z*)-oxime (*Z*)-**1a** resulted in a poor chemical yield (entry 2), due to decomposition of the starting material.[5] The use of triflate, tetrafluoroborate, or perchlorate as a counteranion gave comparable result to that of the triflic imide (entries 3–5), whereas the use of hexafluoroantimonate resulted in a lower yield (entry 6). The catalytic activity depended on the electronic character of the phosphine ligand (entries 7–10), in that the use of relatively electron-deficient triarylphosphines improved the chemical yield (entries 7 and 8). In particular, the reaction using $(4\text{-}F_3CC_6H_4)_3P$ gave **2a** in a good yield (entry 8), whereas $(C_6F_5)_3P$ was inefficient (entry 9). The chemical yield was significantly improved by doubling the loading of the gold catalyst, to afford **2a** in 81% isolated yield (entry 12).[6] The use of CH_2Cl_2 and MeCN was effective to afford **2a** in good yields, whereas the use of MeOH resulted in formation of considerable amounts of nonmethylenated isoxazoline as a byproduct [see the Supplementary Information (SI)]. It should be noted that the *Z*/*E* stereoselectivity at the *exo*-olefin moiety was not significantly affected by the reaction conditions: the *Z*/*E* ratio was about 9:1 in all cases (see SI).

Table 1 Optimization of the Reaction Conditions[a]

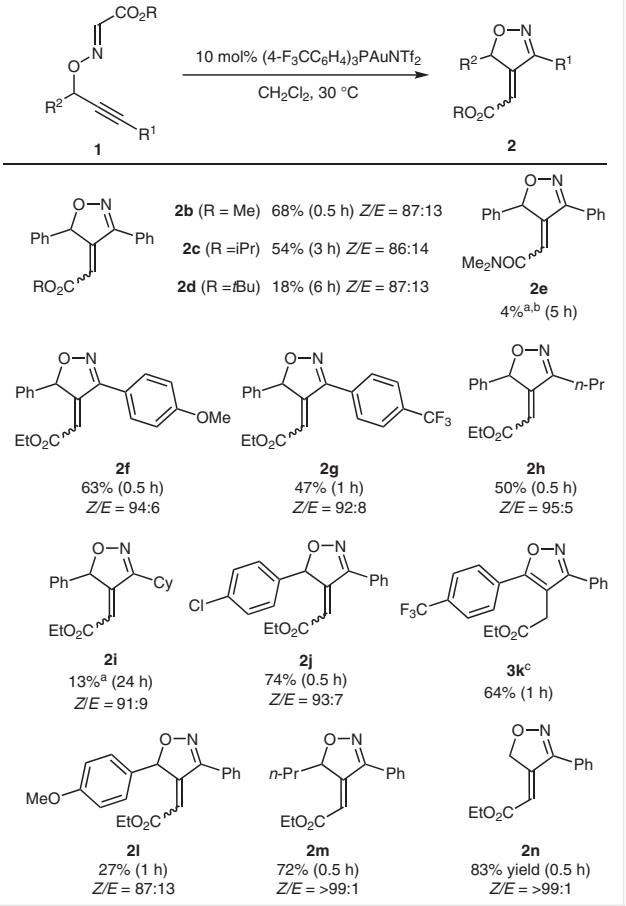


Entry	Au catalyst (mol %)	Time (h)	Yield[b] (%)
1	$Ph_3PAuNTf_2$ (5)	8	46
2[c]	$Ph_3PAuNTf_2$ (5)	24	10
3	Ph_3PAuCl (5), $AgOTf$ (5)	24	41
4	Ph_3PAuCl (5), $AgBF_4$ (5)	8	44
5	Ph_3PAuCl (5), $AgClO_4$ (5)	8	42
6	Ph_3PAuCl (5), $AgSbF_6$ (5)	8	26
7	$(4\text{-}FC_6H_4)_3PAuNTf_2$ (5)	8	50
8	$(4\text{-}F_3CC_6H_4)_3PAuNTf_2$ (5)	8	62
9	$(C_6F_5)_3PAuNTf_2$ (5)	8	4
10	$(4\text{-}MeOC_6H_4)_3PAuNTf_2$ (5)	8	28
11	$Ph_3PAuNTf_2$ (10)	2	76
12	$(4\text{-}F_3CC_6H_4)_3PAuNTf_2$ (10)	2	(81)[d]

[a] Reaction conditions: (*E*)-**1a** (0.2 mmol), gold catalyst, CH_2Cl_2 (0.4 mL), 30 °C.
[b] Determined by ^1H NMR with CH_2Br_2 as an internal standard.
[c] (*Z*)-**1a** was used instead of (*E*)-**1a**.
[d] Isolated yield.

