MECHANISTIC INSIGHTS INTO THE ROLE OF SILVER IN ASYMMETRIC GOLD(I) CATALYZED CYCLOISOMERIZATION OF 1,6-ENE ALLENES

Allison J. Hulchanski

A dissertation submitted to the faculty of the University of North Carolina at Chapel Hill in partial fulfillment of the requirements for the degree of Masters of Arts in the Department of Chemistry.

Chapel Hill
2013

Approved by:

Michel R. Gagnè

Maurice S. Brookhart

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ABSTRACT

Allison J. Hulchanski: MECHANISTIC INSIGHTS INTO THE ROLE OF SILVER IN ASYMMETRIC GOLD(I) CATALYZED CYCLOISOMERIZATION OF 1,6-ENE ALLENES
(Under the direction of Michael R. Gagnè and Maurice S. Brookhart)

This thesis encompasses a series of studies carried out to ascertain the mechanism that axially chiral bis(gold) phosphine catalysts undergo to stereoselectivity cycloisomerize 1,6-ene allenes. The thesis also discusses the role in which silver salts play to not only activate the gold catalysts but their role in catalysis that affects catalyst speciation, stereoselectivity, and formation of dinuclear intermediates. While previous studies into the mechanism of gold(I) catalyzed reactions have focues primarily on monodentate ligated gold catalysts, little is known about the mechanism involved with bis(gold) phosphine based catalysts. In addition, only recently has it been acknowledged that silver may play an active role in catalysis rather than the notion that silver activates gold to become an inactive silver halide byproduct.

The thesis first uses Non-linear effects experiments to determine if oligomers often seen in gold coordination chemistry occur during catalysis. Attempts were made at synthesizing 3-center-2-electron “digold” species often seen in mono-dentate gold catalyzed reaction failed. However, the inability to form stable or isolable “digold” model compounds

suggests that axially chiral bis(gold) phosphine catalysts are too strained to form this type of intermediate.

Also described in this thesis is the study of the role of silver in catalysis. The effect of the amount of silver used to activate the gold catalyst on the enantiomeric excess of the product as well as the catalysts speciation directly shows silver is more than an inactive bystander in catalysis. Titration of silver with bis(gold) phosphine aryl model compounds with silver at low temperatures demonstrate the potential for dinuclear Au-Ag intermediates. Finally, studies removing AgCl byproduct and addition of silver salts with less coordinating counter ions that chloride directly impacted enantiomeric excess of the products suggesting that the proposed dinuclear Au-Ag species is involved in the stereochemistry determining step of the mechanism.

To my family and friends whose love and support have been invaluable and without whom I would not have succeeded.

To my mom for sitting up counless nights as I did school work, her love, and support.

To my sister for always looking out for “Little A” and for being my best friend always

To Elizabeth Bucher for being an amazing roommate, friend and colleague for 4 years of graduate school.

ACKNOWLEDGEMENTS

I would first and foremost like to thank my advisor, Dr. Michel Gagné, for giving me so many incredible opportunities, for sharing his passion for chemistry, and for being so very supportive. Without his support and guidance I would not have made it this far. I cannot thank him enough for all he has done for me. I would also like to thank my co-advisor Dr. Maurice Brookhart who provided support and insight into NMR experiments and mechanistic questions.

I also want to thank the Gagné group for providing ideas, support, and laughs throughout my graduate career. I would like to especially thank Laura Adduci, Michael Bertucci, and Nikki Cochrane for their help editing, bouncing ideas off of, assistance with various lab instrumentation, and most importantly for their friendship. In addition, I would like to express my gratitude to Dieter Weber for helping me understand all things gold chemistry related. I would also like to thank Marc ter Horst for his assistance with Low T NMR, DNMR, 2D NMR, and for always being patient with my questions.

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LIST OF ABBREVIATIONS AND SYMBOLS

◦	degrees
Å	angstroms
Δ	delta
$\Delta G^{\ddagger}$	Gibbs free energy
$\Delta H^{\ddagger}$	enthalpy
$\Delta G^{\ddagger}$	entropy
atm	atmospheres
β	beta
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
br	broad
◦C	degrees Celsius
CD_2Cl_2	deuterated methylene chloride
$CDCl_3$	deuterated chloroform
CD_3NO_2	deuterated nitromethane
d	doublet
δ	chemical shift
E_a	activation energy
ee	enantiomeric excess
EtOAc	ethyl acetate
eq.	equivalents
GC	gas chromatography
GC-MS	gas chromatography mass spectrometry

h	hours
HOTf	triflic acid
Hz	hertz
(I)	monovalent
(III)	trivalent
J	three bond H-H coupling
J_{P-P}	two bond P-P coupling
K	Kelvin
kcal	kilocalorie
m	multiplet
M	Molarity
Me	methyl
Mg	milligram
MHz	megahertz
mL	milliliter
min	minutes
μL	microliter
mmol	millimole
mol %	molar percentage
MS	mass spectrometry
NLE	non-linear effect
NTf	Bis(trifluoromethanesulfonyl)imide
NMR	nuclear magnetic resonance

o-tol	ortho-toluene
OMe	methoxy
OTf	triflate
p-tol	para-toluene
P_2	bidentate phosphine ligand
$P_2Au_2R_2$	bis(gold) phosphine diaryl
Pa	Pascal
Ph	phenyl
ppm	parts per million
psi	pounds per square inch
PTFE	polytetrafluoroethylene
R	gas constant
rac	racemic
RT	room temperature
s	singlet
s^{-1}	per second
t	triplet
T_c	coalescence temperature
THF	tetrahydrofuran
t-Bu	tertiary butyl
TMS	trimethylsilyl
vs	versus
xylyl	3,5-dimethylphenyl

CHAPTER 1: Gold(I) Catalyzed Cycloisomerization and Involvement of *Gem*-diaurated Species in Catalysis

1.1. Introduction: Gold(I) Catalyzed Asymmetric Cycloisomerizations and Current Mechanistic Insights

Transition metal catalyzed C-C bond forming reactions have received a great deal of attention in the last decade, as the search continues for a transition metal catalyzed room temperature reaction that does not require prefunctionalization of each component.[1] Au(I) and Au(III) have shown a preference for forming π-complexes with a variety of unsaturated bonds including; alkenes, alkynes, allenes, carbonyls, and imines.[2] Once electrophilically activated, these unsaturated bonds are susceptible to *intra*- and *inter*molecular nucleophilic attack by oxygen, nitrogen, or C-C multiple bonds to form a variety of cyclic structures.[2] Au(I) is known to form two coordinate complexes with a forced linear geometry.[3] This linear geometry separates the chiral auxiliary approximately 180˚ and 5 Å from the substrate, making the number of asymmetric variants somewhat slower to develop.[3]

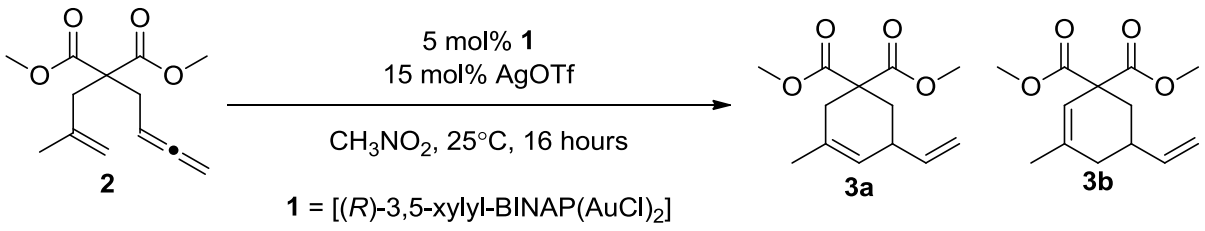
Asymmetric gold catalysis has progressed significantly in the past five years with chiral bis(phosphines) ligands, chiral counterions, chiral N-heterocyclic carbenes, and

monodentate phosphoramidite ligands having been successfully employed for the stereoselective synthesis of a variety carbo- and heterocycles.[4,5] Success has also been found by using several of these asymmetric strategies in combination. Mikami and Toste each observed a synergistic effect that led to an increase in *ee* when combining chiral bis(phosphine) with a chiral counterion.[9,10]

Though there has been exponential growth in the number of reported Au(I) catalyzed reactions, only recently has work investigating the mechanisms of mono-ligated gold(I) reactions revealed the intermediates of digold, π-Au, σ-π-bound digold, Au-vinyl, Au-alkyl, Au-carbene, and Au-Ag structures in various reactions.[7] Despite the burgeoning mechanistic insights into mono-ligated gold(I) catalytic reactions, little is known about the speciation and mechanism of bis(gold) diphosphine catalyzed asymmetric reactions.[3,4,7]

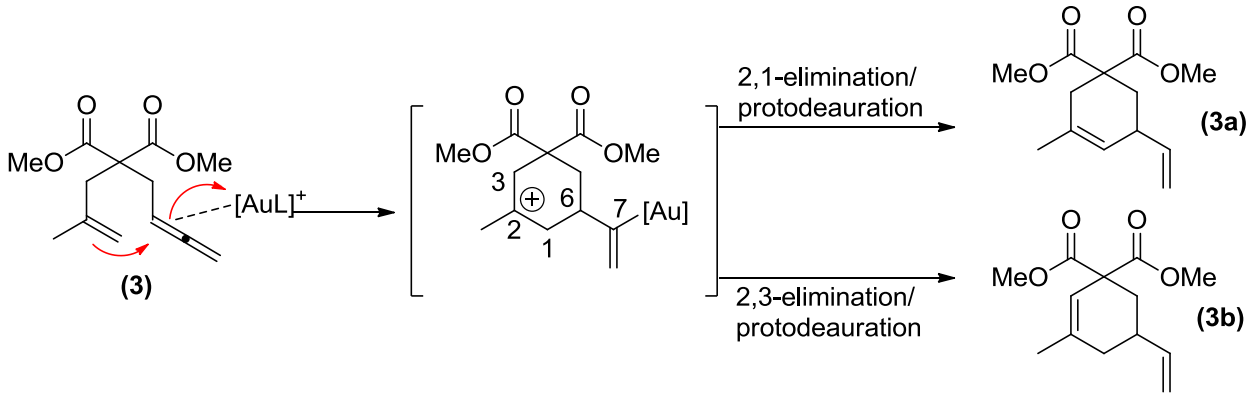
Most proposed bis(gold) phosphine reaction mechanisms are based on *indirect* evidence, literature studies of other proposed monodentate gold-catalyzed, or related transition metal reactions without any *direct* observation or characterization of intermediates.[1] The lack of knowledge of how these transformations proceed and how enantioenrichment occurs is an underdeveloped area of study in the field of gold catalysis.

Au(I) catalysts first came into use in the Gagné group when previously used electrophilic Pt^{II} catalysts for the enantioselective cycloisomerizations of 1,6- and 1,7-dienes were found to be ineffective with a similar system of 1,6-eneallenes.[8] The reactivity of Au(I) with unsaturated bonds allowed for asymmetric cycloisomerization of 1,6-eneallenes to 6-membered rings using (*R*)-3,5-xylyl-BINAP$(AuCl)_2$ **(1)** as the pre-catalyst and AgOTf to activate the catalyst (Scheme 1-1).[9]



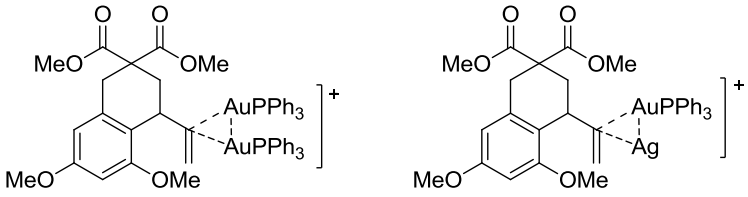
Scheme 1-1. Au(I) catalyzed asymmetric cycloisomerization of 1,6-eneallenes.

