UTILIZING ALLYLIC ALCOHOLS AS BOTH ELECTROPHILES AND NUCLEOPHILES IN GOLD-CATALYZED REACTIONS

By

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To my family and friends

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Ac	Acetyl
(*R*)-BINAPHANE	(*R*, *R*)-1,2-bis[(*R*)-4,5-dihydro-3H-binaptho(1,2-*c*:2',1'-e)phosphineobenzene
MeO-BIPHEP	1,2c:2',1'e)phosphepino]benzene-2,2′-Bis(diphenylphosphino)-6,6′-dimethoxy-1,1′-biphenyl
Boc	*tert*-butylcarbonyl
Bn	benzyl
Bz	benzoyl
Cbz	benzyloxycarbonyl
cod	1,5-cyclooctadiene
DACH-Ph	1,2-Diaminocyclohexane-N,N′-bis(2-diphenylphosphinobenzoyl)
DABCO	1,4-diazabicyclo[2.2.2]octane
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DMPS	dimethylphenylsilyl
DPPBA	diphenylphosphinobenzoic acid
dppe	1,2-bis(diphenylphosphino)ethane
Fmoc	9-fluorenylmethoxycarbonyl
Ns	2-nitrobenzenesulfonyl
Ph	phenyl
PMB	*p*-methoxybenzyl
PMP	*p*-methoxyphenyl
TBD	1,5,7-triazabicyclo-[4.4.0]undec-5-ene
Tf	trifluoromethanesulfonyl
TMS	trimethylsilyl

Troc	2,2,2-trichloroethoxycarbonyl
Ts	p-toluenesulfonyl

Abstract of Dissertation Presented to the Graduate School
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Requirements for the Degree of Doctor of Philosophy

UTILIZING ALLYLIC ALCOHOLS AS BOTH ELECTROPHILES AND NUCLEOPHILES IN GOLD-CATALYZED REACTIONS

By

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Major: Chemistry

Gold-catalysis has emerged as a powerful tool for the synthetic community, allowing for new transformations that are not easily accessed through other methods. Detailed in this dissertation, are the studies leading to a gold-catalyzed dehydrative cyclization to form azacycles via an intramolecular S_N2' type allylic alkylation reaction. Formation of the desired heterocycles occurs through the nucleophilic attack of a tethered nitrogen nucleophile on an allylic alcohol that is rendered electrophilic by a gold-catalyst. During these cyclization studies, an efficient transfer of chirality was observed. Interestingly, with cation stabilizing substituents in the allylic position a competing ionization pathway was observed.

Allylic alcohols are commonly used as electrophiles in dehydrative cyclization reactions, however, their use as nucleophiles is described here in the context of an efficient gold-catalyzed tandem hydroalkoxylation/Claisen rearrangement. This reversal in reactivity posed a significant challenge which required tuning the reaction conditions to circumvent the S_N2' side reactions and allow for selective hydroalkoxylation of the alkyne reaction partner. Fortunately, optimized conditions were found that gave facile

formation of the desired gamma, delta-unsaturated ketones. Successful implementation of this synthetic methodology provides a new protocol for rapidly building complex acyclic ketone products from an allylic alcohol and an alkyne. Additionally, the observed diastereoselectivities for the tandem process have given invaluable insight into the possible mechanistic pathways. During our studies of a gold-catalyzed Claisen rearrangement, an efficient sequential gold-catalyzed enol formation/ruthenium-catalyzed [1,3]-O to –C migration was also developed. The process allows for rapid access to highly functionalized cyclic ketone products in a highly diastereoselective fashion.

CHAPTER 1
SYNTHESIS OF SATURATED HETEROCYCLES VIA METAL-CATALYZED ALLYLIC ALKYLATION REACTIONS

Introduction

The ubiquity of heterocycles in biologically active natural products has led to an ever-growing abundance of methodologies aimed at the production of these cyclic structures. Among these strategies, metal-catalyzed intramolecular allylic alkylations have been particularly fruitful. These facile processes accommodate a broad range of substrates for cyclization under relatively mild conditions with low catalyst loadings. The following chapter is a review of the synthesis of saturated heterocycles via metal-catalyzed allylic alkylation reactions over the past ten years.

Mechanistically, metal-catalyzed allylic alkylation reactions can be placed into three distinct mechanistic categories: π-allyl, formal S_N2' and cationic systems (Figure 1-1). Although these systems can give identical products, their mechanistic pathways vary greatly depending on many factors including: solvent, metal-complex, leaving group, and additives.

π-allyl systems (**1-1**) in general contain nucleophilic/electron rich metal-complexes, and highly reactive leaving groups such as carbonates, halides, etc. Throughout the catalytic cycle, the metal will go through a redox reaction wherein two electrons are lost and regained during the reaction course. More recently, these reactions have focused on the use of new metal-complexes that do not incorporate palladium.

Formal S_N2' reactions (**1-3**) typically involve electrophilic π-acid metal-complex that prefers the formation of a π-complex without alternating oxidation states during the

transformation. These metal-catalyzed intramolecular formal S_N2' reactions constitute a relatively new class of reaction pathway when compared to the well-known π-allyl systems. New methodologies and mechanistic insights are still being reported, which has presented the scientific community with an overwhelming wealth of reports in the past ten years.

Cationic systems (**1-4**) normally incorporate highly electrophilic transition metals that can easily ionize the allyl system by abstracting the leaving group, thereby producing an allyl cation. The metal-complex is usually comprised of a hard metal that coordinates directly to the leaving group. The cationic nature of these systems adds a significant challenge when enantioenriched products are desired.

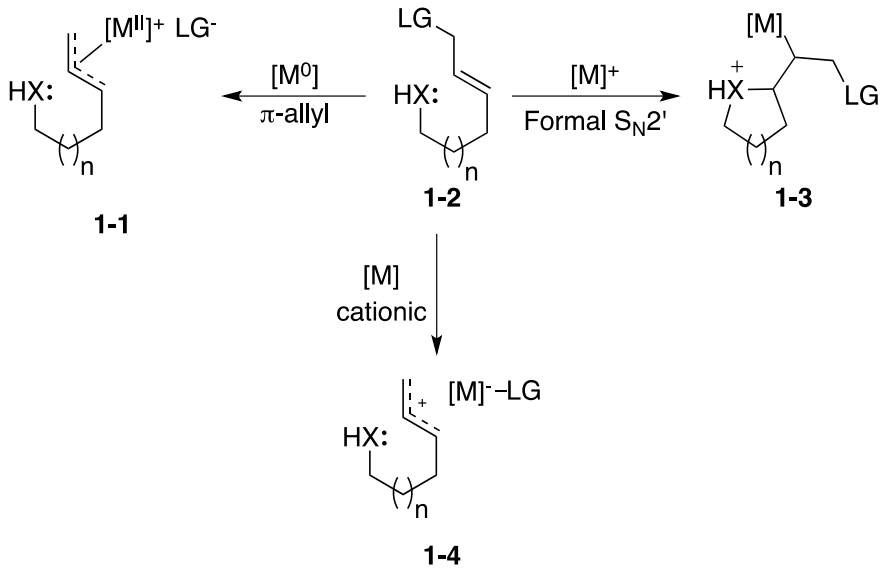


Figure 1-1. Activation modes for π-allyl, formal S_N2', and cationic systems

Over the past decade, various groups have reported these intramolecular cyclizations with numerous substrates and catalyst systems for use in the synthesis of natural products and other biologically relevant compounds. The following chapter is organized chronologically, by which mechanistic pathway was first reported. Each

mechanistic system is then organized by which metal-complex was first employed to promote the desired transformation, and further of those complexes which studies were first reported. This chapter reviews selected examples of saturated heterocycles constructed by carbon-heteroatom bond formation via metal-catalyzed allylic alkylation reactions. For brevity, heterocycles formed through carbon-carbon formation via allylic alkylation reactions will not be discussed in this chapter.

Formation of Saturated Heterocycles via π-allyl Metal Complexes

The following section covers select examples of π-allyl metal intermediates in the formation of heterocycles. These redox processes generally go through the following sequential mechanistic steps: coordination, oxidative addition, and reductive elimination.

