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# Uncovering Subtle Ligand Effects of Phosphines Using Gold(I) Catalysis

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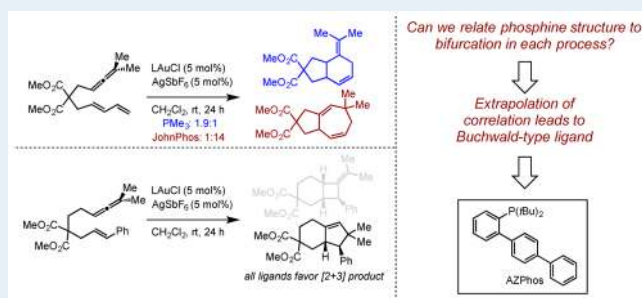
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## Supporting Information

**ABSTRACT:** Herein, we report the integration of simple linear regressions with gold(I) catalysis to interrogate the influence of phosphine structure on metal-catalyzed organic transformations. We demonstrate that observed product ratios in [4 + 3]/[4 + 2] cycloisomerization processes are influenced by both steric and electronic properties of the phosphine, which can be represented by the Au–Cl distance. In contrast, the observed selectivity of a similar [2 + 3]/[2 + 2] cycloisomerization is governed by L/B1, a steric parameter. Using this correlation, we were able to accurately predict the selectivity of a previously untested, Buchwald-type ligand to enhance selectivity for the same transformation. This ligand found further utility in increasing the selectivity of a previously reported gold-catalyzed cycloisomerization/arylation of 1,6-enynes by ~1 kcal/mol.

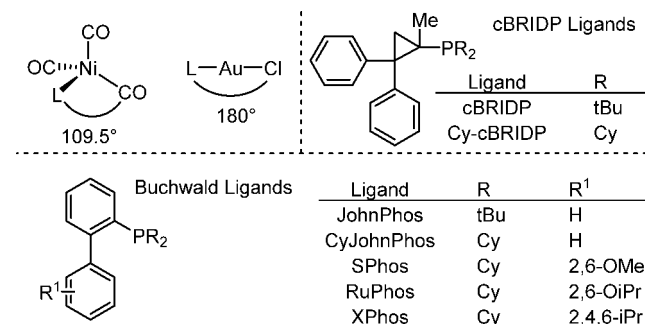
**KEYWORDS:** gold catalysis, cycloisomerization, phosphines, modeling, mechanism, ligand effects



## INTRODUCTION

Phosphine ligands have been demonstrated to be an invaluable ligand class for a multitude of metal-catalyzed organic transformations.<sup>1</sup> Quantitative relationships with phosphines have primarily focused on Tolman's cone angle or electronic parameter, with both being useful measures in correlating direct interactions;<sup>2</sup> however, the indirect interactions involved in determining reaction outcomes are often poorly understood. This is particularly striking in gold(I) catalysis,<sup>3</sup> where fewer steric contacts between substrate and ligand are observed as a function of the linear nature of the gold(I) complexes (Scheme 1).<sup>4</sup> In contrast, the enforced *trans*-relationship of the ligands allows for pronounced electronic effects. Given these features,

**Scheme 1. Geometries of Nickel and Gold Complexes, and Structures of cBRIDP and Buchwald Class Ligands Used in This Study**



