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Au-catalyzed skeletal rearrangement of *O*-propargylic oximes *via* N–O bond cleavage with the aid of a Brønsted base cocatalyst†

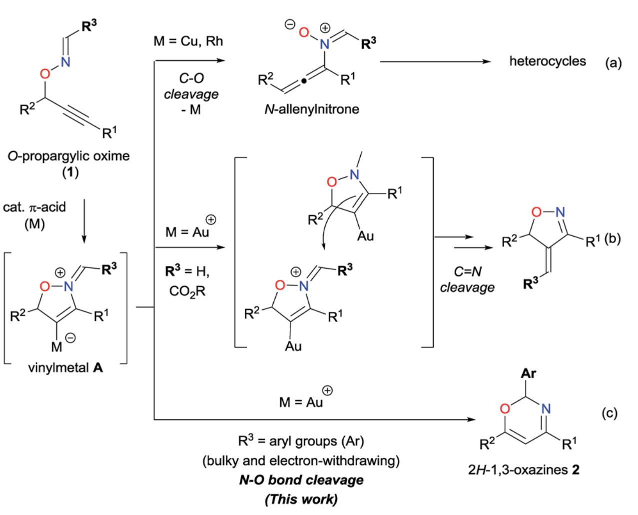
Keigo Shiga,[b] Ilya D. Gridnev,[b] Masahiro Terada[b] and Itaru Nakamura*[a]

O-Propargylic oximes that possess an electron-withdrawing aryl group on the oxime moiety undergo Au-catalyzed skeletal rearrangements *via* N–O bond cleavage to afford the corresponding 2*H*-1,3-oxazine derivatives. Our studies show that the inclusion of a Brønsted base cocatalyst not only accelerates the reaction but also switches pathways of the skeletal rearrangement reaction, realizing divergent synthesis of heterocyclic compounds. Computational studies indicate that the elimination of propargylic proton in the cyclized vinylgold intermediate is rate-determining and both electron-withdrawing substituents at the oxime moiety and base cocatalyst facilitate the proton elimination. Moreover, the protodeauration process proceeds stepwise involving N–O bond cleavage followed by recyclization to construct the oxazine core.

Introduction

π-Acidic metal catalysis is a powerful tool to synthesize a wide variety of heterocyclic compounds in an efficient and environmentally benign manner. In particular, π-acidic metal-catalyzed skeletal rearrangements allow for the rapid construction of highly elaborate organic molecules, inaccessible by conventional methods, through the cleavage of skeletal σ bonds under mild reaction conditions with high functional group compatibility.[1,2] Notably, reaction pathways of catalytic skeletal rearrangements are often changed by metal catalysts as well as functional groups introduced on molecular platforms, such as enynes[1] or propargylic esters,[2] thus leading to functionalized heterocyclic compounds. Therefore, it is beneficial for pharmaceutical science and material science to provide diverse heterocycles by further exploring catalytic skeletal rearrangement reactions with suitable design of starting materials and appropriate choice of π-acidic metal catalysts.

We have recently reported that *O*-propargylic oximes **1** can serve as a unique platform for the skeletal rearrangement reactions to efficiently construct a variety of heterocycles (Scheme 1).[3,4] For example, Cu- and Rh-catalyzed reactions proceeded *via* C–O bond cleavage resulting in *N*-allenylnitrone intermediates that subsequently transformed into azaheterocycles of various ring sizes (Scheme 1a).[3] We further reported on Au-catalyzed reactions of formaldoxime ($R^3 = H$)[4a] and glyoxylate oxime ($R^3 = CO_2R$)[4c] that afforded the corresponding 4-methyleneisoxazolines (Scheme 1b), *via* C=N bond cleavage.[5] Our experimental results imply that these Au-catalyzed reactions proceed *via* an intermolecular nucleophilic attack on the iminium moiety of the long-lived vinylgold intermediate **A** (M = Au), because the C–Au bond is much stronger than the C–Cu due to the relativistic nature of the Au catalyst,[6] resulting in deceleration of the C–O bond cleavage with the elimination of the metal catalyst. Accordingly, we envisaged that oximes that



Scheme 1 π-Acidic metal-catalyzed skeletal rearrangement of *O*-propargylic oximes **1**.