Heterocycle Synthesis via π-allyl Palladium Intermediates

Since the initial discoveries of Tsuji *et al*.[1] and Trost and coworkers,[2] the Tsuji-Trost reaction has stood as one of the most versatile synthetic transformations[3] for the formation of carbon-carbon and carbon-heteroatom bonds. During their syntheses of (±)-desethylibogamine and (+)-ibogamine in the late 1970s, Trost *et al.* reported some of the earliest examples utilizing their methodology to form a carbon-heteroatom bond in an intramolecular fashion.[4] Over the past forty years, intramolecular Tsuji-Trost type cyclizations have become commonplace in the synthesis of heterocycles, and have been utilized in a myriad of natural product syntheses.[5]

Driven by their initial studies toward the construction of the core ring structure of vitamin E,[6] Trost and coworkers extensively studied a palladium-catalyzed intramolecular asymmetric allylic alkylation (AAA) of phenyl allyl carbonates (**1-5**) to form chromans (**1-6**) (Figure 1-2).[7] These highly useful synthons could be formed in

high yield and good enantioselectivities with the use of Pd_2dba_3 and **L1** under mild conditions. In general, the *E*-allylic carbonates give the (*R*)-chroman products while *Z*-allylic carbonates (which usually give higher enantioselectivities) give the (*S*)-chroman products.[7a]

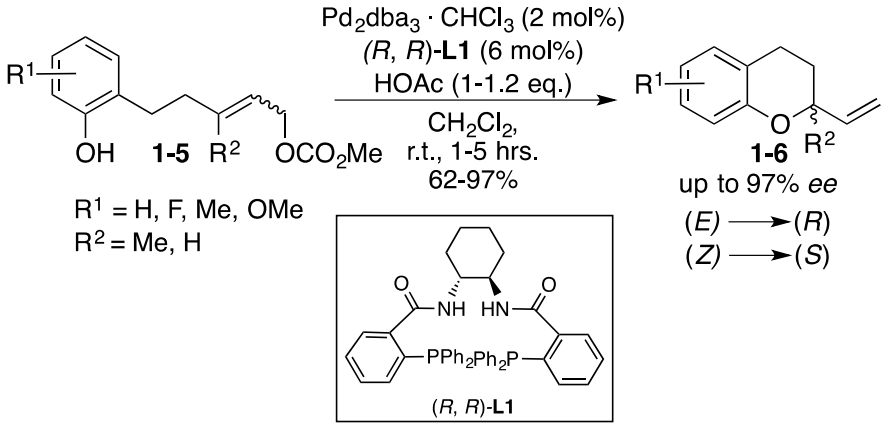


Figure 1-2. Pd-catalyzed synthesis of chromans from phenyl allyl carbonates

Their work culminates in the utilization of these Pd-catalyzed cyclizations in the total syntheses of (+)-clusifoliol[7b] and (-)-siccanin[7c]. Lastly, their mechanistic studies suggest that the enantiodiscriminating step involves the cyclization of the more reactive diastereomeric π-allyl intermediate.[7b]

In 2006, the same group found that similar conditions could be used to achieve a one-pot cascade reaction,[8] forming piperazinone **1-9** from a palladium-catalyzed asymmetric allylic alkylation (AAA) reaction between dicarbonate **1-7** and pyrrole **1-8**. This reaction was further used in the formal total synthesis of (-)-agelastatin A (Figure 1-3). Additional studies revealed that a sequential palladium-catalyzed process gave access to a regioisomer of **1-9**, which was used in the synthesis of the opposite enantiomer, (+)-agelastatin A.

In addition to the use of chiral palladium complexes, enantioenriched starting materials can also furnish products with high enantioselectivity without the use of a chiral catalyst. Spilling and coworkers utilized this strategy by creating a method to form enantioenriched β-ketophosphonates. These versatile synthons are commonly employed in the Horner-Wadsworth Emmons (HWE) olefination, a reaction that is consistently used in natural product syntheses.[9]

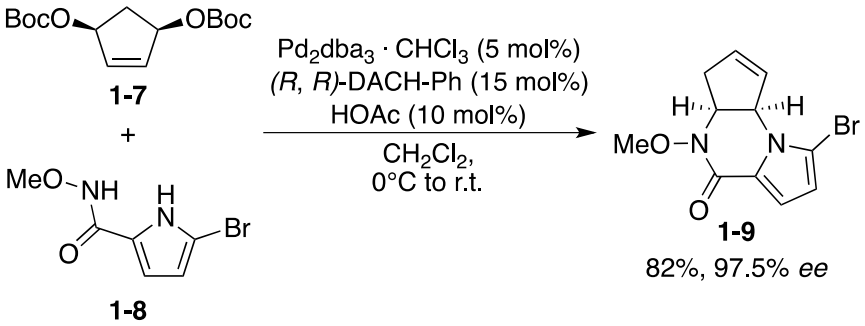


Figure 1-3. Synthesis of piperazinone **8** via Pd-catalyzed intramolecular Tsuji-Trost allylation

As an extension of their previously reported process for vinyl N-heterocyclic phosphonates, Spilling and coworkers reported an attractive method to synthesize vinyl tetrahydropyran and tetrahydrofuran phosphonates.[10] Although 7- and 8-membered rings could not be formed under the reaction conditions, the products obtained for the 5- and 6-membered rings formed with complete transfer of chirality from carbonates **1-10** to the products **1-11** (Figure 1-4).[10b] These vinyl phosphonates are easily transformed into their β-ketophosphonates analogs via a regioselective Wacker oxidation. Their methodology was exemplified in the formal synthesis of (+)-centrolobine,[10b] the synthesis of an Amphidinolide F fragment,[10c] and more recently the synthesis of both diastereomeric nematocidal oxylipids isolated from the Australian sea sponge *Notheia anomala*.[10d]

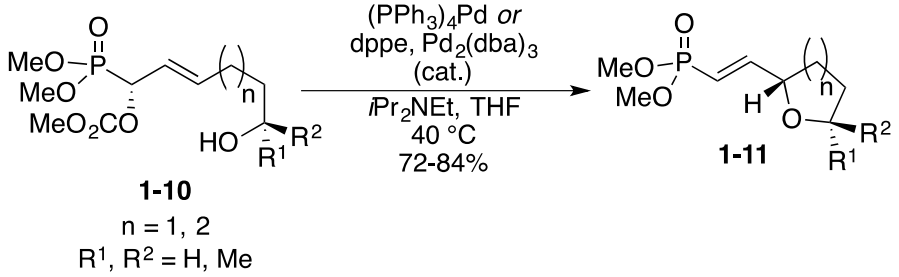


Figure 1-4. Pd-catalyzed synthesis of vinyl tetrahydropyran and tetrahydrofuran phosphonates

As a final example of the synthetic versatility of these palladium-catalyzed intramolecular Tsuji-Trost type reactions, work done by Comins and coworkers demonstrates the ease with which natural products can be constructed using this methodology.[11] Isolated in 1987 by Daly et al.,[12] frog alkaloid (-)-205B is structurally unique when compared to other indolizidine alkaloids. Furthermore, its enantiomer has shown selective inhibition for a receptor that is linked to various neurological diseases.[11] Comins synthesis provides a concise and efficient pathway to the alkaloid **1-14** in eleven steps.[11] An intramolecular Tsuji-Trost reaction using a vinyl amine nucleophile **1-12** gives the product **1-13** in high diastereoselectivity with the bulky $P(^tBu)_3$ ligand (Figure 1-5). It was also found that the use Cs_2CO_3 was critical to the efficiency of the reaction, the use of other bases led to significant decomposition of the substrate. After this key-step the total synthesis of the natural product was easily completed from **1-13** in seven steps.

