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Alkyne Trifunctionalization via Divergent Gold Catalysis: Combining π -Acid Activation, Vinyl–Gold Addition, and Redox Catalysis

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ABSTRACT: Here we report the first example of alkyne trifunctionalization through simultaneous construction of C–C, C–O, and C–N bonds via gold catalysis. With the assistance of a γ -keto directing group, sequential gold-catalyzed alkyne hydration, vinyl–gold nucleophilic addition, and gold(III) reductive elimination were achieved in one pot. Diazonium salts were identified as both electrophiles (N source) and oxidants (C source). Vinyl–gold(III) intermediates were revealed as effective nucleophiles toward diazonium, facilitating nucleophilic addition and reductive elimination with high efficiency. The rather comprehensive reaction sequence was achieved with excellent yields (up to 95%) and broad scope (>50 examples) under mild conditions (room temperature or 40 °C).

INTRODUCTION

Alkynes represent an important group of compounds in chemical synthesis.^{1–6} Over the past decade, alkyne functionalization has gained increasing attention for easy access to complicated molecular scaffolds.^{3,7–10} Although alkyne difunctionalization is more commonly reported, its trifunctionalization has been rare.¹¹ Among the reported examples, rigorous degassing or harsh reaction conditions are generally required, which limits the application of these methods.¹² Moreover, previous literature mainly focused on C–O and C–X bond formation. Therefore, an efficient and practically useful approach for alkyne trifunctionalization is highly desirable.

Throughout the first two decades of this century, gold catalysis has enjoyed the spotlight of organometallic chemistry, mainly due to its exceptional ability to activate alkynes and allenes under mild conditions.^{13–17} The nucleophilic addition toward an alkyne–gold π -complex followed by protodeauration has been applied as an efficient strategy in many important chemical transformations (Scheme1A, paths A and B).^{1,18–22} Recently, with the joint efforts from numerous groups around the world, gold redox

chemistry has gained increasing attention for its unique reactivity, arguably opening a new era of homogeneous gold catalysis.^{23–28} The combination of π -activation and redox chemistry will intrinsically initiate new strategies for efficient and versatile transformations.

With the high oxidation potential between Au^I and Au^{III} (1.4 eV), strong oxidants are usually required in gold redox chemistry, leading to incompatibility with many nucleophiles for gold-activated alkynes.^{29–37} Moreover, protodeauration has been a serious problem for any subsequent transformations using intermediates containing C–Au bonds.^{38–41} Therefore, limited success was achieved combining gold π -activation and redox catalysis.^{42–49} On the other hand, the good electron-donating ability of gold cation toward C==C bond renders vinyl–gold a potentially good nucleophile,

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Scheme 1. Representative Reaction Paths in Gold Catalysis



provided that protodeauration could be prevented. Although few examples have been reported so far, nucleophilic addition of vinyl gold provides an interesting new reaction path that further enriches the versatile reactivity of gold catalysis.^{50–55} Clearly, the possibility of integrating all three gold reaction modes (π -activation, redox catalysis, and vinyl gold nucleophilic addition) is not only mechanistically fascinating but also practically appealing, featuring multiple functionalizations in one step. Herein, we report the concurrent construction of C-O, C-N, and C-C bonds from unactivated alkynes through the divergent gold catalysis. To the best of our knowledge, this is the first example of a transformation that successfully combines three gold reaction modes in a single step. The alkyne trifunctionalization products were obtained with high efficiency (up to 95%) and broad substrate scope (>50 examples) under mild conditions (Scheme 1B).

RESULTS AND DISCUSSION

Reaction Development. To achieve the integration of multiple gold reactivities, the compatibility of vinyl–gold nucleophilic addition (path C) is the most crucial factor. Because of the competing protodeauration, successful vinyl–gold nucleophilic addition examples are extremely rare in the literature, especially in a catalytic fashion. Recently, with the introduction of the γ -keto directing group (DG), our group reported the first intermolecular crossed aldol reaction using synergistic gold/iron catalysis (Figure 1A, room temperature, open air, neutral solution).⁵⁵ Fe(acac)₃ was identified as the critical cocatalyst to effectively prevent C–Au bond from protodeauration. The γ -keto directing group is also crucial as the reaction of phenylacetylene gave only hydration product **3a**' under identical conditions with no aldol product **2a**' observed.

