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

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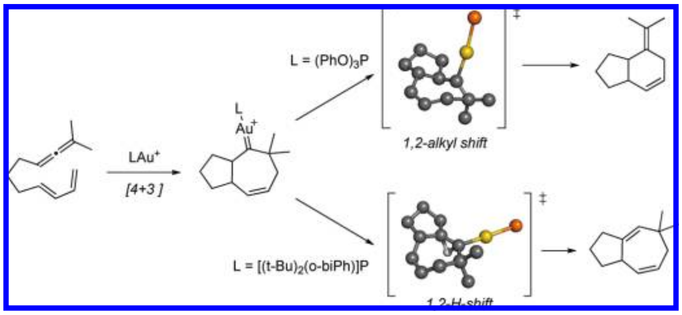
ABSTRACT



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$^+$ 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.[1] Many of these reactions are proposed to proceed via cationic intermediates which, depending on the reaction, display reactivity reminiscent of gold-stabilized carbenes[2] or carbocations.[3] 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,[4] while the corresponding reaction with dienes allowed for ligand-dependent access to either the six- or seven-membered

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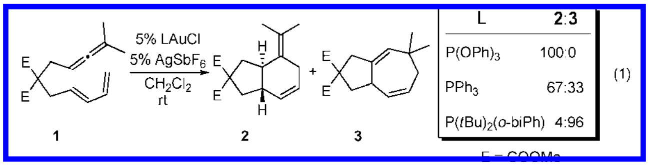
ring products (eq 1).[5] Moreover, evidence was accumulated in support of a stepwise, cationic mechanism in the [2 + 2]-cycloaddition, which contrasted dramatically with the experimental support for concerted [4 + 2]- and [4 + 3]-cycloadditions. To elucidate the factors dictating the reaction pathways, we performed a quantum mechanical study using the M06 flavor[6] 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.



L	2:3
$P(OPh)_3$	100:0
PPh_3	67:33
$P(tBu)_2(o\text{-biPh})$	4:96

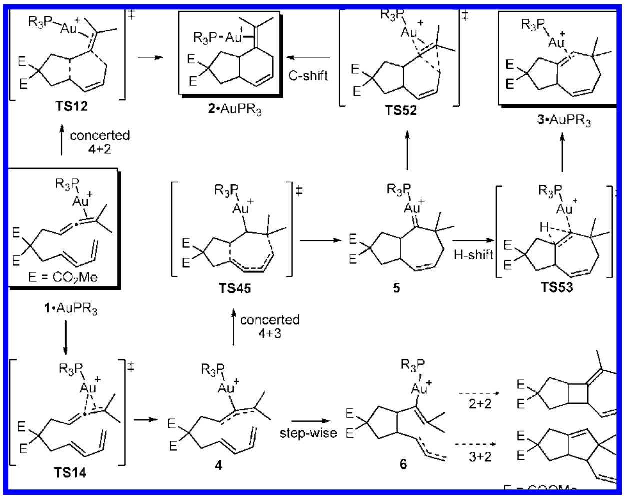
(1)

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-ζ 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_{vib}, S_{vib}). The accuracy of our computational method [M06/LACV3P++**(2f)] was validated against relative binding data for $[IPrAu]^+$ to isobutylene and propene. We calculated a binding free energy difference ΔG = 1.0 kcal/mol in CH_2Cl_2 at −60 °C, which is in excellent agreement with ΔG = 0.97 kcal/mol from ^1H NMR experiments.[7]

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 locate a transition state for the uncatalyzed [4 + 3]. We next turned our attention to the Au(I)-catalyzed reaction using PMe_3 as a ligand. Me_3PAu^+ coordinates to the allene, followed by formation of Au-stabilized allylic cation[8] **4** with an activation free-energy barrier (**TS14**) of $\Delta G^{\ddagger}$ = 6.8 kcal/mol (Scheme 1). Intermediate **4** undergoes a concerted[9] [4 + 3]-cycloaddition via rate-limiting **TS45**[10] at 14.6 kcal/mol (for L = PMe_3) leading to intermediate **5**.

Figure 1. Calculated transition state structures (L = PMe_3) for the concerted [4 + 2]- and [4 + 3]-cycloaddition reaction of dienes and gold-complexed allenes.

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



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**).[11,12] We were able to locate a transition state (**TS12**) for the conversion of **1**•$AuPMe_3$ to **2**•$AuPMe_3$ 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_3, we calculated the relative energies for key intermediates and transition structures for catalysts bearing $P(OPh)_3$, PPh_3, and $P(tBu)_2(o\text{-biPh})$. The phosphite ligand facilitates the [4 + 3]-cycloaddition with respect to PMe_3 and PPh_3 (**TS45**•$AuP(OPh)_3$ is 7.9 and 7.2 kcal/mol lower in energy than for PMe_3 and PPh_3, respectively). In contrast, $[AuP(tBu)_2(o\text{-biPh})]^+$ 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% $(PhO)_3PAuCl$, 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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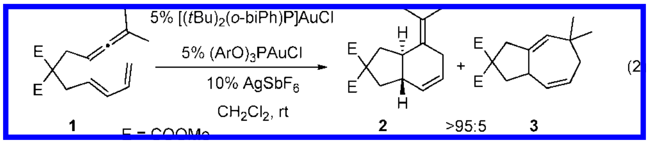
(tBu)$_2$(o-biPh)PAuCl, 10% AgSbF$_6$, CH$_2$Cl$_2$, rt) that resulted in exclusive formation of **2** (eq 2). In addition, [AuP(tBu)$_2$(o-biPh)]$^+$ activates the uncoordinated allenic double bond, promoting a highly asynchronous concerted [4 + 2]-cycloaddition. Our results predict that when di-t-butylbiphenylphosphine 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(tBu)$_2$(o-biPh)]$^+$ 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]$^+$ to C and find that the Au−C bond is much stronger for L = P(OPh)$_3$ [92 kcal/mol in **5**•AuP(OPh)$_3$] than for P(tBu)$_2$(o-biPh) [78 kcal/mol in **5**•AuP(tBu)$_2$(o-biPh)]. Indeed, the carbene intermediate is less stabilized by [AuP(tBu)$_2$(o-biPh)]$^+$, resulting in the observed higher energy for **TS45** compared to the [AuP(OPh)$_3$]$^+$-catalyzed reaction. On the basis of natural bond orbital[13] (NBO) analyses, we find that the gold−carbene bond is composed of weak σ- and π-components. The σ-interaction originates from the C sp^2 lone pair partially overlapping the 6s orbital on gold, which is partially populated by donation from L. In addition, the π-component of the bond is a highly polarized dπ to pπ donation from an Au lone pair to the empty pπ-orbital on C.[14]



