

Gold(I)-Catalyzed Enantioselective
[4 + 2]-Cycloaddition of Allene-dienes

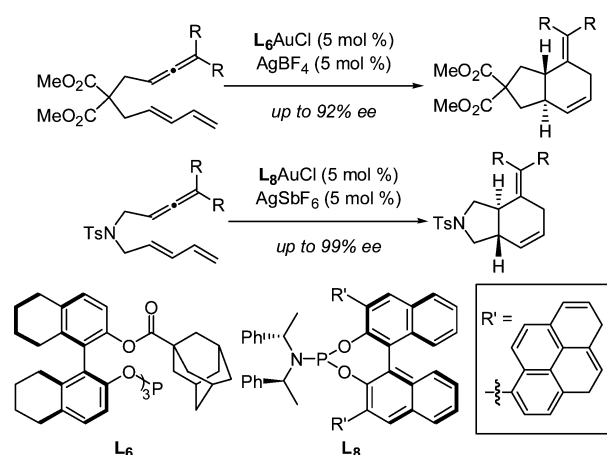
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ABSTRACT



An enantioselective gold(I)-catalyzed intramolecular [4 + 2]-cycloaddition of allenes and dienes is reported. The reactions allow for the asymmetric synthesis of *trans*-hexahydroindenes and pyrrolidine products using C_3 -symmetric phosphitegold(I) and *ortho*-arylphosphoramiditegold(I) complexes as catalysts, respectively.

The nature of the ancillary ligand can have a dramatic impact on the course of gold(I)-catalyzed reactions.¹ Gold(I) complexes of N-heterocyclic carbene,² phosphites,³ and bidentate,⁴ electron-deficient⁵ and bulky⁶ phosphines can display dramatically different reactivity and selectivity. We recently

reported a striking example of ligand-controlled reactivity in which allene-dienes underwent a selective [4 + 2]- or [4 + 3]-cycloaddition catalyzed by gold complexes of phosphites and bulky phosphines, respectively.⁷ With few exceptions,⁸ enantioselective gold(I)-catalyzed transformations

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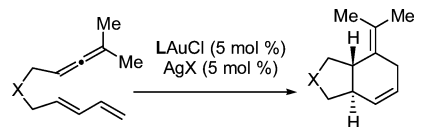
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have largely relied on the use of bis(gold)–phosphine complexes.⁹ Herein we report that, in the course of developing an enantioselective variant of the gold-catalyzed [4 + 2]-cycloaddition, we have uncovered two new ligand platforms for asymmetric gold catalysis.^{9m}

Given the success of bidentate phosphines in gold-catalyzed enantioselective reactions, our initial efforts toward an enantioselective [4 + 2]-cycloaddition focused on the use of chiral diphosphonites¹⁰ as ligands. Unfortunately, the **L**₁ and **L**₂Au(I)-catalyzed reaction of **1** failed to produce any of the desired cycloadduct (Table 1, entries 1 and 2). Moreover, racemic **3** was formed in the chiraphite(**L**₃)Au(I)-catalyzed reaction of **1** (entry 3). As a result of the lack of success experienced with gold complexes of bidentate ligands, we then decided to examine the gold(I) complexes of chiral monodentate phosphite-like ligands as catalysts. While the gold(I) complex of phosphoramidite **L**₄¹¹ did catalyze the desired transformation, it afforded cycloadducts **3** and **4** with low enantiomeric excess (entries 4 and 5).

During the course of our studies, Reetz reported the use of configurationally stable C₃-symmetric monodentate phosphite ligand **L**₅ in the Rh-catalyzed enantioselective hydrogenation of homoallylic alcohols.¹² We were attracted to this type of ligand because the ester moiety appears to extend outward, potentially providing a chiral environment around the gold atom (Figure 1). We were pleased to find that, while only a low degree of enantioinduction was observed with **L**₅Au(I)-catalyzed reaction of **1** (entry 6), this complex catalyzed the formation of cycloadduct **4** in an encouraging 66% ee;¹³ however, a small amount of the competing [4 + 3]-cycloaddition was observed (entry 7). The chemo- and enantioselectivity of this transformation could be improved by changing the solvent from dichloromethane to benzene (entry 8). Employing the H₈-BINOL derived ligand **L**₆ resulted in substantially improved enantioselectivity, yielding **4** in 82% ee in dichloromethane (entry 9). In this case, the use of benzene as solvent resulted in the formation of substantial amounts of the [4 + 3]-cycloadduct (entry 10). The chemoselectivity was restored by replacing the SbF₆⁻

