

Well-Defined Chiral Gold(III) Complex Catalyzed Direct Enantioconvergent Kinetic Resolution of 1,5-Enynes

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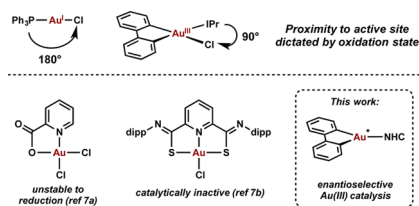
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S Supporting Information

ABSTRACT: The development of a gold(III) catalyzed direct enantioconvergent 1,5-enyne cycloisomerization and kinetic resolution reaction is described. The transformation results in highly enantioenriched bicyclo[3.1.0]hexenes at all levels of conversion, with no racemization or symmetrization taking place during the course of the reaction, and simultaneously affords optically enriched 1,5-enynes. This report marks the first highly enantioselective transformation catalyzed by a well-defined cationic gold(III) catalyst and demonstrates the unique potential of gold(III) complexes in enantioselective catalysis.

Cycloisomerization reactions have been studied extensively because they rapidly and efficiently build structural complexity from much simpler acyclic compounds.¹ The field of homogeneous gold catalysis² has been the subject of intense investigation during the past decade, elevating gold(I) complexes to among the most useful catalysts for a diverse range of cycloisomerization reactions.³ Despite significant progress in the development of enantioselective gold(I) catalysis,^{4,5} challenges still remain largely as a result of the linear geometry that places the active site distant from the chiral information. This challenge can potentially be addressed by employing square-planar geometry gold(III) complexes as catalysts; however, the majority of gold(III) catalyzed reactions employ simple gold halide salts as catalysts or ligands that produce unstable or unreactive complexes (Scheme 1).⁶ We

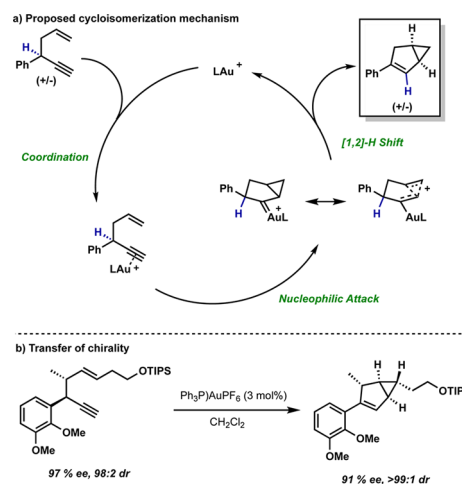
Scheme 1. Ligand Environment of Au^I and Au^{III} Complexes



recently reported on an oxidative addition strategy to prepare well-defined and stable gold(III) catalysts that, as a result of the square-planar geometry, place an ancillary ligand much closer to the active site (Scheme 1).⁷ This new class of organometallic gold(III) complexes takes advantage of a cyclometalated C–C ligand framework to stabilize the catalytically active cationic species, and offers the possibility to leverage an L-type ligand to introduce chiral information.

The gold(I)-catalyzed cycloisomerization of 1,5-enynes was first reported over a decade ago,⁸ but a highly enantioselective variant has yet to be developed.⁹ A challenge inherent to this reaction is that the (*R*) and (*S*) enantiomer of the 1,5-enyne can transform to either the (*R,R*) or the (*S,S*) enantiomer of the bicyclo[3.1.0]hexene, and transfer of chirality has been observed for certain classes of substrates with achiral catalysts (Scheme 2).¹⁰ To develop an enantioselective variant of this cyclo-

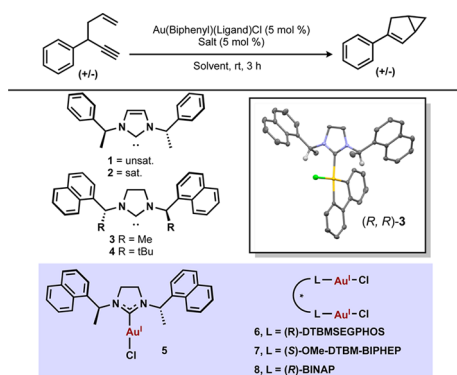
Scheme 2. Proposed Mechanism for Au(I) Catalyzed 1,5-Enyne Cycloisomerization



isomerization, the chiral catalyst ideally will selectively produce one enantiomer of the bicyclo[3.1.0]hexene adduct, overriding the transfer of chirality.

