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Phosphoramidite Gold(I)-Catalyzed Diastereo- and Enantioselective Synthesis of 3,4-Substituted Pyrrolidines

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Abstract

In this article the utility of phosphoramidite ligands in enantioselective Au^I catalysis was explored in the development of highly diastereo- and enantioselective Au^I-catalyzed cycloadditions of allenes. A Au^I-catalyzed synthesis of 3,4-disubstituted pyrrolidines and γ -lactams is described. This reaction proceeds through the enantioselective Au^I-catalyzed cyclization of allenes to form a carbocationic intermediate that is trapped by an exogenous nucleophile, resulting in the highly diastereoselective construction of three contiguous stereogenic centers. A computational study (DFT) was also performed to gain some insight into the underlying mechanisms of these cycloadditions. The utility of this new methodology was demonstrated through the formal synthesis of (–)-isocynometrine.

1. Introduction

The enantioselective synthesis of functionalized pyrrolidines has attracted significant interest due to their abundance in bioactive natural and unnatural products, and use as chiral ligands and organocatalysts.¹ Their importance has inspired the development of diverse methods for their enantioselective construction including transition metal-catalyzed hydroamination,² cycloaddition³ and cycloisomerization reactions.⁴ Despite these advances, enantioselective access to 3,4-substituted pyrrolidines⁵ remains a synthetic challenge. Over the past decade, homogeneous Au^I catalysis has opened the door to a plethora of highly complex molecular frameworks.⁶ The operational simplicity and stability of Au^I complexes to air and moisture has made them, arguably, a leading contender in the field of asymmetric catalysis. As a result, we sought a diastereo- and enantioselective Au^I-catalyzed entry into 3,4-substituted pyrrolidines.

We had previously observed the formation of pyrrolidines during the investigation of the mechanism of the Au^I-catalyzed [2+2]-cycloaddition of allenes. These studies suggested that the *trans*-3,4-substituted pyrrolidines derived from kinetically generated cationic intermediate **A** (Scheme 1);⁷ however, attempts to trap **A** with MeOH using chiral biaryl bisphosphine ligands (**4**) that had been successfully employed in the enantioselective [2+2]-cycloadditions of allenes provided methoxycyclization⁸ product **3a** as a racemate.

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Supporting Information Available. Computational details, experimental procedures and compound characterization data is available free of charge via the Internet at <http://pubs.acs.org>.

Initially introduced by Kagan and Dang in 1971, bidentate chiral phosphines have remained the ligands of choice on many metal-catalyzed synthetic transformations.⁹ Expectedly, this tendency has been extended to the field of enantioselective gold(I) catalysis¹⁰ despite the pronounced preference of gold(I) to form two-coordinate linear complexes rather than the bidentate complexes typical formed with these ligands.^{11,12} These ancillary ligands are also expensive and difficult to synthesize, thwarting optimization efforts.

Recently we and others have shown the utility of tunable monodentate phosphite and phosphoramidite Au^I catalysts in mediating enantioselective cycloadditions.¹³ First introduced to the asymmetric catalysis community in 1994, monodentate chiral phosphoramidites have remained useful ancillary ligands in many transformations.¹² We initially became interested in this ligand class because their modular framework is readily constructed from commercially available enantiomerically pure compounds, thereby allowing for the straightforward preparation of large ligand libraries. We first reported the use of MonoPhos-AuOTf complex on the enantioselective Conia-Ene reaction in 2005 without success.¹⁴ It was not until we explored the enantioselective intramolecular Au^I-catalyzed formal Diels-Alder cycloadditions of allene-dienes that a true need for the development of chiral phosphoramidite Au^I-catalysts transpired. An inspection of MonoPhos-AuCl complex in its solid state suggested that *ortho*-substitution of its BINOL moiety would provide for a more defined steric environment.^{13a} This idea was pursued with success, resulting in the chemoselective synthesis of the desired [4+2]-cycloadducts in excellent enantioselectivities (eq. 1). Consequently, we focus our studies on the Au^I-catalyzed reactions of allenene **1a** with this ligand class. Through these studies we uncovered two highly stereoselective phosphoramidite Au^I catalysts expanding our repertoire of reagents and advancing our efforts in the enantioselective catalytic arena.

