GOLD-CATALYZED CYCLIZATION REACTIONS OF ALLENES

Michael Andrew Tarselli

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 Doctor of Philosophy in the Department of Chemistry.

Chapel Hill
2008

Approved by

Advisor: Professor Michel R. Gagné

Reader: Professor Marcey Waters

Reader: Professor Jeffrey Johnson

Reader: Professor Maurice Brookhart

Reader: Professor Wenbin Lin

ABSTRACT

MICHAEL ANDREW TARSELLI - Gold-Catalyzed Cyclization Reactions of Allenes

(Under the Direction of Prof. Michel R. Gagné)

Cycloisomerization is a so-called "atom-economic" tool to produce complex carbocycles from simple precursors. Gold catalysis is an extension of cation-olefin cyclization utilizing Pt^{2+} that had been a previous focus of our group. As a homogeneous metal catalyst, gold - especially in the (I) oxidation state - is highly carbophilic, exhibits high functional group tolerance, and is not inhibited by trace moisture or air. This combination of attributes is ideal for use of gold as a catalytic C-C bond-forming tool.

Eneallene cycloisomerization catalyzed by gold(I) yields vinylcyclohexenes in a rare example of 6-membered ring formation. However, enantioselective synthesis with gold is challenging due to the linear bonding geometries observed for gold(I) salts. A sufficiently bulky chiral di-gold complex with judicious counterion choice produces the desired vinylcyclohexene in up to 72% yield (77% *ee*).

Allenes tethered to an electron-rich aromatic ring in place of an alkene partner cyclize to form tetrahydronaphthalene skeletons, even at *1 mol% catalyst* loading in commercial-grade solvent. This catalysis was accelerated by more electrophilic phosphite ligands, along with a larger, weakly coordinated counterion ($^{-}SbF_6$). Yields range from 59-94%.

If the tethered arene is non-nucleophilic (Ph) or strongly deactivating (*p*-NO_2), selective hydration of the allene to a methyl ketone is preferred, which provides both a mechanistic rationale and a benchmark for arene nucleophilicity that correlates well with literature. More electrophilic catalyst precursors are able to catalyze the *intermolecular* addition of electron-rich arenes to allenes, although the scope of this transformation was significantly more limited (9 examples, 22-90% yield). This reaction does not proceed with coordinating arenes and sterically demanding allenes.

Cascade cyclization of allenyl epoxides proceeds rapidly under gold(I) catalysis to produce polyethers remniscient of those found in marine and soil polyethers. Initial attempts to cyclize simple allenyl mono- or bis-epoxides led to complex product mixtures, but use of a hydroxyl "trapping group" yields polycycles in 35-65% yield. Carbocation stability ($3^o > 2^o > 1^o$) controls ring formation in the cascade; the resultant polycycles appear to be stereospecific with respect to initial epoxide geometry. The cyclization can be extended to form both fused and linked polyethers from properly-substituted polyepoxides.

To My Family

ACKNOWLEDGEMENTS

Everyone I've known at UNC has had, for better or worse, an impact on my life, and I thank you all for it. Even if you are not specfically named below, know that I am grateful.

I would like to thank Prof. Mike Gagné for rescuing me when I needed a place to go. His ideas, availability, and the freedom he grants to "see where things go" with projects has allowed me to both learn and chase after crazy ideas, some of which wound up in here. Thanks, Mike. Really.

Thanks to my committee (Mike, Brook, Marcey, Jeff, Wenbin) for careful reading of the manuscript and enduring my catalysis talk one more time.

Thanks to all my former teachers and professors. Special thanks to Mr. David Vito (NAHS), Prof. David Adams (UMass) and Prof. Vincent Rotello (UMass). Thanks to my former coworkers at ARIAD and Millennium for looking past my obvious faults and poor grades to see a potential chemist: Dr. Yihan Wang, Dr. William Shakespeare, Dr. Doug Burdi, Dr. Kevin Sprott, Dr. Tracy Jenkins, Dr. Jeff Ciavarri, and Mr. Bob Bennett.

Thanks to all my labmates for assistance and companionship: Dr. Ulf Dreschler, Ali Bayir, Dr. Ray Thibault, Dr. Derek Van Allen, and Dr. Jason Field (UMass); Nick Pelz, Andy Ommen, Dr. Stephane Trudeau, Dr. Sonny Shanmugham, Dr. Heather Burks, and Dr. Josh Sieber (Morken lab, UNC). Thanks to all former and present members of

the Gagné lab, especially Dr. Jeremy Feducia and Dr. Charles Mullen, who showed me the ropes upon arrival in the Gagné lab, and kept me on my toes with ideas and inspiration (also tirades!). Mike Doherty and Mike Rizzo provided energy and laughter, and Dr. Sekhar Korapala, Dr. Colleen Munro-Leighton, Ann Liu, and Steve Andrews make 224 Caudill a great place to work. Best wishes for successful futures to Ann, Steve, Alissa Roland, John Gipson, and Tina Heetderks. My gratitude also to Colleen and Dr. Luke Zuccarello for their proofreading expertise.

Extra special thanks to Jess. You've been a constant source of happiness. Thanks, and much love. Thanks to Anthony and Jaimee Bellissimo for reminding me that good friends are what makes life great.

Finally, thanks to my entire family. To Gram and Gramp, Uncle Doug and Bill, Aunt Nan, Andy, and all the extended cousins, thanks for your love and support. Matt and Mom, you two know I couldn't have made it here without you. Thank you.

"Nothing great was ever achieved without enthusiasm" -Ralph Waldo Emerson

TABLE OF CONTENTS

LIST OF TABLES

LIST OF SCHEMES

LIST OF FIGURES

LIST OF ABBREVIATIONS AND SYMBOLS

1^o	primary
2^o	secondary
3^o	tertiary
^oC	degrees Celsius
Å	Angstrom = 100 pm
Ac	acetyl
α	alpha - going into the page (stereochemistry)
	carbon adjacent to a functionality (regiochemistry)
ADPP	1,1'-azodicarbonyl(dipiperidine)
β	beta - coming out of the page (stereochemistry)
	two carbons away from a functionality
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
BINOL	1,1'-bi-2-naphthol
Boc	*tert*-butoxycarbonyl
Bn	benzyl
n-BuLi	*n*-butyllithium
*t*Bu	*tert*-butyl
cat.	catalytic quantity (substoichiometric)
Cl-TPOP	tri(4-chlorophenyl)phosphite

COSY	$^{1}H/^{1}H$ Correlation Spectroscopy
δ	delta - change from standard value (NMR)
d	doublet (NMR)
DCM	dichloromethane
DEPT	Distortionless Enhancement by Polarization Txfr
DFT	density functional theory (calculations)
DMF	dimethylformamide
DMS	dimethylsulfide
DMSO	dimethylsulfoxide
dr	diastereomeric ratio
DTBM	3,5-di-*tert*-butyl-4-methoxybenzyl
DuPHOS	1,2-bis(2,5-dimethylphospholano)benzene
E	entgegen - opposite (German)
ee	enantiomeric excess
Eq.	Equation
equiv.	equivalents
ESI	electrospray ionization
EtOH	ethanol
EWG	electron-withdrawing group
GC	gas chromatography
GCMS	gas chromatography - mass spectroscopy

HPLC	high performance liquid chromatography
HRMS	high-resolution mass spectrum
Hz	hertz (NMR coupling constants)
L	liter
mL	milliliter (10^{-3} liter)
μL	microliter (10^{-6} liter)
M-	metal (used like R for carbon)
M	molar - 1 mole / liter (concentration)
m-	meta, 1,3-relationship on aromatic
mCPBA	*meta*-chloroperbenzoic acid
Me	methyl
$MgSO_4$	magnesium sulfate
MHz	megahertz
min	minutes
mmol	millimole
MONOPHOS	3,5-Dioxa-4-phospha-cyclohepta [2,1-a; 3,4 a']dinaphthalen-4-yl)dimethylamine
mp	melting point
m/z	mass to charge ratio (mass spectrometry)
υ	nu - frequency (cm^{-1})
NBS	*N*-bromosuccinimide

NMR	nuclear magnetic resonance spectroscopy
nOe	Nuclear Overhauser effect
NTf_2	"bistriflimide"/ *N,N*-bis(trifluoromethanesulfonate)
o-	ortho, 1,2-relationship on aromatic
OMs	"mesylate" / methanesulfonate
OTf	"triflate" / trifluoromethaneulfonate
OTs	"tosylate" / *p*-toluenesulfonate
p-	para-1,4 relationship on aromatic
π	pi - electrons involved in C-C multiple bonds
PF_6	hexafluorophosphate
PNP	tridentate pincer ligand
PPh_3	triphenylphosphine
ppm	parts per million (NMR relative distance)
PPP	Triphos (tridentate pincer ligand)
PTSA	*para*-toluenesulfonic acid
pyr	pyridine
QUINAP	(diphenylphosphino-1-naphthyl)isoquinoline
R-	any unspecified carbon-containing group
RT	room temperature (20-25 degrees Celsius)
s	seconds
s	singlet (NMR)

SbF_6	hexafluoroantimonate
SEGPHOS	5,5'-Bis(diphenylphosphino)-4,4'-bi-1,3 benzodioxole
SFC	supercritical fluid chromatography
σ	sigma - electrons in involved in C-C single bonds
SM	starting material
TBS	*tert*-butyldimethylsilyl
THF	tetrahydrofuran
THP	tetrahydropyran
TMS	trimethylsilyl
Tol	toluene (methylbenzene)
tolBINAP	2,2’-bis(ditolylphosphino)-1,1’-binaphthyl
TPOP	triphenylphosphite
TPP	triphenylphosphine
xylBINAP	2,2’-bis(di-3,5-xylylphosphino)-1,1’-binaphthyl
xyl	xylenes (dimethylbenzene, isomer mixture)
Z	zusammen - together (German)

Chapter 1

Homogeneous Gold Catalysis

1.1 Introduction - Cationic Electrophilic Cyclization

Enzymatic catalysis[1] is the paradigm for the synthesis of complex polycycles from simple olefinic precursors *in vivo*. Steroids,[2] fragrances,[3] and ladder polyether toxins[4] are all examples of the complexity achieved through evolution of specific cyclization enzymes[5] that can guide a polyunsaturated molecule into a preferred cyclization geometry, achieving complete regioselectivity and stereoselectivity. As shown in **Scheme 1-1**, the conversion of squalene **1** to cholesterol **5** occurs by enzymatic oxidation of a terminal trisubstituted olefin to form 2,3-oxidosqualene **2**, which is enzymatically opened *via* a "chair-boat-chair" conformer[1] to form cationic **3** after a stereoselective cascade reaction. Enzyme-assisted methyl and hydride migration occur to produce lanosterol **4**, which serves as the basic [6-6-6-5] tetracyclic steroid architecture.

---

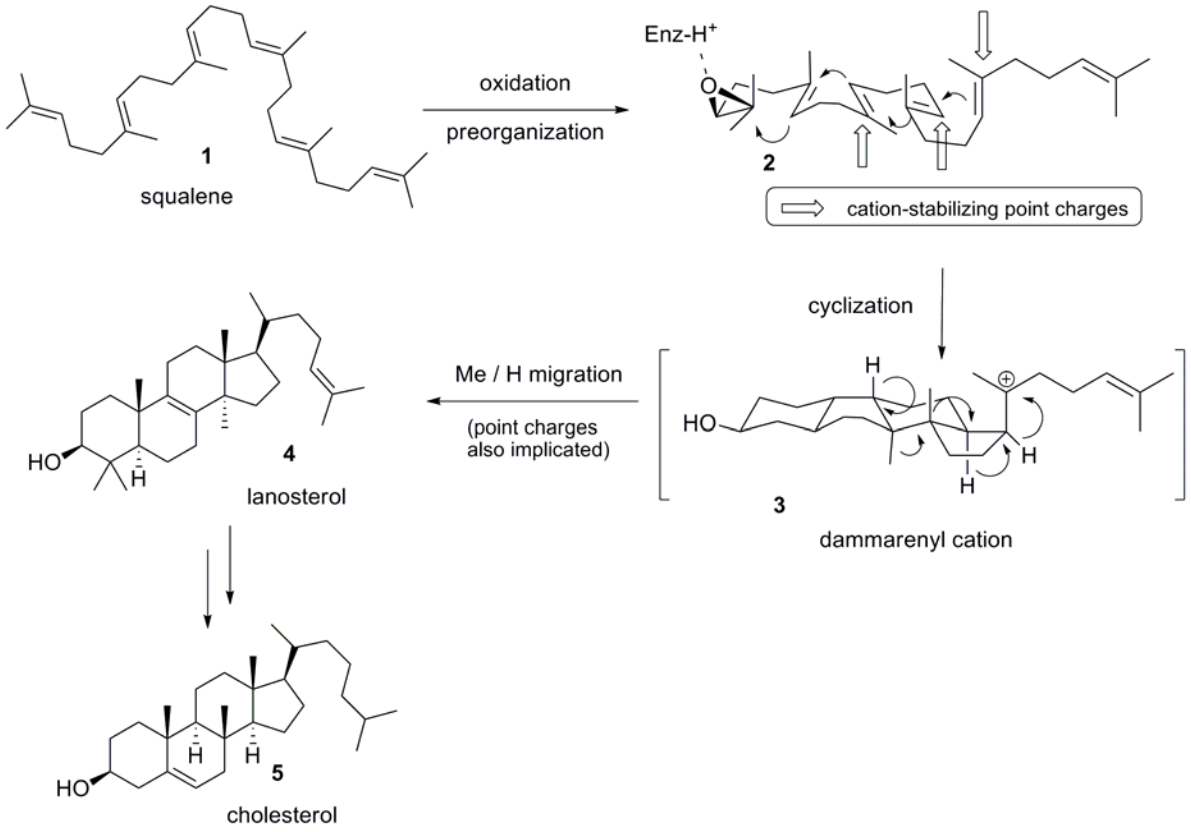
[1] Abe, I.; Rohmer, M.; Prestwich, G. D. *Chem. Rev.* **1993**, *93*, 2189-2206.

[2] Spencer, T. A. *Acc. Chem. Res.* **1994**, *27*, 83-90.

[3] Corey, E. J.; Cane, D. E.; Libit, L. *J. Am. Chem. Soc.* **1971**, *93*, 7017-7021.

[4] a) Alvarez, E.; Candenas, M.-L.; Pérez, R.; Ravelo, J. L.; Martin, J. D. *Chem. Rev.* **1995**, *95*, 1953-1980. b) Faul, M. M.; Huff, B. E. *Chem. Rev.* **2000**, *100*, 2407-2473. c) Inoue, M. *Chem. Rev.* **2005**, *105*, 4379-4405. c) Nakata, T. *Chem. Rev.* **2005**, *105*, 4314-4347.

[5] Wendt, K. U.; Schulz, G. E.; Corey, E. J.; Liu, D. R. *Angew. Chem. Int. Ed.* **2000**, *39*, 2812-2833.



Scheme 1-1. Enzymatic Conversion of Squalene to Cholesterol

Enzymatic stablization of this cyclization in the enzyme cavity by "point charges" is both enticing and controversial. Amino acids such as Tyr and Glu have been implied as π-donor[6] and ion pair stablizers,[7] respectively. Nature's use of anionic stabilizing groups to drive complex polycyclization was first suggested by Cornforth in 1958 and advanced by Johnson, Ourisson, and Nakanishi in the 1980s.[8] Matsuda has recently shown that

[6] Honig, B.; Dinur, U.; Nakanishi, K.; Balogh-Nair, V.; Gawinowicz, M. A.; Arnaboldi, M.; Motto, M. G. *J. Am. Chem. Soc.* **1979**, *101*, 7084-7086.

[7] Johnson, W. S.; Telfer, S. J.; Cheng, S.; Schubert, U. *J. Am. Chem. Soc.* **1987**, *109*, 2517-2518.

[8] Johnson, W. S. *A Fifty Year Love Affair with Organic Chemistry*; American Chemical Society, **1998**.

mutations to alter placement of stabilizing groups can completely change enzyme product distribution.[9]

Chemists attempt to mimic this preorganization and selectivity through use of catalysts, which lower the activation energy of an elementary reaction step.[10] The molecule can therefore react down pathways that were previously kinetically inaccessible, allowing for faster rates and novel product structures. Catalytic carbon-carbon bond-forming reactions can produce less waste, proceed at lower temperatures, improve yields, and potentially control the stereochemistry of the resultant products. Catalysis can be achieved using a variety of different substances, from simple acids and bases (H^+, ^-CN), metals (Fe, Pd, Mg, etc.), small organic molecules (proline, pyridine, DMSO, Ph_3P), and enzymes (squalene cyclase, porcine liver esterase, etc.).

1.2 Gold Catalysis

Homogeneous gold catalysis has enjoyed a renaissance in the last ten years, as evidenced by the large number of reviews currently available on the subject.[11] It is at this point impossible to provide a comprehensive summary of homogeneous gold catalysis, as the

---

[9] Lodeiro, S.; Xiong, Q.; Wilson, W. K.; Kolesnikova, M. D.; Ovak, C. S.; Matsuda, S. P. T. *J. Am. Chem. Soc.* **2007**, *129*, 11213-11222.

[10] Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry - Part A: Structures and Mechanisms*; 4th ed.; Kluwer: New York, 2000. pp. 233-238.

[11] a) Arcadi, A. *Chem. Rev.* **2008**, *108*, 3266-3325. b) Li, Z.; Brouwer, C.; He, C. *Chem. Rev.* **2008**, *108*, 3239-3265. c) Gorin, D. J.; Sherry, B. D.; Toste, F. D. *Chem. Rev.* **2008**, *108*, 3351-3378. d) Widenhoefer, R. A. *Chem. Eur. J.* **2008**, *14*, 5382-5391. e) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180-3211. f) Gorin, D. J.; Toste, F. D. *Nature* **2007**, *446*, 395-403. g) Fürstner, A.; Davies, P. W. *Angew. Chem. Int. Ed.* **2007**, *46*, 3410-3449. h) Hashmi, A. S. K.; Hutchings, G. J. *Angew. Chem. Int. Ed.* **2006**, *45*, 7896-7936.

number of papers has increased exponentially each year since 2004.[12] Gold functions especially well in catalysis due to its excellent functional group tolerance, readily-prepared precatalysts and low sensitivity to moisture or air oxidation. In its +3 oxidation state (**6**), gold possesses a d^8 electron configuration, corresponding to a square planar geometry as is observed with Pt(II), Pd(II), Ir(I), Ru(II), and Rh(I). Gold(III) favors "hard" Lewis basic ligands, such as picolinates or diamines.[13] Gold(I) (**7**) exhibits a d^{10} electronic configuration, which favors coordination of "soft" ligands such as phosphines and C-C π-bonds. Gold(I) coordinates in a linear geometry[14] with two ligands, yielding an L_1-Au-L_2 bond angle of 171-179° (**Figure 1-1**). Thus, the reactive coordination site of the metal is far removed from the chirality-inducing ligand environment, rendering asymmetric catalysis challenging.

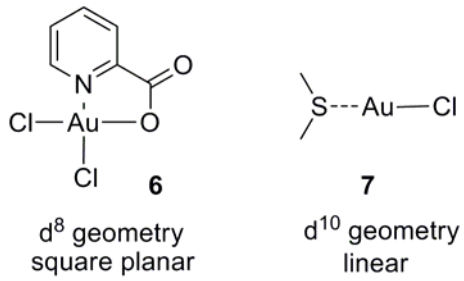


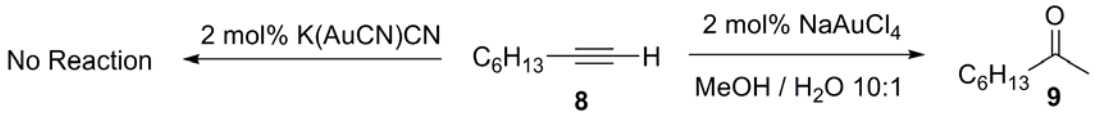
Figure 1-1. Coordination geometry of Au(I) and Au(III)

[12] Toste, F.D. *National Organic Symposium* **2007**, Duke University, Durham, NC

[13] Hashmi, A. S. K.; Weyrauch, J. P.; Rudolph, M.; Kurpejovic, E. *Angew. Chem. Int. Ed.* **2004**, *43*, 6545-6547.

[14] Stork, J. R.; Rios, D.; Pham, D.; Bicocca, V.; Olmstead, M. M.; Balch, A. L. *Inorg. Chem.* **2005**, *44*, 3466-3472.

Gold catalysis began as a heterogeneous process,[15] wherein gold powder or colloidal gold was heated with metallic cocatalysts to achieve surface-based hydrocarbon rearrangements or hydroformylation. Gold(III) was first noted as catalytic in the acetal formation and hydrolysis of phenylacetylene in methanol to acetophenone.[16] However, this process was not initially recognized as catalytic; the only evidence was that the reaction proceeded to 570% yield, based on gold as the limiting reagent! Gold(III) was also found to catalyze hydration of acetylene **8** to ketone **9** as reported by Utimoto in 1991.[17] Interestingly, as shown in **Scheme 1-2**, 2 mol% $NaAuCl_4$ readily catalyzed the reaction, whereas K(AuCN)CN was completely unreactive, even under forcing conditions.



Scheme 1-2. Utimoto Au(III) alkyne hydrolysis (1991)

Scattered reports on homogenous gold(III) catalysis appeared over the next decade,[18] but gold(I) was considered "catalytically dead"[19] due to its propensity to decompose to metallic gold after few turnovers. Teles and coworkers disclosed the first highly active, long-lasting

[15] a) Thompson, D. *Gold Bull.* **1998**, *31*, 112-118. b) Thompson, D. *Gold Bull.* **1999**, *32*, 12-18.

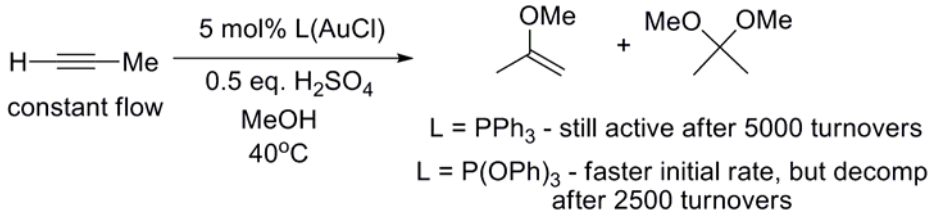
[16] Norman, R. O. C.; Parr, W. J. E.; Thomas, C. B. *J. Chem. Soc. Perkin Trans. I* **1976**, 1983-1987.

[17] a) Fukuda, Y.; Utimoto, K. *J. Org. Chem.* **1991**, *56*, 3729-3731. b)Fukuda, Y.; Utimoto, K. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 2013-2015.

[18] Gasparrini, F.; Giovannoli, M.; Misiti, D.; Natile, G.; Palmieri, G.; Maresca, L. *J. Am. Chem. Soc.* **1993**, *115*, 4401-4402.

[19] Schmidbauer, H. *Naturwiss. Rundsch.* **1995**, *48*, 443.

gold(I) catalyst in 1998.[20] Teles reported that with a suitable Lewis or Brønsted acid cocatalyst, gold(I) cationic catalysts were active for the mono- and bis-methoxylation of propyne with counterion-dependent turnover: less-coordinating anions such as $CH_3SO_3^-$ outperform I^- or Cl^-. The electronic properties of the ligand on gold are also important - electron-poor ligands such as phosphites are more active, but decompose faster (**Scheme 1-3**).



Scheme 1-3. Highly active gold(I) catalysts for homogeneous MeOH addition to alkynes (1998)

Beginning in 2000, a new group of investigators staked "new claims in the gold rush".[21] A review by Dyker[22] published in *Angewandte Chemie* highlighted Hayashi, Teles, and Utimoto's work, but the focus was on $AuCl_3$-catalyzed reactions reported by Hashmi, who, in 2000 demonstrated a synthesis of functionalized phenols (**10**)[23] from furans and alkynes (**9**) (**Scheme 1-4**). This work was later expanded to include picolinic acid-ligated Au(III)

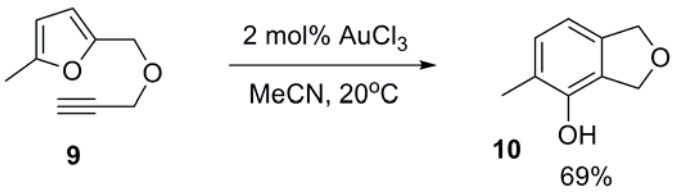
[20] Teles, J. H.; Brode, S.; Chabanas, M. *Angew. Chem. Int. Ed.* **1998**, *37*, 1415-1418.

[21] Hashmi, A. S. K. *Angew. Chem. Int. Ed.* **2005**, *44*, 6990-6993.

[22] Dyker, G. *Angew. Chem. Int. Ed.* **2000**, *39*, 4237-4239.

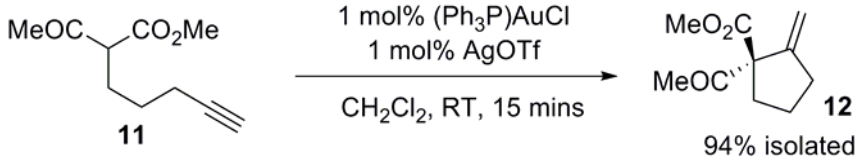
[23] a) Hashmi, A. S. K.; Frost, T. M.; Bats, J. W. *J. Am. Chem. Soc.* **2000**, *122*, 11553-11554. b) Hashmi, A. S. K.; Frost, T. M.; Bats, J. W. *Org. Lett.* **2001**, *3*, 3769-3771.

precatalysts,[24] benzylic C-H activation,[25] and hydroarylation, which will be discussed as a larger part of this dissertation in **Chapter 3**.



Scheme 1-4. Hashmi intramolecular phenol synthesis (2000)

In 2004, Toste and coworkers developed a gold(I)-catalyzed Conia-ene reaction[26] that proceeded at room temperature in commercial-grade solvent, representing a major improvement over the classic thermal reaction. Homogeneous gold catalysis would soon become the major research focus of the Toste group.[11c] Shown in **Scheme 1-5** is cyclization of a pro-nucleophile **11** onto a tethered alkyne to produce cyclopentane **12** in nearly quantitative yield.



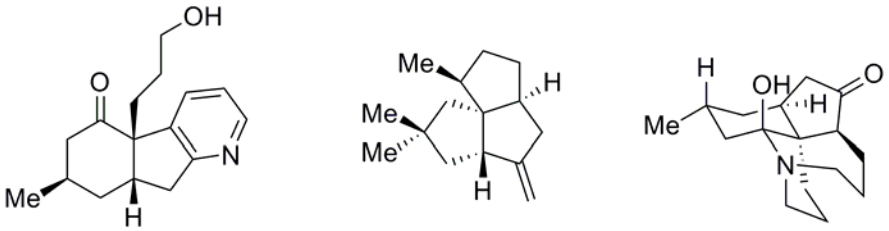
Scheme 1-5. Conia-ene reaction (Toste, 2004)

[24] Hashmi, A. S. K.; Weyrauch, J. P.; Rudolph, M.; Kurpejovic, E. *Angew. Chem. Int. Ed.* **2004**, *43*, 6545-6547.

[25] Hashmi, A. S. K.; Schäfer, S.; Wölfle, M.; Gil, C. D.; Fischer, P.; Laguna, A.; Blanco, M. C.; Gimeno, M. C. *Angew. Chem. Int. Ed.* **2007**, *46*, 6184-6187.

[26] Kennedy-Smith, J. J.; Staben, S. T.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 4526-4527.

Reports on enyne-bicyclohexene cycloisomerization,[27] Münchnone cyclization,[28] and silyl ketene ether addition to alkynes[29] soon followed, showing the exquisite chemoselectivity of gold(I) in its tolerance of imides, silyl ethers, among others. Toste's methodologies have been applied to three total syntheses at present; (+)-fawcettimine,[30] (+)-lycopladine A,[31] and ventricosene[32] (**Figure 1-2**). Gold(I) can now be considered part of the "organic toolbox" for late-stage transformations on advanced material under mild conditions.



(+)-lycopladine A ventricos-7(13)-ene fawcettimine

Figure 1-2. Natural products prepared by the Toste group utilizing gold(I) methodology

[27] Luzung, M. R.; Markham, J. P.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 10858-10859.

[28] Melhado, A. S.; Luparia, M.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 12638-12639.

[29] Minnihan, E. C.; Colletti, S. L.; Toste, F. D.; Shen, H. C. *J. Org. Chem.* **2007**, 6287-6289.

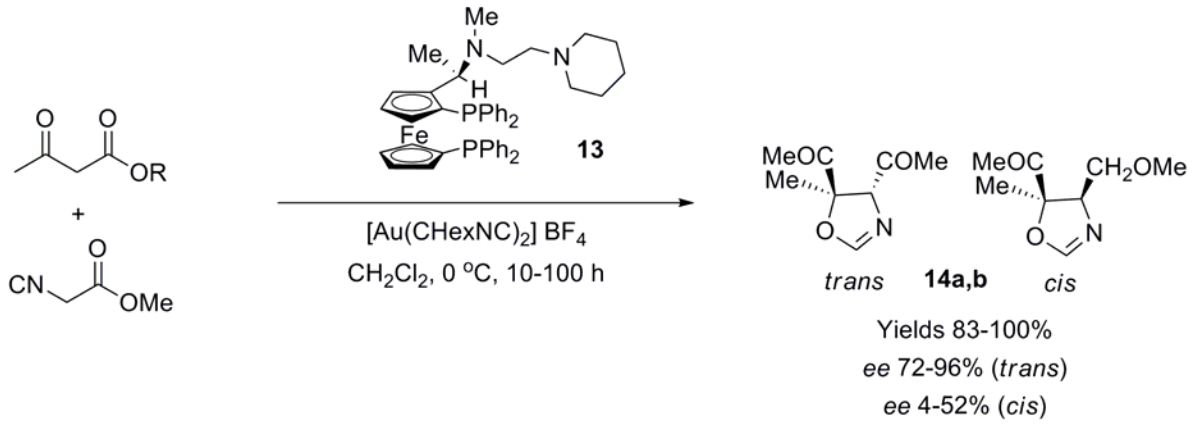
[30] Linghu, X.; Kennedy-Smith, J. J.; Toste, F. D. *Angew. Chem. Int. Ed.* **2007**, *46*, 7671-7673.

[31] Staben, S. T.; Kennedy-Smith, J. J.; Huang, D.; Corkey, B. K.; LaLonde, R. A.; Toste, F. D. *Angew. Chem. Int. Ed.* **2006**, *45*, 5991-5994.

[32] Sethofer, S.; Staben, S. T.; Hung, O. Y.; Toste, F. D. *Org. Lett.* **2008**, *10*, 4315-4318.

1.3 Asymmetric Gold Catalysis

The first example of asymmetric product formation by gold(I) catalysts appeared in the Hayashi-Ito aldol reaction[33] between isocyanoacetates and β-ketoesters, first reported in 1986 (**Scheme 1-6**). This reaction employs a chiral ferrocenyl bis(phosphine) **13** to introduce selectivity, producing mixtures of oxazolines **14a** and **14b** with highly variable enantioselectivity.



Scheme 1-6. Hayashi-Ito Au(I)-catalyzed aldol reaction (1986)

The reaction is thought to proceed as shown in **Figure 1-3**. Hayashi postulated that bidentate ligation of the gold(I) center, followed by isocyanate coordination (reinforced by ammonium-enolate hydrogen bonding) would force the aldehyde to approach on its *si* face, which could account for the high stereospecificity and enantioselectivity.

[33] a) Ito, Y.; Sawamura, M.; Hamashima, H.; Emura, T.; Hayashi, T. *Tetrahedron Lett.* **1989**, *30*, 4681-4683. b) Soloshonok, V. A.; Hayashi, T. *Tetrahedron Lett.* **1994**, *35*, 2713-2716.

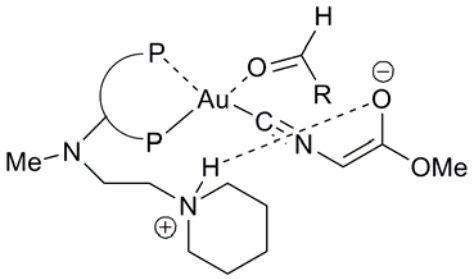


Fig. 1-3. Transition-state model proposed by Hayashi

Four years later, Pastor and Togni characterized a similar catalyst,[34] casting doubt on the transition-state structure proposed by Hayashi. As noted in **Section 1.2**, gold(I) often forms linear complexes with two coordinating ligands. Recrystallization of a ferrocenyl-amine $(AuCl)_x$ catalyst from benzene / diethyl ether resulted in orange platelets, shown to be gold trimers. Togni measured the P7-Au2-Cl5 angle (Fig. 1-3) to be approximately linear, at 178^o (**Figure 1-4**). This observation, while not particularly useful for elucidating Hayashi's results, would heavily influence the design of bis(gold) diphosphine chiral catalysts.[7d] A more recent example of this reaction applied to the formation of imidazolines was reported by Lin in 1999.[35]

[34] Togni, A.; Pastor, S. D.; Rihs, G. *J. Organomet. Chem.* **1990**, *381*, C21-C24.

[35] Zhou, X.-T.; Lin, Y.-R.; Dai, L.-X.; Sun, J.; Xia, L.-J.; Tang, M.-H. *J. Org. Chem.* **1999**, *64*, 1331-1334.

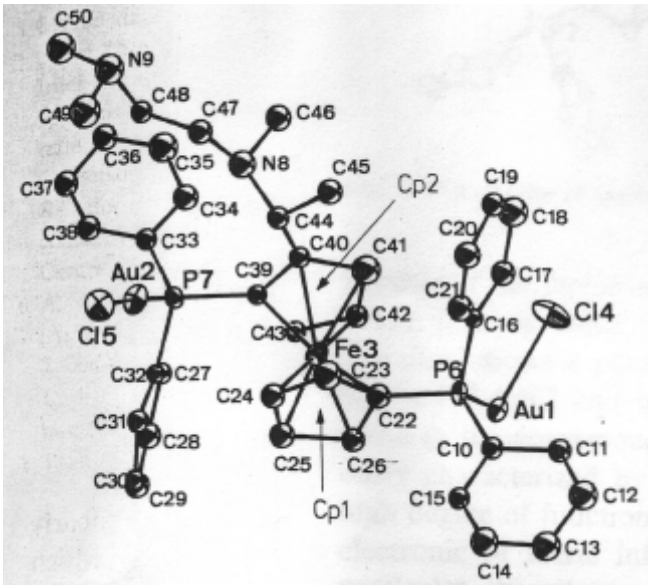


Figure 1-4. Crystal structure of (dppf)$(AuCl)_2$ derivative prepared by Togni (1990)

Crystal structures of enantiopure digold(I) complexes utilizing single-enantiomer commercial ligands were reported by Echavarren in 2005. [36]

[36] Muñoz, M. P.; Adrio, J.; Carretero, J. C.; Echavarren, A. M. *Organometallics* **2005**, *24*, 1293-1300.

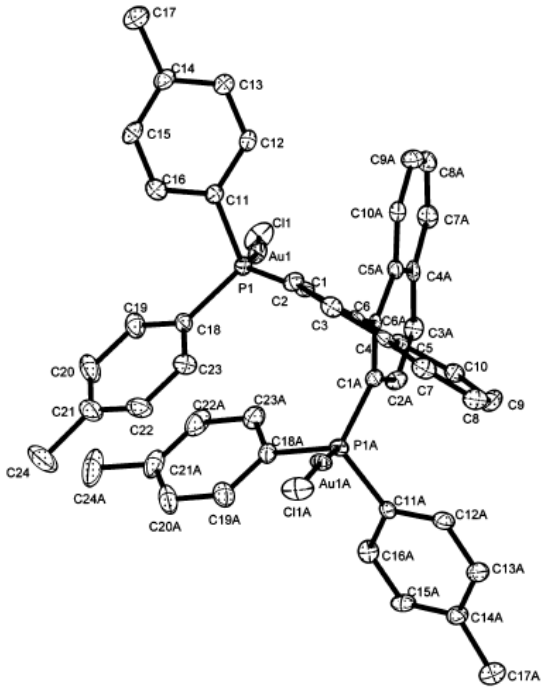
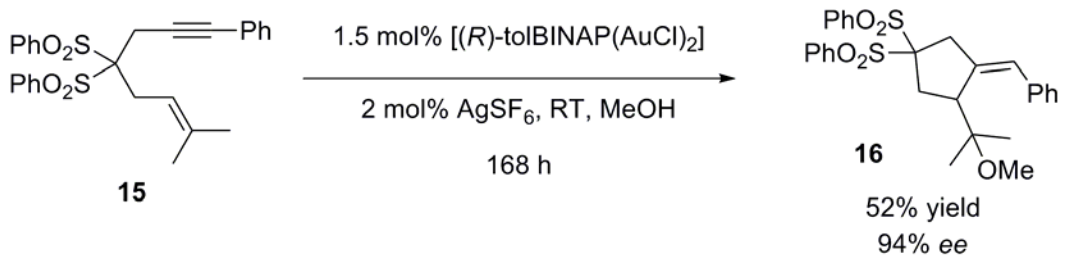


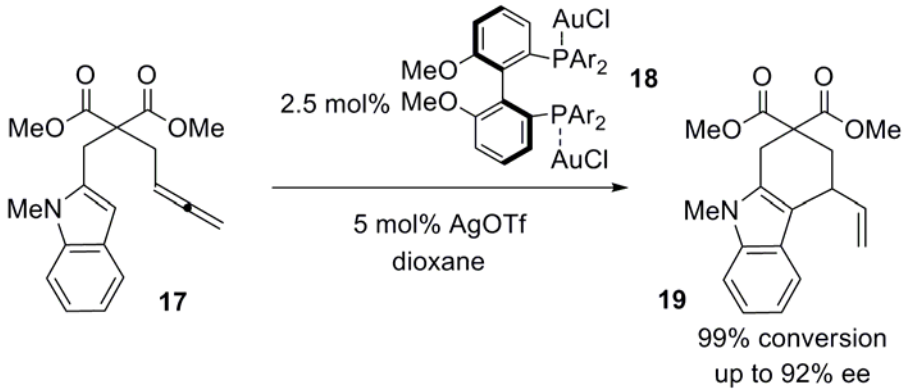
Figure 1-5. Crystal structure of [(*R*)-tolBINAP(AuCl)$_2$] reported by Echavarren (2005)

Bidentate complexes such as [(*R*-tolBINAP)(AuCl)$_2$] (**Figure 1-5**), (*R,R*)-DuPHOS(AuCl)$_2$, as well as complexes of monodentate ligands such as MONOPHOS(AuCl) were shown to catalyze alkoxycyclizations of 1,6-enynes (**15**) into cyclic ethers **16** in 60-92% yield, with *ee* up to 53%.[35] (**Scheme 1-7**). X-ray diffraction of [(*R*-tolBINAP)(AuCl)$_2$] clearly illustrates the linear coordination mode of Au(I): the P-Au-Cl angle is 172.7^o.