Encouraged by this result, we set our goal to explore the possibility of integrating vinyl-gold chemistry with gold redox catalysis by conducting reactions of **1a** and benzaldehyde under various reported gold redox conditions pubs.acs.org/JACS



Figure 1. Vinyl-gold reactivity toward different electrophiles.

(Figure 1B). Initially, the ligand-assisted aryl iodide oxidative addition protocol, recently reported by Bourissou and Patel,⁵⁶⁻⁶¹ was tested. Unfortunately, the dominant hydration product 3a was obtained with no vinyl gold addition product or reductive elimination product observed. Then photoinitiated diazonium activation was also performed, giving similar results with 3a as the dominant product. Both results highlighted the significance and necessity of preventing the rapid protodeauration to access any valid vinyl-gold reactivity. Interestingly, carefully monitoring the reaction under photocatalytic conditions revealed the formation of a new product 4a though in a very low yield. X-ray diffraction identified the structure of this compound as a result of potential vinyl-gold addition toward diazonium. Notably, the aldehyde addition product 2a or 2aa was not obtained in all cases with diazonium presented, suggesting that the diazonium salt might be a more reactive electrophile over aldehvde toward vinvl-gold.

To prevent protodeauration, the $Fe(acac)_3$ cocatalyst strategy was applied to the reaction with diazonium salt. Indeed, addition of 10% $Fe(acac)_3$ raised the yield of **4a** to 34%. Unfortunately, $Fe(acac)_3$ quenched the photocatalytic reactivity and gave almost no conversion over time, suggesting its poor compatibility with photopromoted diazonium activation (see the Supporting Information). Our group has recently reported the base-assisted diazonium activation as an alternative approach to achieve gold oxidation.^{62–65} It is expected that conducting the reaction under basic conditions will not only help diazonium activation but also reduce the rate of protodeauration. As expected, addition of Li_2CO_3 (1 equiv) further improved the yield of **4a** to 79% along with formation of **5a** (reductive elimination product) for the first time.

These exploratory studies were inspiring to us in the following aspects: (A) diazonium is a valid electrophile for vinyl-gold addition (new C-N bond formation strategy); (B) the integration of gold redox catalysis is theoretically feasible (formation of 5a). To develop this new reactivity, we first focused our efforts on the vinyl-gold(I) diazonium

addition. Reactions between **1a** and the aryldiazonium salt were screened under various conditions (see details in the Supporting Information). The combination of $(p-CF_3-C_6H_4)_3PAuNTf_2$ catalyst (5%) and 10% Fe(acac)_3 was identified as the optimal condition, giving the desired product **4a** in 88% isolated yields (5% of **3a**). The performance of some alternative conditions is summarized in Table 1.

Table	1.	Optimization	of	Reaction	Conditions ⁴	,в

R ¹ ─═ ↓ 1 ArN₂BF	$= \underbrace{\begin{array}{c} 5\% [L-Au]NTf_2\\ 10\% Fe(acac)_3\\ \underline{1eq Li_2CO_3}\\ 3 eq H_2O, THF \end{array}} O \underbrace{\begin{array}{c} 0\\ R^1 \end{array}$	$\frac{1}{N}$ Ar + $\frac{0}{R^1}$	+ 0 R ¹	Ar └──N-NHAr
Ar=p-CF ₃ -	C ₆ H ₄ r.t., 6 h 4a	3a		5a
entry	variations	4a (%)	3a (%)	5a (%)
1	none $[L = P(p-CF_3-C_6H_4)_3]$	93 (88) ^c	5	n.d.
2	$L = PPh_3$	83	15	n.d.
3	L = JohnPhos	35	60	trace
4	L = IPr	0	80	n.d.
5	$L = P(ArO)_3$	0	93	n.d.
6	$L = PCy_3$	85	12	trace
7	$L = P(p-F-C_6H_4)_3$	90	6	n.d.
8	Na ₂ CO ₃ instead of Li ₂ CO ₃	34	25	10
9	other bases	<5	<5	n.d.
10	1.0 equiv of H ₂ O	80	12	n.d.
11	5.0 equiv of H ₂ O	78	20	n.d.
12	other solvents ^d	<50	>40	<10
13	40 °C or higher	<78	>8	<15

