

Gold-Catalyzed Cyclization and Subsequent Arylidene Group Transfer of O-Propioloyl Oximes

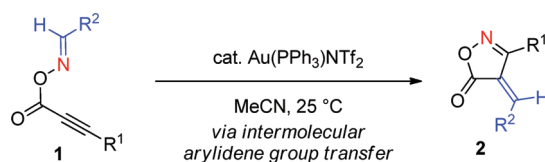
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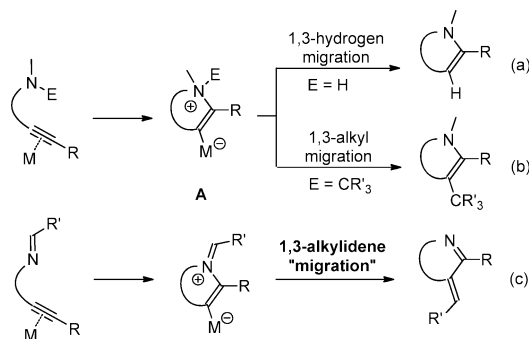
ABSTRACT



Gold-catalyzed cyclizations of O-propioloyl oximes via C–N bond formation followed by arylidene group transfer were successfully carried out to afford the corresponding 4-arylideneisoxazol-5(4H)-ones in good to excellent yields. As an example, (*E*)-benzaldehyde O-3-phenylpropioloyl oxime (**1a**) was reacted in acetonitrile at 25 °C in the presence of Au(PPh₃)NTf₂ (5 mol %) to give 4-benzylidene-3-phenylisoxazol-5(4H)-one (**2a**) in 90% yield. On the basis of crossover experiments, the arylidene “migration” was shown to proceed in an intermolecular manner.

A powerful method of synthesizing nitrogen-containing heterocyclic compounds involves a π -acidic transition-metal-catalyzed cyclization,¹ which is generally initiated by an intramolecular nucleophilic attack by a nitrogen atom onto a carbon–carbon triple bond that possesses an enhanced electrophilicity due to the π -coordinated metal catalyst. In many of these reactions, the resulting vinyl metal species **A** undergoes a subsequent 1,3-migration of a functional group (E) from the nitrogen atom to the sp²-carbon that is bound to the metal catalyst (Scheme 1). In the case of a hydrogen atom (E = H), the 1,3-migration is widely recognized as a

Scheme 1. Formation of Nitrogen-Containing Heterocycles via π -Acidic Transition Metal-Catalyzed Cyclization, Followed by 1,3-Migration Reaction: (a) 1,3-Hydrogen Migration, (b) 1,3-Alkyl Migration, and (c) 1,3-Alkylidene “Migration” (Reported Herein)



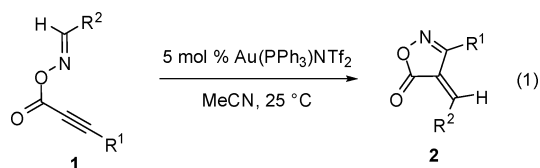
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hydroamination reaction (type a) and has been extensively investigated.² On the other hand, carboamination reactions (type b), which involve the 1,3-migration of carbon functional

groups ($E = CR'_3$) such as acyl, allyl, methyl, methoxy-methyl, ester, and carbamoyl groups, have been recently reported by several groups, including ourselves.^{3,4} To the best of our knowledge, however, a catalytic reaction involving a 1,3-migration of an alkylidene group (type c) has yet to be reported.^{5,6} Herein, we report on the gold-catalyzed cycloisomerizations of *O*-propioloyl aldoximes **1** via C–N bond formation and the subsequent arylidene “migration” to afford the corresponding 4-arylideneisoxazol-5(*4H*)-ones **2** in good to excellent yields under mild conditions (eq 1). We disclosed that the present intriguing arylidene group transfer proceeds via an intermolecular manner, and hence is regarded as the formal 1,3-migration process.



First, as summarized in Table 1, the reaction conditions were optimized using (*E*)-benzaldehyde *O*-3-phenylpropioloyl oxime **1a** as the substrate. Although the use of trivalent gold salts such as AuCl₃ and AuBr₃ gave the desired product **2a** in moderate yields (entries 1 and 2), the combination of Au(PPh₃)Cl and AgOTf was highly effective in promoting the reaction. To investigate the effects of the counteranion, various silver salts were examined (entries 3–6); optimal results (reaction time and yield) were obtained for AgNTf₂ (entry 4), which possesses a weakly coordinated counteranion. Accordingly, preprepared Au(PPh₃)NTf₂ exhibited similarly high catalytic activities (entry 7).⁷ In contrast, the use of AgOTf by itself gave **2a** in a low yield, whereas other metal salts (PtCl₂ and CuCl₈) or a Brønsted acid (HCl) was not effective in catalyzing the reaction. Among the solvents tested, acetonitrile gave the best results (entries 7 and 9–12). For the gold-catalyzed reaction of **1a**, a trace amount of benzaldehyde was detected in the crude products using ¹H NMR.

