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## GOLD-CATALYZED SKELETAL REARRANGEMENT REACTIONS OF *O*-PROPARGYLIC AND *O*-HOMOPROPARGYLIC OXIMES

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**Abstract** – Au-catalyzed skeletal rearrangement reactions of *O*-propargylic oximes, which were derived from the condensation of *N*-propargyloxyamine with either formaldehyde or glyoxylate, afforded the corresponding 4-methylenated isoxazolines via C=N bond cleavage. The obtained isoxazolines underwent carbonyl–ene reactions, generating functionalized isoxazoles in good yields. Moreover, a sequence of Au-catalyzed reactions followed by a carbonyl–ene reaction of enantioenriched substrate produced isoxazoles having a chiral side chain, with excellent levels of chirality transfer. In contrast, the Au-catalyzed reactions of *O*-propargylic oximes bearing an electron-deficient aryl group on the oxime carbon proceeded via N–O bond cleavage, affording oxazines in good yields.

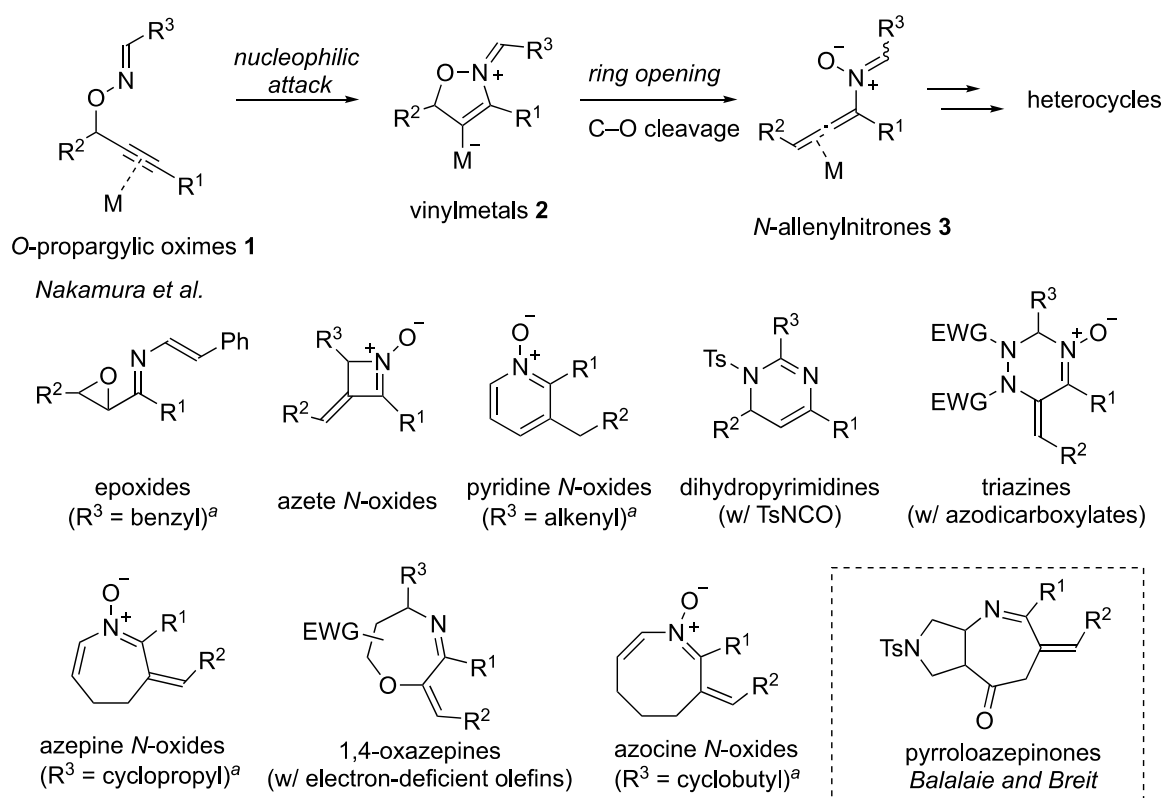
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### 1. INTRODUCTION

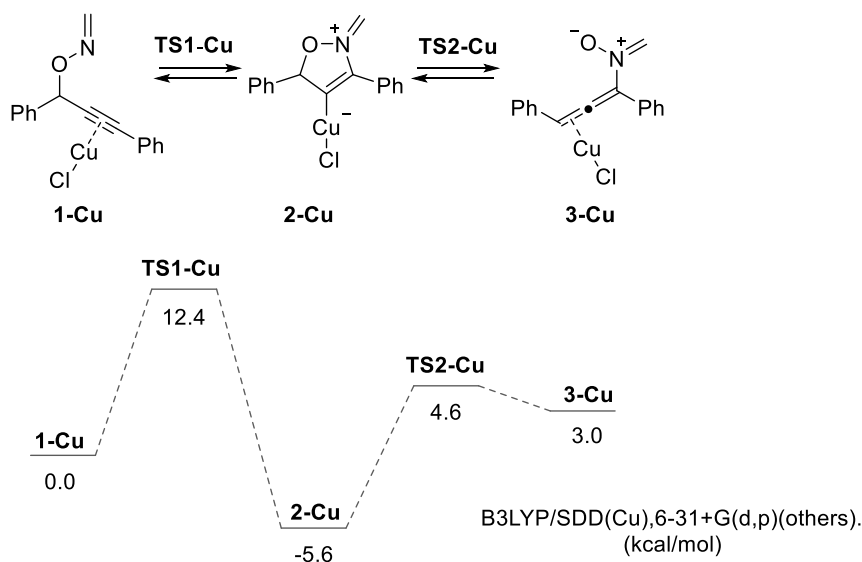
Skeletal rearrangement reactions, which involve the cleavage of skeletal  $\sigma$  bonds such as carbon–carbon, carbon–heteroatom, and heteroatom–heteroatom bonds of readily accessible starting materials, are

attractive methods to rapidly construct multi-substituted molecular skeletons in a single operation<sup>1,2</sup> In particular,  $\pi$ -Lewis acidic metal catalysts have been shown to efficiently promote the transformations by the electrophilic activation of carbon-carbon multiple bonds (e.g., alkynes and allenes) through  $\pi$ -coordination. For this purpose, the efficient synthesis of a wide variety of heterocyclic compounds has been achieved by designing substrates in which a functional group (e.g., amino, hydroxy, carbonyl, imine, olefin, acyloxy, sulfinyl, or *N*-oxidopyridyl) is appropriately positioned from the carbon-carbon multiple bond. We recently reported that *O*-propargylic oximes **1** served as an intriguing platform for skeletal rearrangement reactions by using Cu and Rh catalysts.<sup>3</sup> These reactions yielded nitrogenous heterocycles with three- to eight-membered rings such as epoxides,<sup>4</sup> azete *N*-oxides,<sup>5</sup> pyridine *N*-oxides,<sup>6</sup> dihydropyrimidines,<sup>7</sup> triazines,<sup>8</sup> azepine *N*-oxides,<sup>9</sup> 1,4-oxazepines,<sup>10</sup> and azocine *N*-oxides<sup>11</sup> by functionalization of the substrate at appropriate positions and using external reagents (Scheme 1). More recently, Balalaie and Breit reported an efficient synthesis of pyrrole-fused azepinones using *O*-propargylic oximes as a platform for cascade reactions.<sup>12</sup> These rearrangement reactions proceed via nucleophilic attack of the oxime nitrogen atom on the  $\pi$ -activated carbon-carbon triple bond, resulting in the formation of vinylmetal intermediates **2**. Except in the case of the reaction to synthesize epoxides, which proceeds via N-O bond cleavage,<sup>4</sup> vinylmetal intermediates **2** mainly undergo ring opening involving the cleavage of the C-O bond.



Scheme 1. Cu- and Rh-catalyzed skeletal rearrangement reactions of *O*-propargylic oximes **1**

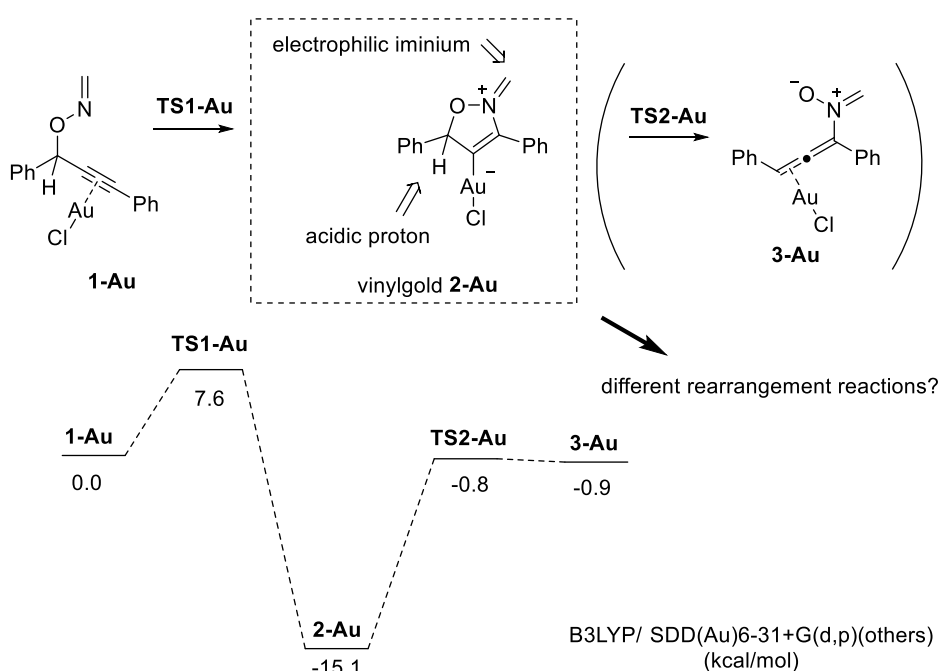
The resulting *N*-allenylnitronone intermediates **3** through the [2,3]-rearrangement of propargylic oximes **1** exhibit versatile reactivities (e.g., act as a nitrogen analogue of vinylallene, 1,3-dipole, and 2-azadiene), realizing the synthesis of a variety of unique heterocycles. Our preliminary DFT calculations for the [2,3]-rearrangement of propargylic oximes **1** to yield *N*-allenylnitronones **3** revealed a lower activation energy of the C–O bond cleavage process than that of the cyclization process (Scheme 2).<sup>13</sup> In addition, the difference in thermodynamic stability between vinylcopper **2-Cu** and *N*-allenylnitronone-copper complex **3-Cu** is 8.6 kcal/mol<sup>-1</sup>, supporting that the generated *N*-allenylnitronone intermediates can be captured both intramolecularly and intermolecularly. This characteristic feature of the energy diagram was reproduced by independent studies by Silva López.<sup>14</sup>



