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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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**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.

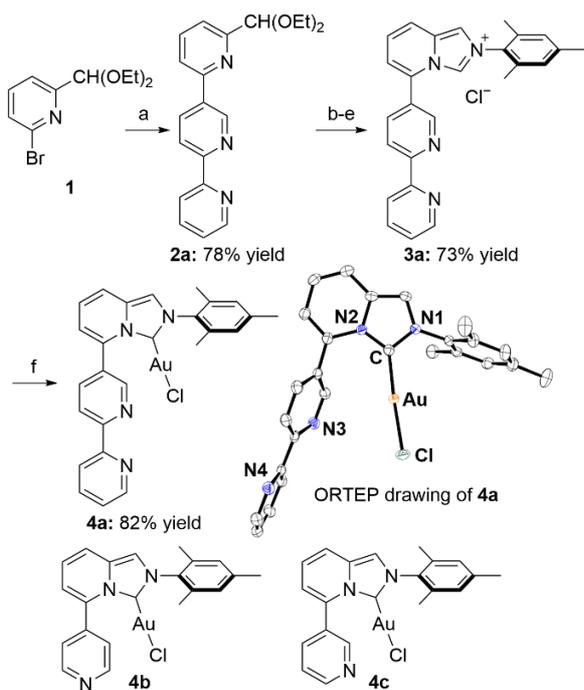
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Cationic gold(I) complexes are well known as effective catalysts for nucleophilic additions toward alkynes with excellent turnover efficiency due to their strong Lewis acidic character and high affinity for alkyne  $\pi$ -systems.<sup>1</sup> Despite the versatile utility of gold catalysts, intermolecular nucleophilic additions of weak oxygen-nucleophiles<sup>2</sup> such as carboxylic acids<sup>3</sup> and phenols<sup>4</sup> 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  $\mu^2$ -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.<sup>3c,g,4b,d,e</sup> 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.<sup>3b</sup> 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.<sup>5</sup> As a platform for the heterobimetallic cooperative catalysis, we synthesized a rigid imidazo[1,5-*a*]pyridin-3-ylidene ligand<sup>6,7</sup> 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.<sup>8</sup> 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)<sub>2</sub> 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<sup>9</sup> 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<sub>3</sub> afforded 5-bipyridylimidazo[1,5-*a*]pyridinium chloride **3a** (73% yield over 4 steps from **2a**). Next, the reaction of **3a** with AuCl·SMe<sub>2</sub> in the presence of K<sub>2</sub>CO<sub>3</sub> in acetone at 60 °C for 3 hours<sup>10</sup> 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), <sup>t</sup>BuLi (1.5 equiv), ZnCl<sub>2</sub> (1.6 equiv), THF/hexane/Et<sub>2</sub>O, -78 °C then 5-bromo-2,2'-bipyridine (1 equiv), Pd(PPh<sub>3</sub>)<sub>4</sub> (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)<sub>3</sub> (1.5 equiv), DCM, r.t., 14 h; (d) HCOOH (excess), Ac<sub>2</sub>O (excess), THF, 0 °C, 3 h; (e) POCl<sub>3</sub> (1.3 equiv), toluene, 100 °C, 21 h; (f) **3a** (1.0 equiv), AuCl-SMe<sub>2</sub> (1.0 equiv), K<sub>2</sub>CO<sub>3</sub> (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.

