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Construction of Heterobimetallic Catalytic Scaffold with a Carbene-Bipyridine Ligand: Gold-Zinc Two-Metal Catalysis for Intermolecular Addition of *O*-Nucleophiles to Non-activated Alkynes

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KEYWORDS: gold catalysis, cooperative catalysis, heterobimetallic complex, nucleophilic addition, DFT calculation

ABSTRACT: A gold(I) complex bearing an imidazo[1,5-*a*]pyridin-3-ylidene ligand with a 2,2'-bipyridine moiety at the C5 position was prepared as a template for constructing heterobimetallic cooperative catalysts. *In situ* generated gold-zinc bimetallic systems enabled intermolecular nucleophilic *anti*-addition of *O*-nucleophiles such as carboxylic acids and phenols toward non-activated internal alkynes. DFT calculations supported the proposed cooperative action of the cationic gold atom and the zinc salt site for activating the alkyne and the carboxylic acid, respectively.

Cationic gold(I) complexes are well known as effective catalysts for nucleophilic additions toward alkynes with excellent turnover efficiency due to their strong Lewis acidic character and high affinity for alkyne π-systems.[1] Despite the versatile utility of gold catalysts, intermolecular nucleophilic additions of weak oxygen-nucleophiles[2] such as carboxylic acids[3] and phenols[4] toward non-activated internal alkynes, which form synthetically valuable enol derivatives with high atom economy, are underdeveloped. As a successful precedent, Nolan and co-workers introduced cationic μ^2-hydroxo-bridged dinuclear gold(I) complexes, which liberate a Lewis acidic cationic gold(I) species and a Brønsted basic hydroxogold(I) complex as components for activating the alkyne and the nucleophile, respectively.[3c,g,4b,d,e] Zhang and co-workers developed gold(I) catalysts coordinated with a phosphine ligand with an amide pendant for hydrocarboxylation of alkynes and proposed that the carboxylic acid is activated through hydrogen-bonding with the amide moiety, directing the *anti*-attack to the gold-bound alkyne.[3b] Regardless of the importance of these contributions, further conceptual advances are demanded for intermolecular *O*-nucleophilic addition to alkynes.

We envisioned that heterobimetallic complexes would be effective catalyst candidates for *O*-nucleophilic addition toward non-activated internal alkynes, expecting cooperative action of the two metal sites for dual activation of electrophiles and nucleophiles as in enzymatic reactions.[5] As a platform for the heterobimetallic cooperative catalysis, we synthesized a rigid imidazo[1,5-*a*]pyridin-3-ylidene ligand[6,7] with a 2,2'-bipyridine moiety at the C5 position and used it for the preparation of a gold(I) carbene complex. The resulting gold complex was converted into heterobimetallic catalysts through *in situ* binding of various hard metals at the bipyridine moiety.[8] The heterobimetallic catalysts thus formed were examined for catalytic activity in the intermolecular addition of *O*-nucleophiles such as carboxylic acids and phenols toward non-activated internal alkynes. Indeed, the catalytic systems showed apparent bimetallic cooperativity with a strong dependence on the nature of the hard metal site, most favoring $Zn(acac)_2$ as a Brønsted base site. DFT calculations supported the proposed cooperative action of the Au-Zn bimetallic catalyst system.

The synthesis of imidazo[1,5-*a*]pyridinium chloride **3a** bearing a bipyridine moiety at the 5-position is outlined in Figure 1. First, Negishi cross-coupling[9] between organozinc species prepared from 2-bromo-6-(diethoxymethyl)pyridine **1** and 5-bromo-2,2'-bipyridine gave terpyridine **2a** in 78% yield. The acetal **2a** was hydrolyzed to an aldehyde and subjected to reductive amination with 2,4,6-trimethylaniline. The *N*-formylation of the resulting amino group with acetic formic anhydride followed by dehydrative cyclization with $POCl_3$ afforded 5-bipyridylimidazo[1,5-*a*]pyridinium chloride **3a** (73% yield over 4 steps from **2a**). Next, the reaction of **3a** with $AuCl\cdot SMe_2$ in the presence of K_2CO_3 in acetone at 60 °C for 3 hours[10] gave, after purification by silica-gel column chromatography, *N*-heterocyclic carbene gold(I) complex **4a** in 82% yield as an air-stable colorless solid. The molecular structure of **4a** was confirmed by single crystal XRD analysis. Similarly, gold(I) complexes with 4-pyridyl or 3-pyridyl pendants (**4b**,**c**) were also synthesized (see Supporting Information).

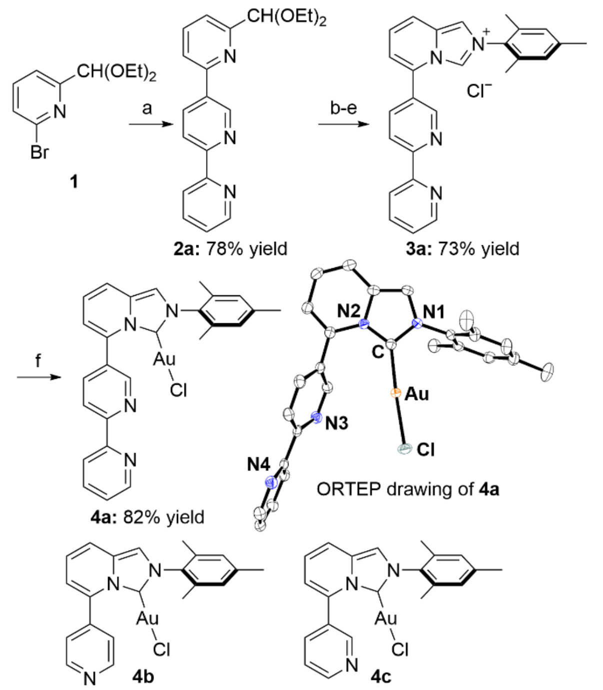
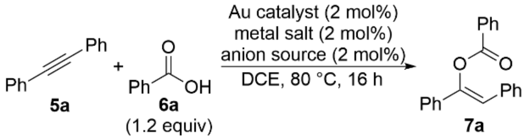


