Synthetic Methods

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Skeletal Rearrangement of *O*-Propargylic Formaldoximes by a Gold-Catalyzed Cyclization/Intermolecular Methylene Transfer Sequence**

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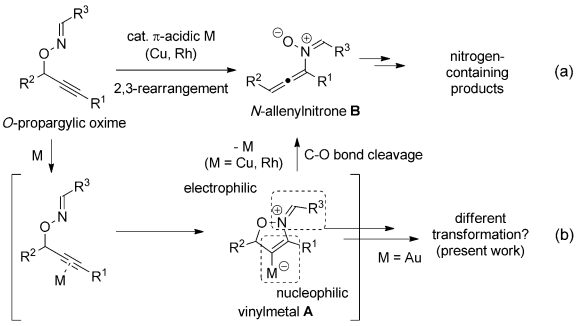
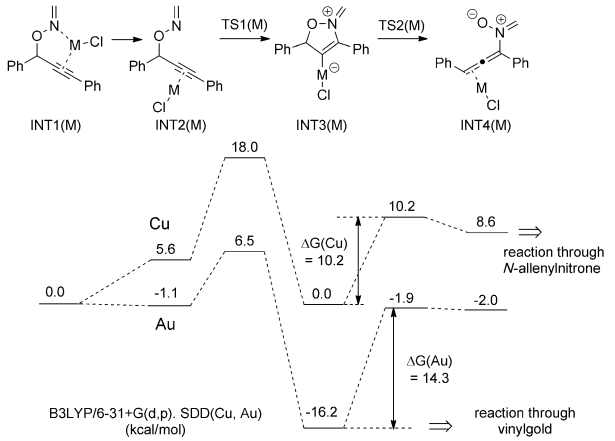
Abstract: *Skeletal rearrangement of O-propargylic formaldoximes, in the presence of gold catalysts, afforded 4-methylene-2-isoxazolines in good to excellent yields by an intermolecular methylene transfer. In addition, the cascade reaction with maleimide in the presence of a gold catalyst afforded isoxazole derivatives by cyclization/methylene transfer and a subsequent ene reaction, whereas that using a copper catalyst gave oxazepines through a 2,3-rearrangement.*

Skeletal rearrangement reactions featuring π-acidic metal catalysts provide an efficient and attractive methodology in the construction of highly functionalized organic molecules from readily available starting materials through cleavage of skeletal σ bonds.[1] Typically, such skeletal rearrangements proceed through several pathways. For divergent organic syntheses, however, it would be desirable to be able to select the reaction pathways using specific metal catalysts.[2]

We have recently reported on the catalytic skeletal rearrangement reactions of *O*-propargylic oximes, which serve as an intriguing platform in the presence of π-acidic copper and rhodium catalysts, for the efficient syntheses of multisubstituted nitrogenous cyclic and acyclic compounds (Scheme 1 a).[3] The transformations proceed primarily through a 2,3-rearrangement step involving the nucleophilic attack of the oxime nitrogen atom onto the π-activated alkyne moiety and subsequent C–O bond cleavage and elimination of the metal catalyst from the resulting vinylmetal intermediate **A**, to form the *N*-allenylnitrone **B** which can undergo further transformations. Our preliminary DFT calculations for the 2,3-rearrangement (Scheme 2) suggested that the activation energy of the C–O bond cleavage process in copper catalysis [ΔG(Cu)] is sufficiently low (10.2 kcal mol^{-1}) to allow efficient generation of the *N*-allenylnitrone INT4(Cu). In contrast, gold catalysts, which are typical π-acidic metals,[4] require higher activation energy for the C–O bond cleavage [ΔG(Au) = 14.3 kcal mol^{-1}] relative to copper catalysts [ΔG(Cu)] because of the significant stabilization of the vinylgold intermediate INT3(Au) by relativistic effect.[5,6] The energetically less favorable C–O bond cleavage in the gold catalysis inspired us to develop a new type of transformation resulting from the long-lived vinylgold intermediate **A** (M = Au) bearing the electrophilic iminium and the nucleophilic vinylgold moieties (Scheme 1 b). Herein, we report the gold-catalyzed reactions of *O*-propargylic formaldoximes (**1**) for the synthesis of 4-methylene-2-isoxazolines (**2**) in good to excellent yields by C=N bond cleavage [Eq. (1)].



Scheme 1. π-Acidic metal-catalyzed 2,3-rearrangement of *O*-propargylic oximes.



Scheme 2. Energy profile for gold- and copper-mediated 2,3-rearrangement of *O*-propargylic formaldoxime.

