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

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Abstract
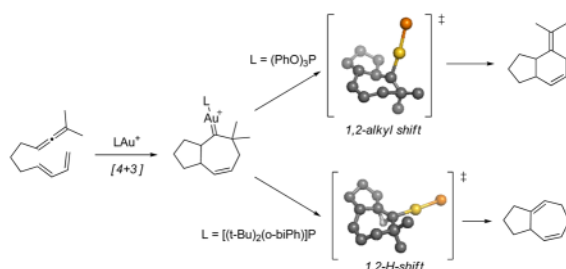
It is shown that [4+3] and [4+2] cycloaddition pathways are accessible in the Au(I) catalysis of allene-dienes. Seven-membered ring gold-stabilized carbenes, originating from the [4+3] cycloaddition process, are unstable and can rearrange *via* a 1,2-H or a 1,2-alkyl shift to yield six- and seven-membered 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-dependant access to either the 6 or 7-membered 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. In order 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.

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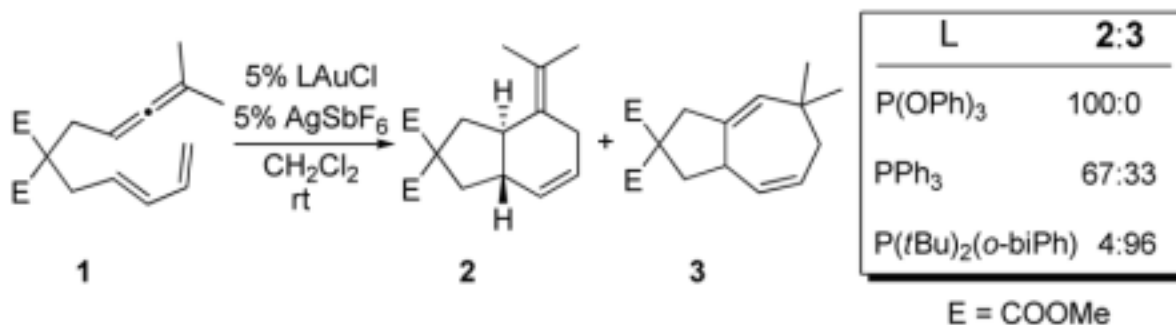
The accuracy of our computational method [M06/LACV3P++**(2f)] was validated against relative binding data for [IPrAu]$^+$ to isobutylene and propene. Geometry optimizations were performed using the M06 functional and the LACVP** basis set. Electronic energies were obtained from single point calculations 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 S. I. for more details). The M06 analytic Hessian was used to obtain vibrational thermodynamic corrections (ZPE, H_{vib}, S_{vib}). We calculated a binding free energy difference $\Delta G = 1.0$ kcal/mol in CH_2Cl_2 at -60 °C, which is in excellent agreement with $\Delta G = 0.97$ kcal/mol from ^{1}H-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 (Figure 1). 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$_3$PAu+ 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**.

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; 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-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^{-1} lower in energy than for PMe$_3$ and PPh$_3$ respectively). In contrast, [Au·P(tBu)$_2$(o-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)$_3$PAuCl, 5% (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 the 4% (3% predicted) of six-

membered ring product (**2**) observed experimentally when [AuP(*t*Bu)$_2$(*o*-biPh)]+ is used a catalyst.

In order 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(*t*Bu)$_2$(*o*-biPh) [78 kcal/mol in **5**·AuP (*t*Bu)$_2$(*o*-biPh)]. Indeed, the carbene intermediate is less stabilized by [AuP(*t*Bu)$_2$(*o*-biPh)]$^+$, resulting in the observed higher energy for **TS45** compared to the [AuP(OPh)$_3$]+-catalyzed reaction. Based on 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]
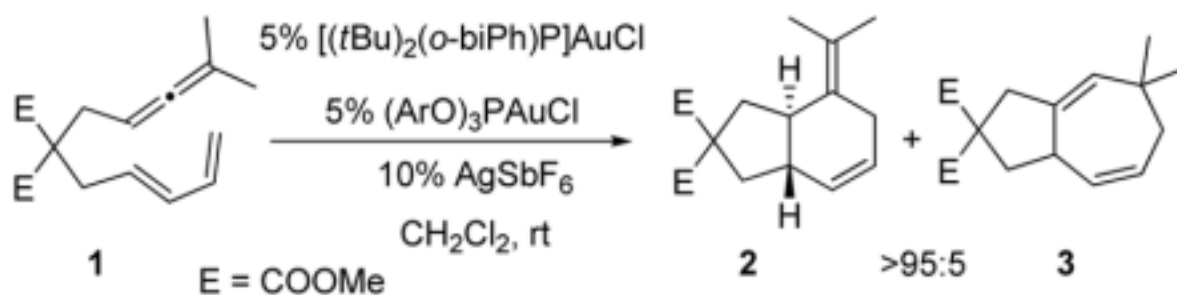

(2)

We next examined **TS52** and **TS53** (Figure 2) with different ligands in order to assess factors that might lead to a preference for 1,2-H or alkyl shift. In all cases, the 7-membered ring in **5** adopts a chair-like 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 C2 σ-lone pair is shifted towards 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(*t*Bu)$_2$(*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(*t*Bu)$_2$(*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.