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[a] Research and Analytical Center for Giant Molecules, Graduate School of Science, Tohoku University, Sendai, 980-8578, Japan. E-mail: itaru-n@tohoku.ac.jp

[b] Department of Chemistry, Graduate School of Science, Tohoku University, Sendai, 980-8578, Japan

† Electronic supplementary information (ESI) available: Experimental and computational details and spectral data are provided. CCDC 1892710 (**2s**). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c9sc00501c

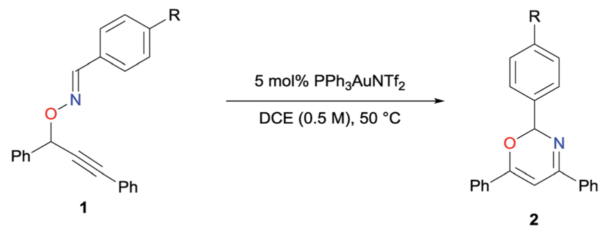
possess a bulky R^3 would decelerate the intermolecular nucleophilic attack and thus favor alternate reactivities of vinylgold intermediate **A**. Herein, we report on the Au-catalyzed reactions of *O*-propargylic oximes **1** having an aryl group at the oxime moiety, which proceed *via* N–O bond cleavage, in affording the corresponding 2*H*-1,3-oxazine derivatives **2** in good to high yields (Scheme 1c).‡,[7]

Results and discussion

Initially, the reaction of oxime **1a**, which possesses a phenyl group at the oxime moiety, was carried out in the presence of PPh_3AuNTf_2 (5 mol%) in 1,2-dichloroethane (DCE) at 50 °C for 24 h, to afford oxazine **2a** in 16% yield (Table 1, entry 1). The efficiency of the present reaction was significantly improved by an electron-deficient aryl group at the oxime moiety (entries 2–4). Particularly, the Au-catalyzed reaction of **1d** having a *p*-nitrophenyl group was complete within 8 h, affording desired product **2d** in an excellent yield (93%, entry 4).

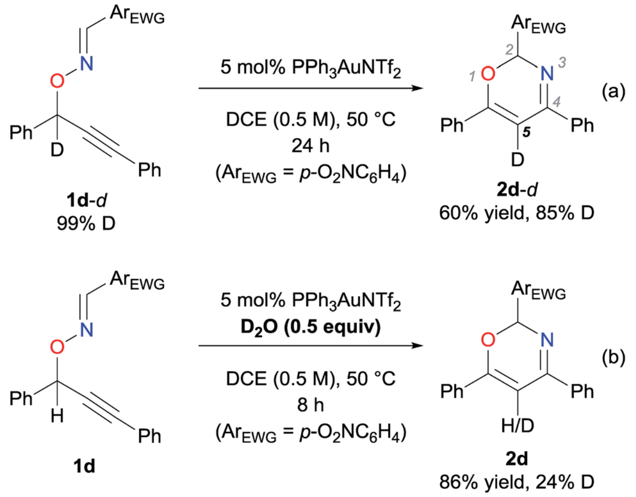
To gain insight into the reaction mechanism, specifically to track the movement of the propargylic hydrogen, experiments were carried out using deuterated substrates (Scheme 2). As shown in Scheme 2a, the Au-catalyzed reaction of **1d**-*d*, which was deuterated (>99%) at the propargylic position, afforded **2d**-*d* with a decreased deuterium content (85% at the 5 position of the oxazine ring) in a 60% yield.§ It is important to note that the reaction of deuterated substrate **1d**-*d* was slower than that of non-deuterated **1d**, and required 24 h for the complete consumption of the deuterated substrate. In contrast, the reaction of the non-deuterated **1d** was carried out in the presence of D_2O (0.5 equivalent) to afford **2d**-*d*, with a deuterium content of 24% (Scheme 2b). These results strongly suggest that the hydrogen was transferred as a proton interconvertible with external water over the course of the reaction. In other words, direct [1,2]-hydrogen shift is unlikely.