Figure 1. Synthesis of gold complexes **4**. (a) **1** (1.4 equiv), ^{n}BuLi (1.5 equiv), $ZnCl_2$ (1.6 equiv), THF/hexane/Et_2O, -78 °C then 5-bromo-2,2'-bipyridine (1 equiv), $Pd(PPh_3)_4$ (5 mol%), THF, reflux, 18 h; (b) **2a** (1 equiv), 1 M HCl aq., acetone, 60 °C, 3 h; (c) 2,4,6-trimethylaniline (1.2 equiv), AcOH (1 equiv), $NaBH(OAc)_3$ (1.5 equiv), DCM, r.t., 14 h; (d) HCOOH (excess), Ac_2O (excess), THF, 0 °C, 3 h; (e) $POCl_3$ (1.3 equiv), toluene, 100 °C, 21 h; (f) **3a** (1.0 equiv), AuCl·SMe_2 (1.0 equiv), K_2CO_3 (2.0 equiv), acetone, 60 °C, 3 h. All hydrogen atoms are omitted for clarity from ORTEP drawing of **4a** showing 50% probability thermal ellipsoids.

We tested the catalytic activity of gold complexes **4** in the hydrocarboxylation of non-activated alkynes. The results are summarized in Table 1. Bimetallic catalysts were prepared *in situ* from **4a**, a hard metal salt, and an anion source. When nucleophilic addition of benzoic acid (**6a**) toward diphenylacetylene (**5a**) as a non-activated alkyne was conducted with **4a**, $Zn(acac)_2$, and $AgNTf_2$ in 1,2-dichloroethane (DCE) at 80 °C for 16 h, enol ether **7a** was obtained in 61% yield (entry 1). When other acetylacetonato-metal salts such as $Cu(acac)_2$, $Ni(acac)_2$, $Pd(acac)_2$, $Co(acac)_2$, $Fe(acac)_2$, $Mn(acac)_3$, and $Cr(acac)_3$ were examined (entries 2-8), the reaction occurred with decreased yield of **7a** (3–23%). The metal alkoxides such as $Ti(O^{i}Pr)_4$, $Y(O^{i}Pr)_3$, and $Mg(O^{t}Bu)_2$ induced almost no reaction (entries 9–11). Additionally, the gold complex **4a** did not cause the reaction in the absence of the metal salt (entry 12). Hence, the hard metal salt had a significant influence on the catalytic activity of **4a**, with $Zn(acac)_2$ being optimal. In contrast, no reaction was observed with gold complexes (**4b**,**c**) with the monopyridyl pendant (entries 13 and 14), indicating the necessity of chelation, thus supporting the cooperative participation of the zinc site for the gold catalysis. Similarly, the gold carbene complex **8a** with a phenyl substituent at the C5 position and its phosphine variant **8b** showed almost no catalytic activity (entries 15 and 16). The addition of 2,2'-bipyridine to the reaction system with **8a** and **8b**, expecting it to act as an external ligand for zinc, showed little effect, indicating the importance of the proximity of the gold and zinc metals for the two-metal cooperativity (entries 17 and 18).

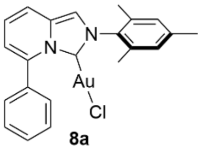
Next, effects of counteranions of the gold complex were investigated. While the replacement of NTf_2^- with BF_4^-, PF_6^-, or SbF_6^- resulted in significant reduction of the product yield (Table 1, entries 19–21), the use of sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate ($NaBAr^F$) as a source of a non-coordinative anion improved the yield to 75% (entry 22). Finally, quantitative yield of **7a** (>99% by ^{1}H NMR analysis, 98% for the isolated product) was obtained by conducting the reaction under high concentration conditions (12 M in DCE) (entry 23). The reaction at a catalyst loading of 0.5 mol% gave **7a** in 80% yield (entry 24). Based on these results, we employed the reaction conditions of entry 23 as the protocol for subsequent experiments exploring the substrate scope.

Table 1. Screening of Reaction Conditions

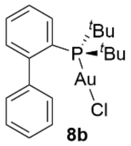


entry	Au catalyst	metal salt	anion source	yield of **7a** [%][a]
1	**4a**	$Zn(acac)_2$	$AgNTf_2$	61
2	**4a**	$Cu(acac)_2$	$AgNTf_2$	18
3	**4a**	$Ni(acac)_2$	$AgNTf_2$	8
4	**4a**	$Pd(acac)_2$	$AgNTf_2$	23
5	**4a**	$Co(acac)_2$	$AgNTf_2$	17
6	**4a**	$Fe(acac)_2$	$AgNTf_2$	3
7	**4a**	$Mn(acac)_3$	$AgNTf_2$	12
8	**4a**	$Cr(acac)_3$	$AgNTf_2$	6
9	**4a**	$Ti(O^{i}Pr)_4$	$AgNTf_2$	2
10	**4a**	$Y(O^{i}Pr)_3$	$AgNTf_2$	1
11	**4a**	$Mg(O^{t}Bu)_2$	$AgNTf_2$	4
12	**4a**	none	$AgNTf_2$	N.D.
13	**4b**	$Zn(acac)_2$	$AgNTf_2$	N.D.
14	**4c**	$Zn(acac)_2$	$AgNTf_2$	N.D.
15	**8a**	$Zn(acac)_2$	$AgNTf_2$	trace
16	**8b**	$Zn(acac)_2$	$AgNTf_2$	trace
17[b]	**8a**	$Zn(acac)_2$	$AgNTf_2$	2
18[b]	**8b**	$Zn(acac)_2$	$AgNTf_2$	1
19	**4a**	$Zn(acac)_2$	$AgBF_4$	23
20	**4a**	$Zn(acac)_2$	$AgPF_6$	40
21	**4a**	$Zn(acac)_2$	$AgSbF_6$	26
22	**4a**	$Zn(acac)_2$	$NaBAr^F$	75
23[c]	**4a**	$Zn(acac)_2$	$NaBAr^F$	>99 (98)[d]
24[c,e]	**4a**	$Zn(acac)_2$	$NaBAr^F$	80