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2. Results and Discussion

2.1 Enantioselective Au^I-Catalyzed [2+2]-Cycloadditions of Allenenes. Scope and Limitations

We began our catalyst screen with BINOL-derived phosphoramidite catalysts **5**. Employing unsubstituted complex (*S,S,S*)-**5a** resulted in low enantioinduction and, contrary to our expectations, introducing substituents in the 3,3'-positions on the BINOL moiety did not significantly improve the selectivity (entries 1-3). Exploring other backbones in our screen showed that VANOL-derived catalyst **7** produced **2b** in a promising 70% ee (entry 6). However, attempts to improve this result by using what we thought would be a more hindered VAPOL backbone (**8**) instead resulted in a lower enantioselectivity (entry 6). However, complex **9a**, containing a simpler spirobiindane-derived phosphoramidite, gave a promising hit (entry 7). Employing its diastereomer (*S,R,R*)-**9a** gave **2b** in lower enantioselectivity confirming that (*R,R,R*)-**9a** corresponds to the match case. We then decided to explore the effect of the amine moiety of **9** on the product's enantioselectivity and catalysts **9b-d** were synthesized and tested. Replacing the bis(1-phenylethyl)amine group for its pyrrolidine counterpart and utilizing a larger amine or a smaller alcohol moiety proved to be ineffective (entries 9-11).

An inspection of complex **9a** (Figure 1) in its solid state suggested that employing 6,6'-disubstituted spirobiindane phosphoramidite ligands might provide a steric environment similar to that found with catalysts **5**.¹⁵ To access our 6,6'-disubstituted spirobiindane phosphoramidite gold(I) complexes we chose to employ a variation of the Beller-Köckritz Suzuki protocol which circumvents the protection and subsequent deprotection of both of SPINOL's alcohol moieties (see Supplementary Information for additional details).¹⁶ Unfortunately, utilizing catalysts **10** on the cycloaddition of allenene **1b** did not result in improved enantioselectivities.

We then decided to examine the scope of the [2+2]-cycloadditions of various allenenes with **9a**. Catalyst **9a** proved to be selective for several allenenes with varying tethers (Table 2, entries 2-4). Notably, bis-sulfone tethered **2c** was obtained in 85% ee (entry 3), a large improvement when compared to that synthesized with **4** (Scheme 1). Nonetheless, catalyst **9a** was unselective towards **1a**, showing a complementary reactivity to **4**. Both electron-withdrawing and -donating substituents as well as distinct substitution patterns on the arene moiety were well tolerated (entries 5-8). Interestingly *cis*-**1b** (entry 9) afforded the same enantiomer as that obtained from its *trans* counterpart in identical selectivity albeit in lower yield. This provides further evidence of the initial formation of **A** (Scheme 1), which, in the absence of an exogenous nucleophile, undergoes cycloreversion forming the more thermodynamically stable *trans*-**1b**. We decided to take a closer look at the hypothesized mechanism by means of a quantum mechanical study using the M06 flavor¹⁷ of density functional theory (DFT) which has been shown¹⁸ to be adequate for the description of organogold catalytic reactions. In doing so, we also hoped to gain some insight into the factors governing the alkoxycyclization reaction pathway leading to the formation of 3,4-substituted pyrrolidines.