Table 1 Au-catalyzed reaction of **1a–d**; substituent effect[a]



Entry	1	R	Time (h)	Yield[b] (%)
1	**1a**	H	24	16[c]
2	**1b**	Br	48	76
3	**1c**	CF_3	15	80
4	**1d**	NO_2	8	93

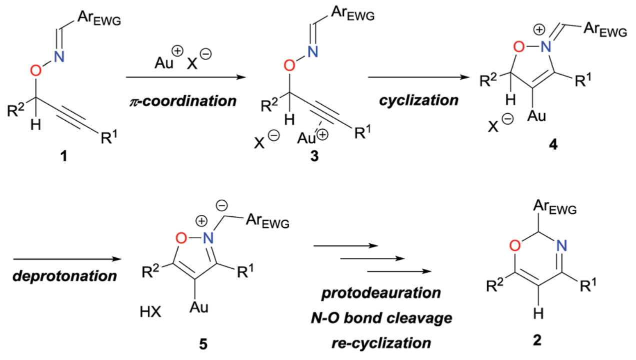
[a] Reaction of **1** (0.2 mmol) were conducted in the presence of PPh_3AuNTf_2 (0.01 mmol) in DCE (0.4 mL) at 50 °C. [b] Isolated yield. [c] 46% of **1a** was recovered.



Scheme 2 Labelling experiments.

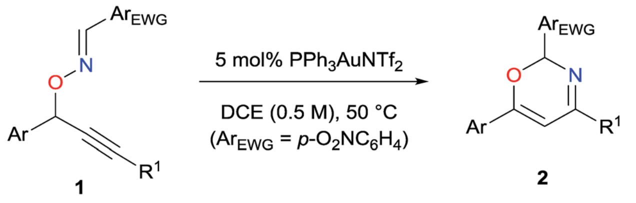
Based on these investigations and our previous studies,[4] a reaction mechanism for the skeletal rearrangement can be outlined as illustrated in Scheme 3. First, the π-acidic Au catalyst is coordinated by the alkyne moiety of **1** to form π-complex **3**. Consequently, the electrophilically activated alkyne moiety undergoes a nucleophilic attack by the oxime nitrogen, leading to the cyclized vinylgold **4**. Next, the propargylic proton is eliminated to form aromatized intermediate **5**, which would further undergo protodeauration, N–O bond cleavage, and re-cyclization, although the order of these processes were unidentifiable at this stage. A strong isotope effect on the reaction rate (Scheme 2a *versus* Table 1, entry 4) would suggest that the rate-determining step is the elimination of the proton from **4** to **5**. Accordingly, a *p*-nitrophenyl group would probably enhance the acidity of the eliminating proton, and facilitate the entire process.

The present transformation was applied toward substrates **1e–s** with various aryl groups at the propargylic position, as listed in Table 2. Substrates **1e–g**, which possess an aryl group at the alkyne terminus, were efficiently converted to the corresponding oxazines **2e–g** in good to excellent yields, regardless of the electronic nature of the aryl group (entries 1–3). 1-



Scheme 3 Outline of the reaction mechanism for Au-catalyzed reaction of *O*-propargylic oximes **1** *via* N–O bond cleavage.

Table 2 Au-catalyzed reactions of **1e–s**[a]



	1	R^1	Ar	Time (h)	2	Yield[b] (%)
1	**1e**	p-MeOC$_6$H$_4$	Ph	8	**2e**	92
2	**1f**	p-ClC$_6$H$_4$	Ph	8	**2f**	94
3	**1g**	p-F$_3$CC$_6$H$_4$	Ph	20	**2g**	86
4	**1h**	1-Cyclohexenyl	Ph	8	**2h**	51
5	**1i**	Cy	Ph	12	**2i**	81
6	**1j**	iPr	Ph	15	**2j**	53
7	**1k**	1-Phenylpentyl	Ph	8	**2k**	61
8	**1l**	*n*Pr	Ph	24	—	<1
9	**1m**	*t*Bu	Ph	6	—	<1[c]
10	**1n**	H	Ph	24	—	<1[d]
11	**1o**	Ph	p-MeOC$_6$H$_4$	8	**2o**	65
12	**1p**	Ph	p-ClC$_6$H$_4$	8	**2p**	92
13	**1q**	Ph	p-F$_3$CC$_6$H$_4$	8	**2q**	91
14	**1r**	4-MeOC$_6$H$_4$	p-F$_3$CC$_6$H$_4$	12	**2r**	93
15	**1s**	Ph	1-Naphthyl	8	**2s**	93