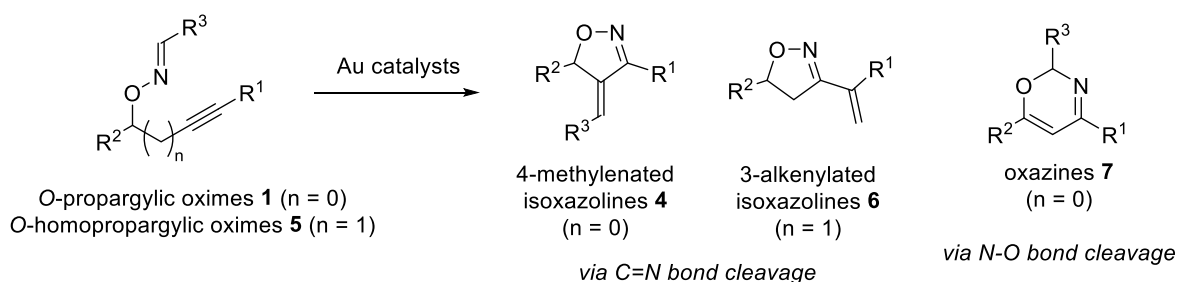
Scheme 2. Reaction profile of Cu-catalyzed [2,3]-rearrangement of *O*-propargylic formaldoxime

In this context, we envisioned that gold catalysts would change the reaction pathway for the skeletal rearrangement of *O*-propargylic oximes, given the influence of relativistic effects,<sup>15</sup> that is, the relativistic contraction of the 6s shell of Au would qualitatively explain the shorter and stronger covalent bond. According to Frenking's calculations,<sup>16</sup> the C–Au bond in phenylgold is stronger than the C–Cu bond in phenylcopper by ca. 6 kcal/mol. Thus, the vinylgold intermediate **2-Au** is expected to be more stable than the vinylcopper intermediate, and the ring-opening process involving C–Au bond cleavage would be decelerated. Indeed, our preliminary calculations indicated that the activation energy of the ring-opening process of vinylgold **2-Au** to generate *N*-allenylnitronone-gold complex **3-Au** is higher than that of the cyclization process from **1-Au** to **TS1-Au** (Scheme 3). Moreover, their energy gap between **2-Au** and **3-Au** is much larger than that between **2-Cu** and **3-Cu** observed in the copper catalysis, suggesting that the capture of the *N*-allenylnitronone intermediate **3-Au** would be more unfavorable in gold catalysis. In other

words, we hypothesized that several types of rearrangement reactions would take place through the long-lived vinylgold intermediate **2-Au** that possesses reactive sites, such as the electrophilic iminium moiety and the acidic proton. In accordance with this hypothesis, we demonstrated that the Au-catalyzed reaction of *O*-propargylic oximes **1** ( $n = 0$ ), which were derived from the condensation of *N*-propargyloxyamine with either formaldehyde ( $R^3 = H$ ) or glyoxylate ( $R^3 = CO_2R$ ), afforded corresponding 4-methylenated 2-isoxazolines **4** (Scheme 4).<sup>13,17</sup> The Au-catalyzed rearrangement reaction, which proceeds via cleavage of the oxime C=N bond, was extended to *O*-homopropargylic oximes **5** ( $n = 1$ ) to afford 3-alkenylated isoxazolines **6**.<sup>18</sup> Moreover, we showed that changing the substituent  $R^3$  to an electron-deficient aryl group dramatically altered the reaction pathway of the Au-catalyzed reaction of *O*-propargylic oximes **1** ( $n = 0$ ), resulting in the selective synthesis of oxazines **7** via N–O bond cleavage.<sup>19</sup> In this review article, we provide an overview of the Au-catalyzed skeletal rearrangement reactions of *O*-propargylic oximes and *O*-homopropargylic oximes for the synthesis of heterocycles containing nitrogen and oxygen atoms.



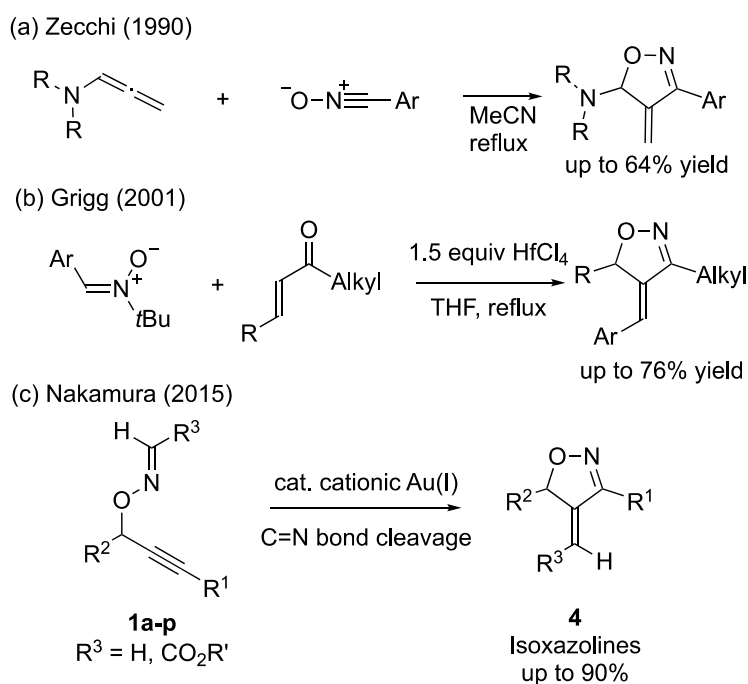
Scheme 3. Working hypothesis drawn from the reaction profile of Au-catalyzed [2,3]-rearrangement



Scheme 4. Synthesis of heterocycles by Au-catalyzed skeletal rearrangement of *O*-propargylic and *O*-homopropargylic oximes

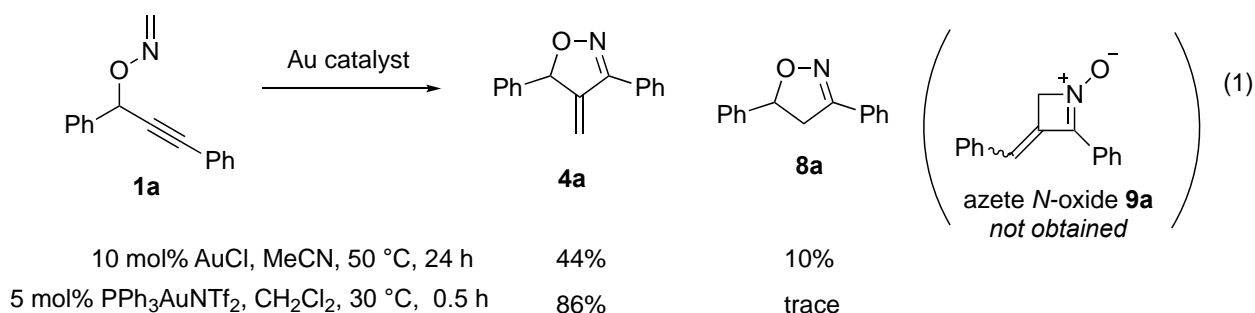
## 2. SYNTHESIS OF ISOXAZOLINES BY GOLD-CATALYZED REACTIONS OF *O*-PROPARGYLIC AND *O*-HOMOPROPARGYLIC OXIMES VIA C=N BOND CLEAVAGE

Isoxazoles and isoxazolines are frequently used in pharmaceutical chemistry and synthetic organic chemistry.<sup>20</sup> In particular, isoxazolines with an *exo*-olefin at the 4-position are expected to serve as efficient synthetic intermediates for the functionalized isoxazoles driven by aromatization. However, due to the inherent instability of the target heterocycles under harsh reaction conditions, only a limited number of synthetic methods for these molecules have been reported to date (Scheme 5). Zecchi reported a synthesis of 5-amino-4-methyleneisoxazolines by [3+2] cycloaddition between allenylamines and nitrile oxides (Scheme 5a).<sup>21</sup> Grigg reported HfCl<sub>4</sub>-mediated reactions between *N*-tert-butyl nitrones and  $\alpha,\beta$ -unsaturated enones for the synthesis of 4-benzylideneisoxazolines (Scheme 5b).<sup>22</sup> Accordingly, our method based on the Au-catalyzed skeletal rearrangement of *O*-propargylic oximes **1a-p** is regarded as an entirely new approach to 4-methylenated isoxazolines **4** under much milder reaction conditions than those used previously (Scheme 5c).

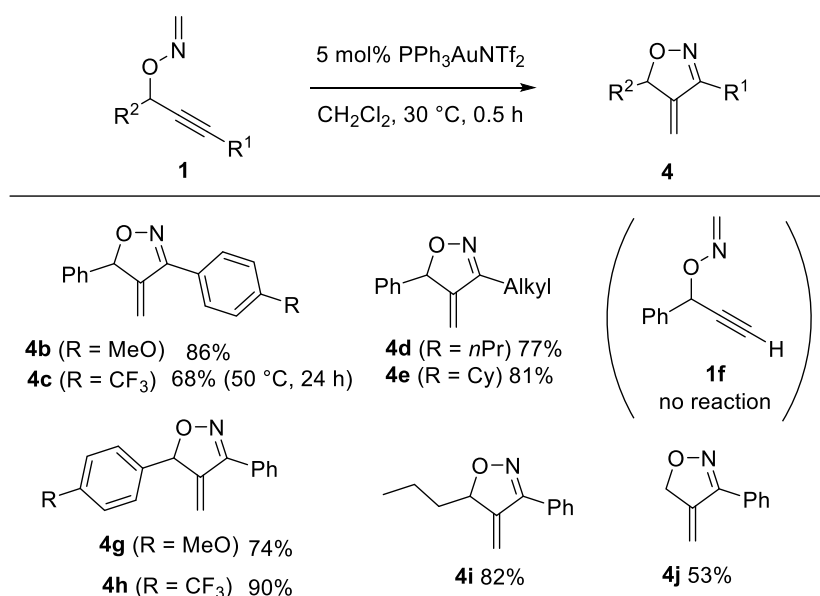


Scheme 5. Representative methods for 4-methylenated 2-isoxazoline synthesis

At the beginning of this investigation, we found that the reaction of *O*-propargylic formaldoxime **1a** in the presence of catalytic amounts of AuCl at 50 °C afforded 4-methylenated isoxazoline **4a** in 44% yield (eq 1), along with non-methylenated isoxazoline **8a** as the byproduct. It should be noted that azete *N*-oxide **9a** (which was derived from 4 $\pi$ -electrocyclization of *N*-allenyl nitron intermediates **3**; Scheme 1) was not obtained. The chemical yield was significantly improved when PPh<sub>3</sub>AuNTf<sub>2</sub> was used as a catalyst at 30 °C.<sup>23</sup>