2.2 Computational Analysis on the Au^I-catalyzed Cycloadditions of Allenenes

The potential energy surface was computed using the model phosphoramidite catalyst (MeO)₂(Me₂N)PAu⁺ as shown in Figure 2. Consistent with our previous predictions,^{18c} our present computational study found a step-wise mechanism where the alkene adds to the gold-coordinated allene, leading to a vinyl-gold in a concerted fashion. There are two stereochemical arrangements for the relative position of the substituents on the formed cyclopentane ring: *cis* (in red) and *trans* (in blue) (Figure 2). Both pathways lead to

intermediates where we found (in the most stable conformation) an interaction between the carbocation and gold that forms a 5-membered metallacycle. This electrostatic interaction results in carbocation stabilization by the full d-shell of the electron-rich gold. On the *cis* pathway the metallacycle ruptures to form the cyclobutane ring, effecting demetallation. Experimentally, exposing isolated **2a** to (PhO)₃PAuBF₄ in the presence of MeOH did not give the alkoxy cyclization product **3a**, demonstrating that the formation of **2a** is irreversible under these reaction conditions (Scheme 2). This result contrasts with Fürstner's findings that when exposed to a NHC-AuCl complex (NHC = *N*-heterocyclic carbene), compound **2a** underwent rearrangement to the thermodynamically favored ring-expanded products, a process that was hypothesized to occur through the regeneration of an **A**-type carbocation.¹⁹

The *trans* pathway exhibits a similar cyclization leading to a 5-membered ring and a carbocation, notably, with a lower barrier than for the *cis* pathway (*trans*: 10.4 kcal/mol vs. *cis*: 13.3 kcal/mol). Moreover, we found a barrier for the addition of MeOH and demetallation²⁰ which is lower than the rate determining barrier for the formation of product via the *cis* pathway. The absence of deuterium loss in the Au^I-catalyzed formation of *d*-**3a** from *d*-**1a** suggests that the alkoxy cyclization product is not formed from the addition of the MeOH to the styrene moiety of a 1,4-diene (**B**) but from a cationic intermediate **A** in agreement with our computational studies (Scheme 2).

Our results suggest that both *cis* and *trans* pathways are competitive, but in the presence of a nucleophile (MeOH), the *trans* pathway is preferred. On the other hand, in the absence of a viable nucleophile, the *cis* pathway is operative. These findings also suggest that a more polar solvent, such as MeNO₂ could further increase the preference for the *trans* pathway, an observation that has been confirmed experimentally (see section 2.3). In addition, we speculate that the interaction between the carbocation and gold may serve to direct the attack of the nucleophile from the opposite side. With a clear view of the underlying mechanism on the Au^I-catalyzed cycloadditions of allenenes we took a closer look at their enantioselective alkoxy cyclization.

2.3 Enantioselective Synthesis of 3,4-disubstituted Pyrrolidines

We first inspected the selectivity of catalyst **9a** on the alkoxy cyclization of **1b** with MeOH, alas **3b** was obtained in low selectivity (Table 3, entry 1). Even though the yield was improved by carrying the reaction in MeNO₂, the enantiomeric excess remained low (entry 2). We then decided to test BINOL-derived phosphoramidites **5**. Catalysts **5a** gave **3b** with low enantioselectivity; however, we found (*S,S,S*)-**5a** to be more selective than its diastereomer (*R,S,S*)-**3a** (Table 1, entries 3-4). Introducing substituents at the 3 and 3' positions of the binaphthol moiety increased the enantiomeric excess (entries 5-11), with 1-pyrenyl-disubstituted catalyst **5c** providing **3b** in up to 76% ee (entry 6). Attempts to improve this result by varying the solvent were unsuccessful (entry 7).²¹ Employing the H₈-BINOL-analog **5c** substantially improved the selectivity and the reaction yield each to 82%. The structures of the Au^I complexes **5c** and **11a** in the solid state help rationalize this boost in enantioselectivity. The larger dihedral angle of **11a** (57.75°) compared to **5c** (53.39°) produces a shortening the Au-C₃_{BINOL} distance to 3.49 Å from 3.63 Å, thereby placing the Au-center in closer proximity to the chiral information (Figure 3). An examination of the solid state structure of **11a** also led us to believe that a 4-pyrenyl moiety instead of its 1-pyrenyl isomer in **11a** would extend the chiral pocket further outward. Indeed, **11b** (Figure 3) catalyzed the cycloaddition/MeOH trapping of **1b** with increased selectivity (88% ee, entry 13). We installed electron-deficient arenes on the 4-pyrenyl moiety of **11b** in an effort to improve efficiency. We came to this hypothesis from the observed high reactivity of **5e**, which allowed us to carry out the reaction at lower temperatures (entries 9-10). Although **11c** mediated the formation of **1a** with better selectivity even at room temperature (92% ee, entry 14), running the reaction at a lower temperature (0°C) produced superior results (entry

