# Ligand-Controlled Access to [4 + 2] and [4 + 3] Cycloadditions in Gold-Catalyzed Reactions of Allene-Dienes

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The utility of homogeneous transition-metal catalysis derives in part from the ability to influence the outcome of the catalyzed reaction by variation of the ancillary ligands.[1] We were initially attracted to LAu(I)X complexes as catalysts because of the potential of controlling reactivity[2] and stereoselectivity[3] by manipulating the neutral (L) and/or anionic (X)[4] ligands. While these ligand effects on catalysis with cationic gold(I) complexes have been demonstrated, examples of ligand variation as a means of achieving divergent reactivity in gold-catalyzed reactions remain elusive.[5,6] In this context, we were intrigued by the observation that in sharp contrast to the selective [2 + 2] cycloaddition of allenenes,[7] the triphenylphosphinegold(I)-catalyzed reaction of allene-diene **1** provided a 2:1 mixture of the [4 + 3][8] and [4 + 2][9] cycloadducts (eq 1). We were therefore attracted to the possibility that either cycloadduct could be accessed by variation of the ligand on the gold(I) catalyst.
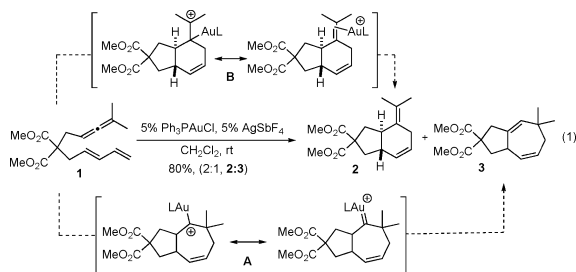
We hypothesized that the product selectivity in gold(I)-catalyzed cycloaddition reactions could be impacted by modulating the relative stability of the cationic transition states generated during the course of the cycloadditions. In particular, fine-tuning of the electronic properties of the catalyst should have a direct impact on the stability of the gold(I) carbenoid intermediate **A** formed in the [4 + 3] cycloaddition.[10] For example, we posited that the pathway leading to the [4 + 3] cycloadduct could be favored by employing electron-rich σ-donor ligands that would increase the relative stability of the pathway leading to **A** while having significantly less impact on the formation of **B**.

In accord with this hypothesis, replacing Ph₃P with the Takasago BRIDP ligands[11] resulted in highly selective formation of the seven-membered ring (Table 1, entries 2−5). Unfortunately, these reactions, as well as those catalyzed by (IPr)gold(I), produced varying amounts of olefin isomerization to cycloheptadiene isomer **3′**. The selectivity was improved to 96:4 in favor of the [4 + 3] cycloadduct **3** using di-*tert*-butylbiphenylphosphinegold(I)[12] as the catalyst (entry 6). Encouraged by these results, we considered that π-acceptor ligands might decrease the relative stability of **A** and therefore divert the reaction to the [4 + 2] cycloadduct. Gratifyingly, the use of arylphosphitegold(I) complexes[5b,13] exclusively produced the formal [4 + 2] cycloaddition product **2** in very good yields after 30 min (entries 8 and 9).

Table 1. Ligand Effects on Product Distribution[a]

entry	ligand (L)	2:3:3′ [b]	% yield[b]
1	Ph₃P	67:33:0	80
2	cy-cBRIDP	22:58:20	66
3	cy-vBRIDP	17:67:16	73
4	cBRIDP	17:73:10	74
5	vBRIDP	7:87:6	80
6	IPr	7:89:4	75
7	di-*tert*-butylbiphenylphosphine	4:96:0	89
8	tris(2,4-di-*tert*-butyl phenyl)phosphite	100:0:0	91
9	(PhO)₃P	100:0:0	89

[a] Reaction conditions: 0.1 M allene-diene, 5 mol % LAuCl, and 5 mol % AgSbF₆ in CH₂Cl₂ at room temperature. [b] Determined by ¹H NMR using 1,3,5-trinitrobenzene as an internal standard.