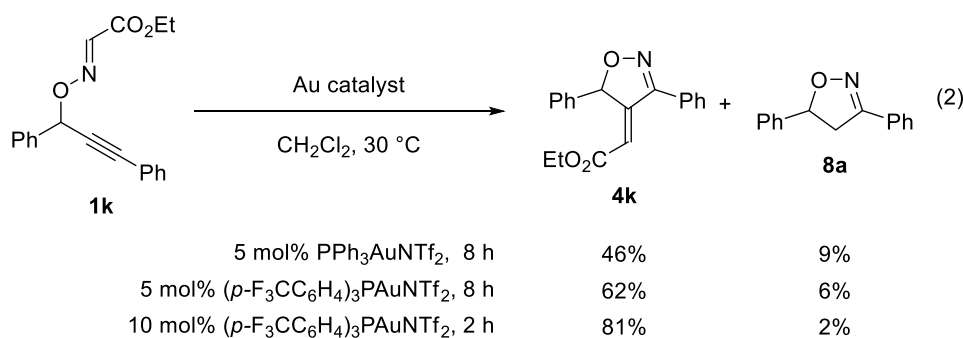


The reaction was applicable to substrates bearing various aryl and alkyl substituents at the alkyne terminus ( $R^1$ ) (Scheme 6). However, the reaction of **1c**, which has an electron-deficient *p*-trifluoromethylphenyl group at  $R^1$ , was exceptionally slow, and **1f** (terminal alkyne) did not react under the present reaction conditions. Various substituents were tolerated at the propargyl position ( $R^2$ ), affording desired products (**4g–i**) in good yields. Moreover, substrate **1j**, which did not have any substituent at  $R^2$ , was effectively converted into achiral isoxazoline **4j** in acceptable yield.

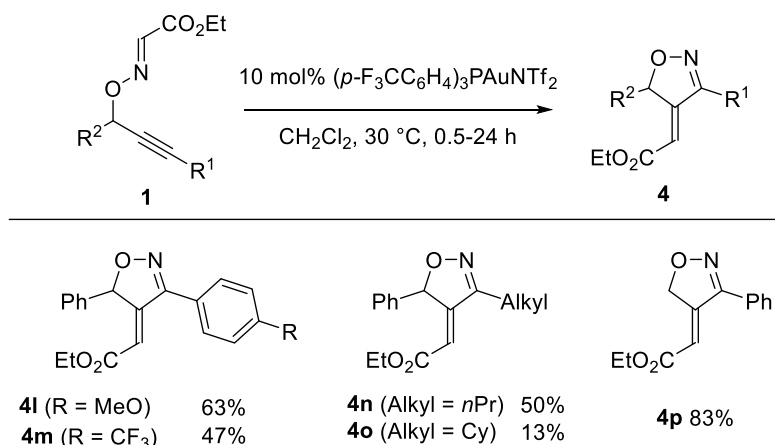


Scheme 6. Scope of Au-catalyzed reactions of *O*-propargylic formaldoximes **1b–j**

When  $\alpha$ -(*N*-propargyloxyimino)acetate **1k**, which bears an ethoxycarbonyl group as a substituent on the oxime carbon, was treated under the reaction conditions for formaldoximes, desired product **4k** was obtained in moderate yield (eq 2).<sup>17</sup> The chemical yield was improved by using triarylphosphine bearing an electron-deficient *p*-trifluoromethylphenyl group on the phosphorus atom as a ligand and by doubling the loading amount of the Au catalyst, with suppressing formation of byproduct **8a** and improving mass balance.

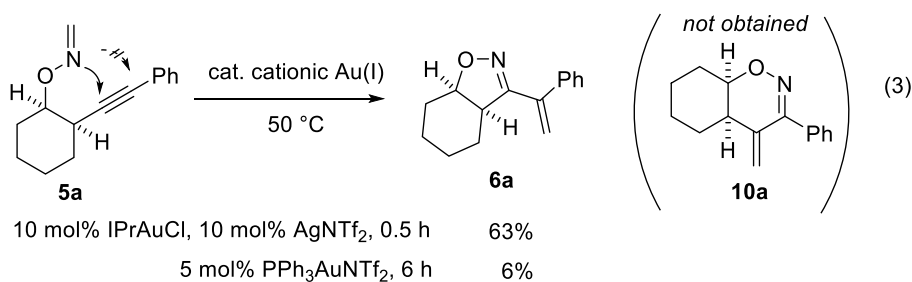


The electron-deficient aryl group at the alkyne terminus R<sup>1</sup> (**1m**) did not significantly affect the reaction efficiency (Scheme 7), unlike the reaction of formaldoxime **1c** (Scheme 6). In contrast, the influence of the bulky cyclohexyl group at R<sup>1</sup> was significant (**1o** versus **1e**), which is likely due to steric repulsion with the ethoxycarbonyl group in the cyclization process (Scheme 1).

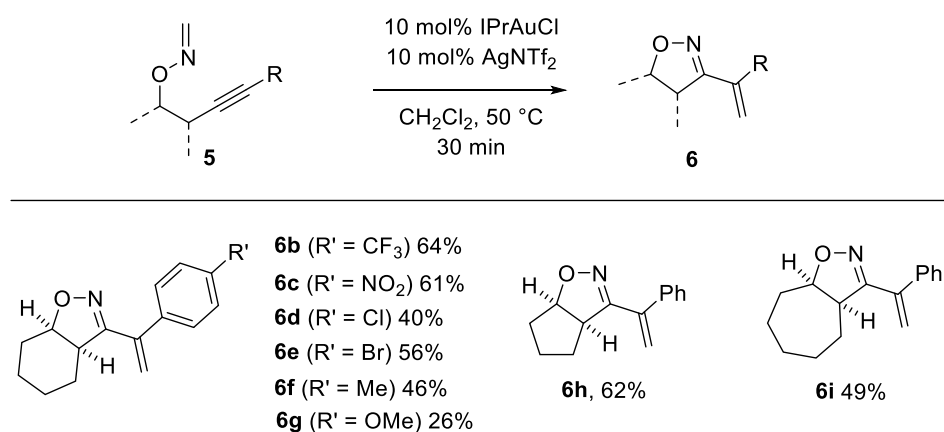


Scheme 7. Scope of Au-catalyzed reactions of  $\alpha$ -(*N*-propargyloxyimino)acetates **1l–p**

The Au-catalyzed skeletal rearrangement reactions were extended to *O*-homopropargylic oximes **5** (eq 3).<sup>18</sup> The reaction of **5a** using IPrAuCl [IPr: 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene] and AgNTf<sub>2</sub> as catalysts afforded cyclohexane-fused isoxazole **6a** via 5-*exo*-cyclization in good yield; dihydrooxazine **10a** derived from 6-*endo*-cyclization was not obtained. The reaction of **5a** using PPh<sub>3</sub>AuNTf<sub>2</sub>, the optimal catalyst for *O*-propargylic formaldoximes **1a–j**, resulted in poor chemical yield and low mass balance.



At the alkyne terminus, electron-withdrawing aryl substituents such as *p*-trifluoromethylphenyl (**5b**) and *p*-nitrophenyl (**5c**) groups were more effective in improving the chemical yield than electron-rich substituents such as *p*-tolyl (**5f**) and *p*-anisyl (**5g**) groups (Scheme 8). It is also noteworthy that the reactive bromo group was compatible in the Au-catalyzed reaction. Not only the cyclohexane ring but also cyclopentane (**5h**) and cycloheptane (**5i**) rings were employed as a tether between the oxime and alkyne moieties.

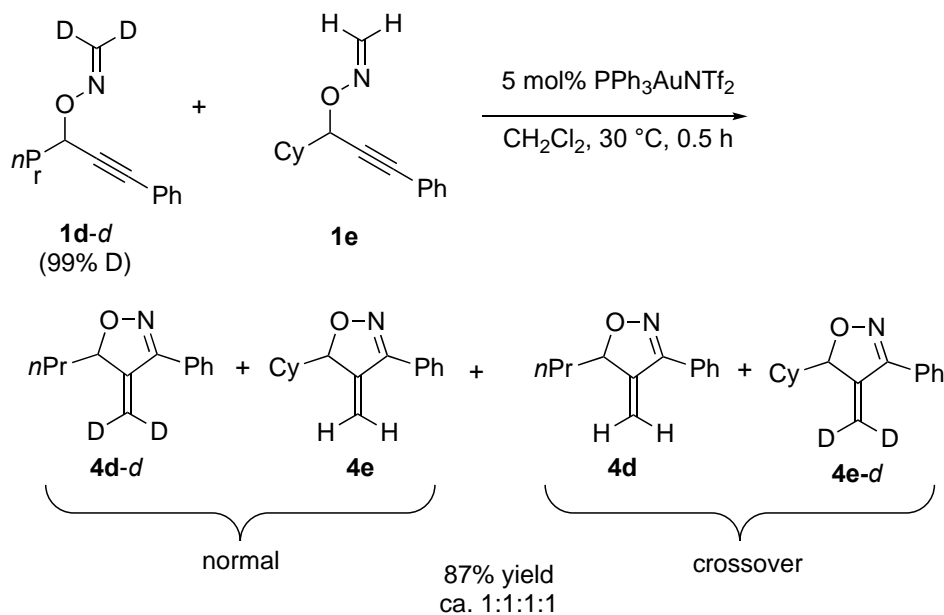


Scheme 8. Scope of Au-catalyzed reactions of *O*-homopropargylic formaldoximes **5**

