

# On the Impact of Steric and Electronic Properties of Ligands on Gold(I)-Catalyzed Cycloaddition Reactions

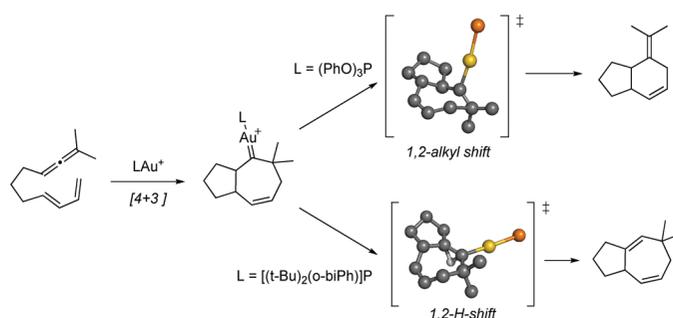
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## ABSTRACT



It is shown that [4 + 3] and [4 + 2] cycloaddition pathways are accessible in the Au(I) catalysis of allene–dienes. Seven-membered ring gold-stabilized carbenes, originating from the [4 + 3] cycloaddition process, are unstable and can rearrange via a 1,2-H or a 1,2-alkyl shift to yield six- and seven-membered products. Both steric and electronic properties of the AuL<sup>+</sup> catalyst affect the electronic structure of the intermediate gold-stabilized carbene and its subsequent reactivity.

Cycloisomerization and cycloaddition reactions catalyzed by cationic gold(I) complexes have been employed effectively to install high degrees of structural complexity under mild conditions.<sup>1</sup> Many of these reactions are proposed to proceed

via cationic intermediates which, depending on the reaction, display reactivity reminiscent of gold-stabilized carbenes<sup>2</sup> or carbocations.<sup>3</sup> This dichotomy is highlighted by the striking differences between the gold-catalyzed intermolecular reaction of allenes–alkenes and allene–dienes: the former generally provided the [2 + 2]-cycloadduct,<sup>4</sup> while the corresponding reaction with dienes allowed for ligand-dependent access to either the six- or seven-membered

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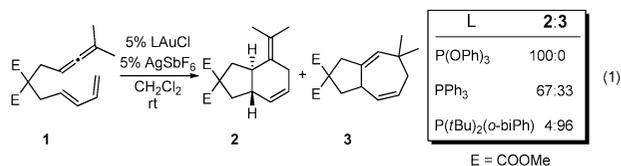
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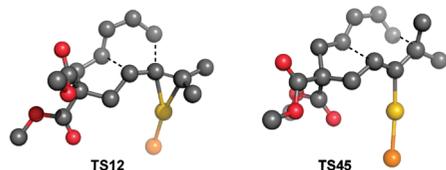
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ring products (eq 1).<sup>5</sup> Moreover, evidence was accumulated in support of a stepwise, cationic mechanism in the [2 + 2]-cycloaddition, which contrasted dramatically with the experimental support for concerted [4 + 2]- and [4 + 3]-cycloadditions. To elucidate the factors dictating the reaction pathways, we performed a quantum mechanical study using the M06 flavor<sup>6</sup> of density functional theory (DFT). In doing so, we hoped to gain insight into not only the mechanism of the [4 + 2]- and [4 + 3]-cycloaddition reactions but also the nature of the Au–C bond in these cationic intermediates and the factors governing their reactivity.



Geometry optimizations were performed using the M06 functional and the LACVP\*\* basis set. Electronic energies were obtained from single-point calculations using the LACV3P++\*(2f) basis set, which includes a double- $\zeta$  f-type polarization function on gold. All other atoms used the 6-311++G\*\* (see Supporting Information for more details). The M06 analytic Hessian was used to obtain vibrational thermodynamic corrections (ZPE,  $H_{\text{vib}}$ ,  $S_{\text{vib}}$ ). The accuracy of our computational method [M06/LACV3P++\*(2f)] was validated against relative binding data for [IPrAu]<sup>+</sup> to isobutylene and propene. We calculated a binding free energy difference  $\Delta G = 1.0$  kcal/mol in CH<sub>2</sub>Cl<sub>2</sub> at –60 °C, which is in excellent agreement with  $\Delta G = 0.97$  kcal/mol from <sup>1</sup>H NMR experiments.<sup>7</sup>

First, we located a transition structure for the uncatalyzed concerted [4 + 2]-cycloaddition process with a barrier of  $\Delta G^\ddagger = 31.1$  kcal/mol. Not surprisingly, we were unable to



**Figure 1.** Calculated transition state structures (L = PMe<sub>3</sub>) for the concerted [4 + 2]- and [4 + 3]-cycloaddition reaction of dienes and gold-complexed allenes.

