



Gold redox catalysis for cyclization/arylation of allylic oximes: synthesis of isoxazoline derivatives†

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Base-assisted diazonium activation has been employed to promote gold(I)/III redox catalysis toward allylic oxime cyclization/aryl coupling. Functional isoxazolines were prepared with good to excellent yields, while the alternative photoactivation method provided trace amounts of the isoxazoline products. This study further broadens the scope of gold redox chemistry.

Homogeneous gold catalysis has been successfully applied in the areas of alkyne, allene, and alkene activation for effective C–C and C–heteroatom bond formation.¹ However, due to the challenge associated with a high oxidation potential of gold, gold redox catalysis has not been well explored until recently.² Typically, strong oxidants such as PIDA or selectfluor have been used in oxidizing Au(I) to Au(III).³ The discovery of diazonium salts as oxidizing agents for gold redox catalysis has recently stimulated the interest of many researchers.⁴ As initially reported by Glorius in 2013, followed by Toste, Shin, Alcaide, Hashimi, and others, photoactivation of diazonium salts leads to the oxidation of Au(I) to Ar–Au(III) intermediates, which promotes sequential C–C multiple bond activation followed by reductive elimination (Scheme 1A).⁵ It is generally believed that the resulting aryl radical from photoactivated diazonium salts initiates gold oxidation.⁶ These seminal studies significantly advanced gold catalysis research since they offered effective reactive species (aryl diazonium) as oxidants in promoting the gold-redox cycle.†

Our group recently reported a Lewis base-promoted gold oxidation process using diazonium salts.⁷ In these reports, inorganic bases were found to be adequate to facilitate diazonium salt activation under thermal conditions (40–60 °C). Herein, we report the successful cyclization of allylic oximes for the preparation of isoxazoline derivatives under mild reaction conditions.

On the other hand, allylic oximes were found to undergo significant decomposition under photoconditions, giving trace amounts of the desired product.

Due to the strong interest in developing a new strategy for heterocycle synthesis under mild conditions, we were curious about the possibility of using the gold-redox strategy for constructing the isoxazoline motif through an allylic oxime cyclization method (Scheme 1B). Notably, isoxazolines and their derivatives are a versatile class of compounds that can be found in numerous natural products and biologically active compounds.⁸ However, due to the poor substrate stability toward transition metal catalysts, there are only limited successful examples reported regarding oxime cyclization.⁹ In 2010, Loh's group reported the first example of Pd-catalyzed allylic oxime cyclization for the dioxygenation of an alkene (O₂ as both oxidant and the second hydroxyl source).¹⁰ Later, Chen's group reported Pd catalyzed allylic oxime cyclization with aryl halides.¹¹ More recently, Zhu and coworkers reported the Pd-catalyzed homoallylic oxime cyclization for the synthesis of 5-methylisoxazoles.¹² Unlike Pd catalysis, gold redox chemistry with aryldiazonium salts does not undergo oxidative addition through an aryl halide pathway. Therefore, gold redox catalysis will offer greater orthogonal functional group tolerance compared to traditional Pd catalysis. One general concern is whether oxime could survive under gold redox conditions with radical labile N–O and C=N bonds. In

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(A) Gold redox catalysis using diazonium salt as oxidant



(B) Challenge in oxime cyclization: radical-labile substrates



Scheme 1 Cyclization of oximes.



Fig. 1 Allylic oxime reactivity with diazonium salt.

fact, when treating allyl oxime **1a** with diazonium **3a** under photocatalytic conditions, no desired product **2a** was observed although **1a** was completely consumed within two hours. With an interest in exploring this useful transformation with gold-redox catalysis, we further evaluated the reactivity of **1a** in the presence of diazonium salt **3a**. The results are summarized in Fig. 1.

Although with reactive N–O and C=C bonds, oxime **1a** showed good stability while exposed to light, giving less than 5% decomposition under blue LED initiation. However, upon treatment with diazonium salt **3a** (1 : 1 mixture of **1a** and **3a**), rapid decomposition occurred at room temperature and 100% of **1a** was consumed with no clear identifiable products observed when exposed to either blue LED or daylight. Slower decomposition was observed (100% decomposition, 5 h) when treating the mixture under darkness. Notably, ¹⁹F NMR studies showed that most of the diazonium salt was consumed (entries 1–4). Unfortunately, these results ruled out the possibility of applying

diazonium salt in gold redox catalysis under photo-activation conditions.