Table 1. Ligand Optimization for the Enantioselective [4 + 2]-Cycloaddition of Allene-dienes

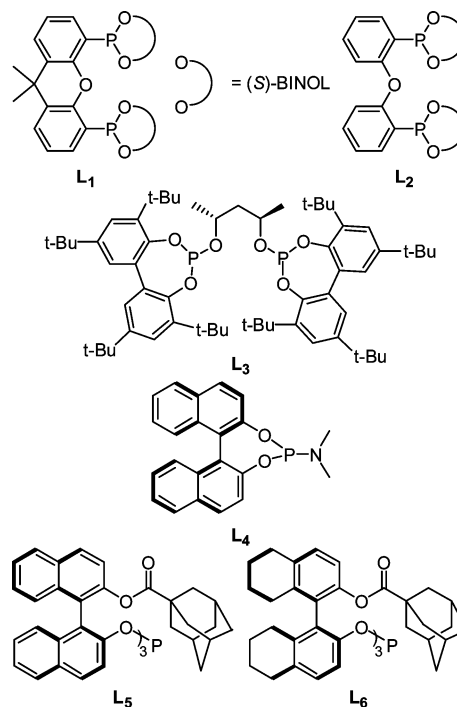


1 X = NTs
2 X = C(CO₂Me)₂

3 X = NTs
4 X = C(CO₂Me)₂

entry	substrate	ligand (L)	X/solvent	yield (%)	ee (%)
1	1	L ₁	SbF ₆ /CH ₂ Cl ₂	NR	--
2	1	L ₂	SbF ₆ /CH ₂ Cl ₂	NR	--
3	1	L ₃	SbF ₆ /CH ₂ Cl ₂	91	0
4 ^a	1	(<i>R</i>)- L ₄	SbF ₆ /CH ₂ Cl ₂	88 ^b	14
5 ^a	2	(<i>R</i>)- L ₄	SbF ₆ /CH ₂ Cl ₂	86	10
6	1	(<i>R</i>)- L ₅	SbF ₆ /CH ₂ Cl ₂	92	-16
7	2	(<i>S</i>)- L ₅	SbF ₆ /CH ₂ Cl ₂	90 ^c	66
8	2	(<i>R</i>)- L ₅	SbF ₆ /C ₆ H ₆	90	-74
9	2	(<i>S</i>)- L ₆	SbF ₆ /CH ₂ Cl ₂	92	82
10	2	(<i>S</i>)- L ₆	SbF ₆ /C ₆ H ₆	92 ^d	nd
11	2	(<i>S</i>)- L ₆	BF ₄ /C ₆ H ₆	87	92
12	1	(<i>S</i>)- L ₆	SbF ₆ /C ₆ H ₆	86	34
13	1	(<i>R</i>)- L ₆	SbF ₆ /CH ₂ Cl ₂	76	-24

^a 10 mol % **L**₄AuCl was used. ^b Isolated as a 13:1 mixture of [4 + 2]- and [4 + 3]-cycloadducts. ^c Isolated as a 24:1 mixture of [4 + 2]- and [4 + 3]-cycloadducts. ^d Isolated as a 7:1 mixture of [4 + 2]- and [4 + 3]-cycloadducts.



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counterion with BF₄⁻, allowing for the **L**₆Au(I)-catalyzed formation of **4** in 92% ee with complete diastereo- and chemoselectivity (entry 11). Unfortunately, significant erosion in the enantiomeric excess was observed in the **L**₆Au(I)-catalyzed reaction of **1**, providing cycloadduct **3** with low enantioselectivity (entries 12 and 13).