15).²² The improved selectivity of **11c** when compared to **11b** at room temperature might be due to an increased bite angle (58.2°) as observed in its solid state (Figure 3). probability level.

In order to examine the scope of the reaction, a variety of allenenes were synthesized and subjected to the optimized conditions for trapping with various alcohols (Table 4). Both electron-donating (entries 1-3) and -withdrawing (entry 4) substituents on the aromatic moiety were well tolerated, as were *ortho*-, *meta*- and *para*-substituents (entries 1-3).²³ The expected cycloadducts were obtained in high yield and enantioselectivity when trapping **1b** with several primary (entries 5-7) and secondary (entry 8) alcohols as nucleophiles. We were pleased to find that even water was a suitable trapping agent and alcohol **3l** was isolated in good yield and enantioselectivity (entry 9). Even a tertiary ether could be synthesized from a trisubstituted olefin in excellent diastereo- (>98:2) and enantioselectivity (92%) (entry 12). The allene moiety was also varied with similar success (entry 13). Accordingly, electron-rich aryl nucleophiles²⁴ could be employed in this transformation, producing the Friedel-Crafts product **3p** in good yield (73%) and enantioselectivity (97%, eq 2).²⁵

Interestingly, *cis*-substituted allenene (*cis*-**1b**) afforded the same **2b** isomer as its *trans*-**1b** counterpart, albeit in lower yield and enantioselectivity (entries 10-11). This observation and the conservation of enantioselectivity regardless of the nucleophile used (Table 4, entries 5-10) suggest that the cyclization is the enantiodetermining step. These findings are in stark contrast with the related 5-*exo-dig* cyclization/trapping of 1,6-enynes for which the nature of the nucleophile significantly affects enantioselectivity.^{8b,24b}

(2)

Additionally, 3,4-disubstituted γ -lactams **13a** and **13b** could be accessed through this methodology in high enantioselectivity (eq 3). The observed reactivity with amide substrate (**12**) prompted us to examine this alkoxy cyclization reaction towards the synthesis of (–)-isocynometrine.

(3)

2.4 Formal Synthesis of (–)-isocynometrine

The utility of this methodology is exemplified by the synthesis of (–)-isocynometrine, an imidazole alkaloid isolated from the *Cynomera* species, known for its antitussive and analgesic properties.²⁶ This alkaloid was first synthesized by Xu and co-workers through a Pd-catalyzed enyne cycloaddition introducing two of the three contiguous stereogenic centers in 53% ee.^{4e} The third stereocenter was then installed by reduction of a phenyl ketone to its secondary carbinol in 2.5:1 dr. In our approach allenene **14** was subjected to the optimized reaction conditions in the presence of water yielding γ -lactam **15** in 83% and 86% ee. The resulting secondary alcohol in **15** was then converted to its benzoyl ester and the trisubstituted olefin was oxidatively cleaved with ozone yielding **17** in 80% (2 steps). The synthesis could then be completed as previously established in the literature to give (–)-isocynometrine.