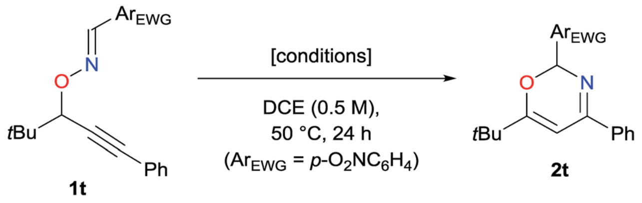
[a] Reaction of **1** (0.2 mmol) were conducted in the presence of PPh$_3$AuNTf$_2$ (0.01 mmol) in DCE (0.4 mL) at 50 °C. [b] Isolated yield. [c] 76% of **1m** was recovered. [d] 28% of **1n** was recovered.

Cyclohexenyl group was tolerated as an alkyne substituent (entry 4). Substrates **1i–k**, which possess a secondary alkyl group at the alkyne terminus, were transformed to the corresponding desired products **2i–k** in good to acceptable yields (entries 5–7). In contrast, **1l–n**, which possess a primary alkyl group, a *t*-butyl group, and a terminal alkyne, respectively, did not afford the corresponding desired products (entries 8–10). As expected, substrates with electron-deficient aryl group substituent at the propargylic position were more effective than that with an electron-rich anisyl substituent, presumably due to the enhanced acidity of the propargyl proton (entries 11–14).

Despite using optimized reaction conditions, the Au-catalyzed reactions of the substrates that possess an alkyl group at the propargylic position did not afford the oxazine; considerable amounts of starting materials were recovered (Table 3, entry 1, see also ESI†). In accordance with our proposed mechanism, the alkyl substituent decreases the acidity of the eliminating proton of the cyclized vinylgold intermediate **4** (Scheme 3). Consequently, we decided to explore the use of other counteranions, which could assist the proton elimination (Table 3, entries 1–3).[8] To our delight, the use of tosylate, instead of triflic imidate in the reaction of **1t** having a *t*-butyl group resulted in efficient formation of **2t** (entry 3), whereas triflate was ineffective (entry 2). More interestingly, we disclosed that pyridine served as an efficient cocatalyst without poisoning the catalytic activities of the π-acidic Au catalyst (entry 4).[9] The reaction using bulkier 2,6-lutidine than pyridine was sluggish, and that using trimethylamine resulted in formation of unidentified byproducts, while KO*t*Bu totally diminished the activity of the gold catalyst (entries 5–7). We selected a combination of PPh$_3$AuNTf$_2$ and pyridine (entry 4) as the reaction conditions for the alkyl-substituted substrate in order to further know the applicability of the intriguing cocatalyst system.

Substrates **1u–w** having a secondary alkyl group were converted to the corresponding products in good to moderate yields by using the gold-pyridine cocatalyst system (Table 4, entries 1–3). In contrast, the reaction of **1x** having a primary alkyl group resulted in the decomposition of starting material **1x**, presumably due to the instability of the corresponding oxazine (entry 4). It should be noted that the reaction of **1y** having a bulky cyclohexyl group at the alkyne terminus was efficiently promoted by the gold-pyridine cocatalyst system (entry 5),

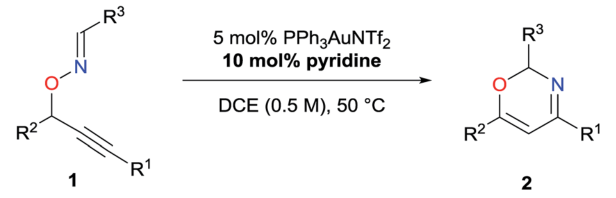
Table 3 Optimization for Au-catalyzed reactions of **1t** having an alkyl group at the propargylic position



Entry	Catalyst (mol%)	Additive (mol%)	Yield[a] (%)	Recovery[a] (%)
1	Ph$_3$PAuNTf$_2$ (5)	—	<1	90
2	PPh$_3$AuCl (5), AgOTf (5)	—	<1	91
3	PPh$_3$AuCl (5), AgOTs (5)	—	90[b]	<1
4	PPh$_3$AuNTf$_2$ (5)	Pyridine (10)	(90)[c]	<1
5	PPh$_3$AuNTf$_2$ (5)	2,6-Lutidine (10)	10	64
6	PPh$_3$AuNTf$_2$ (5)	Et$_3$N (10)	6	33
7	PPh$_3$AuNTf$_2$ (5)	KO*t*Bu (10)	<1	75