Michael Tarselli investigated several mechanistic factors, including: the sensitivity of regioselectivity to counterions, the role of the alkene as the nucleophile, the sensitivity of enantioselectivity to solvent polarity, the dependence of rate on silver-salts and the loss of enantioselectivity when using pre-isolated (*R*)-3,5-xylyl-BINAP(AuOTf)$_2$ **(4).**[9] His studies, combined with the known reactivity of Au(I) toward π-bonds suggested the mechanism first involved silver activation of the pre-catalyst to generate cationic Au(I) that would electrophilically activate the internal allene double bond, followed by nucleophilic attack of the alkene to generate a tertiary carbenium ion.[9] 2,3- or 2,1-elimination of the proton by the counterion and protodeauration of the catalyst would turn over the cycle (Scheme 1-2).[9]



Scheme 1-2. Proposed Au(I) catalyzed cycloisomerization.

This mechanism failed to explain the dependence of rate on the presence of silver-salts and the loss of enantioselectivity when using **4**. Later mechanistic studies on Au(I) catalyzed *intra*molecular hydroarylation of allenes showed the presence of two gold(I) species acting as catalytic resting states in addition to the $Ph_3PAuNTf_2$ catalyst and a gold-vinyl intermediate.[7,10] One isolated resting state was proposed to contain a three-center two-electron bond between two Ph_3PAu^+ units and the internal vinylic carbon, a *gem*-diaurated vinyl or "digold" (Figure 1-1**(E)**).[10] This structure was based on ^1H and ^{31}P NMR data, as well as similar model digolds isolated by Schmidbaur , Fürstner, and Grandberg (Figure 1-2).[7,14,15] The second species was proposed to contain an asymmetric three-center two-electron bond between Ph_3PAu^+, Ag^+, and the internal vinylic carbon (Figure 1-1**(F)**).[13] The structure of species **F** was proposed based on ^1H and ^{31}P NMR data as well as the *intra*- and *inter*molecular Au-Au and Au-Ag bonds or "aurophilic interactions" seen throughout gold literature.[3,7] These interactions are 8-15 kcal/mol bonds formed by the stabilization from d^{10} closed shell interactions and are comparable in strength to strong hydrogen bonding.[3]



(E) **(F)**

Figure 1-1. (**E**) *Gem*-di-aurated vinyl. (**F**) Au-Ag vinyl.

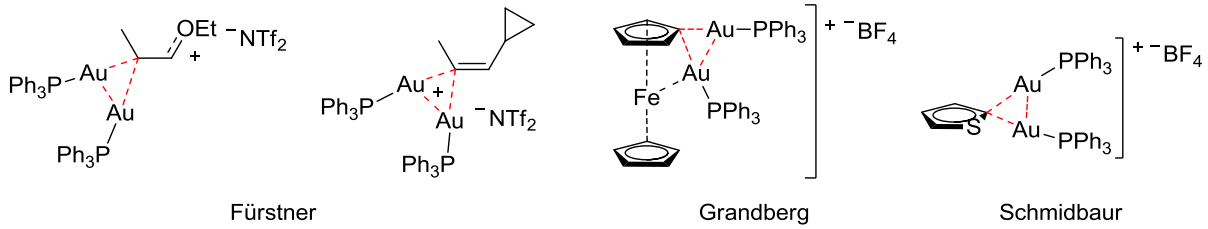
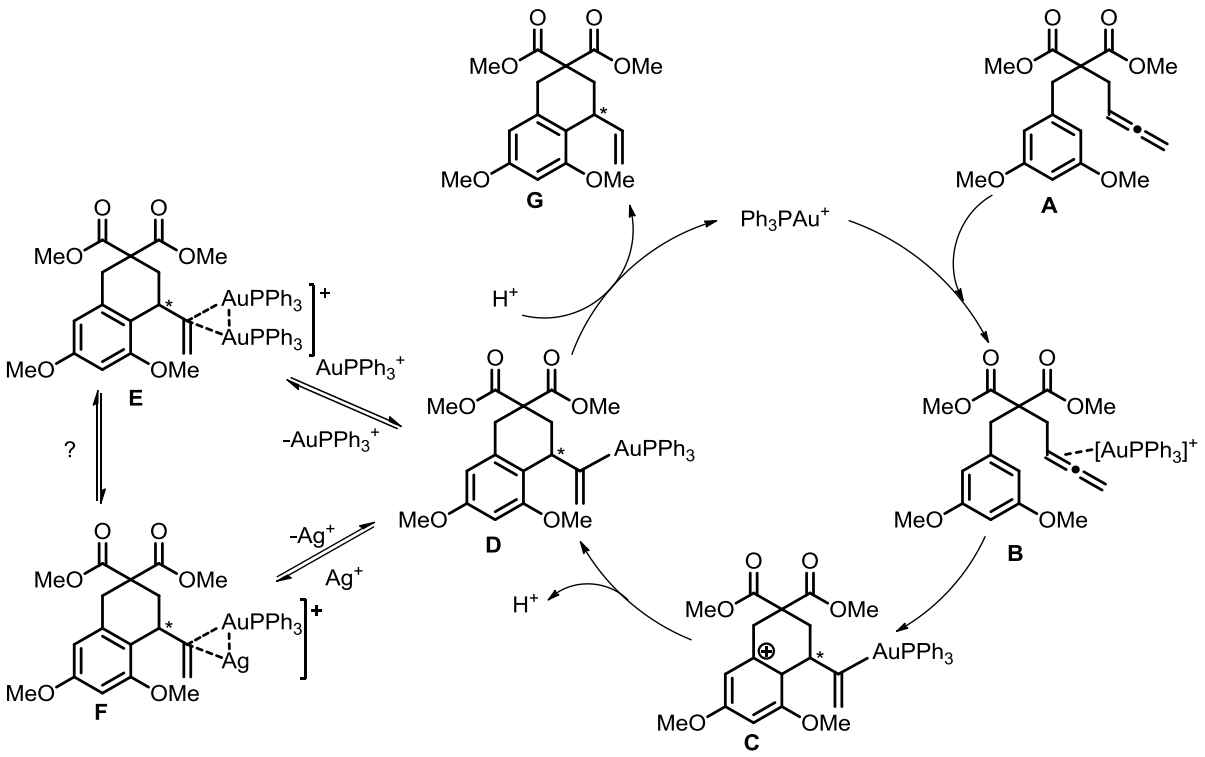


Figure 1-2: 3-center-2-electron bond *gem*-diaurated species found in the literature.[5,14,15]

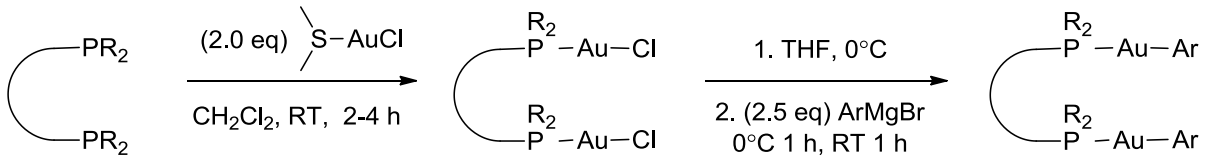
This evidence gives rise to a more complex mechanism for the Au(I) catalyzed hydroarylation of allenes (Scheme 1-3).[7,13] It also raises the question, of whether Au-Au and Au-Ag intermediates are involved in the asymmetric Au(I) catalysis of 1,6-ene allenes to vinylcyclohexenes. One project goal is the isolation of model digold compounds for comparison to initial ^{31}P NMR studies on the **1** catalyzed cycloisomerization of dimethyl-2-(1,2-butadienyl)-2-(cyclohex-1-enylmethyl)-malonate (**2)** because vinyl and aryl digolds have similar ^{31}P chemical shifts.



Scheme 1-3. Proposed mechanism for the hydroarylation of 1,6-eneallenes.

1.2 Diphosphine Au-Au Aryl Complexes as Model Compounds

^{31}P NMR of cyclohexene-allenyl malonate treated with 5 mol% **(1)** and 15 mol% **(2)** in d_3-nitromethane revealed a small amount of diactivated catalyst at 29 ppm, a major peak at 41.3 ppm and five minor signals between 39 and 44 ppm. To determine if any species contained an Au-Au bond, bis(phosphine) gold aryls were targeted as potential model compounds for digold intermediates in the catalytic system based on known gold-vinyl and aryl digold chemical shifts. Based on preparation of **(1)**, various bis-phosphine gold chlorides were prepared and isolated. The bis(phosphine) gold aryls were then formed using a known procedure for transmetallating using alkyl Grignards (Scheme 1-4).

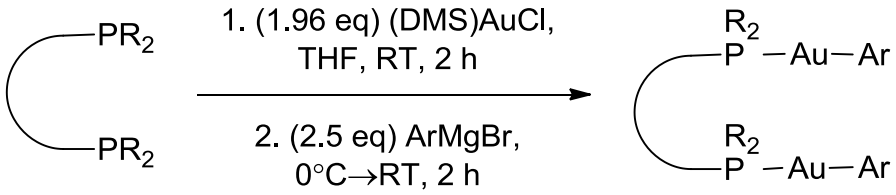


Scheme 1-4. Initial preparation of bis(phosphine) gold aryls.

Bis(phosphine) gold aryls were isolated as white and cream foams but quickly decomposed into yellow-brown oils despite storage in air, moisture, and light free atmospheres and at lowered temperatures. Therefore, various bis(phosphines) and aryl Grignards were used to see if complex stability depended on the ligand, aryl, or both. Initial attempts at purification by recrystallization seemed to only further decompose the compounds. ^{1}H NMR of the compounds showed a mixture of indiscernible species that are assumed to be product, excess protonated Grignard aryls, and various decomposition products. Attempts to simplify preparation of bisphosphine gold aryls and screen various bis(phosphines) efficiently included an attempt at transmetallating the gold starting material, chloro(dimethylsulfide)gold(I) with 2- and 3-biphenyl Grignards. However, this synthesis only resulted in immediate decomposition. An efficient and successful method of preparation combined formation of the bis(phosphine) gold chloride and transmetallation into a one pot synthesis (Scheme 1-5). Using BINAP and 3,5-xylyl-BINAP as the bis(phosphine) a range of aryl and alkyl bis(gold)phosphine were successfully synthesized and isolated via recrystallization from diethyl ether.

Attempts at using Fürstner[14] or Grandberg[15] type synthetic methods for creating bis(gold) phosphine digold model complexes failed, leading to extensive decomposition. Molecular models suggest that axial chiral ligands may create too much strain to achieve the

three-center two electron bonds required to form a digold. Bis(gold) phosphines obtained in the literature generally contain flexible methylene backbones supporting that axially chiral ligands are too strained to feasibly create digold intermediates during catalysis.[15] The inability to make axially chiral bis(gold) phosphines demonstrates that this class of gold catalysts may undergo a different mechanism than traditional bisphosphine based gold catalysis.



