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Diastereoselective Au-Catalyzed Allene Cycloisomerizations to Highly Substituted Cyclopentenones

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Abstract

Site- and regiocontrolled Au-catalyzed allene carbocyclizations furnish highly substituted cyclopentenones in >1:1 *dr*. Significant substitution on the substrate is tolerated, with potential to install five contiguous stereocenters after alkene functionalization. Major challenges include identifying a Au/Cu catalyst that controls both the relative rates of allene epimerization/cyclization and the facial selectivity in addition of a metal enolate to the allene. Experiments to achieve stereodivergent cyclizations and transform key cyclopentenones into useful synthetic building blocks are described.

Graphical Abstract

Methods to rapidly transform simple precursors into complex scaffolds are of continued interest to the synthetic community. The surge of new strategies for the preparation of allenes has stimulated their use as convenient precursors for the introduction of multiple functionalities into the products with high degrees of regio-, chemo-, and stereocontrol.¹ In this context, we have recently described chemoselective, Rh(II)-catalyzed carbene insertions into allylic C–H bonds of **1.1** to yield allenes **1.2**,² which are well-suited for subsequent carbocyclization to furnish cyclopentenones of the form **1.3** (Scheme 1A). However, achieving diastereocontrolled reactions of **1.2** to **1.3** requires a catalyst that epimerizes the allene of **1.2** before C–C bond formation occurs. Once the stereochemistry of the strained bicycle **1.3** is

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Notes

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Supporting Information

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Experimental procedures and full characterization for all new compounds (PDF)

established, transformations of the remaining alkene are expected to occur with high *dr* to deliver highly substituted cyclopentanes present in a host of bioactive molecules, including the antiviral peramivir,³ the neuroprotective compound biloba-lide,⁴ and the Chitinase inhibitor allosamidin⁵ (Scheme 1B).

Examples of Coniaene-like C–C bond formations that occur via intramolecular addition of a carbon nucleophile to a site of unsaturation are known using both Pd⁶ and Au catalysts.⁷ However, these approaches typically use prefunctionalized silyl enol ethers⁸ or do not contain axial chirality in the allene;^{8,9} reported catalyst systems show little or no reactivity with nonterminal alkynes¹⁰ or 1,3-disubstituted allenes. The substitution pattern available using a substrate such as **1.2** would yield more complex cyclopentene scaffolds, provided the *dr* of the metal-catalyzed cycloisomerization is controlled.

Initial investigations focused on Au catalysts known to activate alkynes^{8,10} toward cyclization using **2a** (Table 1) as a 1:1 diastereomeric mixture between *b* and the allene (for an extensive list of catalysts studied in preliminary investigations, see Table S3). While early results utilizing Ph₃PAuCl, AgOTf and TfOH as an additive (see the Supporting Information (SI) for details) were successful, delivering **3a** in 90% yield and 2.5:1 *dr*; these results were not reproducible using a new bottle of Ph₃PAuCl. This led us to consider an impurity in the original Au source might have prevented decomposition of the catalyst to Au(0) or inactive (Ph₃P)₂Au⁺ species.¹¹ Inspired by Gandon and Lafollée's report describing Cu(OTf)₂ as a useful additive for Au catalysis,¹² we found reactivity could be restored using a 1:1 ratio of Ph₃PAuCl and Cu(OTf)₂ in refluxing toluene (Table 1, entry 1 and Table S3) to deliver **3a-anti** as the major product in moderate yield and a *dr* of 1.3. However, a ligand on the Au salt was necessary, as AuCl₃ gave no conversion of **2a** (entry 2). The use of a coordinating anion on Cu (entry 3) shut down the reaction, while Cu(I)OTf (see Table S3) was less effective than Cu(OTf)₂. We propose one function of the Cu(OTf)₂ is to ensure slow release of the active cationic Au species during the reaction,¹² but it likely plays a dual role in aiding the formation of a Cu-enolate species. The impact of the Au:Cu ratio was briefly examined (see Table S4 in the SI for details). The loading of Ph₃PAuCl could be decreased to 2.5 mol %, provided the Cu(OTf)₂ was increased to 25 mol % (entry 4) to furnish **3a** in slightly better *dr* and comparable yield to entry 1. The extended reaction time at the lower Ph₃PAuCl loading likely led to catalyst decomposition, but the more electron-rich Cy₃PAuCl catalyst proved more robust (entry 5), delivering **3a** in a 93% yield and 1.8:1 *dr*.