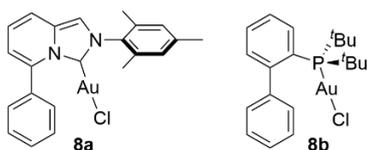
We tested the catalytic activity of gold complexes **4** in the hydrocarboxylation of non-activated alkynes. The results are summarized in Table 1. Bimetallic catalysts were prepared *in situ* from **4a**, a hard metal salt, and an anion source. When nucleophilic addition of benzoic acid (**6a**) toward diphenylacetylene (**5a**) as a non-activated alkyne was conducted with **4a**, Zn(acac)<sub>2</sub>, and AgNTf<sub>2</sub> 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)<sub>2</sub>, Ni(acac)<sub>2</sub>, Pd(acac)<sub>2</sub>, Co(acac)<sub>2</sub>, Fe(acac)<sub>2</sub>, Mn(acac)<sub>3</sub>, and Cr(acac)<sub>3</sub> were examined (entries 2-8), the reaction occurred with decreased yield of **7a** (3–23%). The metal alkoxides such as Ti(O<sup>i</sup>Pr)<sub>4</sub>, Y(O<sup>i</sup>Pr)<sub>3</sub>, and Mg(O<sup>i</sup>Bu)<sub>2</sub> 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)<sub>2</sub> 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<sub>2</sub><sup>-</sup> with BF<sub>4</sub><sup>-</sup>, PF<sub>6</sub><sup>-</sup>, or SbF<sub>6</sub><sup>-</sup> 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<sup>F</sup>) as a source of a non-coordinative anion improved the yield to 75% (entry 22). Finally, quantitative yield of **7a** (>99% by <sup>1</sup>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 <b>7a</b> [%] <sup>a</sup>
1	<b>4a</b>	Zn(acac) <sub>2</sub>	AgNTf <sub>2</sub>	61
2	<b>4a</b>	Cu(acac) <sub>2</sub>	AgNTf <sub>2</sub>	18
3	<b>4a</b>	Ni(acac) <sub>2</sub>	AgNTf <sub>2</sub>	8
4	<b>4a</b>	Pd(acac) <sub>2</sub>	AgNTf <sub>2</sub>	23
5	<b>4a</b>	Co(acac) <sub>2</sub>	AgNTf <sub>2</sub>	17
6	<b>4a</b>	Fe(acac) <sub>2</sub>	AgNTf <sub>2</sub>	3
7	<b>4a</b>	Mn(acac) <sub>3</sub>	AgNTf <sub>2</sub>	12
8	<b>4a</b>	Cr(acac) <sub>3</sub>	AgNTf <sub>2</sub>	6
9	<b>4a</b>	Ti(O <sup>i</sup> Pr) <sub>4</sub>	AgNTf <sub>2</sub>	2
10	<b>4a</b>	Y(O <sup>i</sup> Pr) <sub>3</sub>	AgNTf <sub>2</sub>	1
11	<b>4a</b>	Mg(O <sup>i</sup> Bu) <sub>2</sub>	AgNTf <sub>2</sub>	4
12	<b>4a</b>	none	AgNTf <sub>2</sub>	N.D.
13	<b>4b</b>	Zn(acac) <sub>2</sub>	AgNTf <sub>2</sub>	N.D.
14	<b>4c</b>	Zn(acac) <sub>2</sub>	AgNTf <sub>2</sub>	N.D.
15	<b>8a</b>	Zn(acac) <sub>2</sub>	AgNTf <sub>2</sub>	trace
16	<b>8b</b>	Zn(acac) <sub>2</sub>	AgNTf <sub>2</sub>	trace
17 <sup>b</sup>	<b>8a</b>	Zn(acac) <sub>2</sub>	AgNTf <sub>2</sub>	2
18 <sup>b</sup>	<b>8b</b>	Zn(acac) <sub>2</sub>	AgNTf <sub>2</sub>	1
19	<b>4a</b>	Zn(acac) <sub>2</sub>	AgBF <sub>4</sub>	23
20	<b>4a</b>	Zn(acac) <sub>2</sub>	AgPF <sub>6</sub>	40
21	<b>4a</b>	Zn(acac) <sub>2</sub>	AgSbF <sub>6</sub>	26
22	<b>4a</b>	Zn(acac) <sub>2</sub>	NaBAR <sup>F</sup>	75
23 <sup>c</sup>	<b>4a</b>	Zn(acac) <sub>2</sub>	NaBAR <sup>F</sup>	>99 (98) <sup>d</sup>
24 <sup>c,e</sup>	<b>4a</b>	Zn(acac) <sub>2</sub>	NaBAR <sup>F</sup>	80