^aStandard conditions: 5% (*p*-CF₃C₆H₄)₃PAuNTf₂, 10% Fe(acac)₃, 3 equiv of water, and 0.2 mmol of Li₂CO₃ were added to a THF solution (0.5 mL) of alkyne **1a** (0.2 mmol) and aryldiazonium salt (0.4 mmol), and the reaction was kept stirring at room temperature for 6 h. ^bConversion and yields were determined by ¹⁹F NMR and ¹H NMR spectroscopy by using trifluorobenzene and 1,3,5-trimethoxybenzene correspondingly as internal standard. ^cIsolated yield. ^dSee the Supporting Information.

As shown in Table 1, the primary ligand on gold plays a pivotal role with $P(p-CF_3-C_6H_4)_3AuNTf_2$ giving the best yield, suggesting the balance of electron density on gold is critical (entries 1–7). The $[L-Au-L']^+$ types of catalysts, such as $[LAu(TA)]^+$ and $[LAu(CH_3CN)]^+$, were also tested, giving dominantly hydration product 3a (see the Supporting Information). The choice of base was also proved to be vital. While Li2CO3 was the optimal base, Na2CO3 gave significantly reduced yield of 4a (entry 8), presumably due to the reaction with [Fe] cocatalyst under stronger basic conditions. Some alternative organic and inorganic bases were also tested but gave poor performance (see the Supporting Information). Because the reaction involved both alkyne hydration and vinyl-gold nucleophilic addition, the amount of water should be important to reach the ideal balance between vinyl-gold addition and minimal protodeauration. After screening, 3 equiv of water gave the best result with THF as solvent. Notably, conducting the reaction at elevated temperature (40 $\,^\circ C)$ gave arylhydrazone 5a as the minor product, suggesting the feasibility of the proposed alternative gold redox process (entry 13). With the optimal condition in hand, the substrate scopes of alkynes and aryldiazonium salts were evaluated. The results are summarized in Scheme 2.

An extensive survey of the reaction scope was presented with three variations: diazonium, directing group, and alkyne. pubs.acs.org/JACS

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A series of aryldiazonium salts were prepared as coupling partners with alkyne 1a. In general, the reaction worked well for electron-deficient aryldiazoniums, affording arylhydrazones 4a-4o in good to excellent yields. Electron-rich aryldiazoniums offered <30% yields (4p) due to reduced electrophilicity. Remarkably, with $Fe(acac)_3$ as cocatalyst, the reaction even tolerated weakly acidic functional groups, giving the desired addition product (4i) with little hydration byproducts observed. Variations on γ -keto directing groups have also been evaluated. Most aryl-substituted carbonyl directing groups (DG) are tolerated, giving the desired product in good to excellent yields (4aa-4ai, 4an). The aliphatic carbonyl DG also worked though with slightly reduced yields (4aj, 4ao). Impressively, a variety of substrates containing functional groups, such as cyclopropyl, alkynyl, and allyl groups, gave desired products in good yields (4ak-4am). This result highlighted the mild condition and excellent functional group tolerance of this method.

For many reported gold catalysis, activation of internal alkynes remains a formidable task due to reduced reactivity, especially under mild conditions. In our case, both aryl- and alkyl-substituted internal alkynes provided good to excellent yields (4ba-4bl, 5a). Notably, single regioisomers consistent with the 5-exo-dig activation mechanism were obtained in all cases (no 6-endo-dig products observed). The room temperature activation of internal alkynes highlighted the reactivity boosting effect upon our strategic application of the γ -keto directing group. Similar to our previous observation, extending the keto DG to the δ -position (one extra carbon) led to dramatic reduction of coupling product yield (dominant hydration, see the Supporting Information), emphasizing the choice of the γ -keto directing group in achieving vinyl-gold addition. Having applied the gold/iron dual catalytic system effectively to vinyl-gold diazonium addition, we moved on to the more challenging alkyne trifunctionalization integrating redox catalysis.