Next, the optimal conditions (Table 1, entry 9) were employed to investigate the effects of the substituents at the

Table 1. Optimization of Reaction Conditions

entry	catalyst (mol %)	solvent	time/h	yield/% ^a
1	AuCl ₃ (10)	toluene	21	76
2	AuBr ₃ (10)	toluene	12	69
3	Au(PPh ₃)Cl (10) + AgOTf (10)	toluene	6	84
4	Au(PPh ₃)Cl (10) + AgNTf ₂ (10)	toluene	1	82
5	Au(PPh ₃)Cl (10) + AgClO ₄ (10)	toluene	24	50
6	Au(PPh ₃)Cl (10) + AgBF ₄ (10)	toluene	24	24
7	Au(PPh ₃)NTf ₂ (10)	toluene	1	86
8	AgOTf (10)	toluene	24	13
9	Au(PPh ₃)NTf ₂ (5)	MeCN	0.5	94 (90) ^b
10	Au(PPh ₃)NTf ₂ (5)	THF	1	80
11	Au(PPh ₃)NTf ₂ (5)	CH ₂ Cl ₂	1	87
12	Au(PPh ₃)NTf ₂ (5)	EtOAc	1	87

^a The yields were determined using ¹H NMR with CH₂Br₂ as an internal standard. ^b Isolated yield in parentheses (*Z/E* = 97:3).

alkyne or the oxime moieties (Table 2). For the alkyne terminus group (R¹), an electron-rich *p*-anisyl group accelerated the

Table 2. Au-Catalyzed Cycloisomerization of **1**^a

entry	1	R ¹	R ²	2	time/h	yield/% ^b (<i>Z/E</i>)
1	1b	<i>p</i> -anisyl	Ph	2b	0.25	87 (97:3)
2	1c	<i>p</i> -F ₃ CC ₆ H ₄	Ph	2c	1	81 (92:8)
3	1d	<i>n</i> -Pr	Ph	2d	0.5	78 (96:4)
4	1e	Cy	Ph	2e	4.5	93 (>99:1)
5 ^c	1f	<i>t</i> -Bu	Ph	2f	8	90 (>99:1)
6	1g	Ph	<i>p</i> -anisyl	2g	4.5	88 (>99:1)
7	1h	Ph	<i>p</i> -ClC ₆ H ₄	2h	0.25	69 (94:6)
8	1i	Ph	<i>p</i> -F ₃ CC ₆ H ₄	2i	0.25	50 (92:8)
9	1j	<i>p</i> -tolyl	<i>p</i> -tolyl	2j	0.5	87 (97:3)
10	1k	<i>p</i> -tolyl	<i>p</i> -iPrC ₆ H ₄	2k	0.5	94 (94:6)
11	1l	Ph	Me	-	0.25	decomp

^a The reaction of **1** (0.2 mmol) was carried out in the presence of Au(PPh₃)NTf₂ (5 mol %) in acetonitrile (1 mL) at 25 °C. ^b Isolated yield. ^c At 45 °C.

reaction affording **2b** in a good yield (entry 1), whereas an electron-deficient *p*-(trifluoromethyl)phenyl group resulted in a lower yield (entry 2). Substrates that possess an alkyl R¹ group (**1d**, **1e**, and **1f**) were efficiently converted to the corresponding 3-alkylated isoxazolones (entries 3–5, respectively). In particular, the substrate possessing a bulky *tert*-butyl R²-group (**1f**, entry 5) afforded the desired product **2f** in an excellent yield, albeit requiring a higher reaction temperature. Similarly, substituents on the oxime carbon (R²) exhibited significantly effects