2.5 Computational study on the origin of enantioselectivity

Having established the general mechanism using a model ligand, we used molecular mechanics²⁷ to investigate the conformational landscape starting from the X-ray structure of ligand (*S,S,S*)-**11c** on the fixed coordinates of the intermediates and transition structures. Ligand (*S,S,S*)-**11c** is composed of a (*S,S*) bis(1-phenylethyl)amine fragment and a 3,3'-functionalized (*S*)-octahydro-BINOL. Upon visual analysis of the catalyst-substrate complex, the octahydro BINOL group provides the axial chirality to the catalyst, while the bis(1-phenylethyl)amine group adds steric bulk, increasing the helical pitch. We performed a study of the possible relative rotational orientations of the phosphoramidite ligand and the substrate. Our conformational analysis suggests that the specific stereochemistry of the phenylethyl groups in (*S,S*)-bis(1-phenylethyl)amine may not effect direct enantiomeric discrimination, but may be critical in leveraging the performance of the BINOL moiety. Following our classical mechanics analysis, we subjected two pairs of selected conformations of the full structures of the enantiodetermining transition structures to DFT geometry optimization at the M06/LACVP* level of theory with a C–C distance constraint (1.994 Å as found for the model ligand). This methodology is thought to exhibit enough accuracy to visualize the key structural factors that govern the enantioselectivity.

Our structural analysis suggests that the groups at the 3,3'-positions on BINOL serve to orient the substrate by flanking it. This could explain the increase in enantioselectivity using pyrenyl substituents. The parallel placement of the pyrenyl groups form a channel in which the substrate can adopt two complementary orientations that lead to the different enantiomers. In one of these orientations, the *N*-tosyl pyrrolidine fragment points towards the bis(1-phenylethyl)amine group while the styrenyl and dimethylallyl groups point towards the H₈-BINOL; alternatively, on the other orientation, the styrenyl and dimethylallyl groups point towards the bis(1-phenylethyl)amine group, while the *N*-tosyl pyrrolidine fragment points in the direction of the H₈-BINOL. The enantioselectivity originates from the relative interactions between these groups. We identified the following key ligand structural directives: 1) the aligning of the substrate by the 3,3'-BINOL substituents, 2) the steric interactions provided by the bis(1-phenylethyl)amine group, and the 3) steric interactions provided by the “downward” facing H₄-naphthyl group. We also recognized that a higher dihedral angle of the BINOL group increases the steric interaction of the enantiodiscriminating H₄-naphthyl group, which could explain why increasing the dihedral correlated with higher enantioselectivities.

3. Conclusions

The successful development of newly Au^I-catalyzed transformations depends largely on the ability to design inexpensive ligands that are easy to prepare and tune for a specific chemical transformation. Within this context, this report serves to further demonstrate the potential utility of phosphoramidite ligands in enantioselective Au^I-catalysis. We uncovered two new highly selective catalysts on the cycloadditions of allenes. Commercially available, small, SIPHOS-PE-derived catalyst **9a** proved to be highly selective for the [2+2]-cycloadditions of allenes. Importantly, catalyst **9a** was particularly selective towards nitrogen and bis-sulfone tethered substrates, both of which underwent this transformation with previously reported bis-phosphine-derived **4** in low enantioselectivity. This report also describes a new Au^I-catalyzed cyclization/alkoxylation for the conversion of allenes to *trans*-3,4-disubstituted pyrrolidines and γ -lactams. The reaction allows for the highly diastereo- and enantioselective synthesis of these heterocycles containing three contiguous stereocenters. Central to the success of this effort was the use of bulky mono-phosphorous-Au^I complex **11c**. We also studied these reactions computationally using the M06 functional (DFT) to gain insight into key factors determining the mechanism and the enantioselectivity. The utility of this methodology is demonstrated by the formal synthesis of (–)-isocynometrine.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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20. We also found a barrier of 22.9 kcal/mol for the formation of a cyclobutane ring via the trans pathway.
21. For a full account of all catalysts screened and different reaction conditions used refer to the Supporting Information.
22. Varying the counterion (OTf, SbF₆, PF₆) proved to be inconsequential to the enantioselectivity of the reaction.
23. An aryl substituent on the substrate's olefinic moiety proved to be necessary to achieve reactivity in the [2+2]-cycloaddition and alkoxycyclization reactions. For example, independent reaction of a dimethylsubstituted-olefin containing substrate with 9a and 11c (in the presence of MeOH) in dichloromethane (12 h, rt) resulted in the recovery of the starting material.