Based on 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(*t*Bu)$_2$Ph]+ and predict a **2:3** ratio of 67:33 for this intermediate, which we confirmed experimentally (eq 3).
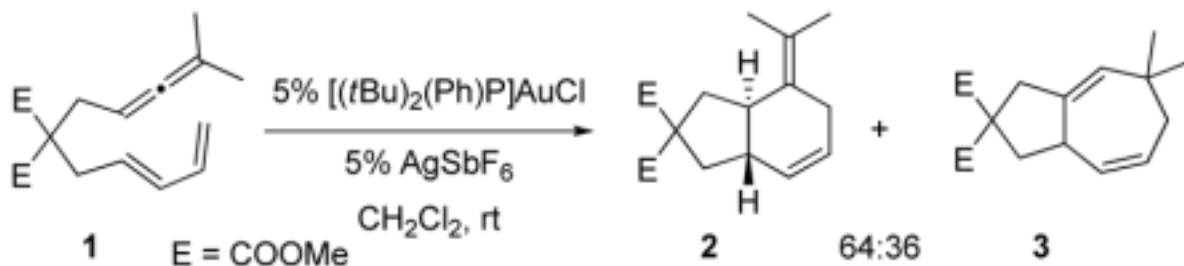
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Our analysis of the gold-catalyzed [4+2]- and [4+3]-cycloaddition reactions finds that both reactions proceed through an initial concerted [4+3]-cycloaddition of a gold-activated allene with a diene. The selectivity for either pathway arises primarily 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 propertes,[14] the sterics of the ligand can dramatically impact Au-C bonding, especially in [AuP(tBu)$_2$(o-biPh)]+-catalyzed reactions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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9. We were able to find stable intermediate 6, presumed to be on the path to step-wise 2+2 and 3+2 cycloaddition pathways. All attempts to locate a step-wise 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 JL. Chem–Eur J 2009;15:3336.

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15. Similar effects have been calculated for transition states for 1,2-H-shifts of singlet carbenes. See: (a) Keating AE, Garcia-Garibay MA, Houk KN. J Phys Chem A 1998;102:8467.and references therein (b) Albu TV, Lynch BJ, Truhlar DG, Goren AC, Hrovat DA, Borden WT, Moss RA. J Phys Chem A 2002;106:5323.