With these results in hand, we examined the scope of the gold(I)-catalyzed cycloaddition reactions. The triarylphosphitegold(I)-catalyzed [4 + 2] cycloaddition showed excellent tolerance for substitution on the diene component (examples **2** and **4−6** in Scheme 1). For example, a 1,1-disubstituted diene underwent the

Scheme 1. [4 + 2] Cycloaddition of Allene-Dienes
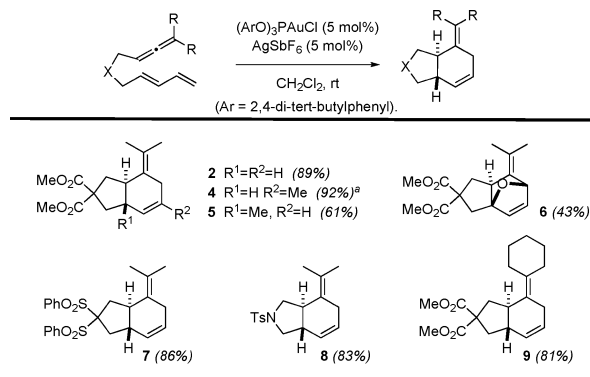
[a] Isolated as a 81:19 mixture of **4**:**10**

gold-catalyzed [4 + 2] cycloaddition to afford cycloadduct **5** containing a quaternary carbon. Variations in the tether were also accepted, as demonstrated by the cycloaddition leading to pyrrolidine **8**. In all cases, the reactions were highly diastereoselective, affording exclusively the *trans*-fused cycloadduct.[14,15] With the exception of the formation of **4**, the arylphosphitegold(I)-catalyzed reaction was highly selective for the [4 + 2] cycloadduct.

The phosphinegold(I)-catalyzed [4 + 3] cycloaddition also showed excellent scope. The reaction also tolerated variation in the tether and the allene and alkene substituents (Scheme 2). For example, a *trans,trans*-1,4-disubstituted diene underwent the gold-catalyzed cycloaddition to afford cycloheptadiene **13** as a single
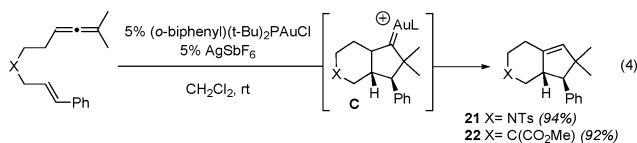
Scheme 2. [4 + 3] Cycloaddition of Allene-Dienes
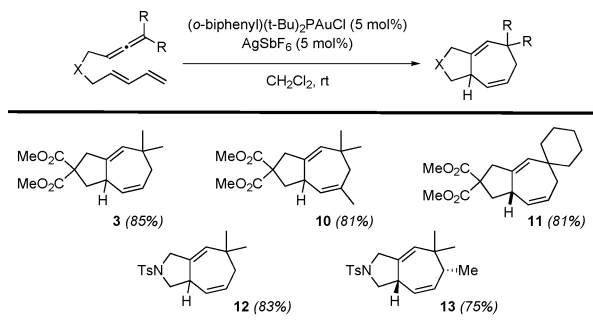
diastereomer. Moreover, in accord with our previous observations,[16] treatment of **1** with 5 mol % IPrAuCl/AgSbF$_6$ in the presence of excess diphenyl sulfoxide led to formation of *trans*-fused bicyclic ketone **14** in 53% yield (eq 2).
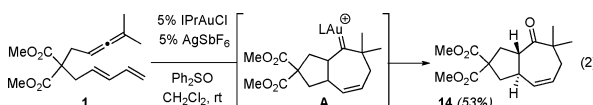
In contrast to the stereochemical outcome of the related [2 + 2] cycloaddition reaction,[7] gold(I)-catalyzed [4 + 2] and [4 + 3] cycloaddition reactions of deuterium-labeled dienes **15** and **16** were stereospecific (eq 3). For example, di-*tert*-butylbiphenylphosphinegold(I)-catalyzed reaction of **15** gave **17** as a single diastereomer (for additional details, see the Supporting Information). This observation suggests that the [4 + 2] and [4 + 3] cycloaddition reactions may proceed through concerted mechanisms;[8] however, a stepwise mechanism involving generation of an allyl cation from the addition of the diene to a gold-activated allene cannot be excluded.[15,17]
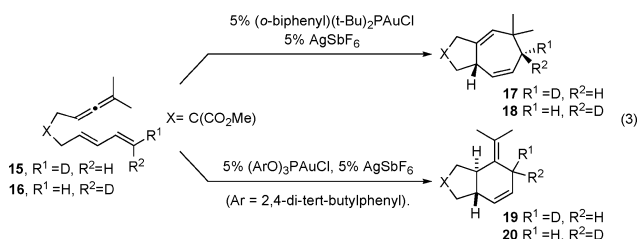
On the basis of these results, we revisited the gold(I)-catalyzed reaction of allenes to determine whether ligand control could be employed to divert the previously reported [2 + 2] cycloaddition reaction[7] toward the [3 + 2] cycloaddition reaction manifold. We were pleased to find that the di-*tert*-butylbiphenylphosphinegold(I)-catalyzed reaction of phenyl-substituted enallenes led to exclusive formation of cyclopentene cycloadducts **21** and **22** as single diastereomers in high yield (eq 4). In this case, the reaction likely proceeds via a stepwise mechanism[18] in which ligand effects stabilize the pathway proceeding through gold(I)-stabilized cation **C**.