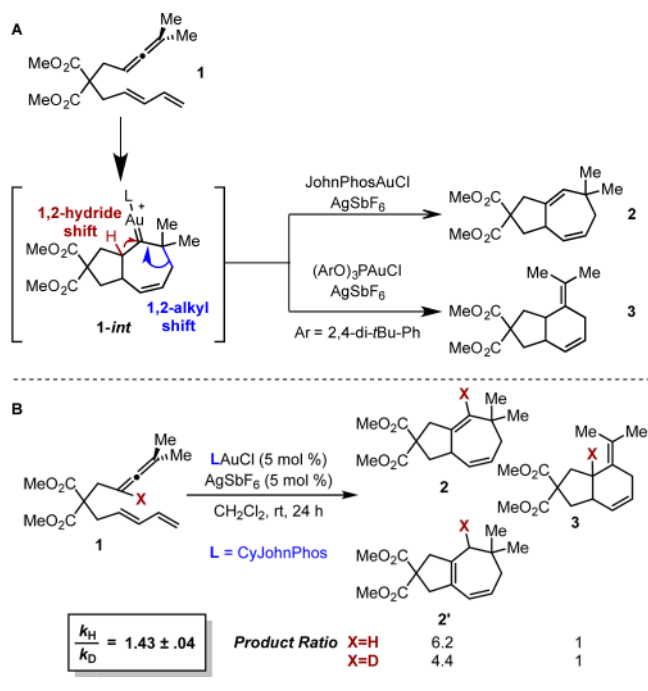
we envisioned gold(I) catalysis as the ideal platform for investigating nonintuitive effects of phosphine structure on reaction outcomes. Herein, we describe the leveraging of a multivariate analysis to reveal subtle ligand interactions resulting in greater mechanistic understanding and ultimately facilitating the prediction of a better performing ligand.<sup>5</sup>

To probe phosphine ligand structure in gold catalysis, we selected the [4 + 3] or [4 + 2] alkene–allene cycloaddition pathways, as the selectivity in this divergent reaction was profoundly dependent on ligand structure.<sup>6</sup> For example, treating allene–dienes with catalytic JohnPhosAuCl/AgSbF<sub>6</sub> to form the catalytically active, cationic, gold complex, primarily resulted in the formation of [4 + 3] cycloheptadiene products. However, use of 2,4-ditert-butyl-phenylphosphite-AuCl/AgSbF<sub>6</sub> as the catalyst led to the generation of [4 + 2] cyclohexene adducts (Scheme 2). This observed regiodivergence resulted in two proposed mechanisms: Initially, an electronic effect of the ligand was implicated as determining the selectivity of the reaction. A subsequent computational study suggested that the product distribution was driven by steric influences of ligand structure on the fate of a common intermediate (*I-int*).<sup>7</sup> The disagreement in proposed pathways and the impact of ligand structure highlights the challenges in investigating subtle ligand effects in gold(I) catalysis.

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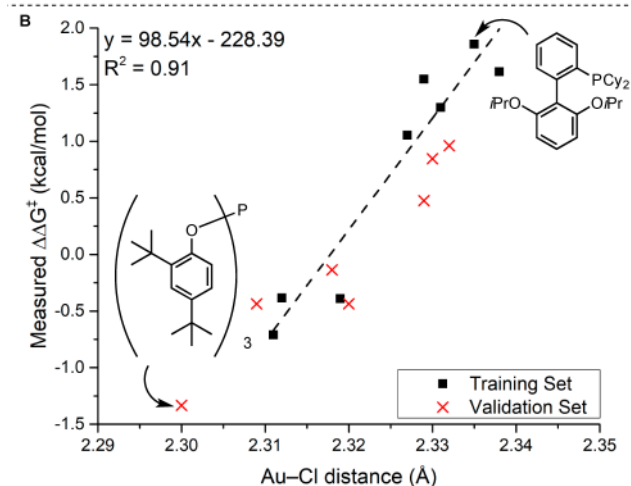
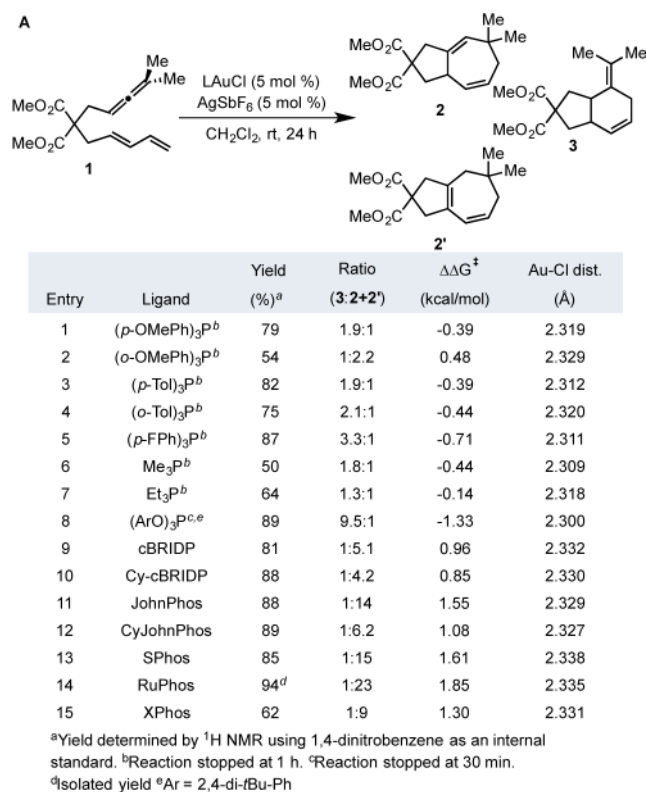
## Scheme 2. Ligand-Controlled Divergence in Gold-Catalyzed Cycloisomerization and Isotopic Labeling Effect