Scheme 1-5. One-pot synthesis of $P_2(AuAr)_2$.

1.3. Experimental

General Information

Dichloromethane, chloroform, diethyl acetate, hexanes, pentanes, and diethyl ether were purchased from Fisher Scientific and used without further purification. Anhydrous THF was purchased from Fisher Scientific in an Acros-Seal bottle and stored under nitrogen. (*S*)-3,5-xylyl-BINAP and (*R*)-3,5-xylyl-BINAP were purchased from Strem Chemicals Inc. and used without further purification. ^{1}H, ^{13}C and ^{31}P NMR data were collected on a Bruker 500 and 600 MHz Avance spectrometer. Chemical shifts are referenced to residual solvent peaks and reported in ppm for ^{1}H and ^{13}C NMR. Chemical shifts are referenced to a phosphoric acid external standard for ^{31}P NMR taken at room temperature and reported in ppm.

General Procedure for Synthesis of $P_2Au_2R_2$ Model Compounds: To a flame dried 100 mL schlenk flask under N_2(g) atmosphere, (*S*)-BINAP (1.0 eq, 0.1625 mmol) and chloro(dimethylsulfide)gold(I) (1.98 eq, 0.3106 mmol) was added and stirred in anhydrous THF (20 mL) at room temperature for 1 hour. The reaction was cooled to 0°C and Grignard (2.5 eq, 0.4100 mmol) was added drop wise. The reaction was then stirred at 0°C for 1 hour then allowed to warm to room temperature over 1 hour becoming a pale yellow solution. The reaction was quenched with H_2O until the solution became cloudy and bubbles stopped forming. The mixture was extracted 4 x 25 mL of Et_2O and dried over potassium sulfate before concentrating to form foam. Product was recrystallized by slow evaporation of Et_2O to form clear, colorless crystals.

Synthesis of (*S*)-BINAP(Au(*p*-tol))$_2$: Complex was prepared according to General Procedure for Synthesis of $P_2Au_2R_2$ Model Compounds. ^{1}H NMR: (600MHz, CD_2Cl_2) δ = 7.98 (d, J_{H-H} = 8.4Hz, 2H), 7.84 (d, J_{H-H} = 8.4H, 2H), 7.74 (m, 4H), 7.49 (t, J_{H-H} = 8.4Hz 2H), 7.38 (t, J_{H-H} = 7.8Hz, 2H), 7.27-7.32 (m, 8H), 7.14 (m, 8H), 7.03 (t, J_{H-H} = 7.2Hz, 4H), 6.97 (s, 2H), 6.96 (s, 1H), 6.81 (t, J_{H-H} = 8.4Hz 2H), 6.59 (d, J_{H-H}=8.4Hz, 2H), 2.28 (s, 6H, CH_3). ^{31}P NMR: (600MHz, CD_2Cl_2, phosphoric acid standard = 0 ppm) = 37.61 ppm (s).

Synthesis of (*S*)-BINAP(AuPh)$_2$: Complex was prepared according to General Procedure for Synthesis of $P_2Au_2R_2$ Model Compounds. ^{1}H NMR: (600MHz, CD_2Cl_2) δ = 7.98 (d, J_{H-H}=12 Hz, 2H), 7.84 (d, J_{H-H}= 12Hz, 2H), 7.74 (m, 4H), 7.49 (t, J_{H-H} = 7.8 Hz, 2H), 7.37 (t, J_{H-H}=7.8Hz, 2H), 7.25-7.31 (m, 8H), 7.1-7.14 (m, 16H), 6.98 (t, J_{H-H} = 7.2 Hz, 2H), 6.79 (t, J_{H-H} = 7.8 Hz, 2H), 6.57 (d, J_{H-H} = 7.8 Hz, 1H). ^{31}P NMR: (600MHz, CD_2Cl_2, phosphoric acid standard = 0 ppm) = 36.56 ppm (s).

Synthesis of (*S*)-BINAP(Au(*o*-tol))$_2$: Complex was prepared according to General Procedure for Synthesis of $P_2Au_2R_2$ Model Compounds. ^{1}H NMR: (600MHz, CD_2Cl_2) δ = 8.03 (d, J_{H-H} = 7.2 Hz, 2H), 7.81 (d, J_{H-H} = 8.4Hz, 2H), 7.71 (m, 4H), 7.48 (t, J_{H-H} = 8.4Hz 2H), 7.31 (t, J_{H-H} = 7.8Hz, 4H), 7.22-7.28 (m, 8H), 7.14 (m, 6H), 6.92-7.06 (m, 10 H), 6.63 (t, J_{H-H} = 8.4Hz, 2H), 6.43 (d, J_{H-H} = 8.4Hz, 2H), 2.29 (s, 6H, CH_3). ^{31}P NMR: (600MHz, CD_2Cl_2, phosphoric acid standard = 0 ppm) = 38.34 ppm (s).

Synthesis of (*S*)-BINAP(Au(4-methoxyphenyl))$_2$: Complex was prepared according to General Procedure for Synthesis of $P_2Au_2R_2$ Model Compounds. ^{1}H NMR: (600MHz, CD_2Cl_2) δ = 7.95 (d, J_{H-H} = 8.4Hz, 2H), 7.84 (d, J_{H-H} = 7.8Hz, 2H), 7.75 (m, 4H), 7.37 (t, J_{H-H} = 7.8 Hz 2H), 7.26-7.31 (m, 8H), 7.27-7.32 (m, 8H), 7.11-7.14 (m, 8H), 7.06 (m, 4H), 6.78 (t, J_{H-H} = 7.8Hz, 2H), 6.71 (d, J_{H-H} = 7.8Hz, 1H), 6.56 (d, J_{H-H} = 8.4Hz. 2H), 3.79 (s, 6H, OCH_3). ^{31}P NMR: (600MHz, CD_2Cl_2, phosphoric acid standard = 0 ppm) = 37.83 ppm (s).

Synthesis of (*S*)-BINAP(Au(3,5-dimethoxyphenyl))$_2$: Complex was prepared according to General Procedure for Synthesis of $P_2Au_2R_2$ Model Compounds. ^{1}H NMR: (600MHz, CD_2Cl_2) δ = 7.98 (d, J_{H-H} = 7.8Hz, 2H), 7.78-7.82 (m, 6H), 7.54 (t, J_{H-H} = 7.2Hz, 2H), 7.33 (t, J_{H-H} = 7.8Hz, 4H), 7.22-7.28 (m, 6H), 7.19 (t, J_{H-H} = 8.4Hz, 4H), 7.09 (t, J_{H-H} = 8.4Hz, 4H), 6.76 (t, J_{H-H} = 7.8Hz 2H), 6.51 (d, J_{H-H} = 8.4Hz, 2H), 6.44 (m, 4H), 3.67 (s, 12H, OCH_3). ^{31}P NMR: (600MHz, CD_2Cl_2, phosphoric acid standard = 0 ppm) = 37.79 ppm (s).

Synthesis of (*S*)-BINAP(Au(3,5-di-^{t}Bu-phenyl))$_2$: Complex was prepared according to General Procedure for Synthesis of $P_2Au_2R_2$ Model Compounds. ^{1}H NMR: (600MHz, CD_2Cl_2) δ = 8.05 (d, J_{H-H} = 9.0Hz, 2H), 7.82 (d, J_{H-H} = 7.8Hz, 2H), 7.74-7.77(m, 4H), 7.57 (t, J_{H-H} = 8.4Hz, 2H), 7.26-7.32 (m, 10H), 7.12 (t, J_{H-H} = 7.8Hz, 4H), 7.02-7.06 (m, 10H),

6.66 (t, J_{H-H} = 7.2Hz 2H), 6.47 (d, J_{H-H} = 8.4Hz, 2H), 1.28 (s, 45H, ^{t}Bu). ^{31}P NMR: (600MHz, CD_2Cl_2, phosphoric acid standard = 0 ppm) = 37.65 ppm (s).

Synthesis of (*S*)-3,5-xylyl-BINAP(AuMe)$_2$: Complex was prepared according to General Procedure for Synthesis of $P_2Au_2R_2$ Model Compounds. ^{1}H NMR: (600MHz, CD_2Cl_2) δ = 8.00 (d, J_{H-H} = 13.2Hz, 2H), 7.93 (d, J_{H-H} = 12.0Hz, 2H), 7.55 (t, J_{H-H} = 10.8Hz, 2H), 7.40 (t, J_{H-H} = 12.0Hz, 2H), 7.24 (m, 6H), 7.01 (d, J_{H-H} = 12.6Hz, 2H), 6.69 (s, 2H), 6.81 (s, 2H), 6.78 (s, 2H), -0.42 (d, J_{H-H} = 12.0Hz, 6H, $AuCH_3$). ^{31}P NMR: (600MHz, CD_2Cl_2, phosphoric acid standard = 0 ppm) = 39.83 ppm (s).

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CHAPTER 2. Non-Linear Effects

2.1. Introductions to Non-Linear Effects

Work in asymmetric catalysis before the 1980's generally assumed that *ee* of the product would vary directly with the *ee* of the chiral auxiliary.[1] Kagan observed deviations from linearity when varying the *ee* of the Sharpless catalyst during the epoxidation of (*E*)-geraniol and noticed the product *ee* did not correlate as expected, developing a non-linear effect (NLE) experiment.[1,2] NLE studies vary the *ee* of the chiral auxiliary and plot it against the resulting product *ee*. The resulting plot gives information about the structure of the catalytically active species and molecularity of the reaction, which provides useful information about the mechanism of an asymmetric reaction.[2]

In a linear system where one chiral auxiliary interacts with one substrate molecule, the product *ee* divided by the *ee* of the auxiliary gives the theoretical or maximum *ee* which is the slope of the expected straight line (Equation 1).[2-5]

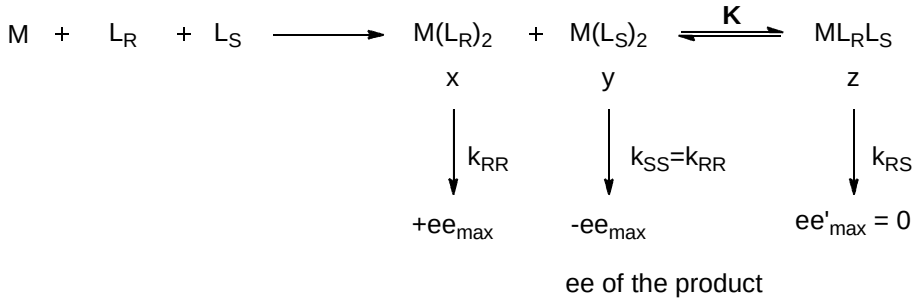
$$ee_{max} = ee_{product}/ee_{auxiliary} \qquad (1)$$

In cases when a non-linear effect is observed, Equation 1 no longer applies unless a correction factor, f, is applied (Equation 2).[2-5] When higher product *ee* than predicted is obtained with non-enantiopure catalyst, a positive NLE "(+)-NLE" has occurred. The

opposite effect, a negative NLE "(-)-NLE", occurs when the product obtained has lower *ee* than predicted.

$$ee_{product} = ee_{max} * ee_{auxiliary} * f \qquad (2)$$

Deviations from linearity occur in higher order systems such as a ML^*_2 where there are two chiral auxiliaries per metal or a dimeric $(ML^*)_2$ species.[1-5] In higher order systems when non-enantiopure chiral auxiliary is present then at least two diastereotopic species, homochiral $(M)L_RL_R$ or $(M)L_SL_S$ as well as a *meso* species $(M)L_SL_R$, are present in equilibrium (Scheme 4).