Au catalyst (2 mol%), metal salt (2 mol%), anion source (2 mol%), **5a** (0.10 mmol) and **6a** (0.12 mmol) in DCE (0.1 mL, 1 M). [a]Determined by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard. [b]2 mol% of 2,2'-bipyridine was added. [c]**5a** (0.4 mmol) and **6a** (0.48 mmol) in DCE (33 μL, 12 M). [d]Isolated yield. [e]0.5 mol% of **4a**, $Zn(acac)_2$, and $NaBAr^F$ were used. N.D. = not detected.



8a

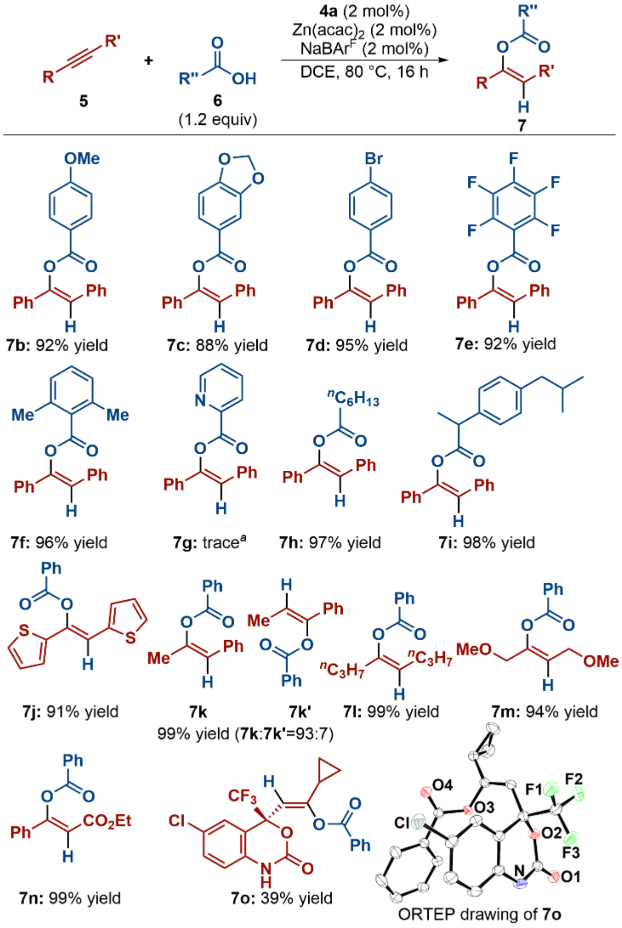


8b

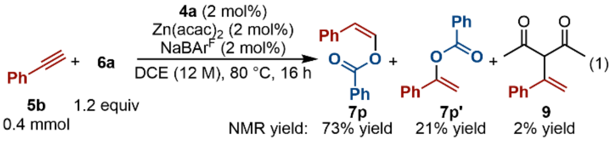
The scope of carboxylic acids and alkynes is summarized in Scheme 1.[11] Electron-donating substituents such as methoxy and methylenedioxy groups on the benzoic acid were compatible with the protocol. The corresponding enol esters **7b** and **7c** were obtained in 92% and 88% yields, respectively. Electron-withdrawing substitutions as in 4-bromo and 2,3,4,5,6-pentafluorobenzoic acids were also compatible, affording **7d** and **7e** in 95% and 92% yields, respectively. The reaction with sterically demanding 2,6-dimethylbenzoic acid gave product **7f** in 96% yield. Pyridine-2-carboxylic acid was nearly unreactive probably due to the inhibitory effect of pyridyl *N*-coordination toward zinc or gold. Aliphatic carboxylic acids, heptanoic acid and ibuprofen, were also competent substrates to give **7h** and **7i** in 97% and 98% yields, respectively. The scope of alkynes was investigated for the reaction with benzoic acid (**6a**). The addition of **6a** to 1,2-di(thiophen-2-yl)ethyne proceeded smoothly, giving **7j** in 91% yield. An unsymmetrical alkyne, 1-phenyl-1-propyne, was transformed to an isomeric mixture in 99% yield (**7k**/**7k'** 93:7). The protocol was applicable to other internal alkynes such as 4-octyne, 1,4-dimethoxy-2-butyne, and ethyl phenylpropiolate, affording *anti*-addition products **7l**, **7m**, and **7n** in 99%, 94%, and 99% yields, respectively. Excellent functional group tolerance of the protocol was demonstrated in the reaction with Efavirenz, a non-nucleoside reverse transcriptase inhibitor, which afforded **7o** in 39% yield as a single constitutional/geometrical isomer. The moderate yield of **7o** was due to a partial conversion of Efavirenz. The molecular structure of **7o** was unambiguously confirmed by single-crystal XRD analysis.