Scheme 1-7. Alkoxycyclization with chiral catalysts

Widenhoefer has prepared heterocycles from hydroalkoxylation and hydroamination of allenes and alkenes, achieving up to 94% *ee* with the rigid (*S*)-DTBM-$(MeO)_2$BIPHEP ligand structure (**18**)[37] (**Scheme 1-8**). Allenyl indoles such as **17** are efficiently cycloisomerized to tetrahydrocarbazole **19**, a target structure in pharmaceutical scaffolds.



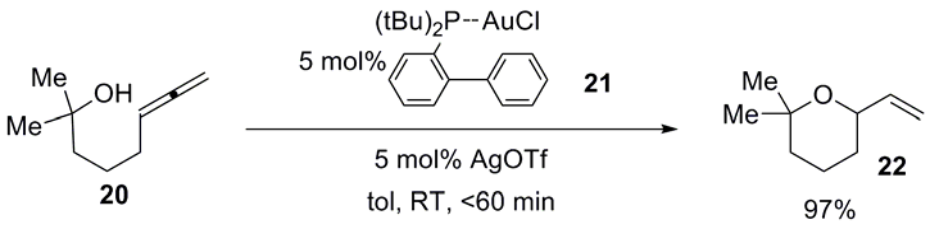
Scheme 1-8. Enantioselective intramolecular gold(I) catalysis of indole-allenes

Widenhoefer was also among the first to realize the highly active nature of the Au[P(*t*-Bu)$_2$(*o*-biphenyl)]Cl catalyst **21**[38] for the addition of arenes, alcohols (**20**), and sulfonamides to allenes (**Scheme 1-9**) to produce cycloisomers, for instance **22**.

---

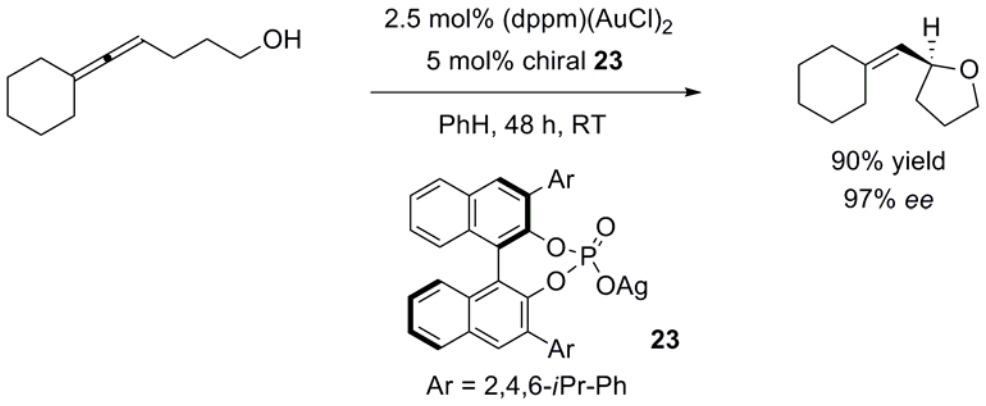
[37] Liu, C.; Widenhoefer, R. A. *Org. Lett.* **2007**, *9*, 1935-1938.

[38] Zhang, Z.; Liu, C.; Kinder, R. E.; Han, X.; Qian, H.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2006**, *128*, 9066-9073.



Scheme 1-9. Hydroalkoxylation of allenes (Widenhoefer, 2007)

Activation of C-C π-bonds by gold(I) promotes nucleophilic attack by "outer-sphere" coordination mechanisms[11] - i.e., the nucleophile and metal do not interact prior to bond formation. If tight ion-pairing is invoked, the gold(I) counterion becomes crucial to controlling regioselectivity and enantioselectivity. In 2007, Toste and coworkers capitalized on this strategy, employing the sterically encumbered counterion **23** with an achiral diphosphine ligand (**Scheme 1-10**) to cyclize allenyl alcohols, observing a dramatic increase in enantioselectivity as solvent polarity decreased.[39]

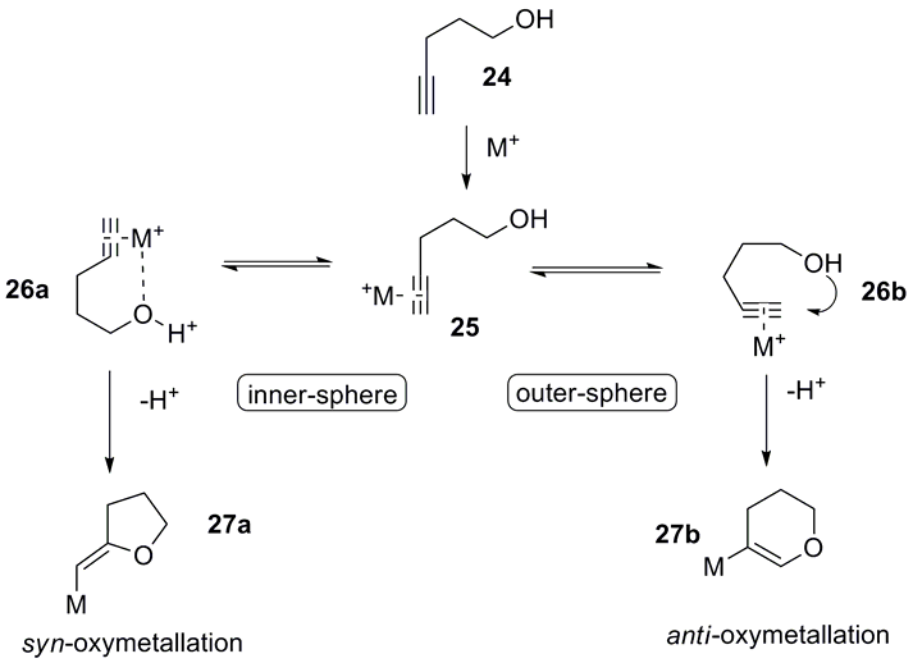


Scheme 1-10. Toste's chiral counterion strategy for enantioselective gold(I) cyclizations

[39] Hamilton, G. L.; Kang, E. J.; Mba, M.; Toste, F. D. *Science* **2007**, *317*, 496-499.

1.4 Research Objectives

A potent strategy for catalytic C-C, C-N, or C-O bond formation involves electrophilic activation (**Scheme 1-11**) of unsaturated carbon-carbon bonds, wherein an electrophilic species (M+) interacts with a π-bond such as alkyn-ol **24**. Metal coordination occurs (**25**), which results in electron density transfer away from the bond, forming cationic character (**26a,b**). If the heteroatom and metal have a bonding interaction (**26a**) prior to cyclization (complexation, oxidative insertion, transmetalation) they can proceed *via* inner-sphere (coordination sphere) mechanisms. At some point in the mechanism, the metal is directly bound to both the π-bond and nucleophile, which implies a greater influence of chiral ligands and metal environment on the reaction.



Scheme 1-11. Electrophilic cyclization *via* inner- and outer-sphere mechanisms

If, instead, the metal is simply "activating" the bond towards nucleophilic attack (**26b**), this is referred to as an outer-sphere mechanism. On the basis of deuterium labeling and kinetic studies, Widenhoefer has proposed that Pt(II)-catalyzed hydroamination of olefins[40] and gold(I)-catalyzed allene hydroalkoxylation[41] both proceed *via* outer-sphere processes. These results, contrary to inner-sphere processes, imply that the metal chirality (if any) does not greatly influence nucleophile bonding (*vide supra*).

Chemists can also control enantioselectivity and *exo* vs. *endo* modes of cyclization[42] through judicious choice of metal and ligand. Intramolecular cycloisomerization, a "green" synthetic method which builds complexity into simple starting materials,[43] is triggered when a metal-coordinated π-bond reacts with a tethered nucleophile, such as a neighboring alkene, epoxide, enolate, or alcohol. The heterocyclic ethers **28a,b** shown below in **Scheme 1-12** illustrate the wide variety of variables chemists can exploit to achieve these desired compounds (*vide infra*).

Initiating groups (**A**) are functionalities able to undergo metal coordination to begin a cyclization cascade. The substitution pattern (**B**) refers to functional groups that promote cyclization - one example is that of a 4,4' disubstitution leading to a chair-like transition

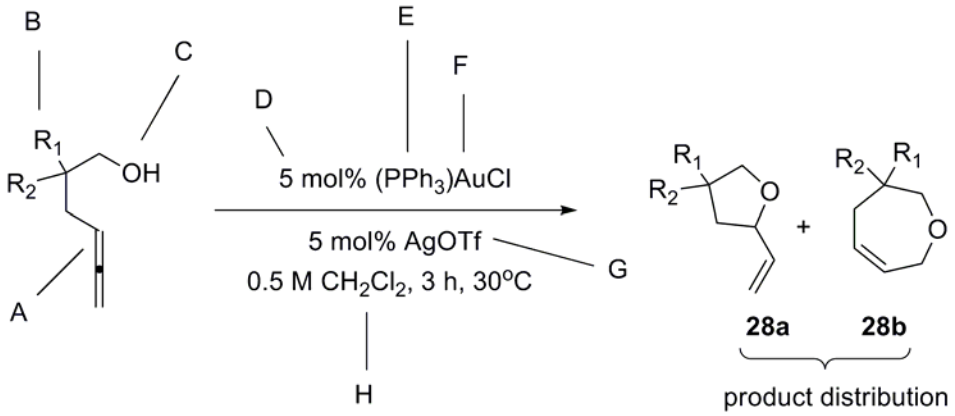
[40] Liu, C.; Han, X.; Wang, X.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2004**, *126*, 3700-3701.

[41] Zhang, Z.; Bender, C. F.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2007**, *129*, 14148-14149.

[42] Baldwin, J. E. *J. Chem. Soc. Chem. Comm.* **1976**, 734-736.

[43] a) Trost, B. M. *Acc. Chem. Res.* **2002**, *35*, 695-705. b) Trost, B. M. *Science* **1991**, *254*, 1471-1477.

state, the so-called "Thorpe-Ingold Effect".[44] "Trapping" groups (**C**) are nucleophilic or pro-nucleophilic groups that can terminate an incipient carbocation. The catalytic load **D** of a reaction is amount of catalyst used. Efficient and "green" catalysis strives to employ transition metals in low catalytic loading.[45] Ligands **E** are Lewis bases which coordinate to the metal center, tuning both the electronic and steric effects of metal reactivity.



Scheme 1-12. Some controllable variables in metal catalysis

A catalyst (**F**) in this context is a Lewis acid (electron-acceptor) able to coordinate to the initiating groups. As previously stated, the counterion **G** has a large effect on the ability of a metal to coordinate with substrate, and can also impact enantioselectivity.[46] Highly coordinating ($^{-}$Cl, $^{-}$OH, $^{-}$CN) or dissociated ($^{-}SbF_6$, $^{-}BF_4$) counterions can affect chemoselectivity and reaction rate dramatically, especially when paired with solvent polarity

[44] Bachrach, S. *J. Org. Chem.* **2008**, *73*, 2466-2468.

[45] Anastas, P.; Warner, J. *Green Chemistry: Theory and Practice*; Oxford University Press: New York, **1998**.

[46] LaLonde, R. A.; Sherry, B. D.; Kang, E.-J.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 2452-2453.

as a variable. Reaction conditions (**H**) include [SM], solvent, time, and temperature, which all affect rate and products obtained.

The work described in the subsequent three chapters was initiated as a logical extension of our group's longstanding interest in Pt(II)-catalyzed cation-olefin reactions[47] (**Chapter 2**). The realization that Au(I) catalysts were more functional-group tolerant and chemoselective towards unsaturated bonds than Pt(II) was accompanied by a movement of the chemistry out of the glovebox and into benchtop work in air with moist, commercial-grade solvent. The catalysts therefore free one to attempt transformations that would hinder Pt(II): chelating heteroatoms, acid-sensitive functionalities, allene hydroarylation (**Chapter 3**), and heteroatomic cascade cyclization (**Chapter 4**).

[47] Chianese, A. R.; Lee, S. J.; Gagné, M. R. *Angew. Chem. Int. Ed.* **2007**, *46*, 4042-4059.

Chapter 2

Gold-Catalyzed Cycloisomerization of 1,6-Eneallenes

2.1 A Little History: Pt(II)- and Pd(II)-Catalyzed Cycloisomerization

The electrophilic cyclization of olefins with divalent palladium[48] or platinum[49] has been a focus of the Gagné group since 2004. These were inspired by pioneering work by Overman on catalysis of the Cope rearrangement by Pd^{2+}.[50] The intiation of these cationic cyclizations with Group 10 metals (Ni, Pd, Pt) are well-studied.[51,52] Coordination of the least substituted olefin in a given system to a Pt^{2+} center cultivates carbocationic character on the β-carbon from the metal (**Scheme 2-1**).[53]

---

[48] a) Koh, J. H.; Mascarenhas, C.; Gagné, M. R. *Tetrahedron* **2004**, *60*, 7405-7410. b) Koh, J. H.; Gagné, M. R. *Angew. Chem. Int. Ed.* **2004**, *116*, 3541-3543. c) Korotchenko, V. N.; Gagné, M. R. *J. Org. Chem.* **2007**, *72*, 4877-4881.

[49] a) Feducia, J. A.; Campbell, A. N.; Doherty, M. Q.; Gagné, M. R. *J. Am. Chem. Soc.* **2006**, *128*, 13290-13297. b) Feducia, J. A.; Campbell, A. N.; Anthis, J. W.; Gagné, M. R. *Organometallics* **2006**, *25*, 3114-3117. c) Kerber, W. D.; Gagné, M. R. *Org. Lett.* **2005**, *7*, 3379-3381.

[50] Overman, L.E.; Knoll, F.M. *J. Am. Chem. Soc.* **1980**, *102*, 685-687.

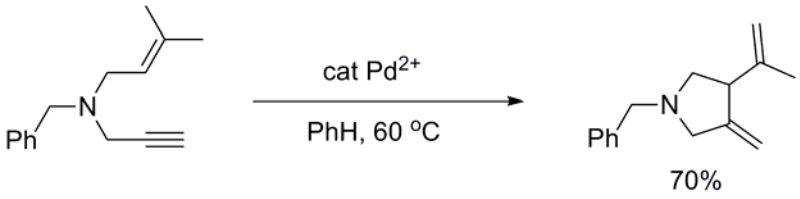
[51] Trost, B. M. *Acc. Chem. Res.* **1990**, *23*, 34-42.

[52] Chianese, A. R.; Lee, S. J.; Gagné, M. R. *Angew. Chem. Int. Ed.* **2007**, *46*, 4042-4059.

[53] Hahn, C.; Cucciolito, M. E.; Vitagliano, A. *J. Am. Chem. Soc.* **2002**, *124*, 9038-9039.

Scheme 2-1. Generic representation of cation-olefin isomerization

This charged species induces a neighboring olefin or heteroatom to form a new bond, relaying a new cation throughout the molecule and prompting new cyclization events. Research in cycloisomerization yields reactions that are atom-efficient (**Scheme 2-2**), catalytic, and produce less waste, all important edicts of the burgeoning field known as "green chemistry".[54]



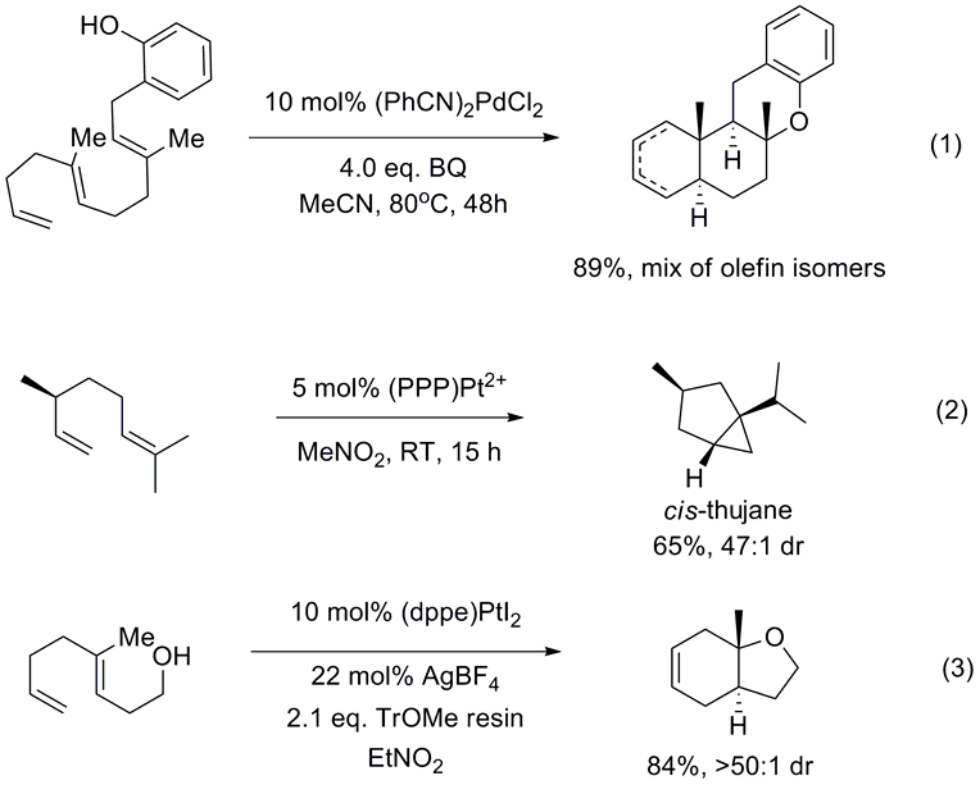
Scheme 2-2. An "atom-economical" cycloisomerization reported by Trost[55]

Three recent examples of this cyclization are shown below. An initial report by Koh and Gagné[1] (**Eq. 1**-see p. 3) demonstrated that oxidative catalysis with Pd(II) or Pt(II) catalysts complexed to PNP or PPP tridentate ligands allowed cycloisomerization of dien- and trienols *via* carbocationic intermediates. Soon after, Kerber and Gagné[2] explored reactions of 1,*n* dienes (n = 6,7) with Pt^{2+} bearing a tridentate pincer ligand (**Eq. 2**). These ligands, which are known to inhibit β-hydride elimination by blocking *cis*-coordination sites on the metal, allow cyclization to take place - the subsequent resultant organometallic σ-

[54] Anastas, P. and Warner, J. "The 12 Principles of Green Chemistry" www.epa.gov/greenchemistry

[55] a) Trost, B. M. *Acc. Chem. Res.* **2002**, *35*, 695-705. b) Trost, B. M. *Science* **1991**, *254*, 1471-1477.

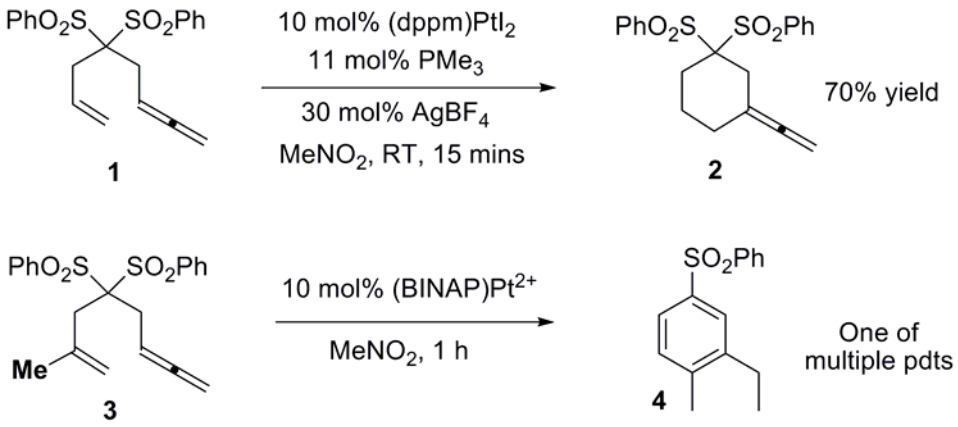
complex then undergoes a 1,2-hydride migration followed by a cyclopropanative migration of the Pt-C bond.



Finally, shown in **Eq. 3** is an example of an oxidative cycloisomerization reported in 2007 by Mullen and Gagné.[56] These reactions are catalyzed by $[P_2Pt][BF_4]_2$ complexes in which regioselective β-hydride elimination is "assisted" by the presence of trityl methyl ether. This ether decomposes under the highly Lewis-acidic reaction conditions, becoming a reservoir for heterolyzed H_2, in the form of a proton from the formed oxonium and a hydride from the metal after oxidation.

[56] a) Mullen, C. A.; Gagné, M. R. *J. Am. Chem. Soc.* **2007**, *129*, 11880-11881. b) Mullen, C. A.; Campbell, A. N.; Gagné, M. R. *Angew. Chem. Int. Ed.* **2008**, *47*, 6011-6014.

Contemporaneously, 1,6-eneallenes were prepared as cyclization substrates in an attempt to extend the aforementioned Pt(II)-initiated cation-olefin cyclizations to produce novel architectures (**Scheme 2-4**). Upon treatment of **1** with dicationic Pt, cycloisomerization proceeded *via* intial coordination to the alkene functionality, and after subsequent β-hydride elimination / reinsertion of the Pt catalyst external allene **2** was formed in 70% yield. This hypothesis was supported by deuterium labeling of the allenyl methine position.[57] Substitution at the allene or alkene (**3** → **4**) generated multiple products, including an aromatized sulfone.

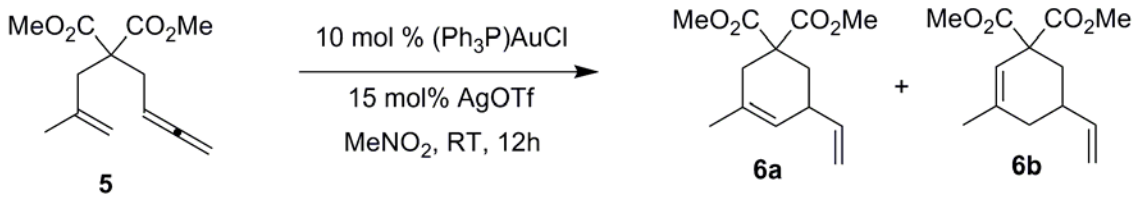


Scheme 2-4. Divergent eneallene reactivity with Pt^{2+}

[57] Chianese, A.R. *unpublished results*

2.2 Reaction Development[58]

Despite the disappointing results of 1,6-eneallene cycloisomerization with Pt^{2+} (**Section 2.1**) the substrates were briefly screened against a number of other common Lewis acids. Allenes are common reactive partners in a host of homogeneous metal-catalyzed reactions, and often lead to novel carbocycles when paired with suitable soft metals, metalloids, or halide sources.[59] Fortunately, gold(I) halide precatalysts activated with silver salts proved suitable for the cycloisomerization of 1,6-eneallenes. As shown in **Scheme 2-5**, compound **5** was found to react with 10 mol% of the catalyst generated from $(Ph_3P)AuCl$ and AgOTf to give vinylcyclohexene(s) **6a** and **6b**, rare six-membered products of 1,6-eneallene cycloisomerization.



Scheme 2-5. Vinylcyclohexenes from gold(I) catalysis

Although numerous studies of 1,6-eneallene cycloisomerizations have been reported (e.g. Rh,[60] Pd,[61] Ru,[62] Ni/Cr[63]), often 5-membered and (less commonly) 7-membered ring

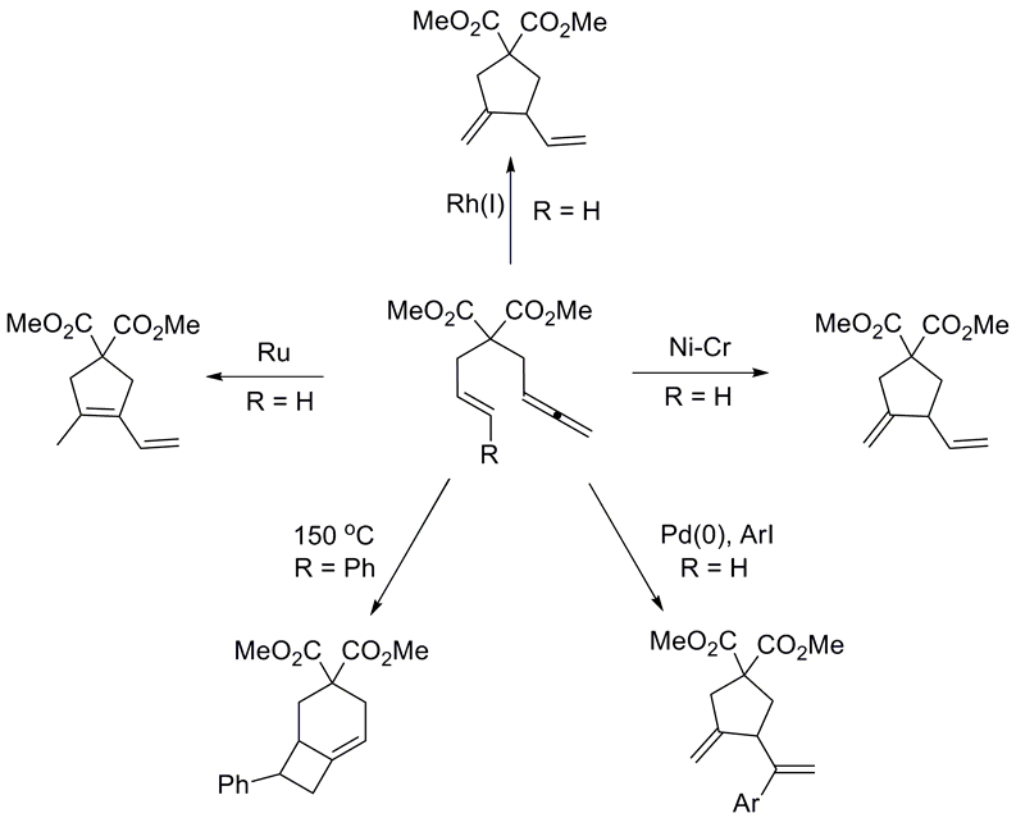
[58] Tarselli, M. A.; Chianese, A. R.; Lee, S. J.; Gagné, M. R. *Angew. Chem. Int. Ed.* **2007**, *46*, 6670-6673.

[59] Ma, S. *Chem. Rev.* **2005**, *105*, 2829-2871.

[60] a) Wender, P. A.; Croatt, M. P.; Deschamp, N. M. *Angew. Chem. Int. Ed.* **2006**, *45*, 2459-2462. b) Makino, T.; Itoh, K. *Tetrahedron Lett.* **2003**, *44*, 6335-6338.

[61] Trost, B. M.; Matsuda, K. *J. Am. Chem. Soc.* **1988**, *110*, 5233-5235.

products are obtained (**Scheme 2-6**). To our knowledge, only a single gold-catalyzed eneallene cycloisomerization existed when we commenced our study; this reaction produced cyclopentadienes from 1,3 eneallenes.[64]



Scheme 2-6. Cyclization modes of 1,6 eneallenes reacting with different metal catalysts

Additionally, these products, although formed as a mixture of alkene isomers, generated a compound with a stereogenic carbon center, allowing us to investigate chiral gold(I) catalysis, which was (in 2006!) still a daunting prospect for reasons outlined in **Chapter 1**. Following this initial lead, we attempted to indentify an optimal chiral phosphine ligand and

---

[62] a) Mukai, C.; Itoh, R. *Tetrahedron Lett.* **2006**, *47*, 3971-3974. b) Kang, S.-K.; Ko, B.-S.; Lee, D.-M. *Tetrahedron Lett.* **2002**, *42*, 6693-6696.

[63] Trost, B. M.; Tour, J. M. *J. Am. Chem. Soc.* **1988**, *110*, 5231-5233.

[64] Lee, J. H.; Toste, F. D. *Angew. Chem. Int. Ed.* **2007**, *47*, 912-914.

to determine whether bisphosphine di(gold) complexes or monodentate ligands were preferred. A preliminary screen of chiral phosphines was therefore initiated (**Table 2-1**).

Table 2-1. Screening of chiral ligands for 1,6-eneallene cycloisomerization

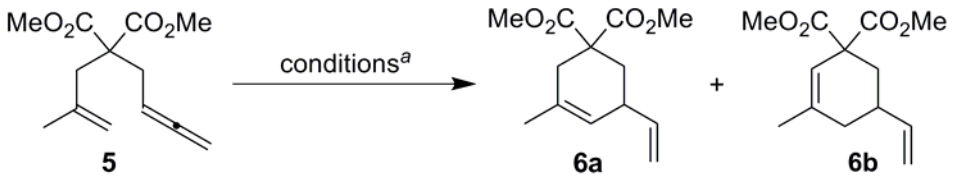
Catalyst[a]	*ee* (%)[b]	Regioselectivity[c]
(S,S)-DIOP($AuCl)_2$	4	1 : 1
(R)-QUINAP(AuCl)	10	1 : 3
(R)-xyl-PHANEPHOS($AuCl)_2$	16	2.5 : 1
(R)-xyl-SOLPHOS($AuCl)_2$	28	3.5 : 1
(R)-SYNPHOS($AuCl)_2$	33	3 : 1
(R)-4,4'-TMS-BINAP($AuCl)_2$	66	1 : 1.5
(SEGPHOS)($AuCl)_2$	66	3.3 : 1
(R)-3,5-xylyl-BINAP($AuCl)_2$	**72**	**3.5 : 1**

[a] General Conditions: 5 mol% catalyst, 15 mol% AgOTf, 0.2M in $MeNO_2$, 12-16 h. Only two products seen by GC after isolation by silica gel chromatography; conversion monitored by ^1H NMR. [b] Average of both regioisomers as measured by chiral GC. [c] GC peak integration.

From this examination [(*R*)-3,5-xylyl-BINAP($AuCl)_2$] was identified as a promising catalyst precursor. Additional optimization studies were carried out with this complex. Interestingly, (*R*)-DTBM-SEGPHOS, previously shown to be optimal in related gold(I) allene chemistry,[65] was unreactive in this system. Also intriguing was the reversed regioselectivity in the (*R*)-QUINAP(AuCl) entry; however, this catalyst exhibited lower enantioselectivity and its optimization was not pursued.

[65] Johansson, M. I.; Gorin, D. J.; Staben, S. T.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 18002-18003.

Table 2-2. Optimization Studies using (*R*)-xylBINAP(AuCl)$_2$



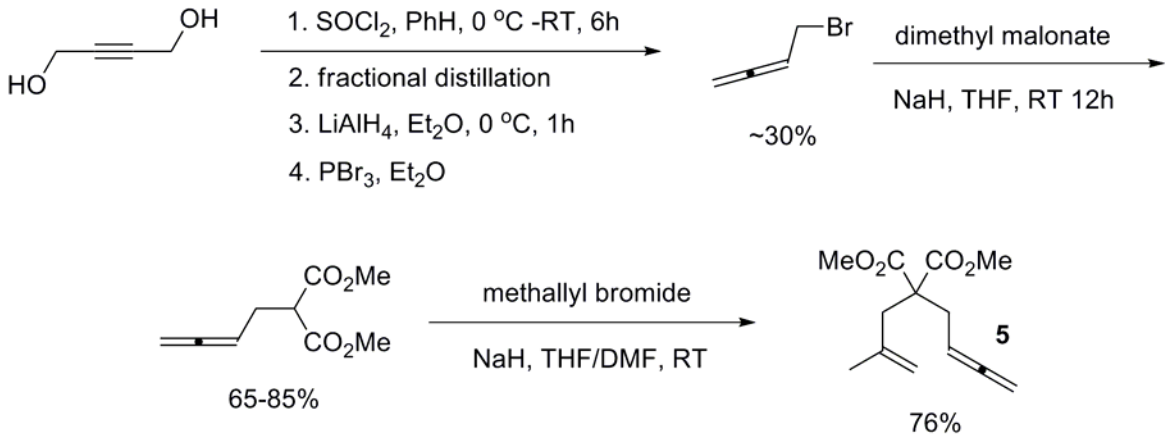
5 **6a** **6b**

Solvent	Activator	Regioselectivity	ee [%][e]
DCM	$AgNTf_2$[b]	2.5 : 1	30%
toluene	$AgNTf_2$	1 : 2	29%
chlorobenzene	$AgNTf_2$	2 : 1	51%
$EtNO_2$	$AgNTf_2$	3 : 1	42%
$MeNO_2$	$AgNTf_2$	**4 : 1**	**65%**
$MeNO_2$	$AgSbF_6$	4 : 3	57%
$MeNO_2$	$AgBF_4$	inc. conversion	30%
$MeNO_2$	AgOTs[c]	**10 : 1**	50%
$MeNO_2$	$AgPF_6$	9 : 1	65%
$MeNO_2$	AgOTf[d]	4 : 1	**72%**

[a] Reaction Conditions: 5 mol% (*R*)-xylBINAP(AuCl)$_2$,15 mol% AgX, 0.1M in **1**, RT,16h. [b] NTf_2 = (bis)trifluoromethanesulfonimide. [c] Ts = toluenesulfonyl [d] Tf = trifluoromethanesulfonate. [e] The *ee* values are averaged from **2a** and **2b** values on chiral GC

As shown in **Table 2-2** the regioselectivity was moderately dependent on solvent polarity, though the enantioselectivities were strongly dependent. Attempts to further optimize these two parameters by modifying the counterion were partially successful; though the counterion that delivered the best regioselectivity for the formation of **2** ($^-$OTs) was not the same as that which provided the best enantioselectivity ($^-$OTf) (**Table 2-1**).

Eneallenes for examining the scope of this chemistry were readily available (**Scheme 2-7**),[66,67] and enabled several structural variations to be examined. Monochlorination of 2-butyn-1,4-diol followed by hydroxyl-directed[68] hydride reduction yielded allenyl alcohol, which could be readily brominated[69] and then used to alkylate activated methylene compounds using sodium hydride in DMF / THF. For synthetic ease, allenylmalonate could also be produced from commercially available dimethyl propargymalonate[70] utilizing a Crabbé reaction[71] modified by Widenhoefer.[72]



Scheme 2-7. Substrate synthesis for 1,6-eneallenes (see Experimental Section)

[66] a) Makino, T.; Itoh, K. *J. Org. Chem.* **2004**, *69*, 395-405. b) Molander, G.; Cormier, E. P. *J. Org. Chem.* **2005**, *70*, 2622-2626.

[67] Wender, P. A.; Croatt, M. P.; Deschamp, N. M. *Angew. Chem. Int. Ed.* **2006**, *45*, 2459-2462.

[68] Hoveyda, A.H.; Evans, D.A.; Fu, G.C. *Chem. Rev.* **1993**, *93* 1307-1370.

[69] Allenylation directly from the alcohol did not proceed using either Sc or Bi catalysts, see: Rueping, M.; Nachtsheim, B. J.; Kuenkel, A. *Org. Lett.* **2007**, *9*, 825-828.

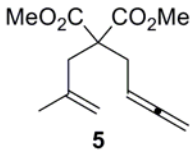
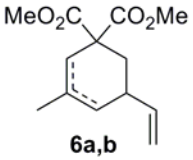
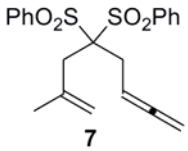
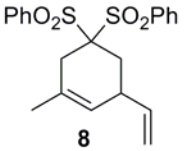
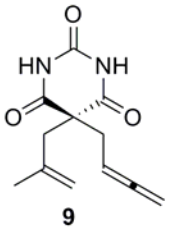
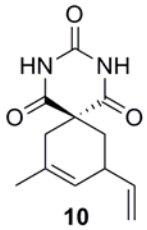
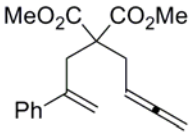
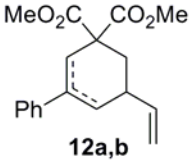
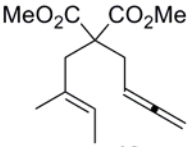
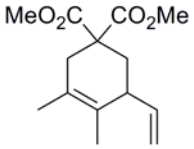
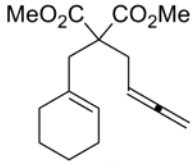
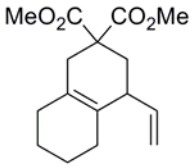
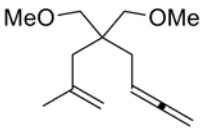
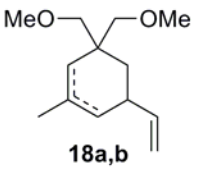
[70] Available from Aldrich and 3B Scientific

[71] Crabbé, P.; Nassim, B.; Robert-Lopes, M.-T. *Org. Syn.* **1985**, *63*, 203-204.

[72] Zhang, Z.; Liu, C.; Kinder, R. E.; Han, X.; Qian, H.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2006**, *128*, 9066-9073.

Alkenes that were only mono-substituted at the internal position were unreactive (**Fig 2-1**, below), though substitution at the alkene terminus was tolerated (**Table 2-3**, **13** and **15**). In the latter cases, this provided sufficient bias to favor one product regioisomer. In the case of methallyl- or phenallyl-substituted substrates (**11** and **15**) lacking this element, a mixture of regioisomers was obtained. This, however, was not universally true as the sulfone (**8**) and urea (**9**) variants of the methallyl substrate were quite regioselective for the 1,2-product.

Table 2-3. Substrate scope for Au(I)-catalyzed 1,6-eneallene cycloisomerization

Substrate	Product	Yield[a] (Isomer Ratio)	ee (%)[d]
 **5**	 **6a,b**	83% (3.5 : 1)[b]	72 (77)
 **7**	 **8**	75%	6
 **9**	 **10**	82%	57
 **11**	 **12a,b**	70% (1.5 : 1)[c]	45
 **13**	 **14**	80%	59
 **15**	 **16**	70%	65
 **17**	 **18a,b**	77% (1 : 1)	64

[a] Isolated yields after silica gel column chromatography. [b] The 1,4 olefin isomer is major. [c] The 1,4 olefin isomer is major. [d] Enantioselectivity measured by chiral GC, see Experimental Section

Enantioselectivities were found to be moderate for most substrates and a slight increase was possible when the reaction was run at 0°C (up to 77% ee). The bis(phenylsulfonyl) linker group was unusual as **7** was obtained in virtually racemic form.[73] Substitution of the olefinic fragment did not seem to greatly affect yield or enantioselectivity, as geminal, styryl, and trisubstituted bonds all gave yields between 70-85%.[10] Evidence for superlative functional group tolerance is demonstrated by **9** and **17**, a pyrimidine-trione and bis(methyl ether), respectively - these substrates would likely decompose under Pt^{2+} conditions.