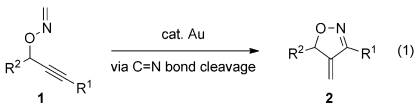


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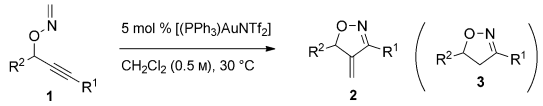
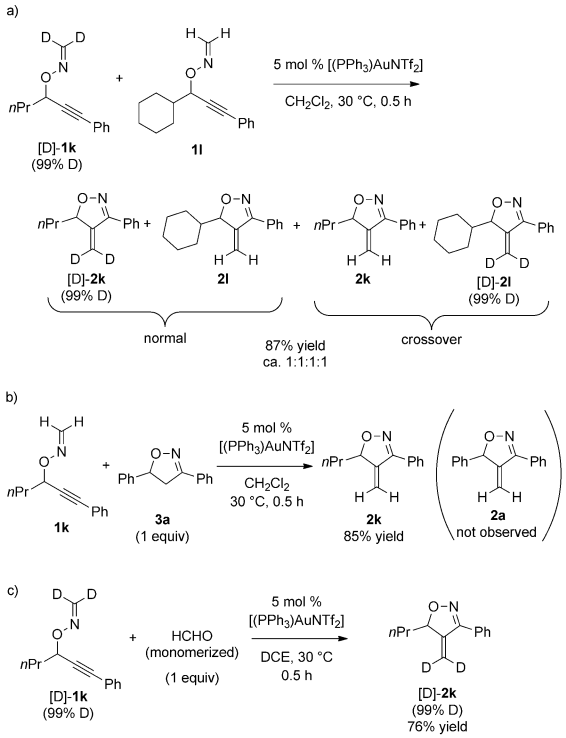
Table 1: Gold-catalyzed reactions of **1**.[a]



Entry	**1**	R^1	R^2	*t* [h]	**2**	Yield [%][b]
1[c]	**1a**	Ph	Ph	24	**2a**	44[d]
2	**1a**	Ph	Ph	0.5	**2a**	86
3	**1b**	*p*-$MeOC_6H_4$	Ph	0.5	**2b**	86
4	**1c**	*p*-MeC_6H_4	Ph	0.5	**2c**	81
5	**1d**	*p*-ClC_6H_4	Ph	0.5	**2d**	87
6[e]	**1e**	*p*-$F_3CC_6H_4$	Ph	24	**2e**	68
7	**1f**	*n*Pr	Ph	0.5	**2f**	77
8	**1g**	Cy	Ph	0.5	**2g**	81
9	**1h**	H	Ph	48	–	< 1[f]
10	**1i**	Ph	*p*-$MeOC_6H_4$	0.5	**2i**	74
11	**1j**	Ph	*p*-$F_3CC_6H_4$	0.5	**2j**	90
12	**1k**	Ph	*n*Pr	0.5	**2k**	82
13	**1l**	Ph	Cy	0.5	**2l**	79
14	**1m**	Ph	H	0.5	**2m**	53

[a] Reactions of **1** (0.4 mmol) were conducted in the presence of $[(PPh_3)AuNTf_2]$ (0.02 mmol) in CH_2Cl_2 (0.8 mL) at 30 °C. [b] Yield of the isolated product. [c] The reaction was carried out in the presence of AuCl (10 mol %) in MeCN at 50 °C. [d] **3a** (10 %) was obtained. [e] The reaction was carried out in 1,2-dichloroethane (DCE) at 50 °C. [f] 60 % of **1h** was recovered. Tf = trifluoromethanesulfonyl.

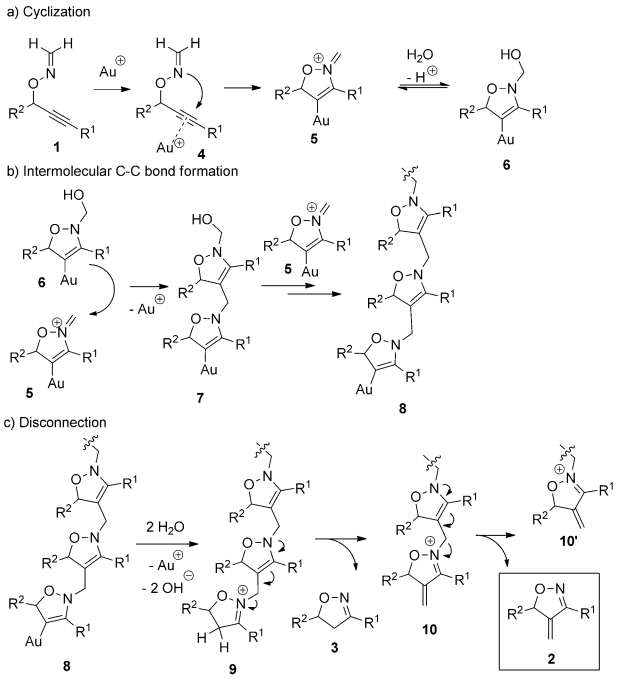


Scheme 3. Mechanistic studies.