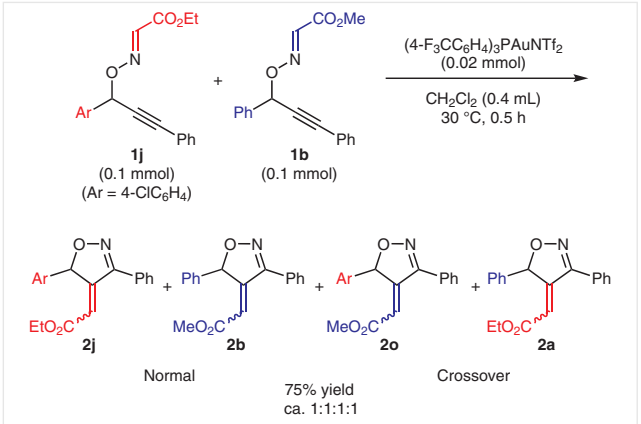
Next, the scope of substrates **1** was examined (Scheme 3). The efficiency of our reaction depended on the bulkiness of the ester group; the methyl ester **1b** and the ethyl ester **1a** were converted into the corresponding products **2b** and **2a** (see also Table 1, entry 12), respectively, in good yields, whereas the *tert*-butyl ester **1d** required a prolonged reaction time to be fully consumed, affording the desired product **2d** in low yield. It should be noted that the *Z*/*E* selectivity at the *exo*-olefin moiety of products **2a–d** was not influenced by the bulkiness of the ester group. The reaction of substrate **1e**, having a dimethylcarbamoyl group instead of an ester group, gave the desired product **2e** in poor yield (4%).[7] Substrate **1f**, having an electron-rich 4-anisyl group at the alkyne terminus (R^1) was converted into the corresponding product **2f** in 63% yield, whereas the reaction of **1g** having an electron-deficient 4-trifluoromethyl group resulted in a lower chemical yield (47%). In terms of alkyl substitution at R^1, **1h**, containing a propyl group was compatible, whereas the reaction of **1i** having a bulky cyclohexyl group was sluggish.[8] An electron-deficient aryl group was tolerated at the propargylic position (R^2) to furnish the corresponding isoxazoline in a good yield. Because **2k** having a 4-(trifluoromethyl)phenyl group at the 5-position of the isoxazoline ring was partially isomerized to the isoxazole **3k** during purification, the crude product **2k** was treated with DBU in one pot to obtain **3k** as a single product in good yield. In contrast, the substrate **1l**, which had an elec-

tron-rich 4-anisyl group at the R^2 position gave **2l** in a low chemical yield of 27%. Moreover, the reaction of **1m** having a less-bulky propyl group at R^2 gave **2m** with excellent *Z*-stereoselectivity. The substrate **1n**, which did not possess any substituents at R^2, was effectively converted into the corresponding product **2n** in 83% yield.



Scheme 3 Au-catalyzed reaction of **1b–m**. *Reaction conditions*: **1** (0.2 mmol), $(4\text{-}F_3CC_6H_4)_3PAuNTf_2$ (10 mol %), CH_2Cl_2 (0.4 mL), 30 °C. Isolated yields of (*Z*)-**2** are reported. The *Z*/*E* ratio was determined by ^{1}H NMR of the crude product. [a] Yield determined by ^{1}H NMR with CH_2Br_2 as internal standard. [b] **1e** was used as an *E*/*Z* mixture (91:9). [c] The crude product **2k** was treated with DBU (1 equiv) in CH_2Cl_2 at 30 °C for 1 h to afford the isoxazole **3k**.