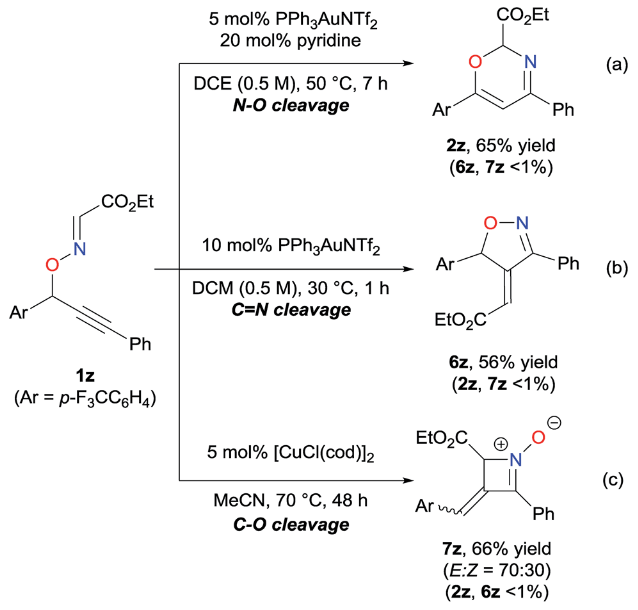
[a] The yields were determined by ^{1}H NMR using dibromomethane as an internal standard. Isolated yield in parentheses. [b] 48 h. [c] 72 h.

Table 4 Au-catalyzed reactions of **1a**, **m**, **u–y** with pyridine cocatalyst[a]



	1	R^1	R^2	R^3	Time (h)	2	Yield[b] (%)
1	**1u**	Ph	iPr	p-$O_2NC_6H_4$	21	**2u**	40
2	**1v**	Ph	Cy	p-$O_2NC_6H_4$	20	**2v**	65
3	**1w**	Ph	Cyclopropyl	p-$O_2NC_6H_4$	24	**2w**	60
4	**1x**	Ph	*n*Pr	p-$O_2NC_6H_4$	24	—	<1
5[c]	**1y**	Cy	*t*Bu	p-$O_2NC_6H_4$	36	**2y**	72
6[d]	**1y**	Cy	*t*Bu	p-$O_2NC_6H_4$	48	**2y**	18[e]
7	**1m**	*t*Bu	Ph	p-$O_2NC_6H_4$	30	**2m**	75[f]
8	**1a**	Ph	Ph	Ph	24	**2a**	28[g]

[a] Reaction of **1** (0.2 mmol) were conducted in the presence of PPh_3AuNTf_2 (0.01 mmol) and pyridine (0.02 mmol) in DCE (0.4 mL) at 50 °C. [b] Isolated yield. [c] $PPh_3PAuNTf_2$ (0.02 mmol) and pyridine (0.02 mmol) were used. [d] PPh_3AuCl (0.02 mmol) and AgOTs (0.02 mol) were used, instead of PPh_3AuNTf_2 and pyridine. [e] Determined by ^1H NMR using dibromomethane as an internal standard. [f] 21% of **1m** was recovered. [g] 44% of **1a** was recovered.



Scheme 4 Divergent synthesis of heterocycles from **1z** *via* skeletal rearrangement.

whereas that using PPh_3AuCl and AgOTs was sluggish (entry 6). Moreover, the substrate **1m**, which has *tert*-butyl and phenyl groups at the alkyne terminus and propargylic position (R^2), respectively, was converted to the desired product **2m** by using the gold-pyridine cocatalyst system (entry 7 *versus* Table 2, entry 9).¶ These results indicate that gold-pyridine cooperative catalyst system is effective for not only the proton elimination process but also the cyclization process when the alkyne substituent is bulky (**3** to **4** in Scheme 3). Probably, pyridine cocatalyst can maintain the π-acidity of the gold catalyst and even enhance the nucleophilicity of the oxime moiety. In addition, chemical yield of the reaction of **1a**, which have a less electron-withdrawing phenyl group at the oxime moiety, was slightly improved from 16% to 28% by the use of the gold-pyridine cocatalyst system (entry 8 *versus* Table 1, entry 1).