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 σ and π character in the carbene. We envision that density from the C2 σ-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 pπ-orbital that overlaps with the empty pπ-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(tBu)$_2$(o-biPh)]$^+$, [AuP(OPh)$_3$]$^+$, and [AuPPh$_3$]$^+$, 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 pπ-orbital by donation from the Au dπ-electrons.[15] The free carbene intermediate undergoes the 1,2-H shift with a barrier of 1.3 kcal/mol.[16] This barrier increases to 6.9 kcal/mol for the [AuP(OPh)$_3$]$^+$-stabilized carbene. In contrast, with [AuP(tBu)$_2$(o-biPh)]$^+$ the barrier only increases to 2.6 kcal/mol indicating that Au dπ-electrons have less overlap with the C pπ-orbital in this transition state.

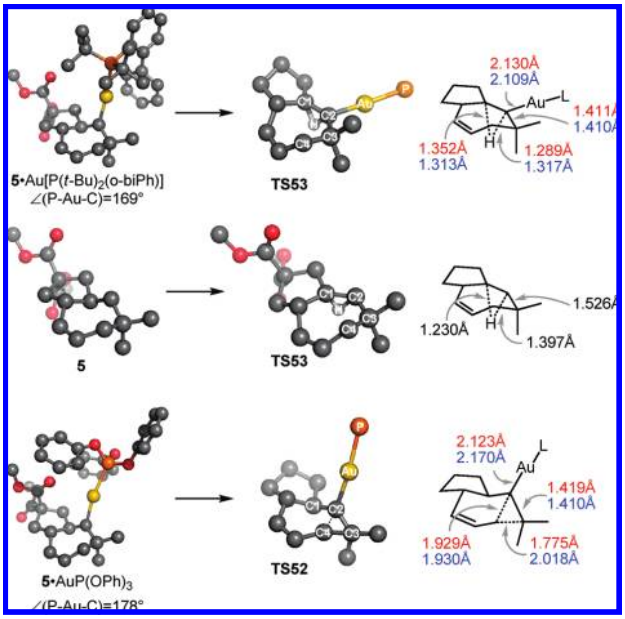
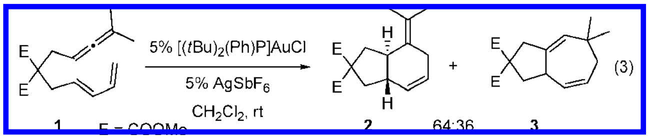


Figure 2. Calculated structures for **5**, **TS53** (L = P(tBu)$_2$(o-biPh) and metal-free), and **TS52** (L = P(OPh)$_3$). Selected bond lengths for **TS53** and **TS52** with L = P(tBu)$_2$(o-biPh) and L = P(OPh)$_3$ shown in red and blue, respectively. Selected bond lengths for **5** and **TS53** for metal-free structures shown in black.

On the basis of previous theoretical and experimental analyses of dialkylbiaryl phosphines,[17] 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 ~169°. This geometric distortion reduces the Au−dπ to C−pπ overlap. In accord with this hypothesis, we calculate a C−Au−P angle of ~176° for [**5**•AuP(tBu)$_2$Ph]$^+$ 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 (ΔG, kcal/mol) Relative to **1·X** at 298 K

X	$AuPMe_3$	$AuP(OPh)_3$	$AuPPh_3$	$AuP(tBu)_2(o\text{-biPh})$	metal-free
4	6.3	−2.4	3.5	5.2	–
TS45	12.4	4.5	11.7	15.1	–
5	−6.8	−10.7	−9.8	−10.1	26.6
TS52	−3.7	−4.7	−4.1	−4.0	–
TS53	−2.8	−3.8	−3.8	−7.5	27.9
2	−38.7	−39.2	−36.2	−34.9	−34.7
3	−40.2	−41.2	−38.6	−38.5	−38.5
TS12	26.6	23.0	25.4	17.3	31.1
pred. **2**:**3**	81:19	81:19	63:37	3:97	–
exp. **2**:**3**	–	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 dπ to pπ interaction in the Au−C bond. Importantly, these results suggest that in addition to electronic properties[14] the sterics of the ligand can dramatically impact Au−C bonding, especially in $[AuP(tBu)_2(o\text{-biPh})]^+$-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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(16) We were unable to locate a transition state for the 1,2-alkyl shift of the free carbene.

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