As shown in Scheme 1A, the alkyne trifunctionalization can be achieved from two slightly different reaction sequences: (1) vinyl-Au^I oxidation to [vinyl-Au^{III}-aryl] followed by reductive elimination and (2) in situ formation of [Ar-Au^{III}] π -acid for alkyne activation followed by reductive elimination.⁶⁶ Although the former strategy is extremely attractive for rapid, simultaneous bond construction, to the best of our knowledge, no catalytic reaction through this path has been realized yet, likely due to various competing side reactions. The vinyl-gold addition to diazonium shown above provided a good platform to explore this new transformation since diazonium could serve as potential oxidant for gold redox chemistry under proper conditions. Very recently, Hashmi's group reported an interesting example of vinyl-gold addition to diazonium for the formation of the C-N bond, which strongly supported this hypothesis.⁶⁷ However, there are two major mechanistic concerns: (A) protodeauration remains the key challenge for any reaction sequence involving Au-C bond, and (B) gold(III) reductive elimination is a fast process due to its high redox potential. On the basis of this analysis, we proposed that in situ formation of [Ar-Au^{III}] for alkyne activation is preferred in a practical sense for alkyne trifunctionalization. To testify this idea, L-AuI-Cl type catalysts were used to react with diazonium salts with the hope to generate active [Au^{III}-Ar] prior to alkyne activation. After tuning several typical reaction parameters, the trifunctionalization product 5a was obtained in excellent

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Scheme 2. Reaction Scope of Difunctionalization^{*a,b*}

Diazonium scope

^aStandard conditions: 5% (p-CF₃-C₆H₄)₃PAuNTf₂, 10% Fe(acac)₃, 3 equiv of water, and 0.2 mmol of Li₂CO₃ were added to a THF solution (0.5 mL) of alkyne 1a (0.2 mmol) and aryldiazonium salt (0.4 mmol), and the reaction was running at room temperature for 6 h. ^bIsolated yields. ^c40 °C.

yields (94% isolated yields) with Cy₃PAuCl as catalyst and 3.0 equiv of diazonium salt under basic conditions (2 equiv of Li₂CO₃) at 40 °C. Results from typical alternative conditions are shown in Table 2 (see detailed screening conditions in the Supporting Information).

First, the typical photocatalytic diazonium activation was not suitable for this transformation (entry 2), forming dominatly ketone 3a as the hydration product. Second, our previously developed base-promoted conditions for thermal activation of diazonium proved essential in this transformation. While Cy₃PAuCl appeared to be the optimal catalyst (entries 3-7), the choice of solvent, base, and amount of water also had huge impacts on the reaction

performance (see detailed screening in the Supporting Information). Higher reaction temperature (>50 °C) significantly raised the hydration rate. Nevertheless, under the optimal condition, the trifunctionalization of alkyne was successfully achieved with high efficiency. Based on this optimal condition, the reaction scope was explored. The results are summarized in Scheme 3.

The reaction scope was also evaluated through three variations: diazonium salts, directing groups, and internal alkynes. A variety of aryldiazonium salts were tested as reaction partner with alkyne 1a. Compared to alkyne difunctionalization, this reaction exhibited a broader scope presumably owing to the higher reactivity of vinyl-gold(III)