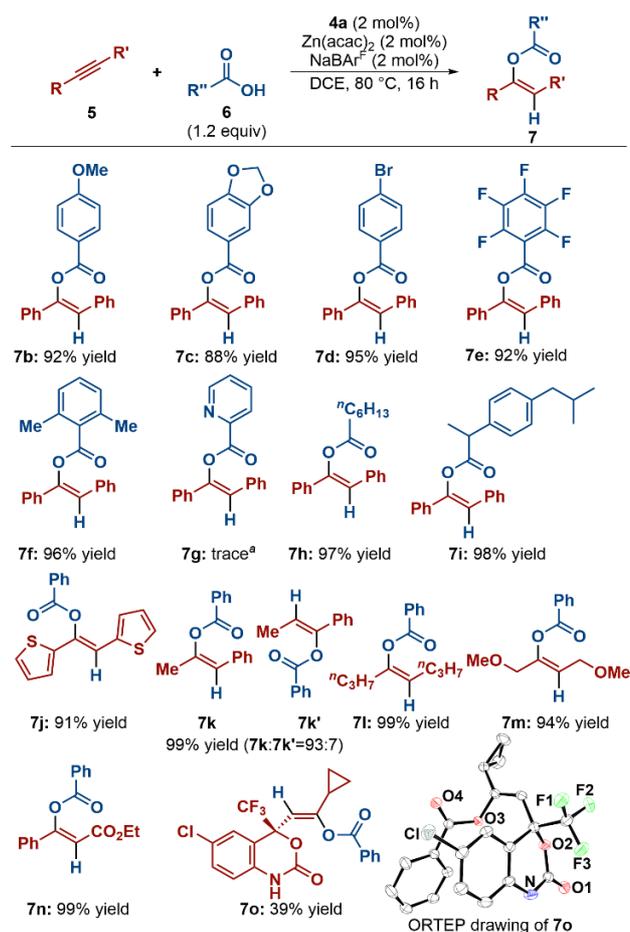
Au catalyst (2 mol%), metal salt (2 mol%), anion source (2 mol%), **5a** (0.10 mmol) and **6a** (0.12 mmol) in DCE (0.1 mL, 1 M). <sup>a</sup>Determined by <sup>1</sup>H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard. <sup>b</sup>2 mol% of 2,2'-bipyridine was added. <sup>c</sup>**5a**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



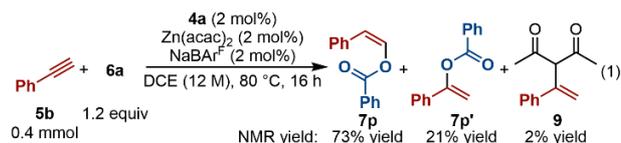
The scope of carboxylic acids and alkynes is summarized in Scheme 1.<sup>11</sup> Electron-donating substituents such as methoxy and methylenedioxy groups on the benzoic acid were compatible with the protocol. The corresponding enol esters **7b** and **7c** were obtained in 92% and 88% yields, respectively. 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<sub>3</sub>-AuCl/AgPF<sub>6</sub> catalyst system.<sup>3a</sup> This interesting regioselectivity is an issue for further investigation.<sup>12</sup>

## Scheme 1. Nucleophilic Addition of Carboxylic Acids to Alkynes



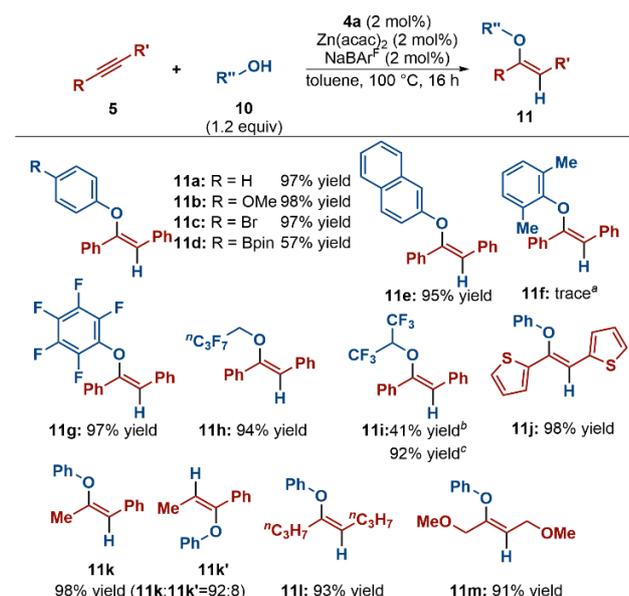
**4a** (2 mol%), Zn(acac)<sub>2</sub> (2 mol%), NaBAR<sup>F</sup> (2 mol%), **5** (0.40 mmol), and **6** (0.48 mmol) in DCE (33 μL). <sup>a</sup>Detected by <sup>1</sup>H NMR analysis.