The uniqueness of the Au-pyridine cooperative catalytic system can be demonstrated by the different pathways for the skeletal rearrangement reactions. In the absence of any cocatalysts, the Au-catalyzed reaction of *O*-propargylic oxime **1z**, which possesses an electron-withdrawing and less bulky ethoxycarbonyl group at the oxime moiety, afforded isoxazoline derivative **6z** through a sequence of cyclization followed by intermolecular methylene transfer (Scheme 4b).[4c] In sharp contrast, in the presence of the cooperative Au-pyridine catalyst system, the reaction of oxime **1z** selectively afforded oxazine **2z** in good yield (Scheme 4a). It is noteworthy that, although a Brønsted base cocatalyst has been typically functioned as an activator of nucleophiles in Au-catalyzed reactions,[10] the base cocatalyst serves as a switch of the reaction pathway in the present cascade reaction. Moreover, the reaction of **1z** using the Cu catalyst afforded the azete-*N*-oxide **7z** *via* C–O bond cleavage (Scheme 4c). Accordingly, our studies reveal that by including or excluding a cocatalyst, as well as choosing appropriate metal catalysts, the skeletal rearrangement reaction can allow for the synthesis of diverse heterocycles from a common starting material through switching among reaction pathways, and can be highly beneficial within the field of drug discovery.

Experimental results indicated that elimination of proton from the propargylic position was rate-determining (Scheme 2). Thus we conducted DFT calculations to further elucidate reaction mechanism, specifically to identify the order of protodeauration, N–O bond cleavage, and re-cyclization processes, which would occur after the deprotonation. The profile for the present skeletal rearrangement reaction was calculated by using **1d** as a model substrate (Fig. 1). All calculations were performed with the Gaussian 16 package (Revision A.03) at the level of ωB97XD/SDD for Au and 6-31G(d,p) for other elements in the solution phase according to the SMD solvation model (dichloroethane). The computations indicated that elimination of a proton by the imidate anion from the cyclized vinylgold intermediate **4d** to form the isoxazolium species **5d** was rate-determining; the free activation energy for this process (**4d** to **TS2d**, Fig. 2) was computed to be 24.4 kcal mol^{-1}. In contrast, an energy barrier for direct [1,2]-hydrogen shift for the vinylgold species **4d** was computed to be much higher than the proton elimination (36.0 kcal mol^{-1}). Subsequent transfer of a proton from Tf_2NH to the gold-bound carbon induced simultaneous ring opening with cleavage of the N–O bond. It is noteworthy that the process was computed to be highly exergonic (56.1 kcal mol^{-1}), which serves as a driving force of the present skeletal rearrangement reaction. While recent theoretical studies have indicated that protodeauration of vinylgold specie proceeds in a concerted manner,[11] our computational studies suggest that protodeauration can proceed stepwise when the