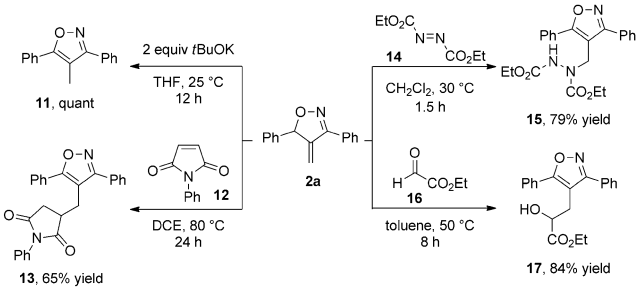
We initially conducted the reaction of the *O*-propargylic formaldoxime **1a** in the presence of AuCl (10 mol %) in MeCN at 50 °C, and it afforded the 4-methylenated isoxazoline **2a** in 44 % yield along with a small amount (10 %) of the isoxazoline **3a**, which does not possess a methylene group (Table 1, entry 1). To our delight, the yields were dramatically improved by conducting the reaction using the cationic $[(PPh_3)AuNTf_2]$ in CH_2Cl_2 at 30 °C (entry 2). In contrast, CuCl did not exhibit any catalytic activities (see the Supporting Information). The reaction can tolerate various aryl and alkyl substituents both at the alkyne terminus (R^1) and the propargylic position (R^2; entries 1–8, and 10–13). As a note, the reaction of **1e**, which possesses a highly electron-deficient *p*-(trifluoromethyl)phenyl group as R^1, required longer reaction times, even when carried out at 50 °C (entry 6). In the case of the terminal alkyne **1h**, the reaction did not afford the desired isoxazoline (entry 9), while the reaction of **1m**, which does not possess any R^2 substituents, afforded the corresponding isoxazoline **2m** in a moderate yield (entry 14). It should be noted, however, that substrates possessing a substituent, such as *n*-propyl or phenyl, at the oxime moiety were not transformed into the desired products under the optimized reaction conditions, thus indicating that, for the present transformation, the migrating group is limited to a nonsubstituted methylene group.

Next, several experiments were carried out to gain insight into the reaction mechanism (Scheme 3). First, crossover experiments were carried out using a 1:1 mixture of **1l** and the equally reactive [D]-**1k**, in which the formyl group was deuterium labelled (Scheme 3 a). The gold-catalyzed reaction afforded equal amounts of normal ([D]-**2k** and **2l**) and crossover products (**2k** and [D]-**2l**), thus clearly indicating that transfer of the methylene group proceeds in an intermolecular manner.[7–9] Secondly, the gold-catalyzed reaction between **1k** and a nonmethylenated isoxazoline (**3a**, 1 equiv) did not afford the expected product **2a** (derived from incorporation of external isoxazoline **3a**); the reaction instead afforded **2k** (derived from starting material **1k**; Scheme 3 b).[8] Thirdly, the reaction was carried out between [D]-**1k** and monomerized formaldehyde, thus resulting in the formation of [D]-**2k**, in which the deuterium content at the methylene moiety was 99 % (Scheme 3 c). The results of the above experiments indicate that the present methylene transfer process does not involve the isoxazoline **3** or formaldehyde, which would be expected to be liberated during the reaction.

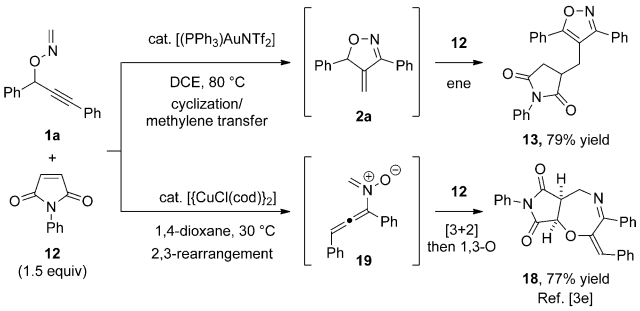
Based on the above experiments, the reaction mechanism can be described as a cyclization/intermolecular C–C bond formation/disconnection sequence, as illustrated in Scheme 4. First, the π-acidic gold catalyst coordinates to the triple bond of **1** to form the π-complex **4**, which is subjected to an intramolecular nucleophilic attack by the oxime nitrogen atom to give the cyclized intermediate **5**. The electrophilic iminium moiety of **5** would react with water which is present in trace amounts in the reaction mixture to form the enaminylgold species **6**. The nucleophilic vinylgold moiety of **6** would then attack the iminium moiety of another **5** to form a C–C bond. Because the C–C bond formation takes place at the vinylgold terminus, the sequential process will continuously generate another intermediate **5**. Concurrently, protonation (because of trace amounts of water) at the nucleophilic vinylgold terminus of **8** would lead to the iminium intermediate **9**. Donation of electrons from the



Scheme 4. A plausible mechanism.