## RESULTS AND DISCUSSION

**[4 + 3]/[4 + 2] Cycloisomerization.** To probe the subtle steric and electronic effects of phosphine ligands in gold catalysis, we initiated our studies by defining a general mechanism that would account for the divergent formation of products in the [4 + 3]/[4 + 2] cycloisomerization reaction. Deuterated **1** was submitted to the reaction, and the resultant product ratio was compared to that generated from the protio variant (Scheme 2A). A significant difference in product ratios between the two reactions ( $k_H/k_D = 1.43 \pm 0.04$ ) was observed, suggesting the involvement of the C–H(D) bond in the selectivity-determining event (Scheme 2B). These data are consistent with the hypothesis that the reaction proceeds through a common intermediate, with divergence in selectivity occurring via either a 1,2-hydride or alkyl shift, which is in agreement with the computationally proposed mechanism.

Having gained evidence for the selectivity-determining step, we sought insight into the nature of the ligand effects on selectivity. To start, an empirical data set was constructed by exploring a diverse range of phosphine ligands, varying in steric and electronic properties for the [4 + 3]/[4 + 2] cycloisomerization reaction in Figure 1A.<sup>8</sup> These results lead to the initial delineation of two general classes of ligands: the Buchwald-type and BRIDP ligands. Tri-*o*-OMePh phosphine (Figure 1A, entries 2, 9–15) lead to preferential formation of **2**, whereas other ligands tested favored the formation of the [4 + 2]-cycloadduct (**3**, Figure 1A, entries 1, 3–8). The bulky Buchwald and BRIDP classes were initially developed for palladium catalysis because of their ability to occupy two coordination sites,<sup>9</sup> therefore, it is tempting to implicate a steric effect in this reaction. However, this hypothesis is complicated by the observation that the utilization of the large, sterically bulky tri-*o*-Tolyl phosphine (Figure 1A, entry 4) resulted in the preferential formation of **3** (Figure 1A). This apparent discrepancy prompted reconsideration of the initial hypothesis



**Figure 1.** (A) Data set design for [4 + 3]/[4 + 2] cycloisomerization. (B) Model showing correlation between measured  $\Delta\Delta G^\ddagger$  and Au–Cl distance.

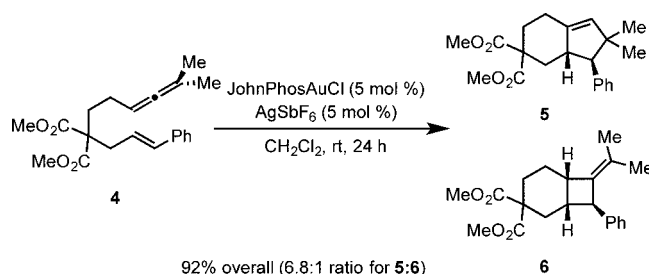
and a deeper investigation of how the ancillary phosphine ligand was influencing the reaction outcome.