Initial investigations began by testing a number of gold(III) catalysts bearing chiral *N*-heterocyclic carbene (NHC) ligands (Table 1).¹¹ The gold(III) complex bearing a saturated NHC ligand catalyzed the formation of the bicyclic adduct in higher enantioselectivity when compared to the unsaturated analog (entries 1–2). Among the saturated NHC ligands, the more sterically encumbered naphthyl-substituted ligand resulted in higher enantioselectivity than the phenyl-substituted ligand (entry 3). Increasing the steric bulk of the NHC ligand by changing the methyl substitution to *t*-butyl resulted in a large drop in enantioselectivity as well as catalytic activity (entry 4). To confirm that *in situ* reductive elimination¹² of biphenylene from the gold(III) species to form an active gold(I) species was

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Table 1. Development of the Enantioselective 1,5-Enyne Cycloisomerization*

entry	catalyst	salt	solvent	conversion (%)	ee (%)
1	1	AgSbF ₆	CH ₂ Cl ₂	100	-24
2	2	AgSbF ₆	CH ₂ Cl ₂	100	-34
3	3	AgSbF ₆	CH ₂ Cl ₂	100	37
4	4	AgSbF ₆	CH ₂ Cl ₂	4	-2
5	5	AgSbF ₆	CH ₂ Cl ₂	23	0
6	6	AgSbF ₆	CH ₂ Cl ₂	100	9
7	7	AgSbF ₆	CH ₂ Cl ₂	100	6
8	8	AgSbF ₆	CH ₂ Cl ₂	100	2
9	2	AgOMs	CH ₂ Cl ₂	0	
10	2	AgTRIP	CH ₂ Cl ₂	0	
11	2	AgOTf	CH ₂ Cl ₂	31	48
12	2	AgNTf ₂	CH ₂ Cl ₂	100	21
13	2	AgPF ₆	CH ₂ Cl ₂	68	44
14	2	AgBF ₄	CH ₂ Cl ₂	91	53
15	2	NaBArF ₂ ₄	CH ₂ Cl ₂	72	19
16	2	AgBF ₄	DMF	0	
17	2	AgBF ₄	MeCN	8	58
18	2	AgBF ₄	THF	68	29
19	2	AgBF ₄	Toluene	41	73
20	2	AgBF ₄	Toluene	61	54

*General reaction conditions: Enyne (1.00 equiv), gold(III) catalyst (0.05 equiv), salt (0.05 equiv), solvent (0.3 M), rt, 3 h. Conversion determined by ¹H NMR spectroscopy, enantiomeric excess (% ee) determined by chiral phase HPLC.

not the operative mechanism, the gold(I) analog was tested and resulted in no enantioselectivity as well as decreased catalytic activity (entry 5). Additionally, the gold(III) catalyst was reisolated from the reaction mixture with no observable reductive elimination to gold(I), and showed the same catalytic activity when resubjected to the reaction conditions (see SI). A range of gold(I) catalysts bearing chiral phosphine ligands were also tested and showed complete conversion to product; however, the enantioselectivity was significantly lower than that obtained with the gold(III) complex as catalyst (entries 6–8).

It has been frequently reported that the identity of the counterion in homogeneous gold catalysis can have a large effect on the outcome of a reaction.¹³ Screening of possible counterions in the gold(III) system revealed that several counterions were incompatible (entries 9–10). Presumably, the decrease in catalyst activity results from tight binding of the counterion to the cationic gold(III) center, which has been shown to have hard Lewis acidity and high oxophilicity.⁶ Ultimately, tetrafluoroborate proved to be the optimal counter-

ion retaining catalytic activity and increasing enantioselectivity (entries 11–15).

We next looked to optimize the solvent conditions, and found low reactivity in solvents that provided poor solubility or were capable of coordination to the cationic gold(III) (entry 16). On the other hand, a significant increase in enantioselectivity was observed when dichloromethane was replaced with toluene as solvent, albeit with a decrease in reactivity (entry 19). When the reaction was run for 16 h, conversion increased but a significant decrease in enantioselectivity was also observed (entry 20).

This decrease in product enantioselectivity with increased conversion suggested a potential kinetic resolution; however, at complete conversion the product remained enantioenriched (*vide infra*). Isolation of the starting 1,5-enyne and analysis by chiral HPLC showed that the enyne was highly enantioenriched in addition to the bicyclo[3.1.0]hexene. Complete optimization of the kinetic resolution resulted in the highest *s*-factor when the reaction was run in CHCl₃ at -40 °C (Table 2).