The reaction of the two equally reactive substrates **1b** and **1j** under the standard reaction conditions afforded equal amounts of the normal products **2b** and **2j** and the crossover products **2a** and **2o** (Scheme 4). Neither the products nor the substrates showed crossover reactions the presence of gold catalysts (see SI), clearly indicating that transfer of the alkoxycarbonylmethylene group took place intermolecularly. In addition, the reaction of **1b** or **1m** in the presence of ethyl glyoxylate or 3,5-diphenylisoxazoline exclusively afforded **2b** or **2m**, derived from the starting material (see SI).



Scheme 4 Crossover experiment

We therefore concluded that the present reaction proceeds through cyclization followed by intermolecular transfer of the alkoxycarbonylmethylene group, sequentially liberating the product **2**, in the same manner of our previous reaction of *O*-propargylic formaldoximes.[4a] The present reaction selectively afforded the (*Z*)-isomer (*Z*)-**2** (Scheme 3). Presumably, because the *exo*-olefin and isoxazoline C=N bond in the (*E*)-isomer are not coplanar due to steric repulsion between the ester group and the substituent R^1 derived from the alkyne terminus of the starting material **1**, the more-stable (*Z*)-isomer was obtained with high stereoselectivity. It should be noted that the reactions of **1m**, which has a less-bulky propyl group at the propargylic position, and of **1n**, which lacks a substituent at R^2, exhibited excellent stereoselectivity. These results also can be explained by relaxation of the steric repulsion between the ester group and R^2 in the (*Z*)-isomer. The use of the gold catalyst with an electron-deficient phosphine ligand, such as $(4\text{-}F_3CC_6H_4)_3P$, gave a better result than that of a catalyst having an electron-rich ligand (Table 1, entry 8 versus entry 10). We assume that the cyclization process requires a higher π-acidity than that in the reaction of formaldoximes due to steric repulsion between the ester group of the (*E*)-oxime and the alkyne substituent R^1 in the cyclization process from **1** to **A** (Scheme 1).[4a] In addition, the electronic character of the gold catalyst might affect the electrophilicity of the iminium moiety of the vinylgold intermediate **A** (Scheme 1) to facilitate intermolecular C–C bond formation. Further mechanistic studies are still underway in our laboratory.

In conclusion, we have successfully synthesized isoxazolines having an alkoxycarbonylmethylene group at the 4-position in an efficient manner. Because there are only a limited number of methods for synthesizing 4-alkylidene-substituted isoxazolines,[9] the present method is useful for constructing densely functionalized heterocycles.

Funding Information

This work was supported by JSPS KAKENHI Grant Number JP16H00996 in Precisely Designed Catalysts with Customized Scaffolding.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1611640.

References and Notes

(1) For selected reviews on gold catalysis, see: (a) Li, Y.; Li, W.; Zhang, J. *Chem. Eur. J.* **2017**, *23*, 467. (b) Harris, R. J.; Widenhoefer, R. A. *Chem. Soc. Rev.* **2016**, *45*, 4533. (c) Yang, W.; Hashmi, A. S. K. *Chem. Soc. Rev.* **2014**, *43*, 2941. (d) Obradors, C.; Echavarren, A. M. *Chem. Commun.* **2014**, *50*, 16. (e) Hashmi, A. S. K. *Angew. Chem. Int. Ed.* **2010**, *49*, 5232. (f) Adcock, H. V.; Davies, P. W. *Synthesis* **2012**, *44*, 3401. (g) Bhunia, S.; Liu, R.-S. *Pure Appl. Chem.* **2012**, *84*, 1749. (h) Lu, B.-L.; Dai, L.; Shi, M. *Chem. Soc. Rev.* **2012**, *41*, 3318. (i) Kirsch, S. F. *Synthesis* **2008**, 3183. (j) Skouta, R.; Li, C.-J. *Tetrahedron* **2008**, *64*, 4917. (k) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180.