We also investigated the effect of the present gold-zinc heterobimetallic catalyst system toward the reaction of a terminal alkyne, phenylacetylene (**5b**), and benzoic acid (**6a**) as model substrates (eq. 1). Interestingly, when the protocol for the internal alkynes was applied to this reaction, an *anti*-Markovnikov addition product with *Z*-configuration was obtained as the major product in 73% yield (**7p**) along with a Markovnikov addition product (**7p'**, 21% yield) and a product of Markovnikov addition of acetylacetone (**9**, 2% yield). This regioselectivity favoring *anti*-Markovnikov addition contrasts with the reported carboxylation with the PPh_3-AuCl/$AgPF_6$ catalyst system.[3a] This interesting regioselectivity is an issue for further investigation.[12]

Scheme 1. Nucleophilic Addition of Carboxylic Acids to Alkynes



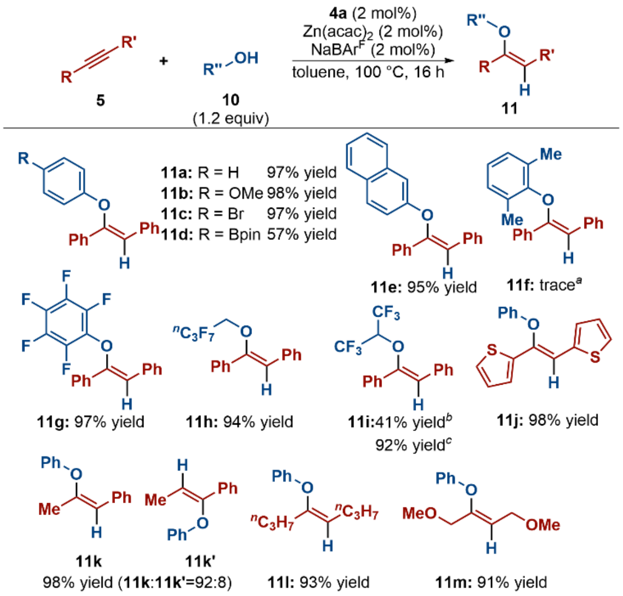
4a (2 mol%), Zn(acac)$_2$ (2 mol%), NaBAr^F (2 mol%), **5** (0.40 mmol), and **6** (0.48 mmol) in DCE (33 μL). [a]Detected by ^{1}H NMR analysis.



The addition of phenols and fluorinated alcohols (**10**) to internal alkynes (**5**) was also investigated. After re-optimizing the reaction conditions, the scope of substrates was investigated under the conditions using the gold complex **4a** (2 mol%), Zn(acac)$_2$ (2 mol%), NaBAr^F (2 mol%) in toluene (12 M) at 100 °C for 16 h (Scheme 2) (see Supporting Information for details). The reaction between phenol (1.2 equiv) and diphenylacetylene (**5a**) gave (*Z*)-(1-phenoxyethene-1,2-diyl)dibenzene **11a** in 97% yield. *p*-Methoxyphenol, *p*-bromophenol, and 2-naphthol were competent with the protocol to afford **11b**, **11c**, and **11e** in 98, 97, and 95% yields, respectively, while a *p*-pinacolatoboron substituent led to a decrease in the yield (57%) of **11d** with the formation of unidentified side products. Sterically hindered 2,6-dimethylphenol gave only a trace amount of **11f**. Pentafluorophenol was a suitable substrate, giving **11g** in 97% yield. The protocol was also applicable to electron-deficient fluorinated alcohols such as 2,2,3,3,4,4,4-heptafluoro-1-

butanol and 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP), giving the corresponding fluoroalkyl enol ethers **11h** and **11i** in 94% and 41% yields, respectively. The use of 3 equiv of HFIP improved the yield of the latter (**11i**) to 92%. Thus, the lower yield with the use of 1.2 equiv of HFIP may have been due to its low boiling point (58 °C).[13] The scope of alkynes was examined using phenol as a model nucleophile. The addition of 1,2-di(thiophen-2-yl)ethyne gave **11j** in 98% yield. 1-Phenyl-1-propyne gave an isomeric mixture (**11k/11k'** 92:8) in 98% yield. 4-Octyne and 1,4-dimethoxy-2-butyne produced **11l** and **11m** in 93% and 91% yields, respectively. Efavirenz showed no reactivity with phenol under the optimized conditions.

Scheme 2. Nucleophilic Addition of Alcohols to Alkynes



4a (2 mol%), Zn(acac)$_2$ (2 mol%), NaBAr^F (2 mol%), **5** (0.40 mmol) and **10** (0.48 mmol) in toluene (33 μL). [a]Detected by ^{1}H NMR analysis. [b]Determined by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard. [c]3.0 equiv of HFIP was used.

To gain information on the gold-zinc heterobimetallic complexes, the interactions between the neutral gold complex **4a** and zinc salts were investigated both in the solid state and in solution phase. Mixing **4a** and ZnCl$_2$ in a DCE/THF mixed solvent gave gold-zinc bimetallic complex **4a-ZnCl$_2$** as a pale yellow powder in 78% yield (Figure 2). Recrystallization of this solid from a DCM/THF solution gave single crystals suitable for XRD analysis. The molecular structure of the gold-zinc bimetallic complex **4a-ZnCl$_2$** as depicted in Figure 2 shows the existence of a linear two-coordinate gold(I) center and a tetrahedral zinc center in a spatially independent manner. Interactions between the pyridine moiety of complexes **4** and zinc salts were also observed in the solution phase (THF-d_8) (see Supporting Information for details).

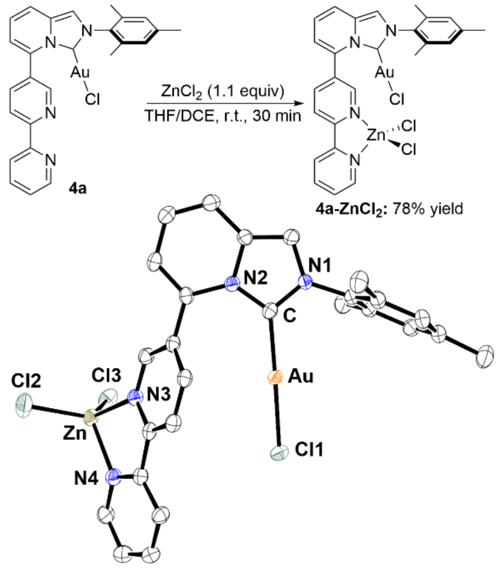


Figure 2. Complexation of gold-zinc bimetallic complex **4a-ZnCl$_2$**. All hydrogen atoms and a solvent molecule are omitted for clarity from the ORTEP drawing of **4a-ZnCl$_2$** showing 50% probability thermal ellipsoids. Selected bond lengths (Å) and angles (deg.) of **12**: Au–Cl 2.2951(9); Au–C 1.992(4); Zn–N3 2.066(3); Zn–N4 2.062(3); C–Au–Cl 178.84(12).