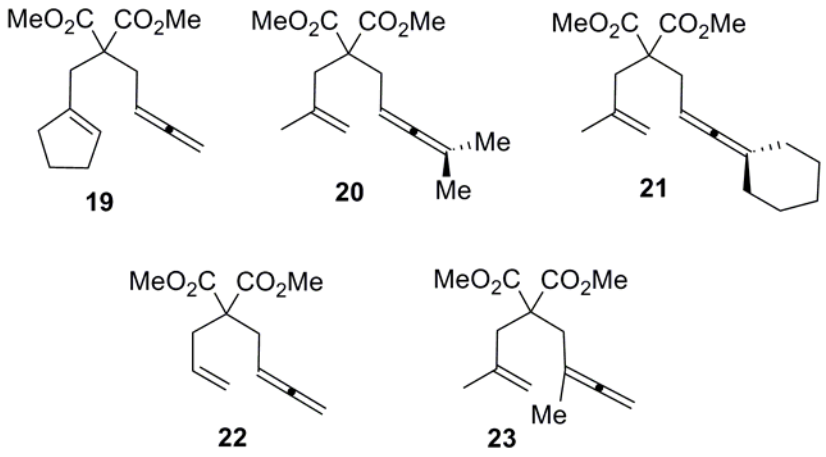


Figure 2-1. Unreactive substrates under the above conditions

Of note are the substrates prepared that did not react under the specified conditions (**Figure 2-1**). Formation of the 6-5 bicycle from a substrate such as **19** did not occur. Additionally, substitution of the allene at the terminus (**20, 21**) lead to a complex mixture of products. This may be due to alternative reaction pathways between the trisubstituted allene

[73] Attempts to improve this result through counterion re-optimization or cooling reaction mixture were not successful.

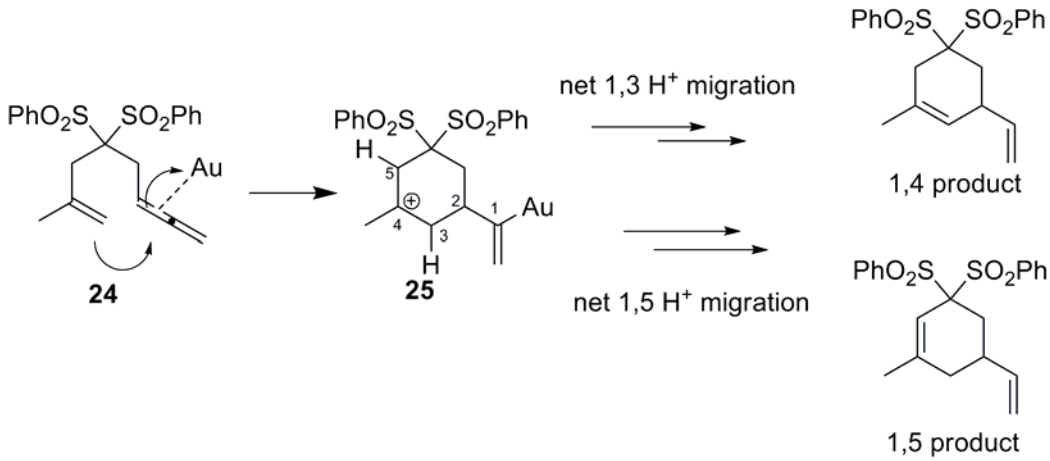
and another functional group in the substrate; an example recently provided by Bäckvall utilizes similar conditions to generate lactones from malonate-allenes.[74] As previously noted, substrates such as **22** cyclize under Pt^{2+} conditions, but sluggishly with gold(I). Geminal substitution of the allene (**23**) resulted in low synthetic yields (<15%); despite interest in formation of a quaternary center, this effort was abandoned.

2.3 Mechanistic Implications

The mechanistic hypothesis explaining the observed reactivity pattern involves the electrophilic activation of the internal allene double bond by Au(I). The formation of a σ-allenyl gold(I) intermediate such as **24** (**Scheme 2-8**) was recently proposed by Widenhoefer.[75] In this scenario the alkene acts as a nucleophile to generate a stablized 3^o carbocation **25**. The catalytic cycle is then completed by 2,3- or 2,1-elimination and protodeauration. In cases where C1 and C2 are each substituted, elimination to the more highly substituted alkene product provides the observed major isomer. The role of the alkene as a nucleophile also explains why internal disubstitution of the alkene is essential, since this ensures the generation of a tertiary carbenium ion in the putative intermediate. This mechanism is also consistent with the observed regiochemical sensitivity to counterions, since they can presumably act as a weak general base in the β-elimination step.

[74] Piera, J.; Krumlinde, P.; Strübing, D.; Bäckvall, J.-E. *Org. Lett.* **2007**, *9*, 2235-2237.

[75] Zhang, Z.; Widenhoefer, R. A. *Org. Lett.* **2008**, *10*, 2079-2081.



Scheme 2-8. Mechanistic proposal for gold(I)-catalyzed cycloisomerization

Asymmetric induction in Au(I)-catalyzed C-C bond-forming processes was rarely observed prior to our work.[76] We hoped to ascertain whether the solid-state environment of the digold catalyst had any relevance to the asymmetric induction. X-ray diffraction-quality crystals were obtained by slow diffusion of pentane into a saturated dichloromethane solution of the dinuclear catalyst precursor. Shown in **Figure 2-2** is the solid-state structure of [(*R*)-3,5-xylylBINAP(AuCl)$_2$].

[76] Widenhoefer, R. A. *Chem. Eur. J.* **2008**, *14*, 5382-5391.

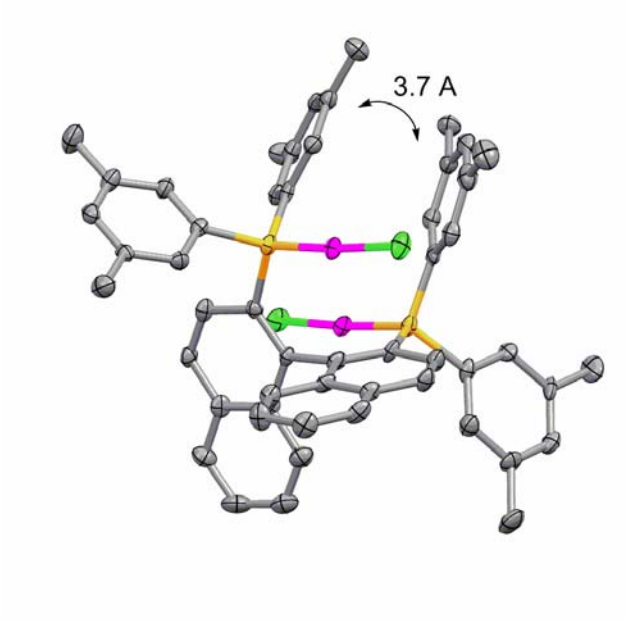


Figure 2-2. [(*R*)-xylylBINAP(AuCl)$_2$]. (gold = pink, chloride = green, carbon = gray, phosphorus = orange, hydrogens omitted for clarity).

Of note is a key π-π stacking interaction between two P-aryl groups (plane to plane distance of 3.7 Å), which serves to rigidify the structure and establish a well-defined chiral cavity. The same conformational preference was observed in (*R*)-TolBINAP(AuCl)$_2$ catalyst[77] and suggests that it may be a common structural feature capable of sculpting the reactive environment of a complex that is otherwise constrained to a linear geometry. Although the picture appears to indicate that a Au-Au interaction[78] is observed, this is misleading, as the Au-Au intramolecular distance is actually >5 Å.[79]

Mechanistic investigations of the cyclization of **5** → **6a,b** led to several observations that complicate the identification of the active catalyst. When 5 mol% of isolated (*R*)-3,5-xylyl-

[77] Muñoz, M. P.; Adrio, J.; Carretero, J. C.; Echavarren, A. M. *Organometallics* **2005**, *24*, 1293-1300.

[78] Schmidbaur, H. *Naturwiss. Rundsch.* **1995**, *48*, 443.

[79] Schmidbaur, H.; Schier, A. *Chem. Soc. Rev.* **2008**, *37*, 1931-1951.

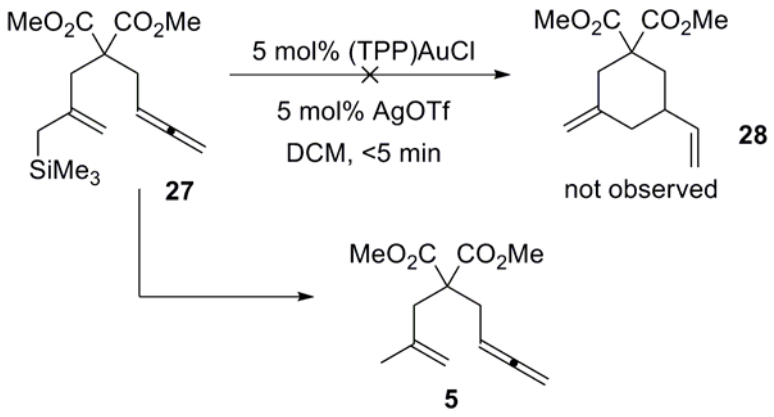
BINAP(AuOTf)$_2$ (**26**)[80] was utilized under the standard conditions, slow reactions and low enantioselectivities were obtained (21 % *ee*, >24 h for completion), contrasting with studies of *in situ*-generated catalysts. Suspecting a role for Ag^+ in these processes, the reactions were repeated using 5 mol% **26** and a 15 mol% excess of AgOTf, and although a fast rate returned, the enantioselectivity remained low (21 % *ee*). Unexpectedly, a control reaction using 5 mol% **26** and added AgCl (15 mol%) increased the *ee* to 34%. A potential explanation has been explored by Malacria and coworkers,[81] who show that presence of halide counterions in the reaction mixture can produce new reaction manifolds in gold chemistry.

A substrate was designed to trap the presumed intermediate carbocation **25** utilizing an intramolecular allylsilane (**27**).[82] It was hypothesized that, after carbocation formation, the allylsilane might eliminate regioselectively to form 1,5-diene **28**. However, preferential desilylation of **27** to **5** was observed in less than five minutes, despite efforts to cool the reaction or run at higher dilution (**Scheme 2-9**).

[80] Prepared by filtration of 2:1 mixture of AgOTf : [*R*-xylBINAP(AuCl)$_2$] through silica plug, and precipitation of concentrated organic with pentane. See Experimental Section for spectral data.

[81] Lemiere, G.; Gandon, V.; Agenet, N.; Goddard, J.-P.; Kozak, A.; Aubert, C.; Fensterbank, L.; Malacria, M. *Angew. Chem. Int. Ed.* **2006**, *45*, 7596-7599.

[82] Terakado, M.; Miyazawa, M.; Yamamoto, K. *Synlett* **1994**, 134-136.



Scheme 2-9. Allylsilane catch substrate

2.4 Reactions of Organogold(I) Complexes

The formation of discrete, isolable organometallic complexes allows further understanding of mechanistic details as well as opportunities to develop new chemistry. As part of the project discussed in **Section 2.3**, we realized that it would be beneficial to develop gold(I) vinyl complexes as mimics of the posited mechanistic intermediate **29** prior to protodeauration (**Figure 2-3**).

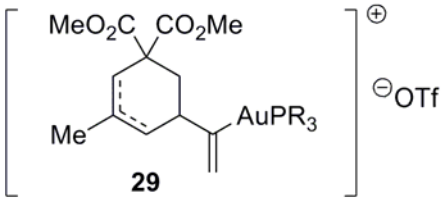
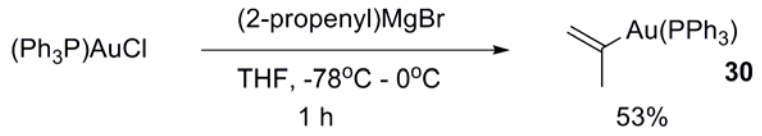


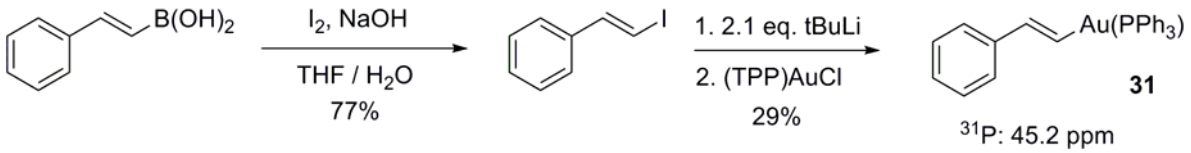
Figure 2-3. A proposed vinylgold(I) intermediate in eneallene cycloisomerization

To achieve this goal, we adopted a variant of a procedure by Toste to produce a gold(I) alkynyl,[83] as well as a procedure by Laguna.[84] Addition of 2-propenyl magnesium bromide to a suspension of $(Ph_3P)AuCl$ in THF yielded 53% of gold(I) vinyl complex **30**, which could be purified by pentane extraction (**Scheme 2-10**).



Scheme 2-10. Addition of propenylmagnesium bromide to gold(I)

While this procedure allowed us to demonstrate that this reaction was feasible, the products after electrophilic deauration (propene, vinyl halides) were difficult to isolate, as volatile gases or low-boiling liquids without chromophores. Thus, treatment of a *trans* vinyl iodide with 2.1 equiv. of *t*-butyllithium in THF at -78°C produced a vinyllithium, which could be intercepted by $(Ph_3P)AuCl$ in THF to produce an isolable gold(I) vinyl, albeit in low yield (**Scheme 2-11**).

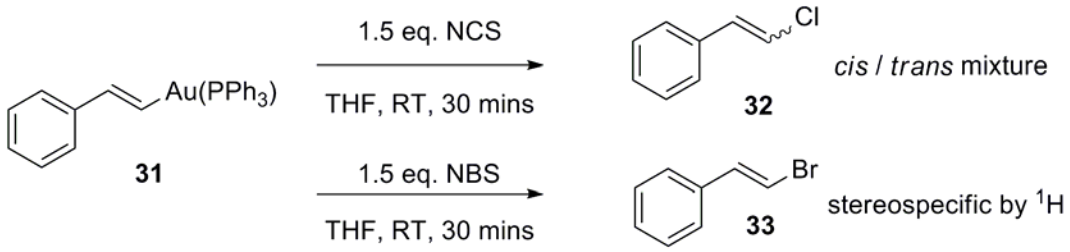


Scheme 2-11: Formation of organometallic gold(I) complexes

[83] Cheong, P. H.-Y.; Morganelli, P.; Luzung, M. R.; Houk, K. N.; Toste, F. D. *J. Am. Chem. Soc.* **2008**, *130*, 4517-4526.

[84] Mohr, F.; Falvello, L. R.; Laguna, M. *Eur. J. Inorg. Chem.* **2006**, 833-838.

This complex was an off-white foam, and was reasonably stable when stored in a dessicator at RT. Complex **31** was then reacted with common X^+ electrophiles, such as *N*-bromosuccinimide and *N*-chlorosuccinimide.[85] The vinyl bromide **33** was generated stereospecifically as an all-*trans* isomer, while the chloride **32** gave a mixture of stereoisomers, which could be ascertained by ^{1}H *J*-coupling values (**Scheme 2-12**).[86] These experiments indicate that halodeauration - and protodeauration, by extension - may proceed by more than one mechanism depending on the electrophile utilized.



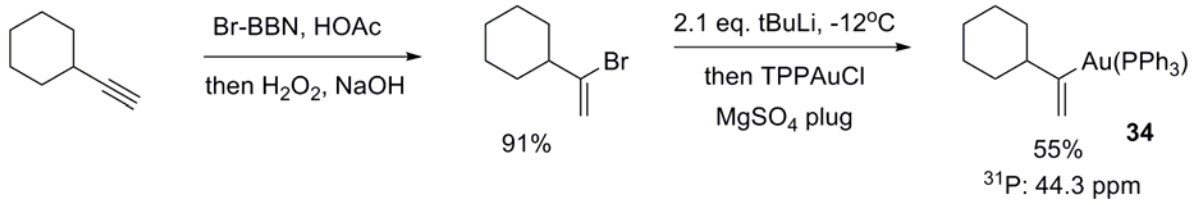
Scheme 2-12. Stereospecific halodeauration

To generate a closer model to our intermediate, a vinylcyclohexane gold complex (**34**) was prepared. **Scheme 2-13** illustrates a two-step synthesis of this organometallic using a protocol reported by Suzuki[87] for haloboration.

[85] Grandberg, K. I. *Russ. Chem. Rev.* **1982**, *51*, 249-264.

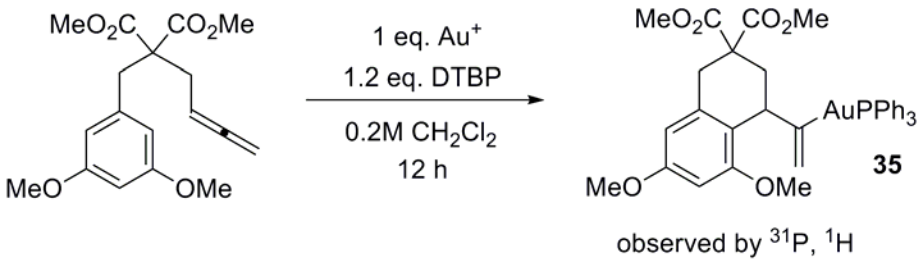
[86] Compounds matched NMR data reported in literature, see: Ye, C.; Shreeve, J. M. *J. Org. Chem.* **2004**, *69*, 8561-8563.

[87] Hara, S.; Dojo, H.; Takinami, S.; Suzuki, A. *Tetrahedron Lett.* **1983**, *24*, 731-734.



Scheme 2-13. Preparation of a (cyclohexylvinyl)gold(I) model system

Attempts to isolate discrete intermediates under the general reaction conditions met with failure, since protodeauration of the C-M bond is facile and rapid, even when using distilled solvents or catalytic base (K_2CO_3). Thus, a suitably strong noncoordinating proton acceptor was needed in order to prevent turnover, since rearomatization is a strong driving force. Currently under investigation in our labs is a protocol reacting aromatic substrates (see **Chapter 3**) with stoichiometric quantities of [(TPP)Au^+]($^-NTf_2$) and 2,6-di-*tert*-butylpyridine toward isolation of a vinylgold complex **35**. Crucial to our postulated mechanism is the ability to ascertain the structure of these compounds in the solid state to probe their role as viable intermediates (**Scheme 2-14**).[88]



Scheme 2-14. Attempts to trap a vinylgold catalytic intermediate (DTBP = 2,6-di-*tert*-butylpyridine)

[88] Tarselli, M. A. and Weber, D. *unpublished results*

2.5 Conclusions

An optimized system to generate chiral cyclohexenes from 1,6-eneallenes was adapted from a chance observation while probing new substrates for Pt(II) cyclization chemistry. The cyclohexenyl product skeleton is unusual as 5- and 7-membered ring products are usually observed for other metal catalysts. The gold catalyst is tolerant of esters, ethers, amides, and a variety of polar and nonpolar solvents. The catalyst is thought to selectively activate the allene over the alkene, generating a carbocationic intermediate which may undergo a solvent- or counterion-mediated elimination to produce the observed products. Studies are underway to isolate potential catalytic intermediates as discrete organometallic entities.

2.6 Experimental

I. General Information: All reactions with air- and water-sensitive compounds were performed in an inert atmosphere glovebox or under Schlenk techniques using unpurified cylinder N_2. Nitromethane was purified from 95% commercial grade material (Aldrich) following IUPAC recommended methods.[89] Toluene, dichloromethane, and diethyl ether were sparged with Ar and dried over activated alumina columns. Tetrahydrofuran was purified by distillation from sodium benzophenone ketyl. If necessary, most commercial organic reagents could be purified by vacuum transfer or distillation before use. Allenyl bromide was prepared according to a procedure developed by Molander.[90] All

[89] Coetzee, J. F.; Chang, T.-H. *Pure Appl. Chem.* **1986**, *58*, 1541-1555.

[90] Molander, G.; Cormier, E. P. *J. Org. Chem.* **2005**, *70*, 2622-2626.

organometallic stocks were titrated prior to use. NMR spectra were acquired with Bruker AMX300, 400, and 500 MHz spectrometers, and shifts are given relative to tetramethylsilane (0.00 ppm). ^{31}P NMR is referenced to 85% H_3PO_4 (0.00 ppm). All coupling constants are reported in Hz. Enantiomeric excess of products **2, 8, 10, 12,** and **14** were measured using a chiral gas chromatograph (Hewlett-Packard) or supercritical fluid chromatography (Berger SFC) for compounds **4** and **6**. GC mass spectra were recorded on an Agilent spectrometer with He carrier gas at 120-150 ^{o}C / 16 mins with FTID detection. High resolution mass spectra were obtained on a Bruker BioTOF II, usually as sodium (M + 23) or ESI+ adducts.

II. General Procedure for Gold Catalyst Formation: In a drybox 2.0 equiv. of (DMS)AuCl were added to 1.02 equiv. of a chiral bidentate ligand in a 1 dram vial equipped with a stirbar. The two components were dissolved in 1 mL DCM and stirred 2-4 hrs. The solution was concentrated to dryness on a rotovap outside the drybox, dried at high vacuum overnight, then analyzed by ^{1}H NMR to verify that no DMS remained in the catalyst. If necessary, the catalyst could be purified by elution through a small silica plug with dichloromethane, and recrystallization from DCM / pentane vapor overnight. Purity (>90%) was assayed by the presence of 1 peak in $[^{1}H]^{31}P$ NMR. The catalysts were stored in a drybox for further use.

(*S,S*)-DIOP(AuCl)$_2$: ^{31}P (162 MHz): δ 26.55

***R*-QUINAP(AuCl)**: ^{31}P (162 MHz): δ 23.87

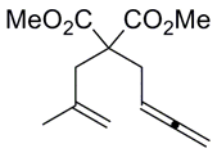
***S*-xyl[PHANEPHOS](AuCl)$_2$:** ^{31}P (162 MHz): δ 32.10

***R*-xylSOLPHOS(AuCl)$_2$:** ^{31}P (162 MHz): δ 20.13

***R*-SYNPHOS(AuCl)$_2$:** ^{31}P (162 MHz): δ 23.35

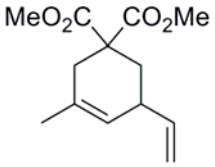
***R*-4,4'-(TMS)$_2$BINAP(AuCl)$_2$:** ^{31}P (162 MHz): δ 25.20

III. **General Cycloisomerization procedure:** In a glove box charged with nitrogen, an oven-dried 1 dram vial was charged with (*R*)-3,5-xylyl-BINAP(AuCl)$_2$ (5.0 mg, 4.2 μmol), silver triflate (3.0 mg, 12.6 μmol), and nitromethane (0.8 mL). After stirring the suspension for 5 min, **1** (20 mg, 84 μmol) was added. A yellow color was usually noted within 10 min, and the reaction was usually blue-grey upon completion. After consumption of starting material (^{1}H NMR), the reaction mixture was loaded directly onto a silica gel column for purification, and eluted with hexanes/ethyl acetate.

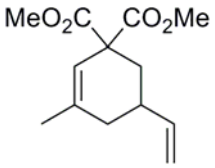


Dimethyl-2-(1,2-butadienyl)-2-(2-methylallyl)malonate (5): To a Schlenk tube charged with 1.2 equiv. 60% NaH emulsion under N_2 was added 2-methallyldimethylmalonate as a 1 M solution in THF. When bubbling ceased and the suspension became a clear solution, allenyl bromide (1.3 equiv.) was added as a 25% solution in Et_2O. The reaction was stirred overnight at RT until TLC indicated consumption of starting material. The reaction was quenched with distilled H_2O, the aqueous extracted with ether (3x), and the organic layer dried over $MgSO_4$. After concentration, a silica gel column with 8 : 1 Hex / EtOAc yielded 45-70% of desired adduct as well as 10% of starting material, each as a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.94 (pent, 1 H, J = 6.0 Hz), 4.86 (s, 1 H), 4.73 (s, 1 H), 4.64 (dd, 2 H,

J = 4.8 Hz), 3.69 (s, 6 H), 2.71 (s, 2 H), 2.61 (dt, 2 H, J_1 = 6.6 Hz, J_2 = 2.4 Hz), 1.63 (s, 3 H). ^{13}C (100 MHz): 209.9, 171.4, 140.3, 115.9, 84.38, 74.57, 57.40, 52.32, 40.03, 31.76, 23.11.

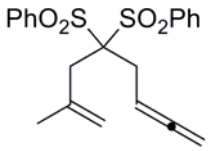


Dimethyl 3-methyl-5-vinylcyclohex-3-ene-1,1'-dicarboxylate [major] (6a): Prepared according to the General Cycloisomerization procedure (*vide supra*). 83% yield as an isomeric mixture with **6b** after silica gel purification in 1:7 EtOAc : Hex. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.69 (m, 1H), 5.23 (s, 1 H), 5.00 (dd, 2 H, J_1 = 24 Hz, J_2 = 16 Hz), 3.71 (s, 6 H), 2.79 (bm, 1 H), 2.52, 2.32 (AB doublet, 2 H, J_1 = 112 Hz, J_2 = 16 Hz), 2.40 (m, 2 H), 1.69 (s, 3 H). ^{13}C (100 MHz): 23.85, 33.86, 35.40, 37.97, 53.06, 114.49, 123.32, 132.33, 141.88, 171.83. Enantiomeric excess (Cyclosil-B column, 20 psi / H_2 carrier gas / 90 ^{o}C – 115 ^{o}C, 70 min.): *ent-1*, 51.6 min.; *ent-2*, 52.4 min. HRMS Expected 261.110 (M + Na), Found 261.106.

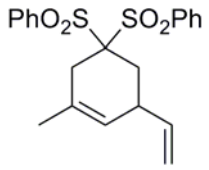


Dimethyl 3-methyl-5-vinylcyclohex-2-ene-1,1'-dicarboxylate [minor] (6b): Prepared according to the General Cycloisomerization procedure (*vide supra*). 83% as isomer mixture with **6a** after silica gel purification in 1:7 EtOAc : Hex. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.69 (m, 1 H), 5.59 (s, 1 H), 5.00 (dd, 2 H, J_1 = 24 Hz, J_2 = 16 Hz), 3.69 (s, 6 H), 2.79 (bm, 1 H), 2.52, 2.32 (AB doublet, 2 H, J_1 = 11.2 Hz, J_2 = 16 Hz), 2.40 (m, 2 H), 1.69 (s, 3 H). ^{13}C (100 MHz): 23.90, 34.12, 35.49, 54.12, 114.31, 118.20, 138.20, 142.02,

172.76. Enantiomeric excess (Cyclosil-B column, 20 psi / H_2 carrier gas / 90 ^oC – 115 ^oC, 70 min.): *ent-1*, 61.2 min.; *ent-2*, 62.7 min. HRMS Expected 261.110 (M + Na), Found 261.106.

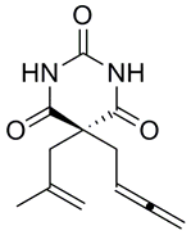


2-(1,2-butadienyl)-2-methylallyl-bis(phenylsulfone) (7): Prepared by reaction of methallylbis(phenylsulfone) (180 mg, 0.54 mmol) with triphenylphosphine (253 mg, 0.96 mmol) and allenyl alcohol (93 mg, 0.59 mmol) in toluene at 0 ^oC, then portionwise addition of 2,2'-azodicarbonyl dipiperidine (200 mg, 0.86 mmol) and stirring at RT overnight. After silica gel purification in 1:2 → 1:1 EtOAc : Hex, 363 mg (55%) was isolated. ^1H NMR (300 MHz): δ 1.82 (s, 3H), 3.05 (s, 2H), 3.19 (dt, 2H), 4.78 (td, 2H), 5.07 (d, 2H), 5.42 (p, 1H), 7.61 (t, 4H), 7.77 (t, 2H), 8.07 (d, 4H). ^{13}C (100 MHz): 24.48, 29.63, 36.57, 75.76, 83.87, 91.48, 118.82, 128.34, 131.48, 134.39, 137.05, 137.69, 209.92. HRMS-ESI+: 425.086 calculated for ($C_{21}H_{22}O_4S_2$ + Na), found 425. 081.

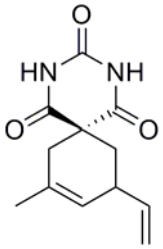


3-Methyl-5-vinylcyclohex-3-ene-1,1'-bis(phenylsulfone) (8): Prepared according to the General Cycloisomerization Procedure (*vide supra*). 82% isolated after 1:1 hexane / ethyl acetate column. ^1H NMR (400 MHz, $CDCl_3$): δ 1.61 (s, 3H), 2.04 (m, 1H), 2.46-2.49 (m, 1H), 2.51 (d, 1H, *J* = 19.2 Hz), 2.87 (d, 1H, *J* = 20 Hz), 3.20 (bm, 1H), 5.05 (m, 2H), 5.26 (s, 1H), 5.59 (p, 1H, *J* = 8 Hz), 7.56 (m, 4H), 7.66 (m, 2H), 8.01 (m, 4H). ^{13}C NMR

(166 MHz): 23.05, 29.39, 29.92, 37.38, 88.18, 115.25, 123.79, 128.48, 128.55, 128.80, 130.58, 131.41, 134.42, 134.48, 135.99, 140.30. HRMS-ESI+: 425.086 calculated for ($C_{21}H_{22}O_4S_2$ + Na), found 425.082. Enantiomeric excess (Berger SFC Chiralcel OD-H, 200 psi, 3% MeOH in CO_2, 1.9 mL/min, 35 ^oC oven and column temp) *ent*-1 = 20.02 min, *ent*-2 = 24.89 min.



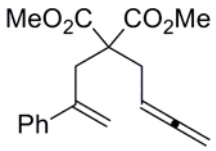
2-Methallyl-2-(1,2-butadienyl) barbituric acid (9): Prepared according to Pohlhaus and Johnson through bis(amidation) of urea with **1** in DMSO / KOtBu.[91] 74% isolated from silica flash column (ethyl acetate) as a white solid. ^1H NMR (400 MHz, $CDCl_3$): δ 1.67 (s, 1H), 2.67-2.71 (m, 4H), 4.72 (bs, 3H), 4.86 (s, 1H), 4.98 (p, 1H). ^{13}C NMR (166 MHz): 23.57, 37.05, 46.07, 56.04, 83.63, 116.08, 138.83, 148.55, 171.52, 209.08.



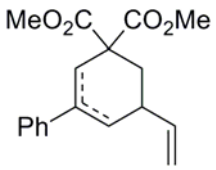
8-Methyl-10-vinyl-2,4-diazaspiro[5.5]undec-7-ene-1,3,5-trione (10): Prepared following General Cycloisomerization Procedure (*vide supra*). ^1H NMR (400 MHz, $CDCl_3$): δ 1.76 (s, 3H), 2.01-2.24 (m, 3H), 2.74-2.91 (m, 2H), 5.04 (dd, 2H), 5.36 (s, 1H), 5.64 (p, 1H), 7.91-8.22 (bd, 2H). ^{13}C NMR (166 MHz): 14.39, 23.44, 36.99, 50.46, 60.10,

[91] Pohlhaus, P. D.; Johnson, J. S. *J. Am. Chem. Soc.* **2005**, *127*, 16014-16015 (SI p.18).

114.62, 122.28, 141.34. Enantiomeric excess (Berger SFC, Chiralcel OD-H column, 200 psi, 1.9% MeOH / CO_2, 2 mL/min, 35 ^oC oven, 38 ^oC column) *ent*-1 = 68.11 min, *ent*-2 = 69.87 min. HRMS(ESI+) Expected 235.108, found 235.110.

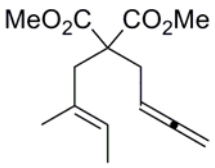


Dimethyl-2-(1,2-butadienyl)-2-(2-phenylmethylallyl)-malonate (11): Prepared as above from allenylmalonate and bromo-alpha-methylstyrene. ^1H NMR (400 MHz, $CDCl_3$): δ 7.19-7.24 (m, 5 H), 5.21, 5.11 (s, 2 H), 4.83 (m, 1 H), 4.59 (m, 2 H), 3.37 (s, 6 H), 3.15 (s, 2 H), 2.50 (d, 2 H, J = 7.8 Hz). ^{13}C (100 MHz): 30.91, 37.09, 52.00, 57.40, 74.61, 84.25, 118.79, 126.87, 127.38, 127.43, 127.99, 128.19, 141.37, 144.25, 170.76, 209.98.

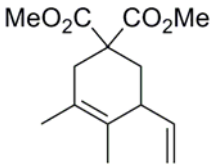


Dimethyl 3-phenyl-5-vinylcyclohex-3-ene-1,1' dicarboxylate (12a,b): Prepared according to the General Cycloisomerization procedure (*vide supra*). 57% isolated yield, as mixture of regioisomers. ^1H NMR (400 MHz, $CDCl_3$): δ 7.31-7.50 (m, 5 H), 5.84 (s, 1 H), 5.75 (m, 1 H), 5.02-5.12 (m, 2 H), 3.72 (s, 6 H), 3.45 (m, 2 H), 3.10, 2.72 (dd, 2 H, J_1 = 152 Hz, J_2 = 16 Hz), 2.53 (m, 3 H). ^{13}C (100 MHz): 32.91, 33.11, 33.38, 35.25, 38.04, 52.02, 52.66, 84.83, 125.5, 125.6, 125.9, 127.4, 128.3, 141.7, 171.5. HRMS Expected 323.126, found 323.123. Enantiomeric excess (Cyclosil-B column, 20 psi / H_2 carrier gas / 159 ^oC –

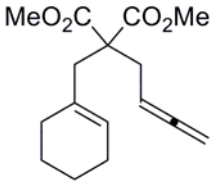
165 ^{o}C (0.1 / min), 120 min.): 8a *ent-1* = 55.84 min, *ent-2* = 56.12 min; 8b *ent*-1 = 63.29 min, *ent*-2 = 64.04 min.



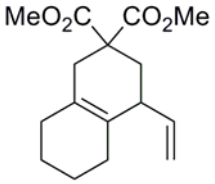
Dimethyl-2-(1,2-butadienyl)-2-(1,2-dimethylallyl)-malonate (13): Prepared as above from 10 and 4-bromo-buta-1,2-diene (5). 61% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.26 (q, 1 H, *J* = 6.8 Hz), 4.92 (m, 1 H), 4.60 (m, 2 H), 3.68 (s, 6 H), 2.55 (m, 2 H), 1.47-1.61 (m, 6 H). ^{13}C (100 MHz): 13.57, 16.32, 24.08, 31.71, 42.14, 52.21, 57.67, 74.47, 84.53, 124.78, 130.25, 171.59, 209.95.



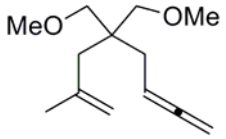
Dimethyl 3,4-dimethyl-5-vinylcyclohex-3-ene-1,1' dicarboxylate (14): Prepared according to the General Cycloisomerization procedure (*vide supra*). 81% isolated yield. ^{1}H NMR: δ 5.51 (m, 1 H), 5.02 (m, 2 H), 3.72 (s, 6 H), 2.79 (m, 1 H), 2.47 (d, 2 H, *J* = 12.4 Hz), 2.32 (m, 2 H), 1.61-1.65 (bs, 6 H). ^{13}C (100 MHz): 16.81, 19.51, 26.15, 32.89, 34.84, 36.60, 43.80, 52.39, 115.72, 124.62, 131.01, 141.34. Enantiomeric excess (Cyclosil-B column, 20 psi / H_2 carrier gas / 110 ^{o}C – 125 ^{o}C, 55 min.): *ent-1* = 55.8 min.; *ent-2* = 57.1 min.



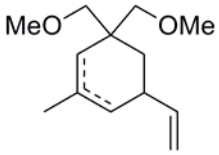
Dimethyl-2-(1,2-butadienyl)-2-(cyclohex-1-enylmethyl)-malonate (15): ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.53 (m, 4H), 1.78 (bs, 2H), 1.97 (bs, 2H), 2.59 (dt, 2H), 2.64 (s, 2H), 3.70 (s, 6H), 4.64 (dt, 2H), 4.95 (p, 1H), 5.47 (s, 1H). ^{13}C NMR (166 MHz): 21.84, 22.78, 25.30, 28.85, 31.77, 40.75, 52.14, 57.38, 74.33, 84.39, 126.94, 132.25, 171.51, 209.77.



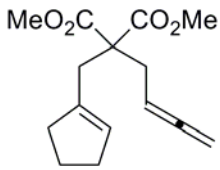
Dimethyl 4-vinyl-3,4,5,6,7,8-hexahydronaphthalene-2,2(1H)-dicarboxylate (16): Prepared according to the General Cycloisomerization procedure (*vide supra*), 70% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.40 (m, 3H), 1.64 (m, 4H), 1.81 (dd, 1H), 1.89 (m, 3H), 2.34 (m, 3H), 2.65 (m, 1H), 3.69 (d, 8H), 5.01 (td, 2H), 5.46 (dt, 1H). ^{13}C NMR (166 MHz): 22.75, 22.99, 28.04, 30.47, 34.74, 35.47, 43.07, 52.42, 116.30, 126.59, 127.90, 141.03. Cyclosil-B column, 20 psi / H_2 carrier gas / 125 ^{o}C –170^{o}C, 55 min.): *ent-1*, 27.6 min.; *ent-2*, 27.9 min. HRMS Expected 265.144 ($M + H^{+}$), Found 265.143.



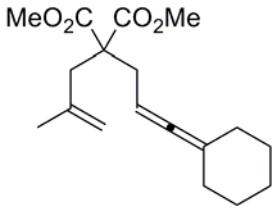
1,3-Dimethoxy-2-(1,3-butadienyl)-2-(methallyl)propane (17): Prepared by lithium aluminum hydride reduction of **5** in ether followed by etherification with NaH / MeI in tetrahydrofuran.[92] Yield: 77% ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.74 (s, 3H), 2.03 (m, 4H), 3.16 (s, 4H), 3.28 (s, 6H), 4.59 (m, 2H), 4.69 (s, 1H), 4.87 (s, 1H), 5.05 (p, 1H). ^{13}C (100 MHz): 24.93, 31.89, 38.86, 42.43, 58.72, 73.31, 74.67, 85.35, 114.71, 142.15, 209.81. HRMS (ESI+) Expected 233.152, found 233.151.



