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Direct Synthesis of Trisubstituted Isoxazoles through Gold-Catalyzed Domino Reaction of Alkynyl Oxime Ethers

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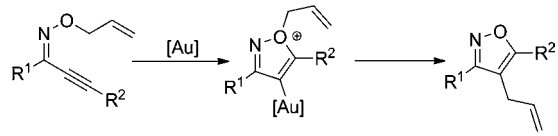
ABSTRACT



Alkynyl oxime ether underwent a gold-catalyzed domino reaction involving cyclization and subsequent Claisen-type rearrangement to afford trisubstituted isoxazoles in a direct, efficient, and regioselective manner. The products were successfully applied to the synthesis of unusual heterocycles as an illustration of the potential utility of the reaction.

Highly substituted isoxazoles are core components of many natural products, biologically active compounds, and functional materials.[1−3] Thus, synthesis of these molecules with high efficiency is highly desirable.[4−11] Although a common and typical strategy for the synthesis of isoxazoles is the [3+2] cycloaddition reaction between alkynes and nitrile oxides, a cycloaddition reaction with internal alkynes for the direct construction of trisubstituted isoxazole has been less frequently reported.[12−14] Furthermore, these methods require harsh conditions and provide poor chemo- and regioselectivities. As an alternative strategy for efficient construction of isoxazoles, Larock recently reported stepwise synthesis

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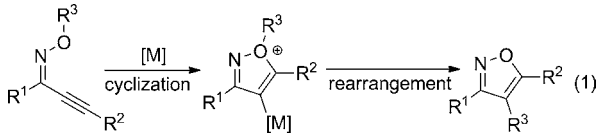
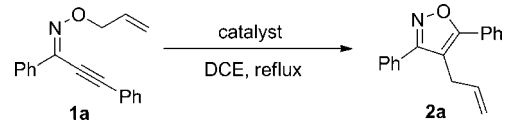
of trisubstituted isoxazoles by electrophilic cyclization of *O*-methyl alkynyl oxime ethers and a subsequent palladium-catalyzed coupling reaction of the resulting 4-haloisoxazole.[15] From the viewpoint of atom economy, the direct and waste-free synthesis of trisubstituted isoxazoles with high chemo- and regioselectivities in one sequence is highly desirable and challenging. We anticipated that π-acidic transition metal-catalyzed cyclization of alkynyl oxime ether would lead to new generation of a vinyl metal intermediate, in which the substituent R^3 could rearrange to the C4 position providing trisubstituted isoxazoles under suitable conditions (eq 1).



π-Acidic transition metal-catalyzed intramolecular addition of a heteroatom to an alkyne and subsequent migration of the substituent is one of the most powerful strategies for the synthesis of heterocyclic compounds.[16] Although these transformations have provided useful access to benzofurans,[17] indoles,[18] benzothiophenes,[19] furans,[20] pyrans,[21] and pyrrolidine,[22] less is known about the synthesis of isoxazoles.[23,24] Moreover, intramolecular addition of the oxygen atom in the oxime ether moiety to alkyne has not yet been reported.[25,26] Herein, we report the direct synthesis of trisubstituted isoxazole through a domino process involving cyclization and subsequent rearrangement in connection with our recent explorations of the domino reaction of conjugated imines.[27]

The *O*-allyl alkynyl oxime ether **1a**, which was prepared by the condensation of 1,3-diphenylprop-2-yn-1-one with *O*-allylhydroxylamine hydrochloride, was initially employed in this study. We expected that the oxonium intermediate would easily undergo Claisen-type [3,3]-sigmatropic rearrangement. Our studies commenced with a survey of catalysts with the goal of identifying effective conditions. When **1a** was treated with 20 mol % of $AgBF_4$ in 1,2-dichloroethane at reflux for 5 h, the expected reaction proceeded successfully to give trisubstituted isoxazole **2a** in 85% yield (Table 1, entry 1). Although Ag(I), Au(I), or Pd(II) catalysts all afforded the desired product, $AuCl_3$ was found to be the most effective catalyst. Thus, the cyclization−rearrangement reaction in the presence of only 5 mol % of $AuCl_3$ proceeded effectively with high yield (entry 5).[28,29]

Table 1. Optimization of Cyclization−Rearrangement Reaction



1a **2a**

entry	catalyst (mol %)	*t* (h)	yield (%)[a]
1	$AgBF_4$ (20)	5	85
2	$AuCl(PPh_3)$ (20)	12	17
3	$PdCl_2(PPh_3)_2$ (20)	12	27
4	$AuCl_3$ (20)	2	90
5	$AuCl_3$ (5)	2	88

[a] Isolated yields.