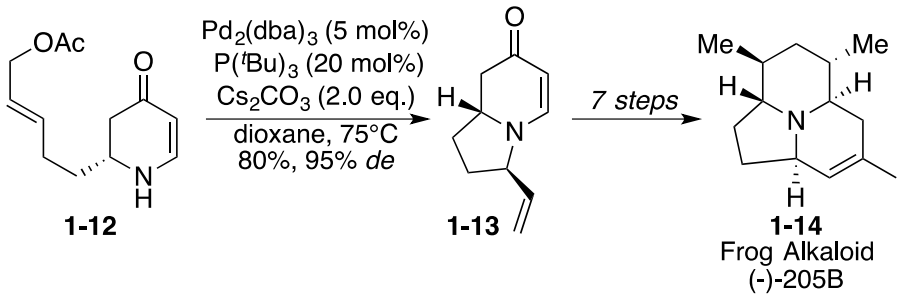
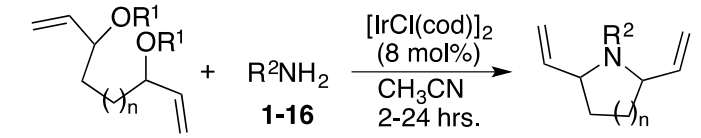


Figure 1-5. Total synthesis of Frog Alkaloid (-)-205B

Heterocycle Synthesis via π-allyl Iridium Intermediates

Approximately forty years after the discovery of the Tsuji-Trost reaction Takeuchi *et al*.[13] and Helmchen and coworkers[14] reported that iridium-complexes were effective catalysts for π-allyl type allylic alkylation reactions. Their pioneering work demonstrated that iridium allylic alkylations preferentially form the branched alkylation products, which is in contrast to the linear alkylation products formed by palladium catalysis. Since these initial reports numerous advances have demonstrated the advantages of iridium complexes in allylic alkylation reactions.[15] Given the latent development of these iridium-catalyzed allylic alkylations, it is not surprising that these complexes were not utilized in the formation heterocycles until the early 2000s.

In 2003, Takemoto *et al.* reported the iridium-catalyzed diallylic amination of bis(allylic carbonates) **1-15** to form various azacycles **1-17** (Figure 1-6).[16] The yields and regioselectivities were high for the reaction, albeit with low diastereoselectivities. More significantly, their report demonstrated the first synthesis of heterocycles via an iridium-catalyzed intramolecular allylic amination strategy.



1-15
n = 1-3
R^1 = Ac, CO_2Me
R^2 = Bn, PMB, Ph

1-17
up to 84%
≤ 2:1 *cis:trans*

Figure 1-6. Iridium-catalyzed sequential allylic amination to form azacycles

Soon after this report, Helmchen and coworkers demonstrated the first enantioselective iridium-catalyzed intramolecular allylic amination.[17] After testing various solvent, ligands, additives, etc., it was found that iridium-complexes with

phosphoramidite ligands of the general structure **L2**[18] have a dramatic impact on both the reactivity and selectivity of the process (Figure 1-7).[17a] Under these conditions, allylic carbonates **1-18** undergo smooth cyclization to their corresponding azacycles **1-19** in up to 99% yield and 97% *ee*. Using similar reaction conditions, they were able to design systems for the enantioselective formations of chromans and an enantioselective sequential inter-/intramolecular allylic amination reaction.[17b]

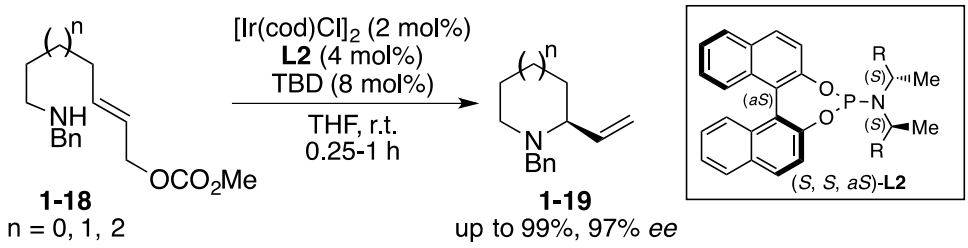


Figure 1-7. First enantioselective iridium-catalyzed intramolecular allylic amination

As an extension of their methodology, the Helmchen group found that these systems could be used as configurational switches to form selectively the 2,6-cis or 2,6-trans piperidines.[17c,d] For example, the isomeric mixture **1-20** can be treated under the same reaction conditions to form either the *cis*-**1-21** or *trans*-**1-22** diastereomeric products depending on which enantiomer of the ligand **L3** is used (Figure 1-8). Although only primary amines were used in these cyclizations, the yields and selectivities were excellent and their methodology has been utilized in the total syntheses of prosopis, dendrobate, and spruce alkaloids.[17d]

More recently, Feringa *et al.* demonstrated a similar process for the construction of tetrahydroisoquinolines.[19] Under their conditions, trifluoroacetylamides **1-23** were readily cyclized into the corresponding tetrahydroisoquinolines **1-24** with high yields and enantioselectivities (Figure 1-9). Their method was also used to synthesize saturated pyrrolidines and piperidines, however, competing β-hydride elimination made the

formation of azepane derivatives quite challenging. The resulting products could then be easily deprotected using K_2CO_3 in MeOH/H_2O, without any appreciable epimerization of the product.

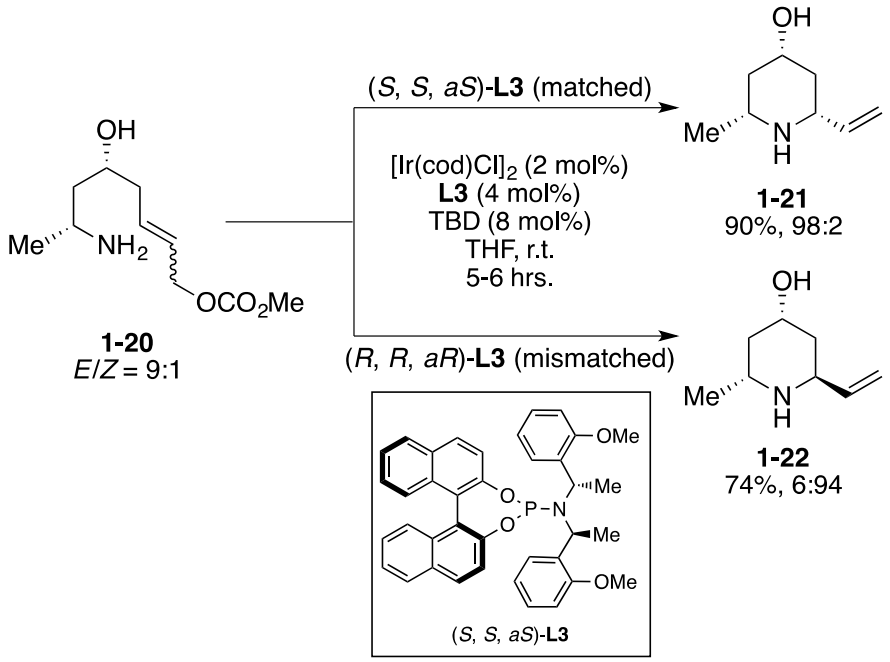


Figure 1-8. Iridium-catalyzed allylic alkylations used as a configurational switch

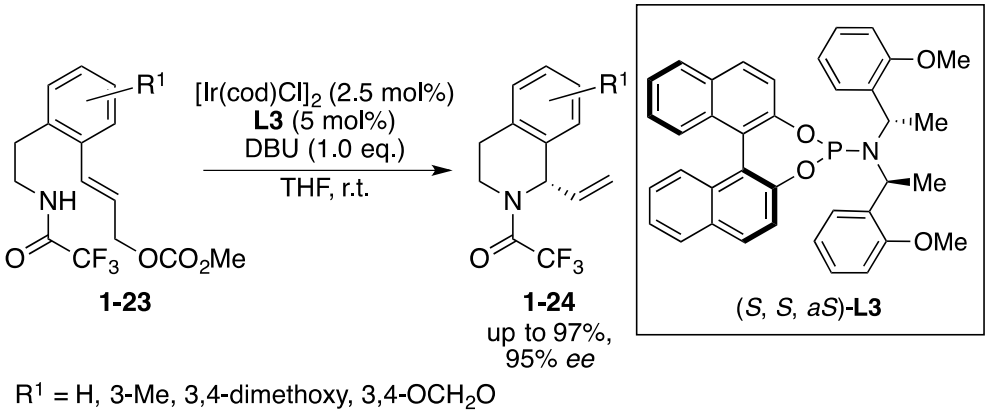


Figure 1-9. Iridium-catalyzed formation of isoquinolines

Heterocycle Synthesis via π-allyl Nickel Intermediates

Examples of nickel-catalyzed intramolecular allylic alkylations to form heterocycles are sparse, however, Berkowitz and coworkers undertook a commendable

study in 2004.[20] Their interests in combinatorial catalysis lead to an *in situ* enzymatic screening (ISES) process that indicated nickel-complexes could be used to form oxazolidinones via an asymmetric allylic amination reaction. During their studies they screened more than twenty five different bis(phosphine)[20a] and P,N-ligands.[20b] Their findings suggest, that best catalyst systems was produced with $Ni(cod)_2$ and (*R*)-MeO-BIPHEP. This complex gave a facile cyclization of **1-25** to **1-26** in an 88% yield with a 75% *ee* (97% *ee* after one recrystallization) (Figure 1-10). After a five-step synthesis the TFA salt of L-glycine **1-27** was obtained in 21% overall yield.