16. We were unable to locate a transition state for the 1,2-alkyl shift of the free carbene.

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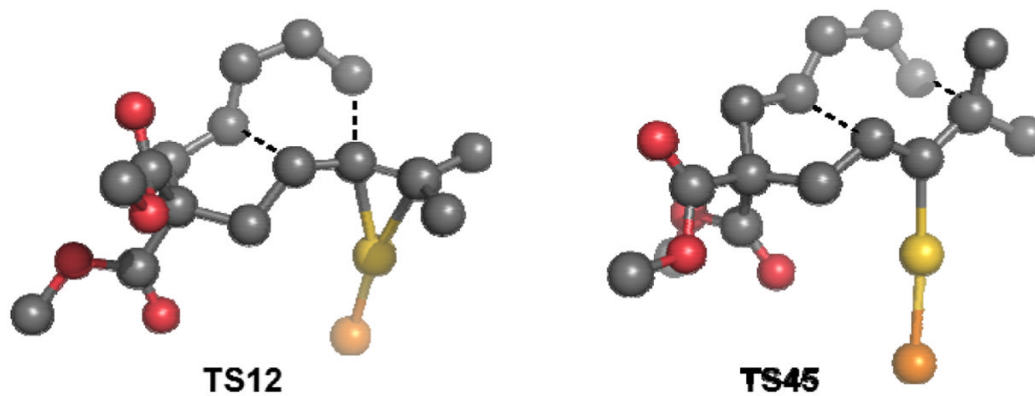
Figure 1.
Calculated transition state structures (L = PMe$_3$) for the concerted [4+2]- and [4+3]-cycloaddition reaction of dienes and gold-complexed allenes.
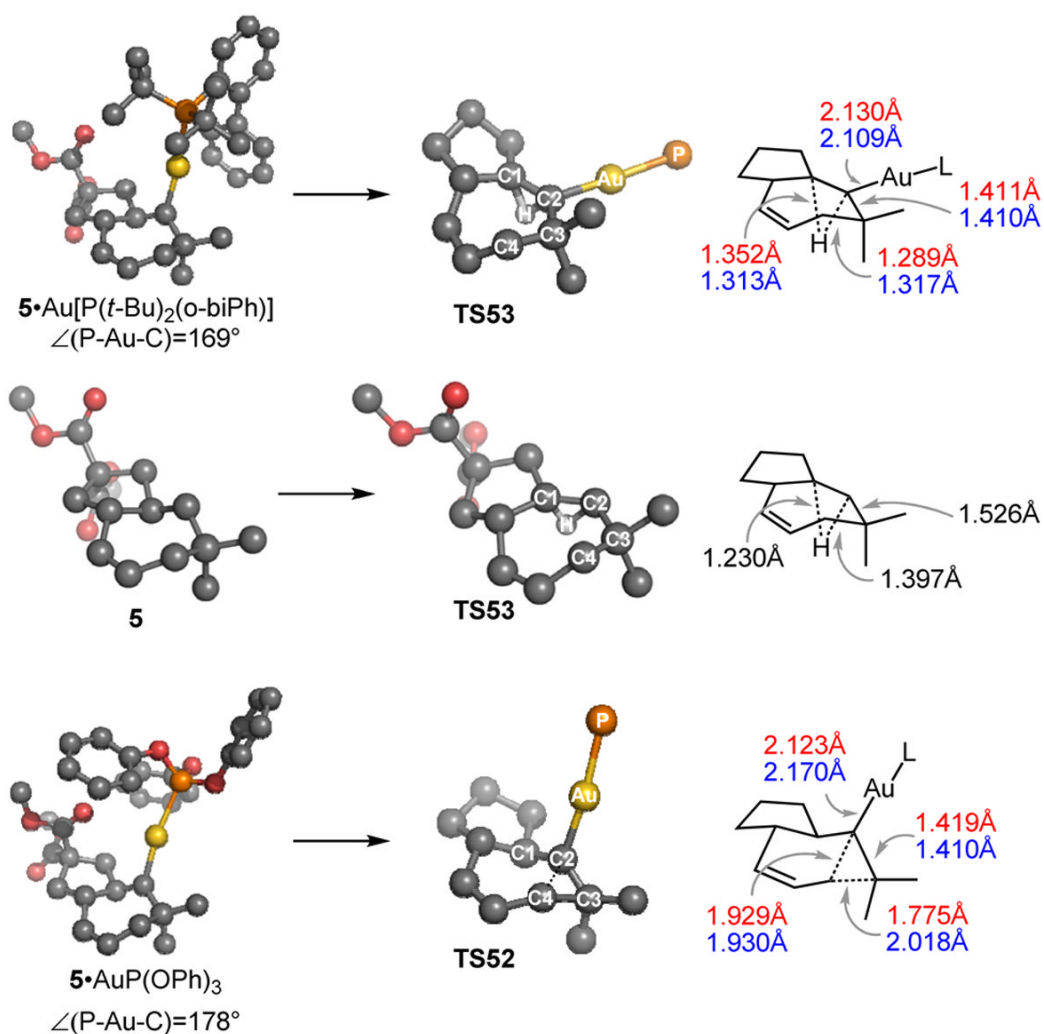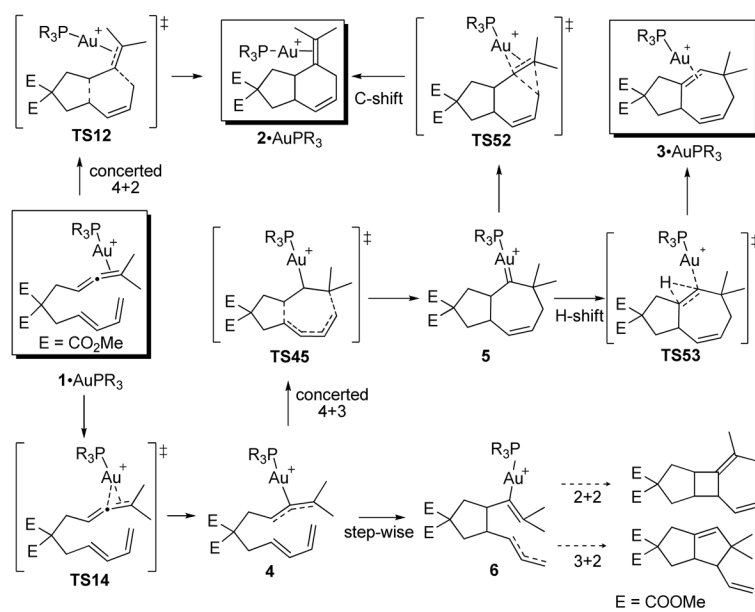
Figure 2.
Calculated structures for **5**, **TS53** (L= P(*t*Bu)$_2$(*o*-biPh) and metal-free), and **TS52** (L=P (OPh)$_3$). Selected bond lengths for **TS53** and **TS52** with L= P(*t*Bu)$_2$(o-biPh) and L=P(OPh)$_3$ shown in red and blue, respectively. Selected bond lengths for **5** and **TS53** for metal-free structures shown in black.

Scheme 1.
Au-catalyzed [4+3] and [4+2]-cycloadditions.

Table 1

Free energies (Δ*G*, kcal/mol) relative to **1·X** at 298 K.

X	AuPMe₃	AuP(OPh)₃	AuPPh₃	AuP(*t*Bu)₂ (*o*-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	–