To examine the scope of the reaction, we treated various *O*-allyl alkynyl oxime ethers **1b**−***l*** with $AuCl_3$ in refluxing 1,2-dichloroethane and obtained the trisubstituted isoxazole **2b**−***l*** in good to high yields (Table 2). Electron-rich or

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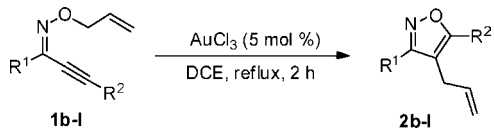
Table 2. Au-Catalyzed Cyclization−Rearrangement Reaction



1b-l 2b-l

entry	substrate	R^1	R^2	product	yield (%)[a]
1	**1b**	4-$MeOC_6H_4$	Ph	**2b**	88
2	**1c**	4-$CF_3C_6H_4$	Ph	**2c**	85
3	**1d**	furyl	Ph	**2d**	80
4	**1e**	cyclohexyl	Ph	**2e**	83
5	**1f**	CO_2Me	Ph	**2f**	53
6	**1g**	Ph	cyclohexyl	**2g**	81
7	**1h**	Ph	*n*Bu	**2h**	90
8[b]	**1i**	Ph	2-BrC_6H_4	**2i**	72
9[b]	**1j**	Ph	allyl	**2j**	83
10	**1k**	Ph	CH_2OTBS	**2k**	99
11	**1*l***	Ph	CH_2OH	**2*l***	78

[a] Isolated yields. [b] Reactions were carried out with $AuCl_3$ (20 mol %).

electron-poor aryl groups, and alkyl groups for R^1, were readily accommodated, producing the expected trisubstituted isoxazoles **2b**−**e** (entries 1−4). Imino ester **1f** was also employed in this reaction, thus affording isoxazole carboxylate **2f** (entry 5). Variation of the substituent on the triple bond terminus was also tolerable (entries 6−11). Remarkably, a 2-bromophenyl group and an allyl group for R^2 were tolerated under the reaction condition; these groups are advantageous for further transformation (entries 8 and 9). It is noteworthy that the unprotected hydroxyl group did not affect the course of the reaction (entry 11).

We next studied the substituent effect on the allyl moiety (Table 3). The additional substituents caused an increase in catalyst loading and prolonged reaction time for complete consumption of the substrate, probably because of steric repulsion. The linear (*E*)-crotylated isoxazole **4a** was regio- and stereoselectively obtained in 42% yield when *O*-1-methylallyl oxime ether **3a** was used as a substrate in the presence of 20 mol % of $AuCl_3$, while the formation of a small amount of branched product was observed by ^1H NMR of the reaction mixture (entry 1). It is noteworthy that the new carbon−carbon bond was generated predominantly at the γ-position in an S_N2' fashion. This result indicated that the migration of the allyl moiety would proceed not through a shift of the allyl cation intermediate,[20c,22,30] but rather through a Claisen-type [3,3]-sigmatropic rearrangement.

The reaction of methallyl derivative **3b** proceeded effectively to afford trisubstituted isoxazole **4b** in 78% yield (entry 2). On the other hand, the methyl group at the terminal position of the allyl moiety led to a decrease in the chemical yield of branched product **4c**, and a significant amount of linear product **4a** was also formed via a 1,3-shift of the crotyl group (entry 3). The gold-catalyzed reaction of **3d**, which

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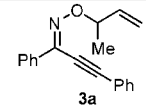
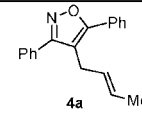
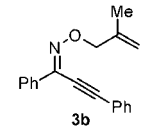
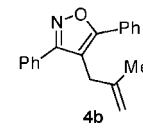
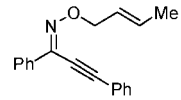
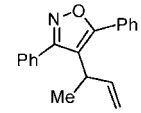
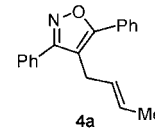
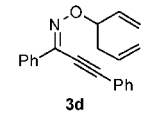
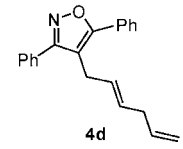
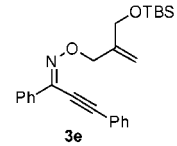
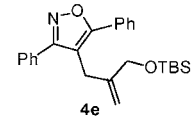
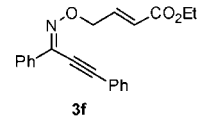
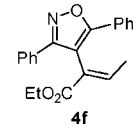
Table 3. Substitution Effect on the Allyl Group

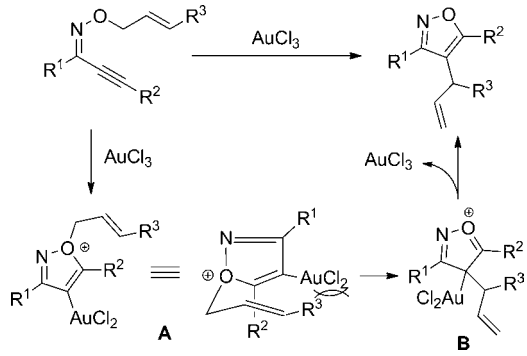
entry	substrate	product	*t* (h)	yield (%)[a]
1[b]	 **3a**	 **4a**	24	42
2[b]	 **3b**	 **4b**	2	78
3[b]	 **3c**	 **4c**  **4a**	24	**4c**: 21 **4a**: 7
4[b]	 **3d**	 **4d**	24	64
5[c]	 **3e**	 **4e**	2	77
6[d]	 **3f**	 **4f**	2	70