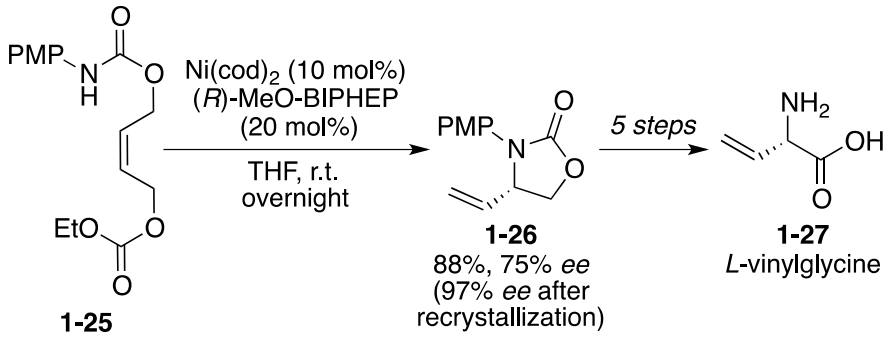


Figure 1-10. Nickel-catalyzed formation of oxazolidinones

Heterocycle Synthesis via π-allyl Ruthenium Intermediates

Pioneering studies by the Tsuji,[21] Watanabe,[22] and Trost[23] research groups demonstrated the practicality of ruthenium-complexes for allylic alkylation reactions, however, their applications in intramolecular heterocyclic formation was not reported until recently.

As an extension of their previously reported methodology for the intermolecular catalytic dehydrative allylation of alcohols,[24] in 2009, Kitamura *et al.* published a very efficient ruthenium-catalyzed dehydrative cyclization to form cyclic ethers.[25] Reactions were performed in various solvents with very low catalyst loadings (as low as 0.0001

mol%) with high yields and enantioselectivities (Figure 1-11). Tetrahydropyrans and furans **1-29**, as well as, chromans could be formed from their corresponding diols **1-28**, however, the formation of seven-membered rings was prevented by the formation of oligomeric side products. The authors suggest that the chlorine atom in ligand **L3** plays two pivotal roles in the reactivity of the complex. Firstly, the inductively withdrawing nature of the chlorine may decrease the energy level of the LUMO, and allow for a more facile redox process. Additionally, a Cp-H•••Cl-R hydrogen bond between the two ligands on the ruthenium could also stabilize the transition state.

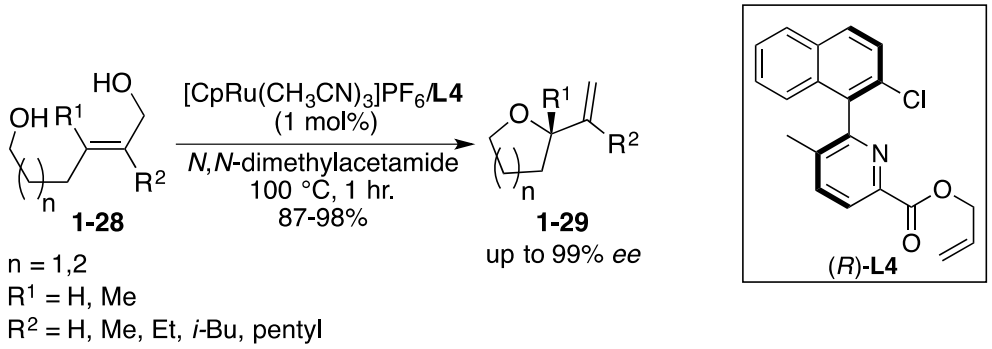


Figure 1-11. Ruthenium-catalyzed formation of cyclic ethers

A few years later, Kitamura's group demonstrated that the same ruthenium-complex could be used in an intramolecular dehydrative cyclization to form azacycles.[26] Various nitrogen heterocycles **1-31** were synthesized from the corresponding allylic alcohols **1-30** with catalyst loadings as low as 0.05 mol% (Figure 1-12).

A variety of protecting groups on the nitrogen could be used, and the yields and enantiomeric ratios were excellent. Interestingly, arene-fused azepane **1-33** could be easily produced from subsequent cyclization of allylic alcohol **1-32**. Conversely, when sulfonamide **1-34** was treated under the optimized conditions, a competing β-hydride elimination dominated resulting in the production of diene **1-35** as the major product. In

the case of the arene-fused azepanes, the authors suggest that the sp^2-carbons of the aniline may permit a better HOMO/LUMO interaction allowing for a higher propensity toward cyclization. The geometric constraints imparted by the aromatic substituent could also give **1-32** a greater predisposition toward cyclization because of it is more geometrically constrained than the alkyl analog **1-35**.

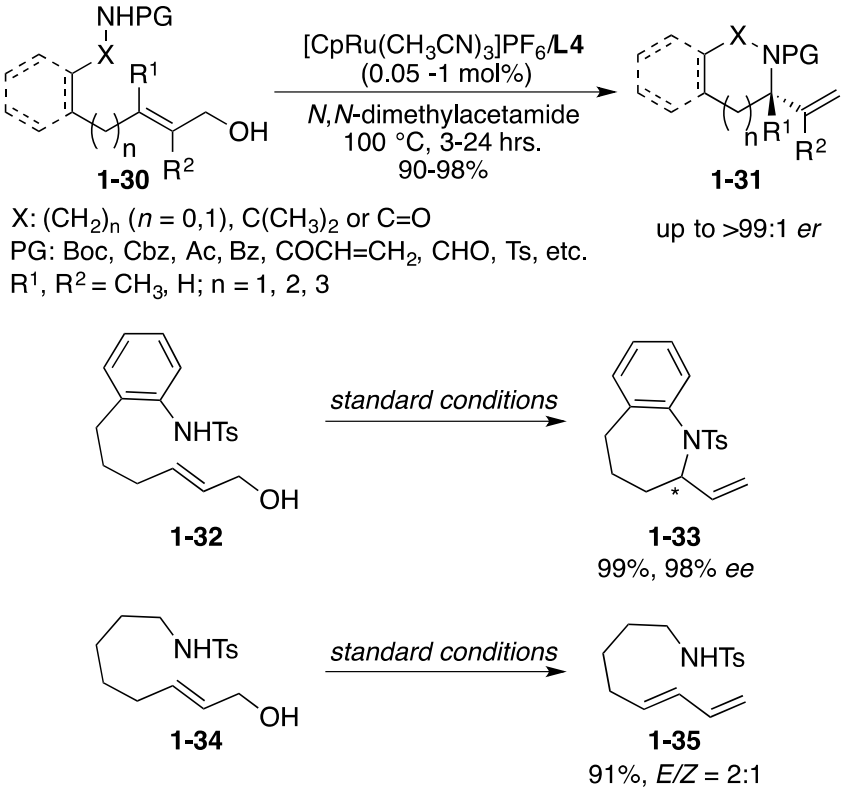


Figure 1-12. Ruthenium-catalyzed formation of azacycles

Formation of Saturated Heterocycles via Formal S_N2' Reactions

Metal-catalyzed formal S_N2' sequences encompass a relatively new reaction class in the formation of heterocycles. In contrast to the mechanistic pathways of the other systems discussed in this chapter, these reactions can produce heterocycles without the formation of a carbocation or a metal-bound cation.