Given that the relationship between ligand and selectivity was not immediately apparent, we sought to find a quantitative correlation<sup>5c,i</sup> between product selectivity and known parameters in order to probe the influence of ligands on reactivity. A training and validation set were designated to provide statistical significance to the analysis. To more accurately quantify ligand size, solid cone angles<sup>5b,c</sup> were utilized in favor of the classic Tolman cone angle. These measures have been shown to be useful in correlating steric effects.<sup>10</sup> However, steric descriptors including cone angle and Sterimol<sup>5a</sup> did not result in satisfying correlations (see Supporting Information). Further investigation identified the calculated Au–Cl bond distance, previously reported by Fey and co-workers,<sup>11</sup> as correlated to the observed

product ratios (Figure 1B). The Au–Cl distance is significantly affected by the electronic, as well as remote steric influence of the ligand and is, therefore, a measure of the “net ( $\sigma$ ) donation,” of the ligand. (For further comparative analysis between parameters, see Figure S1.) Thus, the observed correlation between selectivity and Au–Cl bond distance supports the hypothesis that the gold–carbenoid bond is altered by the electronic contribution of the phosphine, as well as subtle steric influences. This analysis is in agreement with the computationally proposed mechanism involving selectivity determining 1,2-hydride or alkyl shift, with both steric and electronic influences defining the product ratio by significantly altering the  $\Delta G^\ddagger$  for the 1,2-hydride shift in **1-int**, without affecting the energy of the 1,2-alkyl shift.<sup>7a</sup>

**[2 + 3]/[2 + 2] Cycloisomerization.** The simplicity of this correlation prompted us to question the generality of these conclusions in structurally analogous transformations. We previously reported the conversion of **4** to compounds **5** and **6** in 92% overall yield in a 6.8:1 ratio of cycloadducts, respectively (Scheme 3).<sup>6a</sup> The formation of a ratio of

**Scheme 3. Previously Reported Gold-Catalyzed [2 + 3]/[2 + 2] Cycloisomerization**



cycloadducts in the reaction raised the possibility that the ligand effects could be isolated and examined in order to reveal the mechanistic influence of the phosphine ligands.

A similar data set was collected to examine the structure–selectivity relationship in the [2 + 3]/[2 + 2] cycloisomerization (Figure 2). All evaluated ligands demonstrated a preference toward the formation of **5**. It was hypothesized that a comparable relationship between product ratio and Au–Cl distance would be evident if a similar mechanism was operative (Figure 2B). However, the lack of such a correlation led us to re-evaluate what factors may be influencing bifurcation in product formation. Comparison of other phosphine descriptors with the observed product distribution resulted in the determination of a univariate correlation between product ratio and the Sterimol average  $L/B_1$  of the ligand (Figure 2C). Sterimol parameters, originally developed by Verloop and co-workers, use three-dimensional measurements to describe nonspherical substituents.<sup>5a</sup> Thus,  $L/B_1$  likely describes the “depth” of the ligand as well as the steric hindrance proximal to the gold.

On the basis of this model, four possible reaction mechanisms were proposed: (1) Analogous to what was observed with [4 + 3]/[4 + 2] cycloisomerization, the [2 + 3]/[2 + 2] reaction may proceed through concerted formation of a common intermediate, followed by a selectivity-determining 1,2-hydride or 1,2-alkyl shift. (2) Concerted cyclization could be the selectivity determining step, as originally proposed for the [4 + 3]/[4 + 2] cycloisomerization. (3) Stepwise addition of the alkene into the gold–allyl species could precede

cyclization to the five-membered ring intermediate and a selectivity-determining 1,2-hydride or 1,2-alkyl shift, or (4) stepwise addition of the alkene into the gold–allyl species could be followed by a selectivity-determining cyclization directly to either the [2 + 3] or [2 + 2] product (Scheme 4).