### 3. MECHANISTIC STUDIES ON GOLD-CATALYZED REARRANGEMENT REACTIONS VIA C=N BOND CLEAVAGE

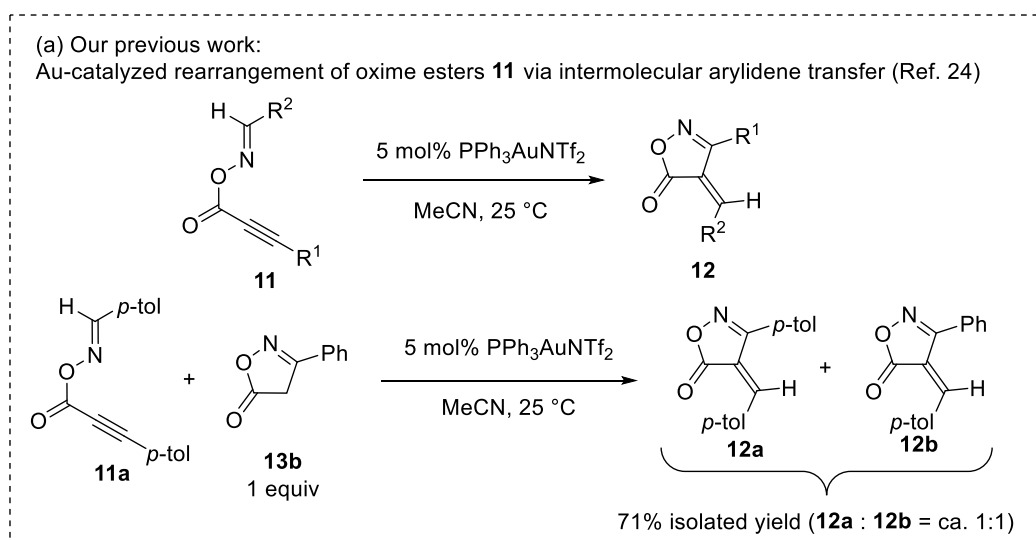
When a mixture of two equally reactive *O*-propargylic formaldoximes **1d-d** and **1e** was treated with catalytic amounts of PPh<sub>3</sub>AuNTf<sub>2</sub>, the reaction afforded not only **4d-d** and **4e**, which were derived from the starting materials (**1d-d** and **1e**, respectively), but almost equal amounts of **4d** and **4e-d** were also obtained as crossover products due to the transfer of the methylene moiety (Scheme 9). It should be noted that the transfer of the methylene group was not observed in the recovered starting materials (**1d-d** and **1e**), or when a mixture of products **4d-d** and **4e** was treated under the same reaction conditions. Since the transfer of the methylene group was also observed in the reaction of  $\alpha$ -(*N*-propargyloxyimino)acetates and *O*-homopropargylic formaldoximes, we concluded that the Au-catalyzed rearrangement reactions via C=N bond cleavage proceed through intermolecular methylene transfer.



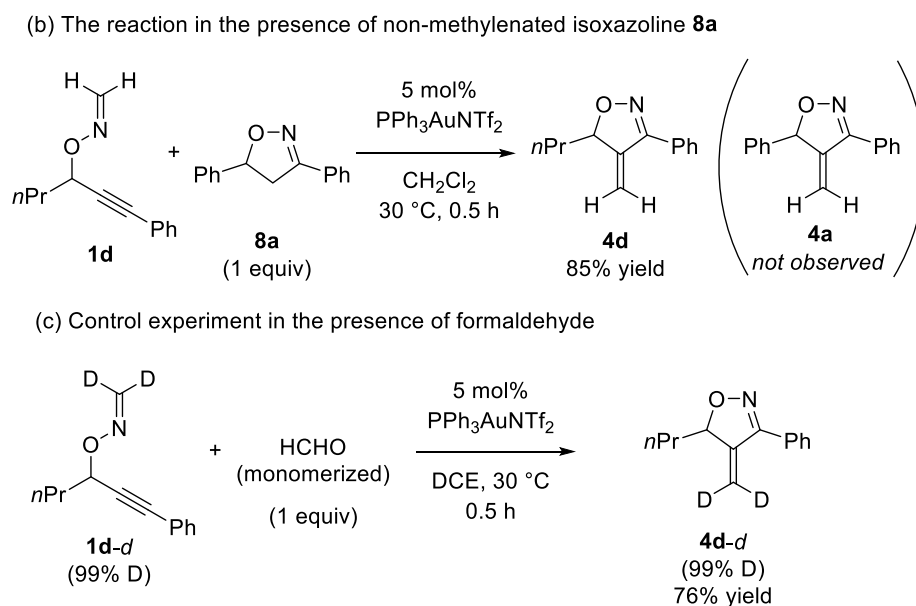


Scheme 9. Crossover experiments

We have previously reported that the Au-catalyzed reactions of oxime esters **11** proceed via intermolecular arylidene transfer mediated by non-methylenated isoxazolones **13**, as confirmed by the control experiment in the presence of **13b** (Scheme 10a).<sup>24</sup> In sharp contrast, however, the reaction of propargylic oxime **1d** in the presence of non-methylenated isoxazoline **8a** under the optimal reaction conditions did not afford expected product **4a** (Scheme 10b). In addition, the reaction of deuterated substrate **1d-d** in the presence of non-deuterated formaldehyde resulted in no decrease in deuterium content at the *exo*-olefin moiety; this eliminated the possibility of external formaldehyde incorporation (Scheme 10c). These results suggest that the methylene group migrates intermolecularly without the aid of non-methylenated isoxazoline **8** and formaldehyde.



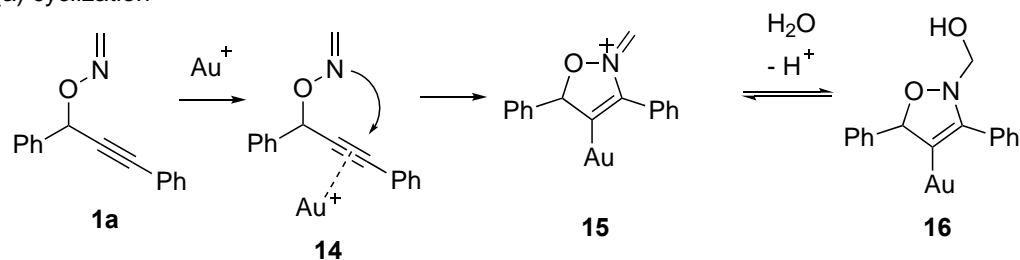
Scheme 10. Mechanistic studies



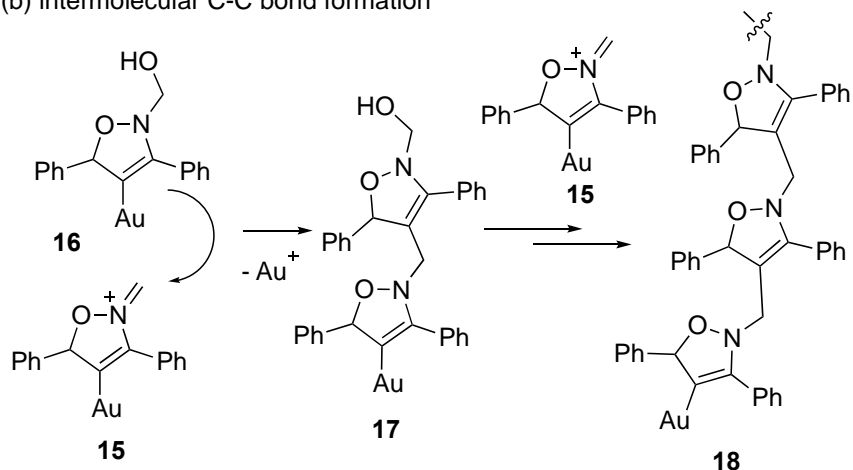
Scheme 10. Mechanistic studies (continued)

On the basis of these experimental results, we propose a mechanism consisting of cyclization, intermolecular C–C bond formation, and product disconnection, as illustrated in Scheme 11. First, the cationic gold catalyst would coordinate to the alkyne moiety of **1a** to form  $\pi$ -complexes **14**. Subsequently, the intramolecular nucleophilic attack of the oxime nitrogen atom on the electrophilically activated carbon–carbon triple bond would lead to the formation of cyclized vinylgold intermediates **15**. Given the high electrophilicity of the iminium moiety, long-lived vinylgold intermediates **15** would partially exist in the enamine form (**16**) as a result of reactions with nucleophilic species such as trace water, **1a**, and **4a** (water molecule is used in the proposed scheme for descriptive purposes). Then, nucleophilic enamine species **16** would intermolecularly attack the iminium moiety of another vinylgold species **15** to form a C–C bond.<sup>25</sup> The regenerated gold catalyst would repeatedly promote this intermolecular C–C bond formation process. Protodeauration and protonation of the enamine moiety would take place at the vinylgold terminus of oligomeric species **18**, which are converted into isoxazoliniums **19**. The donation of electrons from the nitrogen atom of the adjacent isoxazoline ring would cleave the C–N bond, liberating non-methylenated isoxazolines **8a** with the *exo*-methylene group formed at the terminus (**20**). The electron donation process repeatedly takes place, releasing product **4a** from **20**.

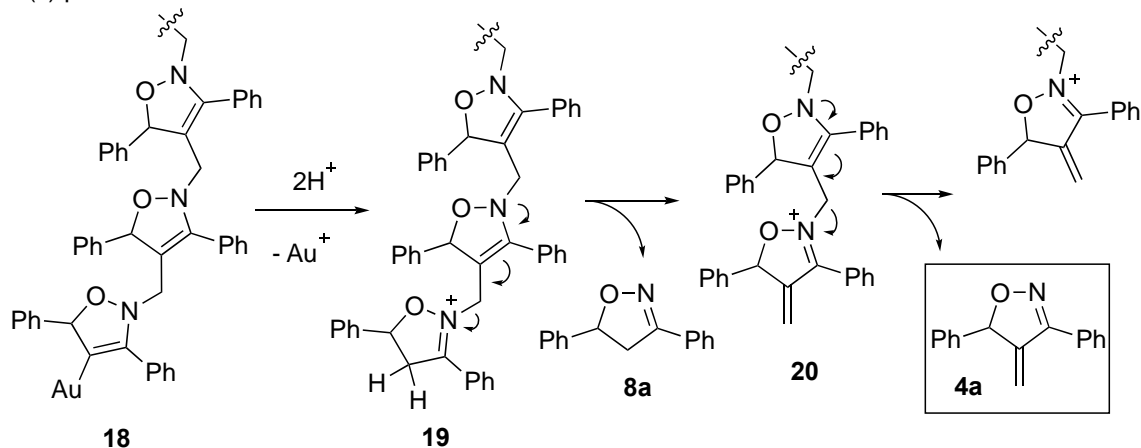
(a) cyclization



(b) intermolecular C-C bond formation



(c) product disconnection

Scheme 11. Proposed mechanism for Au-catalyzed reactions of *O*-propargylic formaldoxime **1a**

When the crude product of the reaction of **1a** using  $\text{PPh}_3\text{AuNTf}_2$  as a catalyst was analyzed by ESI-HRMS, molecular ion peak **Au2** was detected at 929.2564, which corresponded to the sum of two **1a** molecules and one  $\text{PPh}_3\text{Au}$  molecule (Figure 1). Because this ion peak was not observed in the HRMS spectrum of the crude mixture, which was obtained from the treatment of product **4a** under the influence of the gold catalyst, dimeric species **Au2** was likely formed during the Au-catalyzed rearrangement reactions. These results support the scheme of intermolecular C–C bond formation. Although both isolation and structural identification of detected species **Au2** were unsuccessful, the chemical structure of **Au2** are speculated as an imine **21** (Scheme 12).

