

Synergistic Gold and Iron Dual Catalysis: Preferred Radical Addition toward Vinyl–Gold Intermediate over Alkene

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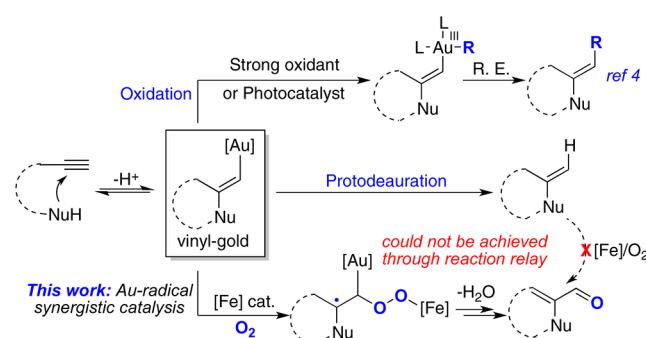
S Supporting Information

ABSTRACT: A dual catalytic approach enlisting gold and iron synergy is described. This method offers readily access to substituted heterocycle aldehydes via oxygen radical addition to vinyl–gold intermediates under Fe catalyst assistance. This system shows good functional group compatibility for the generation of substituted oxazole, indole, and benzofuran aldehydes. Mechanistic evidence greatly supports selective radical addition to an activated vinyl–Au double bond over alkene. This unique discovery offers a new avenue with great potential to further extend the synthetic power and versatility of gold catalysis.

During the past decade, gold complexes have been proven to be one of the most effective catalysts for alkyne activation. In many cases, vinyl–gold complexes are recognized as key intermediates through inter- or intramolecular nucleophilic addition toward alkyne–gold π -complexes.¹ Thus, understanding vinyl–gold complex reactivity is crucial for new reaction discovery.² One of the general reaction pathways of vinyl–gold intermediates is the protodeauration, converting a C–Au bond into C–H bond.³ To further expand the scope, efforts have been made by various research groups in searching for new reactivity of vinyl–Au complexes. One exciting recent breakthrough was the discovery of Au(I)/Au(III) redox cycle originated from vinyl–gold intermediates. Based on this new reaction mode, several new transformations have been achieved through gold-catalyzed alkyne activation followed by vinyl–gold oxidative coupling (under either external oxidants or photocatalytic conditions, Scheme 1).⁴ It is clear that uncovering new reactivity of vinyl–gold complexes will benefit new transformation discovery. Herein, we report the synergistic Au/Fe catalysis as a new strategy to transform vinyl–gold intermediates by iron–oxygen radical addition.⁵

Regarding the combination of gold catalysis and radical chemistry, there are two typical reaction scenarios: (A) reaction relay (sequential alkyne activation and radical addition to alkene) and (B) synergistic catalysis (selective radical addition to vinyl gold over alkene). In theory, synergistic catalysis would facilitate new transformations that could not be achieved through simple stepwise reaction relay. This is particularly important for reactions involving slow protodeauration step. The key concerns were compatibility and orthogonal reactivity of the two catalytic systems. To explore the possibility of this new gold/radical

Scheme 1. Vinyl–Gold As Crucial Intermediates in Gold Catalysis



synergistic catalysis, we selected the gold-catalyzed propargyl amide cyclization as the model reaction.⁶

As shown in Figure 1, gold catalyst promotes the 5-*exo*-dig cyclization of alkyne amide **1a** under mild conditions. The alkene

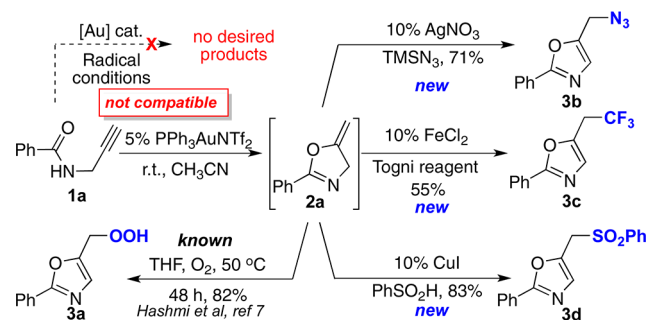


Figure 1. Gold catalysis and radical reaction relay.