Using the conditions described in entries 1 and 4–5 of Table 1, a variety of 1,3-disubstituted allenes were explored. The *n*-pentyl-substituted allene **2a** (Table 2, entries 1–2) delivered **3a** in 93% yield; the stereochemistry at the ring juncture was *syn*, while the 1.8:1 *dr* between the two starred carbons favored the *anti* product. Switching the ester from Et in **2a** to Me in **2b** (entry 3) had little effect, while a less bulky Me-substituted allene **2c** (entries 4–5) furnished **3c** in good yield (entry 5) and poor *dr*; irrespective of the catalyst. A tethered phenyl substituent in **2d** (entry 6) was tolerated; switching to Cy₃PAuCl resulted in a doubling of the *dr* (entry 7) for reasons that were not clear at the time. Changing the nature of the ester in entries 1–3 had little effect, although the bulkier ester in **2e** (entry 8) did improve the *dr*. Branching in the tether adjacent to the allene in **2f** (entry 9) resulted in **3f** with a 6.5:1 *dr*; however, the extra bulk at C3 gave a lower yield. Methyl substitution at the

ring junction in **2g** was well-tolerated (entry 10), yielding two adjacent quaternary, all-carbon stereocenters in **3g**.

A series of 1,1,3-trisubstituted allenes were also subjected to Au(I)-catalyzed carbocyclization. Di-*n*-propyl allene **2h** was converted to **3h** in 62% yield (Table 2, entry 11), while allene **2i**, containing additional branching in the side chain, gave **3i** in 32% yield and 1.1:1 *dr* (entry 12). Moving the third substituent on the allene from C3 to C1 in **2j** (entry 13) gave a 54% yield of **3j** in 2.0:1 *dr* using Ph₃PAuCl. Attempts to increase yield and *dr* with a higher catalyst loading, longer reaction time, or Cy₃PAuCl (entries 14–15) were not successful. However, replacing the C1Me of **2j** with a bulky *tert*-butyldimethylsilyl (TBS) group in **2k** (entry 16) furnished **3k** in 51% yield and a good *dr* of 4.5:1. In contrast, trimethylsilyl (TMS) substitution on the C3 distal allene double bond resulted in rapid protodesilylation to deliver **3a** when subjected to the standard reaction conditions with both Ph₃PAuCl and Cy₃PAuCl (not shown).

At first glance, the *dr* of the cyclopentene products obtained in Table 2 do not appear to respond in any predictable way to changes in the ligand or the allene substitution pattern. However, the ability to obtain a significantly higher *dr* in the product than the starting 1:1 *dr* of the substrate indicates the rate of allene epimerization is faster than carbocyclization. Thus, it is theoretically possible to obtain a single cyclopentene diastereomer if better insight into the important features of this complex system can be obtained.

A partial mechanistic pathway to rationalize the observed stereochemical outcomes in Table 2 is illustrated in Figure 1. In this scenario, **2a** (1:1 *dr*) engages Cu(OTf)₂ to form two Cu-enolate species, **A** and **B**. There are multiple ways in which Au(I) can coordinate to **A** and **B**, as the metal may bind to the C1–C2 or the C2–C3 double bond from either face, depending on allene substitution pattern and substituent size. Nonetheless, literature precedent suggests eventual formation of achiral Au(I) η^1 -allyl cations as intermediates,¹³ represented by species **C–F**. Experimentally, the observation that the juncture between the two five-membered rings is always *syn* has two important implications. First, it supports our proposal that epimerization of Au-coordinated allene¹³ to stereodefined and achiral Au(I) η^1 -allylic cationic intermediates **C–F** occurs at a faster rate than ring closure. Second, it tells us that the copper enolate approaches the Au(I) η^1 -allyl cation on the same face as the proton shown in red in **C–F**. Thus, intermediates **C** and **F** will lead to the **3a-anti** product, while **D** and **E** furnish the **3a-syn** diastereomer. Reversibility in the stereochemical-determining C–C bond-forming step was ruled out by subjecting isolated **3a-anti** and **3a-syn** to the reaction conditions (Ph₃PAuCl and Cu(OTf)₂ in refluxing toluene, Figure 1, bottom) and noting the absence of epimerization.