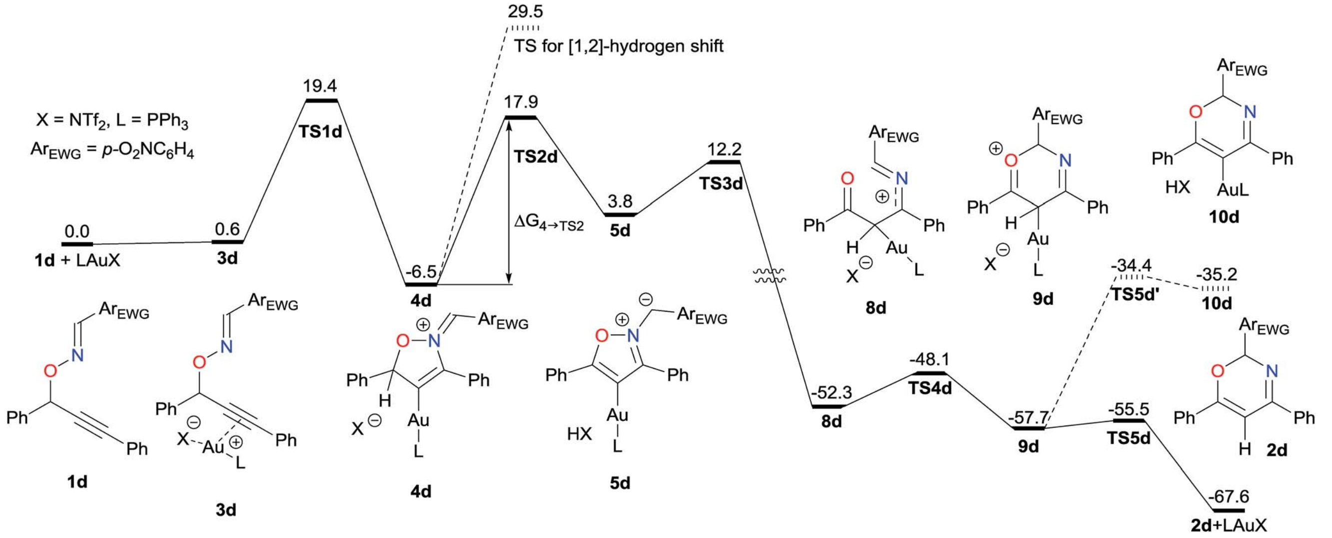


Fig. 1 Energy profile of the Au-catalyzed skeletal rearrangement reaction of **1d** at the level of ωB97XD/SDD for Au and 6-31G(d,p) for other elements.

approach of a proton to the gold-bound carbon atom induces cleavage of a weak covalent bond, such as N–O. Free activation energies for re-cyclization (**8d** to **9d**) and elimination of the gold catalyst were computed to be very low (4.2 and 2.2 kcal mol^{-1}, respectively).‖ Elimination of proton from **9d** to the vinylgold species **10d** was computed to be much slower than elimination of the gold catalyst (23.3 *versus* 2.2 kcal mol^{-1}). This result implies that decrease of the deuterium content in the Au-catalyzed reaction of deuterated substrate **1d**-*d* (Scheme 2a) is primarily due to proton exchange between the eliminated Tf_2ND and external water in the reaction media prior to protonation of **5d**.

Based on the theoretically obtained reaction profile, the activation energy $\Delta G_{\mathbf{4}\rightarrow\mathbf{TS2}}$ of the proton elimination process (**4** to **TS2**) was calculated in order to clarify the substituent effect at the oxime moiety as well as the role of base cocatalyst on this process (Table 5). The activation energy $\Delta G_{\mathbf{4}\rightarrow\mathbf{TS2}}$ for the reaction of **1a** having a phenyl group at the oxime moiety was computed to be much higher than that of **1d** (31.2 kcal mol^{-1} for **1a** *versus* 24.4 kcal mol^{-1} for **1d**), which are in good agreement with our experimental results that the reaction of **1a** required a longer reaction time (24 h *versus* 8 h) to obtain **2a** in a much lower chemical yield (16% *versus* 93%). Thus, the computation well supports our qualitative understanding of the role of electron-withdrawing substituents at the oxime carbon facilitating elimination of the proton by increasing its acidity. In addition, DFT calculations indicated that pyridine approached to a proton on the isoxazoline ring from the opposite side of the imidate anion in the reaction of **1t**, which has an alkyl group at the propargylic position, in the presence of pyridine (Fig. 3). This cooperation of the base cocatalyst significantly reduced the activation energy $\Delta G_{\mathbf{4}\rightarrow\mathbf{TS2}}$ (from 31.9 to 16.3 kcal mol^{-1}, entries 3 and 4). Further elucidation to understand the role of the base

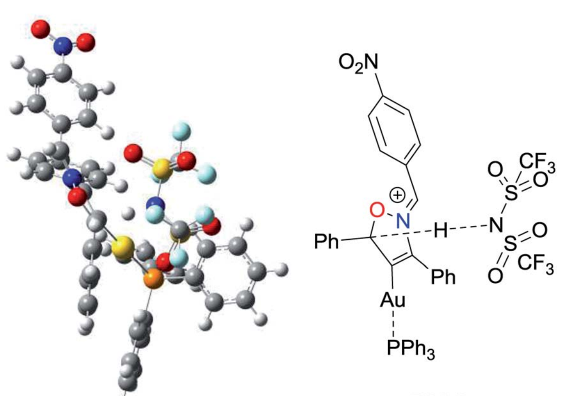
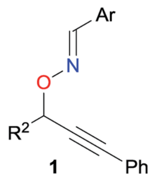


Fig. 2 Transition state **TS2d** of the proton eliminating process in the Au-catalyzed reaction of **1d** at the level of ωB97XD/SDD for Au and 6-31G(d,p) for other elements.