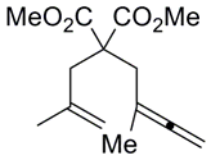
1,1'-(dimethoxymethyl)-3-methyl-5-vinylcyclohex-3-ene (18a,b): Prepared according to the General Cycloisomerization procedure (*vide supra*). 77% isolated with 1:10 ethyl acetate : hexane silica column. ^{1}H NMR (**18a**) (400 MHz, $CDCl_3$): δ 5.78 (m, 1H), 5.23 (s, 1H), 4.95 (m, 2H), 3.20-3.36 (m, 10H), 2.74 (m, 1H), 2.38 (m, 1H), 1.60-1.92 (m, 8H), 1.12 (m, 3H). ^{13}C (100 MHz): 23.82, 29.60, 32.74, 34.48, 36.24, 41.56, 59.26, 73.71, 75.27, 78.68, 112.40, 122.89, 143.05. Enantiomeric excess (Cyclosil-B column, 20 psi / H_2 carrier gas / 80 ^{o}C – 90 ^{o}C, 45 min.): *ent-1* = 31.83 min.; *ent-2* = 32.84 min



Dimethyl-2-(1,2-butadienyl)-2-(cyclopent-1-enylmethyl)-malonate (19): ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.43 (s, 1H), 4.92 (m, 1H), 4.64 (s, 2H), 3.69 (s, 6H), 2.78 (s, 2H), 2.58 (m, 2H), 2.38 (dt, 1H), 2.24 (m, 2H), 2.10 (m, 2H), 1.78 (m, 2H). ^{13}C (100 MHz): 209.9, 171.3, 138.3, 129.5, 84.24, 74.36, 57.18, 52.21, 35.27, 33.68, 32.17, 31.77, 23.59.

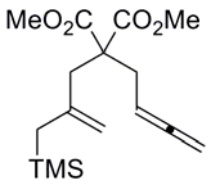


Dimethyl-2-(*gem*-cyclohexenyl-1,2-butadienyl)-2-(2-methylallyl)malonate (21): ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.01 (m, 1H), 5.62 (s, 1H), 5.27 (m, 1H), 4.85 (s, 1H), 4.72 (s, 1H), 3.67 (s, 6H), 2.67 (s, 4H), 2.05 (s, 4H), 1.67 (m, 6H), 1.56 (m, 3H).

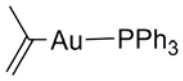


Dimethyl-2-(3-methyl-1,2-butadienyl)-2-(2-methylallyl)malonate (23): ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.83 (s, 1H), 4.69 (s, 1H), 4.57 (dd, 2H), 3.66 (s, 6H), 2.78 (s, 2H), 2.59 (t, 2H), 1.62 (s, 6H).

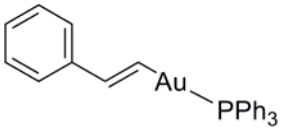
***R*-3,5-xylyl-BINAP(AuOTf)$_2$ (26)**: ^{31}P (162 MHz): δ 17.71. ^{19}F: δ -77.52.



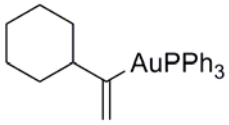
Dimethyl-2-(1,2-butadienyl)-2-(2-trimethylsilylmethallyl)malonate (27): ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.92 (p, 1H), 4.60 (m, 4H), 3.67 (s, 6H), 2.61 (s, 4H), 1.37 (s, 2H), -0.03 (s, 9H).



2-Propenylgold(I) triphenylphosphine (30): ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50-7.42 (m, 15H), 5.69 (s, 1H), 4.96 (s, 1H), 2.11 (s, 3H). ^{31}P (162 MHz): δ 43.49 ppm.



***trans*-beta-styrenylgold(I) triphenylphosphine (31):** ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.73 (d, 1H, J = 15 Hz), 7.57-7.35 (m, 22 H), 6.94 (d, 1H, J = 15 Hz). ^{31}P (162 MHz): δ 45.20 ppm.



1-cyclohexyl-1-[triphenylphosphine gold(I)]-ethylene (34): ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.55-7.42 (m, 15H), 5.60 (d, 1H), 4.87 (s, 1H), 2.38 (m, 1H), 1.74 (t, 3H), 1.60-1.12 (m, 6H). ^{31}P (121 MHz): δ 44.56 ppm.

Chapter 3

Gold(I)-Catalyzed Allene Hydroarylation

3.1 Introduction - The Friedel-Crafts Reaction

The Friedel-Crafts reaction is well-studied in the pantheon of known organic transformations, and much research has been directed towards improvement of the original conditions reported by Charles Friedel and James Crafts in 1877 - Al shavings in benzene at 200 ^{o}C![93] The reaction is formally an electrophilic aromatic substitution where the electrophile is activated through metal complexation (**Scheme 3-1**).

Scheme 3-1. Simplified diagram of the Friedel-Crafts Reaction

Several recent reviews[94] highlight progress towards Friedel-Crafts acylation, alkylation, additions to unsaturated bonds, and even enantioselective variants which now run at or below room temperature with catalytic metals.[95]

---

[93] Olah, G. A. *Friedel Crafts and Related Reactions*; Wiley-Interscience: New York, **1965**.

[94] a) Poulsen, T. B.; Jørgensen, K. A. *Chem. Rev.* **2008**, *108*, 2903-2915. b) Bandini, M.; Melloni, A.; Umani-Ronchi, A. *Angew. Chem. Int. Ed.* **2004**, *43*, 550-556. c) Bandini, M.; Emer, E.; Tommasi, S.; Umani-Ronchi, A. *Eur. J. Org. Chem.* **2006**, 3527-3544. d) Nevado, C.; Echavarren, A. M. *Synthesis* **2005**, 167-182.

The Friedel-Crafts reaction can be described as hydroarylation when the addition of an arene takes place across an unsaturated π-system, such as an alkene, alkyne, allene, or benzyne. Intermolecular hydroarylation has been explored using catalytic Ru, Pt, Pd, and Au for over twenty years.[96] Shown below are several examples of gold-catalyzed hydroarylations to emerge recently. Reetz[97] and coworkers (**Eq. 1**) used a gold(III) catalyst to activate ethynylarenes towards attack by relatively hindered mesitylene. He (**Eq. 2**) reported a similar gold(III) C-H activation of ynoates,[98] discovering that electron-deficient alkynes could even react without solvent. While investigating the mechanism behind his phenol synthesis,[99] Hashmi discovered that furans could be trapped by an exogenous alkyne partner as a bis-aryl adduct[100] instead of undergoing [4+2] thermal cycloaddition (**Eq. 3**).

---

[95] a) Evans, D. A.; Scheidt, K. A.; Fandrick, K. R.; Lam, H. W.; Wu, J. *J. Am. Chem. Soc.* **2003**, *125*, 10780-10781. b) Evans, D. A.; Fandrick, K. R.; Song, H.-J.; Scheidt, K. A.; Xu, R. *J. Am. Chem. Soc.* **2007**, *129*, 10029-10041.

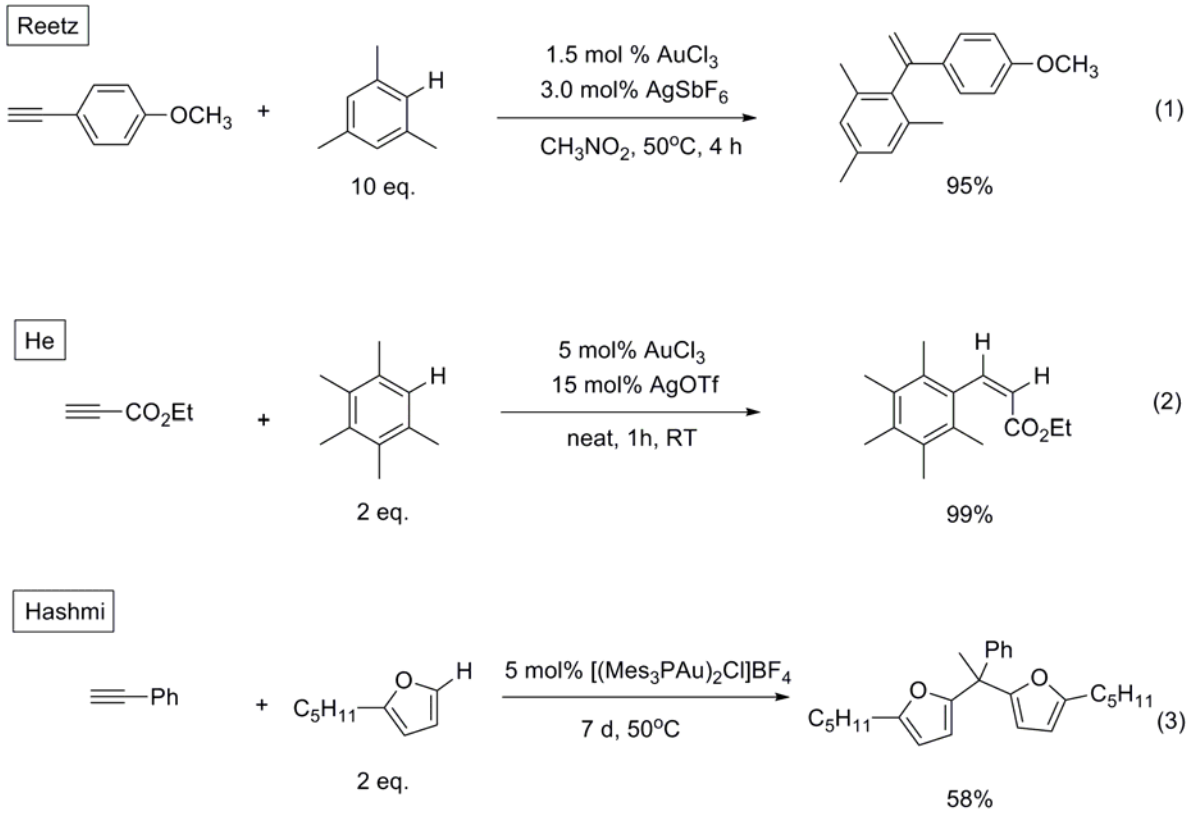
[96] Soriano, E.; Marco-Contelles, J. *Organometallics* **2006**, *25*, 4542-4553.

[97] Reetz, M. T.; Sommer, K. *Eur. J. Org. Chem.* **2003**, 3485-3496.

[98] Shi, Z.; He, C. *J. Org. Chem.* **2004**, *69*, 3669-3671.

[99] Hashmi, A. S. K.; Frost, T. M.; Bats, J. W. *Org. Lett.* **2001**, *3*, 3769-3771.

[100] Hashmi, A. S. K.; Blanco, M. C. *Eur. J. Org. Chem.* **2006**, 4340-4342.



Methods reported for the hydroarylation of allenes have relied mostly on control through intramolecular tethering of the reactive arene to the allene. Shown in the following equations are examples of arenes adding to allenes to form 6-membered rings. Widenhoefer has reported both highly active catalysts[101] based on Buchwald biaryl phosphines,[102] and enantioselective catalysts for the hydroarylation of allenes (**Eq. 4**) with indoles.[103] Ohno[104] disclosed 6-*endo* cyclization of tethered allenes (**Eq. 5**), which can be accelerated by the presence of trace protic acid.

---

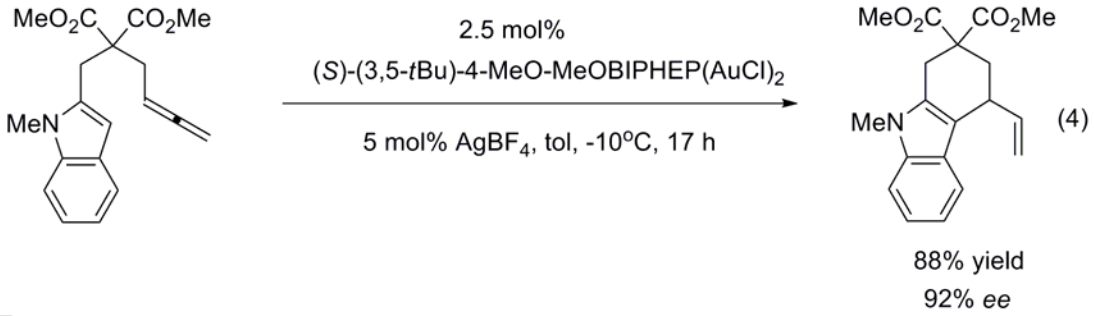
[101] Zhang, Z.; Liu, C.; Kinder, R. E.; Han, X.; Qian, H.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2006**, *128*, 9066-9073.

[102] Barder, T. E.; Biscoe, M. R.; Buchwald, S. L. *Organometallics* **2007**, *26*, 2183-2192.

[103] Liu, C.; Widenhoefer, R. A. *Org. Lett.* **2007**, *9*, 1935-1938.

[104] Watanabe, T.; Oishi, S.; Fujii, N.; Ohno, H. *Org. Lett.* **2007**, *9*, 4821-4824.

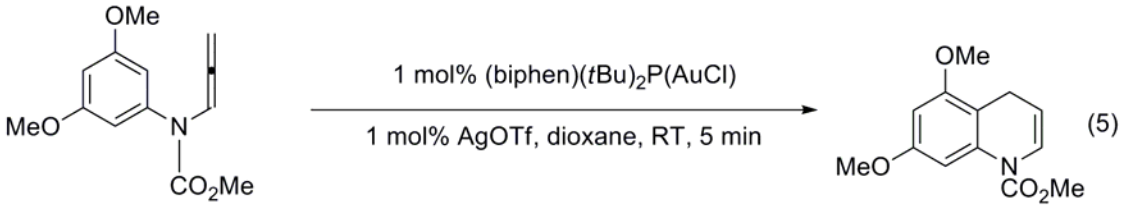
Widenhoefer



(4)

88% yield
92% *ee*

Ohno



(5)

92%

Existing gold-catalyzed hydroarylation reactions are therefore divided into two regimes:

1. Highly nucleophilic arenes (indole, pyrrole) with allenes

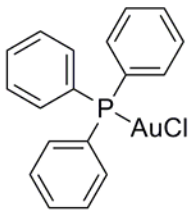
2. Less reactive arenes (benzene, mesitylene) with alkynes

Efforts in our group were focused towards inter- and intramolecular hydroarylation of allenes utilizing a wider range of arene nucleophilicity than previously considered.

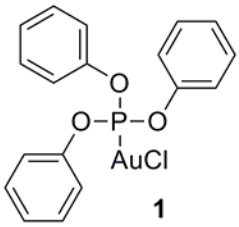
3.2 Gold(I)-Catalyzed *Intramolecular* Hydroarylation of Allenes [105]

While synthesizing substrates for the 1,6 Au(I)-catalyzed eneallene cycloisomerization,[106] a substrate with a trapping arene (3-methoxybenzyl allenyl malonate) was synthesized, and found to participate in the allene cyclization reaction, albeit at slower rates than the corresponding ene-allene with 5 mol% of (*R*)-xylylBINAP(AuCl)$_2$ / AgOTf catalyst. A small screen of more electrophilic catalysts was therefore undertaken to attempt to improve this initial result (**Table 3-1**).

Table 3-1. Reaction screening with electron-deficient ligands

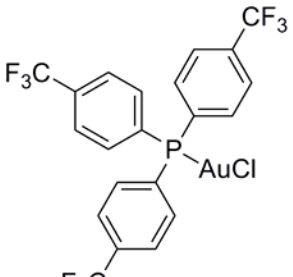


(TPP)AuCl



1

(TPOP)AuCl



(TFMP)AuCl

	(TPP)	(TPOP)	(TFMP)
Electronic Parameter (ν)	2068.9 cm^{-1}	2085.3 cm^{-1}	~2100 cm^{-1}
Cone angle (θ)	145°	128°	145°
Conversion	full, 4 h	**full, 45 mins**	<10%, 3 h

[105] Tarselli, M. A.; Gagné, M. R. *J. Org. Chem.* **2008**, *73*, 2439-2441.

[106] Tarselli, M. A.; Chianese, A. R.; Lee, S. J.; Gagné, M. R. *Angew. Chem. Int. Ed.* **2007**, *46*, 6670-6673.

As noted in **Table 3-1**, the Tolman electronic parameter (υ)[107] continues to increase as ligands become more electron deficient. The Tolman values are derived from a model system of $Ni(CO)_3L$, where the *trans* CO infrared stretching frequency is measured. The higher value indicates a stronger bond between the CO ligand and nickel, i.e., less contribution from phosphine donation into Ni d-orbitals.[108] This, in turn, indicates a more electropositive metal complex. Recent studies[3,4] have suggested that for "soft" Lewis acids, this increase in ligand electrophilicity causes the initiating group (alkyne, allene) to become more electropositive, which increases reactivity: i.e., $(TPOP)Au^+ > (TPP)Au^+$.

The steric contribution cannot be ignored in this consideration, which is represented by the cone angle (θ)[109,110] formed by the phosphorus substituents; a larger cone angle describes a more sterically encumbered ligand environment about the metal. The values presented in **Table 3-1** indicate that triphenylphosphite (TPOP) gold chloride **1** might possess a good balance of these two parameters, and further optimization was performed with this ligand (see **Table 3-2**). Compound **2** was utilized as a test substrate for this optimization, producing **3**, a tetrahydronaphthalene previously synthesized by Cook utilizing In(III) atom-transfer cyclization,[111] and by Ma from allylic alcohols treated with TFA.[112]

---

[107] Tolman, C. A. *Chem. Rev.* **1977**, *77*, 313-348.

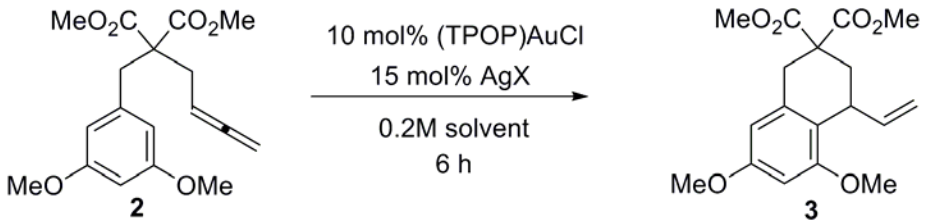
[108] Tolman, C. A. *J. Am. Chem. Soc.* **1970**, *92*, 2953-2956.

[109] Tolman, C. A. *J. Am. Chem. Soc.* **1970**, *92*, 2956-2965.

[110] DeVries, R. A.; Vosejpka, P. C.; Ash, M. L. In *Catalysis of Organic Reactions*; Herkes, F. E., Ed.; Marcel Dekker: New York, **1998**.

[111] a) Hayashi, R.; Cook, G. R. *Org. Lett.* **2006**, *8*, 1045-1048. b) Hayashi, R.; Cook, G. R. *Org. Lett.* **2007**, *9*, 1311-1314.

Table 3-2. Hydroarylation reaction optimization using (TPOP)AuCl as precatalyst



solvent	X^-	conversion (% **3**)
CH_2Cl_2	OTf	**92**
toluene	OTf	52
hexane	OTf	73
Et_2O	OTf	20
THF	OTf	36
$MeNO_2$	OTf	55
CH_2Cl_2	BF_4	**100** (75)
CH_2Cl_2	NTf_2	79 (80)
CH_2Cl_2	PF_6	35 (72)
CH_2Cl_2	SbF_6	89 (**88**)
CH_2Cl_2	OTs	51 (58)
CH_2Cl_2	ClO_4	92 (76)

Arenes for the intramolecular hydroarylation screen were chosen based upon representative examples from the Mayr π-nucleophilicity scale.[113] To devise this chart, Mayr and coworkers reacted arenes under standard conditions with electrophiles, and described the reactivity of each relative to one another in a given reaction (**Eq. 6**).

$$\log k = s(N + E) \tag{6}$$

[112] a) Ma, S.; Zhang, J. *Tetrahedron Lett.* **2002**, *43*, 3435-3438. b) Ma, S.; Zhang, J. *Tetrahedron* **2003**, *59*, 6273-6283.

[113] Mayr, H.; Kempf, B.; Ofial, A. R. *Acc. Chem. Res.* **2003**, *36*, 66-77.

The equation has two variables to describe nucleophilicity (*N,s*), and one to describe electrophilicity (*E*).[114] These values are derived from second-order rate constants of reaction of a variety of nucleophiles with a standardized electrophile set; the slope of the derived line (*s*) indicates the reaction fidelity - usually values between ($0.8 < s < 1.2$) are obtained.

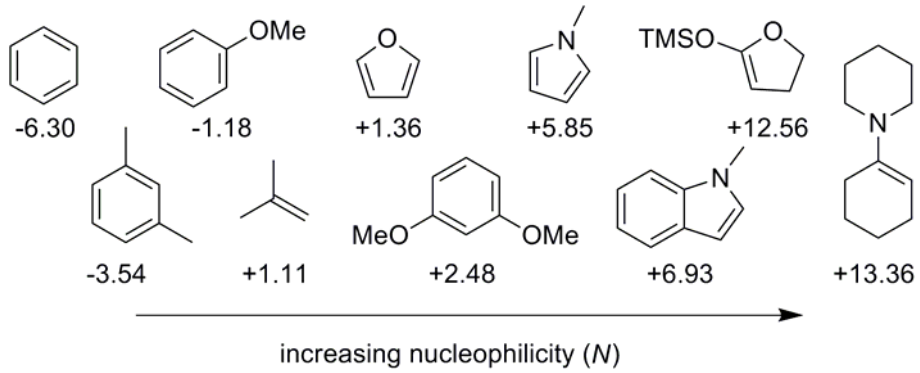
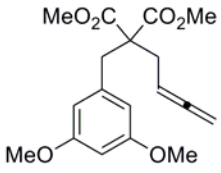
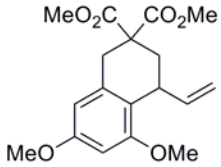
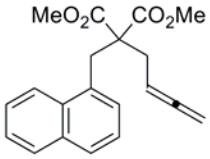
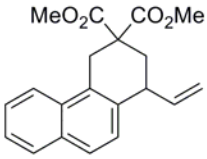
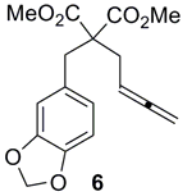
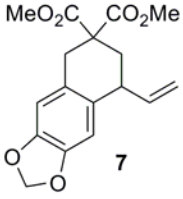
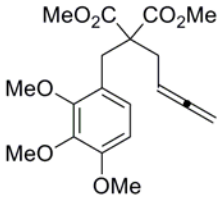
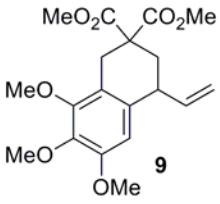
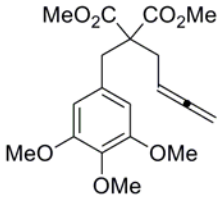
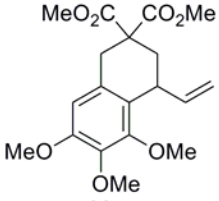
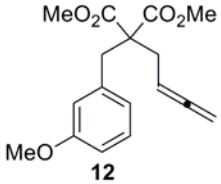
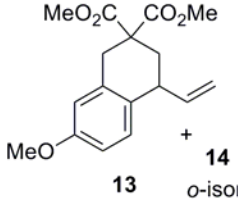
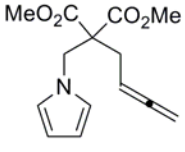
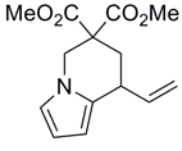


Figure 3-1. Mayr parameters (*N*) to compare arene π-nucleophilicity

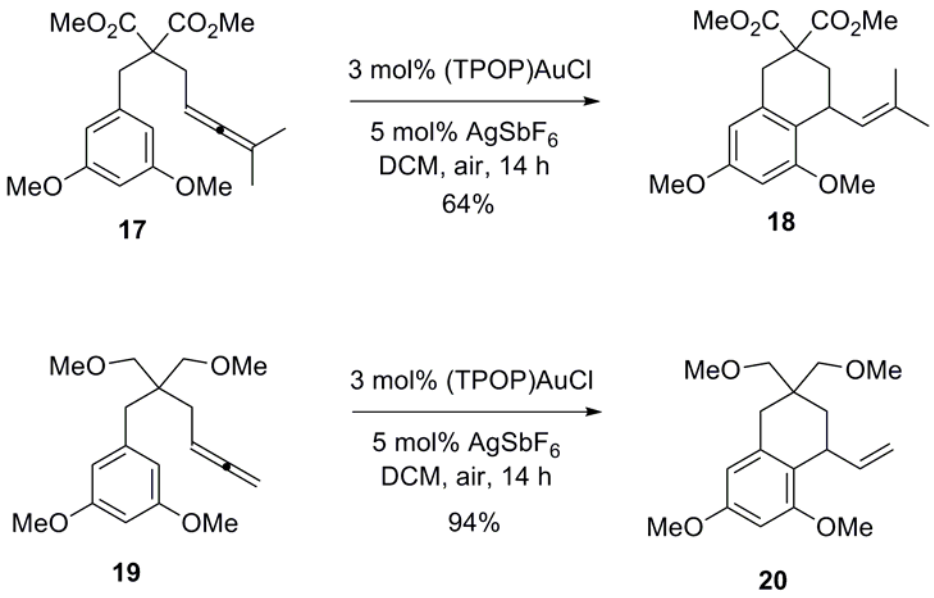
A 3,5-dimethoxyphenyl fragment, with a corresponding Mayr *N* parameter of +2.48 (**Figure 3-1**), is therefore expected to be more nucleophilic (read: more reactive) with the allene-gold electrophilic complex than a xylyl (*N* = -3.54) or furyl (*N* = +1.36) substituent, but not as reactive as an indole (*N* = +6.93). In **Table 3-3**, a number of functional arene-allene substrates are reported, ranging from *N* < 0.00 (napthalene **4**) to *N* = 5.85 (pyrrole **15**). Note that more nucleophilic arenes (**2**, **6**, **15**) proceed with good yield with only 1-3 mol% of catalyst, whereas all other reactions require 5-10 mol% just to proceed overnight.

[114] Mayr, H.; Patz, M. *Angew. Chem. Int. Ed.* **1994**, *33*, 938-957.

Table 3-3. Optimized conditions for allene hydroarylation

entry	substrate	cat.(mol%)	time (h)	product(s)	yield[c]
1	 **2**	3	6	 **3**	85%
2	 **4**	10	16	 **5**	87%
3	 **6**	3	16	 **7**	93%
4	 **8**	5	16	 **9**	59%
5	 **10**	5	16	 **11**	75%
6	 **12**	10	5	 + **14** *o*-isomer **13**	60% (4:1 *p: o*)
7	 **15**	3 1	6 24	 **16**	79% 73%

The chemistry is sufficiently general to permit substitution on the allene fragment (**17** → **18**) and does not require the bis(methylester) functionality to induce cyclization (**19** → **20**, **Scheme 3-2**).



Scheme 3-2. Variation in methylene linker and allene substitution

Interestingly, the Mayr parameters not only tracked well with reactivity, but also gave a cut-off point for reactivity vs. Wacker-type[115] hydrolysis of the allene to the resultant methyl ketone (**Scheme 3-3**). For example, 4-nitrophenyl, 4-tert-butylphenyl, and variously substituted iodo- and bromobenzenes were found to undergo allene hydrolysis readily, with cyclization observed only in the tert-butylphenyl case (~45% conversion to benzocycle with 15 mol% catalyst over 12 h). Heating these reactions to reflux or increasing [SM] (1.0 M) did not affect cyclization rates (**Figure 3-2**).

[115] Phillips, F. C. *Am. Chem. J.* **1894**, *16*, 255-277.

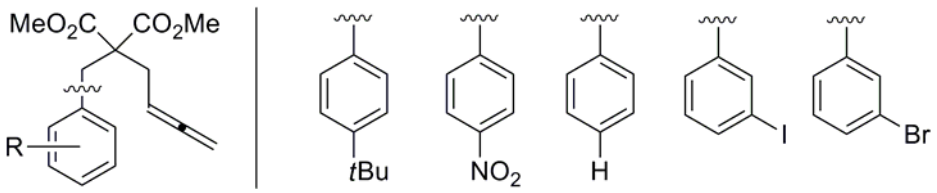
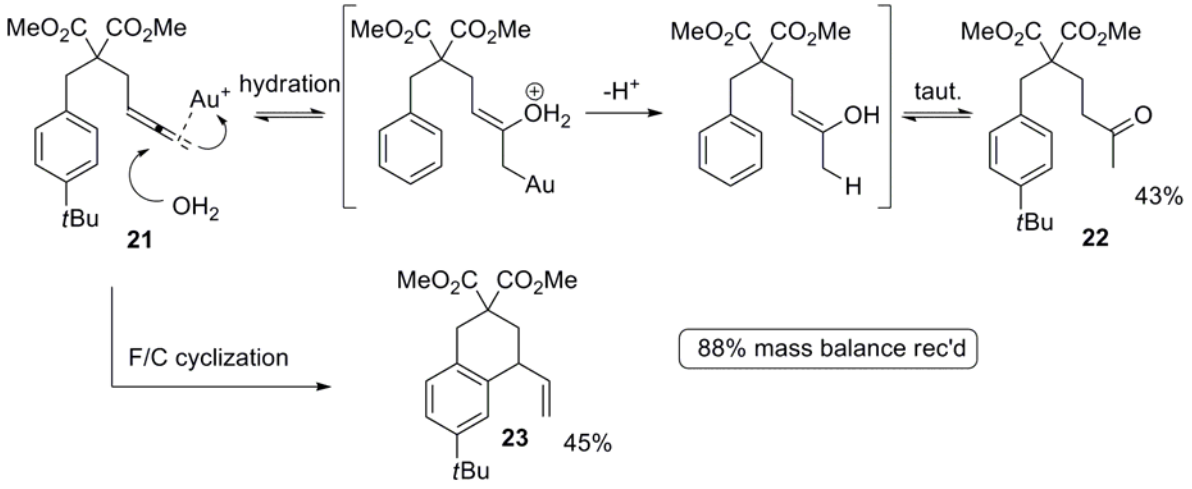


Figure 3-2. Arenes that hydrolyze to methyl ketones under standard conditions

The Mayr π-nucleophilicity parameter for toluene, -4.47, indicates that systems without electron-donating groups on the aromatic ring (Mayr parameter > +1.0) are likely not sufficiently nucleophilic for cyclization to compete with allene hydrolysis (**Scheme 3-3**).



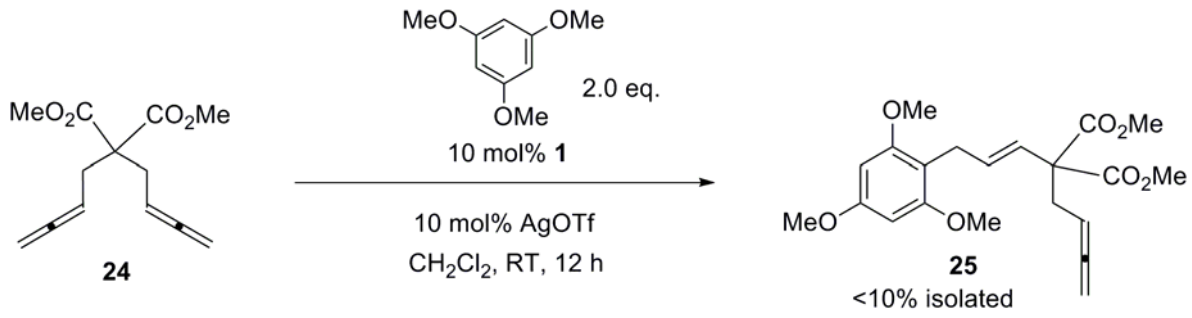
Scheme 3-3. Proposed hydration mechanism to form methyl ketones[116]

Attempts to diminish this hydrolysis utilizing activated 4Å molecular sieves, carbonate salts, or use of rigorously anhydrous solvent resulted only in diminished reactivity.

[116] Jahn, B. O.; Eger, W. A.; Anders, E. *J. Org. Chem.* **2008**, *73*, 8265-8273.

3.3 Gold(I)-Catalyzed *Intermolecular* Allene Hydroarylation[117]

While preparing substrates for allene hydroarylation chemistry, a small fraction of bis(allenyl)malonate **24** was recovered in addition to the desired mono-allene product. When subjected to the optimal conditions - 10 mol% (TPOP)AuCl, 10 mol% AgOTf, CH_2Cl_2 in the presence of an electron-rich arene (1,3,5-trimethoxybenzene) - minimal conversion of **24** to the mono-hydroarylated product **25** was noted (**Scheme 3-4**).



Scheme 3-4. Initial reaction discovery for intermolecular hydroarylation

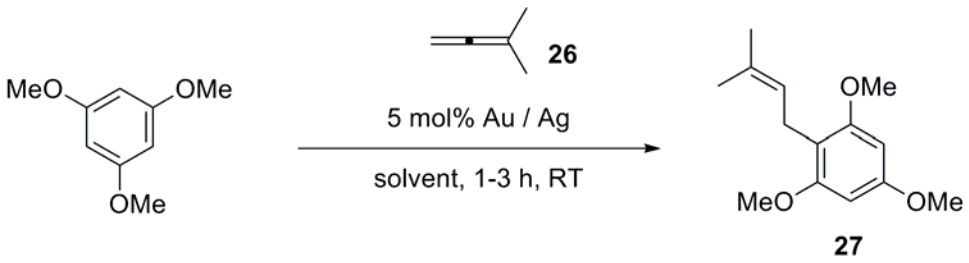
As evidenced by **Scheme 3-4**, only one of two allenes reacts in this chemistry, so the reaction was pared down to reaction of a nucleophilic arene with a simplified monoallene (1,1-dimethylallene **26**[118]) to produce prenylated arene **27**,[119] an intermediate in many plant-derived natural products (**Scheme 3-5**).

---

[117] Tarselli, M. A.; Liu, A.; Gagné, M. R. *Tetrahedron* **2008**, *accepted for publication*.

[118] Available from Aldrich Chemical Co.

[119] Gulácsi, K.; Litkei, G.; Antus, S.; Szántay, C.; Darkó, L. L.; Szelényi, J.; Haskó, G.; Vizi, S. *Arch. Pharm. Med. Chem.* **2001**, *334*, 53-61.



Scheme 3-5. Optimization reaction

Prenylated arenes are ubitquitous in phytochemistry (**Figure 3-3**), and have a wide array of applications in pest control, herbicides, and even human medicine.[120] Caespitin,[121] derrubone,[122] and pawhuskin A[123] are just three of thousands of medicinally relevant phloroglucinol derivatives isolated to date.[124]

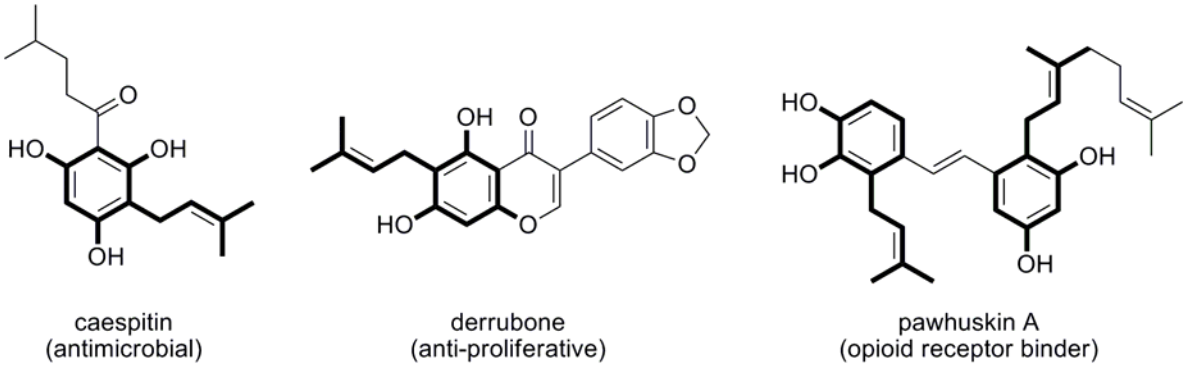


Figure 3-3. Naturally ocurring prenylated phloroglucinols

[120] Mizobuchi, S.; Sato, Y. *Agric. Biol. Chem.* **1985**, *49*, 719-724.

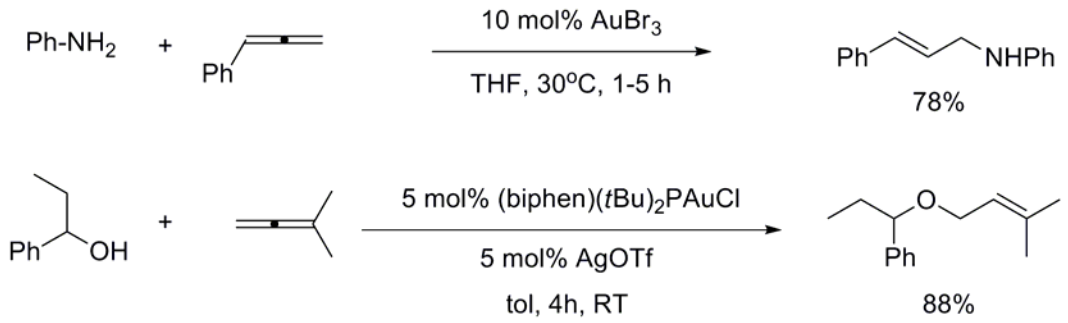
[121] Van der Schyf, C. J.; Dekker, T. G.; Fourie, T. G.; Snyckers, F. O. *Antimicrob. Agents Chemother.* **1986**, *30*, 375-381.

[122] Hastings, J. M.; Hadden, M. K.; Blagg, B. S. J. *J. Org. Chem.* **2008**, *73*, 369-373.

[123] Neighbors, J. D.; Buller, M. J.; Boss, K. D.; Wiemer, D. F. *J. Nat. Prod.*, *ASAP*.

[124] Singh, I. P.; Bharate, S. P. *Nat. Prod. Rep.* **2006**, *23*, 558-591.

As shown by **Table 3-4** (below), substituted gold(I) phosphite complexes are optimal in this reaction. Of interest is that the Buchwald-type ligand listed in entry 6 and the carbene ligand in entry 7 are not as active here as they are in intermolecular hydroamination reported by Yamamoto[125] or hydroalkoxylation reported by Widenhoefer[126] (**Scheme 3-6**).



Scheme 3-6. Yamamoto (2006) and Widenhoefer (2008) intermolecular allene additions

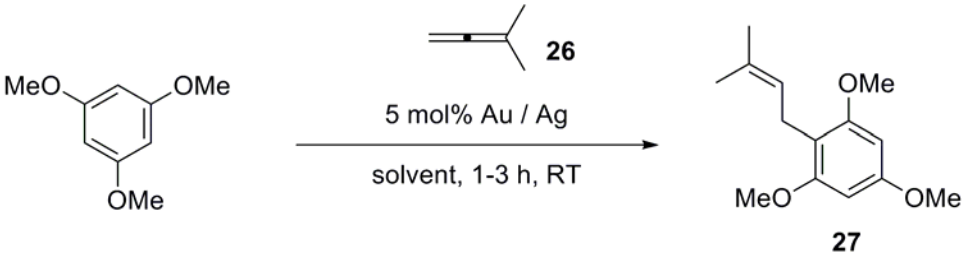
Additionally, the steric component of the phosphite ligands (see **Table 3-1**) plays an interesting role: 4-substituted aryl phosphites were more reactive than substitution in the 2- or 3- position, and electron-withdrawing phosphites led to more reactive catalysts.[127] After the screen, tris(4-chlorophenyl)phosphite gold(I) chloride [$(4\text{-ClPhO})_3\text{PAuCl}$] **28** paired with a highly dissociated $^{-}BF_4$ counterion were the most active catalyst combination.