Formal S_N2' Reactions Catalyzed by Palladium Complexes

Given the vast history of palladium activation in allylic systems it is not surprising that the earliest examples of metal-catalyzed formal S_N2' cyclizations to form heterocycles were performed with palladium-complexes.[27] Hirai and coworkers were the first to exhibit the effectiveness of a palladium(II)-catalyzed formal S_N2' heterocyclization in an enantioselective fashion.[27] The successful chirality transfer from the starting allylic alcohol **1-36** gave the piperidine **1-37** which was shown to have complete transfer of chirality after conversion to the natural product alkaloid **1-38**-(+)-coniine (Figure 1-13).[27a] Throughout the late nineties their group applied these methods to the total synthesis of numerous natural products including: (+)-prosopinine,[27b] (+)-palustrine,[27b] SS20846A,[27c] and 1-deoxymannojirimycin.[27d]

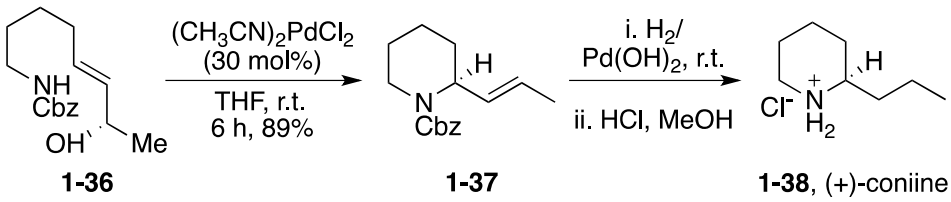


Figure 1-13. Pd(II)-catalyzed transfer of chirality

More recently, Uenishi and coworkers have advanced this strategy to apply to their own methodology in the formation of tetrahydro- and dihydropyrans.[28] These methods were applied directly to the total synthesis of the marine natural product (-)-laulimalide.[28b] During the synthesis a comparison between the Pd(0) and Pd(II)-catalyzed cyclizations in the formation of tetrahydropyran **1-40** and 3,6-dihydropyran **1-42** indicated that Pd(II) was superior (Figure 1-14). For both cyclizations complete chirality transfer was observed, however, in the case of **1-39** the process was much higher yielding with the Pd(II) source due to the competing triene formation found with

the Pd(0) complex. Additionally, cyclization of **1-41** to form pyran **1-42** did not occur under standard Pd(0) conditions. Mechanistically, the cyclization is assumed to go through a *syn*-addition/*syn*-elimination with respect to the palladium-complex.[28b,c] Lastly, fragments **1-40** and **1-42** were successfully used to finish the asymmetric total synthesis of (–)-laulimalide. Uenishi and coworkers have since applied these oxypalladation cyclizations to the construction of several intricate compounds including tetrasubstituted chiral carbon centers,[28c] and more recently in the total synthesis of (-)-apicularen A and its analogues.[28d]

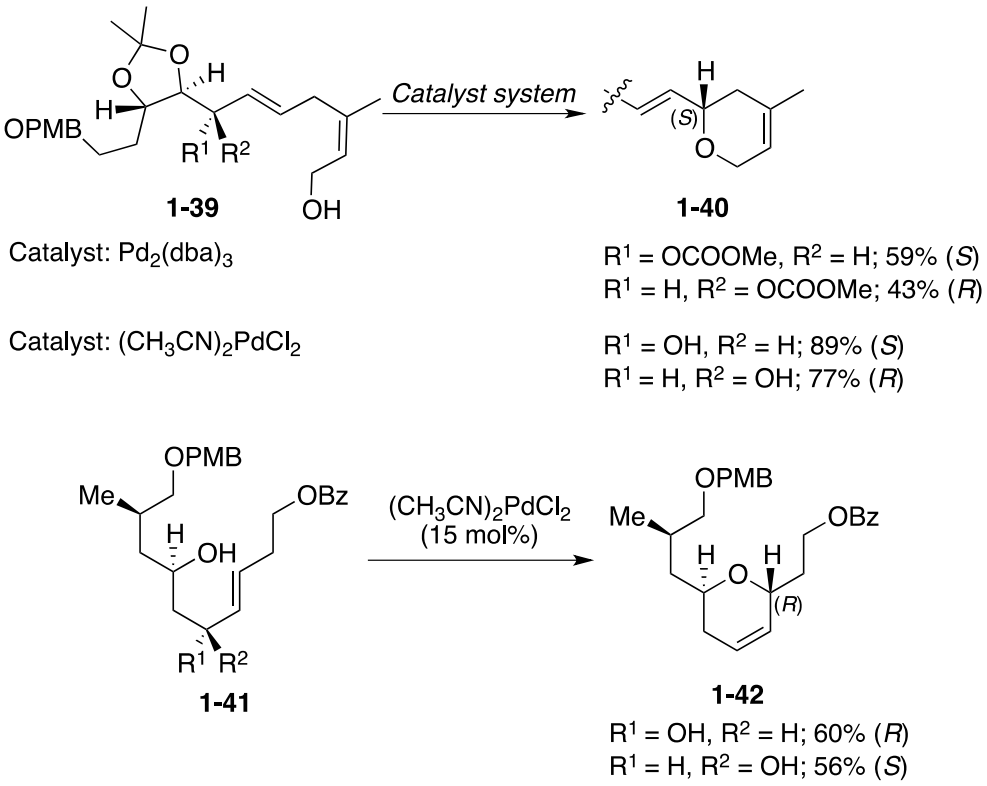


Figure 1-14. Studies in the total synthesis (-)-laulimalide

Shortly after their preliminary reports, their group applied these S_N2' cyclizations to the formation of nitrogen heterocycles.[29] Various nitrogen protecting groups (Cbz, Boc, Ts, Fmoc, etc.) are tolerated, but cyclization with the –Cbz protected amines gave

the best results. Efficient transfer of chirality was also observed for these systems. When the enantioenriched allylic alcohols (*R*)- and (*S*)-**1-43** were treated with 10 mol% of $(CH_3CN)_2PdCl_2$ the 2-vinylpiperidines were produced in 93% and 92% enantiomeric excess, respectively (Figure 1-15). The products (*R*)-**1-44** and (*S*)-**1-44** were further used to synthesize the hydrochloride salts of (*S*)-(+)- and (*R*)-(-)-coniine respectively. These conditions were also found to be highly diastereoselective, which was demonstrated in the cyclization of both epimers of **1-45** to give the product **1-46** with a high diastereoselectivity for both substrates.

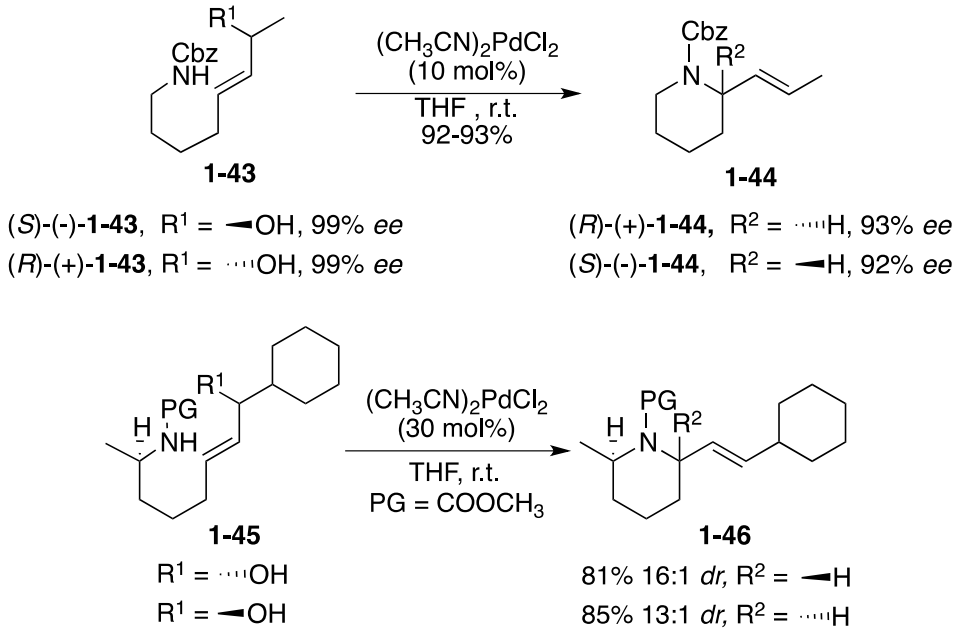


Figure 1-15. Pd(II)-catalyzed formation of piperidines

In 2011, the Uenishi group demonstrated a cascade epoxide ring opening to form bis- and tris- contiguous tetrahydropyran rings.[30] Both epimers of epoxide **43** undergo cyclization in under an hour to form the corresponding bis(tetrahydropyran) **44** with good diastereoselectivity (Figure 1-16). This method can also accommodate both epimers of diepoxide **45** to give the desired tris(tetrahydropyran) compound **46** with

good selectivities. Preliminary mechanistic studies suggest that the sequence is most likely a domino process rather than a stepwise addition.