Scheme 2-1. Formation and reaction of diasteriotopic catalyst species.

"*f*" is determined by the relative reactivity and concentrations of the diastereotopic species (Equation 3). The relative reactivity, g, of the compounds is the ratio of the rates at which the *meso* and homochiral species react with substrate (Equation 4).[1-4] The relative concentrations of the various species is dependent on whether there is irreversible formation of diastereomers (Equation 5) or if fast ligand exchange is occurring with distribution close to thermodynamic equilibrium (Equation 6).[1-4]

$$f = (1 + \beta)/(1 + g\beta) \qquad (3)$$

$$(g = k_{RS}/k_{RR}) \quad (4)$$

$$[\beta = z/(x+y)] \quad (5)$$

$$K = z^2/(xy) \quad (6)$$

$$\beta = \frac{-Kee_{aux}{}^2 \pm \sqrt{4Kee_{aux}{}^2 - K(4 + Kee_{aux}{}^2)}}{2a4 + Kee_{aux}{}^2} \quad (7)$$

In the limits of fast ligand exchange a normal (+)-NLE (Figure 2, Line c) occurs when the reactivity and/or concentration of the *meso* species is lower than that of the homochiral species.[1,2] A normal (-)-NLE (Figure 2-1, Line b) occurs when the reactivity and/or concentration of the homochiral species is lower than that of the *meso* species.[1-4] A reservoir effect (Figure 2-1, Lines d and e) occurs when any of the species are so unreactive that they act as a sink to capture a portion of the chiral auxiliary.[3] If some of the racemic portion of the auxiliary is captured in the sink, the active chiral auxiliary becomes more enantiopure and asymmetric amplification occurs (Figure 2-1, Line d).[3] While if some of the auxiliary in excess is captured, making the active chiral auxiliary more racemic, an extreme (-)-NLE can occur (Figure 2-1, Line e).[3] Occasionally in higher order systems, the relative reactivities and concentrations can balance to make it appear as though a linear effect is occurring, making other mechanistic studies done in conjunction with non-linear effect studies imperative.

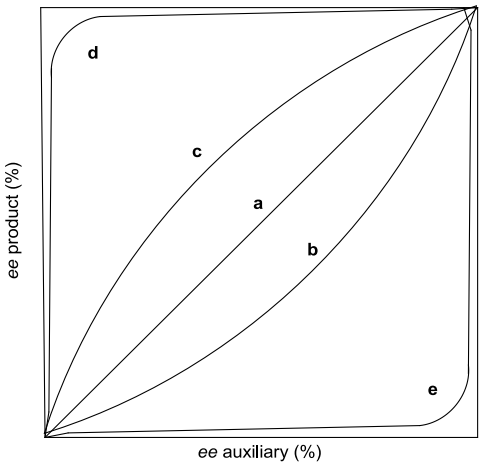


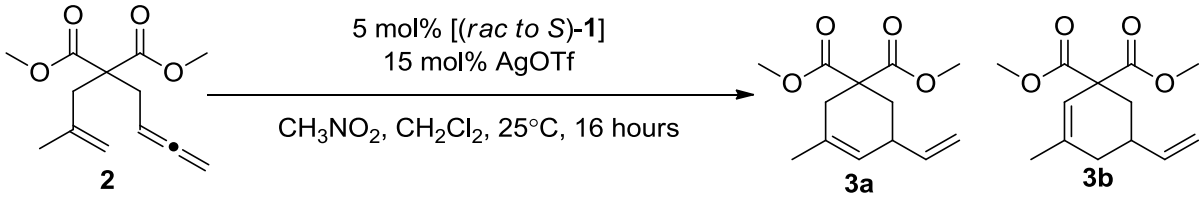
Figure 2-1. Plot of various linear and non-linear effects.

In Au(I) catalyzed asymmetric reactions using chiral bis(phosphines), NLE studies become an important experiment for determining the molecularity of the reaction due to the possibility of the catalyst bridging substrate molecules. It has also been established that bidentate ligands and Au(I) form multinuclear complexes and oligomers due to *inter*-molecular aurophilic interactions. Therefore, to help determine the mechanism and molecularity of the reaction of the cyclization of 1,6-eneallenes, a goal of the project is to run a NLE experiment.

2.2 Results and Conclusions

Two independent non-linear effect experiments were performed on **3** with final product *ee* of **3b** determined via chiral GC. The enantiomers of product **3a** had poor separation in the GC so were not used to determine *ee%*. Results of the studies have a linear trend suggesting the molecularity between ligand and substrate is in a one to one ratio and that oligomers are unlikely in the stereochemistry determining step (Figure 2-2). However, NLE studies alone do not rule out higher order systems where thermodynamics and kinetics

between formation of diastereomers and rate of reaction with substrate are balanced to give the appearance of a linear trend. Current results must be combined with additional kinetic studies to support the theory of a ML* system and linear effect.



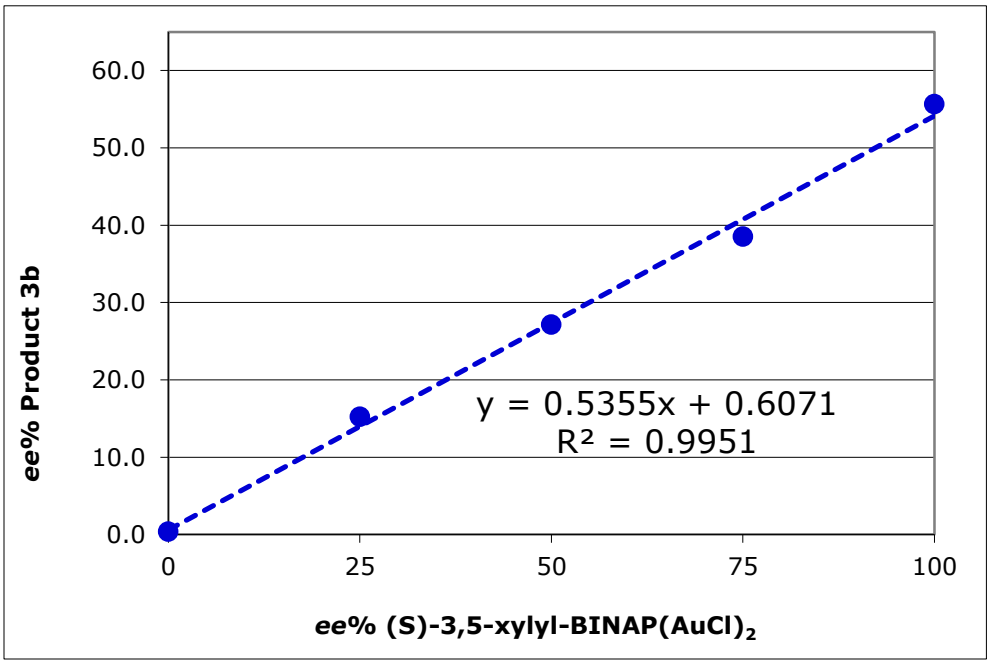


Figure 2-2. Linear Effect observed in the cycloisomerization of 1,6-ene allenes

2.3 Experimental Section

2.3.1. General Information

Gold-catalyzed reactions were carried out in air in 20 mL vials purchased from Fisher Scientific. $AgPF_6$, $AgBF_4$, $AgNTf_2$, AgOTf, AgOTs, and AgCl were purchased from Aldrich and used without purification. The aforementioned silver salts were stored and weighed in a glove box charged with nitrogen before immediately reacted with gold in air for catalysis. CD_3NO_2 was purchased from Cambridge Isotope Laboratories and used without further purification. CH_3NO_2 was purified according to literature procedure[6], dried with MgSO4 overnight and distilled from CaSO4. CD_3NO_2 and CD_3NO_2 were stored over 3 Å molecular sieves. Dichloromethane, chloroform, diethyl acetate, hexanes, pentanes, and diethyl ether were purchased from Fisher Scientific and used without further purification. Anhydrous THF was purchased from Fisher Scientific in an Acros-Seal bottle and stored under nitrogen. (*S*)-3,5-xylyl-BINAP and (R)-3,5-xylyl-BINAP were purchased from Strem Chemicals Inc. and used without further purification. Dimethyl-2-(1,2-butadienyl)-2-(2-methylallyl)malonate[2] (**2**) and $Ph_3PagOTf$[3] were prepared as previously reported.

^1H, ^{13}C and ^{31}P NMR data were collected on a Bruker 500 and 600 MHz Avance spectrometer. Chemical shifts are referenced to residual solvent peaks and reported in ppm for ^1H and ^{13}C NMR. Chemical shifts are referenced to a phosphoric acid external standard for ^{31}P NMR taken at room temperature and reported in ppm. Enantiomeric excess was determined with an Agilent 6890 chiral gas chromatograph outfitted with an Agilent β-Cyclosil column using the following parameters: inlet temperature 75 ˚C, 19.99 psi of helium; oven temperature held at 96 ˚C for 30 min then ramped to 105 ˚C at 0.4 ˚C/min, held for 5 min, then ramped to 120 ˚C at 2.0 ˚C/min, and held for 5 min. The 30 m chiral column with 250 μm diameter was run using 19.99 psi at 3.5 mL/min; the FID detector was held at

250 ˚C with a flow rate of 40 mL/min H_2, 450 mL/min air and makeup flow of 45 mL/min helium.

1.3.2. General Procedure for Catalyst Synthesis

In air, 1.97 eq. of (DMS)AuCl and 1.0 eq. of (*R*)- or (*S*)-3,5-xylyl-BINAP were added to 20 mL vial equipped with a stir bar and dissolved in 5 mL of dichloromethane. The mixture was stirred for 2 to 4 hours before purification via elution through a small silica plug with dichloromethane and recrystallization from dichloromethane/pentanes vapor overnight.

Racemic Mixture of (*R/S*)-3,5-xylyl-BINAP(AuCl)$_2$: In air, 25.1 µL of **(*S*)-1** (0.083M in CH_2Cl_2, 2.5 mol%), 31.9 µL of **(*R*)-1** (0.066M in CH_2Cl_2, 2.5 mol%), and 220.0 µL of AgOTf (0.058M in CH_3NO_2, 14.9 mol%) stock solutions were added to a 20 mL vial. The suspension was stirred for 5 minutes before 450.0 µL of **2** (0.189M in CH_3NO_2, 100.0mol%) was added and the reaction stirred for 16 hours. Products were obtained using preparative TLC (hexanes/EtOAc = 80:10, R_f = 0.), extracted from the silica gel with EtOAc, and rotovaped down to a colorless oil. 0.4% *ee* of **3b**.