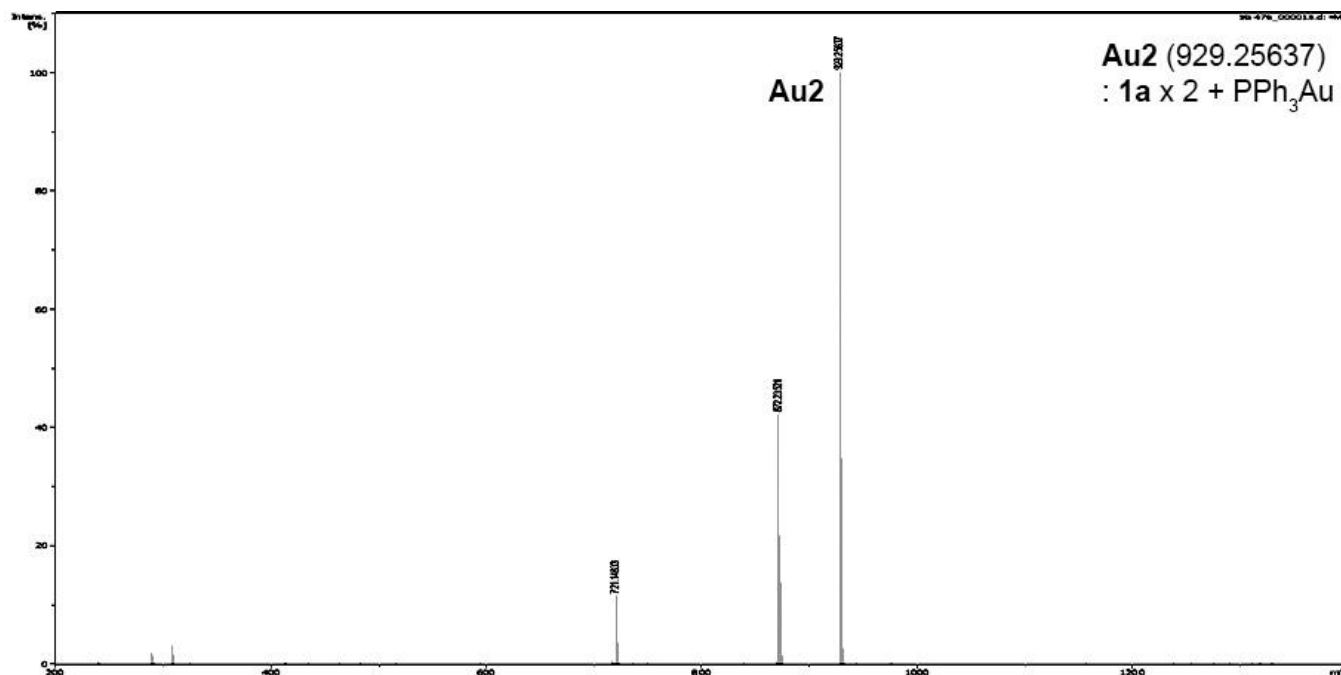
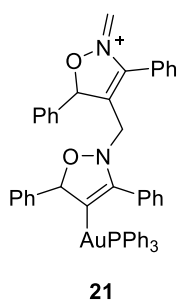


Figure 1. HRMS spectrum of crude product from the Au-catalyzed reaction of **1a**



Scheme 12. A possible structure of the detected species **Au2** in Figure 1

Similar oligomeric species were observed for the Au-catalyzed reaction of *O*-homopropargylic oxime **5a** (Figure 2). The mixture of crude products obtained from the reaction of **5a** using IPrAuCl and AgNTf<sub>2</sub> as catalysts contained trimeric species **H3'** and **Au3'**, of which the ion peaks corresponded to the sums of three **5a** molecules and either a hydrogen atom (**H3'**) or IPrAu (**Au3'**, Figure 2a). In addition, when **5a** was treated with PPh<sub>3</sub>AuCl and AgNTf<sub>2</sub>, molecular peaks **H3'–H5'** (corresponding to three to five **5a** molecules with one hydrogen atom) were observed along with peaks **C3'–C6'** (corresponding to three to six **5a** molecules with one carbon atom and one hydrogen atom). Attempts to obtain product **6a** by treating these oligomeric species (**H3'–H5'**, **C3'–C6'**, and **Au3'**) with external reagents such as gold catalysts, acids, and bases were unsuccessful, implying that these species were not reactive intermediates of the present skeletal rearrangement reactions. As none of these larger oligomers could be observed in the reaction of *O*-propargylic oximes **1**, we speculate that the formation of inactive species **H3'–H5'** and **C3'–C6'** is attributed to the *exo*-cyclization of **22** to **23** (Scheme 13a), that is, oligomerization via intermolecular

C–C bond formation of *exo*-cyclized vinylgold species **23** would lead to the formation of intermediates **24** bearing an alkenyl substituent at the 3-position of the isoxazoline ring. The alkenyl moiety of **24** is flexible to form the *s-cis* conformer, in contrast to **20** that are generated from the *endo*-cyclization of *O*-propargylic oximes **1** and are fixed in the *s-trans* conformation (Scheme 11). Ylides **25** generated by the rapid deprotonation of **24** would readily undergo irreversible  $6\pi$ -electrocyclization reactions from the *s-cis* conformation. The resulting cyclized intermediates **26** are inactive and would not undergo product disconnection. On the basis of the HRMS spectrum shown in Figure 2b, we speculate that the chemical structures of trimers **H3'** and **C3'** are iminium **27** and **28**, respectively (Scheme 13b). This deactivation process reasonably explains the lower chemical yields of the reaction of *O*-homopropargylic oximes **5** compared with those of *O*-propargylic oximes **1**.

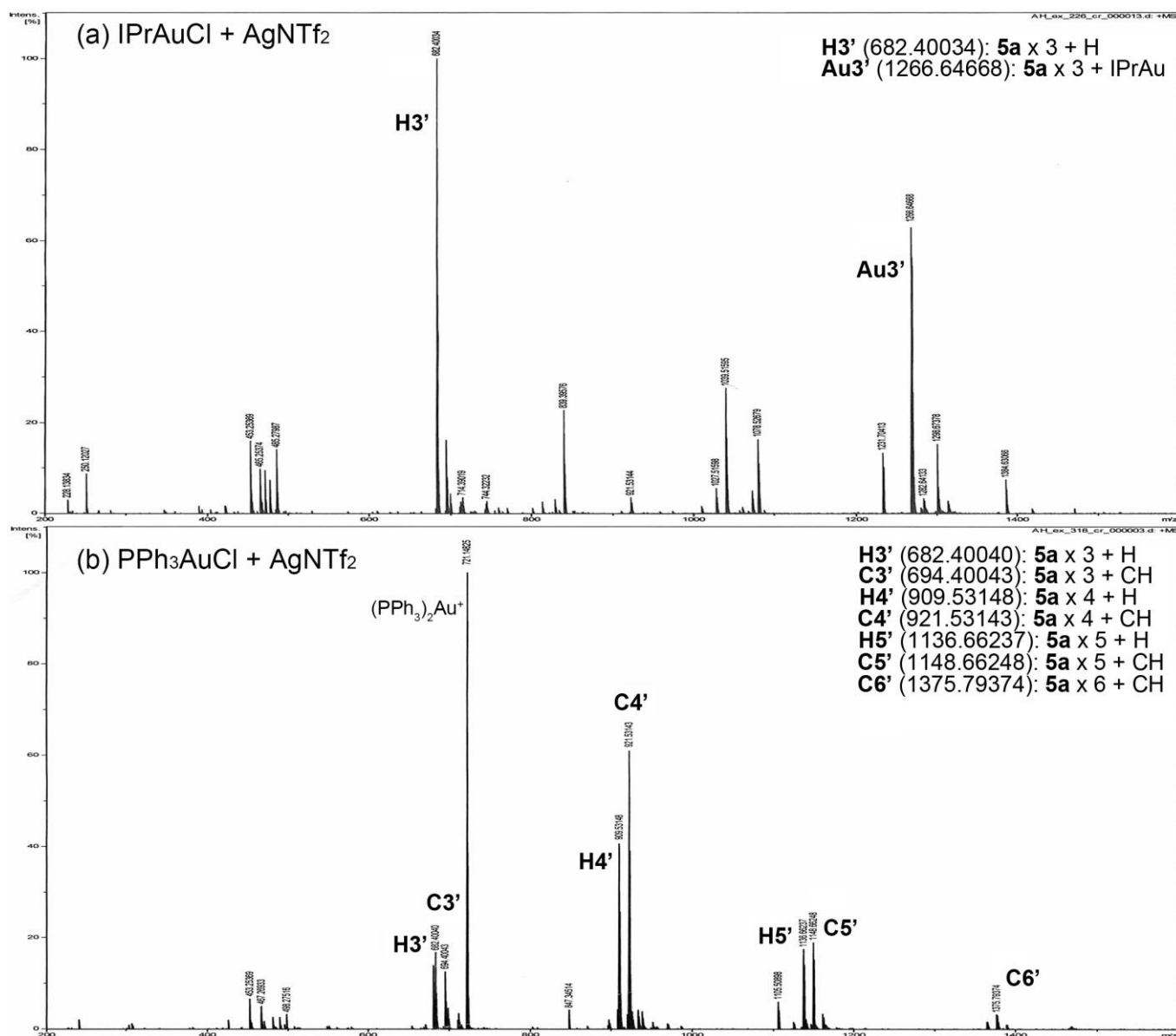
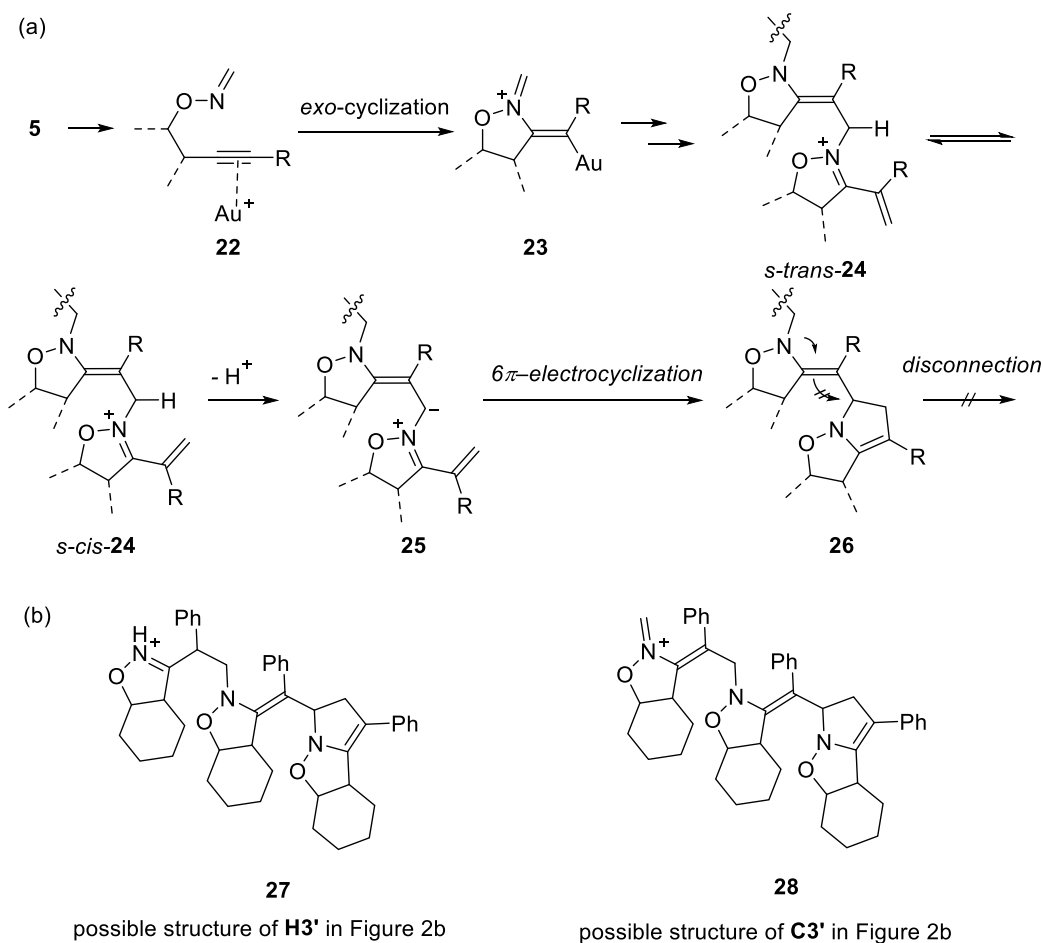