24. For a Pt- and Au-catalyzed enantioselective cyclization/hydroalkylation see: a Toullec PY, Chao C-M, Chen Q, Gladiali S, Genet JP, Michelet V. *Adv. Synth. Catal.* 2008; 350:2401. b Chao C-M, Vitale MR, Toullec PY, Genet J-P, Michelet V. *Chem. Eur. J.* 2009; 15:1319.
25. We attempted to recover both 9a and 11c after their use as catalysts in the corresponding [2+2]-cycloaddition and alkoxycyclization reactions of 1b without success. For successful recycling of related catalysts see ref ^{13a}.
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Scheme 1.
 Au^I-catalyzed Cycloadditions of Allenenes.

Figure 1.
Structure of complex (*R,R,R*)-**9a** in the solid state. Ellipsoids are drawn at the 50% probability level.

Figure 2.

DFT profile for the potential free energy surface for the *cis* (red) and *trans* (blue) cyclization pathways at the M06/LACV3P**++ level of theory corrected for CH₂Cl₂ as solvent in kcal/mol. L = P(OMe)₂(NMe₂).

Scheme 2.
Au^I-cycloadditions of allenenes.

Figure 3.
ORTEP representations of complexes **5c** and **11a-c**. Ellipsoids are drawn at the 50%

Scheme 3.
Enantioselective synthesis of (–)-isocynometrine.

Figure 4.
Views for the matched (top) and mismatched (bottom) structures minimized at the M06/
LACVP* level of theory.

Table 1Ligand Optimization for Phosphoramidite Au^I-catalyzed [2+2]-Cycloaddition of **1b**.^a

entry	Cat.	yield (%) ^b	ee (%) ^c
1	(<i>S,S,S</i>)- 5a	81	34(+)
2	(<i>S,S,S</i>)- 5b	91	14(+)
3	(<i>S,S,S</i>)- 5c	67	56(+)
4	(<i>S,S,S</i>)- 6	34	60(+)
5	(<i>S,S,S</i>)- 7	81	70(+)
6	(<i>R,R,R</i>)- 8	77	64(−)
7	(<i>R,R,R</i>)- 9a	86	90(+) ^d
8	(<i>S,R,R</i>)- 9a	73	52(−)
9	(<i>R,R,R</i>)- 9b	87	32(+)
10	(<i>R,R,R</i>)- 9c	22	4(+)
11	(<i>R</i>)- 9d	88	32(+)
12	(<i>R,R,R</i>)- 10a	66	56(−)
13	(<i>R,R,R</i>)- 10b	---	---

^a Reaction conditions: Cat (5 mol%), AgBF₄ (5 mol%), dichloromethane, 25°C, 24h. Only one diastereoisomer was observed in all cases.^b Isolated yields after silica gel flash column chromatography.^c Enantiomeric excess determined by enantiodiscriminating HPLC (see Supporting Information).^d The enantioselectivity was increased to 99% ee after a simple crystallization.

Table 2

Ligand Optimization for Phosphoramidite Au^I-catalyzed [2+2]-Cycloaddition of **1** with (*R,R,R*)-**9a**.^a

entry	2	X	R	yield (%) ^b	ee (%) ^c
1	a	C(CO ₂ Me) ₂	Ph	75	14
2	b	<i>N</i> -Ts	Ph	86	94
3	c	C(SO ₂ Ph) ₂	Ph	82	85
4	d	<i>N</i> -Boc	Ph	52	81
5	e	<i>N</i> -Ts	2-OMe-C ₆ H ₄	82	80
6	f	<i>N</i> -Ts	3-OMe-C ₆ H ₄	80	91
7	g	<i>N</i> -Ts	4-OMe-C ₆ H ₄	72	80
8	h	<i>N</i> -Ts	4-Cl-C ₆ H ₄	87	97
9 ^d	b	<i>N</i> -Ts	Ph	67	90

^aReaction conditions: Cat (5 mol%), AgBF₄ (5 mol%), dichloromethane, 25°C, 24h. Only one diastereoisomer was observed in all cases. *Trans*-**2** was used in all cases except for those noted.