Table 2. Alkyne	Trifunctionalization	with	Gold	Redox
Catalysis ^{a,b}				

R ¹	$\begin{array}{c} 5\% \ {\rm Cy_3PhAuCl} \\ \underline{2 \ eq. \ Li_2CO_3} \\ 1 \ eq \ H_2O \\ MeCN, \ 40 \ ^oC \\ Ar=p-CF_3-C_6H_4 \end{array} \xrightarrow{\ \ N} \begin{array}{c} {\rm NHAr} \\ R^{\dagger} \\ O \\ {\rm Same } \\ {\rm Sam$	x ray c	↔ f 5a
entry	variation	5a (%)	3a (%)
1	none	95 (94)	2
2	no Li ₂ CO ₃ , Ru(bpy) ₃ PF ₆ , blue LED	0	48
3	PPh ₃ AuCl	90	7
4	JohnPhosAuCl	trace	35
5	IPrAuCl	10	50
6	(ArO) ₃ PAuCl	0	0
7	(4-CF ₃ C ₆ H ₄) ₃ AuCl	85	12
8	3.0 equiv of H ₂ O	88	8
9	other solvents ^c	<89	>8
10	Na ₂ CO ₃ instead of Li ₂ CO ₃	30	15
11	other bases ^c	<10	<15
12	50 °C or higher	<67	>20

^aStandard conditions: 5% Cy₃PAuCl, 1 equiv of water, and 0.4 mmol of Li₂CO₃ were added to a MeCN solution (0.6 mL) of alkyne 1a (0.2 mmol) and aryldiazonium salt (0.6 mmol), and reaction was running at 40 °C for 3 h. ^bConversion and yields were determined by ¹⁹F NMR and ¹H NMR spectroscopy using trifluorobenzene and 1,3,5-trimethoxybenzene correspondingly as internal standard. ^cSee the Supporting Information.

intermediates. In general, the reaction worked well for both electron-deficient and electron-rich aryldiazonium salts. The reaction of electron-deficient diazonium salts afforded arylhydrazones 5a-5i with good to excellent yields while the electron-rich diazonium salt gave a moderate yield (5j). Interestingly, ortho- and meta-substituted aryldiazonium salts, which were unsatisfactory substrates in the base-promoted gold-redox process, worked well in this transformation (5k-5n). Disubstitued aryldiazonium salts also exhibit decent reactivity (50-5r). Furthermore, substrates with diverse γ carbonyl DG including both aryl (including heterocycles) and aliphatic substituents displayed good to excellent yields (5aa-5an). Notably, although Ar-Au^{III} is a superior π -acid which can activate alkenes, great chemoselectivity was observed with carbon-carbon double bond remaining intact in this transformation (5al). Some other functional groups such as cyclopropyl and alkynyl also survived under the reaction condition, exemplifying mildness and robustness of this transformation. Significantly, when treating internal alkynes with aryldiazonium 1a, azo compounds containing a quaternary carbon center were formed (5ba-5bq). The electron-deficient aryl-substituted internal alkynes dominantly went through 5-exo-dig cyclization, providing azo compounds in good to excellent yields (5ba-5bg, 5bj-5bm). In contrast, less electron-deficient aryl-substituted internal alkynes afforded azo products in slightly reduced yields as 5:1 and 3.5:1 regioisomers (1,4-diketones from 5-exo addition vs 1,5diketones from 6-endo addition), respectively (5bh and 5bi). The electron-rich aryl-substituted internal alkyne (5bo) gave exclusively 1,5-diketone in a good yield. Impressively, internal alkynes with cyclic ketone directing group reacted with diazonium salts, giving the desired product 5bq in modest yield but with good diastereoselectivity. This result featured stereoselectivity improvement of vinyl gold nucleophilic addition by the 5-exocyclization mechanism besides the

aforementioned "boosting effect". On the other hand, the low diastereoselectivity of product **Sbp** was likely an outcome of α -carbon epimerization.

Mechanistic Studies and Functional Group Conversions. Under photochemical (blue LED) or thermal conditions, arylgold(III) species were formed by treating aryldiazonium with the gold(I) chloride complex.^{66,68} To gain more mechanistic insight, we monitored the reaction with nESI-MS (Figure 2A). Diagnostic signals of $[Au^{III}-Ar]$ catalyst and key intermediates **A** and **B** were all successfully captured, whereas their structure compositions confirmed by CID (MS-MS, see details in the Supporting Information). These HRMS results greatly supported the proposed reaction sequence with formation of $[Au^{III}-Ar]$ followed by alkyne π -activation, vinyl–gold nucleophilic addition toward diazonium salts, and finally Au^{III} reductive elimination.