For gaining mechanistic insights into the gold-zinc cooperative catalysis, DFT calculations were conducted at the M06/SDD,6-311+G(d,p)/SMD(DCE)//M06/SDD,6-31G(d) level of theory with the Gaussian 16 package.[14] Gold-zinc complexes were calculated as mono-cationic species without BAr^{F-} anions. The relative energies were corrected for Gibbs free energy and reported in kcal/mol (Figure 3).

The cationic gold complex **Int-1** including alkyne **5a** is formed through the coordination of the bipyridine moiety of **Int-0** to Zn(OBz)$_2$ generated from Zn(acac)$_2$ and benzoic acid. This complexation is an exergonic process by 18.4 kcal/mol. The nucleophilic *anti*-attack of the zinc benzoate toward the alkyne moiety activated by the gold atom proceeds through **TS$_{1\text{-}2}$** with an energy barrier of 24.7 kcal/mol. This step is 15.9 kcal/mol endergonic to afford alkenyl gold(I) intermediate **Int-2**. Alternatively, the benzoate can act as a base to deprotonate benzoic acid. Thus, **Int-1** captures another benzoic acid molecule through hydrogen-bonding at the benzoate oxygen atom to form **Int-3**. The bound benzoic acid undergoes deprotonation coupled with nucleophilic *anti*-attack toward the alkyne moiety through **TS$_{3\text{-}4}$** with an energy barrier of 21.5 kcal/mol, producing alkenyl gold(I) complex **Int-4**. The difference in the relative energies between **TS$_{1\text{-}2}$** and **TS$_{3\text{-}4}$** is only 0.6 kcal/mol indicating that nucleophilic attack could occur through either **TS$_{3\text{-}4}$** or **TS$_{1\text{-}2}$**. **Int-2** is transformed to more stable **Int-4** (ΔG = –4.7 kcal/mol) through ligand exchange on the zinc atom from the enol ester to an external benzoic acid molecule. **Int-4** alters its conformation to **Int-5**, then undergoes protonation at the alkenyl gold moiety through **TS$_{5\text{-}6}$** to form product-bound gold(I) complex **Int-6**. Since **TS$_{5\text{-}6}$** is ca. 4 kcal/mol lower in energy than **TS$_{1\text{-}2}$** and **TS$_{3\text{-}4}$**, the protonation should be faster than the nucleophilic attack.