[125] a) Nishina, N.; Yamamoto, Y. *Angew. Chem. Int. Ed.* **2006**, *45*, 3314-3317. b) Nishina, N.; Yamamoto, Y. *Synlett* **2007**, 1767-1770.

[126] Zhang, Z.; Widenhoefer, R. A. *Org. Lett.* **2008**, *10*, 2079-2081.

[127] The 4-bromo and 4-fluorophosphite catalysts were also prepared, and gave lower yields than the corresponding 4-chlorophosphite catalyst.

Table 3-4. GC optimization for new catalyst system

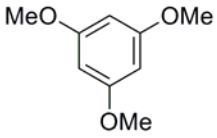
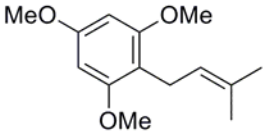
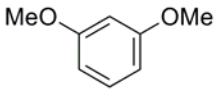
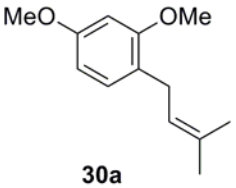
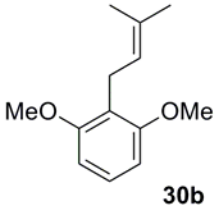
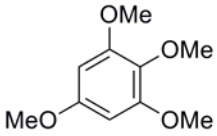
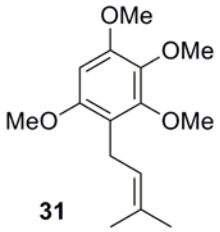
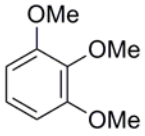
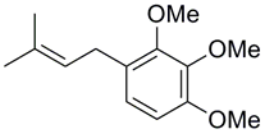
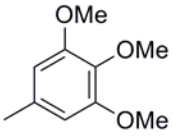
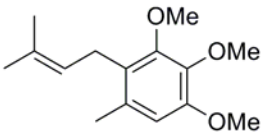


Entry	Solvent[a]	Gold Source	Silver Source	Time	Conversion[b]
1[c]	THF	$(PhO)_3P(AuCl)$	AgOTf	0.5 h	2%
2	Toluene	$(PhO)_3P(AuCl)$	AgOTf	0.5 h	16%
3	Et_2O	$(PhO)_3P(AuCl)$	AgOTf	0.5 h	8%
4	**CH_2Cl_2**	$(PhO)_3P(AuCl)$	AgOTf	0.5 h	**54%**
5	MeCN	$(PhO)_3P(AuCl)$	AgOTf	0.5 h	<1%
6	CH_2Cl_2	(*t*-Bu_2-*o*-biphenyl)P(AuCl)	AgOTf	48 h	52%
7	CH_2Cl_2	(IMes)AuCl	AgOTf	20 h	55%
8[d]	CH_2Cl_2	$(PhO)_3P(AuCl)$	$AgSbF_6$	10 h	86%
9	CH_2Cl_2	$(PhO)_3P(AuCl)$	$AgNTf_2$	10 h	79%
10	CH_2Cl_2	$(PhO)_3P(AuCl)$	**$AgBF_4$**	10 h	**92%**
11	CH_2Cl_2	(2,4-diMe-$PhO)_3P(AuCl)$	$AgBF_4$	1 h	88%
12	CH_2Cl_2	(2-Ph-$PhO)_3P(AuCl)$	$AgBF_4$	1 h	80%
13	CH_2Cl_2	(4-Cl-$PhO)_3P(AuCl)$ **28**	$AgBF_4$	<1 h	**>95%**

a. Solvents dried by passage through alumina column with Ar (tol, Et_2O, CH_2Cl_2), or distilled from Na^0 (THF) or CaH_2 (MeCN). *b.* Integrated against remaining SM by GC. *c.* Entries 1-7 run with 1 : 1 arene to allene molar ratio. *d.* Entries 8-13 run with 2 : 1 arene to allene ratio.

Table 3-5 shows results of screening nucleophilic arenes, with the arene used in excess (2.0 equiv.). Prenylation of poly-methoxybenzenes is facile, and produces monoprenylated compounds **29-33** at room temperature with 5 mol% catalyst loading.

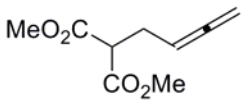
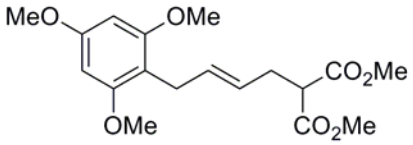
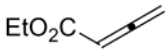
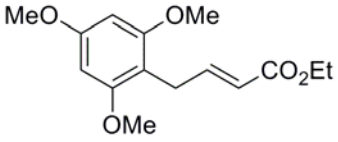
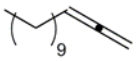
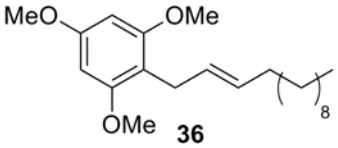
Table 3-5. Addition of electron-rich arenes to allenes

Arene	Time	Product	Yield[a, b]
	4 h	 **29**	67%
	4 h	 **30a**  **30b**	71% 6 : 1[c]
	18 h	 **31**	53%
	16 h	 **32**	65%
	12 h	 **33**	75%

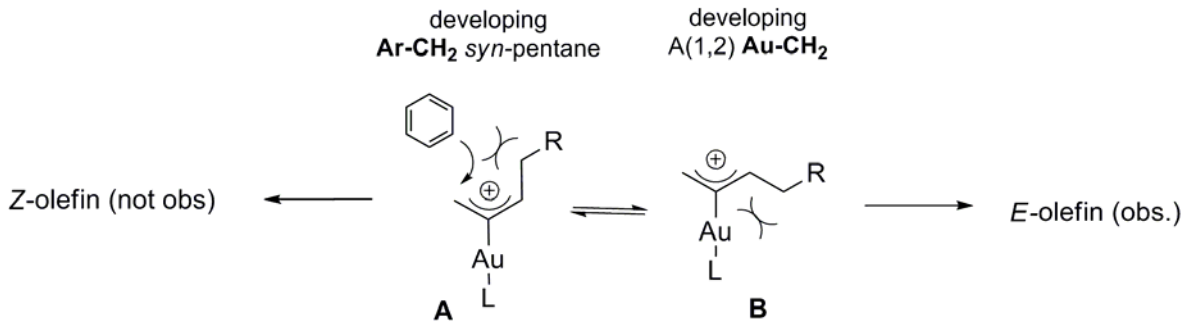
a. General procedure: 2.0 eq. arene and 1.0 eq. allene were added to 5 mol% of preactivated gold catalyst **28** in a 2-mL screwtop vial, using anhydrous CH_2Cl_2 at room temperature for the time indicated. *b.* Isolated yield after silica gel chromatography in ethyl acetate : hexanes. *c.* Inseparable mixture

Other allenes also participate with 1,3,5-trimethoxybenzene, producing **34-36** with stereospecific *E*-geometry allylic functionalities (**Table 3-6**).

Table 3-6. Results with monosubstituted allene partners

Allene	Time	Product	Yield
	12 h	 **34**	51%
	12 h	 **35**	90%
	16 h	 **36**	22%

Selectivity for the *E*-isomer in this case is puzzling - this isomer presumably forms from a transition state in which the gold catalyst suffers an unfavorable A(1,2) interaction with the alkyl chain (**Scheme 3-7, A**). Perhaps the more limiting interaction is actually a developing *syn*-pentane interaction suffered by the arene (**B**) upon approach to the gold(I) σ-allyl species.



Scheme 3-7. Potential intermediates in gold-catalyzed intermolecular hydroarylation

3.4 Limitations of Intermolecular Method

In an attempt to extend these promising intermolecular results to a more general arene class (i.e. nitrogen heterocycles, oxygen heterocycles, nonactivated arenes - **Figure 3-4**).

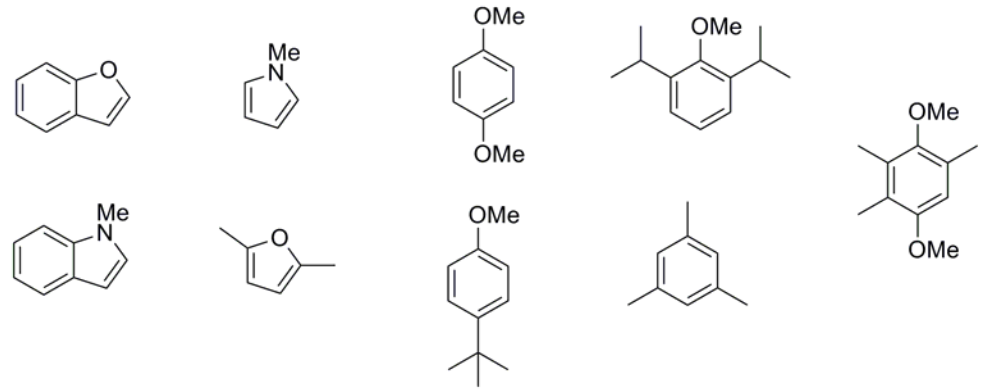


Figure 3-4. Unreactive arenes for intermolecular hydroarylation

Unfortunately, despite increasing catalyst loading, concentration, heating to reflux, or addition of acidic cocatalyst, conversion to prenylated products with 1,1'-dimethylallene remained low (0-25%).

Additionally, the allene steric requirement was found to be exceptionally sensitive. Large α-substituents (Ph, Bn, *c*-Hex)[128] were not compatible with this reaction, and no conversion from the allene was observed, even with the techniques previously mentioned (**Figure 3-5**).

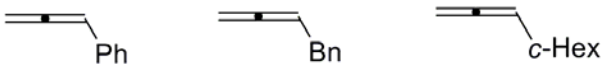


Figure 3-5. Unreactive allenes with large steric demand

Under forcing conditions, phosphite-gold catalyst **28** decomposes to metallic gold(0) which can be seen plating out on the sides of the reaction vessel after only 10 minutes. Control reactions with Au(III) catalysts show that they are not capable of catalyzing this reaction, indicating that destruction of the Au(I) oxidation state likely halts further reaction. A gold(III)-gold(I) redox pathway has been implicated in previous studies.[129]

3.5 Conclusions

Intermolecular and intramolecular gold-catalyzed hydroarylations of allenes were developed. The intramolecular version was found to be accelerated by non-coordinating counterions ($^{-}BF_4$, $^{-}SbF_6$) and more electrophilic precatalysts (TPOP vs. TPP). The intermolecular reaction proceeded with more electrophilic halophosphite catalysts, and

[128] Allenes were formed by reaction of the corresponding vinyl / styrenyl compound with dibromocarbene and base-catalyzed decomposition, see: Ngai, M.-Y.; Skucas, E.; Krische, M. J. *Org. Lett.* **2008**, *10*, 2705-2708.

[129] Hashmi, A. S. K.; Blanco, M. C.; Fischer, D.; Bats, J. W. *Eur. J. Org. Chem.* **2006**, 1387-1389.

generated products of traditional allylation without prefunctionalization (using allyl halides or metalated arenes). These reactions represent dramatic improvements over traditional hydroarylation methods, which often require high temperatures or stoichiometric heavy metals to proceed.

3.6 Experimental Procedures

Representative Cycloisomerization Procedure: To a 1 dram vial charged with a stirbar, **1** (27.2 mg, 0.05 mmol, 1.0 eq.), and $AgSbF_6$ (24.0 mg, 0.07 mmol, 1.4 eq.) was added dichloromethane (1.0 mL) by syringe, at which point a white-grey suspension formed. After 2 minutes, **2** (168 mg, 0.5 mmol, 10 eq.) was added by pipette. The suspension turned deep green within 20 minutes. After 6 h, the reaction was loaded directly onto a silica flash column, and purified with 1:7 ethyl acetate / hexanes. Yield: 85% of **3** as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.23 (s, 2H), 5.74 (m, 1H), 4.90 (d, 1H, J = 10.4 Hz), 4.68 (d, 1H, J = 17.2 Hz), 3.77 (s, 3H), 3.70 (s, 3H), 3.66 (s, 3H), 3.64 (s, 3H), 3.34 (d, 1H, J = 16 Hz), 2.99 (d, 1H, J = 16.4 Hz), 2.48 (m, 1H), 2.29 (m, 1H). ^{13}C (100 MHz): 171.8, 171.7, 159.1, 158.6, 141.3, 135.8, 113.3, 104.3, 97.1, 55.3, 55.2, 52.6, 52.4, 35.4, 35.0, 34.3. HRMS-ESI+: 357.131 Calculated for ($C_{18}H_{22}O_6$ + Na), found 357.131.

Triphenylphosphite gold(I) chloride (1): Adapted from conditions reported by Toste[130] et. al: To (DMS)AuCl (200 mg, 0.68 mmol) obtained from a drybox and taken up in anhydrous dichloromethane (5 mL) was added triphenylphosphite (214 mg, 0.69 mmol) dropwise as a

[130] Johansson, M. J.; Gorin, D. J.; Staben, S.T.; Toste, F. D. *J. Am. Chem. Soc.*, **2005**, *127*, 18002-18003.

0.2 mL CH_2Cl_2 solution. When all ligand had been consumed (TLC), the reaction was filtered with a 0.2 μm syringe filter, pushed through a small silica plug with ethyl acetate, concentrated to a white foam, and recrystallized in CH_2Cl_2 / pentane by vapor crystallization. Clear, colorless rectangular crystals, 350 mg (80%). Melting point: 101°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41-7.19 (m, 15H) ^{13}C (100 MHz): 130.4, 126.6, 121.1, 121.1. ^{31}P (166 MHz): 109.9. HRMS-ESI+: 580.975 Calculated for ($C_{18}H_{15}O_3PAuCl$ + K), found 580.975.

Dimethyl-2-(1,2-butadienyl)-2-(3,5-dimethoxybenzyl)malonate (2): Off-white crystalline solid, 64%. Melting point: 49°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.29 (s, 1H), 6.22 (s, 2H), 4.96 (m, 1H), 4.70 (m, 2H), 3.70 (d, 6H), 3.17 (s, 2H), 2.52 (d, 2H, *J* = 7.2 Hz). ^{13}C (100 MHz): 210.3, 170.9, 160.6, 138.0, 108.2, 99.1, 84.6, 74.9, 59.1, 55.2, 52.4, 38.1, 31.2. HRMS-ESI+: 357.131 Calculated for ($C_{18}H_{22}O_6$ + Na), found 357.129.

Dimethyl-2-(1,2-butadienyl)-2-(methylene-2-naphthyl)malonate (4): Light brown oil, 78%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02 (d, 1H, *J* = 8 Hz), 7.79 (d, 1H, *J* = 8 Hz), 7.71 (d, 1H, *J* = 7.6 Hz), 7.44-7.33 (m, 4H), 5.05 (p, 1H), 4.70 (m, 2H), 3.76 (s, 2H), 3.55 (s, 6H), 2.57 (m, 2H). ^{13}C (100 MHz): 210.2, 171.2, 133.9, 132.8, 132.4, 128.8, 128.3, 127.8, 125.8, 125.4, 125.1, 123.8, 84.8, 75.0, 59.2, 52.3, 33.6, 32.1. HRMS ESI+: 347.126 Calculated for ($C_{20}H_{20}O_4$ + Na); found 347.123.

1-Vinyl-3, 3-bis(methoxycarbonyl)-1,2,3,4-tetrahydrophenanthrene (5): ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.02 (d, 1H), 7.79 (d, 1H, *J* = 7.5 Hz), 7.64 (d, 1H, *J* = 8.7 Hz), 7.49 (m,

2H), 7.30 (d, 1H, J = 8.7 Hz), 5.75 (m, 1H), 5.22 (m, 2H), 3.95 (d, 1H, J = 16.8 Hz), 3.79 (s, 3H), 3.73 (m, 1H), 3.66 (s, 3H), 3.42 (d, 1H, J = 16.8 Hz), 2.68 (ddd, 1 H, J_1 = 12 Hz, J_2 = 5.7 Hz, J_3 = 1.8 Hz), 2.11 (dd, 1 H, J_1 = 13.5 Hz, J_2 = 10.7 Hz). ^{13}C (100 MHz): 172.3, 171.3, 141.4, 133.3, 132.4, 132.0, 128.5, 128.3, 126.8, 126.5, 126.2, 125.4, 123.0, 116.8, 53.4, 52.9, 52.8, 41.9, 34.6, 31.4. HRMS-ESI+: 347.126 Calculated for ($C_{20}H_{20}O_4$ + Na), found 347.125.

Dimethyl-2-(1, 2-butadienyl)-2-(piperonyl)-malonate (6): Clear oil, 86%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.66 (d, 1H, J = 8 Hz), 6.53 (m, 2H), 4.97 (p, 1H), 4.71 (m, 2H), 3.69 (s, 3H), 3.16 (s, 2H), 2.50 (m, 2H). ^{13}C (100 MHz): 210.2, 171.0 147.5, 146.6, 129.3, 123.1, 110.2, 108.1, 100.9, 84.5, 75.0, 59.2, 52.4, 37.6, 31.1. HRMS-ESI+: 341.100 Calculated for ($C_{17}H_{18}O_6$ + Na), found 341.097.

Dimethyl 8-vinyl-7, 8-dihydronaphtho[2,3-d][1,3]dioxole-6,6(5H)-dicarboxylate (7): ^{1}H NMR (400 MHz, $CDCl_3$): 6.61 (s, 1H), 6.55 (s, 1H), 5.85 (s, 2H), 5.64 (m, 1H), 5.13 (m, 2H), 3.71 (s, 3H), 3.66 (s, 3H), 3.37 (m, 1H), 3.25 (d, 1H), 3.04 (d, 1H), 2.52 (m, 1H), 1.93 (m, 1H). ^{13}C (100 MHz): 172.0, 171.1, 146.4, 146.3, 141.4, 129.3, 126.4, 116.4, 108.4, 100.8, 53.6, 52.8, 52.7, 41.5, 35.1. HRMS-ESI+: 341.100 Calculated for ($C_{17}H_{18}O_6$ + Na), found 341.100.

Dimethyl-2-(1, 2-butadienyl)-2-(2,3,4-trimethoxybenzyl)malonate (8): Clear oil, 42%. ^{1}H NMR (400 MHz, $CDCl_3$): 6.71 (d, 1H, J = 8.4 Hz), 6.52 (d, 1H, J = 8.8 Hz), 5.10 (p, 1H), 4.62 (dt, 2H, J_1 = 5.4 Hz, J_2 = 2.4 Hz), 3.79-3.78 (m, 9H), 3.68 (s, 6H), 3.19 (s, 2H),

2.42 (m, 2H). ^{13}C (100 MHz): 210.0, 171.3, 152.9, 152.9, 142.1, 125.6, 121.7, 107.0, 85.0, 74.4, 60.7, 60.6, 59.1, 55.9, 52.2, 32.1, 31.5. HRMS-ESI+: 387.142 Calculated for ($C_{19}H_{24}O_7$ + Na), found 387.144.

Dimethyl-6,7,8-trimethoxy-4-vinyl-3,4-dihydronaphthalene-2,2(1H) dicarboxylate (9): ^{1}H NMR (400 MHz, $CDCl_3$): 6.44 (s, 1H), 5.68 (m, 1H), 5.14 (m, 2H), 3.84 (s, 3H), 3.82 (s, 3H), 3.74 (s, 3H), 3.72 (s, 3H), 3.66 (s, 3H), 3.45 (d, 1H, J = 15.6 Hz), 3.35 (m, 1H), 2.81 (d, 1H, J = 16.8 Hz), 2.51 (m, 1H), 1.94 (dd, 1H, J_1 = 13.2 Hz, J_2 = 11.6 Hz). ^{13}C (100 MHz): 172.3, 171.3, 151.7, 151.0, 141.2, 140.7, 131.6, 119.8, 116.6, 107.3, 60.8, 60.5, 55.9, 53.1, 52.8, 52.6, 41.5, 34.9, 28.9. HRMS-ESI+: 403.116 Calculated for ($C_{19}H_{24}O_7$ + K), found 403.119.

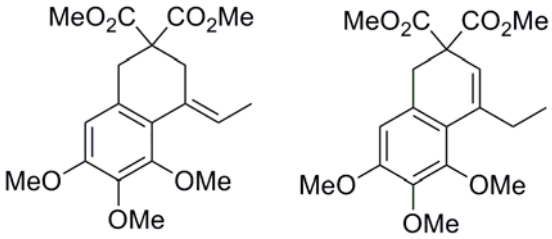
Dimethyl-2-(1,2-butadienyl)-2-(3,4,5-trimethoxybenzyl)malonate (10): Off-white solid, 74%. Melting point: 88-89 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$): 6.32 (s, 2H), 4.97 (m, 1H), 4.74 (m, 2H), 3.85 (s, 9H), 3.79 (s, 6H), 3.19 (s, 2H), 2.56 (m, 2H). ^{13}C (100 MHz): 211.0, 171.1, 153.6, 131.2, 108.7, 84.7, 75.4, 60.8, 59.1, 56.1, 53.2, 38.5, 31.5. HRMS-ESI+: 387.142 Calculated for ($C_{19}H_{24}O_7$ + Na), found 387.144.

Dimethyl-5,6,7-trimethoxy-4-vinyl-3,4-dihydronaphthalene-2,2(1H)-dicarboxylate (11): (10:1:1 inseparable mixture of olefin isomers) **Major -** ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.40 (s, 1H), 5.76 (m, 1H), 4.93 (d, 1H, J = 10.2 Hz), 4.72 (d, 1H, J = 17.1 Hz), 3.78, 3.76, 3.62 (s, 15H), 3.27 (d, 1H), 2.98 (m, 1H), 2.41 (m, 1H), 2.22 (m, 1H). ^{13}C (100 MHz): 171.8,

171.6, 152.3, 151.9, 141.8, 140.6, 129.4, 122.1, 113.7, 107.1, 60.6, 55.8, 52.8, 52.6, 52.4, 35.9, 35.0, 34.3. HRMS-ESI+: 403.116 Calculated for ($C_{19}H_{24}O_7$ + K), found 403.117.

Minor isomers - ^{1}H NMR (400 MHz, $CDCl_3$): 6.52 (s, 1H), 6.39 (s, 1H), 3.80 (s, 3H), 3.73 (s, 3H), 3.66 (m, 3H), 3.15 (s, 2H), 2.64 (q, 2H), 1.77 (d, 3H), 1.01 (t, 3H).

*The minor olefin isomers are consistent with the following structures:



Dimethyl-2-(1,2-butadienyl)-2-(3-methoxybenzyl)malonate (12): Clear oil, 48%. ^{1}H NMR (400 MHz, $CDCl_3$): 7.14 (t, 1H), 6.74 (d, 1H), 6.69 (m, 1H), 5.00 (m, 1H), 4.71 (m, 2H), 3.73 (s, 4H), 3.69 (s, 6H), 3.22 (s, 2H), 2.51 (m, 2H). ^{13}C (100 MHz): 210.2, 171.0, 159.5, 137.3, 129.3, 122.3, 115.8, 112.4, 84.5, 75.0, 59.1, 55.1, 52.4, 37.9, 31.2. HRMSESI+: 305.139 Calculated for ($C_{17}H_{20}O_5$ + H), found 305.142.

Dimethyl-7-methoxy-4-vinyl-3,4-dihydronaphthalene-2,2(1H)-dicarboxylate (13): ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.05 (d, 1H), 6.68 (dd, 1H), 6.64 (s, 1H), 5.66 (m, 1H), 5.14 (m, 2H), 3.76-3.67 (3s, 9H), 3.42 (bm, 1H), 3.40 (d, 1H), 3.13 (d, 1H), 2.55 (m, 1H), 1.97 (dd, 1H). ^{13}C (100 MHz): 172.1, 171.2, 158.1, 141.4, 134.5, 129.6, 128.2, 116.2, 113.3, 112.7, 55.2, 53.5, 52.8, 52.7, 40.7, 35.3, 35.2. HRMS-ESI+: 327.121 Calculated for ($C_{17}H_{20}O_5$ + Na), found 327.117.

Dimethyl-2-(1,2-butadienyl)-2-(*N*-pyrrolo)malonate (15): Light yellow oil, 72%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.54 (s, 2H), 6.09 (s, 2H), 4.96 (m, 1H), 4.75 (m, 2H), 4.46 (s, 2H), 3.73 (s, 6H), 2.58 (m, 2H). ^{13}C (100 MHz): δ 210.3, 169.7, 122.6, 107.8, 84.8, 75.5, 59.5, 55.0, 53.5, 52.1, 50.6. HRMS-ESI+: 264.124 Calculated for ($C_{14}H_{17}O_4N$ + H), found 264.123.

5, 5-Dicarbomethoxy-5:6:7:8-tetrahydro-8-vinyl pyrrocoline (16): ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.55 (d, 1H), 6.13 (t, 1H, J = 2.8 Hz), 5.84 (d, 1H, J = 1.6 Hz), 5.78 (m, 1H), 5.19 (d, 1H, J = 16.8 Hz), 5.10 (d, 1H, J = 10 Hz), 4.60 (dd, 1H, J_1 = 12.4 Hz, J_2 = 1.2 Hz), 4.08 (d, 1H, J = 12.4 Hz), 3.76 (s, 3H), 3.73 (s, 3H), 3.49 (m, 1H), 2.65 (ddd, 1H, J_1 = 12 Hz, J_2 = 5.6 Hz, J_3 = 1.2 Hz), 1.98 (dd, 1H, J_1 = 13.4 Hz, J_2 = 8 Hz) ^{13}C (100 MHz): 169.8, 169.3, 139.2, 129.3, 121.7, 119.5, 116.0, 108.7, 108.5, 105.7, 54.2, 53.2, 53.2, 48.4, 36.5, 33.7. HRMS-ESI+: 286.106 Calculated for ($C_{14}H_{17}NO_4$ + Na), found 286.107.

Dimethyl-2-(2-methyl-2,3-pentadienyl)-2-(3,5-dimethoxybenzyl)malonate(17):
Colorless oil, 73%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.28 (s, 1H), 6.23 (d, 2H, J = 2 Hz), 4.83 (septet, 1H, J = 3.2 Hz), 3.699 (s, 6H), 3.68 (s, 3H), 3.18 (s, 2H), 2.48 (d, 2H), 1.67 (d, 6H, J = 2.8 Hz). ^{13}C (100 MHz): δ 204.0, 171.0, 160.6, 138.3, 108.1, 98.9, 95.5, 83.1, 59.1, 55.1, 52.3, 37.8, 31.7, 20.6. HRMS-ESI+: 385.163 calculated for ($C_{20}H_{26}O_6$ + Na), found 385.165.

Dimethyl-5,7-dimethoxy-4-(2-methyl-2-propenyl)-3,4-dihydronaphthalene-2,2(1H)-dicarboxylate (18): ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.24 (s, 2H), 4.79 (d, 1H, J= 9.3 Hz),

3.88 (dd, 1H), 3.77 (s, 3H), 3.69 (s, 3H), 3.66 (s, 3H), 3.63 (s, 3H), 3.28 (d, 1H, *J*= 15 Hz), 3.07 (d, 1H, *J*= 15.9Hz), 2.52 (m, 1H), 1.99 (m, 1H), 1.72 (s, 3H), 1.62 (s, 3H). ^{13}C (100 MHz): δ 172.4, 171.5, 158.8, 158.7, 135.2, 130.0, 128.7, 119.8, 104.4, 97.3, 55.4, 55.2, 53.2, 52.5, 35.7, 35.5, 31.0, 30.0, 25.7, 17.7. HRMS-ESI+: 401.137 Calculated for ($C_{20}H_{26}O_6$ + K), found 401.137.

1,3-Dimethoxy-2-(1,3-butadienyl)-2-(3,5-dimethoxybenzyl)propane(19): Prepared from $LiAlH_4$ reduction of **2**, followed by bisether formation with NaH / MeI (54%, 2 steps, clear oil). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.38 (d, 2H, *J* = 2.1 Hz), 6.31 (t, 1H, *J* = 2.1 Hz), 5.09 (p, 1H, *J* = 6.6 Hz), 4.65 (dt, 2H), 3.75 (s, 6H), 3.31 (s, 6H), 3.09 (s, 4H), 2.57 (s, 2H), 2.01 (dt, 2H). ^{13}C (100 MHz): δ 210.1, 160.3, 140.2, 108.8, 98.4, 85.6, 74.1, 73.6, 58.9, 55.2, 43.2, 37.9, 31.5. HRMS-ESI+: 329.173 Calculated for ($C_{18}H_{26}O_4$ + Na), found 329.176.

5,7-Dimethoxy-2,2-dimethoxymethyl-4-(2-methyl-2-propenyl)-3,4-dihydronaphthalene (20): ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.30 (d, 1H, *J* = 2.4 Hz), 6.25 (s, 1H), 5.88 (m, 1H), 4.87 (m, 2H), 3.77 (s, 3H), 3.74 (s, 3H), 3.65 (m, 1H), 3.32 (s, 3H), 3.26 (s, 3H), 3.13 (s, 2H), 2.57 (d, 2H, *J* = 5.6 Hz). ^{13}C (100 MHz): 158.8, 158.6, 143.4, 137.9, 119.0, 112.1, 105.2, 96.6, 75.2, 59.3, 59.1, 55.3, 55.2, 39.0, 35.2, 35.1, 34.2. HRMS-ESI+: 307.191 Calculated for ($C_{18}H_{26}O_4$ + H), found 307.190.

Dimethyl-2-(1,3-butadienyl)-2-(4-*tert*-butylbenzyl)malonate (21): Clear, colorless oil, 84%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.25 (d, 2H, *J*=8.4 Hz), 6.99 (d, 2H, *J*=8.1Hz), 5.01 (p, 1H), 4.71 (dt, 2H, J_1 = 6.6Hz, J_2 = 2.7Hz), 3.71 (s, 6H), 3.22 (s, 2H), 2.50 (dt, 2H, J_1 =

7.8Hz, J_2 = 2.7Hz), 1.27 (s, 9H). ^{13}C (100 MHz): 210.2, 171.1, 149.8, 132.6, 129.6, 125.2, 84.6, 74.8, 59.2, 52.3, 37.5, 34.4, 31.3, 31.3. HRMS-ESI+: 353.173 Calculated for ($C_{20}H_{26}O_4$ + Na), found 353.172.

Dimethyl-2-(4-tert-butylbenzyl)-2-(3-oxobutyl)malonate (22): ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.24 (d, 2H), 6.95 (d, 2H), 3.69 (s, 6H), 3.18 (s, 2H), 2.47 (t, 2H, *J* =8 Hz), 2.09 (s, 3H), 2.04 (t, 2H, *J*= 7.6 Hz), 1.26 (s, 9H). ^{13}C (100 MHz): 208.0, 171.5, 149.9, 132.4, 129.5, 125.3, 58.2, 52.4, 39.1, 38.9, 34.4, 31.3, 29.9, 26.4. HRMS-ESI+: 371.183 Calculated for ($C_{20}H_{28}O_5$ + Na), found 371.184.

Dimethyl-7-*tert*-butyl-4-vinyl-3,4-dihydronaphthalene-2,2(1H)-dicarboxylate (23): ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.15 (d, 2H), 7.04 (d, 1H, *J*=8.4 Hz), 5.74 (m, 1H), 5.18 (m, 2H), 3.73 (s, 3H), 3.68 (s, 3H), 3.48 (m, 1H), 3.36 (d, 1H, *J*=16.4 Hz), 3.15 (d, 1H, *J*= 16.4Hz), 2.56 (m, 1H), 2.00 (dd, 1H), 1.25 (s, 9H). ^{13}C (100 MHz): δ 172.2, 171.3, 149.0, 141.3, 135.4, 130.1, 128.4, 125.3, 123.7, 116.5, 53.4, 52.8, 52.8, 41.5, 35.2, 34.6, 34.5, 31.4. HRMS-ESI+: 369.147 Calculated for ($C_{20}H_{26}O_4$ + K), found 329.145.

General Procedure for Intermolecular Hydroarylation - To a 5-mL vial charged with a stirbar was added **28** (9.6 mg, 15 μmol) and $AgBF_4$ (3.0 mg, 15 μmol), and dichloromethane (1.0 mL) by syringe, resulting in a light grey suspension. After stirring for 2 minutes, 1,3,5-trimethoxybenzene (100 mg, 0.6 mmol) was added, resulting in a color change to light orange. After stirring 2 additional minutes, **26** (20.0 mg, 0.3 mmol) was added dropwise by microsyringe. Stirring was continued until GC / TLC (product Rf 0.5 in 1:7 ethyl acetate :

hexanes) analysis indicated complete consumption of the allene. The reaction was concentrated, loaded directly onto a silica flash column and eluted with 1:10-1:8 ethyl acetate : hexanes to yield **27** (67% yield) Clear oil. ^{1}H NMR (300 MHz): δ 6.13 (s, 2H), 5.16 (t, 1H), 3.79 (s, 9H), 3.26 (d, 2H), 1.75 (s, 3H), 1.65 (s, 3H). ^{13}C (100 MHz): 159.9, 158.7, 130.6, 123.5, 111.0, 90.9, 55.7, 55.3, 25.8, 21.8, 17.6.

Tri(4-chlorophenyl)phosphite gold(I) chloride (**28**) White crystalline solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.37 (d, 2H, J = 9 Hz), 7.12 (dd, 2H, J_1 = 9 Hz, J_2 = 1.8 Hz). ^{13}C (100 MHz): δ 147.6, 132.5, 130.6, 122.3 (d). ^{31}P (121 MHz): δ 112.0.

2-Methyl-4-(2,4-dimethoxyphenyl)-but-2-ene(30a) / **2-Methyl-4-(2,6-dimethoxyphenyl)-but-2-ene (30b)**: 6:1 mixture, inseparable by column chromatography. **30a** ^{1}H NMR (400 MHz): 1.68 (s, 3H), 1.71 (s, 3H), 3.22 (d, 2H), 3.77 (s, 3H), 3.79 (s, 3H), 5.26 (t, 1H), 6.42 (m, 2H), 7.01 (d, 1H). **30b** ^{1}H NMR (400 MHz): 1.65 (s, 3H), 1.74 (s, 3H), 3.32 (d, 2H), 3.79 (s, 3H), 3.80 (s, 3H), 5.19 (t, 1H), 6.53 (d, 2H), 7.09 (t, 1H). ^{13}C NMR (100 MHz) (mixture): 159.1, 158.1, 129.4, 123.3, 123.0, 122.6, 103.9, 98.6, 55.8, 55.3, 27.8, 25.8, 17.7.

2-Methyl-4-(1,2,3,5-tetramethoxyphenyl)-but-2-ene (31): ^{1}H NMR (400 MHz): δ 6.24 (s, 1H), 5.11 (t, 1H), 3.82 (s, 3H), 3.81 (s, 3H), 3.77 (s, 3H), 3.23 (d, 2H), 1.72 (s, 3H), 1.62 (s, 3H). ^{13}C (100 MHz): 153.6, 152.4, 151.6, 130.7, 123.6, 116.5, 100.0, 93.1, 60.9, 60.9, 56.3, 56.1, 25.7, 22.6, 17.7. HRMS (ESI+): Expected 289.1416, Observed 289.1422 ($M + Na^+$)

2-Methyl-4-(1,2,3-trimethoxyphenyl)-but-2-ene (32): Clear oil. ^{1}H NMR (400 MHz): δ6.80 (d, 1H), 6.59 (d, 1H), 5.24 (t, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.82 (s, 3H), 3.25 (d,

2H), 1.72 (s, 6H). ^{13}C (100 MHz): 152.0, 151.8, 142.5, 131.9, 127.9, 123.5, 123.3, 107.5, 60.7, 56.0, 28.2, 25.7, 17.1.

2-Methyl-4-(5-methyl-1,2,3-trimethoxyphenyl)-but-2-ene (33): ^{1}H NMR (400 MHz): 1.66 (s, 3H), 1.75 (s, 3H), 2.22 (s, 3H), 3.26 (d, 2H), 3.79-3.83 (m, 9H), 5.02 (t, 1H), 6.48 (s, 1H). ^{13}C (100 MHz): 151.8, 151.1, 140.5, 131.8, 131.0, 126.3, 123.2, 109.6, 60.9, 60.8, 55.9, 25.6, 19.6, 17.8.

Dimethyl-2-(*E*-4-(1,3,5-trimethoxyphenyl)-but-2-enyl)malonate (34): Clear oil. ^{1}H NMR (300 MHz): δ 6.09 (s, 2H), 5.58 (dt, 1H, J = 15.3 Hz), 5.29 (dt, 1H, J = 15.0 Hz), 3.78 (s, 3H), 3.75 (s, 6H), 3.65 (s, 6H), 3.35 (t, 1H, J = 7.5 Hz), 3.20 (d, 2H, J = 6 Hz), 2.51 (t, 2H, J = 14.7 Hz). ^{13}C (100 MHz): 169.4, 159.5, 158.7, 132.3, 124.5, 109.4, 90.8, 55.7, 55.3, 52.2, 52.1, 31.9, 25.6. HRMS (ESI+): Expected 375.1482, Observed 375.1482 ($M + Na^{+}$).

Ethyl-*E*-4-(1,3,5-trimethoxyphenyl)-but-2-enoate (35): Clear oil. ^{1}H NMR (300 MHz): δ 7.01 (dt, 1H, J_1 = 15.6 Hz, J_2 = 6 Hz), 6.10 (s, 2H), 5.66 (dt, 1H, J = 15.3 Hz), 4.11 (m, 2H), 3.79 (s, 3H), 3.76 (s, 6H), 3.42 (dd, 2H), 1.23 (t, 3H). ^{13}C (100 MHz): 167.2, 160.1, 158.8, 148.1, 129.3, 120.6, 116.7, 106.6, 104.2, 90.6, 59.9, 55.3, 25.5, 14.3. HRMS (ESI+): Expected 281.1389, observed 281.1387 ($M + H^{+}$).

1-(1,3,5-trimethoxyphenyl)-2*E*-triskadecene (37): Clear oil. ^{1}H NMR (400 MHz): δ 0.85 (t, 4H), 1.22 (m, 22H), 1.90 (m, 2H), 3.22 (d, 2H), 3.79 (m, 12H), 5.40 (m, 2H), 6.12 (s, 2H). ^{13}C (100 MHz): 159.3, 158.8, 130.0, 128.3, 90.9, 55.8, 55.3, 32.5, 31.9, 29.6, 29.5,

29.3, 29.2, 25.7, 22.7, 14.1. HRMS (ESI+): Expected 371.2562, Observed 371.2583 (M + Na^+).