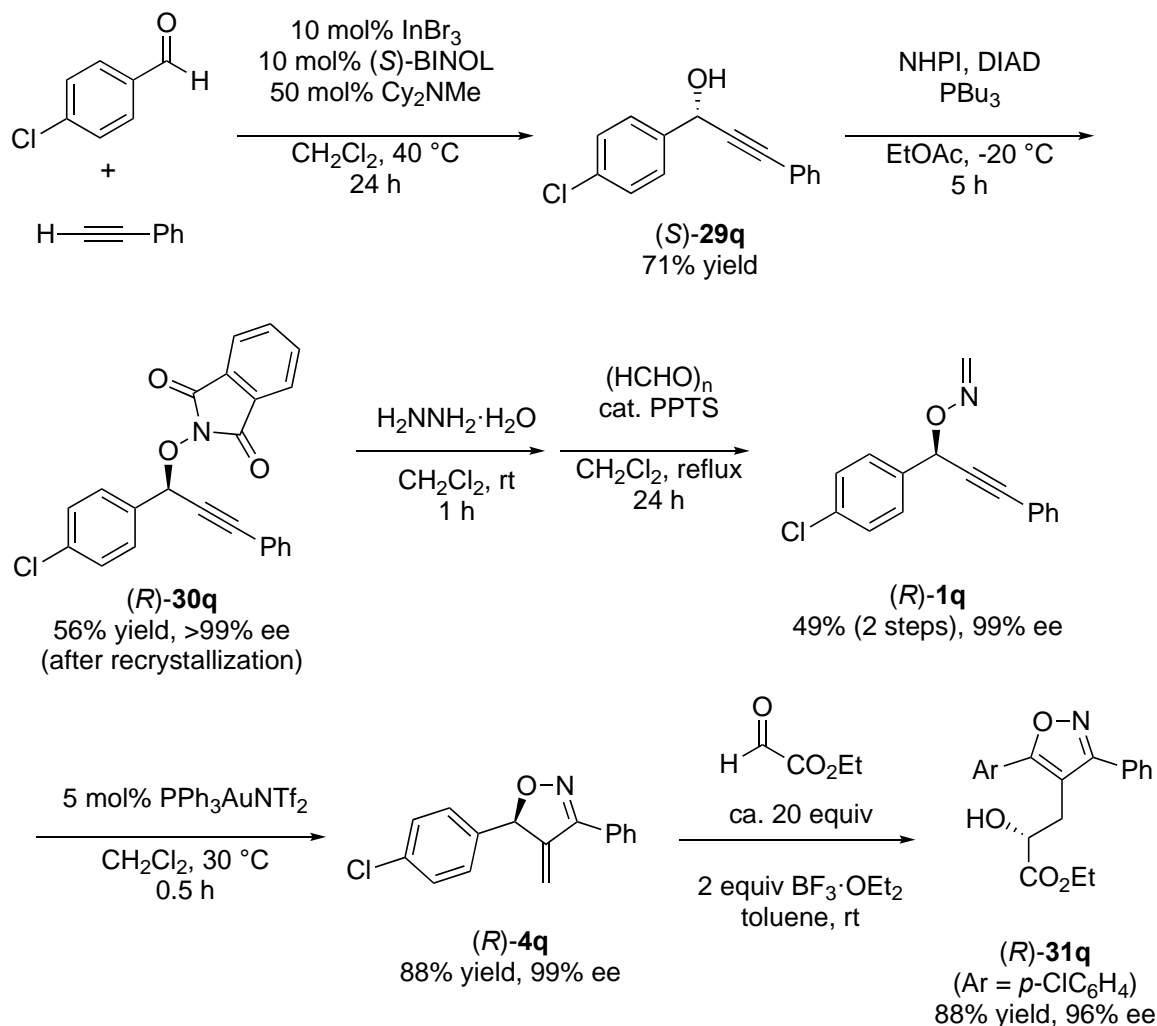
Figure 2. HRMS spectra of byproducts obtained from Au-catalyzed reaction of **5a**

Scheme 13. Mechanistic considerations for the reaction of **5**

#### 4. CHIRALITY TRANSFER IN GOLD-CATALYZED REACTIONS OF *O*-PROPARGYLIC OXIMES

We developed a synthetic protocol for isoxazoles having a chiral side chain on the basis of the Au-catalyzed rearrangement reactions of enantioenriched *O*-propargylic oximes, which were readily accessible from the corresponding aldehydes (Scheme 14). For example, Shibasaki's asymmetric alkynylation reaction of *p*-chlorobenzaldehyde using catalytic amounts of  $\text{InBr}_3$  and (*S*)-BINOL afforded chiral propargylic alcohol (*S*)-**29q** with an excellent level of enantioselectivity.<sup>26</sup> The subsequent Mitsunobu reaction with *N*-hydroxyphthalimide (NHPI) and recrystallization afforded enantiomerically pure *N*-propargyloxypthalimide (*R*)-**30q**. Then, the one-pot deprotection of the phthaloyl group of (*R*)-**30q** followed by condensation with formaldehyde gave (*R*)-**1q**, the enantioenriched substrate for the subsequent Au-catalyzed rearrangement reaction. This reaction proceeded with complete preservation of chirality at the propargylic carbon, and the resulting 4-methylenated isoxazoline (*R*)-**4q** underwent a carbonyl-ene reaction with ethyl glyoxylate by the aid of  $\text{BF}_3 \cdot \text{OEt}_2$  with an excellent level of chirality transfer, affording isoxazole (*R*)-**31q** having a chiral side chain at the 4-position of the isoxazole ring. The *R*-configuration

indicates that the aromatization-driven carbonyl–ene reaction proceeds in an *endo* manner. As chiral isoxazoles have recently attracted attention as pharmacophores, our protocol is potentially useful for the synthesis of a new class of enantioenriched isoxazoles.

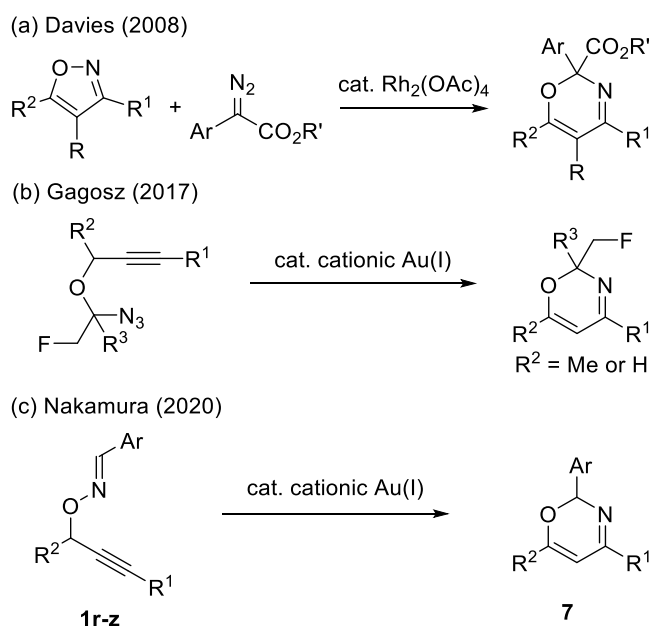


Scheme 14. Synthesis of chiral isoxazoles via Au-catalyzed skeletal rearrangement

## 5. SYNTHESIS OF OXAZINES BY GOLD-CATALYZED REARRANGEMENT REACTIONS OF *O*-PROPARGYLIC OXIMES VIA N–O BOND CLEAVAGE

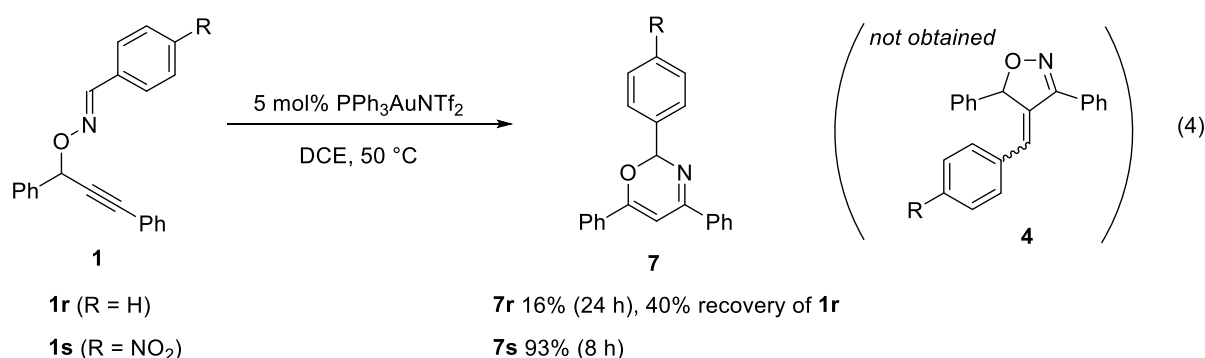
2*H*-1,3-Oxazines have not drawn as much attention as heterocyclic compounds, presumably because of their low accessibility. Recently, two efficient methods for the construction of the oxazine ring using transition metal catalysts have been reported, namely, rhodium-catalyzed carbene insertion into the isoxazole N–O bond reported by Davies (Scheme 15a),<sup>27</sup> and Au-catalyzed dinitrogenative cyclization of  $\alpha$ -propargyloxy- $\beta$ -haloalkylazides reported by Gagosz (Scheme 15b).<sup>28</sup> However, there is still room for the development of synthetic methods to generate different classes of oxazines from readily available substrates with high functional group compatibility. In this context, we have reported that the Au-catalyzed

skeletal rearrangement reaction of *O*-propargylic oximes **1r-z** bearing an aryl substituent on the oxime carbon afforded oxazines **7** via N–O bond cleavage (Scheme 15c).