product **2a** can be isolated. Hashmi et al. reported the oxidation of **2a** by molecular oxygen over time to give oxazole peroxide **3a**.⁷

To test the reaction compatibility with gold catalyst, we explored reactions of alkene **2a** with various radical species. As shown in Figure 1, new and mild radical conditions were developed for access to synthetically attractive oxazole derivatives, including azide (**3b**), CF₃ (**3c**), and sulfone (**3d**).⁸ Notably, oxazole derivatives are very important building blocks in medicinal and biological research, and these new strategies

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offered practical and efficient ways to synthesize this class of compounds.⁹ However, direct treatment of **1a** with the combination of gold catalyst and these newly developed radical conditions gave complex reaction mixtures with no desired product observed. Clearly, the compatibility between gold catalyst and radical conditions is one crucial challenge for the development of the proposed synergistic catalysis.

The recent successes in photocatalyst promoted gold redox chemistry suggested good compatibility between gold complexes and photocatalysts.¹⁰ Inspired by those results, we tested the reactivity of **1a** with the combination of gold and photo catalysts under 1 atm O₂. Interestingly, as shown in Figure 2A, besides the

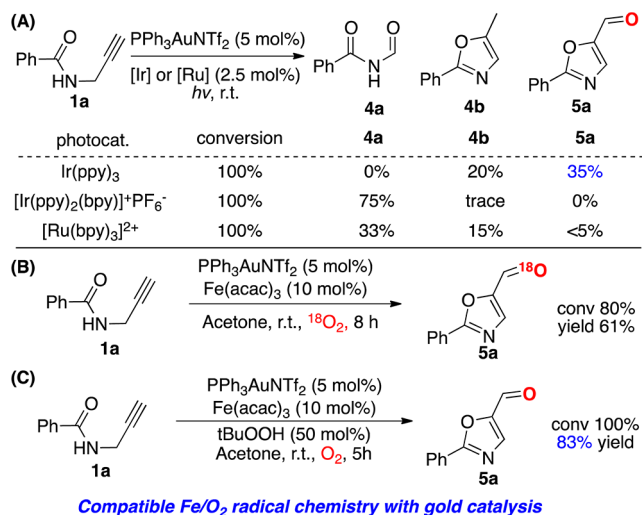


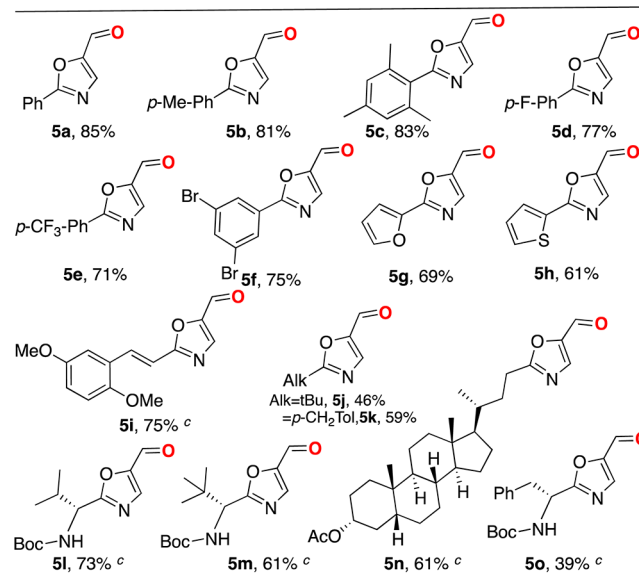
Figure 2. Fe/O₂ as compatible conditions with gold catalysis.

ring opening product **4a** and aromatization product **4b**, the oxazole-aldehyde **5a** was obtained, albeit in low yield. These results suggested good compatibility of oxygen radical with gold catalyst. To improve the reaction performance, we directed our attention toward searching for other oxygen radical initiation conditions.¹¹ As shown in Figure 2B, Fe(acac)₃ was identified as the optimal catalyst (see detailed screening conditions in SI), which promoted the oxidation of **1a** to oxazole-aldehyde **5a** (80% conversion and 61% yield) simply with 1 atm molecular oxygen at room temperature. In addition, ¹⁸O-labeled experiment confirmed that the aldehyde oxygen was originated from O₂. Finally, addition of 50% *t*BuOOH helped the reaction to reach completion, giving **5a** in 83% isolated yield, which highlighted the great compatibility of the Fe/O₂ radical conditions with gold catalysis (Figure 2C).