locate a transition state for the uncatalyzed [4 + 3]. We next turned our attention to the Au(I)-catalyzed reaction using PMe<sub>3</sub> as a ligand. Me<sub>3</sub>PAu<sup>+</sup> coordinates to the allene, followed by formation of Au-stabilized allylic cation<sup>8</sup> **4** with

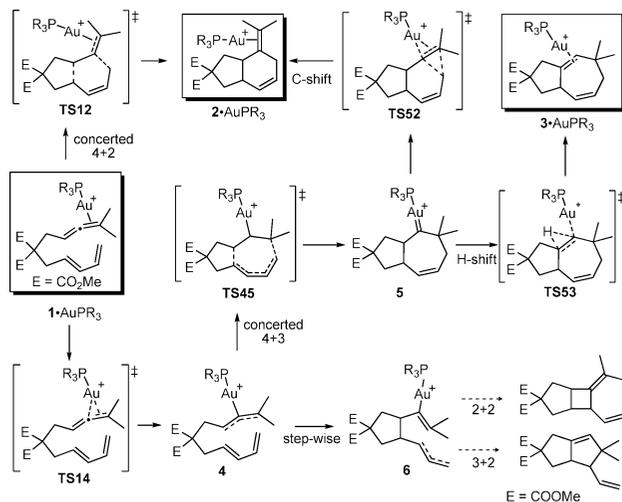
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an activation free-energy barrier (TS14) of  $\Delta G^\ddagger = 6.8$  kcal/mol (Scheme 1). Intermediate **4** undergoes a concerted<sup>9</sup>

### Scheme 1. Au-Catalyzed [4 + 3]- and [4 + 2]-Cycloadditions



[4 + 3]-cycloaddition via rate-limiting TS45<sup>10</sup> at 14.6 kcal/mol (for L = PMe<sub>3</sub>) leading to intermediate **5**.

Our results suggest that intermediate **5** is a key bifurcation point in the pathways leading to the formation of six- and seven-membered ring products **2** and **3** via a 1,2-alkyl shift (TS52) or via a 1,2-hydrogen shift (TS53).<sup>11,12</sup> We were able to locate a transition state (TS12) for the conversion of 1·AuPMe<sub>3</sub> to 2·AuPMe<sub>3</sub> by a direct [4 + 2]-cycloaddition (Figure 1); however, this process is 13.9 kcal/mol higher in energy than the rate-determining barrier for the pathway via intermediate **5**.

Having established the mechanism using PMe<sub>3</sub>, we calculated the relative energies for key intermediates and transition structures for catalysts bearing P(OPh)<sub>3</sub>, PPh<sub>3</sub>, and P(*t*Bu)<sub>2</sub>(*o*-biPh). The phosphite ligand facilitates the [4 + 3]-cycloaddition with respect to PMe<sub>3</sub> and PPh<sub>3</sub> (TS45·AuP(OPh)<sub>3</sub> is 7.9 and 7.2 kcal/mol lower in energy than for PMe<sub>3</sub> and PPh<sub>3</sub>, respectively). In contrast, [AuP(*t*Bu)<sub>2</sub>(*o*-biPh)]<sup>+</sup> catalyzed reaction shows the highest activation barrier of 9.9 kcal/mol for the [4 + 3]-cycloaddition (TS45). This difference in activation energy was confirmed by a catalyst competition experiment (5% (PhO)<sub>3</sub>PAuCl, 5%

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(9) We were able to find stable intermediate **6**, presumed to be on the path to stepwise 2 + 2 and 3 + 2 cycloaddition pathways. All attempts to locate a stepwise pathway leading to **2** and **3** led to concerted TS45.

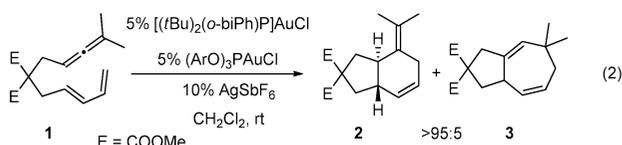
(10) In contrast, a related DFT study of Pt- and Au-catalyzed [4 + 3]-cycloaddition suggests “a 1,2-hydride shift on the generated carbene intermediate as the rate-limiting step”. See: Trillo, B.; López, F.; Montserrat, S.; Castedo, L.; Lledós, A.; Mascareñas, J. L. *Chem.—Eur. J.* **2009**, *15*, 3336.