Scheme 5. Derivatization of **2a**. DCE = 1,2-dichloroethane, THF = tetrahydrofuran.



Scheme 6. Catalyst-controlled cascade reactions.

nitrogen atom of the adjacent isoxazoline ring would result in the cleavage of the C–N bond and formation of an *exo* C=C bond, thus liberating the nonmethylenated isoxazoline **3**. Electron donation from an adjacent isoxazoline ring would continue and sequentially disconnect **2**. Significant deceleration resulting from an electron-deficient substituent at the alkyne terminus (Table 1, entry 6) suggests that the decreased nucleophilicity of the olefin moiety of **6** and **7** strongly affects the intermolecular C–C bond-forming process.[10] Although the nucleophilicity of the nonmethylenated isoxazoline **3** by itself is insufficient to attack the iminium moiety, the enhanced nucleophilicity resulting from the corresponding vinylgold intermediates **6** and **7** enables the intermolecular introduction of a methylene group. This synthetic methodology featuring metal-catalyzed cyclization followed by intermolecular methylene transfer may serve as an efficient approach to introduce a methylene group (and hopefully other alkylidene groups) to less nucleophilic heterocycles that are inert for Knoevenagel condensation.

Accordingly, **2** can be further derivatized into various multisubstituted isoxazole derivatives (Scheme 5). For example, **2a** was quantitatively isomerized into the isoxazole **11** using *t*BuOK. Alternatively, **2a** underwent an ene reaction with various compounds, such as maleimide **12**, azodicarboxylate **14**, and glyoxylate **16**, to afford the corresponding functionalized isoxazoles **13**, **15**, and **17**, respectively, in good to excellent yields.[11]

In addition, the gold-catalyzed one-pot reaction of **1a** in the presence of **12** proceeded via the isoxazoline **2a** by a cyclization/methylene transfer followed by an ene reaction, thus affording the corresponding isoxazole **13** (Scheme 6). This result is in sharp contrast to our previously reported copper-catalyzed cascade reaction, which proceeds through the *N*-allenylnitrone intermediate **19** by a 2,3-rearrangement, thus leading to the oxazepine derivative **18** (Scheme 6).[3e] These results strongly support our initial hypothesis that the metal catalysts can control the pathway of the skeletal rearrangement reactions of *O*-propargylic oximes (Scheme 2).[12]

In conclusion, we have successfully developed a novel approach for the formation of 4-methylenated isoxazoline derivatives by a reaction sequence of cyclization and an unprecedented intermolecular methylene transfer, under mild reaction conditions. Although such compounds are highly useful for synthesis of functionalized isoxazolines and isoxazoles, which are commonly found in biologically active compounds and serve as important synthetic intermediates,[13] there are only a limited number of reports on preparation of the 4-methylenated isoxazoline.[14] Therefore, the present cyclization/intermolecular methylene transfer sequence is highly useful for construction of these molecular frameworks.

Experimental Section

1a (94.1 mg, 0.4 mmol) in CH_2Cl_2 (0.8 mL) was added to $[(PPh_3)AuNTf_2]$ (14.8 mg, 0.02 mmol) in a V-vial under an argon atmosphere. The mixture was stirred at 30 °C for 0.5 h and then passed through a short pad of silica gel with CH_2Cl_2 (50 mL). The solvents were evaporated in vacuo and the crude product was purified by flash silica-gel column chromatography using hexane/EtOAc (10:1) as eluent to give product **2a** (81.1 mg, 86 %).

Keywords: copper · gold · heterocycles · rearrangements · synthetic methods

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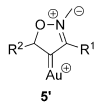
[6] Indeed, transformations of *O*-propargylic oximes that we previously reported were not promoted by gold catalysts; decomposition of substrates was observed. See Ref. [3c].

[7] As a note, we confirmed that, under the reaction conditions, crossover of methylene group did not occur between starting materials [D]-**1k** and **1l**, and between products [D]-**2k** and **2l.** See the Supporting Information.



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[8] We have previously reported that the gold-catalyzed reaction of *O*-propiolyl oxime proceeds via an intermolecular arylidene transfer, mediated by liberated isoxazolone: a) I. Nakamura, M. Okamoto, M. Terada, *Org. Lett.* **2010**, *12*, 2453 – 2455. Indeed, isoxazolone is sufficiently nucleophilic to undergo Knoevenagel condensation: b) D. Renard, H. Rezaei, S. Z. Zard, *Synlett* **2002**, 1257 – 1260.

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[10] Alternatively, it is also possible that the C–C bond formation would take place through the gold carbenoid—ylide species **5′**, which is a resonance form of vinylgold species **5**. To date, however, attempts to capture the expected carbenoid intermediate **5** using external olefins, such as styrene, have been unsuccessful.

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