Given the promising results and with optimized reaction conditions, we set out to examine the scope of the enanti-

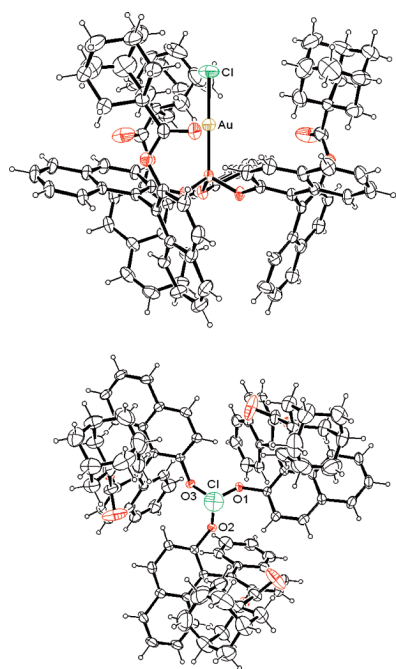


Figure 1. X-ray structure of (*S,S,S*)-**L**₅AuCl. Side view (top) and view along the C₃ axis of the chiral complex (bottom).

oselective gold(I)-catalyzed [4 + 2]-cycloaddition reaction. Substitution on the diene component was well tolerated, efficiently providing **5** and **6** in 88% and 82% ee, respectively (Table 2, entries 2 and 3). Accordingly, a 1,1-disubstituted

Table 2. Asymmetric Gold(I)-Catalyzed Cycloadditions of Allene-dienes with **L**₆AuCl



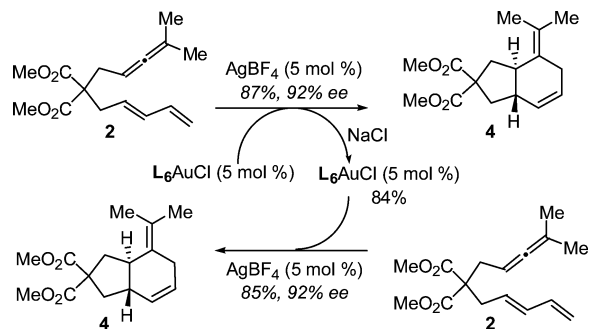
entry	R ¹	R ²	R ³	R ⁴	product	yield (%)	ee (%)
1	Me	Me	H	H	4	87	92
2	Me	Me	H	Me	5	70 ^a	88
3	Me	Me	Me	H	6	50	82
4	Me	-(CH ₂) ₄ -	H	H	7	93	86
5	Me	-(CH ₂) ₅ -	H	H	8	92	82
6	Bn	Me	H	H	9	94	83 ^b

^a Reaction resulted in a 85:15 mixture of [4 + 2]- and [4 + 3]-cycloaddition products. The yield is that of **5** after isolation. ^b Reaction carried out in CH₂Cl₂ at -30 °C.

diene underwent the gold(I)-catalyzed cycloaddition to afford cycloadduct **6** containing a quaternary stereogenic center (entry 3). Variation in the allene provided **7** and **8** with little decrease in enantiomeric excess (entries 4 and 5). In all cases, the reactions were highly diastereoselective, affording exclusively the *trans*-fused bicyclo[4.3.0]nonane ring system.

With the exception of the formation of **5**, the reaction was also highly selective for the [4 + 2]-cycloadduct with no observable formation of the isomeric [4 + 3]-counterparts. Importantly, silica gel chromatography of the crude reaction allowed not only for the purification of the desired product but also for the recovery of the **L**₆AuCl complex in up to 84% yield (Scheme 1). The recovered catalyst could be reused with no observable erosion in the enantioselectivity of the product.