Various alkyne-amides **1** were prepared to evaluate the reaction scope. The results are summarized in Table 1.

Good substrate compatibility was observed with this new dual-catalytic system. First, substrates with EWGs and EDGs in the benzene ring on compound **1** all furnished the oxazole aldehyde in good yields (**5a–5f**). Heteroaromatic substrates (**5g**, **5h**) and aliphatic substituted propargyl amides (**5i**, **5j**) also worked well. Notably, this reaction proceeded well with high efficiency and selectivity even with α,β -unsaturated amide (**5i**). Moreover, to further evaluate the synthetic utility and generality of this system, we subjected natural amino acid derivatives (**5l**, **5m**, **5o**) and bioactive molecule (**5n**) to this system. The desired oxazoles were obtained with good to excellent yields, further highlighting the generality and great potential of this new catalytic system.

Table 1. Reaction Scope for Synthesis of Oxazole Aldehydes^a



^aGeneral reaction conditions: **1** (0.2 mmol), PPh₃AuNTf₂ (5 mol %), Fe(acac)₃ (10 mol %), *t*BuOOH (50 mol %) in acetone (0.4 M) with O₂ balloon, rt. ^bIsolated yield. ^cWith ditBuXphosAuNTf₂ (5 mol %), EtOAc (0.4 M), 50 °C, 5 h.

To explore whether this transformation went through synergistic catalysis or stepwise reaction relay, we monitored the reaction kinetics under various conditions using NMR (¹H and ¹⁹F).

As shown in Figure 3, interesting reaction kinetics was observed. In the reaction of **1e** to **5e** with the combination of gold

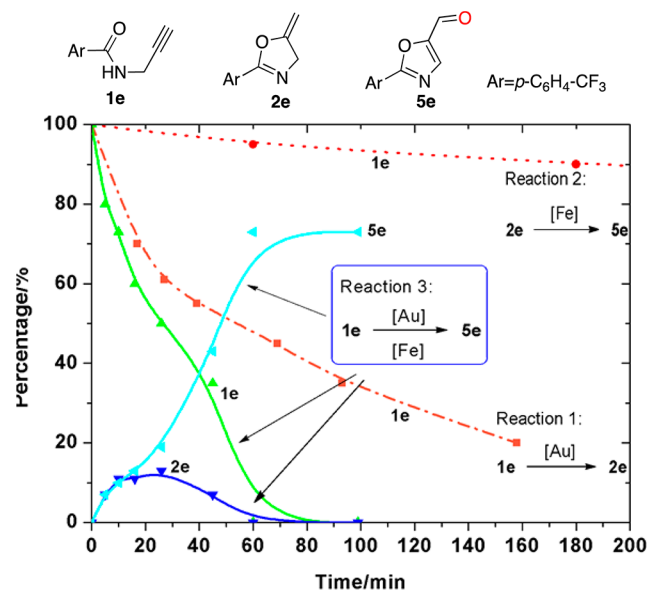


Figure 3. Reaction kinetic profiles under various conditions (see detailed reaction conditions in SI).

and iron catalysts (reaction 3), a faster rate was seen than either the Fe/O₂ promoted oxidation of **2e** to **5e** (reaction 2) or the gold-catalyzed cyclization of **1e** to **2e** (reaction 1). The oxidation of **2e** to aldehyde **5e** showed a more dramatic decrease in reaction rate (more than 48 h) compared to the combined catalysis (see full reaction kinetic in SI). This insight strongly

ruled out the possibility of a stepwise catalytic relay under the reaction conditions. To explore the identity of reaction intermediates, we attempted to isolate L–Au–vinyl intermediates. Notably, it has been reported in literature that PPh_3Au –vinyl complex was unstable at room temperature and could not be isolated. Thus, more stable IPrAu –vinyl complex was prepared and subjected to Fe/O_2 catalytic system.¹²

As shown in Figure 4, reaction of **1e** with $[\text{IPrAu}]^+$ and $[\text{Fe}]/\text{O}_2$ in catalytic fashion gave the desired aldehyde in poor yield