In conclusion, we have demonstrated that high selectivity can be achieved in gold(I)-catalyzed intramolecular [4 + 2] and [4 + 3] cycloaddition reactions of allene-dienes. The studies presented herein lend further support to the hypothesis that gold(I) complexes are capable of stabilizing adjacent carbocations, such as **A** and **C**, and that this stabilization can be modulated by adjusting the electronic properties of the ancillary ligands. Since this class of intermediate is prevalent in gold(I)-catalyzed transformations,[19] the development of reactions that take advantage of this ligand-controlled reactivity is ongoing and will be reported in due course.

Supporting Information Available: Experimental procedures, compound characterization data, and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) van Leeuwen, P. W. N. M. *Homogenous Catalysis: Understanding the Art*; Kluwer Academic Publishers: Dordrecht, The Netherlands, 2004; Chapter *1*. (b) van Leeuwan, P. W. N. M.; Kamer, P. C. J.; Reek, J. N. H.; Dierkes, P. *Chem. Rev.* **2000**, *100*, 2741. (c) Tolman, C. A. *Chem. Rev.* **1977**, *77*, 313.
(2) (a) Teles, J. H.; Brode, S.; Chabanas, M. *Angew. Chem., Int. Ed.* **1998**, *37*, 1415. (b) For a review of ligand effects in Au catalysis, see: Gorin, D. J.; Sherry, B. D.; Toste, F. D. *Chem. Rev.* **2008**, *108*, 3351.
(3) (a) Ito, Y.; Sawamura, M.; Hayashi, T. *J. Am. Chem. Soc.* **1986**, *108*, 6405. (b) For a review of stereoselective Au catalysis, see: Widenhoefer, R. A. *Chem.—Eur. J.* **2008**, *14*, 5382.
(4) (a) LaLonde, R. L.; Sherry, B. D.; Kang, E. J.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 2452. (b) Hamilton, G. L.; Kang, E. J.; Mba, M.; Toste, F. D. *Science* **2007**, *317*, 496.
(5) (a) Lemière, G.; Gandon, V.; Agenet, N.; Goddard, J.-P.; de Kozak, A.; Aubert, C.; Fensterbank, L.; Malacria, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 7596. (b) Gorin, D. J.; Watson, I. D. G.; Toste, F. D. *J. Am. Chem. Soc.* **2008**, *130*, 3736. (c) Xia, Y.; Dudnik, A. S.; Gevorgyan, V.; Li, Y. *J. Am. Chem. Soc.* **2008**, *130*, 6940.
(6) For selected examples of ligand-controlled divergent reactivity, see: (a) Trost, B. M.; Rhee, Y. H. *J. Am. Chem. Soc.* **2002**, *124*, 2528. (b) Makino, T.; Itoh, K. *J. Org. Chem.* **2004**, *69*, 395. (c) Kezuka, S.; Okado, T.; Niou, E.; Takeuchi, R. *Org. Lett.* **2005**, *7*, 1711. (d) Gray, B. L.; Schreiber, S. L. *J. Comb. Chem.* **2007**, *9*, 1028. (e) Walczak, M. A. A.; Wipf, P. *J. Am. Chem. Soc.* **2008**, *130*, 6924.