25% Enantiomeric Excess of (*S*)-3,5-xylyl-BINAP(AuCl)$_2$: In air, 31.3 µL of **(*S*)-1** (0.083M in CH_2Cl_2, 3.1 mol%), 23.9 µL of **(*R*)-1** (0.066M in CH_2Cl_2, 1.9 mol%), and 220.0 µL of AgOTf (0.058M in CH_3NO_2, 14.9 mol%) stock solutions were added to a 20 mL vial. The suspension was stirred for 5 minutes before 450.0 µL of **2** (0.189M in CH_3NO_2, 100.0mol%) was added and the reaction stirred for 16 hours. Products were obtained using preparative TLC (hexanes/EtOAc = 80:10, R_f = 0.), extracted from the silica gel with EtOAc, and rotovaped down to a colorless oil. 15.2% *ee* of **3b**.

50% Enantiomeric Excess (*S*)-3,5-xylyl-BINAP(AuCl)$_2$: In air, 37.6 µL of **(*S*)-1** (0.083M in CH_2Cl_2, 3.8 mol%), 16.0 µL of **(*R*)-1** (0.066M in CH_2Cl_2, 1.3 mol%), and 220.0 µL of AgOTf (0.058M in CH_3NO_2, 14.9 mol%) stock solutions were added to a 20 mL vial. The suspension was stirred for 5 minutes before 450.0 µL of **2** (0.189M in CH_3NO_2, 100.0mol%) was added and the reaction stirred for 16 hours. Products were obtained using preparative TLC (hexanes/EtOAc = 80:10, R_f = 0.), extracted from the silica gel with EtOAc, and rotovaped down to a colorless oil. 28.1% *ee* of **3b**.

75% Enantiomeric Excess (*S*)-3,5-xylyl-BINAP(AuCl)$_2$: In air, 43.9 µL of **(*S*)-1** (0.083M in CH_2Cl_2, 4.4 mol%), 8.0 µL of **(*R*)-1** (0.066M in CH_2Cl_2, 0.6 mol%), and 220.0 µL of AgOTf (0.058M in in CH_3NO_2, 14.9 mol%) stock solutions were added to a 20 mL vial. The suspension was stirred for 5 minutes before 450.0 µL of **2** (0.189M in CH_3NO_2, 100.0mol%) was added and the reaction stirred for 16 hours. Products were obtained using preparative TLC (hexanes/EtOAc = 80:10, R_f = 0.), extracted from the silica gel with EtOAc, and rotovaped down to a colorless oil. 38.6% *ee* of **3b**.

100% Enantiomeric Excess (*S*)-3,5-xylyl-BINAP(AuCl)$_2$: In air, 50.1 µL **(*S*)-1** (0.083M in CH_2Cl_2, 4.4 mol%) and 220.0 µL of AgOTf (0.058M in CH_3NO_2, 14.9 mol%) stock solutions were added to a 20 mL vial. The suspension was stirred for 5 minutes before 450.0 µL of **2** (0.189M in CH_3NO_2, 100.0mol%) was added and the reaction stirred for 16 hours. Products were obtained using preparative TLC (hexanes/EtOAc = 80:10, R_f = 0.), extracted from the silica gel with EtOAc, and rotovaped down to a colorless oil. 55.7% *ee* of **3b**.

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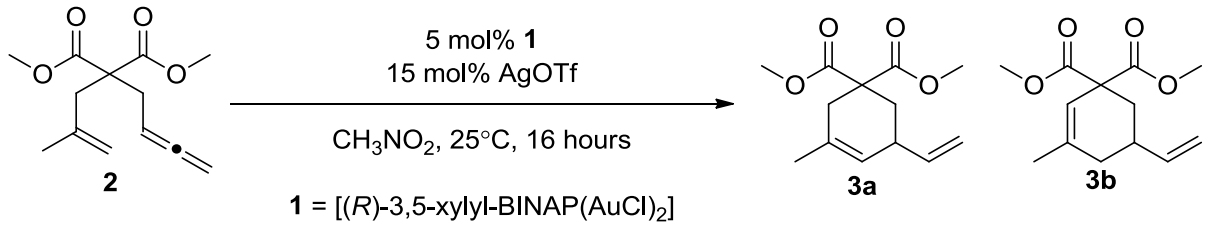
CHAPTER 3. Effects of Silver in Catalysis

3.1. Introduction to Silver Effects

Often in gold(I) catalysis silver(I) salts are used to abstract halides from gold, allowing organogold π–complexes to form.[1,2] The comon belief has been that after activating gold, silver precipitates as AgCl to become an unreactive biproduct. However, recent work has shown that contrary to popular belief , silver may play a role in catalysis influencing rate, selectivity, or form Au-Ag intermediates.[3]

When the (*R*)-3,5-xylyl-BINAP(AuCl)$_2$ **(1)** catalyzed system for the asymmetric cycloisomerization of 1,6-eneallenes was developed, the role that silver played outside of activating the gold catalyst was not yet understood. It was also assumed that the active form of the catalyst was the diactivated **4** because this species was independently isolated and characterized by ^{1}H and ^{31}P NMR. However, **4** was significantly less reactive and selective than the *in situ* generated catalytic species.[3f]



Scheme 3.1. Standard reaction conditions for the cycloisomerization of **2**.[3f]

Recent work by Zhang *et al.* using (*R*)-C_1-tunephos$(AuCl)_2$ for intermolecular tandem cyclization and [3+3] cycloadditions of 2-(1-alkynyl)-2-alken-1-ones with nitrones showed that one equivalent of silver-salt, not two as generally assumed, provided the highest enantioselectivities.[3a] Like Zhang, Mikami *et al* observed that one equivalent of silver-salt provided the highest enantioselectivies in his system.[3h] Meanwhile, Mikami also observed independently synthesized diactivated (*R*)-DM-BIPHEP$(AuCl)_2$ **(5)** afforded lower rates and selectivities than diactived **(5)**.[3h] Attempts at isolation of a monoactivated gold complex by reacting one equivalent of **(5)** and one equivalent of chiral silver-phosphate afforded three species by ^{31}P NMR. The species were in a 0.5/1.0/0.3 ratio and were determined to be **5**, monoactivated **5**, and diactivated **5**.[3h] Toste also observed that when varying the metal-to-anion ratios in catalytic tests with non-coordinating counterions, that the monoactivated gold complex may be the catalytically active species.[3i] These findings support a project goal of determining if a mono- or diactivated **1** is the active form of the catalyst in the studied system. Studies on the impact of varied amounts of **2** and its impact on product *ee* and independent synthesis and characterization the monoactivated form of **1** will help achieve this research goal.

3.2. Effects of Amount of Silver on Enantioselectivity and Catalyst Speciation

Previously in the Gagnè group it was observed that both enantioselectivity and rate were dependant on *in situ* activation of the catalyst and the presence of a slight excess of silver salt.[3f] To determine the effect of excess silver triflate on enantioselectivity, catalytic reactions were set up with 5 mol% (*R*)-**1** and increasing amounts of silver triflate. It was observed that

the highest product *ee*% was achieved with 15 mol% AgOTf and that further increase of silver caused a decrease in the enantioselectivity of the products [Figure 3-2].

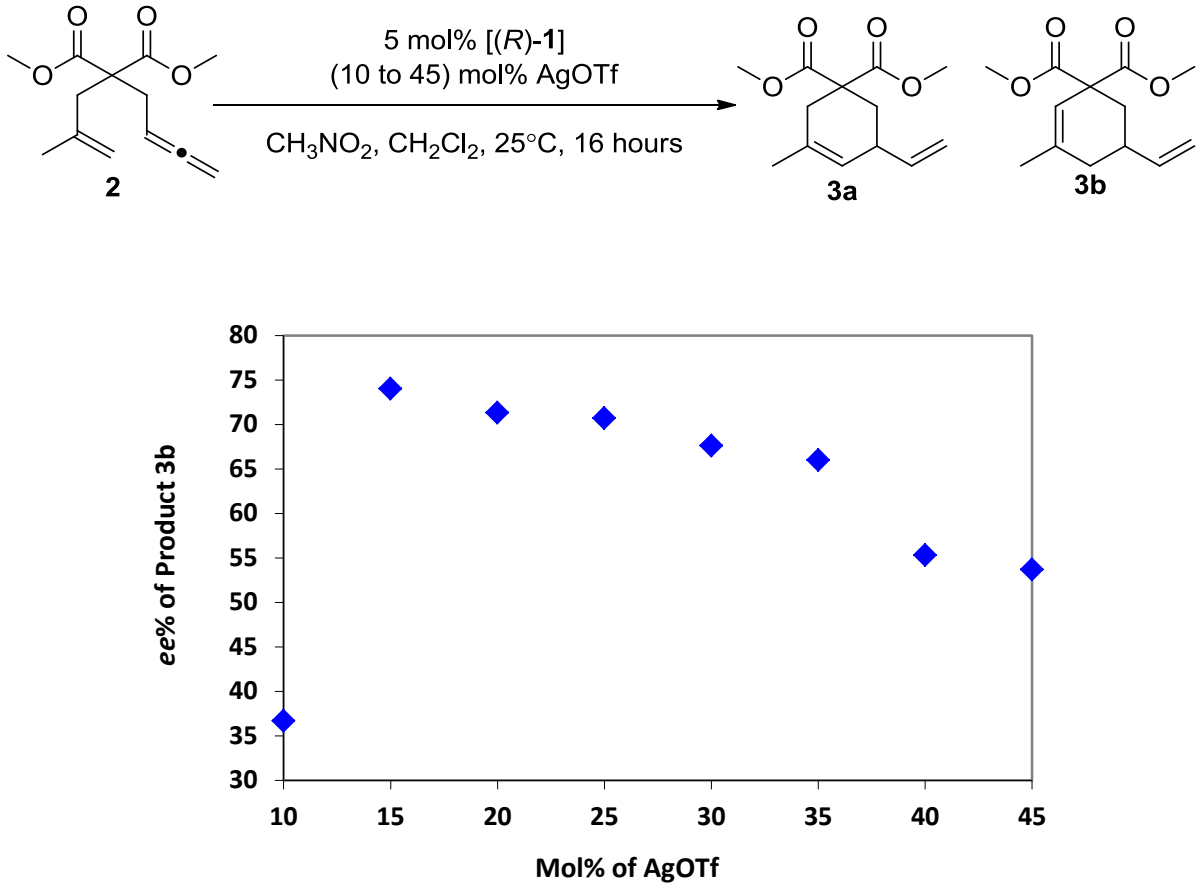


Figure 3-1. Effect of the amount of AgOTf on the enanteoselectivity of **3b**.