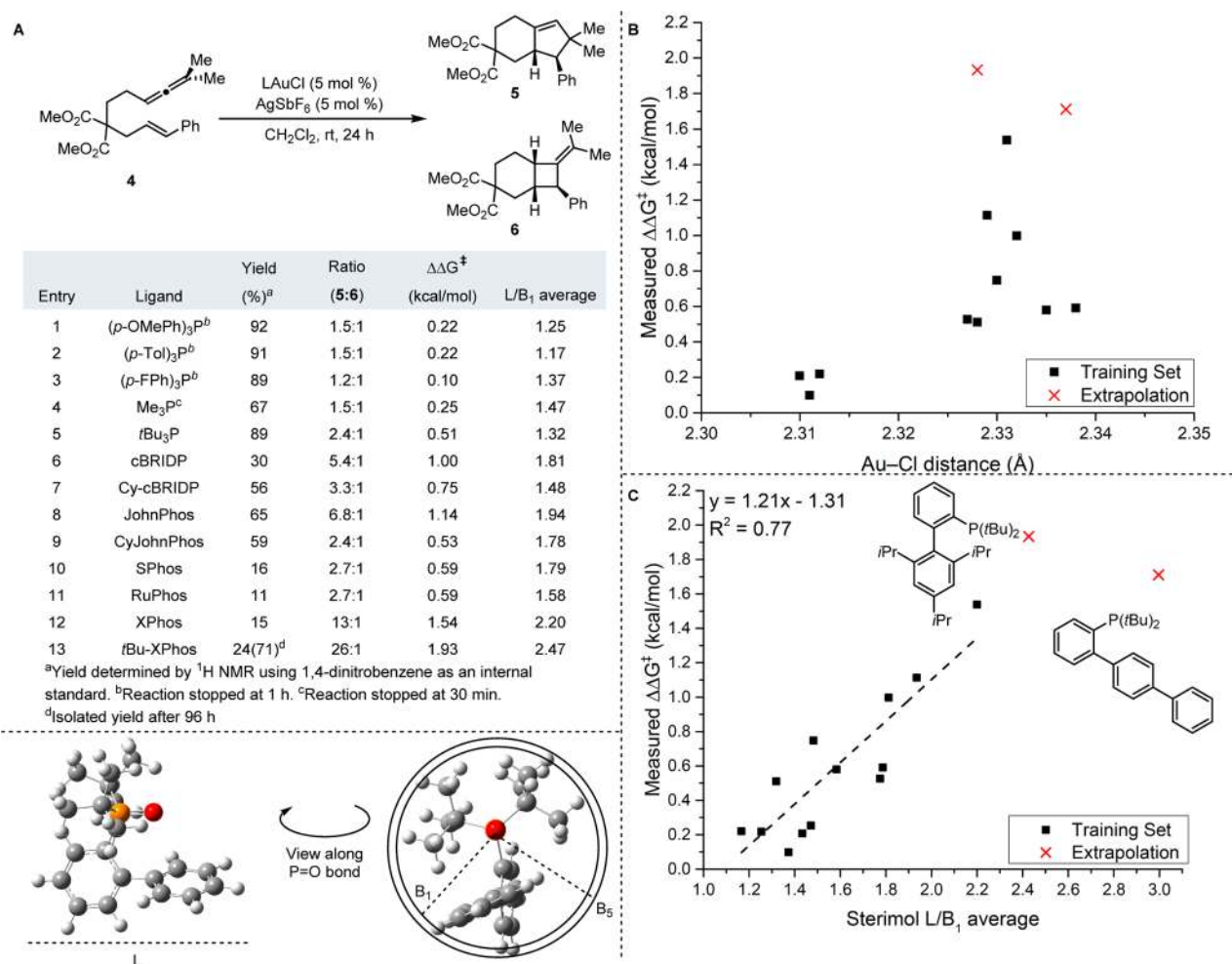
As a means to explore these possible pathways, the deuterated isotopomer of **4** was synthesized. Unlike the [4 + 3]/[4 + 2] cycloisomerization, this reaction displayed little-to-no change in selectivity, suggesting that a 1,2-hydride/1,2-alkyl shift is not involved in the selectivity-determining step, thus eliminating mechanisms 1 and 3 from consideration (Scheme 5).