Scheme 15. Representative methods of *2H*-1,3-oxazine synthesis

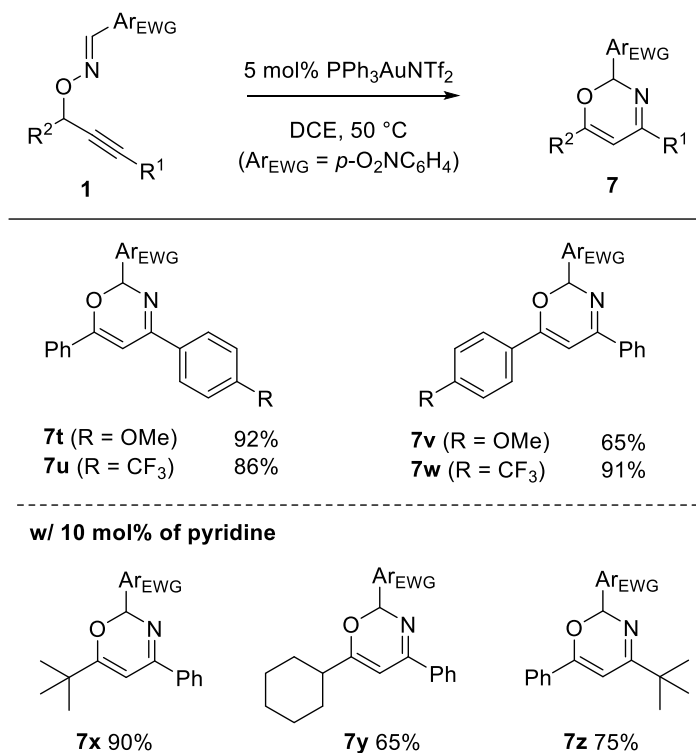
When *O*-propargylic oxime **1r** bearing a phenyl substituent on the oxime carbon was treated with  $\text{PPh}_3\text{AuNTf}_2$  in 1,2-dichloroethane (DCE), the reaction afforded oxazine **7r** albeit in low chemical yield (eq 4); isoxazoline **4** derived from C=N bond cleavage was not obtained. The chemical yield was dramatically improved by changing the substituent to a *p*-nitrophenyl group (**1s**).



The electronic character of the substituent R<sup>1</sup> at the alkyne terminus did not significantly affect the reactivity of **1** (Scheme 16, **1t** versus **1u**). In contrast, the reaction of **1v**, which has an electron-donating *p*-anisyl group at the propargylic position (R<sup>2</sup>), was less efficient than that of **1w**, which has an electron-withdrawing *p*-trifluoromethylphenyl group at R<sup>2</sup>. Moreover, substrates **1x** and **1y** having an alkyl group at R<sup>2</sup> were not converted into the desired products under the conditions optimized for aryl-substituted substrates **1r-w**. To

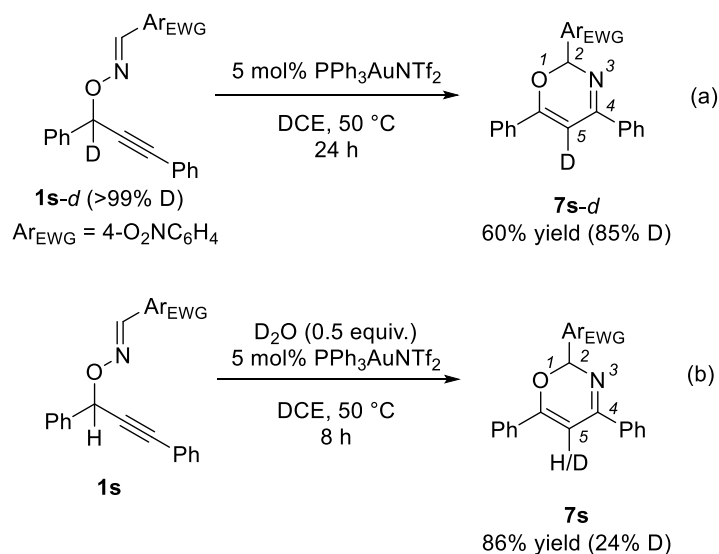


our delight, the use of pyridine as a cocatalyst effectively promoted these reactions, affording 6-alkyl-oxazines **7x** and **7y** in good yields.<sup>30</sup> Moreover, the Au-pyridine hybrid catalyst was effective for the reaction of **1z**, which has a bulky *tert*-butyl group at the alkyne terminus, whereas the reaction of **1z** without the pyridine cocatalyst did not proceed at all.



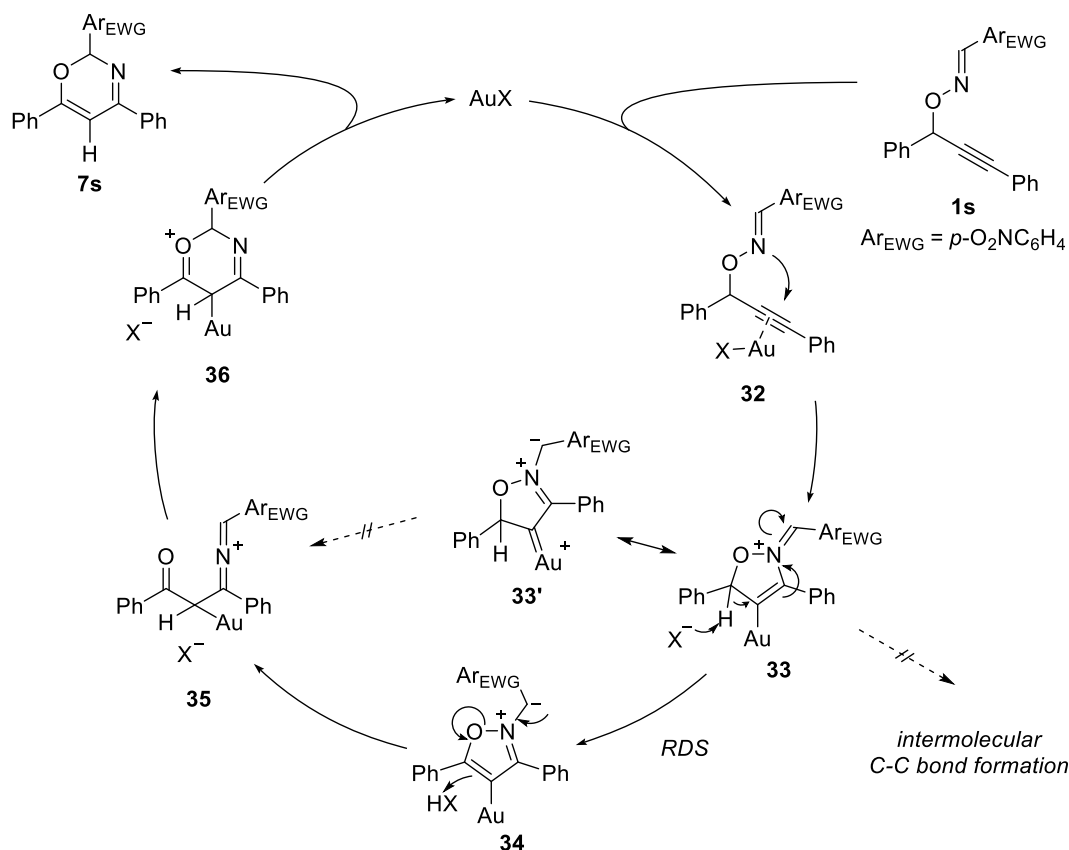
Scheme 16. Scope of Au-catalyzed reactions of **1t–z** via N-O bond cleavage

The reaction of deuterium-labeled **1s-d** at the propargylic position (>99% D) yielded deuterated product **7s-d**, in which the oxazine ring was deuterated at the 5-position (Scheme 17a). It is noteworthy that the deuterium content was decreased to 85%, and the reaction time was prolonged. In addition, the reaction of non-labeled substrate **1s** in the presence of heavy water resulted in partial deuteration at the 5-position (Scheme 17b). Because the deuterium content of **7s-d** was unchanged when treated with water (H<sub>2</sub>O) under the same reaction conditions, external water is likely incorporated during the migration process of the hydrogen atom (Scheme 17b).