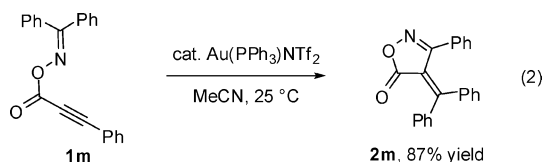
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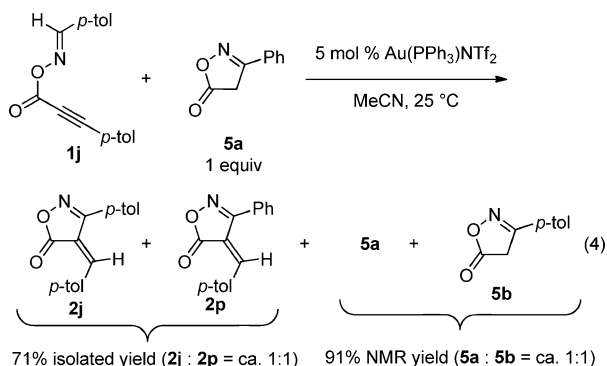
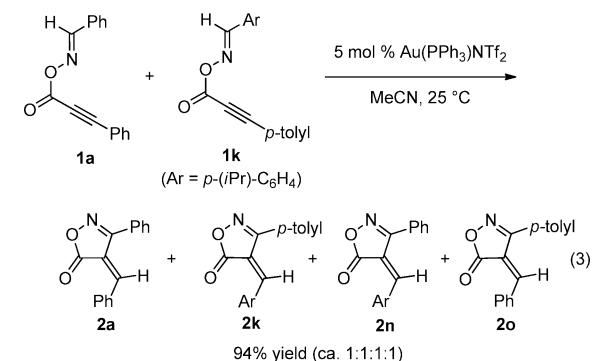
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on the reaction; an electron-donating *p*-anisyl R²-group afforded **2g** in a good yield (entry 6), whereas electron-withdrawing R²-groups decreased the chemical yields due to the competitive decomposition of the starting materials (entries 7 and 8). In contrast, the reaction of the substrate **1l** having an alkyl group at the oxime moiety did not afford the desired product; **1l** was quickly decomposed under the reaction conditions (entry 11). Furthermore, the present methodology was applied to ketoxime **1m** to afford **2m** in a good yield (eq 2).

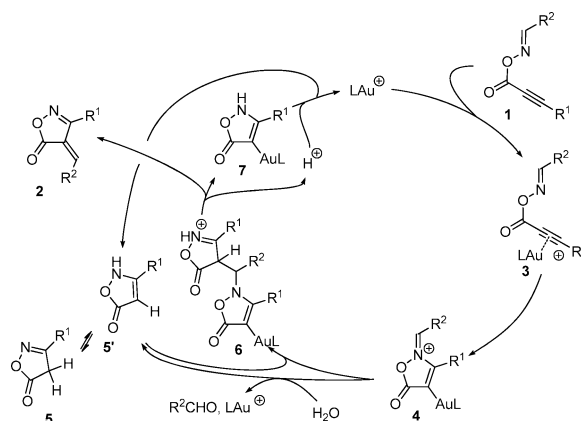


To gain insight into the mechanism, the reaction was carried out using a 1:1 mixture of **1a** and **1k** under the optimal reaction conditions. The resulting mixture of normal products **2a** and **2k** and crossover products **2n** and **2o** (ca. 1:1:1:1, as determined by GC–MS) clearly suggested that the 1,3-arylidene “migration” proceeds in an intermolecular manner, in sharp contrast to that of the 1,3-alkyl migration.⁴ In the presence of 3-phenylisoxazolone **5a**, the reaction of **1j** afforded an approximately 1:1 mixture of **2j** and **2p**, whereas, in the presence of benzaldehyde (1 equiv), the reaction of **1j** afforded solely **2j**; in other words, isoxazolone **5** is generated as the reactive intermediate in the arylidene-transfer process.



Based on our results, a mechanism for the gold-catalyzed reaction of **1** is proposed (Scheme 2): first, cyclized vinyl gold intermediate **4** is formed via nucleophilic attack by the

Scheme 2. Proposed Mechanism



nitrogen atom of the oxime group onto the electrophilic alkyne moiety of **1**, which is coordinated to the π -acidic gold catalyst. In the initial stage, 5-isoxazolone **5** and its enamine tautomer **5'** are formed.⁹ As a note, trace amounts of water may cause the hydrolysis of **4** to presumably form an aldehyde along with the gold catalyst. The intermolecular nucleophilic attack by **5'** onto the iminium moiety of another molecule of **4** would lead to intermediate **6**. β -Elimination and subsequent protodemetalation would yield product **2**, while regenerating the gold catalyst and 5-isoxazolone **5**. The arylidene group transfer would occur via effective combination between the highly electrophilic iminium intermediate **4** and the highly nucleophilic isoxazolone species **5'**, which are generated *in situ* during the reaction. The high *Z* selectivity is probably because the *E* isomer is destabilized due to steric repulsion between R¹ and R².

In conclusion, we have developed a method to synthesize 4-arylideneisoxazolones from *O*-propioloyl oximes via cyclization, followed by intermolecular arylidene group transfer, under mild conditions. Investigations to gain further insight into the reaction mechanism are ongoing in our laboratories.

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Supporting Information Available: Experimental procedures and characterization of **1**, **2**, and **5b**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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