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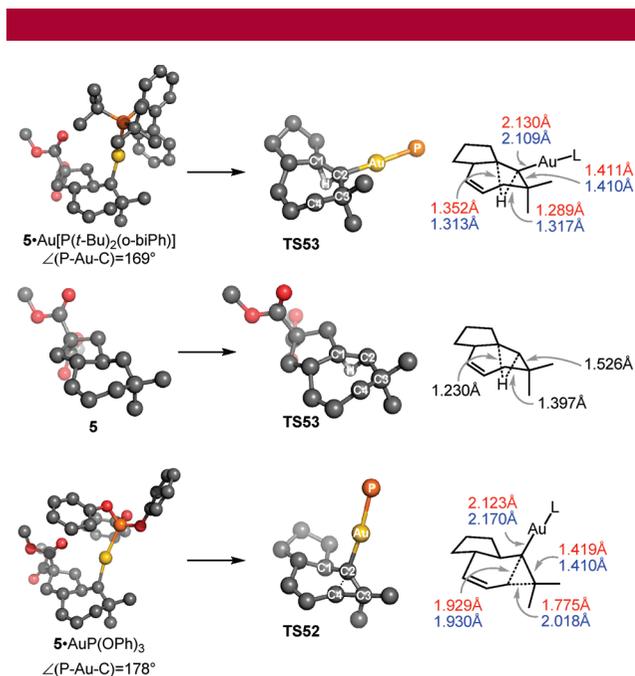
(*t*Bu)<sub>2</sub>(*o*-biPh)PAuCl, 10% AgSbF<sub>6</sub>, CH<sub>2</sub>Cl<sub>2</sub>, rt) that resulted in exclusive formation of **2** (eq 2). In addition, [AuP(*t*Bu)<sub>2</sub>(*o*-biPh)]<sup>+</sup> activates the uncoordinated allenic double bond, promoting a highly asynchronous concerted [4 + 2]-cycloaddition. Our results predict that when di-*t*-butylbiphenylphosphine is used as the ligand the [4 + 2]-cycloaddition pathway (**TS12**, 17.3 kcal/mol) becomes competitive with the [4 + 3] (**TS45**, 15.1 kcal/mol). Thus, our calculations suggest that a [4 + 2] pathway is responsible for 4% (3% predicted) of six-membered ring product (**2**) observed experimentally when [AuP(*t*Bu)<sub>2</sub>(*o*-biPh)]<sup>+</sup> is used a catalyst.

To account for the differences in activation energy for the cycloaddition (**TS45**), we considered the effects that the different ligands have on the Au–C bond. We calculated snap-bond energies for [AuL]<sup>+</sup> to C and find that the Au–C bond is much stronger for L = P(OPh)<sub>3</sub> [92 kcal/mol in **5**•AuP(OPh)<sub>3</sub>] than for P(*t*Bu)<sub>2</sub>(*o*-biPh) [78 kcal/mol in **5**•AuP(*t*Bu)<sub>2</sub>(*o*-biPh)]. Indeed, the carbene intermediate is less stabilized by [AuP(*t*Bu)<sub>2</sub>(*o*-biPh)]<sup>+</sup>, resulting in the observed higher energy for **TS45** compared to the [AuP(OPh)<sub>3</sub>]<sup>+</sup>-catalyzed reaction. On the basis of natural bond orbital<sup>13</sup> (NBO) analyses, we find that the gold–carbene bond is composed of weak  $\sigma$ - and  $\pi$ -components. The  $\sigma$ -interaction originates from the C sp<sup>2</sup> lone pair partially overlapping the 6s orbital on gold, which is partially populated by donation from L. In addition, the  $\pi$ -component of the bond is a highly polarized  $d\pi$  to  $p\pi$  donation from an Au lone pair to the empty  $p\pi$ -orbital on C.<sup>14</sup>



We next examined **TS52** and **TS53** (Figure 2) with different ligands to assess factors that might lead to a preference for 1,2-H or alkyl shift. In all cases, the seven-membered ring in **5** adopts a chairlike conformation. Consequently, this geometry is essentially conserved in transition structures **TS52** for the alkyl shift. The 1,2-alkyl shift involves both  $\sigma$  and  $\pi$  character in the carbene. We envision that density from the C2  $\sigma$ -lone pair is shifted toward C3, contributing to the resulting double bond. In turn, C4 migrates with the C3–C4 electron pair, which at the transition structure (**TS52**) forms an occupied  $p\pi$ -orbital that overlaps with the empty  $p\pi$ -orbital at C2. Thus, the alkyl shift is relatively insensitive to ligand effects and occurs with barriers of 6.1, 6.0, and 5.7 kcal/mol for [AuP(*t*Bu)<sub>2</sub>(*o*-biPh)]<sup>+</sup>, [AuP(OPh)<sub>3</sub>]<sup>+</sup>, and [AuPPh<sub>3</sub>]<sup>+</sup>, respectively.