In order to probe the role of either a concerted or stepwise mechanism during the selectivity-determining step, we turned to a Hammett analysis. It was hypothesized that the stepwise mechanism would result in a linear Hammett plot when compared to  $\sigma_{\text{para}}^+$ . Rather, the relative rates of reaction correlated well to  $\sigma_{\text{para}}$  with a significant slope of  $-3.65$ . These data suggest that a distinct carbocation is not likely formed in the reaction but that there is a considerable accumulation of positive charge in the transition state (Figure 3). We therefore exclude the possibility of a stepwise cyclization (4) and propose the mechanism proceeds through a concerted cyclization (2) from gold-coordinated **4**.<sup>12</sup>

As a robust correlation was identified between known parameters and reaction selectivity, virtual screening commenced to identify a ligand that would improve the reaction selectivity. As the product ratio correlates to the  $L/B_1$  of the ligand, two pathways were foreseen to increase selectivity:  $B_1$  could be decreased by exchanging the cyclohexyl rings for *tert*-butyl groups in XPhos, or  $L$  could be increased by extension of the biaryl ring in JohnPhos (Scheme 6). As an example of the former, *t*BuXPhos resulted in a product ratio of 26:1 ( $\Delta\Delta G^\ddagger = 1.93$  kcal/mol), slightly higher than predicted (17:1,  $\Delta\Delta G^\ddagger = 1.68$  kcal/mol). A novel ligand with an extended  $L$  value, (ditertbutyl-terphenyl)phosphine (AZPhos, **10**), was predicted to produce a 31:1 product ratio ( $\Delta\Delta G^\ddagger = 2.03$  kcal/mol) favoring **5**, an extrapolation of 1 kcal/mol from the training set. The observed selectivity of 17:1 ( $\Delta\Delta G^\ddagger = 1.68$  kcal/mol) is lower than expected; however, this ratio is within the range of predictions. These extrapolations demonstrate the power of using small data sets to provide nonintuitive results.

#### Extension of New Ligand to Arylation of 1,6-Enynes.

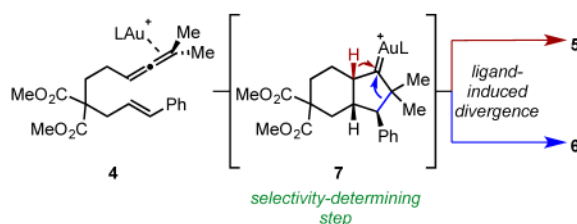
Having synthesized AZPhosAuCl and demonstrated its ability to catalyze the [2 + 3]/[2 + 2] cycloisomerization with improved selectivity, we sought to extend its utility in other gold-catalyzed processes. Given that the use of this ligand improved selectivity in a reaction presumably proceeding through a gold–carbenoid intermediate, we selected a previously reported transformation that also suggested a gold–carbenoid intermediate and possessed selectivity between two potential products. In this context, Echavarren and coworkers described a gold-catalyzed transformation, wherein site-selectivity of arylation in a 1,6-enyne cycloisomerization was controlled by the choice of ligand (Scheme 7).<sup>13</sup> The proposed mechanism involved a selectivity-determining attack of the indole nucleophile to a gold-stabilized cyclopropyl carbonyl cation **12** either at the gold–carbenoid carbon or the cyclopropyl carbon, eventually resulting in products **13** or **14**, respectively. It was hypothesized that the increased sterics of AZPhos would limit the direct attack on the carbene thus increasing selectivity. When JohnPhos was used, the ligand most similar to AZPhos, the reaction proceeded with an



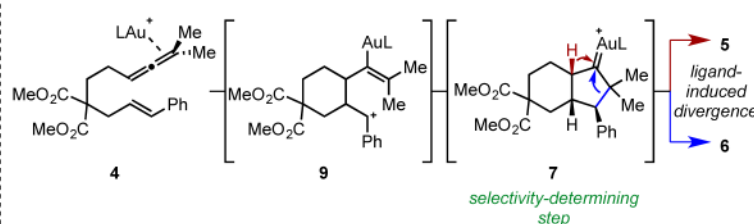
**Figure 2.** (A) Data set design for [2 + 3]/[2 + 2] cycloisomerization. (B) Model showing correlation between measured  $\Delta\Delta G^\ddagger$  and Au–Cl distance. (C) Model showing correlation between measured  $\Delta\Delta G^\ddagger$  and L/B<sub>1</sub> average.

