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

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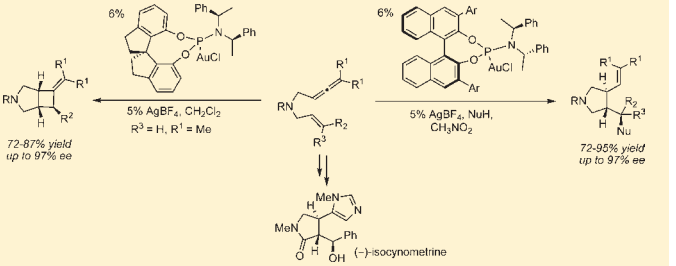
Supporting Information

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 allenenes. 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 allenenes 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.



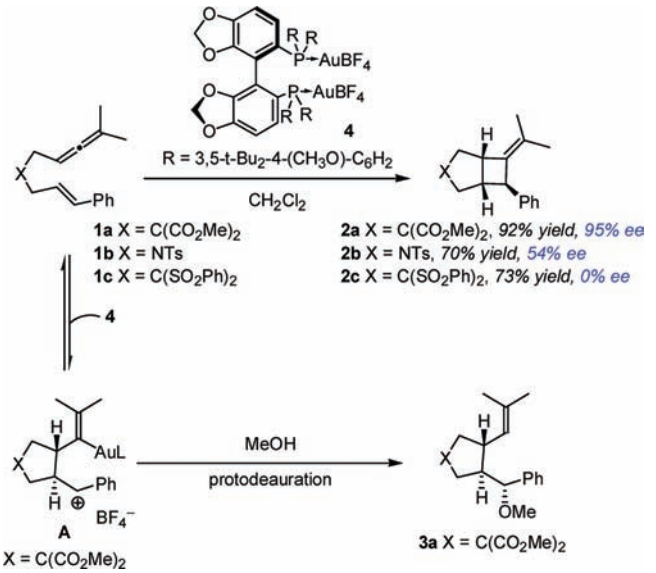
1. INTRODUCTION

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] cycloaddition,[3] and cycloisomerization reactions.[4] Despite these advances, enantioselective access to 3,4-substituted pyrrolidines[5] 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 allenenes. 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 allenenes provided methoxycyclization[8] product **3a** as a racemate.

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) catalysis[10] despite the pronounced preference of gold(I) to form two-coordinate linear complexes rather than the

Scheme 1. Au^I-Catalyzed Cycloadditions of Allenenes



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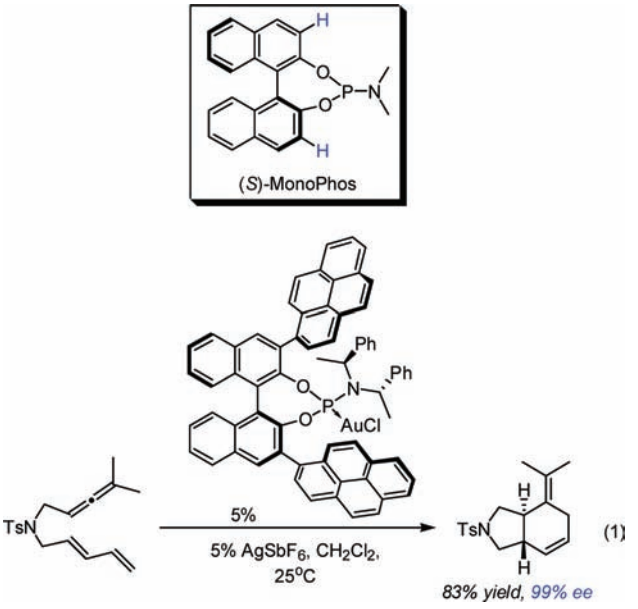
bidentate complexes typical formed with these ligands.[11,12] These ancillary ligands are also expensive and difficult to synthesize, thwarting optimization efforts.

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 a 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 the 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).