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 re-investigated under the conditions using the gold complex **4a** (2 mol%), Zn(acac)<sub>2</sub> (2 mol%), NaBAR<sup>F</sup> (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*-pinacoloboron 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-

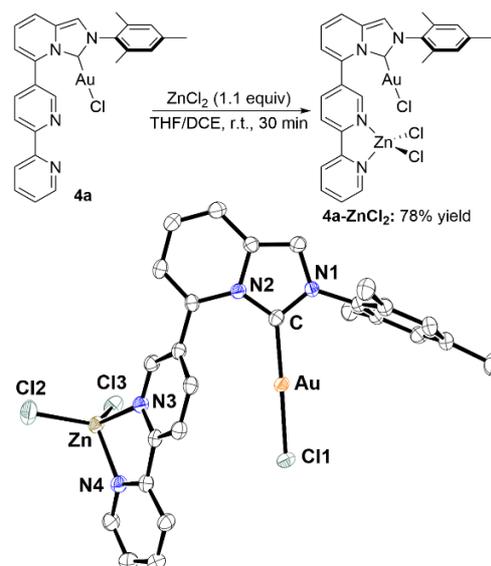
butanol and 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP), giving the corresponding fluoroalkyl enol ethers **11h** and **11i** in 94% and 41% yields, respectively. The use of 3 equiv of HFIP improved the yield of the latter (**11i**) to 92%. Thus, the lower yield with the use of 1.2 equiv of HFIP may have been due to its low boiling point (58 °C).<sup>13</sup> 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%),  $\text{Zn}(\text{acac})_2$  (2 mol%),  $\text{NaBAR}^{\text{F}}$  (2 mol%), **5** (0.40 mmol) and **10** (0.48 mmol) in toluene (33  $\mu\text{L}$ ). <sup>a</sup>Detected by <sup>1</sup>H NMR analysis. <sup>b</sup>Determined by <sup>1</sup>H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard. <sup>c</sup>3.0 equiv of HFIP was used.