#### Scheme 4. Possible Pathways for Regioselective [2 + 3]/[2 + 2] Cycloisomerization

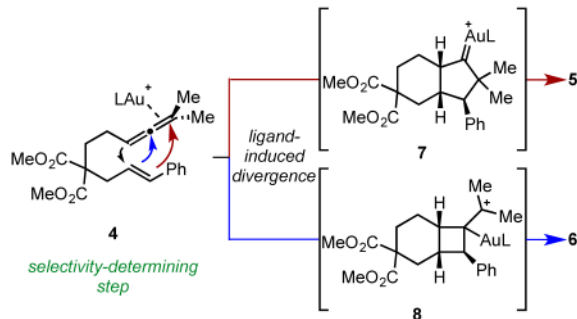
1. Concerted cyclization/shift determines selectivity



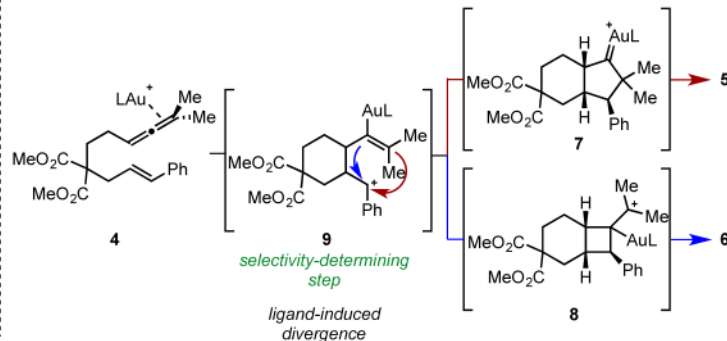
3. Stepwise cyclization/shift determines selectivity



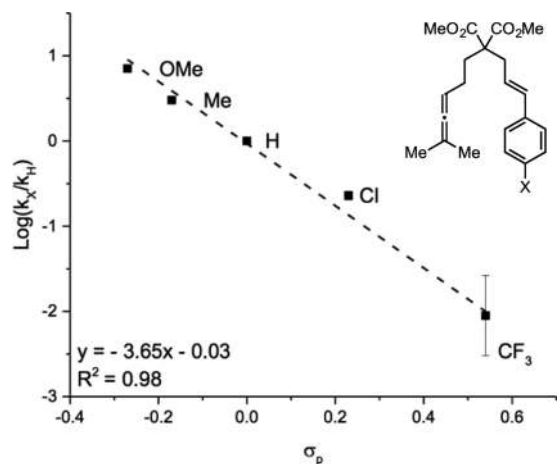
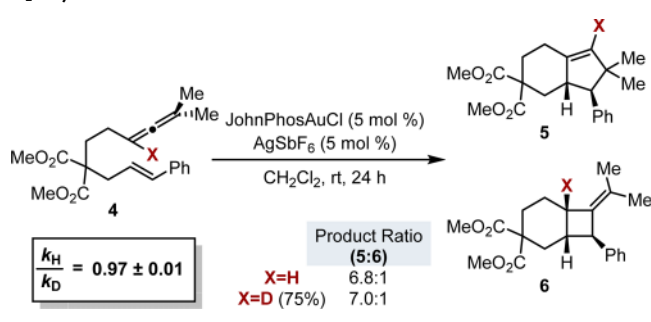
2. Concerted/cyclization determines selectivity