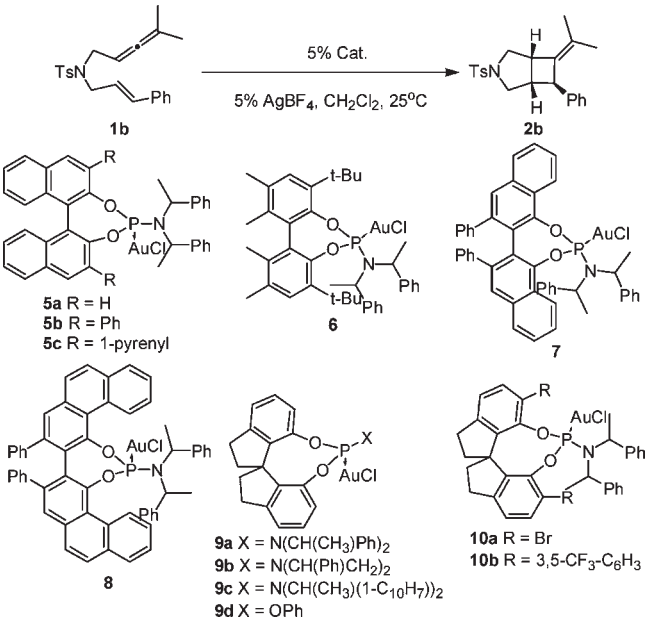


Consequently, we focus our studies on the Au^{I}-catalyzed reactions of allenene **1a** with this ligand class. Through these studies we uncovered two highly stereoselective phosphoramidite Au^{I} catalysts expanding our repertoire of reagents and advancing our efforts in the enantioselective catalytic arena.

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 (Table 1, entries 1−3). Exploring other backbones in our screen showed that VANOL-derived catalyst **7** produced **2b** in a promising 70% ee (entry 5). 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).

Table 1. Ligand Optimization for Phosphoramidite Au^{I}-Catalyzed [2 + 2]-Cycloaddition of 1b[a]



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

[a] Reaction conditions: Cat. (5 mol %), $AgBF_4$ (5 mol %), dichloromethane, 25 °C, 24 h. 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.

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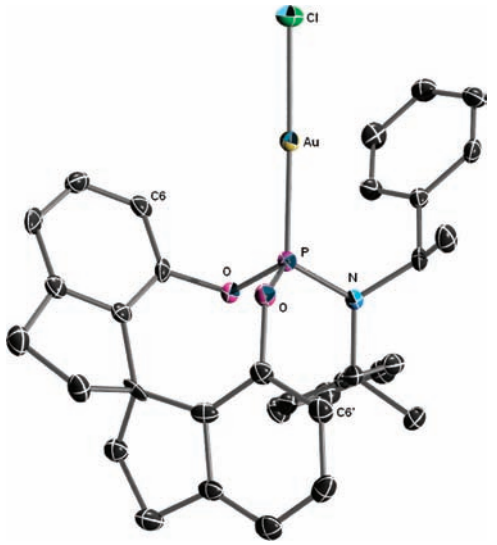


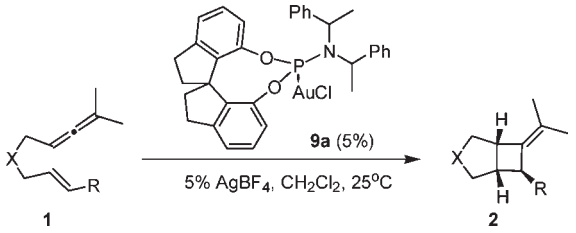
Figure 1. Structure of complex (*R*,*R*,*R*)-**9a** in the solid state. Ellipsoids are drawn at the 50% probability level.

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 Supporting 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 toward **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 functional[17] of the density functional theory (DFT) which has been shown[18] 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 $(MeO)_2(Me_2N)PAu^+$ as shown in Figure 2. Consistent with our previous predictions,[18c] our present computational study found a stepwise

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**	$C(CO_2Me)_2$	Ph	75	14
2	**b**	*N*-Ts	Ph	86	94
3	**c**	$C(SO_2Ph)_2$	Ph	82	85
4	**d**	*N*-Boc	Ph	52	81
5	**e**	*N*-Ts	2-OMe-C_6H_4	82	80
6	**f**	*N*-Ts	3-OMe-C_6H_4	80	91
7	**g**	*N*-Ts	4-OMe-C_6H_4	72	80
8	**h**	*N*-Ts	4-Cl-C_6H_4	87	97
9[d]	**b**	*N*-Ts	Ph	67	90

[a] Reaction conditions: Cat. (5 mol %), $AgBF_4$ (5 mol %), dichloromethane, 25 °C, 24 h. Only one diastereoisomer was observed in all cases. *trans*-**2** was used in all cases except for those noted. [b] Isolated yields after silica gel flash column chromatography. [c] Enantiomeric excess determined by enantiodiscriminating HPLC (see Supporting Information). [d] From *cis*-**1b**.