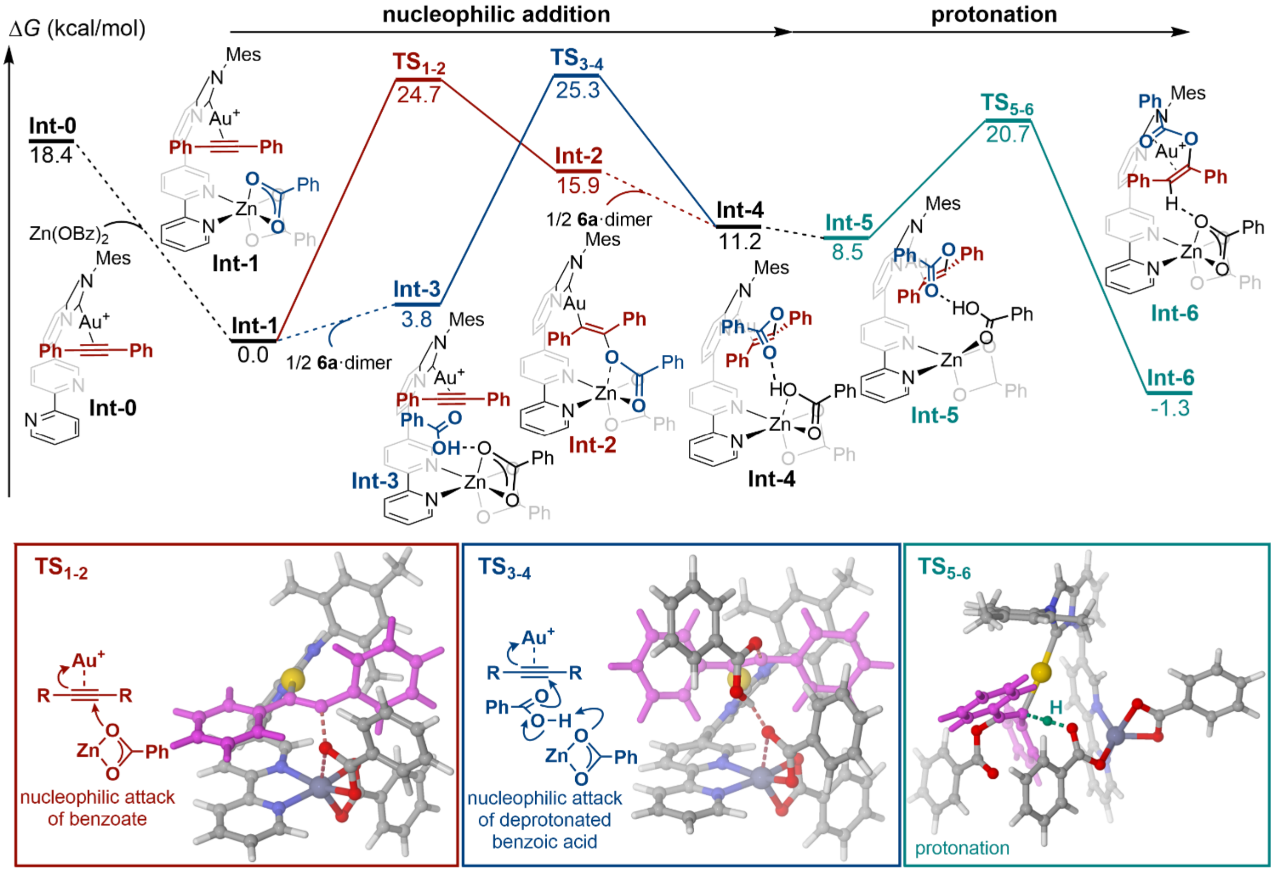


Figure 3. Energy diagram for nucleophilic addition of **6a** toward **5a**. DFT calculations were conducted at the M06/SDD,6-311+G(d,p)/SMD(DCE)//M06/SDD,6-31G(d) level of theory. The relative energies were corrected for the Gibbs free energies and reported in kcal/mol.

In summary, heterobimetallic cationic gold(I) catalyst systems with a 5-(2,2'-bipyrid-5-yl)imidazo[1,5-*a*]pyridin-3-ylidene ligand allowed intermolecular additions of carboxylic acids and phenols across non-activated internal alkynes. The activity of the heterobimetallic systems was highly dependent on the nature of the hard metal site, with Zn(acac)$_2$ being optimal. The molecular structure of the heterobimetallic gold-zinc complex was revealed by single-crystal XRD analysis. DFT calculations supported a proposed cooperative action of the cationic gold(I) atom and the zinc site for the intermolecular nucleophilic *anti*-addition of benzoic acid toward diphenylacetylene.

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Author Contributions

All authors have given approval to the final version of the manuscript.

ASSOCIATED CONTENT

Supporting Information. This material is available free of charge via the Internet at http://pubs.acs.org.

Detailed experimental procedures, analytical data, computational details, and NMR spectra (PDF)

Crystallographic data for **4a**, **4b**, **4c**, **4a-ZnCl$_2$**, and **7o** (CIF)

CCDC 2162186-2162190 contain the supplementary crystallographic data for **4a**, **4b**, **4c**, **4a-ZnCl$_2$**, and **7o**.

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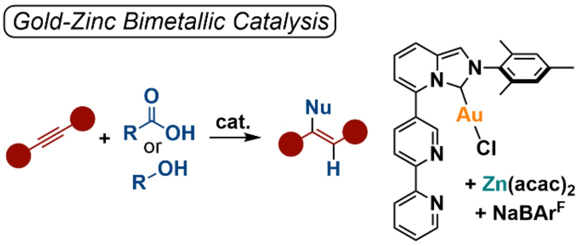
REFERENCES