While taking *insitu* NMR of these catalytic reactions it was observed that increasing the amount of silver triflate also had an effect on the speciation of the catalyst. Careful addition of one to two equivalents of AgOTf to **1** shows a major ^{31}P signal at 32 ppm for (*S*)-3,5-xylyl-BINAP(AuOTf)$_2$ [Figure 3-3], with mono- and unactivated catalysts insoluable in nitromethane and therefore unobserved. As additional silver triflate was added, a broad signal

was observed at 23 ppm as the amount of silver increased. This observation and the well documented gold-silver metallophilic interactions suggests that a gold-silver species may form in the presence of excess silver salt during catalysis.[3-5]

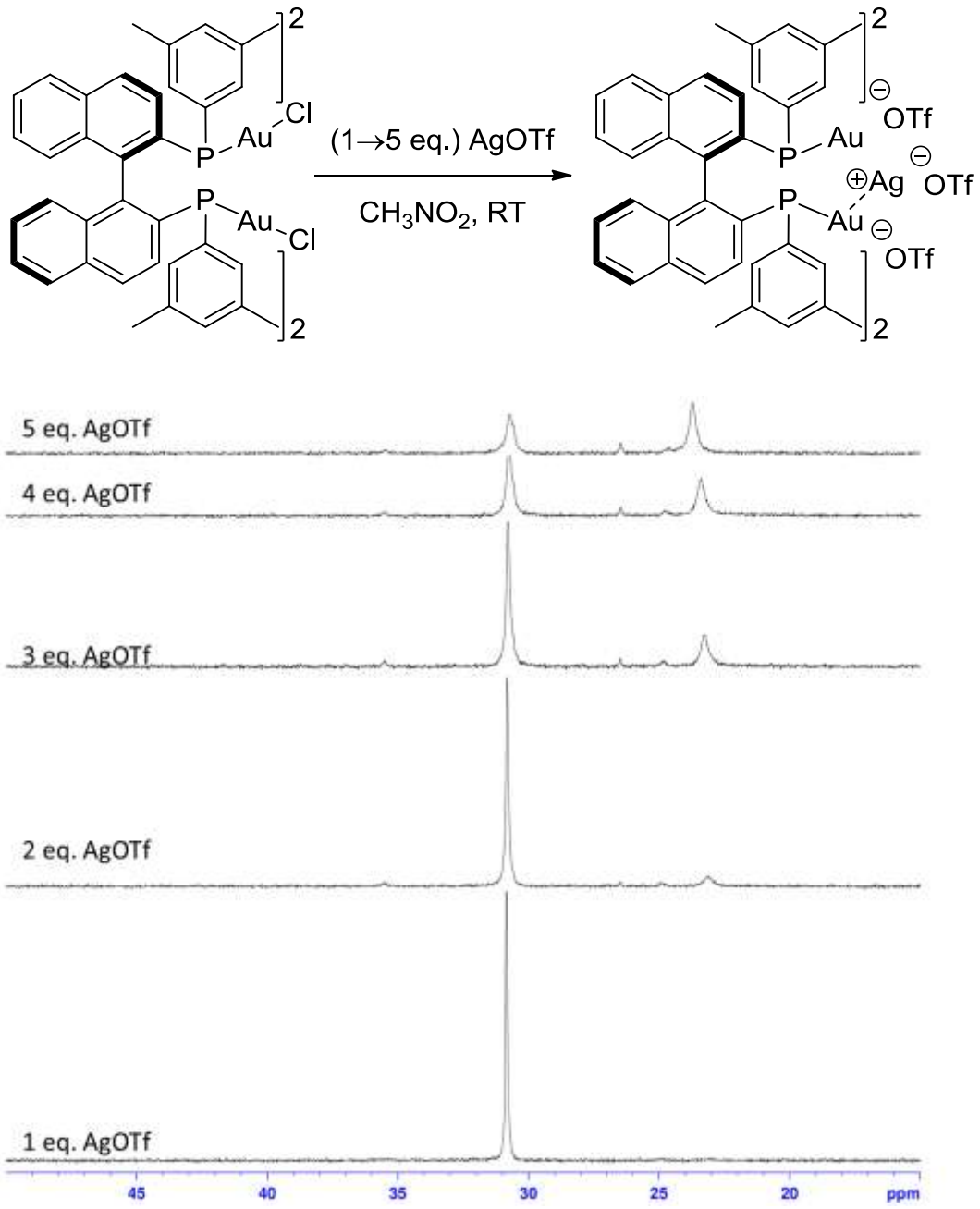


Figure 3-2. Effect of the equivalents of AgOTf on catalyst speciation.

3.3. Model Au-Ag Compounds and Low Temperature Dynamic NMR

As increasing equivalents of AgOTf added for *in situ* catalyst activation impacted both product enantioselectivity and catalyst speciation, it was hypothosized that a dinuclear Au-Ag intermediate may be an intermediate in catalysis. Previous work by Laguna provides evidence for gold-silver metallophilic interactions in solution supporting the possibility of a gold-silver intermediate in our system.[5] In addition, work by Jones, Straub, and others show the role of gold-silver intermediates mono-gold(I) catalyzed reactions.[6] To see if a gold-silver intermediate was possible in a bis(gold) phosphine system, 1.25 equivalents of $Ph_3PAgOTf$ was added to a solution of (*S*)-BINAP(Au(*p*-tol))$_2$ in dichloromethane and observed at varying temperature with ^{31}P NMR. At 295K [Figure 4d] one signal at 41 ppm with an integration of 2 was observed for the BINAP back bone along with a doublet of doublets at 15 ppm with an integration of 1 for the Ph_3PAg that was split twice by the spin ½ isotopes of silver, ^{107}Ag and ^{109}Ag.[7] At lower temperatures the signal at 41 ppm BINAP signal began to broaden and at 185K split into two signals at 43.89 and 37.13 ppm. This observation suggests that at low temperatures the phosphorus in the BINAP backbone loose their C_2 symmetry due to coordination of silver to one gold atom. The coalescence of the BINAP signals at 200 K is consistant with a dynamic process where the silver exchanges between the two gold atoms.[7,8]

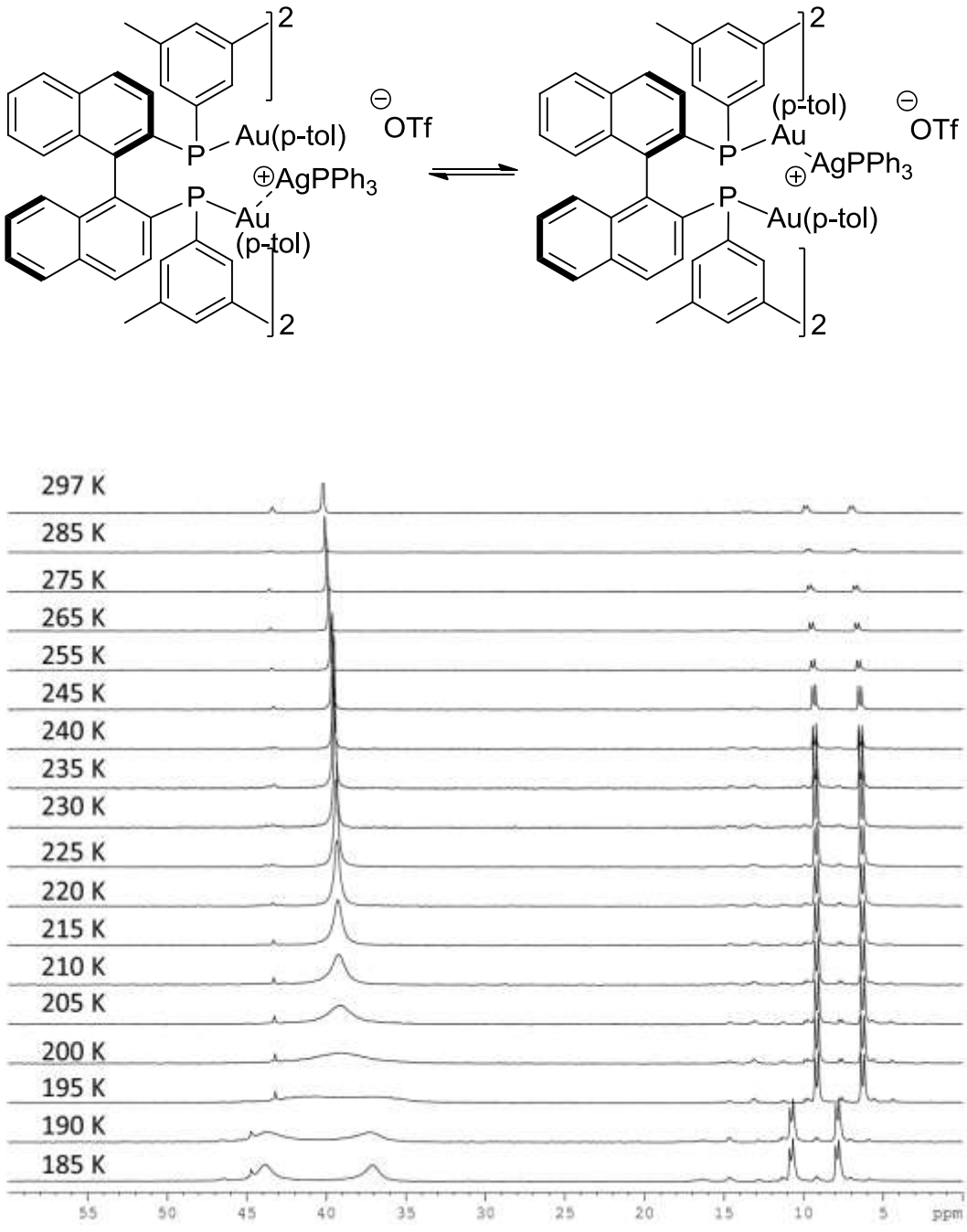


Figure 3-3. a) (*S*)-BINAP(Au(*p*-tol))$_2$ and 1.25 eq. of $Ph_3PAgOTf$ at 185 K and temperature raised to 295 K. T_c determined to be 200K.

To determine if exchange happens via an associative or dissociative mechanism Arrhenius and Eyring plots wer created, Figure 5 and Figure 6. Using the intercept it was determined that $\Delta S^{\ddagger}$ = 24.2 e.u. A large, positive gain in entropy in the transition state suggests that silver exchages between gold atoms via a dissociative mechanism as seen in Scheme 2.

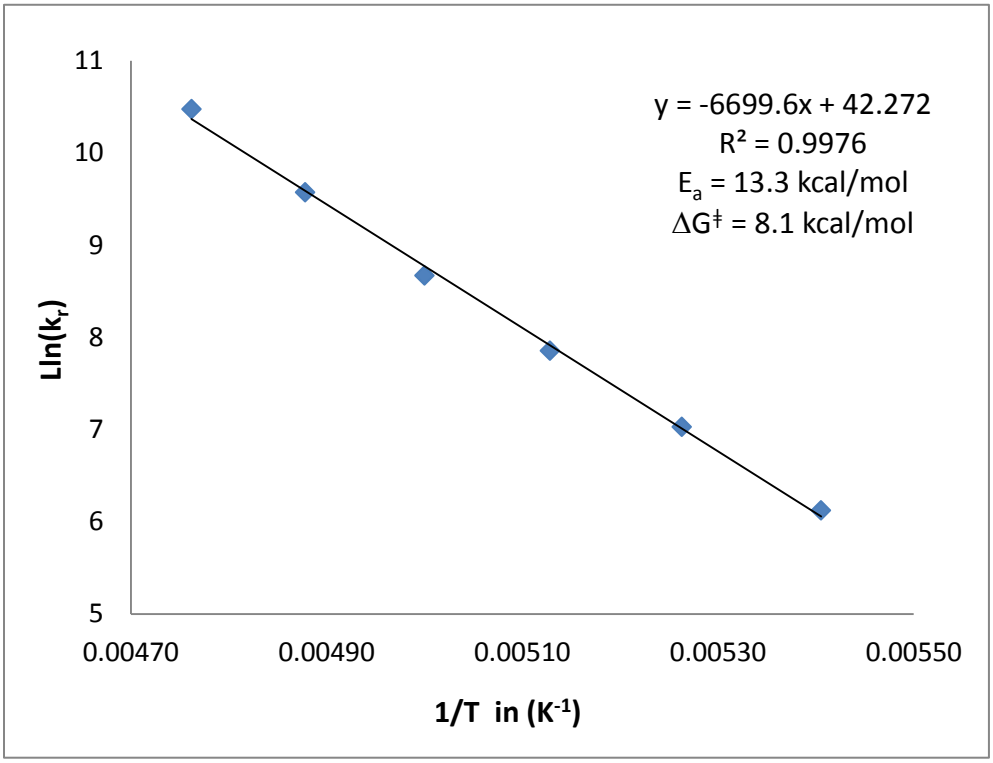


Figure 3-4. Arrhenius plot showing the temperature dependence of $Ph_3PAgOTf$ exchange between gold atoms on (*S*)-BINAP(Au(*p*-tol))$_2$.