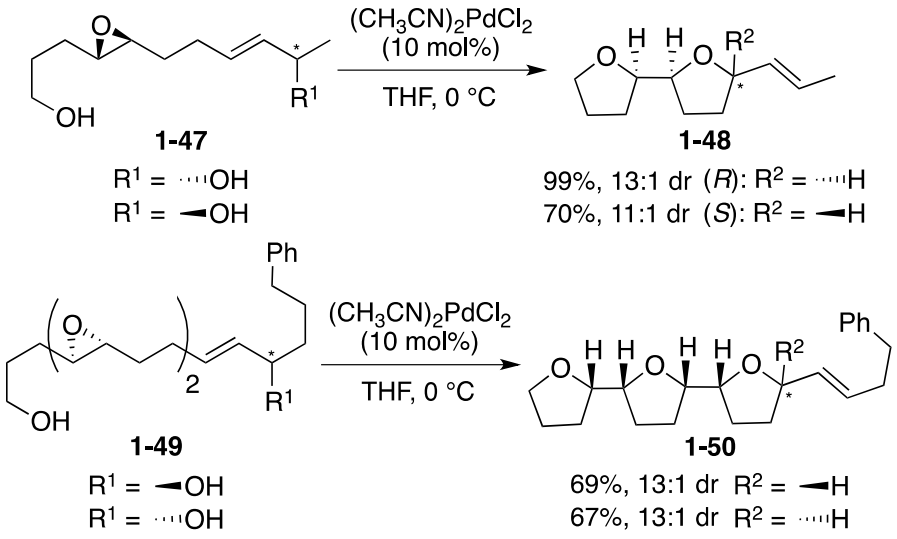


Figure 1-16. Pd(II)-catalyzed formation contiguous furan rings

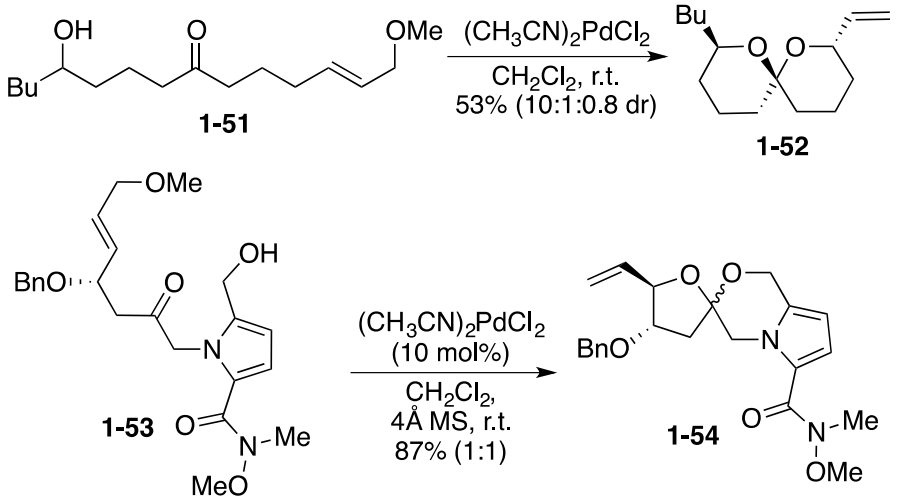


Figure 1-17. Pd(II)-catalyzed spiroketalization in the synthesis of acortatarin A

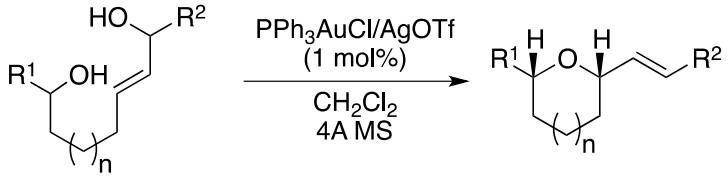
Recent studies by Aponick and coworkers have revealed a facile spiroketalization methodology utilizing a palladium(II)-catalyzed S_N2' cyclization (Figure 1-17).[31] These spiroketalizations occur at room temperature, transforming ketodiol **1-51** to the cyclization product **1-52** in a 53% yield. Most notably they were able to apply this method to the key step in their total synthesis of acortatarin A.[31b] Treatment of allylic

ether **1-53** with 10 mol% of $(CH_3CN)_2PdCl_2$ produced the desired spiroketal **1-54** in an 87% yield as a 1:1 mixture of epimers which were further elaborated to obtain the desired natural product.

Formal S_N2' Reactions Catalyzed by Gold Complexes

Gold-catalysis is an ever-expanding field that has recently brought about many changes in the scientific community.[32] With low catalyst loadings and high functional group tolerance gold-complexes have become a competitive alternative to traditionally used transition metals.

In 2008, Aponick and coworkers were the first to demonstrate a gold-catalyzed dehydrative formal S_N2' cyclization to form *cis*-tetrahydropyrans and furans.[33] The process is selective for the *cis*-cyclic ethers **1-56** from monoallylic diols **1-55** with high diastereoselectivities and yields using very low catalyst loadings (Figure 1-18). With ease of the substrate syntheses and catalyst loadings as low as 0.1 mol%, the production of gram-scale quantities of these tetrahydropyrans and furans was readily achieved. Further experimentation demonstrated that the cyclizations did not proceed through a cationic mechanism but rather through formal S_N2' pathway.



1-55
n = 0,1

1-56
77-99%
up to >25:1 *dr*

Figure 1-18. Gold-catalyzed dehydrative cyclization to form cyclic ethers

With respect to heterocyclic formation our group[34] as well as others[35] have made significant extensions to these methods including the synthesis of substituted

chromenes,[34c] a stereoselective 2-vinyl-morpholine methodology,[35a] and applications to the total synthesis of (+)-isoaltholactone,[35b] to name a few.

In 2011, the Aponick group reported an efficient transfer of chirality for the cyclization of monoallylic diols **1-57** to form tetrahydropyrans and morpholines **1-58** and **1-59** (Figure 1-19).[34d] Selective access to either enantiomer can be achieved from substrates that differ only by the olefin geometry, allowing for selective access to either stereoisomer. This synthetically practical process provides the desired products in high yields with excellent diastereo- and enantioselectivities. Later that year, a comparative study showed that in lieu of allylic alcohols, allylic ethers could also be used to furnish these 2-vinyltetrahydropyran products.[34e]

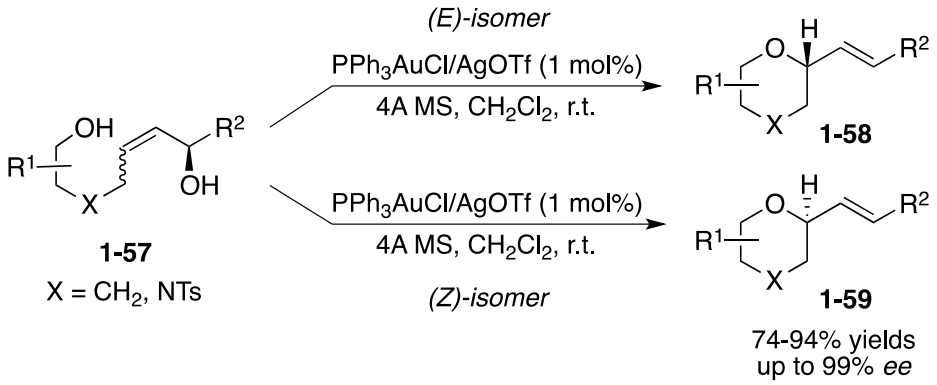


Figure 1-19. Gold-catalyzed chirality transfer process

In 2011, Widenhoefer and coworkers demonstrated an efficient transfer of chirality in the gold-catalyzed intramolecular amination to form azacycles.[35c] The yields and diastereoselectivities are high in selected cases, however, substrates are limited to alkyl amine nucleophiles **1-60** that require higher temperatures (60-100 °C) for cyclization to the desired azacycles **1-61** (Figure 1-20). Additionally, treating amine **1-62** under their optimized conditions produced the desired piperidine **1-63** with a complete

transfer of chirality. The enantiopurity and absolute configuration of **1-63** was then confirmed by the synthesis of the hydrochloric acid salt of (*S*)-(+)-coniine.