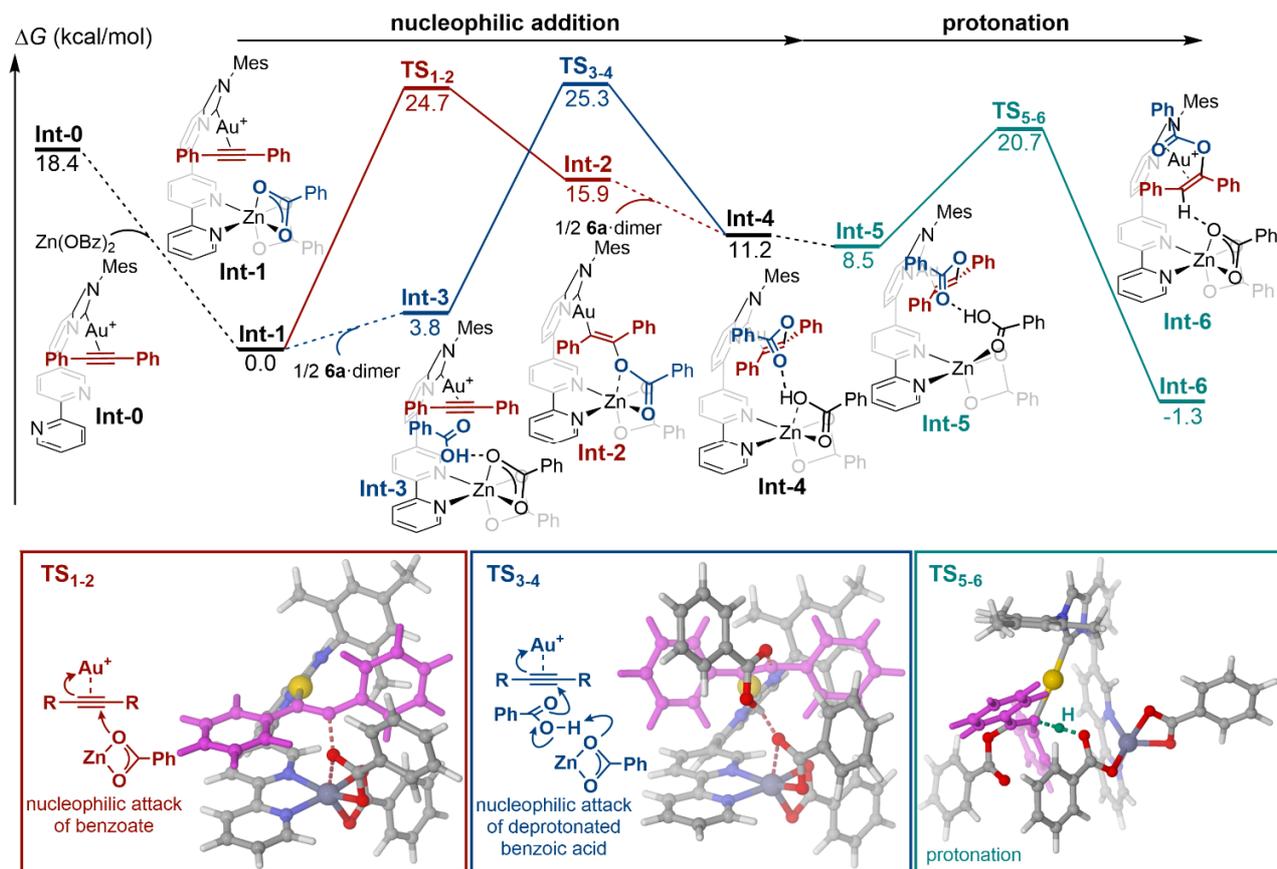
To gain information on the gold-zinc heterobimetallic complexes, the interactions between the neutral gold complex **4a** and zinc salts were investigated both in the solid state and in solution phase. Mixing **4a** and  $\text{ZnCl}_2$  in a DCE/THF mixed solvent gave gold-zinc bimetallic complex **4a-ZnCl<sub>2</sub>** 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<sub>2</sub>** 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*<sub>8</sub>) (see Supporting Information for details).



**Figure 2.** Complexation of gold-zinc bimetallic complex **4a-ZnCl<sub>2</sub>**. All hydrogen atoms and a solvent molecule are omitted for clarity from the ORTEP drawing of **4a-ZnCl<sub>2</sub>** showing 50% probability thermal ellipsoids. Selected bond lengths (Å) and angles (deg.) of **12**: Au-Cl1 2.2951(9); Au-C 1.992(4); Zn-N3 2.066(3); Zn-N4 2.062(3); C-Au-Cl1 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.<sup>14</sup> Gold-zinc complexes were calculated as mono-cationic species without  $\text{BAR}^{\text{F}}$  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  $\text{Zn}(\text{OBz})_2$  generated from  $\text{Zn}(\text{acac})_2$  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<sub>1,2</sub>** 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<sub>3,4</sub>** with an energy barrier of 21.5 kcal/mol, producing alkenyl gold(I) complex **Int-4**. The difference in the relative energies between **TS<sub>1,2</sub>** and **TS<sub>3,4</sub>** is only 0.6 kcal/mol indicating that nucleophilic attack could occur through either **TS<sub>3,4</sub>** or **TS<sub>1,2</sub>**. **Int-2** is transformed to more stable **Int-4** ( $\Delta G = -4.7$  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<sub>5,6</sub>** to form product-bound gold(I) complex **Int-6**. Since **TS<sub>5,6</sub>** is ca. 4 kcal/mol lower in energy than **TS<sub>1,2</sub>** and **TS<sub>3,4</sub>**, 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)<sub>2</sub> 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<sub>2</sub>**, and **7o** (CIF) CCDC 2162186-2162190 contain the supplementary crystallographic data for **4a**, **4b**, **4c**, **4a-ZnCl<sub>2</sub>**, and **7o**.

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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)<sub>2</sub> (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.

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Gold-Zinc Bimetallic Catalysis