Table 2. Enyne Cycloisomerization *s*-Factor Optimization*

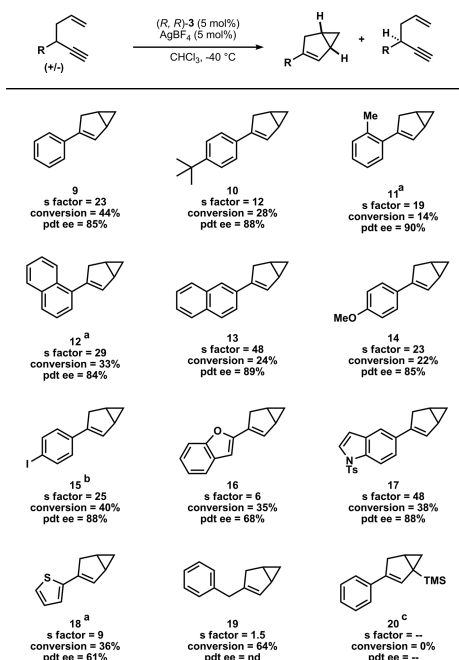
entry	solvent	temperature (°C)	conversion (%)	<i>s</i> -factor
1	CH ₂ Cl ₂	rt	30	6
2	CH ₂ Cl ₂	0	31	9
3	CH ₂ Cl ₂	-20	46	12
4	CH ₂ Cl ₂	-30	55	14
5	CH ₂ Cl ₂	-40	51	21
6	CH ₂ Cl ₂	-50	0	
7	CH ₂ Cl ₂	-40	51	21
8	PhCl	-40	14	18
9	DCE	-40	44	16
10	CHCl ₃	-40	44	23

*General reaction conditions: enyne (1.00 equiv), gold(III) catalyst (0.05 equiv), AgBF₄ (0.05 equiv), solvent (0.3 M), 3 h. Conversion determined by ¹H NMR spectroscopy, enantiomeric excess (ee) determined by chiral phase HPLC. Selectivity (*s*-factor) calculated as $s = \ln[(1 - C)(1 - ee_{SM})] / \ln[(1 - C)(1 + ee_{SM})]$.

With optimized reaction conditions in hand, the scope of the transformation was explored (Table 3). Substrates with more sterically hindered ortho substitution required higher temperatures but maintained similarly high levels of enantioselectivity and *s*-factor (enyne 11 and 12). Despite the potential for nonproductive coordination to the hard Lewis-acidic cationic gold(III), we found that heteroarene substrates were tolerated and in one case greatly exceeded the selectivity of the model substrate (enyne 16–18). Substrates in which the propargyl substitution was changed from aryl to alkyl were compatible with the reaction but with a decreased selectivity (enyne 19). On the other hand, the use of a silyl-substituted alkyne dramatically slowed the rate of reaction and resulted in no kinetic resolution or product enantioselectivity (enyne 20).

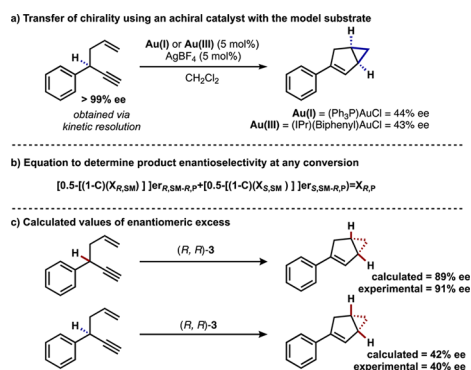
To further explore the interplay between the kinetic resolution and the enantioselective product formation, we first isolated enantioenriched starting material and subjected it to the reaction conditions with an achiral gold(I) and gold(III) catalyst. The bicyclo[3.1.0]hexene product was isolated with 44% and 43% enantiomeric excess respectively, indicating that the reaction proceeded with some, but not complete, chirality transfer (Scheme 3). Additionally, when the racemic starting

Table 3. Scope of the Enantioconvergent Kinetic Resolution*



*General reaction conditions: enyne (1.00 equiv), catalyst (0.05 equiv), AgBF₄ (0.05 equiv), AgBF₄ (0.05 equiv), solvent (0.3 M), 3 h. Conversion determined by ¹H NMR spectroscopy, ee determined by chiral phase HPLC. Selectivity (*s*-factor) calculated as $s = \ln[(1 - C)(1 - ee_{SM})] / \ln[(1 - C)(1 + ee_{SM})]$. ^a-20 °C for 3 h. ^b-30 °C for 3 h. ^c60 °C for 24 h.