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 five-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 demetalation. Experimentally, exposing isolated **2a** to $(PhO)_3PAuBF_4$ in the presence of MeOH did not give the alkoxycyclization 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 an 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 five-membered ring and a carbocation, notably, with a lower barrier than that 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 demetalation[20] 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 alkoxycyclization 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).

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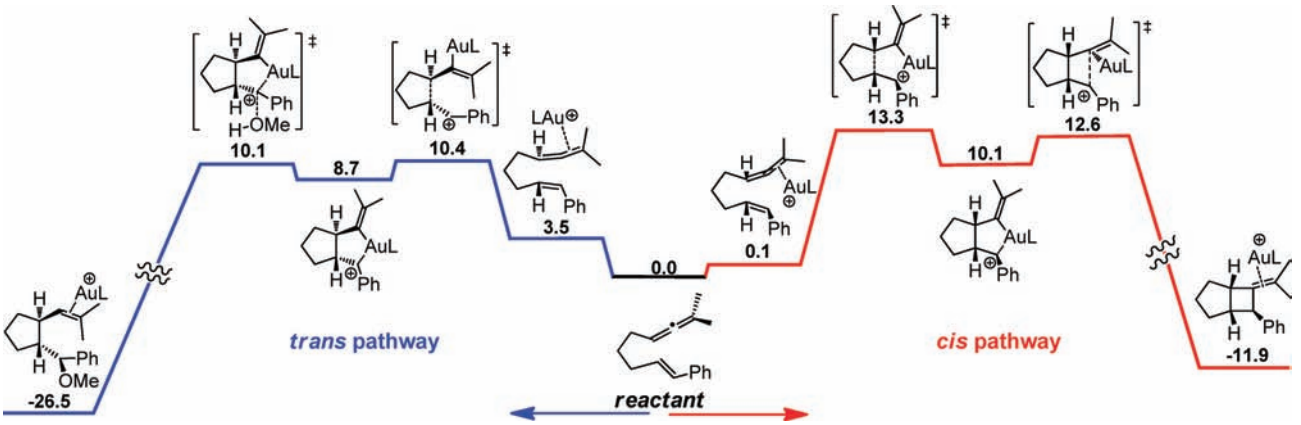
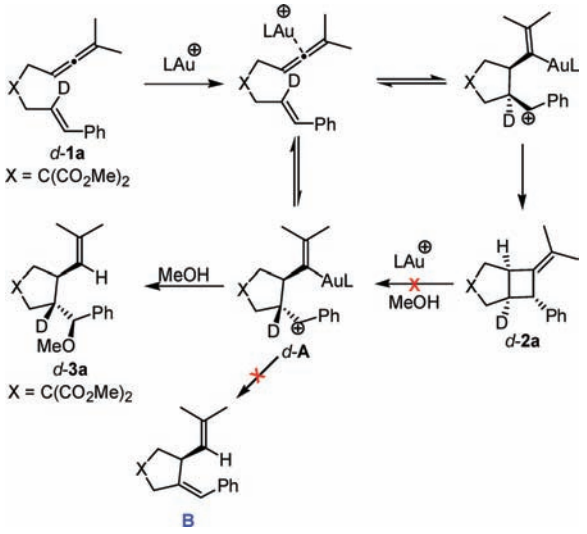


Figure 2. DFT profile for the potential free energy surface for the *cis* (red) and *trans* (blue) cyclization pathways at the M06/LACV3P**++ level of theory corrected for CH_2Cl_2 as solvent in kcal/mol. L = $P(OMe)_2(NMe_2)$.

Scheme 2. Au^I-Cycloadditions of Allenenes



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 $MeNO_2$, 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 alkoxycyclization.

2.3. Enantioselective Synthesis of 3,4-Disubstituted Pyrrolidines. We first inspected the selectivity of catalyst **9a** on the alkoxycyclization 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 $MeNO_2$, 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*)-**5a** (Table 3, 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 H_8-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 of 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).

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).