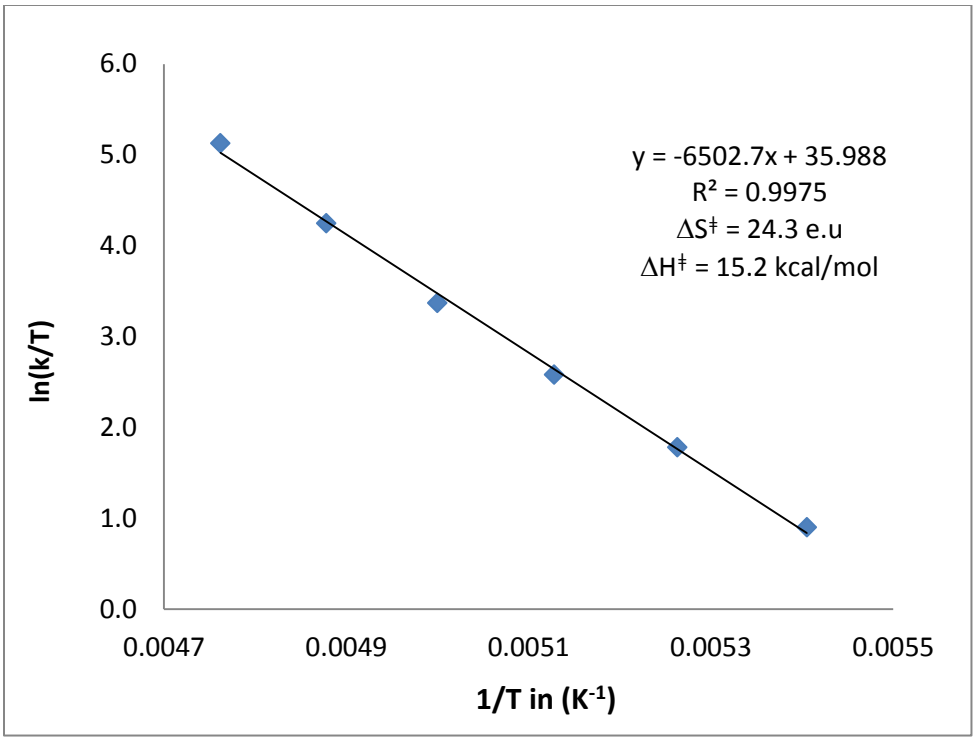
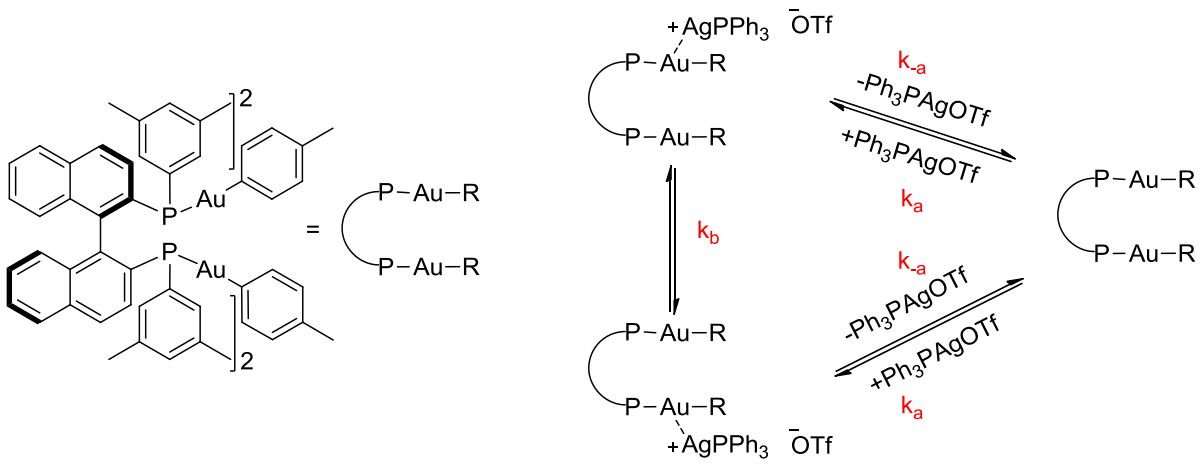
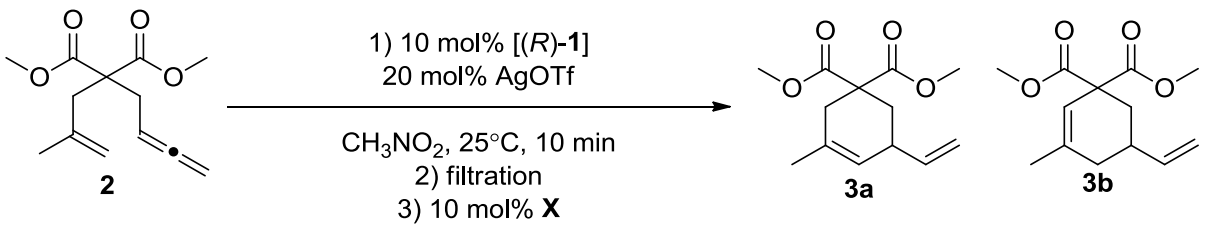


Figure 3-5. Eyring plot showing the temperature dependence of $Ph_3PAgOTf$ exchange between gold atoms on (*S*)-BINAP(Au(*p*-tol))$_2$.



Scheme 3-2. Dissociation mechanism of Ph_3Ag^+ exchange between gold atoms.

With a dinuclear Au-Ag model compound observed in solution, it was postulated that this species could be involved in the stereochemistry determining step. A dinuclear Au-Ag catalyst could aslo explain why excess silver with a less coordinating conterion than the AgCl generated during activation is needed to achieve good enantioselectivity. To prove this hypothesis, a series of catalytic reactions were undergone where 10 mol% of (*R*)-**1** was activated with 20 mol% of AgOTf and then the resulting AgCl precipitate was filtered off *insitu* using a syringe filter. The resulting solution of 10 mol% (*R*)-3,5-xylyl-BINAP$(AuOTf)_2$ was mixed with 10 mol% of silver additive before reacting with **2**. Without any 10 mol% silver added to the *insitu* generated (*R*)-3,5-xylyl-BINAP$(AuOTf)_2$, *ee*% of the product dropped to 45% from an *ee*% of 72% normally observed under standard reaction conditions.[15] Silver additives with tightly binding counter ions also appeared to cause a drastic decrease in enantioselvtivity, with 10% AgCl additive giving the lowest selectivity of 34% (Table 3-1). Use of silver additives with loosely binding counterions gave product enantioselectivity between 69 to 77%. The necessity of excess silver with a loosly coordinating counterion to achieve high enantioselectivity suggests a dinuclear Au-Ag intermediate is involved during the stereochemistry determining step.



Entry	10 mol% AgX[a]	*ee*% of **3b**[b]
1	None	45
2	Ag (*R*)-(-)-1,1′-binaphthyl-2,2′-diyl phosphate[10]	51
3	Ag (*S*)-(-)-1,1′-binaphthyl-2,2′-diyl phosphate[10]	53
4	$AgSbF_6$	71
5	$AgBF_4$	74
6	$AgPF_6$	77
7	$AgNTf_2$	69
8	AgOTf	74
9	AgOTs	70
10	AgCl	34

Table 3-1. Effects of 10 mol % of silver additive on the enantioselectivity of **3b** as determined by chiral GC. [a] AgCl(s) generated during activation of 10 mol% **1** with 20 mol% AgOTf is removed by syringe filter before addition of 10 mol % of silver additive. [b] Only regioisomer **3a** was not used due to poor separation of enantiomers in the chiral GC.

Our studies have shown that in a bis(gold) phosphine system that 1) gold oligamers and aggregates are unlikely as an Linear Effect is observed. 2) Failed attempts at creating a bisphosphine digold model compound suggests that strain in the backbone of an axially chiral ligand may prevent digold intermediates from forming. 3) The change of catalyst speciation and loss of C_2 symmetry in ^{31}P NMR in the presence of excess silver cation suggests that an equilibrium between a gold-silver catalyst and free silver cation. 4) A large and positive $\Delta S^{\ddagger}$ of 24.3 e.u. suggests a dissociative mechanism of silver exchange between gold atoms on bis(gold) phosphines. 5) The impact of excess silver with a loosly coordinating counterion to on enantioselectivity suggests that a silver cation is needed to interact with one gold atom during the stereochemistry determining step. These observations support the theory of the presence of a gold-silver intermediate in the gold(I) catalyzed cycloisomerization of 1,6-ene allenes. These new insights into the role of silver in asymmetic catalysis by bis(gold) phosphine has could greatly impact how silver is viewed and used to affected stereochemisty in this class of reactions.

3.4. Experimental

3.4.1. Effects of Increasing AgOTf on Enantiomeric Excess of 3b

10 mol% AgOTf and 5 mol% (*R*)-1: In air, 200.0 µL of **(*R*)-1** (0.015M in CH_2Cl_2, 0.003 mmol, 3.6 mg), 66.7 µL of AgOTf (0.09M in CH_3NO_2, 0.006 mmol, 1.5 mg), and 233.3 µL of CH_3NO_2 were added to an NMR tube. The suspension was stirred for 5 minutes before 600.0 µL of **2** (0.100M in CH_3NO_2, 0.060 mmol, 14.3 mg) was added and the reaction stirred for 16 hours. Products were obtained using preparative TLC (hexanes/EtOAc = 80:10, R_f =

0.), extracted from the silica gel with EtOAc, and rotovaped down to a colorless oil. 36.7% *ee* of **3b**.

15 mol% AgOTf and 5 mol% (*R*)-1: In air, 200.0 µL of **(*R*)-1** (0.015M in CH_2Cl_2, 0.003 mmol, 3.6 mg), 100.0 µL of AgOTf (0.09M in CH_3NO_2, 0.009 mmol, 2.3 mg), and 200.0 µL of CH_3NO_2 were added to an NMR tube. The suspension was stirred for 5 minutes before 600.0 µL of **2** (0.100M in CH_3NO_2, 0.060 mmol, 14.3 mg) was added and the reaction stirred for 16 hours. Products were obtained using preparative TLC (hexanes/EtOAc = 80:10, R_f = 0.), extracted from the silica gel with EtOAc, and rotovaped down to a colorless oil. 74.0% *ee* of **3b**.