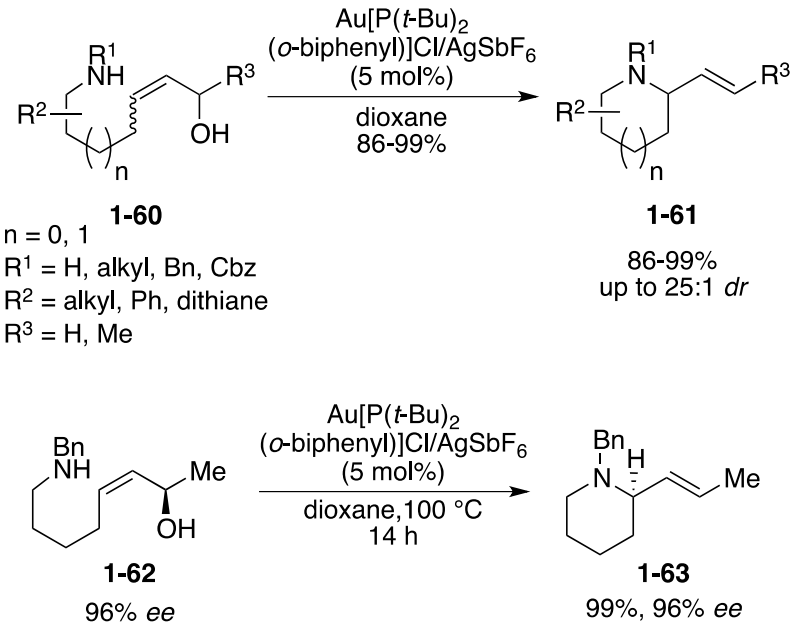


Figure 1-20. Gold-catalyzed formation of azacycles

Soon after, Widenhoefer and coworkers reported a highly effective enantioselective intramolecular amination catalyzed by a chiral bis(gold)phosphine complex.[35b] The new method accommodates a wide range of carbamates **1-64** to give the desired piperidines and piperazines **1-65** in high yields and enantioselectivities with the use of a bis(gold)phosphine complex prepared from bisphosphine **L4** (Figure 1-21). Further experiments demonstrated a net *syn*-displacement of the allylic alcohol by the incoming carbamate nucleophile.

Mechanistic studies by the Aponick and Ess groups has given an unequivocal insight into the mechanism of these gold-catalyzed dehydrative cyclization.[34f] Their experimental and computational studies illustrate the importance of hydrogen bonding with respect to both reactivity and stereoselectivity in the cyclization of **1-66** to **1-67**.

Between the three transition states **TS-*anti*,** **TS-*syn***, and **TS-*concerted*** the lowest calculated energy state is **TS-*anti* (**Figure 1-22). Their results suggest the cyclizations must go through a non-concerted *anti*-alkoxyauration/*anti*-elimination mechanism, which is accelerated by and stereochemically defined through the intramolecular hydrogen bonding between the allylic alcohol and the incoming hydroxyl nucleophile.

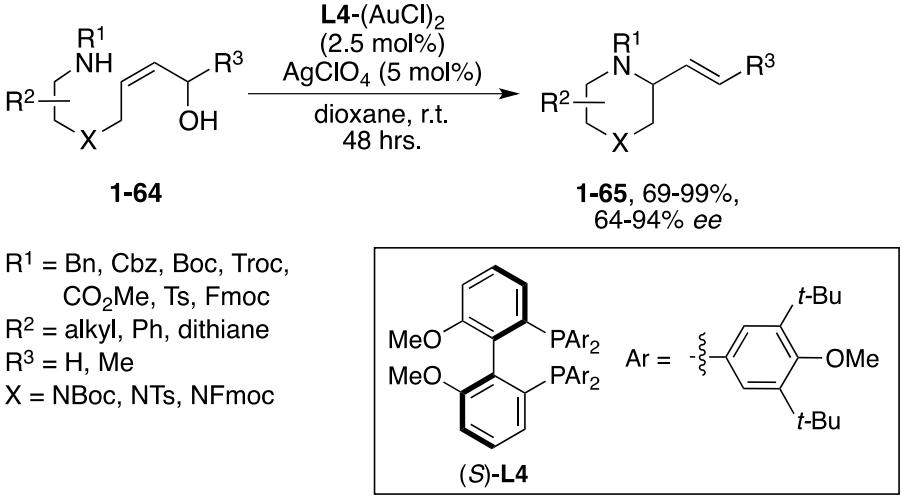


Figure 1-21. Enantioselective formation of azacycles by a bis(phosphine)gold-complex

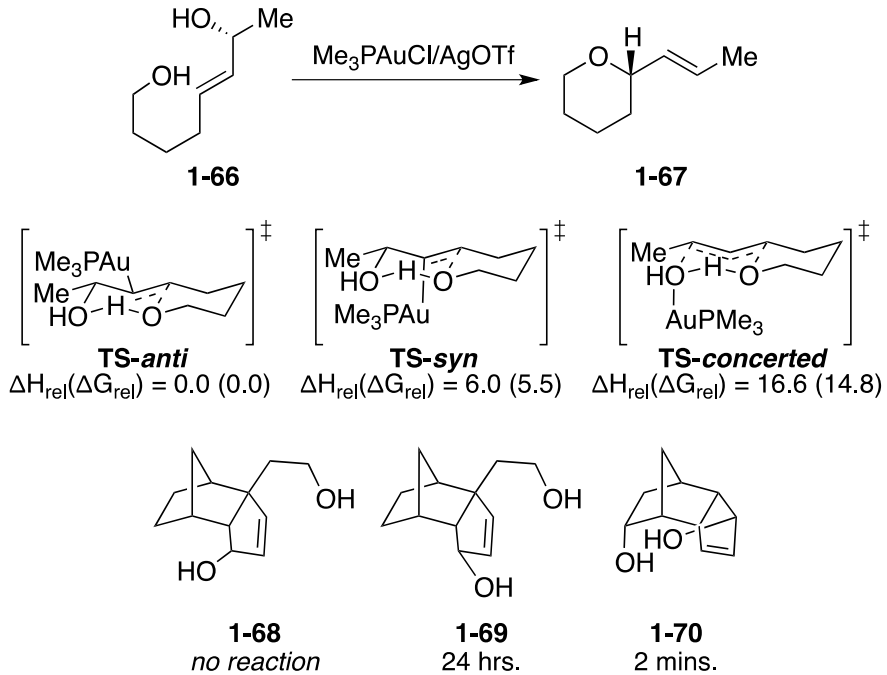
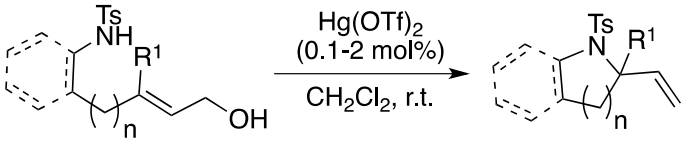


Figure 1-22. Pivotal role of hydrogen bonding, and evidence for *anti*-addition in gold-catalyzed dehydrative cyclizations of monoallylic diols

Experimentally, this concept was demonstrated in the gold-catalyzed cyclizations of bicyclic diols **1-68**-**1-70**. The requisite distance for these intramolecular hydrogen-bonding interactions cannot be achieved with substrate **1-68** and consequently no desired cyclization was observed under the optimized conditions. In contrast, as this interaction and the ability of the catalyst to affect an *anti*-addition become more accessible, the desired cyclization becomes much more facile (compare cyclizations of **1-69** and **1-70**, Figure 1-22).