(7) Luzung, M. R.; Mauleón, P.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 12402.
(8) Pt-catalyzed [4 + 3]: (a) Trillo, B.; López, F.; Gulías, M.; Castedo, L.; Mascareñas, J. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 951. During the preparation of this manuscript, a related NHCAu(I)-catalyzed [4 + 3] cycloaddition was reported: (b) Trillo, B.; López, F.; Montserrat, S.; Ujaque, G.; Castedo, L.; Lledós, A.; Mascareñas, J. L. *Chem.—Eur. J.* **2009**, *15*, 3336.
(9) Rh-catalyzed [4 + 2]: Wender, P. A.; Jenkins, T. E.; Shigeaki, S. *J. Am. Chem. Soc.* **1995**, *117*, 1843.
(10) The choice of ligand has been shown to have an impact on the reactivity of Rh carbenoid intermediates: (a) Padwa, A.; Austin, D. J.; Price, A. T.; Semones, M. A.; Doyle, M. P.; Protopopova, M. A.; Winchester, W. R.; Tran, A. *J. Am. Chem. Soc.* **1993**, *115*, 8669. (b) Mehía-Oneto, J. M.; Padwa, A. *Tetrahedron Lett.* **2004**, *45*, 9115, and references therein.
(11) Suzuki, K.; Hori, Y.; Nishikawa, T.; Kobayashi, T. *Adv. Synth. Catal.* **2007**, *349*, 2089.
(12) Nieto-Oberhuber, C.; López, S.; Echavarren, A. M. *J. Am. Chem. Soc.* **2005**, *127*, 6178.
(13) López, S.; Herrero-Gómez, E.; Pérez-Galán, P.; Nieto-Oberhuber, C.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 6029.
(14) This was established by X-ray analysis of [4 + 2] cycloadduct **7** (see the Supporting Information).
(15) The formal intramolecular [4 + 2] cycloaddition of allyl cations and dienes also provides the endo cycloadduct: (a) Gassman, P. G.; Singleton, D. A. *J. Am. Chem. Soc.* **1984**, *106*, 6085. (b) Gassman, P. G.; Singleton, D. A. *J. Org. Chem.* **1986**, *51*, 3075.
(16) Witham, C. A.; Mauleón, P.; Shapiro, N. D.; Sherry, B. D.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 5838.
(17) This would require rapid trapping of the allyl cation. For an excellent discussion of the stereochemical course of allyl cation cycloadditions, see: Hoffman, H. M. R. *Angew. Chem., Int. Ed.* **1984**, *23*, 1.
(18) (a) Giguere, R. J.; Tassely, S. M.; Rose, M. I.; Krishnamurthy, V. V. *Tetrahedron Lett.* **1990**, *31*, 4577. (b) Harmata, M. *Tetrahedron* **1997**, *53*, 6235.
(19) (a) Fürstner, A.; Davies, P. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 2. (b) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 31. (c) Gorin, D. J.; Toste, F. D. *Nature* **2007**, *446*, 395. (d) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Rev.* **2008**, *108*, 3326.

JA901649S