^bIsolated yields after silica gel flash column chromatography.

^cEnantiomeric excess determined by enantiodiscriminating HPLC (see Supporting Information).

^dFrom *cis*-**1b**.

Table 3

Ligand Optimization for the Au^I-catalyzed Cycloaddition/Alkoxylation of Allenes.^a

entry	Catalyst	temp.	yield (%) ^b	ee (%) ^c
1 ^d	(<i>R,R,R</i>)- 9	rt	42	20(+)
2	(<i>R,R,R</i>)- 9	rt	72	28(+)
3	(<i>R,S,S</i>)- 5a	rt	41	10(−)
4	(<i>S,S,S</i>)- 5a	rt	74	19(+)
5	(<i>R,R,R</i>)- 5b	rt	75	38(+)
6	(<i>S,S,S</i>)- 5c	rt	80	76(−)
7 ^d	(<i>S,S,S</i>)- 5c	rt	75	70(−)
8	(<i>S,S,S</i>)- 5d	rt	17	34(−)
9	(<i>R,R,R</i>)- 5e	rt	84	53(+)
10	(<i>R,R,R</i>)- 5e	−15 °C	86	70(+)
11	(<i>R,R,R</i>)- 5f	rt	87	49(+)
12	(<i>R,R,R</i>)- 11a	rt	82	82(+)
13	(<i>S,S,S</i>)- 11b	rt	86	88(−)
14	(<i>S,S,S</i>)- 11c	rt	86	92(−)
15	(<i>S,S,S</i>)- 11c	0 °C	95	94(−)

^aReaction conditions: LAuCl (5 mol%), AgBF₄ (5 mol%), MeOH (9 equiv), nitromethane, rt, 24h. In all experiments a small amount (<9%) of the corresponding [2+2]-cycloaddition product was also produced. The diastereoselectivity was >98:2 in all cases.

^bIsolated yields after silica gel flash column chromatography.

^cEnantiomeric excess determined by enantiodiscriminating HPLC (see Supporting Information).

^dReaction run in dichloromethane.

Table 4

Substrate Scope for Au^I-catalyzed Cycloaddition/Alkoxylation of Allenes with **11c**.^a

entry	Substrate	NuH	3	yield %	ee %

1	$\underline{R^1}, \underline{R^2}$ 2-OMe-C ₆ H ₄ , H	MeOH	d	73	96
2	3-OMe-C ₆ H ₄ , H	MeOH	e	92	96
3	4-OMe-C ₆ H ₄ , H	MeOH	f	90	94
4	4-Cl-C ₆ H ₄ , H	MeOH	g	68	86
5	Ph, H	EtOH	h	90	92
6	Ph, H	HOCH ₂ (C(CH ₃) ₃)	i	72	94
7	Ph, H	HOCH ₂ (HC=CH ₂)	j	84	94
8	Ph, H	HOCH(CH ₃) ₂	k	81	96
9	Ph, H	H ₂ O	l	85	96
10	Ph, H	MeOH	b	95	94
11	H, Ph	MeOH	b	39	86
12	Ph, Me	MeOH	m	83	92

13		MeOH	n	76	94

entry	Substrate	NuH	3	yield %	ee %
14		MeOH		86	72

^aReaction conditions: **11c** (6 mol%), AgBF₄ (5 mol%), trapping agent (Nu) (9 equiv), 24h. For entries 5–10 the reaction was run at 0°C, all others were run at room temperature. In all experiments a small amount (<9%) of the corresponding [2+2]-cycloaddition product was also produced. The diastereoselectivity was >98:2 in all cases. Isolated yields after silica gel flash column chromatography. Enantiomeric excess determined by enantiodiscriminating HPLC (see Supporting Information).