[a] Isolated yields. [b] Reactions were carried out with $AuCl_3$ (20 mol %) in DCE at reflux. [c] Reaction was carried out with $AuCl_3$ (5 mol %) in DCE at reflux. [d] Reactions were carried out with $AuCl_3$ (5 mol %) followed by treatment with Et_3N (3 equiv).

bears an additional allyl group, provided unconjugated diene (*E*)-**4d** in 64% yield (entry 4). Interestingly, substrate **3e** bearing a silyloxymethyl group efficiently underwent the domino reaction with use of 5 mol % of $AuCl_3$ to yield the corresponding isoxazole **4e** (entry 5). Possibly, the chelation of the oxygen atom in **3e** enhanced the reactivity of the catalyst. The cyclization/rearrangement reaction can be applied to the electron-deficient allyl moiety. The reaction of crotonate **3f** with 5 mol % of $AuCl_3$ followed by stereoselective isomerization by Et_3N afforded the functionalized isoxazole **4f** in 70% yield (entry 6).

On the basis of the above results, a possible reaction pathway is shown in Scheme 1. It commences with the addition of an oxygen atom to an Au(III)-activated C−C triple bond, generating an oxonium intermediate **A**, which would undergo Claisen-type rearrangement to form intermediate **B**. The subsequent aromatization of **B** would afford isoxazole and liberate the catalytic gold species. In the case

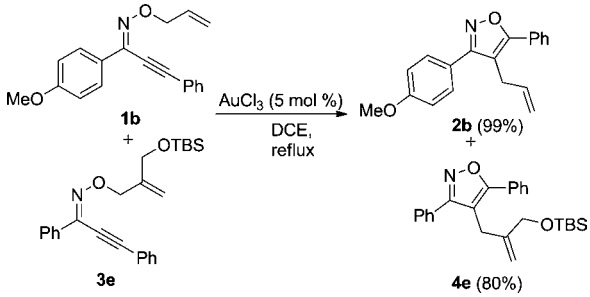
Scheme 1. Possible Reaction Pathway



of **3c**, steric repulsion between the methyl group and the gold moiety might decrease the chemical yield of **4c**.

The proposed reaction pathway was partially supported by the results of a crossover experiment (Scheme 2).

Scheme 2. Crossover Reaction of **1b** and **3e**

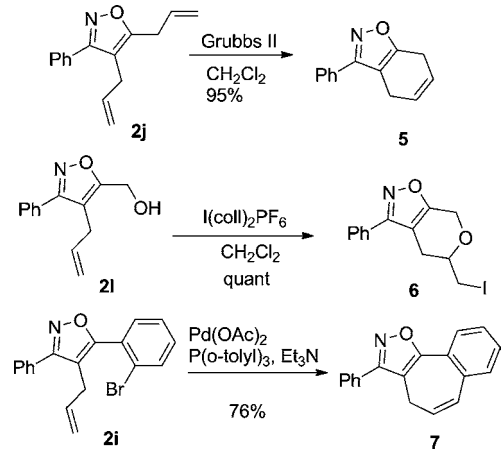


Treatment of an equimolar mixture of **1b** and **3e** with 5 mol % of $AuCl_3$ gave **2b** and **4e** in 99% and 80% yields, respectively, without any crossover products. This result indicates that the transfer of the allyl moiety proceeds in an intramolecular manner.

To demonstrate the synthetic utility of the trisubstituted isoxazoles as highly versatile building blocks, we investigated further transformations into a variety of different heterocycles (Scheme 3). The 3,4-diallylisoxazole **2j** was transformed into dihydrobenzisoxazole **5** by ring closing metathesis with an excellent yield.[31] Iodoetherification of **2*l*** with bis(2,4,6-collidine)iodonium hexafluorophosphate proceeded smoothly

(31) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18.

Scheme 3. Synthetic Application



to afford pyrano[4,3-*d*]isoxazole **6**, which could be used for further functionalization of the carbon−iodine bond.[32] Palladium-mediated intramolecular Heck reaction of **2i** provided 4*H*-benzo[3,4]cyclohept[1,2-d]isoxazole **7** with a 76% yield and high regioselectivity.[33]

In summary, we have developed a novel method for the synthesis of trisubstituted isoxazoles from alkynyl oxime ether. The trisubstituted isoxazoles were produced via gold-catalyzed cyclization followed by an allyl oxonium Claisen-type rearrangement. The present method was successfully applied to the synthesis of unusual heterocycles. The domino reaction is characterized by mild conditions, is straightforward, and allows for the efficient construction of functionalized isoxazoles.

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Supporting Information Available: Experimental procedure, characterization data, and ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

OL100803E

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(33) Söderberg, B. C. G.; Hubbard, J. W.; Rector, S. R.; O'Neil, S. N. *Tetrahedron* **2005**, *61*, 3637.