Scheme 3. Contribution of Chirality Transfer to Enantiomeric Excess



material was reacted under our conditions to complete conversion, the product was enantioenriched. This observation stands in contrast to a standard kinetic resolution where there would be no enantioenrichment at complete conversion. Moreover, the inherent chirality transfer of the cycloisomerization must be overridden when using the chiral gold(III) catalyst for one enantiomer of starting material, and enforced in the case of the other enantiomer.

The decrease in the enantiomeric excess of the bicyclo[3.1.0]-hexene over the course of the reaction implies that each enantiomer of starting material must also be transforming to product with different enantiomeric ratios. This phenomenon can be modeled and used as a predictive system (Scheme 3b, see SI). Given the enantiomeric excess data from at least two different values of conversion, it is possible to solve for the enantiomeric ratios that each starting material is converting to

product. Using this method, the (*R*)-enyne starting material was found to transform to the bicyclo[3.1.0]hexene product with 89% ee catalyzed by (*R,R*)-3, whereas the (*S*)-enyne converted to the same product with 42% ee under our optimized reaction conditions (Scheme 3c). These values were then compared to experimental values and found to be in close agreement (see SI). Using this data, it was possible to create a model to determine product enantioenrichment at any conversion, which was compared to a similar plot for a standard kinetic resolution (Figure 1). From the comparison, it is clear that the

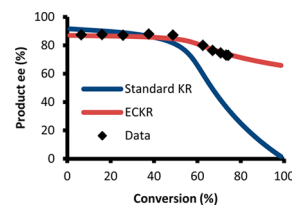
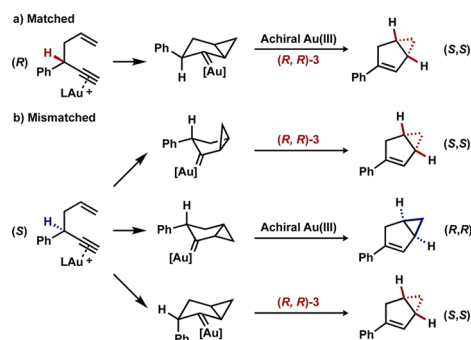


Figure 1. Enantioselectivity of a kinetic resolution with $s = 23$ (blue) and enantioselectivity of the enantioconvergent kinetic resolution with $s = 23$ (data = black, model = red).

enantioconvergent kinetic resolution results in more highly enantioenriched product at synthetically useful conversions (above 40%) when s factors are identical, while simultaneously maintaining the high levels of starting material enantioenrichment seen in a standard kinetic resolution.¹⁴

The previously proposed mechanism for this reaction accounts for the chirality transfer of the reaction by considering the half-chair transition states (Scheme 4). In the matched case

Scheme 4. Direct Enantioconvergence of the 1,5-Enyne Cycloisomerization Reaction



the (*R*)-enyne preferentially forms the (*S,S*)-bicyclo[3.1.0]-hexene, and this preference is reinforced when the transformation is performed with (*R,R*)-3 as the catalyst (Scheme 4). In the mismatched case the (*S*)-enyne preferentially forms the (*R,R*)-bicyclo[3.1.0]hexene. However, the chiral gold(III) catalyst overrides this preference and the major product becomes the (*S,S*)-bicyclo[3.1.0]hexene. These observations can be best explained by examining the selectivity determining transition state. The chiral catalyst either induces the large phenyl substituent to be in the axial position of the half-chair or it induces the cyclopropane ring to fold in to a half-boat conformation. Because both enantiomers of starting material convert to the same enantiomer of product without any racemization or symmetrization processes, this gold(III)-catalyzed cycloisomerization reaction falls under the rare class of direct enantioconvergent transformations.¹⁵

In summary, we have developed an enantioconvergent kinetic resolution that allows access to enantioenriched 1,5-enynes and bicyclo[3.1.0]hexenes that has not been shown to be possible with gold(I). This transformation represents a rare mode of direct enantioconvergent kinetic resolution wherein product enantioenrichment is increased at synthetically useful conversions and starting material enantioenrichment is maintained when compared to a standard kinetic resolution. More importantly, these transformations mark the first highly enantioselective reactions catalyzed by a well-defined gold(III) complex and set the stage for further exploration and development.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.7b06025.

Experimental details and characterization data (PDF)
Crystallographic data for 3 (CIF)

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Notes

The authors declare no competing financial interest.

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