4. Stepwise/cyclization determines selectivity

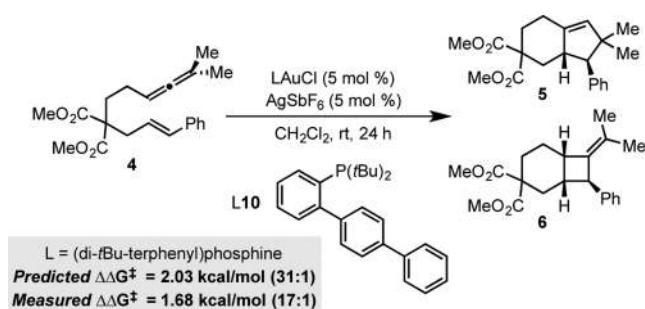


## Scheme 5. Deuterium Effect on Selectivity for [2 + 3]/[2 + 2] Cycloisomerization

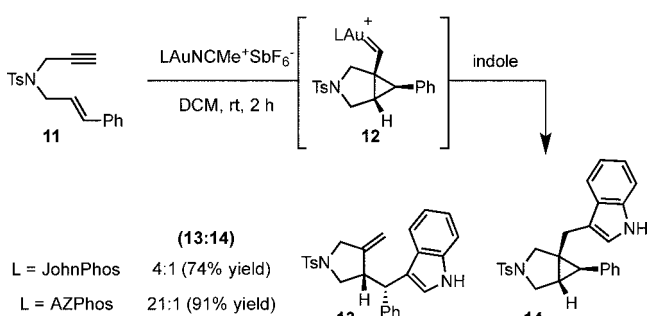


**Figure 3.** Hammett plot of  $\text{Log}(k_x/k_H)$  vs  $\sigma_{\text{para}}$  for gold-catalyzed [3 + 2]/[2 + 2] cycloisomerization. All data points are an average of three runs. See Supporting Information for further details.

## Scheme 6. Testing of Novel Ligand



## Scheme 7. Application of New Ligand in Arylation of 1,6-Enyne Cycloisomerization



observed 4:1 selectivity toward the ring-open product **13** over the cyclopropanated product **14**. Subjecting enyne **11** to the AZPhosAu(I)-catalyzed reaction produced a 21:1 selectivity of **13:14** in 91% overall yield. This result supports the broader utility of this ligand toward other ligand-controlled chemical transformations.

## CONCLUSIONS

The extraction of detailed mechanistic information from ligand effects in gold catalysis remains an omnipresent challenge. Commonly, the factors that influence the selectivity of an organometallic transformation are nonintuitive, and uncovering these small intricacies can be difficult. In this work, we have deployed a combination of classical, physical organic experiments and modern data analysis tools to provide detailed insight into the relationship between ligand structure and selectivity in gold(I)-phosphine-catalyzed cycloisomerization reactions.

Initial modeling of a [4 + 3]/[4 + 2] cycloisomerization reaction led to the hypothesis that the ligand's effect on the bond length is a key factor governing selectivity between 1,2-hydride and 1,2-alkyl shifts. In contrast, the case of the [2 + 3]/[2 + 2] cycloisomerization, a correlation was observed between the average L/B<sub>1</sub> and the product ratios, indicating a significant ligand steric effect. The complex nature of controlling factors in these two similar reactions demonstrates the aptitude of utilizing this methodology in gold(I) catalysis to identify nonobvious trends and influences. Drawing on insights from these correlations, a novel ligand was predicted that improved the selectivity in the [2 + 3]/[2 + 2] cycloisomerization. This ligand also performed exceptionally well in a disparate transformation that was proposed to involve gold-carbenoid intermediates. Current work to exploit this modeling strategy to both extract valuable mechanistic information and improve reaction performance in other gold-catalyzed processes is ongoing and will be reported in due course.

## ASSOCIATED CONTENT

## Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.7b00757.

Experimental details and compound characterization data (PDF)

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## Author Contributions

<sup>†</sup>A.H.C and Z.L.N. contributed equally.

## Notes

The authors declare no competing financial interest.

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(8) Validation of kinetic selectivities was performed for all ligand classes. Reactions were monitored by <sup>1</sup>H NMR to see if product ratios were constant over time and if decomposition pathways were observed; reactions would be stopped at appropriate times to accurately reflect kinetic selectivity.

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and isomerization of the *cis* isomer, were inconclusive. See [Supporting Information](#) for details.

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