As discussed above, our group had initiated a chemical activation approach as an alternative for diazonium salt promoted gold redox catalysis. We argued that a base will assist the *in situ* N₂ extrusion process to promote the oxidation of Au(I) to Au(III)–Ar, thereby, slowing down the radical generation which decomposes the oxime.^{7,13} With this in mind, we found that addition of 2 eq. Li₂CO₃ did slow down **1a** decomposition: 10% conversion of **1a** in 6 h under daylight (entry 5). Meanwhile, ¹⁹F NMR studies showed that only a little amount of diazonium salt was consumed in the presence of Li₂CO₃. This further suggests that Li₂CO₃ could potentially prevent the diazonium salt from decomposition to the aryl radical. Encouraged by this result, we evaluated the proposed cyclization–arylation under various conditions, including the choices of catalysts, solvents, bases, and reaction temperatures. Eventually, 7.5% PPh₃AuCl, 5 eq. Li₂CO₃ in CH₃CN as a solvent was identified as the optimal conditions, giving the desired product **2a** in 78% NMR yield (74% isolated yield). Comparison of various reaction conditions is summarized in Table 1.

As shown above, the gold catalyst was found to be crucial for the allylic oxime cyclization since no conversion of the substrate was observed without gold (entry 2). Conducting the reaction in the absence of a base gave complete conversion with no appreciable amount of the desired product. Li₂CO₃ (5 eq.) was identified as the optimal choice for this transformation (entries 5 and 6). Notably, although crude ¹H NMR of the reaction mixture indicated a very ‘clean’ reaction, the overall yield was around 75%. Meanwhile, the addition of excess diazonium salt was found to lead to lower yield (entry 9). Also, acetonitrile was the only solvent suitable for this transformation; switching to other solvents like 1,2-dichloroethane or toluene gave no desired product. This is due to the poor solubility of the diazonium salt in these solvents, even at increased temperature. To emphasize the uniqueness of our chemical activation method, photochemical conditions were

Table 1 Selected initial optimization reactions

Entry	Reaction conditions varies from standard ^a	Conv'n 1a (%)	Yield ^b 2a (%)	Yield ^b 2a' (%)
1	None	100	78	0
2	No [Au]	0	—	—
3	No [ArN ₂][BF ₄]	18	—	—
4	No base	100	Trace	—
5	NaHCO ₃ 2 eq.	95	58	0
6	Li ₂ CO ₃ 2 eq.	100	74	0
7	5% PPh ₃ AuCl	90	51	0
8	5 eq. [ArN ₂][BF ₄]	100	65	—
9 ^c	No [Au], UVA or Blue LED, degassed MeOH	100	0	0
10 ^c	10% PPh ₃ AuCl, degassed MeOH or MeCN, 12 W blue LEDs, RT	100	<5	0
11 ^c	10% PPh ₃ AuCl, 2.5% [Ru(bpy) ₃](PF ₆) ₂ degassed MeOH or MeCN, 12 W blue LEDs, RT	100	<5	0

^a General reaction conditions: **1a** (0.33 mmol), [Au] (0.025 mmol) diazonium salt (0.66 mmol) and base (1.65 mmol) in CH₃CN (0.4 M), 60 °C.
^b Yield was based on ¹H NMR with 1,3,5-trimethoxybenzene as an internal standard. ^c Solvents were degassed using the freeze-pump-thaw method.



Scheme 2 Substrate scope for allylic oxime. General reaction conditions: **1a** (0.33 mmol), [Au] (0.025 mmol), diazonium salt (0.66 mmol), and base (1.65 mmol) in CH₃CN (0.4 M), 60 °C; isolated yield.

used for the cyclization in the presence of diazonium salt. The substrate readily decomposed in the presence of diazonium salts under this method. The standard photoactivation conditions using gold and [Ru(bpy)₃](PF₆)₂ in degassed methanol did not provide a significant amount of desired isoxazoline as confirmed by ¹H NMR analysis of the crude reaction mixture. This result suggests that the photoactivation condition is unsuitable for the oxime substrates in the presence of diazonium salt. With the optimal reaction conditions in hand, we applied it to a series of allylic oximes (Scheme 2).