Scheme 17. Mechanistic studies

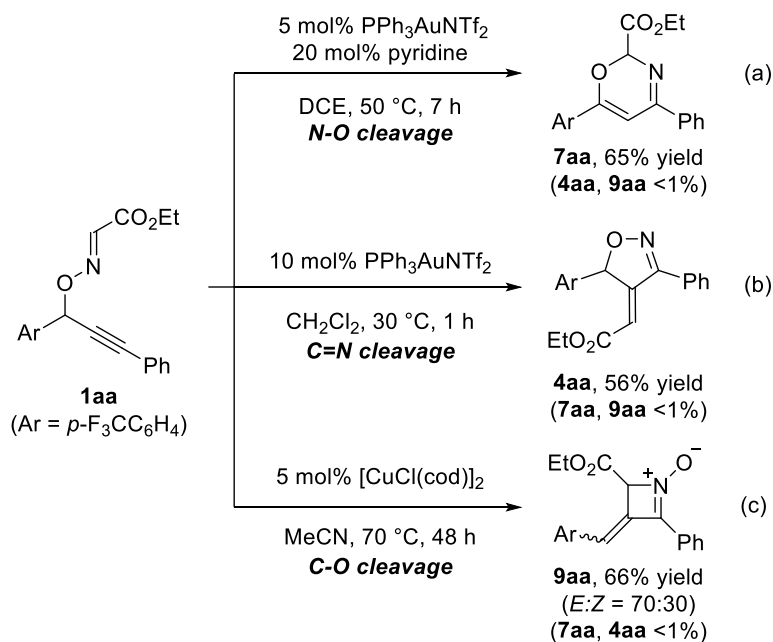
A proposed mechanism for the Au-catalyzed reactions of **1s** for the synthesis of oxazines **7s** is shown in Scheme 18. The reaction is initiated by *5-endo*-cyclization through a nucleophilic attack of the oxime nitrogen atom on the  $\pi$ -activated alkyne moiety. The nucleophilic attack on the iminium moiety of resulting vinylgolds **33**, which occurs in the reaction of *O*-propargylic formaldoximes **1a**, would be hampered by the bulky aryl group. Instead, deprotonation takes place by the action of the counteranion or the pyridine cocatalyst to form isoxazolium intermediates **34**. Subsequent protonation at the gold-bound carbon of **34** induces ring opening involving the cleavage of the N–O bond. The following re-cyclization of **35** leads to six-membered ring intermediates **36**. Finally, elimination of the gold catalyst gives **7**. Although vinylgold intermediates **33** are expected to exhibit a carbene character (**33'**), the loss of deuterium content in the Au-catalyzed reaction of deuterium-labeled substrate **1s-d** (Scheme 17a) suggests that the concerted [1,2]-hydrogen rearrangement (which ideally proceeds without loss of deuterium) is unlikely. The bulky *p*-nitrophenyl group on the oxime carbon not only prevent nucleophilic attack on the iminium moiety of vinylgold intermediates **33**, but its electron-withdrawing nature also facilitates the elimination of the proton from **33**, leading to the formation of **34**. Our DFT calculations indicated that the deprotonation process is the rate-determining step of the present rearrangement reactions. The deceleration of the reaction of deuterium-labeled substrate **1s-d** agreed with the calculations.



Scheme 18. Proposed mechanism for Au-catalyzed rearrangement reactions of **1s** via N–O bond cleavage

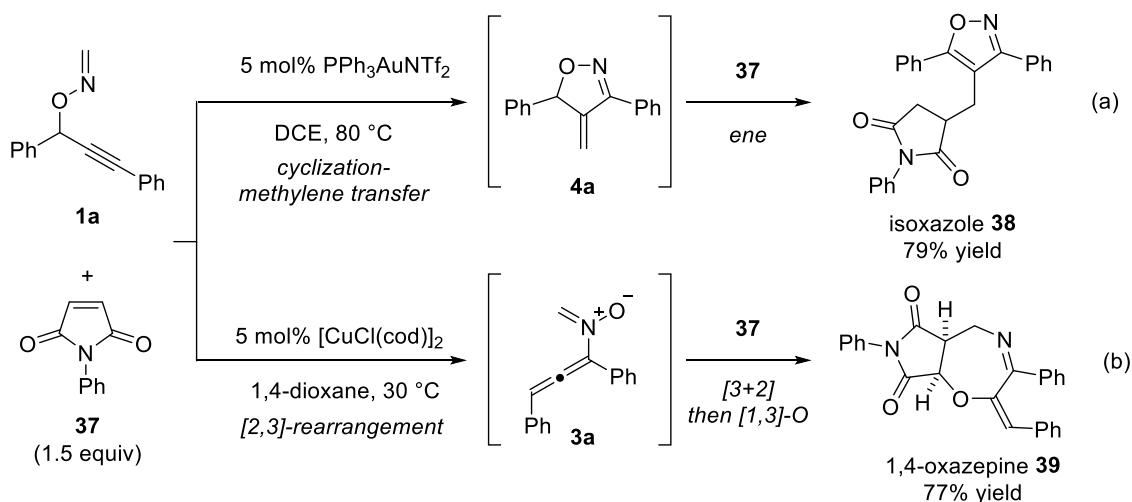
## 6. DIVERGENT SYNTHESIS OF HETEROCYCLES BY $\pi$ -LEWIS ACIDIC METAL-CATALYZED SKELETAL REARRANGEMENT

The divergent synthesis of heterocyclic compounds is a desirable way to achieve the rapid construction of chemical libraries from a single starting material by changing the catalysts and the reaction conditions.<sup>31</sup> We used  $\pi$ -Lewis acidic skeletal rearrangement reactions to divergently synthesize four-, five-, and six-membered heterocycles from  $\alpha$ -(*N*-propargyloxy)acetate **1aa** bearing an electron-withdrawing ethoxycarbonyl group, which was less bulky than *p*-nitrophenyl group, on the oxime carbon. The reaction of **1aa** using gold-pyridine hybrid catalysts selectively afforded oxazine **7aa** (Scheme 19a). In contrast, the Au-catalyzed reaction of **1aa** in the absence of the pyridine cocatalyst exclusively led to the formation of isoxazoline **4aa** via C=N cleavage (Scheme 19b). Moreover, the reaction of **1aa** using the copper catalyst [CuCl(cod)]<sub>2</sub> instead of the gold catalyst predominantly proceeded via C–O bond cleavage, affording azete *N*-oxide **9aa** through [2,3]-rearrangement followed by 4 $\pi$ -electrocyclization (Scheme 19c; see also Scheme 2).

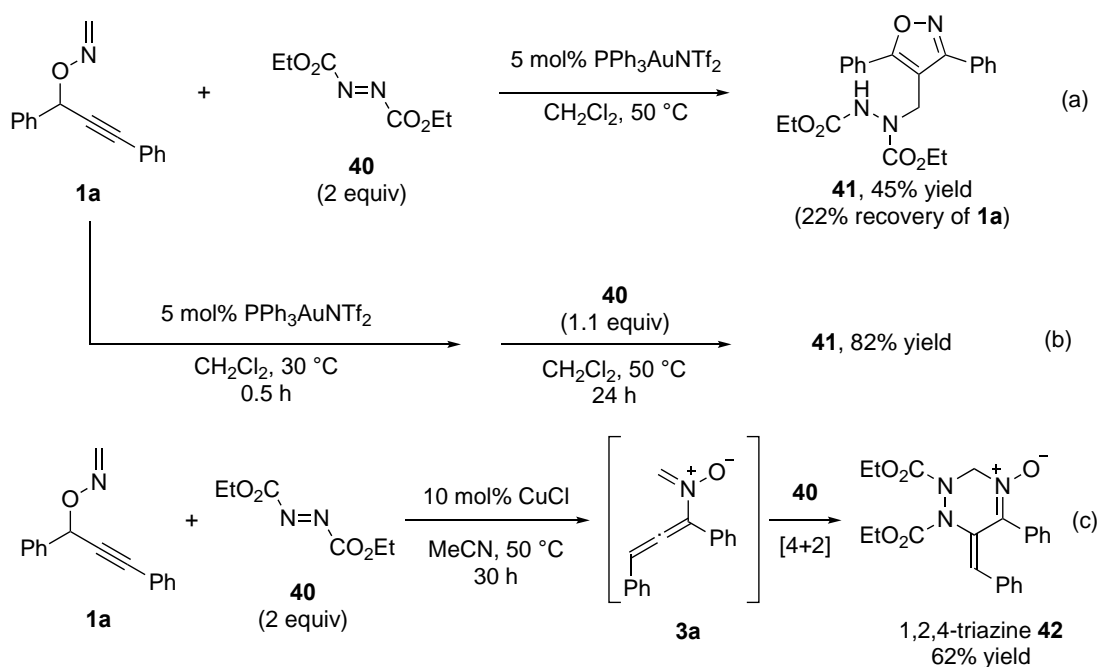


Scheme 19. Divergent synthesis of heterocycles by  $\pi$ -Lewis acidic metal-catalyzed skeletal rearrangement of **1aa**

Divergent synthesis was also achieved by intermolecular cascade reactions with external reagents. For example, the reaction of *O*-propargylic formaldoxime **1a** and *N*-phenylmaleimide **37** in the presence of the gold catalyst proceeded via capture of in situ-generated isoxazoline **4a** by an ene reaction with **37**, affording isoxazole **38** in good yield (Scheme 20a). In contrast, the reaction of **1a** and **37** using the copper catalyst proceeded via [3+2] cycloaddition, in which the generated *N*-allenylnitron intermediate **3a** functioned as a 1,3-dipolar intermediate to react with **37**, producing 1,4-oxazepine **39** (Scheme 20b). Diethyl azodicarboxylate **40** also served as an efficient reagent for divergent synthesis (Scheme 21). The Au-catalyzed reaction of **1a** and **40** proceeded via cyclization-intermolecular methylene transfer followed by an ene reaction to afford isoxazole **41**. Although azodicarboxylate **40** deactivated the gold catalyst during the reaction (Scheme 21a), the yield was significantly improved by carrying out the reaction in one pot, i.e., adding **40** to the vessel after running the Au-catalyzed reaction for 30 min (Scheme 21b). In contrast to the Au-catalyzed reaction, the Cu-catalyzed reaction of **1a** and **40** proceeded via [4+2] cycloaddition, in which intermediate **3a** was employed as 2-azadiene to form 1,2,4-triazine **42** in a selective manner (Scheme 21c). The results of the divergent synthesis support our initial hypothesis that the control of vinylmetal intermediates **2** (Scheme 1) can modify the skeletal rearrangement reaction of *O*-propargylic oximes.



Scheme 20. Divergent heterocyclic synthesis by intermolecular cascade reaction of **1a** and *N*-phenylmaleimide **37**



Scheme 21. Divergent heterocyclic synthesis by reaction of **1a** and diethyl azodicarboxylate **40**

## 7. PERSPECTIVES

We have developed new methods for the synthesis of multiply substituted heterocycles by Au-catalyzed rearrangement reactions. The key feature of these methods is to adequately control the reactivity of vinylmetal intermediates by choosing the appropriate  $\pi$ -Lewis acidic metal catalysts, thereby enabling unique transformations. In addition, the mild reaction conditions of the Au-catalyzed reactions allow for the synthesis of new classes of heterocycles such as 4-methylenated isoxazolines **4**, which readily isomerize under harsh conditions. There is no doubt that the steady development of organic synthetic methods will

enable the preparation of complex starting materials. We expect that new heterocyclic compounds can be efficiently synthesized through new skeletal rearrangement reactions utilizing more well-designed substrates.

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25. Alternatively, vinylgold intermediate **15** could react directly with the iminium moiety of another vinylgold intermediate to form a C-C bond. However, we believe that this is unlikely because vinylgold **15** connects directly with the iminium moiety, which would greatly reduce its nucleophilicity. In fact, the Au-catalyzed reaction of **1s** in the presence of water did not yield **8a** derived from the protodeauration of vinylgold **15** (Scheme 16b), indicating the low nucleophilicity of vinylgold intermediate **15**.
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