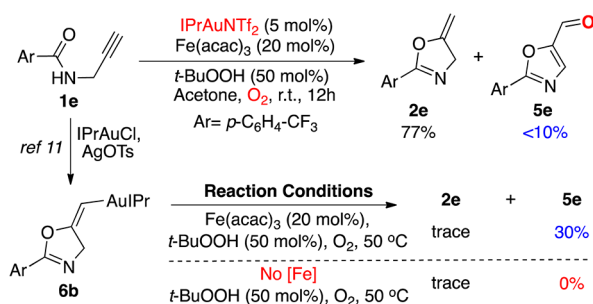


Figure 4. Mechanistic investigation.

(<10%). In contrast, reaction of vinyl–gold **6b** with Fe/O_2 under the standard condition gave the desired aldehyde **5e** in a better yield. This result strongly suggested that the vinyl–gold was the active reaction intermediate and that a synergistic dual catalysis was occurring. Treating **6b** with $t\text{BuOOH}$ alone (without iron catalyst) gave no aldehyde **5e**, which confirmed the importance of iron catalyst in promoting the oxygen radical reaction toward vinyl–gold. Moreover, addition of 1 equiv TEMPO in the reaction mixture quenched the reaction completely, which was consistent with the proposed radical mechanism. All evidence strongly suggested the iron-activated oxygen radical addition to vinyl gold as the key step in this dual catalytic transformation.

With this synergistic catalysis mechanism revealed, we put our attention into the evaluation of more challenging cyclization. As shown in Figure 5, gold-catalyzed *5-exo-dig* cyclization should be a good strategy for the preparation of substituted indole and benzofuran.¹³ However, these transformations generally proceeded poorly, making the overall strategy impractical.¹⁴

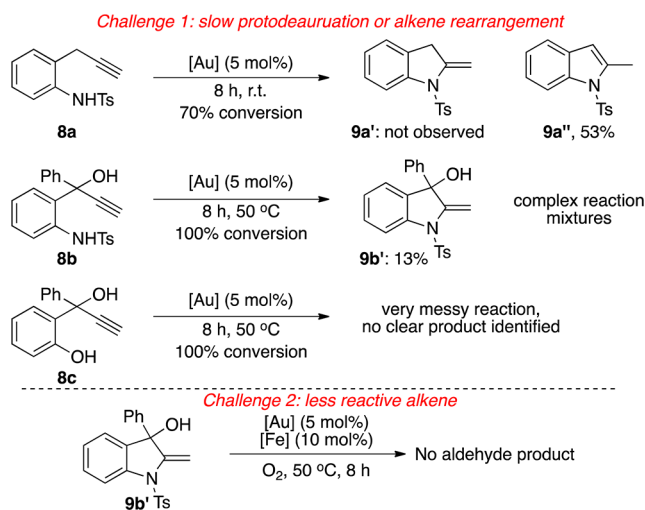


Figure 5. Challenges in gold-catalyzed cyclization.

The major challenge for this synthetic route was the slow protodeauration, which led to the poor yields of the cyclization products. In addition, some alkene products were not reactive enough to be oxidized by the Fe/O_2 condition. For example, charging **9b'** with Fe/O_2 gave no desired product even with extended reaction time or at elevated temperature. To our great satisfaction, these challenges were simply overcome by this new synergistic catalytic system. As shown in Figure 6, charging **8b**

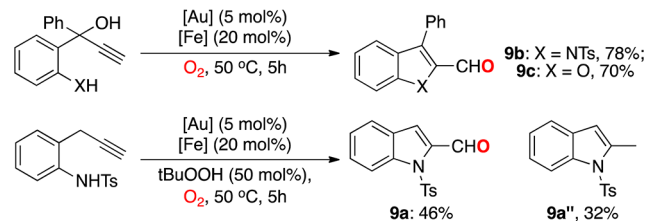
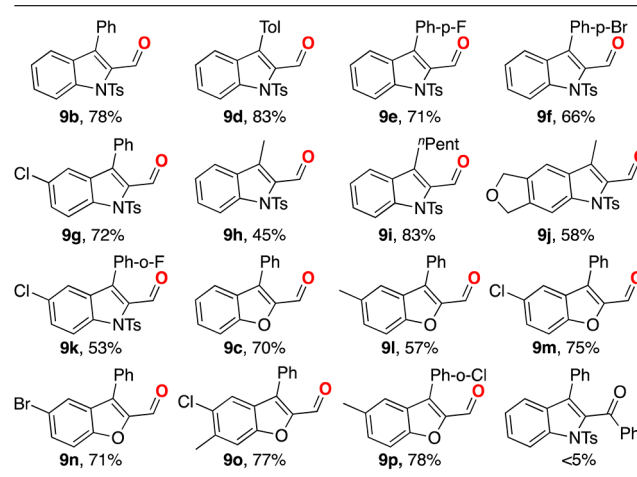