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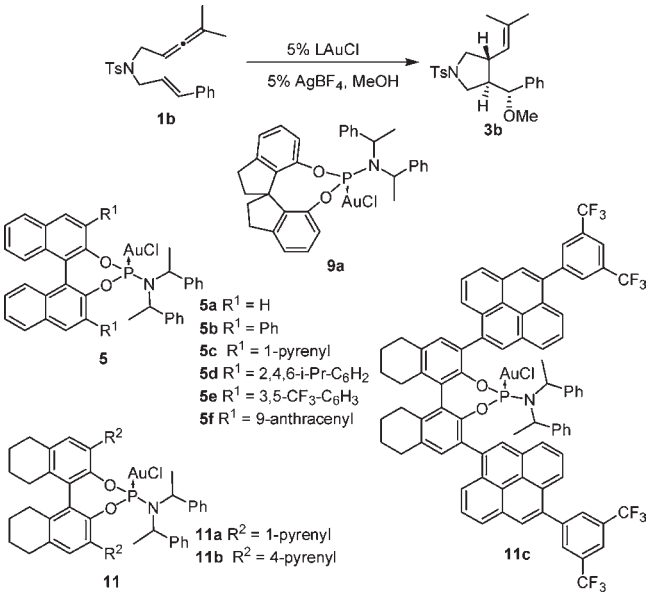
Table 3. Ligand Optimization for the Au^I-Catalyzed Cycloaddition/Alkoxylation of Allenenes[a]

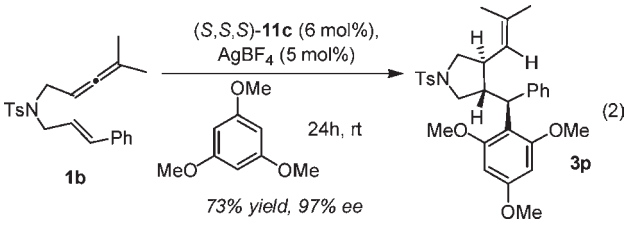


entry	catalyst	temp	yield (%)[b]	ee (%)[c]
1[d]	(*R*,*R*,*R*)-**9a**	rt	42	20(+)
2	(*R*,*R*,*R*)-**9a**	rt	72	28(+)
3	(*R*,*S*,*S*)-**5a**	rt	41	10(−)
4	(*S*,*S*,*S*)-**5a**	rt	74	19(+)
5	(*R*,*R*,*R*)-**5b**	rt	75	38(+)
6	(*S*,*S*,*S*)-**5c**	rt	80	76(−)
7[d]	(*S*,*S*,*S*)-**5c**	rt	75	70(−)
8	(*S*,*S*,*S*)-**5d**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

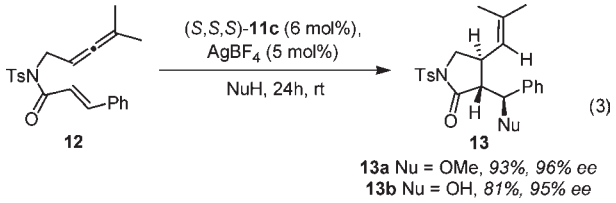
[a] Reaction conditions: LAuCl (5 mol %), $AgBF_4$ (5 mol %), MeOH (9 equiv), nitromethane, rt, 24 h. In all experiments a small amount (<9%) of the corresponding [2 + 2]-cycloaddition product was also produced. The diastereoselectivity was >98:2 in all cases. [b] Isolated yields after silica gel flash column chromatography. [c] Enantiomeric excess determined by enantiodiscriminating HPLC (see Supporting Information). [d] Reaction run in dichloromethane.

Accordingly, electron-rich aryl nucleophiles[24] 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-exodig* cyclization/trapping of 1,6-enynes for which the nature of the nucleophile significantly affects enantioselectivity.[8b,24b]



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



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% yield and 86% ee (Scheme 3). 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% yield (two 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 mechanics[27] 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

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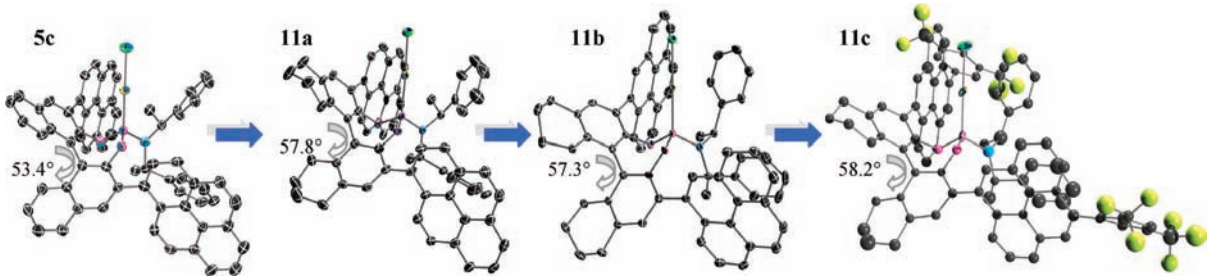
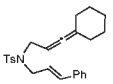
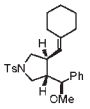
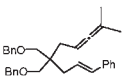
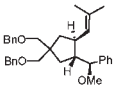


Figure 3. ORTEP representations of complexes **5c** and **11a**−**c**. Ellipsoids are drawn at the 50% probability level.