Chapter 4

Gold(I)-Catalyzed Cascade Cyclization of Allenyl Epoxides

4.1 Introduction - Polyether Natural Products

In addition to sesquiterpene and diterpene carbocycles (see **Chapter 1**), a curious class of toxins is produced both by dinoflagellates in sea water and by soil bacteria.[131] These highly oxygenated polycycles, which usually contain common structural elements such as *trans*-fused medium-ring ethers, are hypothesized to arise from polyene precursors - like the terpenoids - that are then oxidized to polyepoxides prior to enzymatic cyclization.[132]

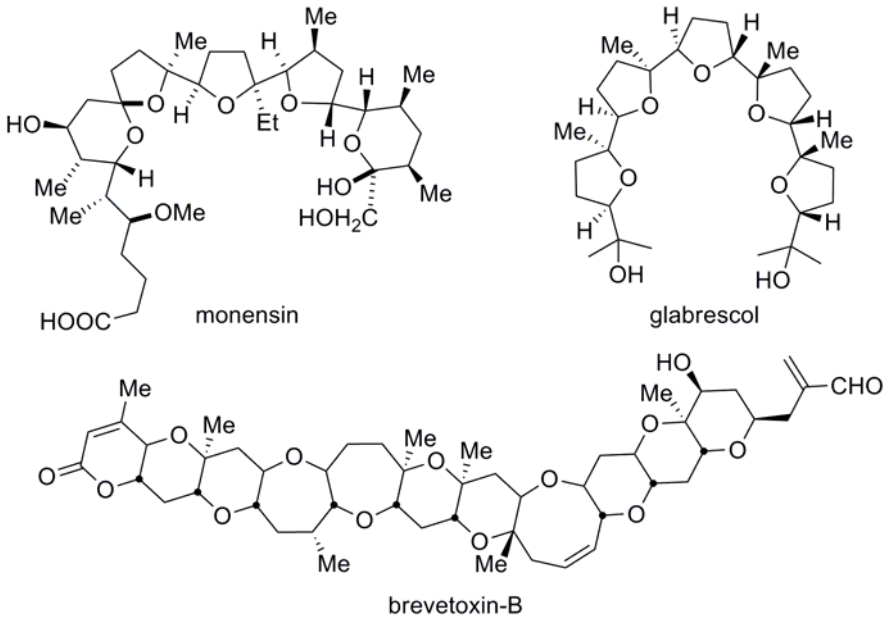


Figure 4-1. Polyether natural products proposed to arise from polyepoxide cascades

[131] Nicolaou, K. C.; Frederick, M. O.; Aversa, R. J. *Angew. Chem. Int. Ed.* **2008**, *47*, 7182-7225.

[132] Cane, D. E.; Celmer, W. D.; Westley, J. W. *J. Am. Chem. Soc.* **1983**, *105*, 3594-3600.

Shown in **Figure 4-1** are three such products, monensin,[133] from *Streptomyces cinamonensis*, a soil bacterium; glabrescol,[134] from *Spathelia glabrescens*, a Jamaican plant; and brevetoxin B,[135] from *Karenia brevis*, a dinoflagellate implicated in red tide poisoning.

Involvement of polyepoxide intermediates in the biosynthesis of natural products found in marine algae and soil fungi was first illustrated in 1981 by Nakanishi, Clardy, and coworkers.[136] The model specified that selective enzymatic oxidation of long-chain terpenoids, followed by enzymatic cyclization, would yield discrete polyether products. Shown in **Scheme 4-1** are two potential enzymatic pathways that a polyepoxide could adopt for cyclization: an electrophile-initiated cascade, or a nucleophile-opening cascade. While the precursor molecules for these putative cyclizations have not yet been detected among marine isolates, the repetitive *trans* bridged "ladder" toxins and the *exo*-selective polyethers found in the monensin antibiotic class strongly implicate polyepoxide intermediates.

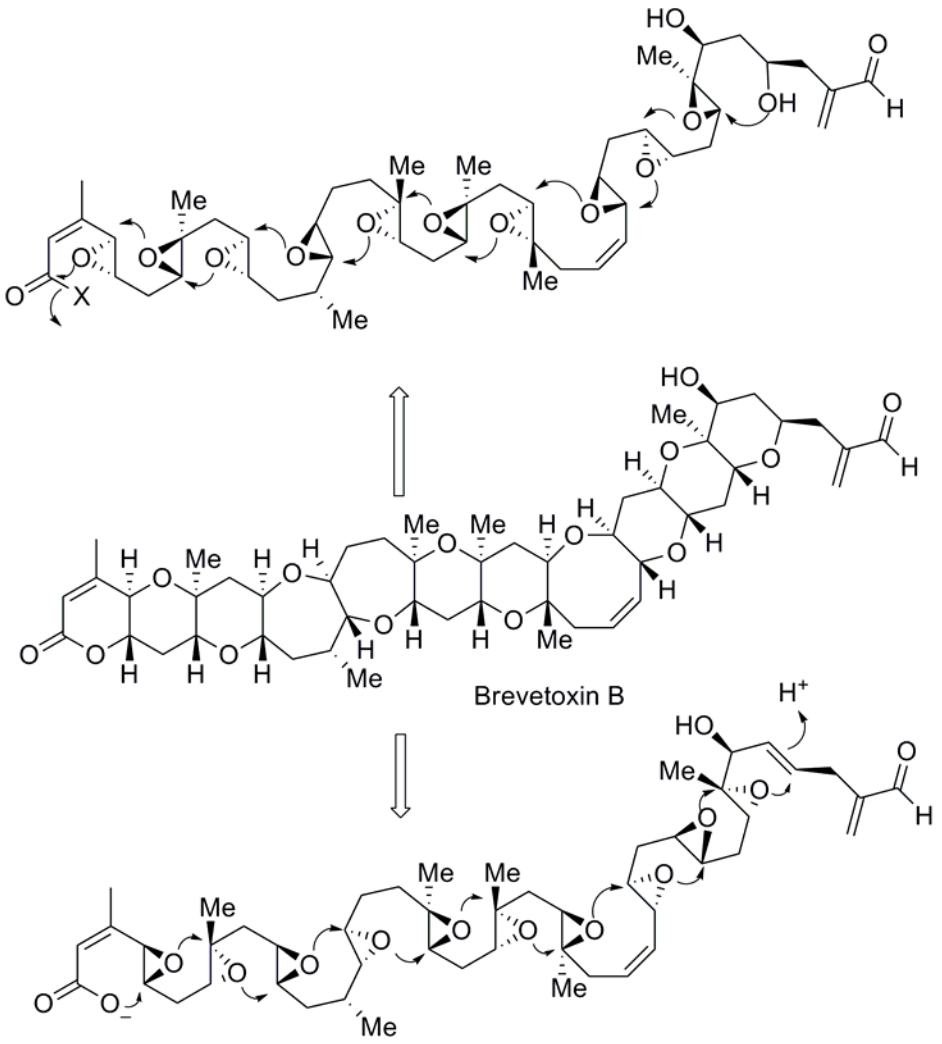
---

[133] a) Schmid, G.; Fukuyama, T.; Akasaka, K.; Kishi, Y. *J. Am. Chem. Soc.* **1979**, *79*, 259-260. b) Fukuyama, T.; Wang, C.-L. J.; Kishi, Y. *J. Am. Chem. Soc.* **1979**, *79*, 260-261. c) Fukuyama, T.; Akasaka, K.; Karanewsky, D. S.; Wang, C.-L. J.; Schmid, G.; Kishi, Y. *J. Am. Chem. Soc.* **1979**, *101*, 262-263.

[134] Harding, W. W.; Lewis, P. A.; Jacobs, H.; McLean, S.; Reynolds, W. F.; Tay, L.-L.; Yang, J.-P. *Tetrahedron Lett.* **1995**, *36*, 9137-9140.

[135] a) Matsuo, G.; Kawamura, K.; Hori, N.; Matsukura, H.; Nakata, T. *J. Am. Chem. Soc.* **2004**, *126*, 14374-14376. b) Nicolaou, K.C. *Angew. Chem. Int. Ed.* **1996**, *35*, 588.

[136] Lin, Y.-Y.; Risk, M.; Ray, S. M.; Van Engen, D.; Clardy, J.; Golik, J.; James, J. C.; Nakanishi, K. *J. Am. Chem. Soc.* **1981**, *103*, 6773-6775.



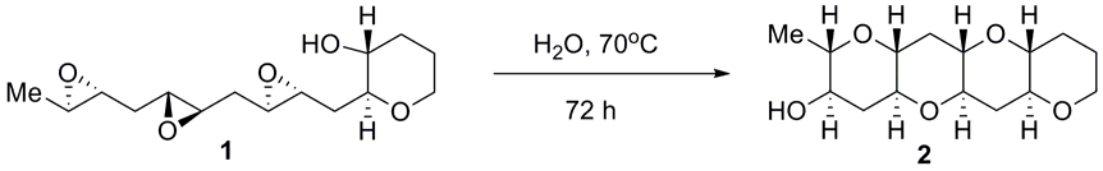
Scheme 4-1. Nucleophilic and electrophilic polyepoxide models

Circumstantial evidence for both nucleophilic and electrophilic cascade mechanisms has been found. The cationic initiation invokes an enzyme similar to squalene-hopene cyclase[137] that may catalyze epoxide opening or carbonyl activation to initiate the cascade. Lerner and coworkers[138] showed that such an enzyme could be designed by culturing

[137] Wendt, K. U.; Schulz, G. E.; Corey, E. J.; Liu, D. R. *Angew. Chem. Int. Ed.* **2000**, *39*, 2812-2833.

[138] Janda, K. D.; Shevlin, C. G.; Lerner, R. A. *Science* **1992**, *259*, 490-493.

antibodies incubated with an N-oxide mimic of the pyran-forming transition state. In support of the nucleophilic mechanism, Jamison and coworkers have recently shown that a suitably-constructed polyepoxide **1** can spontaneously cyclize in water (**Scheme 4-2**), producing *trans*-fused ladder system **2**.[139] The templating effect of the initial *trans*-substituted cyclohexanol ring was critical to the stereospecific formation of ladder structures. A similar phenomenon has been previously noted by the Jamison group when forming the same tetrad with "disappearing" silyl directing groups.[140]



Scheme 4-2. Opening of polyepoxides in water with mild heating

The selectivity for THP vs. THF ring opening of the starting epoxy alcohols was found to be 6:1 selective for the THP ring with mild heating in water near pH 7.0. The model for selectivity in straight water has been proposed to involve hydrogen-bond assistance from two molecules of water in the cyclization event (**Figure 4-2**).

[139] Vilotijevic, I.; Jamison, T. *Science* **2007**, *317*, 1189-1192.

[140] Simpson, G. L.; Heffron, T. J.; Merino, E.; Jamison, T. F. *J. Am. Chem. Soc.* **2006**, *128*, 1056-1057.

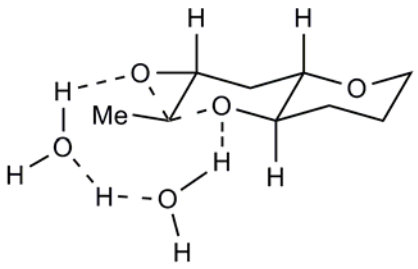
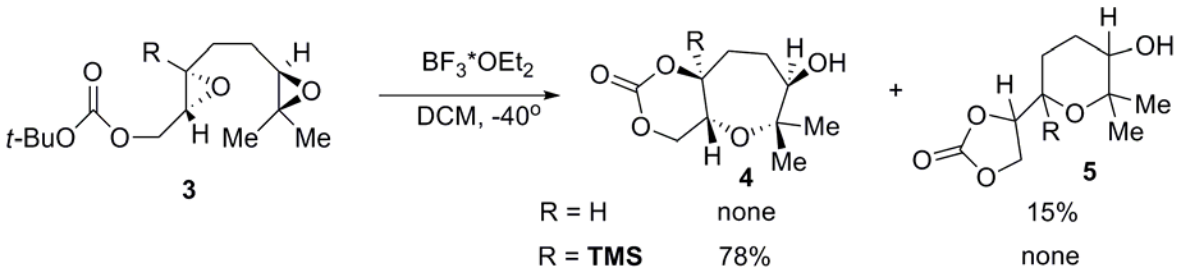


Figure 4-2. Hydrogen bond-assisted epoxide opening favors THP production

Harnessing electrophilic epoxide cascades to generate natural product-like polyethers has been well-explored by several research groups.[141] Among them, McDonald and coworkers[142] have shown that Lewis acidic activation of the terminal oxirane of polyepoxide **3** by $BF_3{\cdot}OEt_2$ yields fused polyethers (**Scheme 4-3**) stereospecifically, favoring *endo* cyclization product **4** when a suitable silyl ether directing group is used.



Scheme 4-3. Lewis-acid mediated *endo* cyclization of bis-epoxides with carbonate trap

[141] Valentine, J. C.; McDonald, F. E. *Synlett* **2006**, 1816-1828.

[142] Valentine, J. C.; McDonald, F. E.; Neiwert, W. A.; Hardcastle, K. I. *J. Am. Chem. Soc.* **2005**, *127*, 4586-4587.

This synthetic approach has recently been applied to the total synthesis of three natural products: durgamone, *ent*-nakorone, and *ent*-abudinol B (**Figure 4-3**).[143]

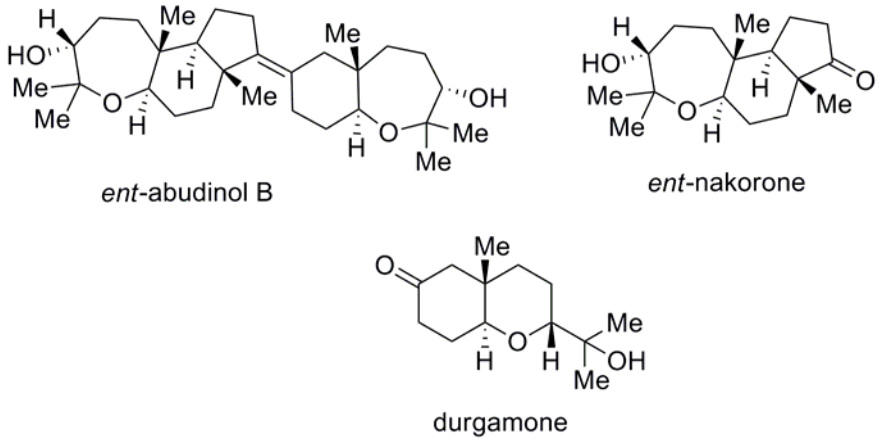
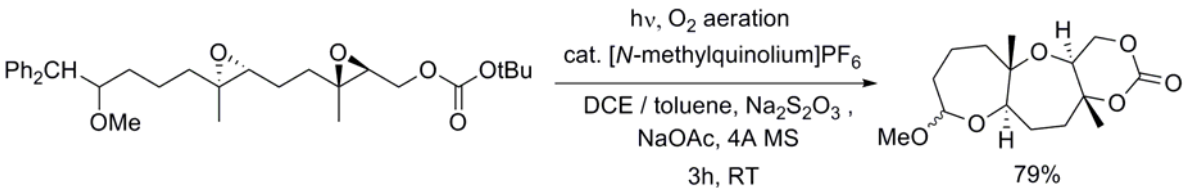


Figure 4-3. Natural products synthesized using epoxide cascades (McDonald, 2007)

Related cascades to form large polyethers from epoxide precursors utilizing an oxidative mechanism have recently been reported by Floreancig.[144] These cyclizations, which include several *endo*-specific polyethers, are initiated by oxidation of a terminal diphenylmethylene group, which can be oxidized away using O_2 as terminal oxidant to form an oxo-carbocationic initiation point for cyclization (**Scheme 4-4**).

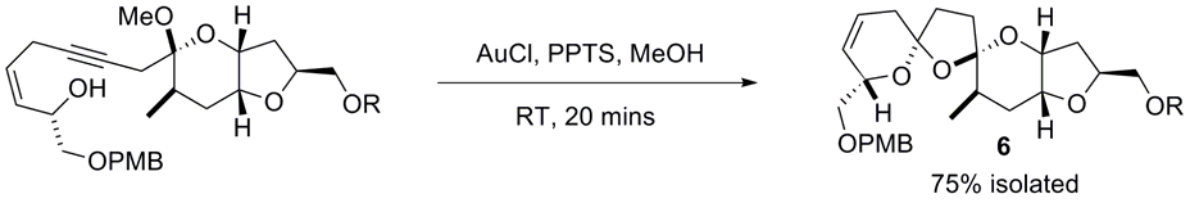
[143] Tong, R.; Valentine, J. C.; McDonald, F. E.; Cao, R.; Fang, X.; Hardcastle, K. I. *J. Am. Chem. Soc.* **2007**, *129*, 1050-1051.

[144] Wan, S.; Gunayadin, H.; Houk, K. N.; Floreancig, P. E. *J. Am. Chem. Soc.* **2007**, *129*, 7915-7923.



Scheme 4-4. Oxidative initiation of polyether cascades (Floreancig, 2007)

A single example of a gold-catalyzed cascade to assemble a highly oxygenated natural product skeleton - the azaspiracid core - was reported in 2007 by Forsyth and coworkers.[145] **Scheme 4-5** illustrates the complex cascade route which "stitched together" two of the four oxygenated rings of **6** in a single step.



Scheme 4-5. Spiroketalization to generate the azaspiracid core

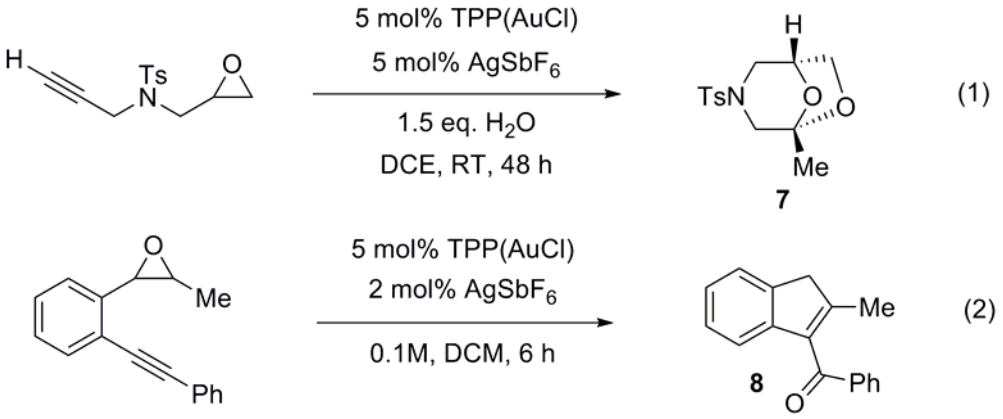
This reaction is accomplished *via* selective alkyne activation by the gold(I) cation in the presence of primary alcohols, ethers, and electron-rich aromatics - gold is a highly carbophilic π-acid.[146]

[145] Li, Y.; Zhou, F.; Forsyth, C. *Angew. Chem. Int. Ed.* **2007**, *46*, 279-282.

[146] Fürstner, A.; Davies, P. W. *Angew. Chem. Int. Ed.* **2007**, *46*, 3410-3449.

4.2 Gold-Catalyzed Cascades[147]

As shown above, gold-catalyzed cascades have successfully been accessed using alkynes as initiating groups. Additionally, epoxide cascades generate complex polyether structures upon treatment with strong Lewis acids. We therefore sought a method that might encompass both the high functional-group tolerance and "soft" nature of gold(I) and the high reactivity of polyepoxide systems. This approach has already achieved some success in a report by Shi[148] in 2006, detailing alkyne-activated epoxide cyclization to form bicyclic ethers **7** (**Eq. 1**), along with a recent report from Liu and coworkers[149] to form ketones through oxygen migration (**Eq. 2**).

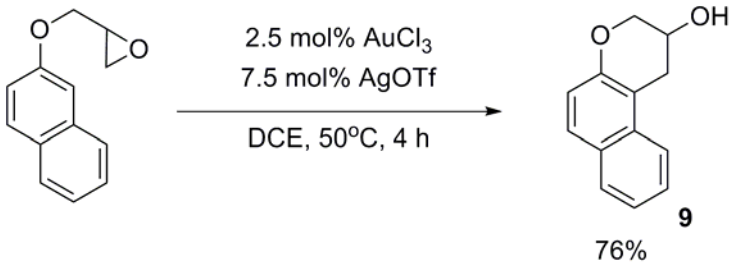


[147] Tarselli, M.A.; Gagné, M.R. *J. Am. Chem. Soc.* **2008** *submitted*

[148] Dai, L.-Z.; Qi, M.-J.; Shi, Y.-L.; Liu, X.-G.; Shi, M. *Org. Lett.* **2007**, *9*, 3191-3194.

[149] Lin, G.-Y.; Li, C.-W.; Hung, S.-H.; Liu, R.-S. *Org. Lett.* **2008**, *10*, 5059-5062.

A number of other reported gold-catalyzed epoxide reactions proceed *via* initial epoxide-activation, followed by trapping of the weakened epoxide σ-bond with aromatic[150] or heteroatomic[151] traps (**Scheme 4-6**) to yield secondary alcohols such as **9**. These reactivity patterns are more commonly observed with the more oxophilic gold(III) catalysts than with gold(I).[152]



Scheme 4-6. An example of gold(III) "epoxide-first" activation

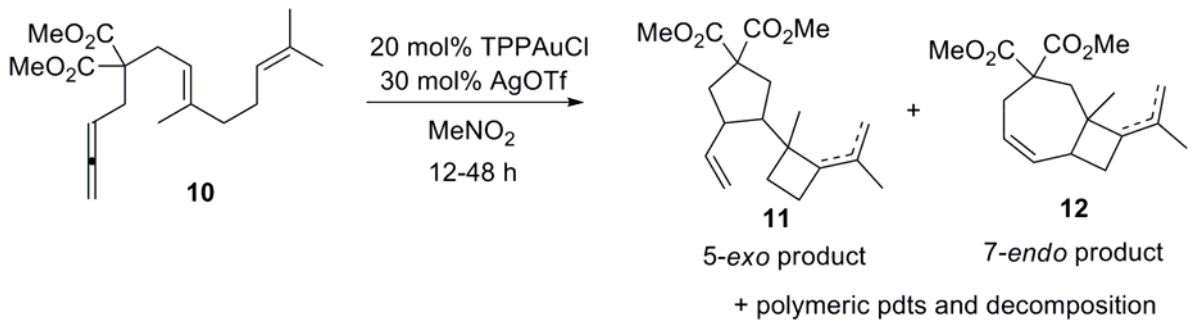
We first looked at the allene-epoxide cyclizations using readily accessible substrates derived from common terpene alcohols (nerol, geraniol). These substrates were prepared as were substrates for gold(I)-eneallene cycloisomerization (see **Chapter 2**). Upon treatment of a suitable poly-ene allene substrate **10** with catalytic gold(I), 50-60% conversion to cyclized products **11** and **12** was observed by GCMS and crude NMR (**Scheme 4-7**). While this reaction was successful in that it provided proof-of-concept, it required 20 mol% catalyst and more than 12 h to advance, and resulted in a mixture of >5 olefin-containing products at the correct m/z, even under optimal conditions.

---

[150] Shi, Z.; He, C. *J. Am. Chem. Soc.* **2004**, *126*, 5964-5965.

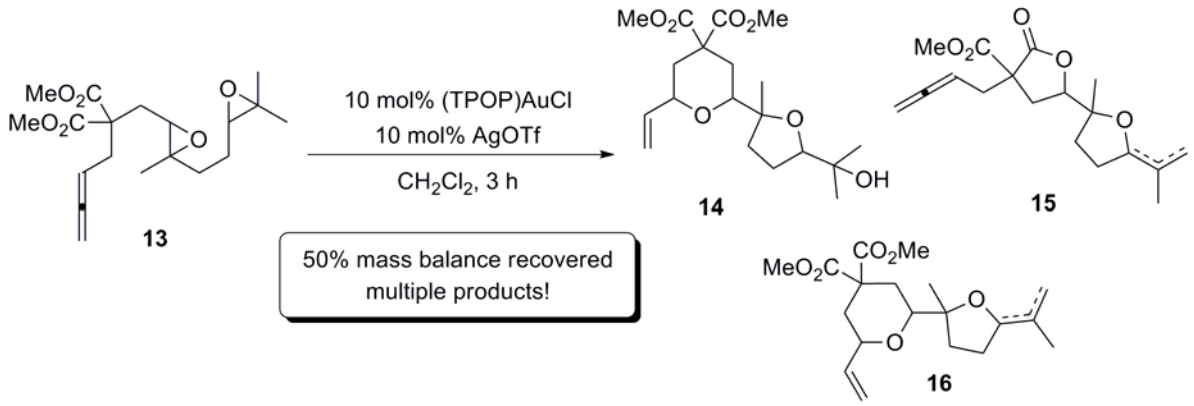
[151] Li, Y.; Tang, P.; Chen, Y.; Yu, B. *J. Org. Chem.* **2008**, *73*, 4323-4325.

[152] *Gold: Progress in Chemistry, Biochemistry, and Technology*; Schmidbaur, H., Ed.; Wiley & Sons: New York, **1999**.



Scheme 4-7. Cascade cyclization of polyene-allenes

Inspired by McDonald's work with polyepoxides, these substrates were oxidized with 2.5 eq. of *meta*-chloroperbenzoic acid (mCPBA) to yield bisepoxide **13** (**Scheme 4-8**). A much more rapid cycloisomerization was then observed upon treatment with 10 mol% Au(I) in CH_2Cl_2 - the reaction reached full conversion in less than 3 h! An inseparable mixture of polycyclic products (**14**, **15**, **16**) could be observed by GCMS.[153]

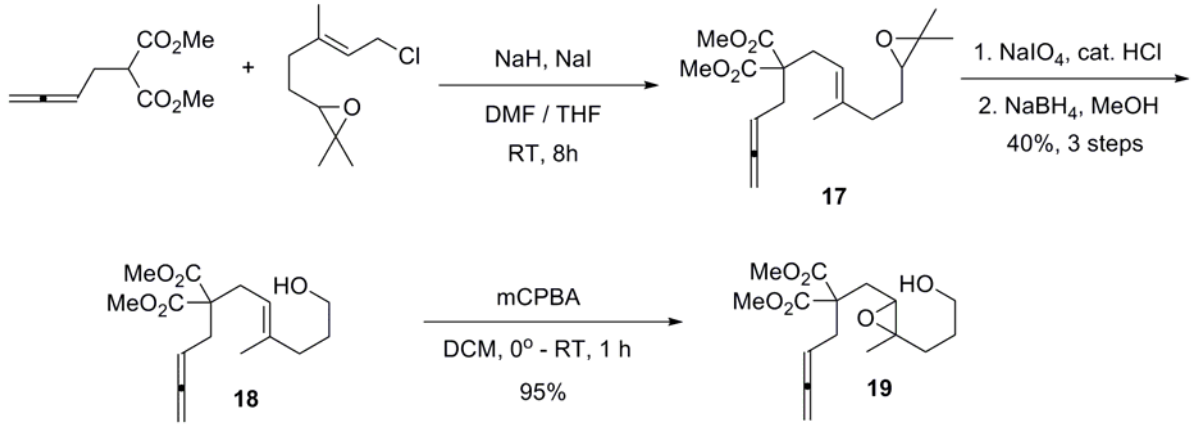


Scheme 4-8. Cascade cyclization of polyepoxides generates multiple products

Unfortunately, despite many months of optimization, this cyclization could not be pushed towards a single product in synthetically useful yields. As noted by W.S.

[153] Crude proton NMR confirmed the presence of several different vinyl groups, indicating cyclization had indeed occurred.

Johnson,[154] cascade cyclizations are dependent on both the *initiating group* and the *terminating group* to proceed with control and selectivity. We therefore devised a synthesis of a similar substrate that could terminate with an intramolecular hydroxyl trap. **Scheme 4-9** outlines such a protocol, with allylation of dimethyl allenylmalonate to form terminal epoxide **17**, which could be oxidatively cleaved using *in situ* generated periodic acid and reduced to generate alcohol **18.** This intermediate was treated with mCPBA at low temperature to give epoxide **19**.



Scheme 4-9. Optimized synthesis of allene-epoxide-alcohol cascade substrate

Once substrate **19** was in hand, cyclizations conditions were optimized for conversion to **20** along with a favorable ratio of **20** : **21**. The following variables were altered: gold precatalyst, silver source, and solvent polarity[155] (**Table 4-1**). Not shown in the Table are

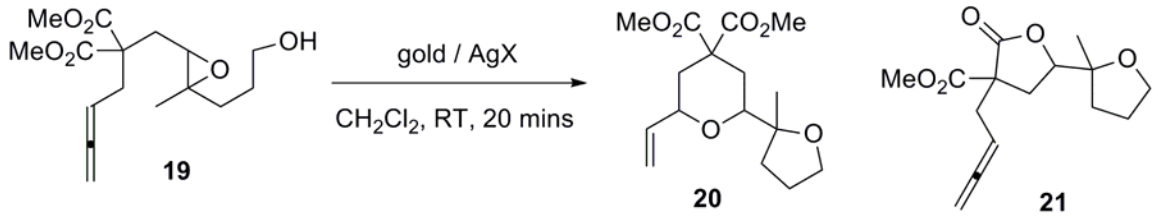
[154] Johnson, W. S. *A Fifty Year Love Affair with Organic Chemistry*; American Chemical Society, **1998**.

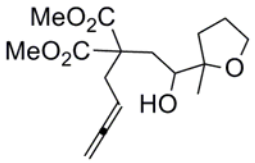
[155] Dichloromethane proved optimal; other solvents tested ($MeNO_2$, Tol, PhH, THF, DCE, 1,2-dichlorobenzene) led to multiple products or poor conversion.

catalysts that favored the lactone byproduct **21**[156] (>5:1). This product presumably arises from Au^+ or Ag^+ activation, epoxide opening, and transesterification of the resultant metal alkoxide with a methyl ester.

[156] These include: $(2\text{-Ph-PhO})_3PAuCl$, $(2,4\text{-diMe-PhO})_3PAuCl$, $(furyl)_3PAuCl$, $(EtO)_3PAuCl$, and $(t\text{-Bu})_2(biphen)PAuCl$, all with AgOTf as cocatalyst.

Table 4-1. Optimization using malonate-geraniol derived epoxy alcohol



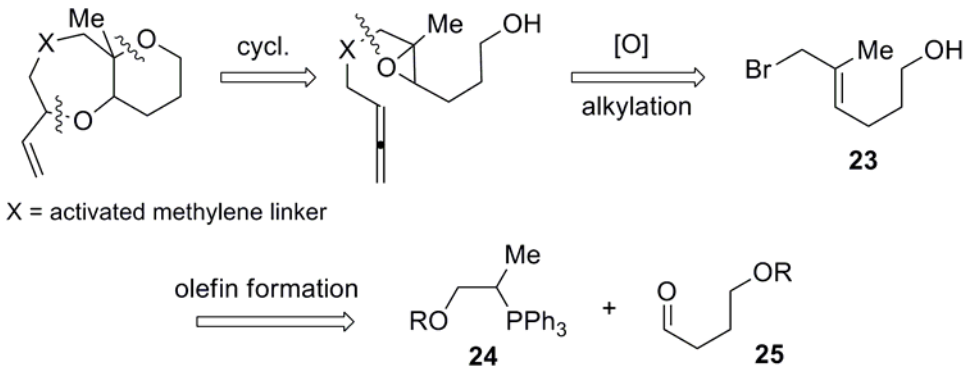
Conditions	Ratio **20** : **21**[a]	
10 mol% Cy_3PAuCl / AgOTf	1.0	1.0
5 mol% (*R*)-xylBINAP$(AuCl)_2$ / AgOTf	low conversion[b]	
5 mol% (dppe)$(AuCl)_2$ / AgOTf	low conversion	
5 mol% $EtPh_2PAuCl$ / AgOTf	1.0	4.3
5 mol% Ph_3PAuCl / AgOTf	1.0	3.0
10 mol% [(TPP)Au] (NTf_2)[c]	1.0	1.4
10 mol% [(TPOP)Au] (NTf_2)	1.2	1.0
5 mol% [(TPOP)Au] (NTf_2) + 20% K_2CO_3	2.0	1.0
5 mol% [(TPOP)Au] (NTf_2) + 40% K_2CO_3	1.0	2.0
5 mol% [(TPOP)Au] (NTf_2) + 5% K_2CO_3	3.0	1.0
5 mol% (4-Cl-TPOP)AuCl / AgOTf	1.0	1.0
5 mol% (4-MeO-TPOP)AuCl / AgOTf	1.0	1.2
5 mol% (4-CN-TPOP)AuCl / AgOTf	1.0	3.0
5 mol% (TPOP)AuCl / $AgBF_4$	--	sole pdt
5 mol% (TPOP)AuCl / AgOTs	1.0	2.5
5 mol% (TPOP)AuCl / $AgSbF_6$	3.5	1.0
5 mol% (TPOP)AuCl / AgOTf	**>5.0**	**1.0**
5 mol% AgOTf	--	sole pdt
5 mol% TfOH	--	sole pdt
10 mol% AgCl	 **22**	

Reactions run on 15 mg scale in golvebox under N_2 atmosphere. *a*) Ratios of 6-5 pdt : lactone obtained by ^1H NMR integration. *b*) low conversion indicates <25% over 1 h. *c*) Complexes formed from $AgNTf_2$ + LAuCl and purified by short plug of silica gel

In general, phosphite-gold catalysts outperformed phosphines, but there was not a clear trend between electron-rich and electron-poor ligand architectures. The added base was inspired by Pale and coworkers, who report optimization of a hydroalkoxylation to form aurones.[157] Compound **22** was observed only in the absence of gold or strong acid. Under the optimal conditions [(TPOP)AuCl and AgOTf in CH_2Cl_2 at room temperature] cyclization was reasonably selective (>5:1) for the 6-5 bicyclic product. This product was not observed in the absence of gold(I).

To this point in the chemistry, geraniol-derived sidechains had predominantly been used due to their synthetic accessibility. To better mimic the structure of natural polyether products, we attempted the synthesis of olefinic sidechains with a methyl positioned strategically to favor *endo* cyclization.[144] Unfortunately, there is not a straightforward route to these compounds from existing terpenoid compounds (**Scheme 4-10**). We believed that the non-oxidized alkylation partner **23** could instead be prepared by a *trans*-selective olefination, which would take place between a stabilized Wittig reagent **24** and a protected alcohol **25**.

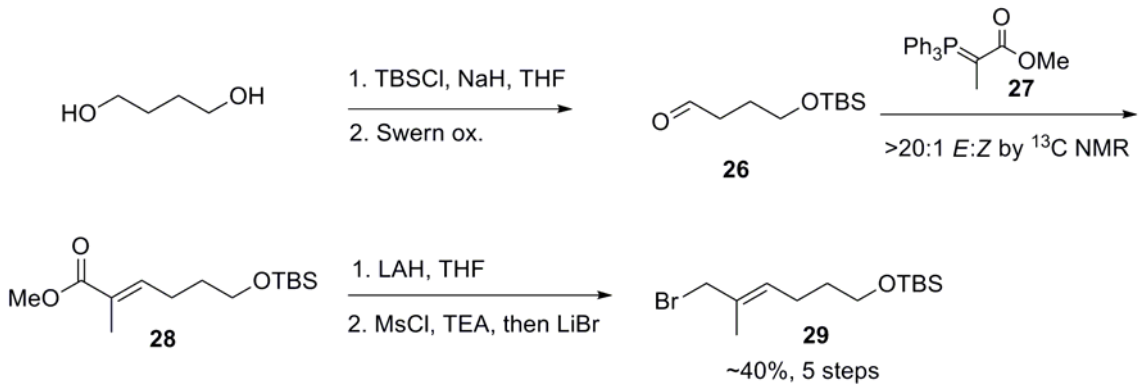
[157] Harkat, H.; Blanc, A.; Weibel, J.-M.; Pale, P. *J. Org. Chem.* **2008**, *73*, 1620-1623.



Scheme 4-10. Retrosynthetic concept for *endo* cyclization

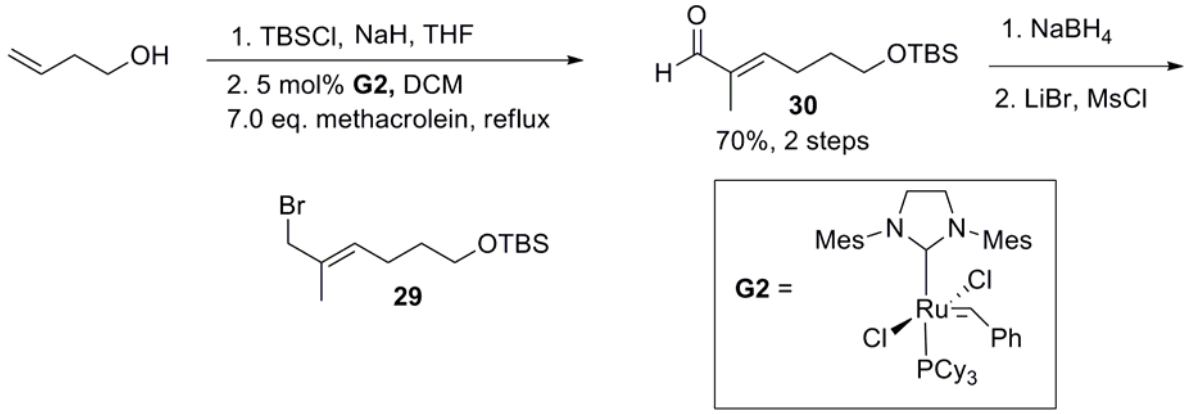
The synthesis of **29** commenced as follows (**Scheme 4-11**): 1,4-butanediol was deprotonated with one equivalent of sodium hydride in THF at 0 ^{o}C, followed by addition of TBS-Cl in THF by cannula. The resultant monoprotected alcohol was usually clean enough to attempt direct oxidation without purification. Following the Swern oxidation, **26** reacted with stabilized Wittig reagent **27** to give the expected *trans* enoate **28** as the major product (>20:1). Reduction of the ester functionality to an allylic alcohol, followed by a procedure reported by Corey[158] to convert the allylic alcohol into **29** resulted in an orange oil, which was sufficiently pure for use in the next step.

[158] Huang, A. X.; Xiong, Z.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 9999-10003.