(2) For pioneering works, see: (a) Trost, B. M.; Tanoury, G. J. *J. Am. Chem. Soc.* **1988**, *110*, 1636. (b) Chatani, N.; Morimoto, T.; Muto, T.; Murai, S. *J. Am. Chem. Soc.* **1994**, *116*, 6049. For reviews, see: (c) Wang, Q.; Shi, M. *Synlett* **2017**, *28*, 2230. (d) Dorel, R.; Echavarren, A. M. *J. Org. Chem.* **2015**, *80*, 7321. (e) Michelet, V. *Top. Curr. Chem.* **2015**, *357*, 95.

(3) For pioneering works, see: (a) Rautenstrauch, V. *J. Org. Chem.* **1984**, *49*, 950. (b) Mainetti, E.; Mouriès, V.; Fensterbank, L.; Malacria, M.; Marco-Contelles, J. *Angew. Chem. Int. Ed.* **2002**, *41*, 2132. For reviews, see: (c) Boyle, J. W.; Zhao, Y.; Chan, P. W. H. *Synthesis* **2018**, *50*, 1402. (d) Fensterbank, L.; Malacria, M. *Acc. Chem. Res.* **2014**, *47*, 953. (e) Mauleon, P.; Toste, F. D. In *Modern Gold Catalyzed Synthesis*, Chap. 4, Hashmi, S. K.; Toste, F. D., Ed.; Wiley-VCH: Weinheim, **2012**, 75.

(4) (a) Nakamura, I.; Gima, S.; Kudo, Y.; Terada, M. *Angew. Chem. Int. Ed.* **2015**, *54*, 7154. (b) Gima, S.; Nakamura, I.; Terada, M. *Eur. J. Org. Chem.* **2017**, 4375.

(5) Identifiable byproducts were not obtained from the reaction of (*Z*)-**1a**. It is therefore unclear at the present stage why the reaction of (*Z*)-**1a** resulted in a low chemical yield.

(6) **Ethyl (2*Z*)-(3,5-Diphenylisoxazol-4(5*H*)-ylidene)acetate [(*Z*)-2a]; Typical Procedure**
Oxime (*E*)-**1a** (61.5 mg, 0.2 mmol) in CH_2Cl_2 (0.4 mL) was added to $(4\text{-}F_3CC_6H_4)_3PAuNTf_2$ (18.9 mg, 0.02 mmol) in a V-vial under argon, and the mixture was stirred at 30 °C for 2 h. The mixture was then passed through a short pad of silica gel, eluting with CH_2Cl_2 (50 mL). The solvents were evaporated in vacuo, and the crude product was purified by flash column chromatography [silica gel, hexane–EtOAc (8:1)] to give a colorless liquid; yield: 50 mg (81%, *Z*/*E* = 90:10). IR (neat): 3063, 3033, 2981, 2939, 2903, 1709, 1641, 1494, 1455, 1444, 1367, 1331, 1310, 1299, 1269, 1199, 1130, 1096, 1077, 1035, 1007, 912, 899, 873 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.67–7.62 (m, 2 H), 7.55–7.50 (m, 3 H), 7.39–7.31 (m, 5 H), 6.76 (d, *J* = 3.2 Hz, 1 H), 6.32 (d, *J* = 3.2 Hz, 1 H), 4.06 (q, *J* = 7.3 Hz, 2 H), 1.14 (t, *J* = 7.3 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.22, 157.47, 155.10, 137.69, 130.36, 129.07, 128.70, 128.63, 128.33, 127.58, 127.39, 115.57, 88.03, 60.83, 14.01. HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{19}H_{17}NNaO_3$: 330.1101; found: 330.1100.

(7) A substrate having a trichloromethyl group was not converted into the desired product under the optimal reaction conditions; 60% of the starting material was recovered. Preparations from substrates having a cyano or keto group instead of an ester group failed.

(8) The reaction of **1i** at 50 °C afforded the desired product **2i** in 12% yield.

(9) (a) Dunn, P. J.; Graham, A. B.; Grigg, R.; Higginson, P.; Sridharan, V.; Thornton-Pett, M. *Chem. Commun.* **2001**, 1968. (b) Broggini, G.; Bruché, L.; Zecchi, G.; Pilati, T. *J. Chem. Soc., Perkin Trans. 1* **1990**, 533.