The key to stereocontrolled reaction is to understand how the allene substitution pattern, Au catalyst, and Lewis acid additive work together to influence which of the four proposed intermediates **C–F** (Figure 1) are favored. **C** and **E** are favored when the allene is monosubstituted at C3 in order to minimize A^{1,3} strain. However, steric clashing between [Au] and the lactone must also be considered; **C** and **D** minimize this interaction, especially as the size of [Au] increases. As **C** minimizes both A^{1,3} strain and [Au]/substrate interactions, we propose this is the lowest energy species leading to *anti* product, while **D** is

the lowest energy intermediate expected to deliver the *syn* product. According to this model, increasing catalyst bulk with 1,3-disubstituted allenes should have little impact on the *dr*. Indeed, only a slight increase in *dr* resulted when moving from Ph₃PAuCl to Cy₃PAuCl (Table 2, entries 1–2 and 4–5). However, as C3 becomes larger, preference for both **C** and the *anti* product should increase. This is indeed the case for **3d–f** (Table 2, entries 6–9); however, if the bulk is too far removed, this effect is lost. The increase in *dr* was particularly noteworthy in **2f**, where additional A^{1,3} strain due to the *i*Pr group resulted in a 6.5:1 *dr* of **3f**. Disubstitution at C3 of **2h–i** (Table 2, entries 11–12) disables the ability to relieve A^{1,3} strain, and essentially no *dr* is observed. In contrast, additional substitution at C1, especially when R is bulky (compare entries 13–15 vs 16), is expected to further increase preference for **C** over **D**, resulting in increased preference for the *anti* product. This is what is observed, with reaction of **2k** (entry 16) yielding **3k** in 4.5:1 *dr*. The effect of the Au(I) ligand is still under investigation.

To test whether our model has predictive power, we reasoned incorporation of a *gem*-dimethyl group on the lactone ring of **2l** (Table 3) should disfavor **E** and **F** due to increased steric interactions between the ring and the Au catalyst. Product formation should proceed more readily from **C**, as opposed to **D**, due to decreased steric effects as the enolate approaches the Au(I) η^1 -allyl cation to form the new C–C bond. In the event, treatment of **2l** with Ph₃PAuCl furnished **3l** in 70% yield and 2.6:1 *dr* (entry 1). Switching to the more sterically demanding Cy₃PAuCl (entry 2) gave **3l** in excellent 89% yield and 6.6:1 *dr*, a marked increase over the analogous allene precursor **2a**. These reactions could be carried out on gram scale, with isolated yields closely tracking with NMR yields (see the SI for details), highlighting another strategy to exploit interactions between substrate and catalyst to influence *dr*. Computational studies are in progress to inform other strategies to achieve highly stereocontrolled allene carbocyclizations.

Previous reports¹⁴ have shown that the additive identity in Au-catalyzed Coniaene type cyclizations may influence stereo-selectivity. With this in mind, we were curious if changing the metal additive could select for the *syn* diastereomer in reactions of **2l** (Table 4). All reactions were complete in 24 h. Interestingly, although In(OTf)₃ (entry 1) was less effective than Cu(OTf)₂, a switch in the *dr* from 6.6:1 *anti* to 1.2:1 *syn* was noted. Sn(OTf)₂ (entry 2) gave a higher yield and similar *dr*, while Zn(OTf)₂ further improved the preference for **3l-syn** in good yield (entry 3). Eu(OTf)₃ (entry 5) gave the best balance of *dr* and yield in this limited screen, producing **3l-syn** as the major diastereomer in 83% yield and 1.9:1 *dr*. Presumably, the nature of the Lewis acid additive shifts the equilibrium between the cationic η^1 -allylic intermediates **C–F**; further investigations into the exact role of the metal additive and its impact on stereoselectivity are currently being pursued.

Conversion of the cyclopentene products to highly substituted cyclopentanes was briefly explored (Scheme 2). Substrate **3m** was prepared in the same manner as **3l** (Table 4), with the exception that **E** = CO₂Me. Both **3l–m** could be enriched to >19:1 *dr* by standard purification by column chromatography. The concave nature of the 5,5-bicyclic rings of **3l** and **3m** were leveraged to selectively functionalize one face of the alkene over the other to furnish substituted cyclopentanes in a highly diastereocontrolled manner. Treatment of **3m**

with *m*CPBA delivered epoxide **4** in excellent *dr*, while diol **6** was obtained in >19:1 *dr* under the Upjohn dihydroxylation conditions. Hydroboration of **31** with BH₃·THF, followed by oxidation with NaBO₃·4H₂O, produced the alcohol **8** in 64% yield and >19:1 *dr*. The pendant methyl ester moiety of **3m** could be removed by heating in DMSO with LiCl and H₂O to furnish lactone **5**. Using conditions described previously by Du Bois, treatment of **5** with catalytic Rh₂(tfacam)₄ (tfacam₄ = CF₃CONH), PhI(OAc)₂, and 1,1,1-trichlorosulfamate ester (TcesNH₂) provided aziridine **7** in 66% yield and >19:1 *dr*.¹⁵