1. Yamamoto, Y.; Gridnev, I. D.; Patil, N. T.; Jin, T. Alkyneactivation with Brønsted acids, iodine, or gold complexes, and its fate leading to synthetic application. *Chem. Commun.* **2009**, 5075–5087.
2. Recent reviews, (a) Praveen, C. Carbophilic activation of π-systems via gold coordination: Towards regioselective access of intermolecular addition products. *Coord. Chem. Rev.* **2019**, *392*, 1–34. (b) Cadierno, V. Metal-Catalyzed Synthesis and Transformations of *β*-Haloenol Esters. *Catalysts* **2020**, *10*, 399. (c) Leung, C. H.; Baron, M.; Biffis, A. Gold-Catalyzed Intermolecular Alkyne Hydrofunctionalizations—Mechanistic Insights. *Catalysts* **2020**, *10*, 1210. (d) González-Belman, O. F.; Brotons-Rufes, A.; Tomasini, M.; Falivene, L.; Caporaso, L.; Jiménez-Halla, J. O. C.; Poater, A. Towards Dual-Metal Catalyzed Hydroalkoxylation of Alkynes. *Catalysts* **2021**, *11*, 704.
3. Examples for gold-catalyzed nucleophilic addition of carboxylic acids to non-activated alkynes, (a) Chary, B. C.; Kim, S. Gold(I)-Catalyzed Addition of Carboxylic Acids to Alkynes. *J. Org. Chem.* **2010**, *75*, 7928–7931. (b) Wang, Y.; Wang, Z.; Li, Y.; Wu, G.; Cao, Z.; Zhang, L. A general ligand design for gold catalysis allowing ligand-directed anti-nucleophilic attack of alkynes. *Nat. Commun*. **2014**, *5*, 3470. (c) Dupuy, S.; Gasperini, D.; Nolan, S. P. Highly Efficient Gold(I)-Catalyzed Regio- and Stereoselective Hydrocarboxylation of Internal Alkynes. *ACS Catal.* **2015**, *5*, 6918–6921. (d) González-Liste, P. J.; García-Garrido, S. E.; Cadierno, V. Gold(I)-catalyzed addition of carboxylic acids to internal alkynes in aqueous medium. *Org. Biomol. Chem.* **2017**, *15*, 1670–1679. (e) León, F.; González-Liste, P. J.; García-Garrido, S. E.; Arribas, I.; Rubio, M.; Cadierno, V.; Pizzano, A. Broad Scope Synthesis of Ester Precursors of Nonfunctionalized Chiral Alcohols Based on the Asymmetric Hydrogenation of *α*,*β*-Dialkyl-, *α*,*β*-Diaryl-, and *α*-Alkyl-*β*-aryl-vinyl Esters. *J. Org. Chem.* **2017**, *82*, 5852–5867. (f) Francos, J.; Moreno-Narváez, M. E.; Cadierno, V.; Sierra, D.; Ariz, K.; Gómez, J. Gold(I) Complexes with Ferrocenylphosphino Sulfonate Ligands: Synthesis and Application in the Catalytic Addition of Carboxylic Acids to Internal Alkynes in Water. *Catalysts* **2019**, *9*, 955. (g) Darmandeh, H.; Löffler, J.; Tzouras, N. V.; Dereli, B.; Scherpf, T.; Feichtner, K.-S.; Broeck, S. V.; Van Hecke, K.; Saab, M.; Cazin, C. S. J.; Cavallo, L.; Nolan, S. P.; Gessner, V. H. Au···H−C Hydrogen Bonds as Design Principle in Gold(I) Catalysis. *Angew. Chem., Int. Ed.* **2021**, *60*, 21014–21024.
4. Examples for gold-catalyzed nucleophilic addition of phenols to non-activated alkynes, (a) Kuram, M. R.; Bhanuchandra, M.; Sahoo, A. Gold-Catalyzed Intermolecular Hydrophenoxylation of Unactivated Internal Alkynes. *J. Org. Chem.* **2010**, *75*, 2247–2258. (b) Oonishi, Y.; Gómez-Suárez, A.; Martin, A. R.; Nolan, S. P. Hydrophenoxylation of Alkynes by Cooperative Gold Catalysis. *Angew. Chem., Int. Ed.* **2013**, *52*, 9767–9771. (c) Richard, M. E.; Fraccica, D. V.; Garcia, K. J.; Miller, E. J.; Ciccarelli, R. M.; Holahan, E. C.; Resh, V. L.; Shah, A.; Findeis, P. M.; Stockland, R. A. Acid, silver, and solvent-free gold-catalyzed hydrophenoxylation of internal alkynes. *Beilstein J. Org. Chem.* **2013**, *9*, 2002–2008. (d) Gómez-Suárez, A.; Oonishi, Y.; Martin, A. R.; Nolan, S. P. Scope and limitations of the dual-gold-catalysed hydrophenoxylation of alkynes. *Beilstein J. Org. Chem.* **2016**, *12*, 172–178. (e) Gómez-Suárez, A.; Oonishi, Y.; Martin, A. R.; Vummaleti, S. V. C.; Nelson, D. J.; Cordes, D. B.; Slawin, A. M. Z.; Cavallo, L.; Nolan, S. P.; Poater, A. On the Mechanism of the Digold(I)–Hydroxide-Catalysed Hydrophenoxylation of Alkynes. *Chem. Eur. J.* **2016**, *22*, 1125–1132. (f) Lazreg, F.; Guidone, S.; Gómez-Herrera, A.; Nahra, F.; Cazin, C. S. J. Hydrophenoxylation of internal alkynes catalysed with a heterobimetallic Cu-NHC/Au-NHC system. *Dalton. Trans.* **2017**, *46*, 2439–2444. (g) González-Belman, O. F.; Jiménez-Halla, J. O. C.; Nahra, F.; Cazin, C. S. J.; Poater, A. The role of the metal in the dual-metal catalysed hydrophenoxylation of diphenylacetylene. *Catal. Sci. Technol.* **2018**, *8*, 3638–3648. (h) Ramos, M.; Poater, J.; Villegas-Escobar, N.; Gimferrer, M.; Toro-Labbé, A.; Cavallo, L.; Poater, A. Phenoxylation of Alkynes through Mono- and Dual Activation Using Group 11 (Cu, Ag, Au) Catalysts. *Eur. J. Inorg. Chem.* **2020**, 1123–1134.
5. (a) Van Den Beuken, E. K.; Feringa, B. L. Bimetallic catalysis by late transition metal complexes. *Tetrahedron* **1998**, *54*, 12985–13011. (b) Park, J.; Hong, S. Cooperative bimetallic catalysis in asymmetric transformations. *Chem. Soc. Rev.* **2012**, *41*, 6931–6943. (c) Matsunaga, S.; Shibasaki, M. Recent advances in cooperative bimetallic asymmetric catalysis: dinuclear Schiff base complexes. *Chem. Commun.* **2014**, *50*, 1044–1057. (d) Xiong, N.; Zhang, G.; Sun, X.; Zeng, R. Metal-Metal Cooperation in Dinucleating Complexes Involving Late Transition Metals Directed towards Organic Catalysis. *Chin. J. Chem.* **2020**, *38*, 185–201.
6. Lewis acid-organic base cooperative catalysis with imidazo[1,5-*a*]pyridin-3-ylidene ligand has been developed for intramolecular nucleophilic addition of alkyne-tethered carboxylic acids: Rawat, V. K.; Higashida, K.; Sawamura, M. Use of Imidazo[1,5-*a*]pyridin-3-ylidene as a Platform for Metal-Imidazole Cooperative Catalysis: Silver-Catalyzed Cyclization of Alkyne-Tethered Carboxylic Acids. *Adv. Synth. Catal.* **2021**, *363*, 1631–1637.
7. Iglesias-Sigüenza, J.; Izquierdo, C.; Díez, E.; Fernández, R.; Lassaletta, J. M. Chirality and catalysis with aromatic N-fused heterobicyclic carbenes. *Dalton. Trans.* **2016**, *45*, 10113–10117.
8. Examples of heterobimetallic complexes constructed by the combination of NHC and *N*-heteroaromatic ligands, (a) Rubio, M.; Jellema, E.; Siegler, M. A.; Spek, A. L.; Reek, J. N. H.; de Bruin, B. Supramolecular NHC ligands: on the influence of Zn^{II}-templates on the activity of Rh^{I}(cod) complexes in 'carbene polymerization'. *Dalton. Trans.* **2009**, 8970–8976. (b) Strasser, C. E.; Catalano, V. J. "On−Off" Au(I)···Cu(I) Interactions in a Au(NHC)$_2$ Luminescent Vapochromic Sensor. *J. Am. Chem. Soc.* **2010**, *132*, 10009–10011. (c) Mondal, M.; Ranjeesh, T. K.; Gupta, S. K.; Choudhury, J. Labile coordination approach for the modulation of the electronic properties of ruthenium(II) and iridium(III) complexes within an "N-heterocyclic carbene (NHC)–pyridyl" dynamic platform. *Dalton. Trans.* **2014**, *43*, 9356–9362. (d) Bertrand, B.; Citta, A.; Franken, I. L.; Picquet, M.; Folda, A.; Scalcon, V.; Rigobello, M. P.; Gendre, P. L.; Casini, A.; Bodio, E. Gold(I) NHC-based homo- and heterobimetallic complexes: synthesis, characterization and evaluation as potential anticancer agents. *J. Biol. Inorg. Chem.* **2015**, *20*, 1005–1020. (e) Boselli, L.; Carraz, M.; Mazères, S.; Paloque, L.; González, G.; Benoit-Vical, F.; Valentin, A.; Hemmert, C.; Gornitzka, H. Synthesis, Structures, and Biological Studies of Heterobimetallic Au(I)–Ru(II) Complexes Involving N-Heterocyclic Carbene-Based Multidentate Ligands. *Organometallics* **2015**, *34*, 1046–1055. (f) Gatus, M. R. D.; Bhadbhade, M.; Messerle, B. A. Highly versatile heteroditopic ligand scaffolds for accommodating group 8, 9 & 11 heterobimetallic complexes. *Dalton. Trans.* **2017**, *46*, 14406–14419. (g) Kaub, C.; Lebedkin, S.; Li, A.; Kruppa, S. V.; Strebert, P. H.; Kappes, M. M.; Riehn, C.; Roesky, P. W. Bimetallic d^{10}-Metal Complexes of a Bipyridine Substituted N-Heterocyclic Carbene. *Chem. Eur. J.* **2018**, *24*, 6094–6104. (h) Teng, Q.; Huynh, H. V. (Hetero)bimetallic and Tetranuclear Complexes of Pincer-Bridged N-Heterocyclic Carbene Ligands. *Organometallics* **2018**, *37*, 4119–4127. (i) Simler, T.; Möbius, K.; Müller, K.; Feuerstein, T. J.; Gamer, M. T.; Lebedkin, S.; Kappes, M. M.; Roesky, P. W. Mono- and Dinuclear Coinage Metal Complexes Supported by an Imino-Pyridine-NHC Ligand: Structural and Photophysical Studies. *Organometallics* **2019**, *38*, 3649–3661.
9. Using the reported procedure after modification, Carroll, J.; Woolard, H. G.; Mroz, R.; Nason, C. A.; Huo, S. Regiospecific Acylation of Cycloplatinated Complexes: Scope, Limitations, and Mechanistic Implications. *Organometallics* **2016**, *35*, 1313–1322.
10. Using the reported procedure after modification, Callado, A.; Gómez-Suárez, A.; Martin, A. R.; Slawin, A. M. Z.; Nolan, S. P. Straightforward synthesis of [Au(NHC)X] (NHC = *N*-heterocyclic carbene, X = Cl, Br, I) complexes. *Chem. Commun.* **2013**, *49*, 5541–5543.
11. General procedure of nucleophilic addition of carboxylic acids to alkynes: In a nitrogen-filled glove box, **4a** (5.0 mg, 0.008 mmol, 2 mol%) and NaBAr^{F} (7.1 mg, 0.008 mmol, 2 mol%) were placed