Scheme 4-11. Synthesis of "moved methyl" allylic bromide[159]

The above protocol was later streamlined for synthetic utility and time savings. Shown in **Scheme 4-12** is an alternative route, utilizing a Grubbs **G2**[160]-catalyzed cross-metathesis[161] to install the requisite trisubstituted enal, utilizing methacrolein as the olefin "donor" in place of the Wittig salt.



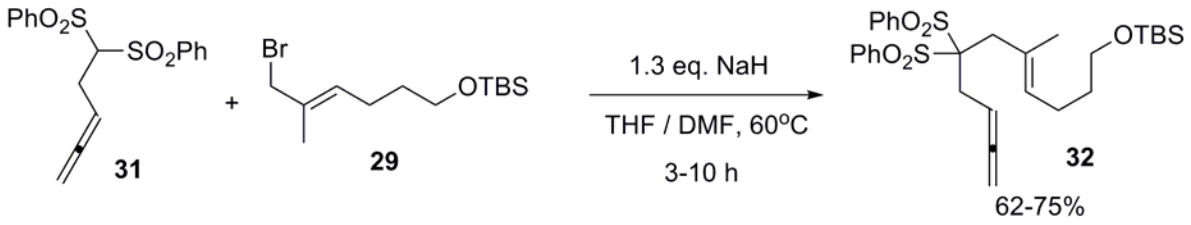
Scheme 4-12. Modified route to isomeric allylic bromide

[159] This route was developed with the help of John Gipson (Gagné lab).

[160] **G2** is available commericially from Aldrich Chemical Co. and Materia, Inc.

[161] Tsai, A. S.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2008**, *130*, 6316-6317.

A variety of activated methylene groups were considered for use as "linkers" for the allene and epoxy-alcohol substrate fragments; bis(phenylsulfonyl)methane was finally chosen for ease of synthesis, stability to the cyclization conditions, and potential for crystalline products.[162] Alkylations of activated methylene groups are facile, and substitution does not seem to greatly hinder the reaction (**Scheme 4-13**).



Scheme 4-13. Alkylation of sulfonyl-allene with allylic bromide

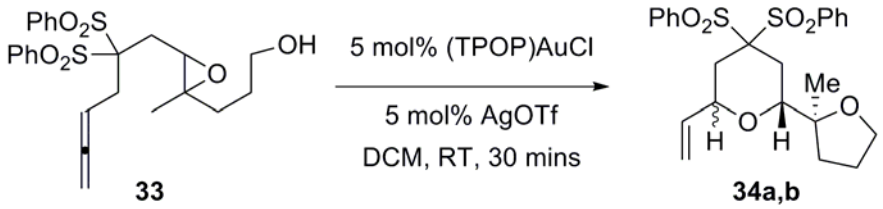
Deprotection of the silyl protecting group with TBAF in THF, followed by epoxidation with mCPBA proceeded without incident to yield **37** (**Table 4-2**, *vide infra*).

4.3 Stereochemistry of Cyclizations

We wanted to construct a potentially crystalline analogue of the cyclization product observed in the geranyl-derived malonate substrate **19**, and thus made the sulfone analog **33**. Upon cyclization with 5 mol% of (TPOP)AuCl / AgOTf, two diastereomers (**34a,b**) were isolated (**Scheme 4-14**) after purification over silica gel followed by HPLC purification,

[162] Lu, P.; Ma, S. *Org. Lett.* **2007**, *9*, 5319-5321.

yielding products enriched enough in one diastereomer to permit full characterization and begin stereochemical determination.



Scheme 4-14. Catalysis of sulfone substrate yields diastereomers separable by HPLC

Initial analysis by NMR confirmed a 2.5 : 1 ratio of diastereomers, each possessing a unique resonance for the allylic proton as a complex multiplet, even in C_6D_6 - **34a** (major) - 4.68 ppm; **34b** (minor) 5.10 ppm. Homonuclear decoupling of the multiplet by irradiation at the vinylic position[163] simplified this signal to a doublet of doublets (dd), with coupling constants: J_1 =11.1-11.6 Hz and J_2 = 2.5 Hz for both diastereomers. These constants would be indicative of a rigid tetrahydropyran chair structure (**Figure 4-4**).

[163] Special thanks to Dr. David Harris for help with this experiment. Irradiation of 4.68 ppm resonance with -43 dB of attenuation successfully resolved the splitting pattern with baseline resolution (500 MHz Bruker).

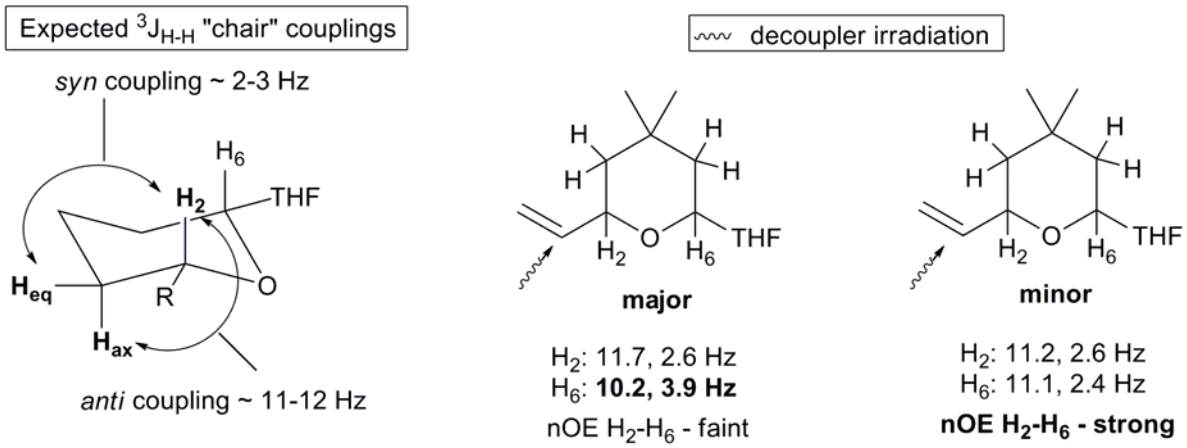


Figure 4-4. Comparison of coupling constants from **34a** and **34b**

The Karplus curve[164] predicts that, if we have a rigid *cis*-2,6-disubstituted tetrahydropyran, the vicinal coupling constants ($^3J_{H-H}$) should be similar for the H_2 and H_6 protons with their respective adjacent methylenes (**Figure 4-4**). However, as noted in **Figure 4-5** the major isomer instead has coupling constants more consistent with a twist-boat conformer,[165] which could be present in the 2,6-disubstituted *trans* tetrahydropyran.

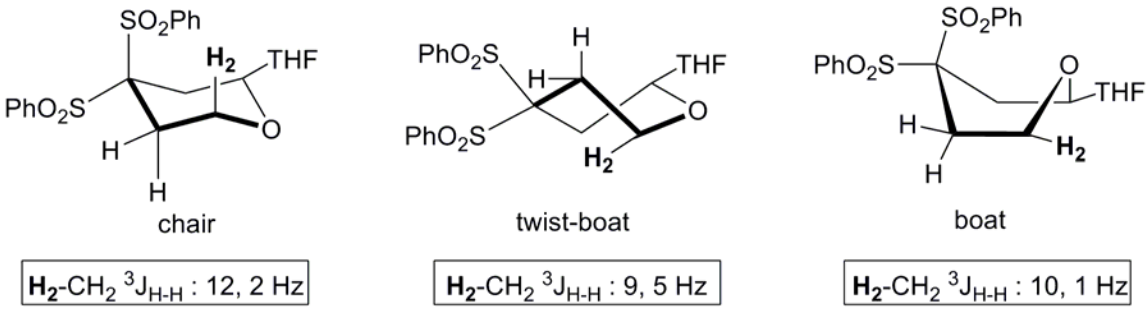
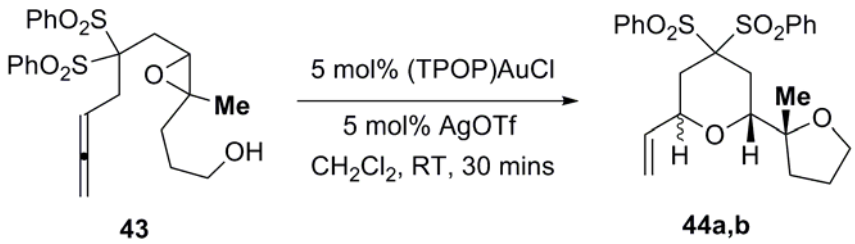


Figure 4-5. Potential $^3J_{H-H}$ values for other THP conformations

[164] a) Karplus, M. *J. Am. Chem. Soc.* **1963**, *85*, 2870-2871. b) Friebolin, H. *Basic One- and Two-Dimensional NMR Spectroscopy*; Wiley-VCH: Heidelberg, **2005**.

[165] Special thanks to Prof. Michael Crimmins for help with this analysis.

The *anti* relationship between the Me and "H_2" proton was suggested by the lack of a strong nOE between these groups, which suggested that the differentiating stereocenter between **34a** and **34b** was indeed the allylic position. Therefore, the Stork-Eschenmoser[166] postulate, initially developed to explain cationic diene cyclization, can be adapted to these polyepoxide cascades, with initial epoxide stereospecificity conserved during the cyclization event. As confirmation of this phenomenon, cyclization of neryl-derived (*Z*-olefin → epoxide) compound **43** results in a major and minor product that were difference from **34a** and **34b.**



43 **44a,b**

Scheme 4-15. Cyclization of neryl isomer yields *syn* relationship between Me and H_6

In contrast to these stereoisomers, **44a,b** exhibited a strong nOE between H_6 and the THF quaternary methyl group (**Scheme 4-15**), suggesting a complementary stereospecific epoxide ring-opening.

To confirm the relative stereochemistry of **34a,** we sought to grow single crystals to probe its structure by X-ray crystallography. Shown in **Figure 4-6** is the crystal structure obtained from the major diastereomer, confirming a *trans* pyran and twist-boat structure.

[166] a) Stork, G.; Burgstahler, A. W. *J. Am. Chem. Soc.* **1955**, *77*, 5068-5077. b) Gamboni, G.; Schniz, H.; Eschenmoser, A. *Helv. Chim. Acta* **1954**, *37*, 964-971.

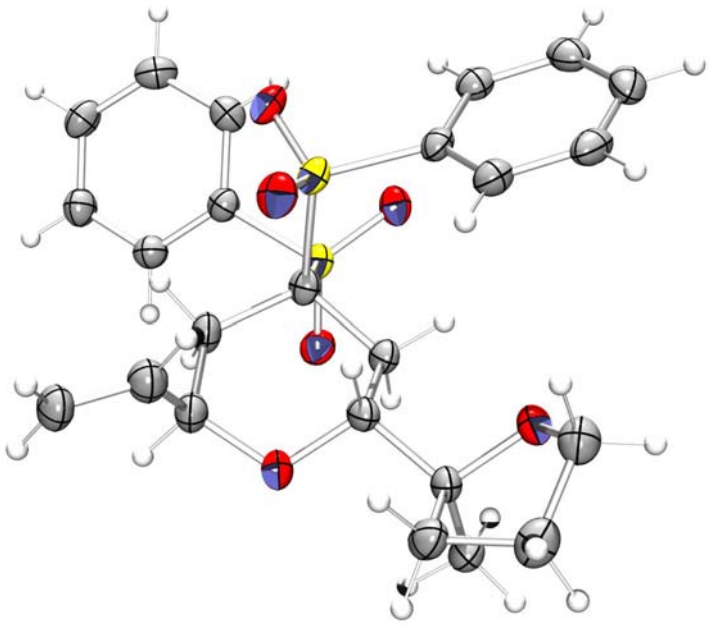


Figure 4-6. Crystal structure of compound **34a**, clearly indicating trans ether bridge. Sulfur = yellow, oxygen = red, carbon = gray, hydrogen = white

The formation of the major diastereomer **34a** is a product of a pseudo-axial allene orientation in the transition state after gold coordination. Although this intermediate may appear at first glance to have several disfavored steric interactions (**Figure 4-7**), several groups - including ours - have documented this curious "axial initiator" phenomenon in other catalyzed cation-olefin cyclizations.[167]

[167] a) Johnson, W. S.; Telfer, S. J.; Cheng, S.; Schubert, U. *J. Am. Chem. Soc.* **1987**, *109*, 2517-2518. b) Koh, J. H.; Gagné, M. R. *Angew. Chem. Int. Ed.* **2004**, *116*, 3541-3543. c) Seiders II, J. R.; Wang, L.; Floreancig, P. E. *J. Am. Chem. Soc.* **2003**, *125*, 2406-2407.

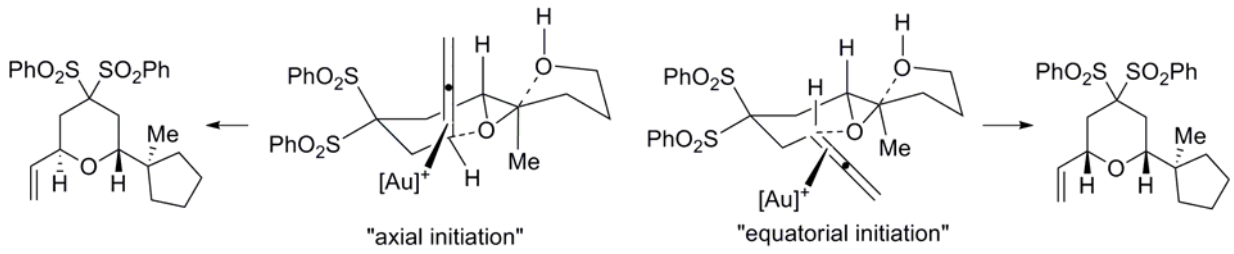
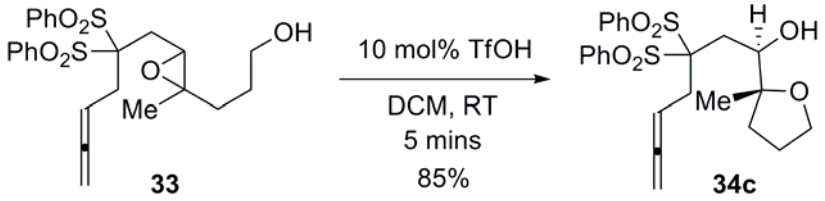


Figure 4-7. Transition state model for cyclization indicating preference for pseudo-axial orientation

A control experiment run to test for acidic background reactions helps to confirm the stereospecificity of this cyclization. When substrate **33** was exposed to 10 mol% TfOH in DCM for 5 min, the resultant epoxide-opened product (**34c**) was obtained as a single diastereomer (**Scheme 4-16**). Cyclization of this secondary alcohol with gold and silver salts led to a 1 : 1 ratio of diastereomers **34a** and **34b**. This piece of evidence argues that the above cascade mechanism is not proceeding by initial epoxide-opening followed by hydroalkoxylation, since the authentic gold-catalyzed reaction from **33** → **34** yields 2.2 : 1 dr.

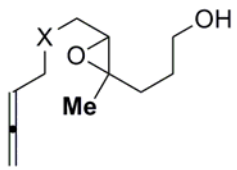
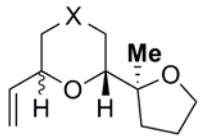
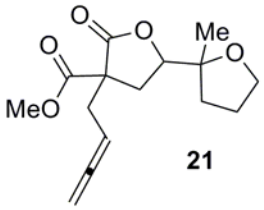
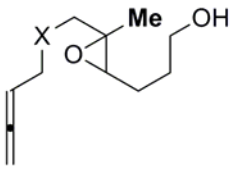
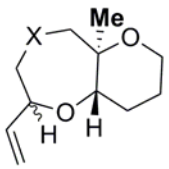
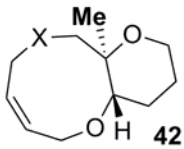
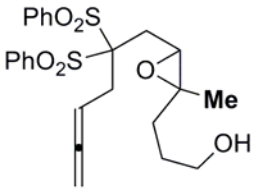
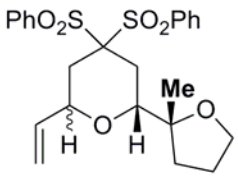


Scheme 4-16. Control reaction of **33** yields single diastereomer of alcohol

4.4 Discussion and Comments on Mechanism

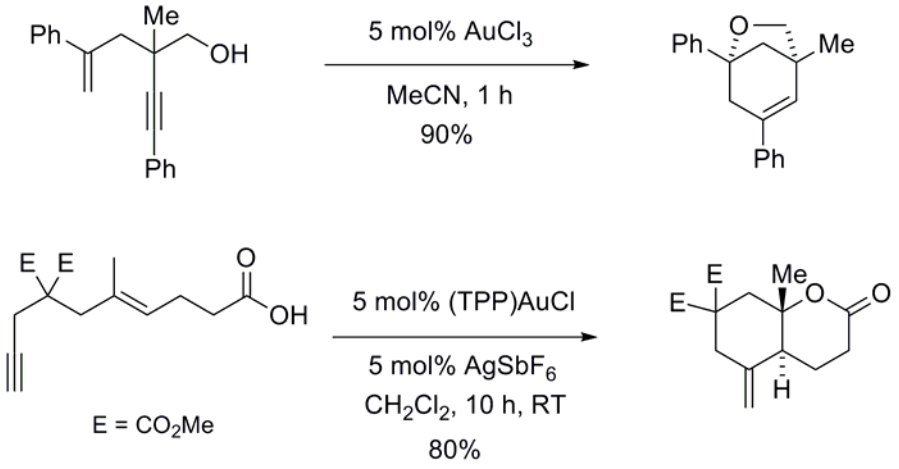
Table 4-2 (below) shows the scope of the proposed cyclization. Sulfones, sulfonamides and ethers cyclize without difficulty; however, the malonate-linked substrates form a small amount of lactone byproduct, mentioned previously (**Table 4-1**). The reaction proceeds in ambient air and is not sensitive to moisture. Yields ranged from 35-65%, and substrate-controlled diastereoselectivity is modest. In specific cases, the product is isolated as a single diastereomer (**20**, **42**).

Table 4-2. Results of allene-epoxide-alcohol cycloisomerization

Substrate		Product(s)	Yield[a]	Selectivity (α : β)
				
33	X = $(PhSO_2)_2C$	**34a,b**	65%	2.2 : 1[c]
35	X = O	**36a,b**	60%	8 : 1
19	X = $(MeO_2C)_2C$	**20**	65%[d]	*e*
		 **21**		
				
37	X = $(PhSO_2)_2C$	**38a,b**	35%	7 : 1
39	X = NTs	**40a,b**	59%[b]	4 : 1
41	X = $(MeO_2C)_2C$	 **42**	35%	*e*
 **43**		 **44a,b**	45%	2.5 : 1

General conditions: 5 mol% $(PhO)_3PAuCl$ / 5 mol% AgOTf in DCM at RT for 15-45 min. *a.* Isolated yields after silica gel chromatography. *b.* ~10% of **42** (X = NTs) generated. *c.* <10% of the 9-endo product also formed. *d.* Yield includes 15% of lactone byproduct under optimized conditions. *e.* Single diastereomer by NMR

Of note in this chemistry are the [5.4.0] bicycles **38** and **40**, which form due to *endo*-selective epoxide cyclization. This selectivity switch presumably arises from intermediates where the most stabilized cations are generated, another component of the Stork-Eschenmoser construct. Similar studies conducted by Kozmin[168] and later Fürstner[169] have augmented experimental evidence for this pathway in gold-catalyzed cascades (**Scheme 4-17**).



Scheme 4-17. Cascade reactions obeying Stork-Eschenmoser reported by Kozmin (top, 2005) and Furstner (bottom, 2008)

Of even greater interest is the formation of [7.4.0] bisether **42**. Although allene-based methods for generation of medium-ring ethers have been developed over the past 20 years,[170] to the best of our knowledge, this is the only example generated by cascade catalysis *in situ*. The presumed model for this selectivity arises from 1,3-diaxial interactions

[168] Zhang, L.; Kozmin, S. A. *J. Am. Chem. Soc.* **2005**, *127*, 6962-6963.

[169] Fürstner, A.; Morency, L. *Angew. Chem. Int. Ed.* **2008**, *47*, 5030-5033.

[170] a) Brummond, K. M.; Chen, H.; Mitasev, B.; Casarez, A. D. *Org. Lett.* **2004**, *6*, 2161-2163. b) Ferrer, C.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2006**, *45*, 1105-1109. c) Makino, T.; Itoh, K. *J. Org. Chem.* **2004**, *69*, 395-405. d) Kang, S.-K.; Ko, B.-S.; Ha, Y.-H. *J. Org. Chem.* **2001**, *66*, 3630-3633.

(**45**) between the methyl ester and the methyl group of the trisubstituted epoxide (**Figure 4-8**). It is reasonable to expect that the molecule may bend out of a perfect chair-type transition structure to alleviate steric strain, which might diminish orbital overlap between the π^* orbital of the proximal allene bond, thus encouraging preferential bonding with the distal bond as shown in **46**.

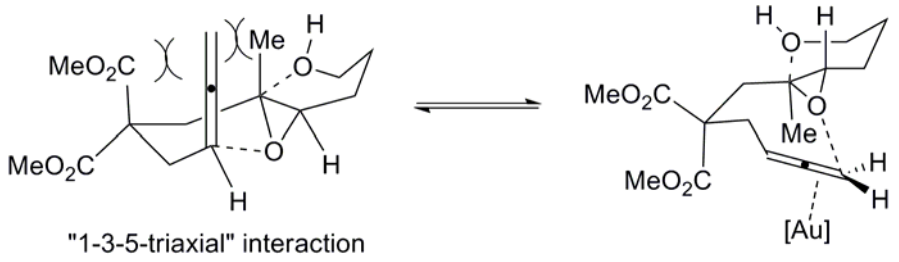


Figure 4-8. Possible transition-state interactions in [7.4.0] bisether formation

The selective formation of unsaturated 9-membered rings is critical to the formation of many synthetic precursors to natural products. Shown in **Figure 4-9** are two such examples, intermediates from the syntheses of the asbestinins (**47**) and ciguatoxin core (**48**), from Crimmins[171] and Inoue, respectively. Interestingly, the 9-membered ring of ciguatoxin CTX3C is critical to the potency and toxicity of this compound.[172]

[171] Crimmins, M. T.; Ellis, J. M. *J. Org. Chem.* **2008**, *73*, 1649-1660.

[172] a) Inoue, M.; Lee, N.; Miyazaki, K.; Usuki, T.; Matsuoka, S.; Hirama, M. *Angew. Chem. Int. Ed.* **2008**, *47*, *ASAP*. b) Inoue, M.; Hirama, M. *Acc. Chem. Res.* **2004**, *37*, 961-968.

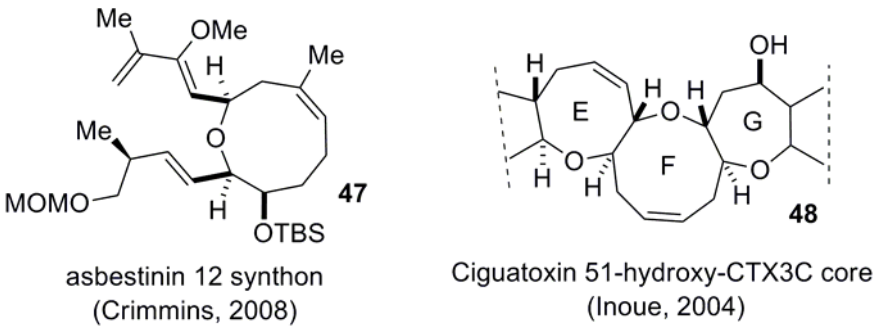
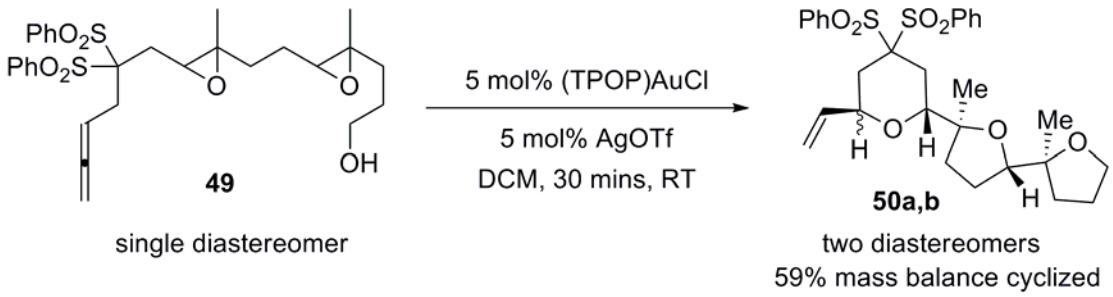


Figure 4-9. Nine-membered ring intermediates in natural products

Recently, we have applied the optimized cyclization conditions to triepoxide **49**, which cyclizes to form two diastereomers **50a,b** (**Scheme 4-18**).



Scheme 4-18. Tricyclic compounds from polyepoxide cascades

The bis(epoxide) diastereomers **49** resulting from achiral epoxidation of a diene-sulfone are separable by silica gel chromatography (1 : 1 EA / Hex), and only one stereoisomer has been exposed to catalytic conditions. As this is a recent result, we do not yet know if these conditions are optimal for polycyclization, nor what diastereomer of bis(epoxide) we are reacting. Currently, efforts are underway to synthesize a known epoxide stereoisomer by way of the Shi epoxidation[173] in order to simplify stereochemical analysis.

[173] Wang, Z.-X.; Shu, L.; Frohn, M.; Tu, Y.; Shi, Y. *Org. Syn.* **2003**, *80*, 9-13.

4.5 Conclusions

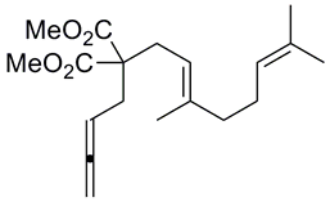
A method for the formation of polycyclic ethers by gold-catalyzed allene-epoxide cycloisomerization is described. The reaction proceeds in ambient air and is not sensitive to moisture. The reaction is tolerant of sulfonamides, sulfones, and ether linkages, but forms a lactone byproduct when a malonate linker is used. Movement of the methyl group located on the trisubstituted epoxide changes the product regioselectivity, favoring the product where positive charge resides on the more highly-substituted carbon. The chemistry has been shown amenable to polycyclization, and represents an entry into the notoriously difficult-to-make oxonine (9-membered ether) ring class.

4.6 Experimental Section

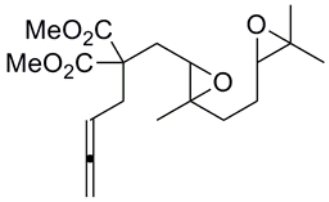
I. General Information: Reactions sensitive to trace moisture were performed using Schlenk techniques under N_2 with glassware flame-dried under vacuum. Tetrahydrofuran was purified by distillation from sodium benzophenone ketyl. Anhydrous dichloromethane and ether were dried using alumina-packed solvent purification columns under a positive flow of Ar gas. Methacrolein and allenyl bromides were purified by vacuum transfer or distillation prior to use. Silica flash chromatography was performed with 60Å Silicycle silica gel. All organometallic stocks were titrated prior to use. NMR shifts (δ) are given relative to tetramethylsilane (0.00 ppm). Spectra are calibrated to residual solvent protons with $CDCl_3$ = 7.24 ppm, C_6D_6 = 7.15. All coupling constants are reported in Hz. HPLC purification was performed on a Varian PrepStar SD-1 with a Dynamax UV-1 absorbance detector set at 254 nm. Elution was conducted with an appropriate mixture of hexanes :

ethyl acetate at 15 mL/min at 25 bar on a Berger Cyano 60 Å prep column. High resolution mass spectra (HRMS) were obtained from the University of Illinois mass spectrometry lab (Dr. Furong Sun). The m/z ratios are reported as sodium (M + 22.989), potassium (M + 39.098) or protonated (M + 1.008) adducts.

II. Substrate Synthesis

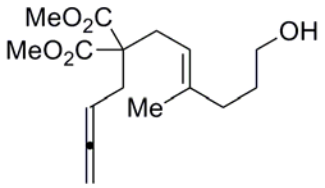


Geranyl Allenyl Dimethylmalonate (10): ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.03 (m, 1H), 4.92 (m, 2H), 4.62 (dt, 2H), 3.68 (s, 6H), 2.65 (d, 2H), 2.57 (m, 2H), 2.05-1.99 (m, 4H), 1.72 (s, 3H), 1.59 (s, 3H), 1.57 (s, 3H).



6*E*-9,9'-bis(carbomethoxy)-2,6-dimethyl-11,12-dien-2,6-bisepoxide (13): To a solution of **10** cooled to 0°C in ice water is added *meta*-chloroperbenzoic acid (3.0 eq.) portionwise over 10 minutes. When TLC (1:1 EA: Hex) indicates complete conversion, the reaction is quenched with 5 mL sat'd. $NaHCO_3$ and 5 mL $Na_2S_2O_3$. The aqueous layer is extracted with ether (3x), washed with bicarbonate and brine, and dried over $MgSO_4$. Purified by flash chromatography in 1:1 EA : Hex to yield **13** as a clear oil, 65%. ^{1}H NMR (300 MHz,

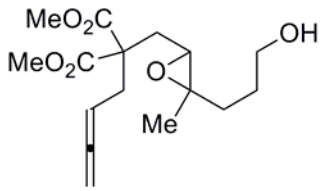
$CDCl_3$): δ 4.97 (p, 1H), 4.65 (m, 2H), 3.72 (s, 3H), 3.71 (s, 3H), 2.77-2.65 (m, 4H), 2.24 (m, 1H), 2.06 (m, 1H), 1.65-1.52 (m, 4H), 1.30 (s, 3H), 1.28 (s, 6H).



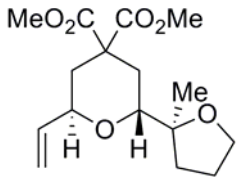
4*E*-7,7'-bis(carbomethoxy)-4-methyl-4,9,10-trien-1-ol (**18**): To a suspension of sodium hydride (60% in mineral oil, 1.2 eq.) in THF was added slowly at room temperature dimethylallenylmalonate (1.0 eq.) The suspension was stirred for 10 minutes, at which point it became a light yellow solution. Geranyl bromide monoepoxide (1.5 eq.) was added in 10 mL THF, and the resulting suspension was stirred for 12 h at RT. Water was added, and the layers separated. The aqueous residue was extracted 3x with 10 mL diethyl ether. The combined organic layers were washed with water, brine, and dried over $MgSO_4$.

The resultant dark yellow oil was taken up in 10:1 THF / H_2O, treated with $NaIO_4$ (1.5 eq.) in one portion, followed by 5 drops of concentrated HCl. The light yellow solution becomes a white suspension formed within 10 minutes. After 1.5 h, the reaction is neutralized with $Na_2S_2O_3$ and $NaHCO_3$, partitioned, the aqueous layer extracted 3x with diethyl ether, and the combined organic layers washed with bicarbonate and brine. After drying over $MgSO_4$, filtering, and concentrating, a light yellow oil results. The crude aldehyde is observed by ^1H NMR at 9.74 ppm.

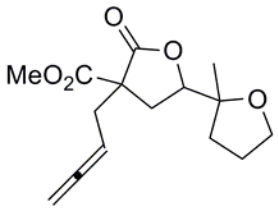
The crude oil from periodate cleavage is dissolved in MeOH, and cooled to -10 ^{o}C in brine / ice bath. $NaBH_4$ is added in portions over 10 minutes, resulting in a bubbling suspension. After 30 minutes, the reaction is warmed slowly to RT, and stirred for an additional 20 minutes. The reaction is diluted with 20 mL Et_2O, 10 mL of NH_4Cl solution is added (slowly!) and the aqueous layer extracted 3x with diethyl ether. Washes of water (10 mL) and brine (10 mL) are followed by drying over $MgSO_4$ and evaporation. Column chromatography on silica gel (1:2 EtOAc / Hex → 1:1) yields **18** as a colorless, viscous oil, 41% (3 steps). ^{1}H (400 MHz, $CDCl_3$): δ 4.98 (m, 2H), 4.64 (m, 2H), 3.69 (s, 6H), 3.59 (t, 2H), 2.64 (d, 2H), 2.56 (d, 2H), 2.02 (t, 2H), 1.61 (m, 5H). ^{13}C (166 MHz, $CDCl_3$): 210.0, 171.4, 139.0, 117.9, 84.35, 74.53, 62.41, 57.92, 52.31, 36.18, 32.02, 30.96, 30.69, 16.02.



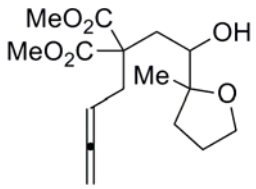
4*E*-7,7'-bis(carbomethoxy)-4-epoxy-4-methyl-9,10-dien-1-ol (19): Clear oil. ^{1}H (400 MHz, $CDCl_3$): δ 4.91 (m, 1H), 4.59 (m, 2H), 3.67 (s, 3H), 3.66 (s, 3H), 3.53 (t, 2H), 2.71 (dd, 1H), 2.65 (dt, 2H), 2.34 (bs, 1H), 2.23 (dd, 1H), 1.97 (dd, 1H), 1.61-1.48 (m, 4H), 1.18 (s, 3H). ^{13}C (100 MHz, $CDCl_3$): 210.1, 171.1, 84.14, 74.77, 62.41, 60.35, 59.31, 56.69, 52.63, 52.51, 34.81, 32.84, 27.81, 16.47. HRMS (TOF MS ES+): Calculated for ($C_{16}H_{24}O_6$ + Na) 335.1471, found 335.1463.



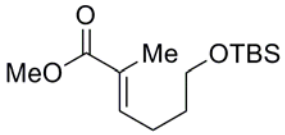
(2*R*,6*S*)-2-((*S*)-2-methyltetrahydrofuran-2-yl)-6-vinyl-4,4'-bis(carbomethoxy)-tetrahydropyran (20): Representative Procedure for Cyclization - To a 20 mL scintillation vial preloaded with 2.3 mg AgOTf (0.05 equiv.) and 4.6 mg (TPOP)AuCl (0.05 equiv.) as white solids is added 1.0 mL of dichloromethane. A white-grey suspension forms within 5 min. 56 mg of **19** is added by pipette, and the pipette tip washed with 0.3 mL fresh DCM into the reaction. Conversion is monitored by TLC (1:1 EA : Hex Rf 0.25 → 0.7). After 15-30 min., the reaction is loaded directly onto a silica column and eluted with 1:3 EA : Hex to obtain **20** as a clear oil. ^{1}H (400 MHz, $CDCl_3$): δ 5.79 (m, 1H), 5.22 (d, 1H), 5.07 (d, 1H), 3.89 (ddd, 1H), 3.82 (m, 2H), 3.74 (s, 3H), 3.68 (s, 3H), 3.30 (dd, 1H, J_1 = 11.6 Hz, J_2 = 1.6 Hz), 2.31 (dd, 2H), 2.01 (m, 1H), 1.86 (m, 2H), 1.67-1.58 (m, 3H), 1.15 (s, 3H). ^{13}C NMR (100 MHz): 171.7, 171.1, 138.3, 114.8, 83.59, 78.81, 74.38, 68.30, 53.51, 52.83, 52.69, 35.92, 34.65, 30.64, 26.09, 22.26.



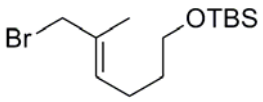
Lactone (21): Formed under acid or AgOTf catalysis from **19.** ^{1}H (400 MHz, $CDCl_3$): δ 5.05 (m, 1H), 4.73 (m, 2H), 4.39 (t, 1H), 3.87 (m, 2H), 3.76 (s, 3H), 2.69-2.51 (m, 3H), 2.31 (dd, 1H), 1.94 (m, 3H), 1.72 (m, 1H), 1.21 (s, 3H). GCMS: MW 280.3.



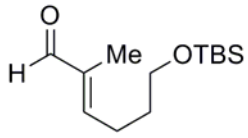
Alcohol (22): ^{1}H (400 MHz, $CDCl_3$): δ 4.92 (m, 1H), 4.63 (m, 2H), 3.91-3.73 (m, 3H), 3.69 (s, 6H), 3.61 (d, 1H), 2.85 (m, 1H), 2.65 (m, 1H), 2.36 (s, 1H), 2.15 (d, 1H), 2.01-1.82 (m, 4H), 1.53 (m, 1H), 1.12 (s, 3H)



2*E*-Methyl-(6-*tert*-butyldimethylsiloxy-2-methyl-hex-2-enoate) (28): light yellow oil. ^{1}H (400 MHz, $CDCl_3$): δ 6.78 (td, 1H), 3.73 (s, 3H), 3.62 (t, 2H), 2.23 (q, 2H), 1.83 (s, 3H), 1.65 (m, 2H), 0.89 (s, 9H), 0.05 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): 168.6, 142.1, 127.8, 104.2, 62.29, 51.54, 31.63, 26.30, 25.10, 18.23, 12.25, -5.39.

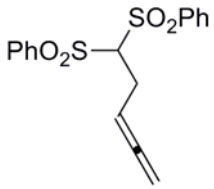


6-*tert*-butyldimethylsiloxy-2-methyl-hex-enyl bromide (29): ^{1}H (400 MHz, $CDCl_3$): δ 5.60 (t, 1H), 3.95 (s, 2H), 3.57 (t, 2H), 2.07 (q, 2H), 1.74 (s, 3H), 1.55 (m, 2H), 0.87 (s, 9H), 0.02 (s, 6H).

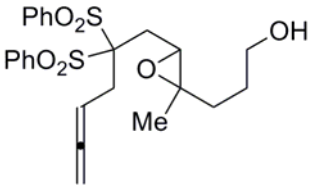


6-*tert*-butyldimethylsiloxy-2-methyl-hex-2-enal (30): To a mixture of methacrolein (8.7 mL, 0.1 mol, 7.0 eq., distilled before use) and TBS-protected 4-penten-1-ol (3 g, 15 mmol,

1.0 eq.) is added **G2** (191 mg, 1.5 mol%). The resultant dark red solution is evacuated and refilled with nitrogen 2x, then set to reflux on a 50°C bath for 8h. The reaction is cooled to room temperature, concentrated, loaded directly onto a silica gel column with ethyl acetate, and eluted with 1:10 EA : Hex. 82%, orange oil. ^{1}H (400 MHz, $CDCl_3$): δ 9.38 (s, 1H), 6.52 (t, 1H), 3.63 (t, 2H), 2.43 (t, 2H), 1.75-1.70 (m, 6H), 0.87 (s, 9H), 0.03 (s, 6H). *trans* selectivity was assayed by ^{13}C NMR after LAH reduction to be (>12 : 1), measured by integration of signals at 125.9 vs. 124.8.