Scheme 1. Recovery of **L**₆AuCl



As a result of the low enantiomeric excess observed in the cycloaddition leading to pyrrolidine **3** (Table 1, entries 12 and 13) we returned to chiral phosphoramiditegold(I) complexes as catalysts. Our initial studies pointed to the fact that the latter catalyst could potentially be more selective in the cycloadditions of *N*-Tos tethered substrates (Table 1, entries 4 and 5). Thus, when the phosphoramidite dimethylamine moiety was changed to a bis(phenylethyl)amine ((*S,S,S*)-**L**₇),¹⁴ the gold(I)-catalyzed reaction produced **3** with a modest improvement in enantioselectivity to 21% ee (89% yield). Examination of the X-ray crystal structure of **L**₄AuCl (Figure 2) suggested that *ortho*-

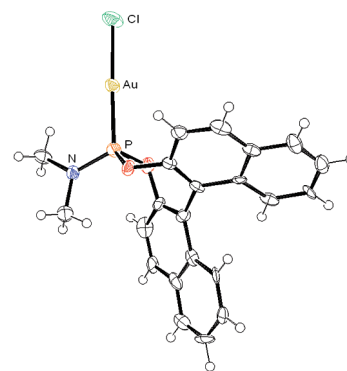


Figure 2. X-ray structure of (*S*)-**L**₄AuCl.

substitution on the phosphoramidite ligands¹⁵ might provide a steric environment similar to that found with phosphites **L**₅ and **L**₆. After a systematic study of various substituents, we were

(14) The gold(I)-catalyzed reaction of **1** using (*R,S,S*)-**L**₇ as the ligand afforded **3** in 92% yield and 0% ee.

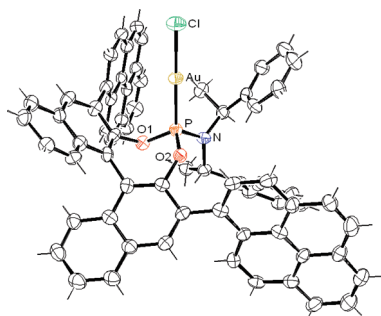
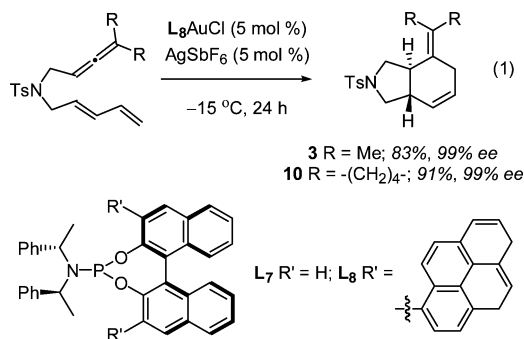


Figure 3. X-ray structure of (*S,S,S*)-**L**₈AuCl.

pleased to find that the gold(I) complex of pyrenyl-substituted ligand **L**₈ (Figure 3) catalyzed the formation of **3** in 83% yield and with a markedly improved 99% ee (eq 1).¹⁶ Similarly, varying the allene moiety also produced pyrrolidine **10** in 91% yield and an excellent 99% ee.¹⁷



In conclusion, we have demonstrated that high enantioselectivity can be achieved for gold(I)-catalyzed intramolecular [4 + 2] cycloaddition reactions of diene-allenes. Two complementary catalyst systems have been developed: *C*₃-symmetric phosphitegold(I) complexes are employed for the enantioselective synthesis of *trans*-hexahydroindenes, and pyrrolidine products are prepared using *ortho*-arylphosphoramiditegold(I) complexes as catalysts. These studies demonstrate that, despite the linear geometry of gold(I) complexes, chiral monodentate phosphorus-based ligands can be employed in asymmetric gold(I) catalysis.⁸ Application of these phosphite and phosphoramiditegold(I) complexes in other enantioselective transformations is ongoing and will be reported in due course.

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Supporting Information Available: Experimental procedures and compound characterization data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(16) For additional *ortho*-substituted phosphoramiditegold(I) complexes that were examined, see Supporting Information.

(17) Chiral phosphoramiditegold(I)-catalyzed reactions of **2** gave **4** with only modest enantioselectivity (up to 54% ee). **L**₈AuCl/AgSbF₆ catalyst system reacted sluggishly with **2**.