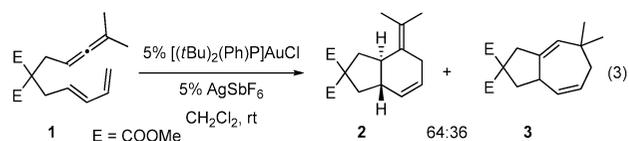
In contrast, our results suggest that the barrier for the 1,2-H shift is affected (and raised relative to the metal-free case) by increased population of the C  $p\pi$ -orbital by donation from the Au  $d\pi$ -electrons.<sup>15</sup> The free carbene intermediate



**Figure 2.** Calculated structures for **5**, **TS53** (L = P(*t*Bu)<sub>2</sub>(*o*-biPh) and metal-free), and **TS52** (L = P(OPh)<sub>3</sub>). Selected bond lengths for **TS53** and **TS52** with L = P(*t*Bu)<sub>2</sub>(*o*-biPh) and L = P(OPh)<sub>3</sub> shown in red and blue, respectively. Selected bond lengths for **5** and **TS53** for metal-free structures shown in black.

undergoes the 1,2-H shift with a barrier of 1.3 kcal/mol.<sup>16</sup> This barrier increases to 6.9 kcal/mol for the [AuP(OPh)<sub>3</sub>]<sup>+</sup>-stabilized carbene. In contrast, with [AuP(*t*Bu)<sub>2</sub>(*o*-biPh)]<sup>+</sup> the barrier only increases to 2.6 kcal/mol indicating that Au  $d\pi$ -electrons have less overlap with the C  $p\pi$ -orbital in this transition state.

On the basis of previous theoretical and experimental analyses of dialkylbiaryl phosphines,<sup>17</sup> we hypothesized that steric effects of the biaryl were responsible for this difference. The distal aryl causes a repulsive steric interaction with the gold atom and with the substrate. As a consequence, the P–Au–C angle in the complexes bearing the biarylphosphine ligand is  $\sim 169^\circ$ . This geometric distortion reduces the Au– $d\pi$  to C– $p\pi$  overlap. In accord with this hypothesis, we calculate a C–Au–P angle of  $\sim 176^\circ$  for [5•AuP(*t*Bu)<sub>2</sub>(*o*-biPh)]<sup>+</sup> and predict a 2:3 ratio of 67:33 for this intermediate, which we confirmed experimentally (eq 3).



Our analysis of the gold-catalyzed [4 + 2]- and [4 + 3]-cycloaddition reactions finds that both reactions proceed

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(15) Similar effects have been calculated for transition states for 1,2-H shifts of singlet carbenes. See: (a) Keating, A. E.; Garcia-Garibay, M. A.; Houk, K. N. *J. Phys. Chem. A* **1998**, *102*, 8467, and references therein. (b) Albu, T. V.; Lynch, B. J.; Truhlar, D. G.; Goren, A. C.; Hrovat, D. A.; Borden, W. T.; Moss, R. A. *J. Phys. Chem. A* **2002**, *106*, 5323.

**Table 1.** Free Energies ( $\Delta G$ , kcal/mol) Relative to **1·X** at 298 K

<b>X</b>	AuPMe <sub>3</sub>	AuP(OPh) <sub>3</sub>	AuPPh <sub>3</sub>	AuP( <i>t</i> Bu) <sub>2</sub> ( <i>o</i> -biPh)	metal-free
<b>4</b>	6.3	-2.4	3.5	5.2	-
<b>TS45</b>	12.4	4.5	11.7	15.1	-
<b>5</b>	-6.8	-10.7	-9.8	-10.1	26.6
<b>TS52</b>	-3.7	-4.7	-4.1	-4.0	-
<b>TS53</b>	-2.8	-3.8	-3.8	-7.5	27.9
<b>2</b>	-38.7	-39.2	-36.2	-34.9	-34.7
<b>3</b>	-40.2	-41.2	-38.6	-38.5	-38.5
<b>TS12</b>	26.6	23.0	25.4	17.3	31.1
pred. <b>2:3</b>	81:19	81:19	63:37	3:97	-
exp. <b>2:3</b>	-	100:0	67:33	4:96	-

through an initial concerted [4 + 3]-cycloaddition of a gold-activated allene with a diene. The selectivity for either pathway arises primarily from a preference for either 1,2-H or 1,2-alkyl shifts in the gold-stabilized carbene intermediate. We conclude that the impact of the gold catalyst on migratory aptitude is a consequence of the relative strength of the  $d\pi$  to  $p\pi$  interaction in the Au–C bond. Importantly, these results suggest that in addition to electronic properties<sup>14</sup> the

sterics of the ligand can dramatically impact Au–C bonding, especially in [AuP(*t*Bu)<sub>2</sub>(*o*-biPh)]<sup>+</sup>-catalyzed reactions.

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**Supporting Information Available:** Supplied are XYZ coordinates. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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