in a screw vial containing a magnetic stirring bar. After addition of dry DCE (0.3 mL), the reaction mixture was stirred for 10 minutes. The resulting solution was filtered through a glass-fiber pad packed into a pipette, and the filtrate was added to $Zn(acac)_2$ (2.1 mg, 0.008 mmol, 2 mol%) and **6** (0.40 mmol, if boiling point of **6** is higher than 220 °C) in a screw vial containing a magnetic stirring bar. After stirring for 30 minutes, all volatile compounds were removed under reduced pressure. **7** (0.48 mmol), **6** (0.40 mmol, if boiling point of **6** is lower than 220 °C), and dry DCE (33 μL) were added to the mixture, and the reaction vial was sealed with a screw-cap and removed from the glove box. After stirring at 80 °C for 16 hours, the resulting mixture was quenched by passage through a short pad of silica. The crude mixture was purified by silica-gel column chromatography.

12. Ruthenium-catalyzed (*Z*)-selective *anti*-Markovnikov nucleophilic addition of carboxylic acids toward terminal alkynes was reported, in which ruthenium vinylidene complexes are proposed as the intermediates, Doucet, H.; Martin-Vaca, B.; Bruneau, C.; Dixneuf, P. H. General Synthesis of (*Z*)-Alk-1-en-1-yl Esters via Ruthenium-Catalyzed anti-Markovnikov trans-Addition of Carboxylic Acids to Terminal Alkynes. *J. Org. Chem.* **1995**, *60*, 7247–7255.
13. Purcell, K. F.; Stikeleather, J. A.; Brunk, S. D. Linear enthalpy-spectral shift correlations for 1,1,1,3,3,3-hexafluoro-2-propanol. *J. Am. Chem. Soc.* **1969**, *91*, 4019–4027.
14. Gaussian 16, Revision C.01, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, G. A. Petersson, H. Nakatsuji, X. Li, M. Caricato, A. V. Marenich, J. Bloino, B. G. Janesko, R. Gomperts, B. Mennucci, H. P. Hratchian, J. V. Ortiz, A. F. Izmaylov, J. L. Sonnenberg, D. Williams-Young, F. Ding, F. Lipparini, F. Egidi, J. Goings, B. Peng, A. Petrone, T. Henderson, D. Ranasinghe, V. G. Zakrzewski, J. Gao, N. Rega, G. Zheng, W. Liang, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, K. Throssell, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. J. Bearpark, J. J. Heyd, E. N. Brothers, K. N. Kudin, V. N. Staroverov, T. A. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. P. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, J. M. Millam, M. Klene, C. Adamo, R. Cammi, J. W. Ochterski, R. L. Martin, K. Morokuma, O. Farkas, J. B. Foresman, and D. J. Fox, Gaussian, Inc., Wallingford CT, 2019.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