In conclusion, we have demonstrated that highly complex cyclopentane scaffolds can be accessed in only a few steps from diastereomeric mixtures of allene precursors. Equilibrium control over the addition of a metal enolate to an activated allene drives a diastereocontrolled carbocyclization reaction. The success of this transformation hinges on the slow delivery of the fragile cationic gold species via triflate exchange with a Cu(OTf)₂ or other Lewis acidic triflate source. Factors including minimization of A^{1,3} strain and steric interactions between the substrate and the Au(I) catalyst are proposed to be the primary factors driving the stereoselectivity. Subsequent transformations of the alkene products show the variety of functionalization patterns that can be accessed via this carbocyclization methodology.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.
 Proposed model for stereochemical induction.

Scheme 1.
Proposed Allene Carbocyclization to Cyclopentenones

Scheme 2.
Elaboration to Highly Substituted Cyclopentanes

Table 1

Selected Studies of Au-Catalyzed Carbocyclizations

entry	Au cat (mol %)	additive (mol %)	time (h)	NMR yield (%) ^a	dr
1	Ph ₃ PAuCl (5)	Cu(OTf) ₂ (5)	2	72	1.3:1
2	AuCl ₃ (5)	Cu(OTf) ₂ (5)	2	0	–
3	Ph ₃ PAuCl (5)	Cu(OAc) ₂ (5)	2	0	–
4	Ph ₃ PAuCl (2.5)	Cu(OTf) ₂ (25)	24	68	1.6:1
5	Cy ₃ PAuCl (2.5)	Cu(OTf) ₂ (25)	24	93	1.8:1

^aYield determined by relative integration to mesitylene internal standard.

Table 2

Scope of the Allene Carbocyclization

entry	product	[Au]	xy	time (h)	yield (%) ^a	<i>d</i> ^b
1	2a	PPh ₃ AuCl	2.5:25	24	68	1.6:1
2	3a	PCy ₃ AuCl	2.5:25	24	93	1.8:1
3	2b	PPh ₃ AuCl	5:5	2	68	2.0:1
4	2c	PPh ₃ AuCl	2.5:25	24	78	1.0:1
5	3c	PCy ₃ AuCl	2.5:25	24	60	1.2:1

entry	product	[Au]	xy	time (h)	yield (%) ^a	<i>d_D</i>
6		PPh ₃ AuCl	1:5	2	72	2.1:1
7		PCy ₃ AuCl	2.5:2.5	24	67	4.0:1
8		PCy ₃ AuCl	2.5:2.5	24	74	4.6:1
9		PCy ₃ AuCl	2.5:2.5	24	39	6.5:1

entry	product	[Au]	xy	time (h)	yield (%) ^a	<i>d</i> ^b
10	2g	PCy ₃ AuCl	2.5:25	24	54 ^c	3.6:1
11	2h	PPh ₃ AuCl	5:5	2	62	n/a
12	2i	PCy ₃ AuCl	2.5:25	24	32	1.1:1
13	2j	PPh ₃ AuCl	1:10	12	54	2.0:1
14		PPh ₃ AuCl	2.5:25	24	37	1.8:1
15		PCy ₃ AuCl	2.5:25	24	30	1.4:1

entry	product	[Au]	xy	time (h)	yield (%) ^a	d ^b
16	<p>2k</p>	PPH ₃ AuCl	5:5	2	21	4.5:1

^a¹H NMR yield with mesitylene as internal standard.^b *anti:syn*.^c Isolated yield.

Table 3

Impact of Tether Substitution on the *dr*

entry	[Au]	X:Y	time (h)	yield (%) ^a	<i>dr</i> (<i>anti:syn</i>)
1	PPh ₃ AuCl	2.5:25	24	70	2.6:1
2	PCy ₃ AuCl	2.5:25	24	89	6.6:1

^a¹H NMR yields using mesitylene as the internal standard.

Table 4Impact of the Lewis Acid Additive on the *dr*

entry	Lewis acid	time (h)	yield (%) ^a	<i>dr</i> (<i>syn:anti</i>)
1	In(OTf) ₃	24	43	1.2:1
2	Sn(OTf) ₂	24	70	1.5:1
3	Zn(OTf) ₂	24	62	1.9:1
4	Yb(OTf) ₃	24	56	1.7:1
5	Eu(OTf) ₃	24	83	1.9:1

^a¹H NMR yields using mesitylene as the internal standard.