As shown in Scheme 2, both aromatic and aliphatic substrates were evaluated for the reaction. Good yields and high reaction efficiency could be observed when aryl groups were used (**2a–2j**). The presence of electron withdrawing groups appeared to be more favorable with respect to the isolated yield (**2e–2g**). Also, the naphthyl group afforded a good yield (**2i**). In the case of electron donating substituent **2h**, a modest yield was achieved. Compared to **2j**, the more sterically hindered **2b** provided a lower yield, suggesting that sterics played a role. However, the aliphatic substrate gave a much lower yield for this reaction (**2k**). Also, the homoallylic oxime was found to be viable for this reaction giving a good yield of 5,6-dihydro-4*H*-1,2-oxazine derivative (**2l**). This is a significant step towards broadening the scope of this reaction; owing to the fact that oxazines are also known to be a highly desirable class of heterocycles. The 7 or 8 membered-ring analogs could not be observed under the reported reaction conditions.

Furthermore, a series of diazonium salts were investigated (Scheme 3); electron poor aryl diazonium salts could also be

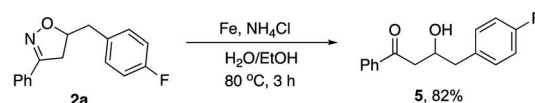


Scheme 3 Substrate scope for diazonium salt. General reaction conditions: **1a** (0.33 mmol), [Au] (0.025 mmol), diazonium salt (0.66 mmol), and base (1.65 mmol) in CH₃CN (0.4 M), 60 °C; isolated yield.

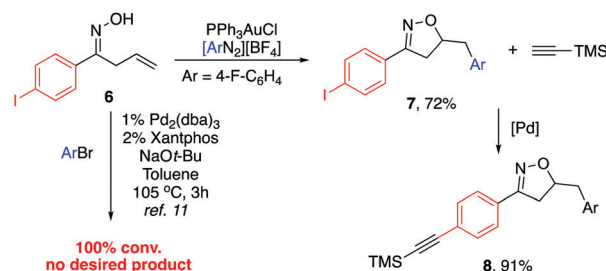
enlisted, giving the desired products in high yields (**4a–h**). The iodo-substituted diazonium salt **4e** was also successfully applied with modest yield. This result highlights the orthogonal reactivity under gold catalysis, compared with previously reported Pd catalysis conditions. However, electron rich diazonium salts failed to give the desired product due to the instability of the diazonium species.

Although the substituted isoxazolines are in themselves useful compounds, we carried out their reduction to the corresponding hydroxyl ketones (Scheme 4a). Isoxazoline **2a** was subjected to reductive N–O bond cleavage followed by subsequent hydrolysis of the resulting imine. This reductive ring opening was achieved with up to 82% yield. To further demonstrate the synthetic utility, we synthesized the *p*-iodo substituted aromatic substrate **6**, which was further subjected to our reaction conditions. The desired isoxazoline **7** was obtained with 72% yield (Scheme 4b). Notably, when treating **6** under previously reported Pd-catalyzed conditions, no desired product was observed with 100% conversion. The fast oxidative addition of the C–I bond led to the side reaction pathway. This result clearly indicated the orthogonal catalytic reactivity between Pd and Au. The following Sonogashira

a) Reduction of Isoxazoline



b) orthogonal reactivity



Scheme 4 Isoxazoline reactivity.

reaction of 7 afforded alkyne substituted aromatic isoxazoline 8, allowing an extended synthetic handle.

In conclusion, gold-redox chemistry has been applied for the cyclization/functionalization of allylic oximes in the presence of aryl diazonium salts. This transformation gives access to aryl functionalized 2-isoxazolines in good to excellent yields. Moreover, we believe that the apparent compatibility of Au redox chemistry with oximes will provide an alternate route towards the synthesis of isoxazoline derivatives.

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Conflicts of interest

There are no conflicts to declare.

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