Table 4. Substrate Scope for Au^{I}-Catalyzed Cycloaddition/Alkoxylation of Allenenes with 11c[a]

entry	Substrate	NuH	3	yield %	ee %
					
	R^1, R^2				
1	2-OMe-C_6H_4, H	MeOH	**d**	73	96
2	3-OMe-C_6H_4, H	MeOH	**e**	92	96
3	4-OMe-C_6H_4, H	MeOH	**f**	90	94
4	4-Cl-C_6H_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_2O	**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		76	94
14		MeOH		86	72

[a] Reaction conditions: **11c** (6 mol %), AgBF4 (5 mol %), trapping agent (Nu) (9 equiv), 24 h. 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).

as found for the model ligand) (Figure 4). 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 forms 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 toward the bis(1-phenylethyl)amine group while the styrenyl and dimethylallyl groups point toward the H_8-BINOL; alternatively, on the other orientation, the styrenyl and dimethylallyl groups point toward the bis(1-phenylethyl)amine group, while the *N*-tosyl pyrrolidine fragment points in the direction of the H_8-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 H_4-naphthyl group. We

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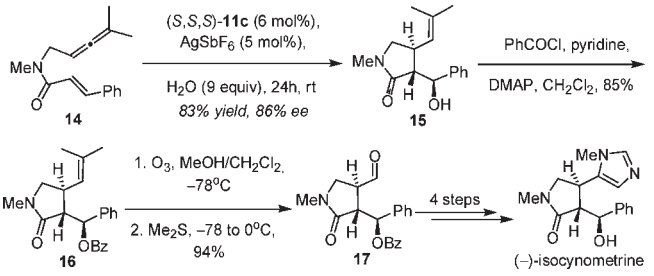
Scheme 3. Enantioselective Synthesis of (−)-Isocynometrine



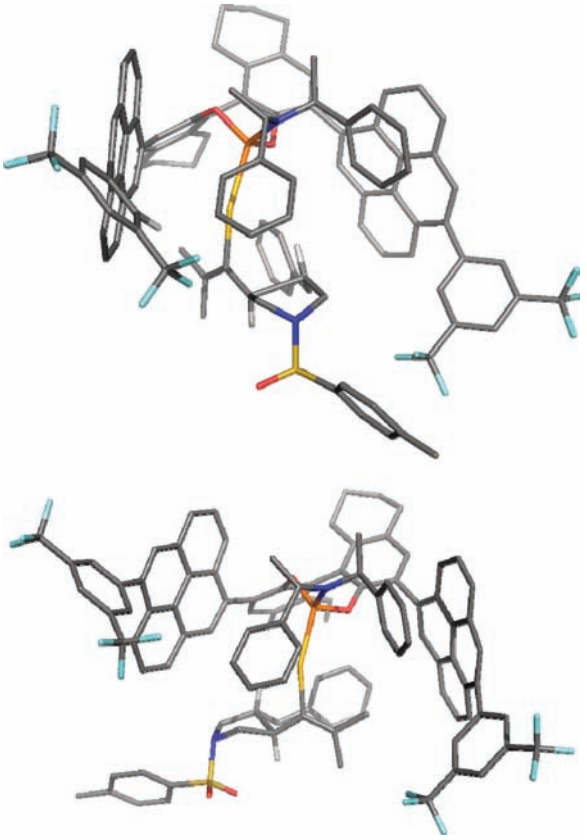


Figure 4. Views for the matched (top) and mismatched (bottom) structures minimized at the M06/LACVP* level of theory.

also recognized that a higher dihedral angle of the BINOL group increases the steric interaction of the enantiodiscriminating H_4-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 for the cycloadditions of allenenes. Commercially available, small, SIPHOS-PE-derived catalyst **9a** proved to be highly selective for the [2 + 2]-cycloadditions of allenenes. Importantly, catalyst **9a** was particularly selective toward 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 allenenes 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 monophosphorus−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.

■ ASSOCIATED CONTENT

Supporting Information. Computational details, 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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(22) Varying the counterion (OTf, SbF_6, PF_6) 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 dimethyl-substituted 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.

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