Table 5 Free activation energy $\Delta G_{\mathbf{4}\rightarrow\mathbf{TS2}}$ for the proton elimination process in Au-catalyzed reaction of **1**



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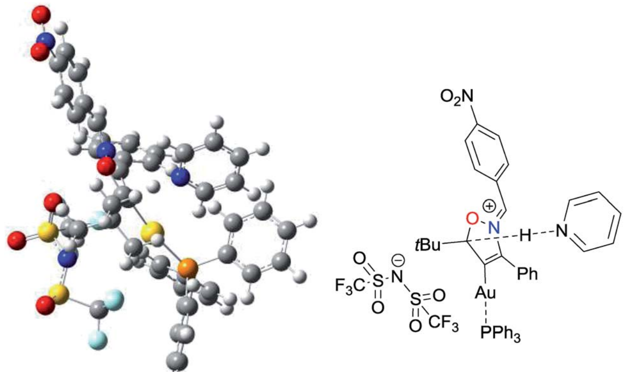
Entry	1	R^2	Ar	Activation energy^b (kcal mol^{-1})
1	**1d**	Ph	*p*-$O_2NC_6H_4$	24.4
2	**1a**	Ph	Ph	31.2
3	**1t**	*t*Bu	*p*-$O_2NC_6H_4$	31.9
4	**1t**	*t*Bu	*p*-$O_2NC_6H_4$	16.3^a

[a] With pyridine. [b] At the level of ωB97XD/SDD for Au and 6-31G(d,p) for other elements.



TS2t-py

Fig. 3 Transition state **TS2t-py** of the proton elimination process in the Au-catalyzed reaction of **1t** in the presence of pyridine at the level of ωB97XD/SDD for Au and 6-31G(d,p) for other elements.

cocatalyst in the present transformation is underway in our laboratory.

Conclusions

We have successfully developed an novel approach for the synthesis of 2*H*-1,3-oxazine derivatives *via* Au-catalyzed skeletal rearrangement. Although oxazine derivatives exist within biologically active compounds,[12] and serve as synthetic intermediates for nitrogenous compounds,[13] syntheses of such compounds have remained challenging due to the instability of oxazines under thermal and acidic conditions.[13a,13c,14] From a synthetic viewpoint, our methodology offers the potential toward the syntheses of various oxazines under mild reaction conditions.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Notes and references

‡ We have previously reported on the Cu-catalyzed rearrangements of *O*-propargylic phenylacetaldoximes *via* N–O bond cleavage to afford *N*-styryl epoxyimines. (a) I. Nakamura, T. Iwata, D. Zhang, M. Terada, *Org. Lett.*, 2012, **14**, 206–209. Although we have proposed the copper carbenoid species as the intermediate, it is more likely that the reaction proceeds *via* formal hydroamination, followed by [1,3]-oxygen rearrangement (Scheme S1†), according to our continued investigations and reports from other groups (b) D.-L. Mo, L. L. Anderson, *Angew. Chem. Int. Ed.*, 2013, **52**, 6722–6725; (c) I. Nakamura, T. Jo, Y. Ishida, H. Tashiro, M. Terada, *Org. Lett.*, 2017, **19**, 3059–3062. See also ref. 3e. Further mechanistic studies to elucidate the reaction mechanisms of the Cu-catalyzed reactions are currently underway in our laboratories.

§ Incorporation of deuterium was not observed when the product **2d** was treated with D_2O in the presence of the gold catalyst. See ESI.†

¶ The reaction of **1l** and **1n** by using gold-pyridine cocatalyst system did not afford the desired products; **1l** was decomposed under the reaction conditions, while **1n** was partially recovered (71%).

‖ It is alternatively possible that the intermediate **8d** undergoes elimination of the gold catalyst before re-cyclization (6π-electrocyclization), of which activation energy were 6.6 and 8.6 kcal mol^{-1}, respectively. See ESI.†

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