Figure 6. Achieving cyclization via synergistic catalysis.

and **8c** with the combined gold and iron catalyst gave the desired aldehydes in good yields under mild conditions with only 1 atm O_2 . Reaction of **8a** under the dual catalytic conditions gave aldehyde **9a** in 46% yield along with indole **9a''** (32%), suggesting the fast double rearrangement. Various propargyl alcohols were then prepared to verify the reaction scope. The results are summarized in Table 2.

Table 2. Reaction Scope for Synergistic Catalysis^{a,b}



^aGeneral conditions for indole aldehyde synthesis: **8** (0.2 mmol), ditBuXphosAu(CH_3CN)SbF₆ (5 mol %), FeCl_2 (10 mol %) in EtOAc (0.4 M) with O_2 balloon, 50 °C, 5h. General conditions for benzofuran aldehyde synthesis: **8** (0.2 mmol), JackiephosAuNTf₂ (3 mol %), FeCl_2 (10 mol %) in 1,4-dioxane (0.4 M) with O_2 balloon, 50 °C, 5h. ^bIsolated yield.

Again, this dual catalytic system indicated good substrate compatibility. Various indole and benzofuran aldehydes were prepared in good yields directly from alkyne **8**. Both electron-rich (**9d**, **9l**) and electron-deficient (**9e–9g**, **9k**, **9m**, **9n**, **9p**) substituents were suitable for this transformation. Halogen functional groups (**9f**, **9n**) were also tolerated, which may offer a potential synthetic handle for further functionalization. The aliphatic substituents (**9h–9j**) were also compatible in this reaction, giving the desired products. Substrates with internal alkyne did not work under the standard conditions with starting material recovered.

Although the exact mechanism of the Fe/O₂ radical addition step is uncertain at this moment (detailed investigation is current undergoing), the observed results are consistent with the proposed oxygen radical addition toward vinyl–gold. First, addition of oxygen radical to vinyl–gold will form a new reactive species that may help gold catalyst turnover (overcome slow protodeauration). Second, with 10 d-electrons, Au(I) cation can donate an electron toward the C=C double bond. Thus, the π bond in vinyl–gold complex has a higher electron density than the π bond in alkene. As a result, vinyl–gold will be more reactive toward electron-deficient oxygen radical.¹⁵ Overall, the success of achieving these challenging transformations not only provided a highly efficient and economical approach (the only waste is water) to prepare substituted indole and benzofuran but also demonstrated the synergistic catalysis of gold and radical chemistry, which would enhance the versatility of gold catalysis.

In summary, we report herein a successful example of selective radical addition to vinyl–gold as a new general strategy for synergistic gold-radical catalysis. This chemistry allows vinyl–gold as the reactive intermediate to successfully bypass protodeauration. As a result, new transformations, which previously could not be achieved through stepwise reaction relay, were successfully achieved. Applications of this new reaction concept for other challenging transformations are currently undergoing.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, and NMR spectra. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b05415.

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Notes

The authors declare no competing financial interest.

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- (14) With ditBuXphosAu(CH₃CN)SbF₆ (5 mol%) in CH₃CN, the yield of cyclized alkene **9b'** is only 14%. However, with ditBuXphosAu(CH₃CN)SbF₆ (5 mol%) and FeCl₂ (10 mol%) in DMSO, the reaction got 90% yield of alkene **9b'**. See detailed information in SI.

- (15) Based on the experimental results, a proposed reaction mechanism is provided in SI.