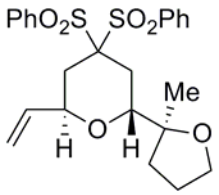


(1,2-Butadienyl)-bis(phenylsulfonyl)methane (31): Prepared by Mitsunobu reaction between allenyl alcohol and bis(phenylsulfonyl)methane [PPh_3, ADPP, THF, RT]. White crystalline solid. ^{1}H (400 MHz, $CDCl_3$): δ 7.94 (m, 4H), 7.69 (m, 2H), 7.57 (m, 4H), 5.14 (p, 1H), 4.70 (m, 2H), 4.54 (t, 1H), 2.87 (m, 2H).

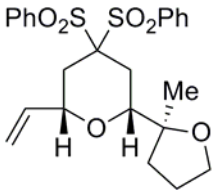


4*E*-7,7'-bis(phenylsulfonyl)-4-epoxy-4-methyl-9,10-dien-1-ol (33): White foam. Hygroscopic! ^{1}H (400 MHz, $CDCl_3$): δ 8.06 (d, 4H), 7.74 (q, 2H), 7.57 (m, 4H), 5.31 (m, 1H), 4.77 (m, 2H), 3.64 (m, 2H), 3.29 (t, 1H), 3.08 (m, 2H), 2.63 (dd, 1H, J_1 = 16 Hz, J_2 = 4.8 Hz), 2.30 (dd, 1H, J_1 = 16 Hz, J_2 = 4.4 Hz), 1.72-1.58 (m, 5H), 1.24 (s, 3H). ^{13}C NMR

(100 MHz, $CDCl_3$): 210.4, 136.6, 136.4, 134.9, 131.5, 131.4, 128.8, 128.7, 89.65, 83.35, 75.97, 62.35, 61.64, 57.87, 34.52, 30.09, 29.80, 27.63, 16.77. HRMS (TOF MS ES+): Calculated for ($C_{24}H_{28}O_6S_2$ + Na) 499.1211, found 499.1225.

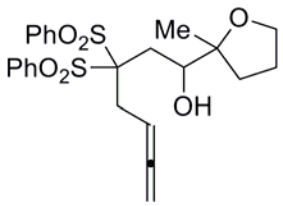


(2*R*,6*S*)-2-((*S*)-2-methyltetrahydrofuran-2-yl)-6-vinyl-4,4'-bis(phenylsulfonyl)-tetrahydropyran (major-34a): Prepared following Representative Procedure, see **20.** White foam. ^1H (400 MHz, $CDCl_3$): 8.06 (d, 2H), 7.99 (d, 2H), 7.73 (q, 2H), 7.61 (m, 4H), 5.75 (m, 1H), 5.29 (d, 1H), 5.17 (d, 1H), 4.68 (m, 1H), 4.02 (dd, 1H), 3.85 (m, 2H), 2.29 (m, 3H), 2.15 (dd, 1H), 1.94 (m, 2H), 1.66 (m, 1H), 1.14 (s, 3H). ^{13}C (100 MHz, C_6D_6): 141.2, 138.3, 134.1, 131.9, 131.6, 115.3, 83.62, 74.08, 70.73, 68.1, 35.87, 31.67, 26.65, 25.76, 20.49. HRMS (TOF MS ES+): Calculated for ($C_{24}H_{28}O_6S_2$ + Na) 499.1225, found 499.1207.

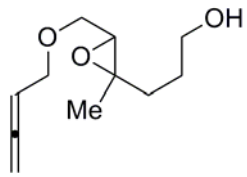


(2*R*,6*R*)-2-((*S*)-2-methyltetrahydrofuran-2-yl)-6-vinyl-4,4'-bis(phenylsulfonyl)-tetrahydropyran (minor-34b): White foam. ^1H (400 MHz, C_6D_6): 8.30 (m, 2H), 8.09 (d, 2H), 7.12-6.94 (m, 6H), 5.70 (m, 1H), 5.26 (d, 1H), 5.10 (m, 1H), 4.99 (d, 1H), 4.45 (dd, 1H, J_1 = 11.1 Hz, J_2 = 2.4 Hz), 3.68 (m, 2H), 2.90-2.45 (m, 4H), 2.05 (m, 1H), 1.64-1.50 (m, 4H), 1.21 (s, 3H). ^{13}C NMR (C_6D_6, 125 MHz): 138.1, 137.0, 136.5, 134.1, 133.9, 131.9,

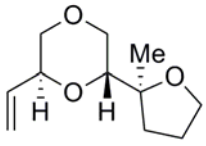
131.8, 131.6, 128.7, 115.3, 86.99, 83.31, 77.35, 73.84, 68.07, 36.09, 32.15, 26.10, 26.04, 20.83. HRMS (TOF MS ES+): Calculated for ($C_{24}H_{28}O_6S_2$ + Na) 499.1225, found 499.1207.



Acid-catalyzed product (34c): ^{1}H (400 MHz, $CDCl_3$): δ 8.05 (d, H), 7.68 (t, 2H), 7.56 (t, 4H), 5.29 (m, 1H), 4.68 (m, 2H), 4.15 (m, 1H), 3.90-3.75 (m, 2H), 3.47 (d, 1H), 3.14 (m, 2H), 2.82 (d, 1H), 2.24 (dd, 1H), 1.92 (m, 3H), 1.64 (m, 2H), 1.14 (s, 3H).

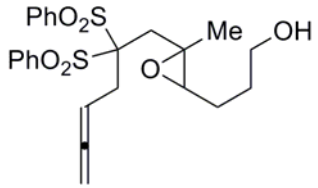


2*E*-epoxy-6-hydroxy-3-methylhexyl 2,3-butadienyl ether (35): Clear oil. ^{1}H (400 MHz): δ 5.19 (p, 1H), 4.76 (m, 2H), 4.03 (m, 2H), 3.59 (m, 3H), 3.52 (dd, 1H), 2.96 (t, 1H), 2.24 (bs, 1H), 1.62 (m, 4H), 1.25 (s, 3H). ^{13}C (166 MHz): 209.4, 87.4, 75.8, 69.0, 68.3, 62.3, 61.2, 60.1, 34.7, 27.8, 16.6 HRMS (TOF MS ES+): Calculated for ($C_{11}H_{18}O_3$ + Na) 221.1157, found 221.1154.

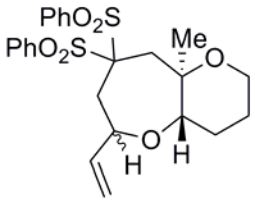


(2*R*,6*S*)-2-((*S*)-2-methyltetrahydrofuran-2-yl)-6-vinyl-1,4-dioxane (36a): Prepared following Representative Procedure, see **20.** Clear oil. ^{1}H (300 MHz, $CDCl_3$): 5.69 (m, 1H), 5.31 (dd, 1H, J_1 = 16.8 Hz, J_2 = 1.8 Hz), 5.15 (dt, 1H, J_1 = 10.8 Hz, J_2 = 1.5 Hz), 4.11

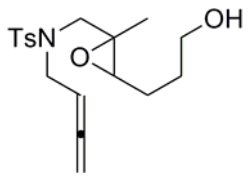
(m, 1H), 3.83 (m, 4H), 3.69 (dd, 1H, J_1 = 11.4 Hz, J_2 = 2.7 Hz), 3.51 (dd, 1H, J_1 = 10.2 Hz, J_2 = 2.4 Hz), 3.34 (t, 1H, J = 11.1 Hz), 3.15 (t, 1H, J = 11.1 Hz), 2.06 (m, 1H), 1.87 (m, 2H), 1.59 (m, 1H), 1.16 (s, 3H). ^{13}C (100 MHz, $CDCl_3$): 134.4, 116.8, 82.54, 79.83, 76.39, 70.42, 68.26, 67.02, 35.30, 25.99, 22.22.



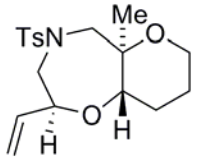
4*E*-7,7'-bis(phenylsulfonyl)-4-epoxy-5-methyl-9,10-dien-1-ol (37): ^{1}H (400 MHz, $CDCl_3$): δ 7.99 (d, 2H), 7.86 (d, 2H), 7.66 (m, 2H), 7.53 (m, 4H), 5.17 (p, 1H), 4.72 (m, 2H), 3.61 (m, 2H), 3.30-3.21 (m, 2H), 3.10 (m, 1H), 2.74 (d, 1H), 2.25 (d, 1H), 1.99 (s, 2H), 1.72 (m, 4H), 1.46 (s, 3H). ^{13}C (100 MHz, $CDCl_3$): 210.3, 137.6, 137.0, 134.8, 131.4, 131.35, 128.8. HRMS (TOF MS ES+): Calculated for ($C_{24}H_{28}O_6S_2$ + Na) 499.1211, found 499.1225.



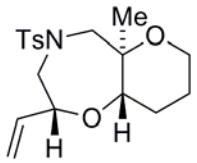
[5.4.0] bis-ether (38a): Prepared following Representative Procedure, see **20.** White foam. ^{1}H (300 MHz, C_6D_6): 8.24-8.10 (m, 4H), 7.01 (m, 6H), 5.54 (m, 1H), 4.85 (m, 2H), 3.48 (d, 1H, J = 16.8 Hz), 3.31 (t, 2H), 2.72 (d, 1H), 2.57 (d, 1H, J = 16.2 Hz), 2.35 (t, 1H), 2.28 (t, 1H), 1.69 (m, 2H), 1.16 (s, 3H).



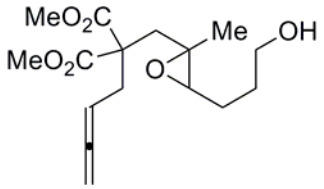
***N*-(1,2-butadienyl)-*N*-(2*E*-epoxy-6-hydroxy-2-methyl)-toluenesulfonamide (39):** ^{1}H (300 MHz, $CDCl_3$): δ 7.57 (d, 2H), 7.20 (d, 2H), 4.72 (m, 1H), 4.56 (m, 2H), 3.87-3.71 (ddd, 2H), 3.57 (t, 2H), 3.15 (dd, 2H), 2.78 (m, 1H), 2.32 (s, 3H), 1.68-1.49 (m, 4H), 1.24 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 209.5, 143.5, 137.0, 129.7, 127.1, 85.09, 76.15, 62.01, 61.67, 59.70, 53.00, 47.33, 29.39, 24.94, 21.43, 14.85. HRMS (TOF MS ES+): Calculated for ($C_{18}H_{25}NO_4S$ + Na): 374.1402, found 374.1401.



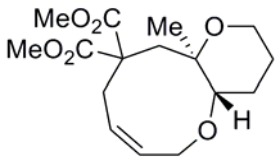
[5.4.0] sulfonamide (major-40a): Prepared following Representative Procedure, see **20.** Light yellow oil. ^{1}H (500 MHz, C_6D_6): 7.57 (d, 2H), 6.69 (d, 2H), 5.48 (m, 1H), 5.10 (d, 1H), 4.90 (d, 1H), 4.19 (b, 1H), 3.98 (dd, 1H, J_1 = 11 Hz, J_2 = 1.5 Hz), 3.77 (d, 1H, J_1 = 11 Hz), 3.55 (q, 1H), 3.51 (t, 1H, J = 7Hz), 3.40 (q, 1H), 2.18 (d, 1H), 1.95 (t, 1H), 1.85 (s, 3H), 1.57 (m, 2H), 1.31 (m, 2H), 1.28 (s, 3H). ^{13}C (125 MHz, C_6D_6): 142.9, 135.8, 133.4, 129.5, 116.3, 83.67, 75.48, 69.65, 68.46, 53.29, 50.58, 26.01, 25.76, 20.88, 14.50. HRMS (TOF MS ES+): Calculated for ($C_{18}H_{25}NO_4S$ + Na): 374.1402, found 374.1390.



(**40b**): ^{1}H (300 MHz, C_6D_6): 7.58 (d, 2H), 6.73 (d, 2H), 5.48 (m, 1H), 5.12 (d, 1H), 4.90 (d, 1H), 4.56 (t, 1H), 4.20 (dd, 1H, J_1 = 11 Hz, J_2 = 1.5 Hz), 4.02 (m, 1H), 3.78 (dt, 1H), 3.59 (m, 2H), 2.00 (d, 1H), 1.99 (t, 1H), 1.87 (s, 3H), 1.61 (m, 1H), 1.45 (m, 3H), 0.98 (s, 3H). ^{13}C NMR (C_6D_6, 125 MHz): 142.9, 135.9, 133.5, 129.5, 116.3, 76.09, 74.83, 70.32, 68.59, 51.98, 49.93, 26.22, 24.86, 20.88, 19.45. HRMS (TOF MS ES+): Calculated for ($C_{18}H_{25}NO_4S$ + Na): 374.1402, found 374.1390.

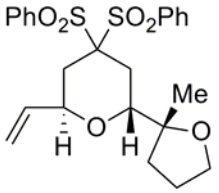


4*E*-7,7'-bis(phenylsulfonyl)-4-epoxy-5-methyl-9,10-dien-1-ol (41): ^{1}H (400 MHz, $CDCl_3$): δ 4.89 (p, 1H), 4.56 (m, 2H), 3.63 (bs, 6H), 3.56 (t, 2H), 2.64 (m, 2H), 2.58-2.49 (m, 2H), 2.27 (d, 1H), 2.02 (d, 1H), 1.62-1.45 (m, 4H), 1.11 (s, 3H). ^{13}C (100 MHz, $CDCl_3$): 209.1, 171.1, 84.47, 74.74, 63.79, 62.07, 58.37, 56.64, 52.20, 41.06, 33.06, 29.42, 24.94, 17.28.

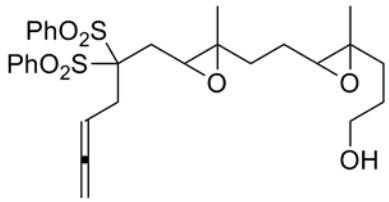


(4aS,11aR,Z)-dimethyl-11a-methyl-4,4a,6,9,11,11a-hexahydro-2H-pyrano[3,2-b] oxonine-10,10(3H)- dicarboxylate (42): Prepared following Representative Procedure, see **20.** Clear oil. ^{1}H (300 MHz, $CDCl_3$): δ 5.62 (m, 2H), 3.90-3.80 (m, 7H), 3.77 (s, 3H), 3.68

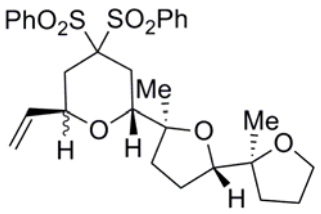
(s, 1H), 3.28 (s, 3H), 2.82 (dd, 1H), 2.61 (dd, 1H), 2.42 (d, 1H), 2.25 (d, 1H), 1.93 (m, 4H), 1.38 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): 170.8, 131.7, 127.5, 85.70, 83.26, 72.63, 68.88, 57.85, 56.08, 53.22, 38.16, 36.39, 27.10, 26.10, 23.49. HRMS: Calculated for ($C_{16}H_{24}O_6$ + Na) = 335.1471, found 335.1462.



(2*R*,6*S*)-2-((*R*)-2-methyltetrahydrofuran-2-yl)-6-vinyl-4,4'-bis(phenylsulfonyl)-tetrahydropyran (major-44a): Prepared following Representative Procedure, see **20.** ^{1}H (300 MHz, C_6D_6): 8.23 (dd, 4H, J_1 = 6.3 Hz, J_2 = 1.8 Hz), 7.03 (m, 9H), 5.70 (m, 1H), 5.33 (d, 1H), 5.00 (d, 1H), 4.81 (m, 1H), 4.48 (dd, 1H), 3.73 (t, 2H), 3.28 (dd, 1H), 2.68 (m, 4H), 2.29 (m, 1H), 1.59 (m, 2H), 1.32 (m, 2H), 1.02 (s, 3H).



***rac*-(4*E*,8*E*)-11,11'-bis(phenylsulfonyl)-4,8-dimethyl-4,8-diepoxy-pentadeca-13,14-dien-ol (49):** ^{1}H (300 MHz, C_6D_6): 8.05 (d, 4H), 7.71 (q, 2H), 7.61 (q, 4H), 5.28 (m, 1H), 4.74 (m, 2H), 3.62 (q, 2H), 3.27 (t, 1H), 3.08 (m, 2H), 2.80-2.60 (bm, 2H), 2.30 (m, 1H), 1.82-1.54 (m, 11 H), 1.24 (m, 6H).



(2*R*,6*S*)-2-[(*S*)-2-methyl-5*S*-(*S*-2-methyltetrahydrofuranyl)]-tetrahydrofuran-2-yl]-6-vinyl-4,4'-bis(phenylsulfonyl)-tetrahydropyran (mixture, 50a,b): Prepared following Representative Procedure, see **20.** Off-white semi-solid. ^{1}H (300 MHz, C_6D_6): 8.18 (t, 4H), 8.15 (m, 1H), 8.09 (d, 3H), 7.36 (t, 3H), 7.05 (m, 7H), 5.73 (m, 1H), 5.29 (d, 2H), 5.15 (m, major diastereomer, 0.9), 5.03 (d, 2H), 4.75 (m, minor diastereomer, 0.35), 4.49 (d, 2H), 3.95 (m, 4H), 3.74 (m, 4H), 3.10-2.88 (m, 2H), 2.78-2.38 (m, 3H), 1.96 (m, 3H), 1.68 (m, 8H), 1.45 (m, 5H), 1.21 (s, 6H), 1.19 (s, 6H).

BIBLIOGRAPHY

Abe, I.; Rohmer, M.; Prestwich, G. D. *Chem. Rev.* **1993**, *93*, 2189-2206.

Alvarez, E.; Candenas, M.-L.; Pérez, R.; Ravelo, J. L.; Martin, J. D. *Chem. Rev.* **1995**, *95*, 1953-1980.

Anastas, P.; Warner, J. *Green Chemistry: Theory and Practice*; Oxford University Press: New York, 1998.

Antoniotti, S.; Genin, E.; Michelet, V.; Genêt, J.-P. *J. Am. Chem. Soc.* **2005**, *127*, 9976-9977

Arcadi, A. *Chem. Rev.* **2008**, *108*, 3266-3325.

Aubert, C.; Buisine, M.; Malacria, M. *Chem. Rev.* **2002**, *102*, 813-834.

Bachrach, S. *J. Org. Chem.* **2008**, *73*, 2466-2468.

Baldwin, J. E. *J. Chem. Soc. Chem. Comm.* **1976**, 734-736.

Bandini, M.; Emer, E.; Tommasi, S.; Umani-Ronchi, A. *Eur. J. Org. Chem.* **2006**, 3527-3544.

Barder, T. E.; Biscoe, M. R.; Buchwald, S. L. *Organometallics* **2007**, *26*, 2183-2192.

Brummond, K. M.; Chen, H.; Mitasev, B.; Casarez, A. D. *Org. Lett.* **2004**, *6*, 2161-2163

Cane, D. E.; Celmer, W. D.; Westley, J. W. *J. Am. Chem. Soc.* **1983**, *105*, 3594-3600.

Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry - Part A: Structures and Mechanisms*; 4th ed.; Kluwer: New York, 2000.

Cheong, P. H.-Y.; Morganelli, P.; Luzung, M. R.; Houk, K. N.; Toste, F. D. *J. Am. Chem. Soc.* **2008**, *130*, 4517-4526.

Chianese, A. R.; Lee, S. J.; Gagné, M. R. *Angew. Chem. Int. Ed.* **2007**, *46*, 4042-4059.

Coetzee, J. F.; Chang, T.-H. *Pure Appl. Chem.* **1986**, *58*, 1541-1555

Corey, E. J.; Cane, D. E.; Libit, L. *J. Am. Chem. Soc.* **1971**, *93*, 7017-7021.

Crabbé, P.; Nassim, B.; Robert-Lopes, M.-T. *Org. Syn.* **1985**, *63*, 203-204.

Crimmins, M. T.; Ellis, J. M. *J. Org. Chem.* **2008**, *73*, 1649-1660.

Dai, L.-Z.; Qi, M.-J.; Shi, Y.-L.; Liu, X.-G.; Shi, M. *Org. Lett.* **2007**, *9*, 3191-3194.

DeVries, R. A.; Vosejpka, P. C.; Ash, M. L. In *Catalysis of Organic Reactions*; Herkes, F. E., Ed.; Marcel Dekker: New York, 1998.

Dyker, G. *Angew. Chem. Int. Ed.* **2000**, *39*, 4237-4239.

Evans, D. A.; Scheidt, K. A.; Fandrick, K. R.; Lam, H. W.; Wu, J. *J. Am. Chem. Soc.* **2003**, *125*, 10780-10781.

Evans, D. A.; Fandrick, K. R.; Song, H.-J.; Scheidt, K. A.; Xu, R. *J. Am. Chem. Soc.* **2007**, *129*, 10029-10041.

Faul, M. M.; Huff, B. E. *Chem. Rev.* **2000**, *100*, 2407-2473.

Feducia, J. A.; Campbell, A. N.; Doherty, M. Q.; Gagné, M. R. *J. Am. Chem. Soc.* **2006**, *128*, 13290-13297.

Feducia, J. A.; Campbell, A. N.; Anthis, J. W.; Gagné, M. R. *Organometallics* **2006**, *25*, 3114-3117.

Ferrer, C.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2006**, *45*, 1105-1109.

Friebolin, H. *Basic One- and Two-Dimensional NMR Spectroscopy*; Wiley-VCH: Heidelberg, 2005.

Fukuda, Y.; Utimoto, K. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 2013-2015.

Fukuyama, T.; Wang, C.-L. J.; Kishi, Y. *J. Am. Chem. Soc.* **1979**, *79*, 260-261.

Fukuyama, T.; Akasaka, K.; Karanewsky, D. S.; Wang, C.-L. J.; Schmid, G.; Kishi, Y. *J. Am. Chem. Soc.* **1979**, *101*, 262-263.

Fürstner, A.; Davies, P. W. *Angew. Chem. Int. Ed.* **2007**, *46*, 3410-3449.

Fürstner, A.; Morency, L. *Angew. Chem. Int. Ed.* **2008**, *47*, 5030-5033

Gamboni, G.; Schniz, H.; Eschenmoser, A. *Helv. Chim. Acta* **1954**, *37*, 964-971.

Gasparrini, F.; Giovannoli, M.; Misiti, D.; Natile, G.; Palmieri, G.; Maresca, L. *J. Am. Chem. Soc.* **1993**, *115*, 4401-4402.

Gorin, D. J.; Sherry, B. D.; Toste, F. D. *Chem. Rev.* **2008**, *108*, 3351-3378.

Gorin, D. J.; Toste, F. D. *Nature* **2007**, *446*, 395-403.

Grandberg, K. I. *Russ. Chem. Rev.* **1982**, *51*, 249-264.

Gulácsi, K.; Litkei, G.; Antus, S.; Szántay, C.; Darkó, L. L.; Szelényi, J.; Haskó, G.; Vizi, S. *Arch. Pharm. Med. Chem.* **2001**, *334*, 53-61.

Hahn, C.; Cucciolito, M. E.; Vitagliano, A. *J. Am. Chem. Soc.* **2002**, *124*, 9038-9039.

Hamilton, G. L.; Kang, E. J.; Mba, M.; Toste, F. D. *Science* **2007**, *317*, 496-499.

Hara, S.; Dojo, H.; Takinami, S.; Suzuki, A. *Tetrahedron Lett.* **1983**, *24*, 731-734.

Harkat, H.; Blanc, A.; Weibel, J.-M.; Pale, P. *J. Org. Chem.* **2008**, *73*, 1620-1623.

Harding, W. W.; Lewis, P. A.; Jacobs, H.; McLean, S.; Reynolds, W. F.; Tay, L.-L.; Yang, J.-P. *Tetrahedron Lett.* **1995**, *36*, 9137-9140.

Hashmi, A. S. K.; Frost, T. M.; Bats, J. W. *J. Am. Chem. Soc.* **2000**, *122*, 11553-11554.

Hashmi, A. S. K.; Frost, T. M.; Bats, J. W. *Org. Lett.* **2001**, *3*, 3769-3771.

Hashmi, A. S. K.; Weyrauch, J. P.; Rudolph, M.; Kurpejovic, E. *Angew. Chem. Int. Ed.* **2004**, *43*, 6545-6547.

Hashmi, A. S. K. *Angew. Chem. Int. Ed.* **2005**, *44*, 6990-6993.

Hashmi, A. S. K.; Blanco, M. C. *Eur. J. Org. Chem.* **2006**, 4340-4342.

Hashmi, A. S. K.; Hutchings, G. J. *Angew. Chem. Int. Ed.* **2006**, *45*, 7896-7936.

Hashmi, A. S. K.; Schäfer, S.; Wölfle, M.; Gil, C. D.; Fischer, P.; Laguna, A.; Blanco, M. C.; Gimeno, M. C. *Angew. Chem. Int. Ed.* **2007**, *46*, 6184-6187.

Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180-3211.

Hastings, J. M.; Hadden, M. K.; Blagg, B. S. J. *J. Org. Chem.* **2008**, *73*, 369-373.

Honig, B.; Dinur, U.; Nakanishi, K.; Balogh-Nair, V.; Gawinowicz, M. A.; Arnaboldi, M.; Motto, M. G. *J. Am. Chem. Soc.* **1979**, *101*, 7084-7086.

Huang, A. X.; Xiong, Z.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 9999-10003.

Inoue, M. *Chem. Rev.* **2005**, *105*, 4379-4405.

Inoue, M.; Hirama, M. *Acc. Chem. Res.* **2004**, *37*, 961-968.

Inoue, M.; Lee, N.; Miyazaki, K.; Usuki, T.; Matsuoka, S.; Hirama, M. *Angew. Chem. Int. Ed.* **2008**, *47*, *ASAP*.

Ito, Y.; Sawamura, M.; Hamashima, H.; Emura, T.; Hayashi, T. *Tetrahedron Lett.* **1989**, *30*, 4681-4683.

Jahn, B. O.; Eger, W. A.; Anders, E. *J. Org. Chem.* **2008**, *73*, 8265-8273.

Janda, K. D.; Shevlin, C. G.; Lerner, R. A. *Science* **1992**, *259*, 490-493.

Johansson, M. I.; Gorin, D. J.; Staben, S. T.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 18002-18003.

Johnson, W. S.; Telfer, S. J.; Cheng, S.; Schubert, U. *J. Am. Chem. Soc.* **1987**, *109*, 2517-2518.

Johnson, W. S. *A Fifty Year Love Affair with Organic Chemistry*; American Chemical Society, 1998.

Kang, S.-K.; Ko, B.-S.; Lee, D.-M. *Tetrahedron Lett.* **2002**, *42*, 6693-6696.

Kang, S.-K.; Ko, B.-S.; Ha, Y.-H. *J. Org. Chem.* **2001**, *66*, 3630-3633.

Karplus, M. *J. Am. Chem. Soc.* **1963**, *85*, 2870-2871.

Kennedy-Smith, J. J.; Staben, S. T.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 4526-4527.

Kerber, W. D.; Gagné, M. R. *Org. Lett.* **2005**, *7*, 3379-3381.

Koh, J. H.; Gagné, M. R. *Angew. Chem. Int. Ed.* **2004**, *116*, 3541-3543.

Koh, J. H.; Mascarenhas, C.; Gagné, M. R. *Tetrahedron* **2004**, *60*, 7405-7410.

Korotchenko, V. N.; Gagné, M. R. *J. Org. Chem.* **2007**, *72*, 4877-4881.

LaLonde, R. A.; Sherry, B. D.; Kang, E.-J.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 2452-2453.

Lee, J. H.; Toste, F. D. *Angew. Chem. Int. Ed.* **2007**, *47*, 912-914.

Lemiere, G.; Gandon, V.; Agenet, N.; Goddard, J.-P.; Kozak, A.; Aubert, C.; Fensterbank, L.; Malacria, M. *Angew. Chem. Int. Ed.* **2006**, *45*, 7596-7599.

Li, Z.; Brouwer, C.; He, C. *Chem. Rev.* **2008**, *108*, 3239-3265.

Li, Y.; Zhou, F.; Forsyth, C. *Angew. Chem. Int. Ed.* **2007**, *46*, 279-282.

Li, Y.; Tang, P.; Chen, Y.; Yu, B. *J. Org. Chem.* **2008**, *73*, 4323-4325.

Lin, Y.-Y.; Risk, M.; Ray, S. M.; Van Engen, D.; Clardy, J.; Golik, J.; James, J. C.; Nakanishi, K. *J. Am. Chem. Soc.* **1981**, *103*, 6773-6775.

Lin, G.-Y.; Li, C.-W.; Hung, S.-H.; Liu, R.-S. *Org. Lett.* **2008**, *10*, 5059-5062

Linghu, X.; Kennedy-Smith, J. J.; Toste, F. D. *Angew. Chem. Int. Ed.* **2007**, *46*, 7671-7673

Liu, C.; Widenhoefer, R. A. *Org. Lett.* **2007**, *9*, 1935-1938.

Liu, C.; Han, X.; Wang, X.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2004**, *126*, 3700-3701.

Lodeiro, S.; Xiong, Q.; Wilson, W. K.; Kolesnikova, M. D.; Ovak, C. S.; Matsuda, S. P. T. *J. Am. Chem. Soc.* **2007**, *129*, 11213-11222.

Luzung, M. R.; Markham, J. P.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 10858-10859.

Lu, P.; Ma, S. *Org. Lett.* **2007**, *9*, 5319-5321.

Ma, S. *Chem. Rev.* **2005**, *105*, 2829-2871.

Makino, T.; Itoh, K. *Tetrahedron Lett.* **2003**, *44*, 6335-6338.

Makino, T.; Itoh, K. *J. Org. Chem.* **2004**, *69*, 395-405.

Matsuo, G.; Kawamura, K.; Hori, N.; Matsukura, H.; Nakata, T. *J. Am. Chem. Soc.* **2004**, *126*, 14374-14376.

Mayr, H.; Kempf, B.; Ofial, A. R. *Acc. Chem. Res.* **2003**, *36*, 66-77.

Mayr, H.; Patz, M. *Angew. Chem. Int. Ed.* **1994**, *33*, 938-957.

Melhado, A. S.; Luparia, M.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 12638-12639.

Minnihan, E. C.; Colletti, S. L.; Toste, F. D.; Shen, H. C. *J. Org. Chem.* **2007**, 6287-6289.

Mizobuchi, S.; Sato, Y. *Agric. Biol. Chem.* **1985**, *49*, 719-724.

Mohr, F.; Falvello, L. R.; Laguna, M. *Eur. J. Inorg. Chem.* **2006**, 833-838.

Molander, G.; Cormier, E. P. *J. Org. Chem.* **2005**, *70*, 2622-2626.

Mullen, C. A.; Gagné, M. R. *J. Am. Chem. Soc.* **2007**, *129*, 11880-11881.

Mullen, C. A.; Campbell, A. N.; Gagné, M. R. *Angew. Chem. Int. Ed.* **2008**, *47*, 6011-6014.

Mukai, C.; Itoh, R. *Tetrahedron Lett.* **2006**, *47*, 3971-3974.

Muñoz, M. P.; Adrio, J.; Carretero, J. C.; Echavarren, A. M. *Organometallics* **2005**, *24*, 1293-1300.

Nakata, T. *Chem. Rev.* **2005**, *105*, 4314-4347.

Neighbors, J. D.; Buller, M. J.; Boss, K. D.; Wiemer, D. F. *J. Nat. Prod.*, *ASAP*.

Nicolaou, K. C.; Frederick, M. O.; Aversa, R. J. *Angew. Chem. Int. Ed.* **2008**, *47*, 7182-7225.

Norman, R. O. C.; Parr, W. J. E.; Thomas, C. B. *J. Chem. Soc. Perkin Trans. I* **1976**, 1983-1987.

Olah, G. A. *Friedel Crafts and Related Reactions*; Wiley-Interscience: New York, 1963-1965.

Overman, L.E.; Knoll, F.M. *J. Am. Chem. Soc.* **1980**, *102*, 685-687.

Piera, J.; Krumlinde, P.; Strübing, D.; Bäckvall, J.-E. *Org. Lett.* **2007**, *9*, 2235-2237.

Pohlhaus, P. D.; Johnson, J. S. *J. Am. Chem. Soc.* **2005**, *127*, 16014-16015 (SI p.18).

Poulsen, T. B.; Jørgensen, K. A. *Chem. Rev.* **2008**, *108*, 2903-2915.

Reetz, M. T.; Sommer, K. *Eur. J. Org. Chem.* **2003**, 3485-3496.

Rueping, M.; Nachtsheim, B. J.; Kuenkel, A. *Org. Lett.* **2007**, *9*, 825-828.

Schmid, G.; Fukuyama, T.; Akasaka, K.; Kishi, Y. *J. Am. Chem. Soc.* **1979**, *79*, 259-260.

Schmidbaur, H. *Naturwiss. Rundsch.* **1995**, *48*, 443.

Schmidbaur, H.; Schier, A. *Chem. Soc. Rev.* **2008**, *37*, 1931-1951.

Gold: Progress in Chemistry, Biochemistry, and Technology; Schmidbaur, H., Ed.; Wiley & Sons: New York, 1999.

Seiders II, J. R.; Wang, L.; Floreancig, P. E. *J. Am. Chem. Soc.* **2003**, *125*, 2406-2407.

Sethofer, S.; Staben, S. T.; Hung, O. Y.; Toste, F. D. *Org. Lett.* **2008**, *10*, 4315-4318.

Shi, Z.; He, C. *J. Org. Chem.* **2004**, *69*, 3669-3671.

Simpson, G. L.; Heffron, T. J.; Merino, E.; Jamison, T. F. *J. Am. Chem. Soc.* **2006**, *128*, 1056-1057.

Singh, I. P.; Bharate, S. P. *Nat. Prod. Rep.* **2006**, *23*, 558-591.

Soloshonok, V. A.; Hayashi, T. *Tetrahedron Lett.* **1994**, *35*, 2713-2716.

Soriano, E.; Marco-Contellos, J. *Organometallics* **2006**, *25*, 4542-4553.

Spencer, T. A. *Acc. Chem. Res.* **1994**, *27*, 83-90.

Staben, S. T.; Kennedy-Smith, J. J.; Huang, D.; Corkey, B. K.; LaLonde, R. A.; Toste, F. D. *Angew. Chem. Int. Ed.* **2006**, *45*, 5991-5994.

Stork, G.; Burgstahler, A. W. *J. Am. Chem. Soc.* **1955**, *77*, 5068-5077.

Stork, J. R.; Rios, D.; Pham, D.; Bicocca, V.; Olmstead, M. M.; Balch, A. L. *Inorg. Chem.* **2005**, *44*, 3466-3472.

Tarselli, M. A.; Chianese, A. R.; Lee, S. J.; Gagné, M. R. *Angew. Chem. Int. Ed.* **2007**, *46*, 6670-6673.

Tarselli, M. A.; Gagné, M. R. *J. Org. Chem.* **2008**, *73*, 2439-2441.

Tarselli, M. A.; Liu, A.; Gagné, M. R. *Tetrahedron*, accepted for special issue, **2008**

Tarselli, M. A.; Gagné, M. R. *J. Am. Chem. Soc.* **2008**, *submitted*.

Teles, J. H.; Brode, S.; Chabanas, M. *Angew. Chem. Int. Ed.* **1998**, *37*, 1415-1418.

Terakado, M.; Miyazawa, M.; Yamamoto, K. *Synlett* **1994**, 134-136.

Thompson, D. *Gold Bull.* **1998**, *31*, 112-118.

Thompson, D. *Gold Bull.* **1999**, *32*, 12-18.

Togni, A.; Pastor, S. D.; Rihs, G. *J. Organomet. Chem.* **1990**, *381*, C21-C24.

Tolman, C. A. *Chem. Rev.* **1977**, *77*, 313-348.

Tolman, C. A. *J. Am. Chem. Soc.* **1970**, *92*, 2953-2956.

Tolman, C. A. *J. Am. Chem. Soc.* **1970**, *92*, 2956-2965.

Tong, R.; Valentine, J. C.; McDonald, F. E.; Cao, R.; Fang, X.; Hardcastle, K. I. *J. Am. Chem. Soc.* **2007**, *129*, 1050-1051.

Trost, B. M.; Tour, J. M. *J. Am. Chem. Soc.* **1988**, *110*, 5231-5233.

Trost, B. M.; Matsuda, K. *J. Am. Chem. Soc.* **1988**, *110*, 5233-5235.

Trost, B. M. *Acc. Chem. Res.* **1990**, *23*, 34-42.

Trost, B. M. *Science* **1991**, *254*, 1471-1477.

Trost, B. M. *Acc. Chem. Res.* **2002**, *35*, 695-705.

Tsai, A. S.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2008**, *130*, 6316-6317.

Valentine, J. C.; McDonald, F. E. *Synlett* **2006**, 1816-1828.

Valentine, J. C.; McDonald, F. E.; Neiwert, W. A.; Hardcastle, K. I. *J. Am. Chem. Soc.* **2005**, *127*, 4586-4587.

Van der Schyf, C. J.; Dekker, T. G.; Fourie, T. G.; Snyckers, F. O. *Antimicrob. Agents Chemother.* **1986**, *30*, 375-381.

Vilotijevic, I.; Jamison, T. *Science* **2007**, *317*, 1189-1192.

Wan, S.; Gunayadin, H.; Houk, K. N.; Floreancig, P. E. *J. Am. Chem. Soc.* **2007**, *129*, 7915-7923.

Wang, Z.-X.; Shu, L.; Frohn, M.; Tu, Y.; Shi, Y. *Org. Syn.* **2003**, *80*, 9-13.

Watanabe, T.; Oishi, S.; Fujii, N.; Ohno, H. *Org. Lett.* **2007**, *9*, 4821-4824

Wender, P. A.; Croatt, M. P.; Deschamp, N. M. *Angew. Chem. Int. Ed.* **2006**, *45*, 2459-2462.

Wendt, K. U.; Schulz, G. E.; Corey, E. J.; Liu, D. R. *Angew. Chem. Int. Ed.* **2000**, *39*, 2812-2833.

Widenhoefer, R. A. *Chem. Eur. J.* **2008**, *14*, 5382-5391.

Ye, C.; Shreeve, J. M. *J. Org. Chem.* **2004**, *69*, 8561-8563.

Zhang, L.; Kozmin, S. A. *J. Am. Chem. Soc.* **2005**, *127*, 6962-6963.

Zhang, Z.; Liu, C.; Kinder, R. E.; Han, X.; Qian, H.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2006**, *128*, 9066-9073.

Zhang, Z.; Widenhoefer, R. A. *Org. Lett.* **2008**, *10*, 2079-2081.

Zhang, Z.; Bender, C. F.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2007**, *129*, 14148-14149.

Zhou, X.-T.; Lin, Y.-R.; Dai, L.-X.; Sun, J.; Xia, L.-J.; Tang, M.-H. *J. Org. Chem.* **1999**, *64*, 1331-1334.