Apart from its mechanistic novelty, the resulting 1,4diketone products contain versatile functional groups, which make them interesting building blocks for complex molecular skeleton construction. It is well-known that 1,4-diketone is a good synthon for the synthesis of hetereocycles through double condensation by reacting with amine or hydrazine.^{69,70} This approach was further confirmed by the example shown in Figure 2B: treating 4a with Lawesson's reagent produces hydrozone-substituted thiophene 6a, a corrector of a mutant cystic fibrosis transmembrane conductance regulator (CFTR), in excellent yield.⁷¹ To explore the synthetic applications of this new method, we put our efforts into exploring new transformations that are uniquely associated with the resulting products from the following three perspectives: (1) selective carbonyl reduction over hydrazone, (2) effective protocol for directing group removal, and (3) selective hydrazone reduction to the N-N bond.

For effective transformations of the resulting products, one practical concern is the selective reduction of ketone (C=O)over C=N and N=N, or vice versa. After exploring multiple typical reduction conditions, we are pleased to identify Pd/ C/H₂ as an optimal condition for selective imine-ketone reduction (5a to 6b, 90%). In addition, NaBH₄ was identified as the optimal reagent for ketone reduction over imine, giving 6c in 93% yields. Interestingly, the resulting diol 6c could be readily coverted into substituted THF 6d, bearing an imine moiety with no hydration. The result greatly enriched good synthetic potential of this method by introducing multiple functional groups in one simple step. Notably, the hydrazones (6a-6d) were all assigned as E isomer based on X-ray single crystals of starting material 5a. Although the γ -ketone directing group is an useful synthetic handle as demonstrated above, it could be more attractive if an effective directing group removal strategy could be developed to further extend the synthetic applications. After extensive condition screening, aqueous HCl (3 N) was identified as the practical condition for γ -ketone dissociation, giving hydrazones (7a-7c) in good to excellent yields. Notably, this method not only gives an effective approach to prepare hydrazones bearing more reactive aldehyde (traditional condensation will not work) but also allows the rapid construction formation of alkyl-aryl hydrazone (7b, 7c), which could be readily converted into the substituted cinnoline 8 by using reported conditions (two steps, high yields). The hydrazones (7b, 7c) were assigned as Z configuration based on the literature reported.⁷²

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Scheme 3. Reaction Scope of Alkyne Trifunctionalization^{*a,b*}



"Standard conditions: 5% Cy₃PAuCl, 1 equiv of water, and 0.4 mmol of Li_2CO_3 were added to a MeCN solution (0.6 mL) of alkyne 1a (0.2 mmol) and aryldiazonium (0.6 mmol), and the reaction was running at 40 °C for 3 h. ^bIsolated yields.

Finally, while the reduction of N–N to NH_2 is a wellstudied process with numerous conditions reported, $^{73-75}$ it is important to develop practical conditions for selective N=N hydrogenation to the N–N single bond with C=O presented. After exploring multiple typical reduction conditions, we are pleased to discover that the azo compounds



Figure 2. Derivatization and proposed mechanism.

bearing tertiary carbon (such as **5ba**, prepared from internal alkynes) could be readily reduced to the N–N single bond product 7d without further reduction of C=O (92%). This example highlights the diverse substitution pattern (two different aryl groups) of the reporting method and provides a practical synthesis of substituted hydrazine and amine derivatives.

CONCLUSION

In summary, we disclosed herein a divergent gold catalysis for alkyne trifunctionalization. The overall sequence combined gold π -activation, vinyl gold nucleophilic addition, and gold(III) reductive elimination. Aryldiazonium salts were identified as the effective electrophile and oxidant. Besides the ability to construct complex molecular motifs within simple steps, this new method demonstrated a new strategy to apply vinyl-Au^{III} as effective nucleophiles for the construction of new bonds. This new design principle of gold catalysis could certainly be applied to other gold-promoted chemical transformations, which is currently under investigation in our lab.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.1c01811.

Experimental procedures, characterization data, and crystallographic data (PDF)

Accession Codes

CCDC 2044472–2044479 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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