20 mol% AgOTf and 5 mol% (*R*)-1: In air, 200.0 µL of **(*R*)-1** (0.015M in CH_2Cl_2, 0.003 mmol, 3.6 mg), 133.3 µL of AgOTf (0.09M in CH_3NO_2, 0.012 mmol, 3.1 mg), and 166.7 µL of CH_3NO_2 were added to an NMR tube. The suspension was stirred for 5 minutes before 600.0 µL of **2** (0.100M in CH_3NO_2, 0.060 mmol, 14.3 mg) was added and the reaction stirred for 16 hours. Products were obtained using preparative TLC (hexanes/EtOAc = 80:10, R_f = 0.), extracted from the silica gel with EtOAc, and rotovaped down to a colorless oil. 71.3% *ee* of **3b**.

25 mol% AgOTf and 5 mol% (*R*)-1: In air, 200.0 µL of **(*R*)-1** (0.015M in CH_2Cl_2, 0.003 mmol, 3.6 mg), 166.7 µL of AgOTf (0.09M in CH_3NO_2, 0.015 mmol, 3.8 mg), and 133.3 µL of CH_3NO_2 were added to an NMR tube. The suspension was stirred for 5 minutes before 600.0 µL of **2** (0.100M in CH_3NO_2, 0.060 mmol, 14.3 mg) was added and the reaction stirred for 16 hours. Products were obtained using preparative TLC (hexanes/EtOAc = 80:10, R_f =

0.), extracted from the silica gel with EtOAc, and rotovaped down to a colorless oil. 70.7% *ee* of **3b**.

30 mol% AgOTf and 5 mol% (*R*)-1: In air, 200.0 µL of **(*R*)-1** (0.015M in CH_2Cl_2, 0.003 mmol, 3.6 mg), 200.0 µL of AgOTf (0.09M in CH_3NO_2, 0.018 mmol, 4.6 mg), and 100.0 µL of CH_3NO_2 were added to an NMR tube. The suspension was stirred for 5 minutes before 600.0 µL of **2** (0.100M in CH_3NO_2, 0.060 mmol, 14.3 mg) was added and the reaction stirred for 16 hours. Products were obtained using preparative TLC (hexanes/EtOAc = 80:10, R_f = 0.), extracted from the silica gel with EtOAc, and rotovaped down to a colorless oil. 67.6% *ee* of **3b**.

35 mol% AgOTf and 5 mol% (*R*)-1: In air, 200.0 µL of **(*R*)-1** (0.015M in CH_2Cl_2, 0.003 mmol, 3.6 mg), 233.3 µL of AgOTf (0.09M in CH_3NO_2, 0.021 mmol, 5.4 mg), and 66.7 µL of CH_3NO_2 were added to an NMR tube. The suspension was stirred for 5 minutes before 600.0 µL of **2** (0.100M in CH_3NO_2, 0.060 mmol, 14.3 mg) was added and the reaction stirred for 16 hours. Products were obtained using preparative TLC (hexanes/EtOAc = 80:10, R_f = 0.), extracted from the silica gel with EtOAc, and rotovaped down to a colorless oil. 66.0% *ee* of **3b**.

40 mol% AgOTf and 5 mol% (*R*)-1: In air, 200.0 µL of **(*R*)-1** (0.015M in CH_2Cl_2, 0.003 mmol, 3.6 mg), 266.7 µL of AgOTf (0.09M in CH_3NO_2, 0.024 mmol, 6.1 mg), and 33.3 µL of CH_3NO_2 were added to an NMR tube. The suspension was stirred for 5 minutes before 600.0 µL of **2** (0.100M in CH_3NO_2, 0.060 mmol, 14.3 mg) was added and the reaction stirred for 16 hours. Products were obtained using preparative TLC (hexanes/EtOAc = 80:10, R_f =

0.), extracted from the silica gel with EtOAc, and rotovaped down to a colorless oil. 55.3% *ee* of **3b**.

45 mol% AgOTf and 5 mol% (*R*)-1: In air, 200.0 µL of **(*R*)-1** (0.015M in CH_2Cl_2, 0.003 mmol, 3.6 mg) and 300.0 µL of AgOTf (0.09M in CH_3NO_2, 0.027 mmol, 6.9 mg) were added to an NMR tube. The suspension was stirred for 5 minutes before 600.0 µL of **2** (0.100M in CH_3NO_2, 0.060 mmol, 14.3 mg) was added and the reaction stirred for 16 hours. Products were obtained using preparative TLC (hexanes/EtOAc = 80:10, R_f = 0.), extracted from the silica gel with EtOAc, and rotovaped down to a colorless oil. 53.7% *ee* of **3b**.

3.4.2. Effects of Excess AgOTf on Catalyst Speciation in ^{31}P NMR

1.0 eq. AgOTf and 1.0 eq. (*S*)-1: In air, **(*S*)-1** (0.0083 mmol, 10.0 mg) was weighed into an NMR tube then 104.3 µL of AgOTf (0.08M in CH_3NO_2, 0.0083 mmol, 2.1 mg) and 445.7 µL of CH_3NO_2 were added. The suspension was stirred for 5 minutes before ^{31}P NMR spectra was taken on a 600 MHz Bruker NMR. ^{31}P NMR: (600MHz, CH_3NO_2, phosphoric acid standard) = 30.84 ppm (s).

2.0 eq. AgOTf and 1.0 eq. (*S*)-1: In air, **(*S*)-1** (0.0083 mmol, 10.0 mg) was weighed into an NMR tube then 208.5 µL of AgOTf (0.08M in CH_3NO_2, 0.0167 mmol, 4.3 mg) and 341.5 µL of CH_3NO_2 were added. The suspension was stirred for 5 minutes before ^{31}P NMR spectra was taken on a 600 MHz Bruker NMR. ^{31}P NMR: (600MHz, CH_3NO_2, phosphoric acid standard) = 30.84 ppm (s) and 23.12 ppm (s) peaks in a ratio of 7.18 : 1.0

3.0 eq. AgOTf and 1.0 eq. (*S*)-1: In air, **(*S*)-1** (0.0083 mmol, 10.0 mg) was weighed into an NMR tube then 312.8 µL of AgOTf (0.08M in CH_3NO_2, 0.0250 mmol, 6.4 mg) and 237.2 µL

of CH_3NO_2 were added. The suspension was stirred for 5 minutes before ^{31}P NMR spectra was taken on a 600 MHz Bruker NMR. ^{31}P NMR: (600MHz, CH_3NO_2, phosphoric acid standard) = 30.78 ppm (s) and 23.26 ppm (s) peaks in a ratio of 2.55 : 1.0

4.0 eq. AgOTf and 1.0 eq. (*S*)-1: In air, **(*S*)-1** (0.0083 mmol, 10.0 mg) was weighed into an NMR tube then 417.0 µL of AgOTf (0.08M in CH_3NO_2, 0.0334 mmol, 8.6 mg) and 133.0 µL of CH_3NO_2 were added. The suspension was stirred for 5 minutes before ^{31}P NMR spectra was taken on a 600 MHz Bruker NMR. ^{31}P NMR: (600MHz, CH_3NO_2, phosphoric acid standard) = 30.74 ppm (s) and 23.40 ppm (s) peaks in a ratio of 1.49 : 1.0

5.0 eq. AgOTf and 1.0 eq. (*S*)-1: In air, **(*S*)-1** (0.0083 mmol, 10.0 mg) was weighed into an NMR tube then 521.3 µL of AgOTf (0.08M in CH_3NO_2, 0.0417 mmol, 10.7 mg) and 28.7 µL of CH_3NO_2 were added. The suspension was stirred for 5 minutes before ^{31}P NMR spectra was taken on a 600 MHz Bruker NMR. ^{31}P NMR: (600MHz, CH_3NO_2, phosphoric acid standard) = 30.73 ppm (s) and 23.69 ppm (s) peaks in a ratio of 0.75 : 1.0

3.4.3. Low Temperature Experiments of Au-Ag Model Compound

In air, (*S*)-BINAP(Au(*p*-tol))$_2$ (24.2 mg, 0.0202 mmol) was weighed into an NMR tube and dissolved in 0.2 mL of CH_2Cl_2 then cooled to -78 ˚C. In air, $Ph_3PAgOTf$[9] (13.1 mg, 0.0252 mmol, 1.25 eq.) was weighted into a 20 mL vial, dissolved in 0.6 mL of CH_2Cl_2, and transferred to the NMR tube. ^{31}P NMR was recorded on a 500 MHz Bruker starting at 185 K and taken every 5 K to 245 K and every 10 K from 245 K to 297 K.

3.4.4. Dynamic NMR Analysis:

Using spectra acquired at 185 K and TopSpin 3.1 DNMR software a module was created by manually fitting line broadening, rate, and intensity to ^{31}P peaks at 43.89 and 37.13 ppm then having the software line fit the data. Exchange rates were collected at the following temperatures: 185 K, 190 K, 195 K, 200 K (coalescence temperature), 205 K, and 210 K by allowing the software to adjust line broadening (LB), intensity, and rate (k). Values found for k at 185 to 210 K are listed in Table. Arrhenius and Erying plots were used to determine: E_a, $\Delta G^{\ddagger}$, $\Delta H^{\ddagger}$, and $\Delta S^{\ddagger}$.

Temp (K)	1/T (K^{-1})	k (s^{-1})	Ln(k)	Ln(k/T)	$\Delta G^{\ddagger}$ (kcal/mol)
185	0.0054	455.7	6.12	0.90	8.40
190	0.0053	1127.4	7.03	1.78	8.30
195	0.0051	2575.3	7.85	2.58	8.21
200	0.0050	5811.9	8.67	3.37	8.10
205	0.0049	14332.8	9.57	4.25	7.95
210	0.0048	35407.6	10.47	5.13	7.78

Table 3.2: Table of exchange rates and $\Delta G^{\ddagger}$ as determined at temperatures between 185 K and 210 K using DNMR line shape analysis with TopSpin 3.1 software.

3.3.5. 10 mol% Silver Additive Cycloisomerization Procedure

In air, (*R*)-1 (15.1 mg, 0.0126 mmol) and AgOTf (6.5 mg, 0.0250 mmol) were added to a 20 mL vial then dissolved in 0.5 mL of CD2NO2. The slurry was stirred for 5 minutes before the mixture was pushed through a 0.2 μm PTFE syringe filter into a 20 mL vial containing

$AgSbF_6$ (4.4 mg, 0.0126 mmol). The syringe filter was rinsed twice with (0.25 mL CD3NO2). The slurry was stirred for five minutes then 250 µL of **1** (0.5M in CD_2NO_2, 30.0 mg, 0.1258 mmol) was added. The reaction was stirred for 8 hours and turned dark blue-grey upon completion. Products were obtained using preparative TLC (hexanes/EtOAc = 80:10, R_f = 0.), extracted from the silica gel with EtOAc, and rotovaped down to a colorless oil. Enantiomeric excess of regioisomer **3a** (major product): *ent-1*, 51.6 min.; *ent-2*, 52.4 min. Enantiomeric excess of regioisomer **3b** (minor product): *ent-1*, 61.2 min.; *ent-2*, 62.7 min. Enantiomeric excess is reported using only enantiomers of **3b** as poor separation of enantiomers of **3a** limits it use.

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