Formal S_N2' Reactions Catalyzed by Mercury Complexes

Nishizawa and coworkers have recently reported efficient mercury-catalyzed dehydrative cyclizations to form various saturated azacycles and indolines.[36] In 2008, they were able to demonstrate that sulfonamides **1-71** underwent facile ring closure to form the desired 2-vinylazacycles **1-72** in high yields with very low catalyst loadings (Figure 1-23).[36a] Allylic alcohols and ethers also underwent the desired cyclization, however, allylic esters were unable to cyclize under the optimized conditions.



1-71
n = 0, 1, 2, 3
R^1 = H, Me

1-72
25-99%

Figure 1- 23. Mercury-catalyzed dehydrative cyclization to form azacycles

The same group then established an enantioselective version of these cyclizations using the chiral (R)-BINAPHANE ligand with $Hg(OTf)_2$ (Figure 1-24).[36b] After screening various ligands and nitrogen protecting groups, it was determined that the highest enantioselectivities were achieved with *tert*-butyl substituted sulfonamides.

Treating sulfonamides **1-73** with the chiral mercury-complex at low temperatures gave the desired indolines **1-74** in high yields with moderate to good enantioselectivities. Sulfonamide products **1-74** could be easily deprotected with anisole in a solution of TFA/CH_2Cl_2, without appreciable epimerization of the product.

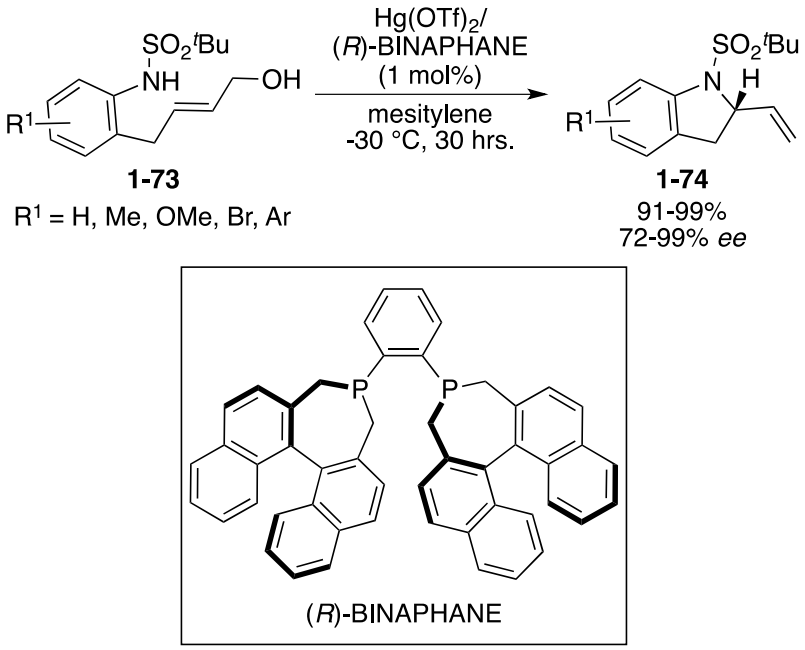
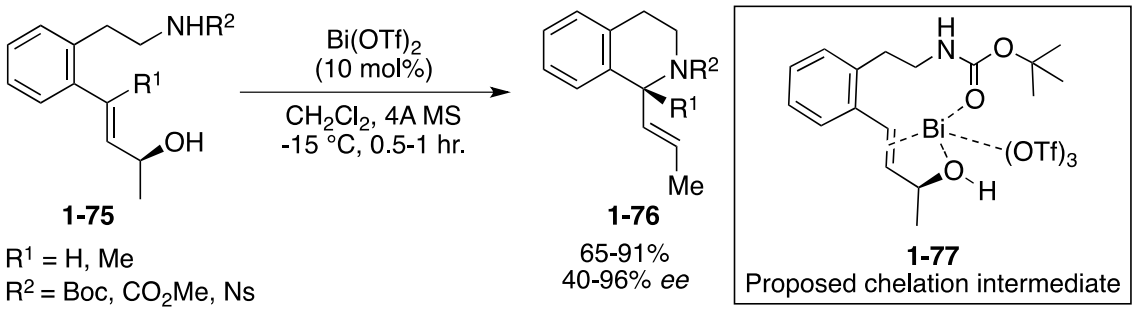


Figure 1-24. Mercury-catalyzed enantioselective formation of indolines

Formal S_N2' Reactions Catalyzed by Bismuth Complexes

During their investigations of a chirality transfer in metal-catalyzed intramolecular allylic aminations Kawai/Uenishi *et al*. screened over ten different metals to find that bismuth (III) triflate gave the best results.[37] Under their optimized bismuth-catalyzed conditions enantiopure allylic alcohols **1-75** could be treated under relatively mild conditions to form the desired tetrahydroisoquinolines **1-76** (Figure 1-25).[37a] Boc-protected amines achieved the highest selectivities, while substituted olefins (where R^1 = Me) were found to significantly lower the enantiomeric ratio. Interestingly, under their previously reported palladium conditions (analogous to those found in Figure 1-14) good

enantioselectivity was given only at -20 °C, however, the reactivity degraded forming only 20% of the desired product. From these findings a chelation intermediate, **1-77**, was proposed to rationalize the higher selectivities obtained with carbamate starting materials.



1-75

R^1 = H, Me
R^2 = Boc, CO_2Me, Ns

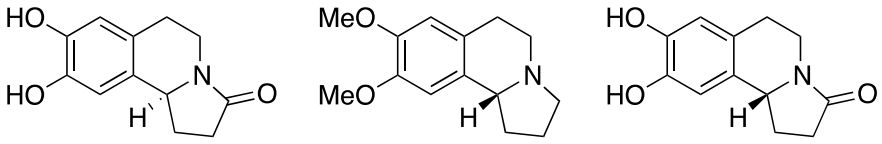
1-76

65-91%
40-96% *ee*

1-77
Proposed chelation intermediate

Figure 1-25. Bismuth-catalyzed chiral transfer to form tetrahydroisoquinolines

In 2011, an extension of the bismuth methodology was reported to include substituted tetrahydroisoquinolines, and give further insight into the mechanism of the reaction.[37b] Later that year, a variety of tetrahydroisoquinoline natural product alkaloids were prepared that showcase their methodology, these include: (*S*)-(-)-trolline, (*R*)-(+)-crispine A, and (*R*)-(+)-oleracein (Figure 1-26).[37c]



(*S*)-(-)-Trolline (*R*)-(+)-Crispine A (*R*)-(+)-Oleracein

Figure 1-26. Tetrahydroisoquinoline natural products

Formation of Saturated Heterocycles via Cationic Intermediates

The use of cationic intermediates in the synthesis of heterocycles has become more prominent over the past ten years. Much like the intermediates found in π-allyl systems an allyl cation is produced, however, the metal is not covalently associated with the cation making enantioinduction rather difficult.

Ionization using Magnesium Complexes

During a total synthesis of (-)-*cis*-clavicipitic acid, Jia and coworkers made a serendipitous discovery.[38] Deprotection of bis(carbamate) **1-78** using $Mg(ClO_4)_2$ was followed by an unexpected magnesium-promoted cyclization to give the desired azepane **1-79** with reasonable selectivity for the *cis*-isomer (Figure 1-27).[38a] This process provided simple access to the desired natural product after several steps. The magnesium-promoted process was later used in a one-pot tandem palladium catalyzed Heck reaction/magnesium promoted dehydrative cyclization in the total syntheses of aurantioclavine and clavicipitic acid.[38b]

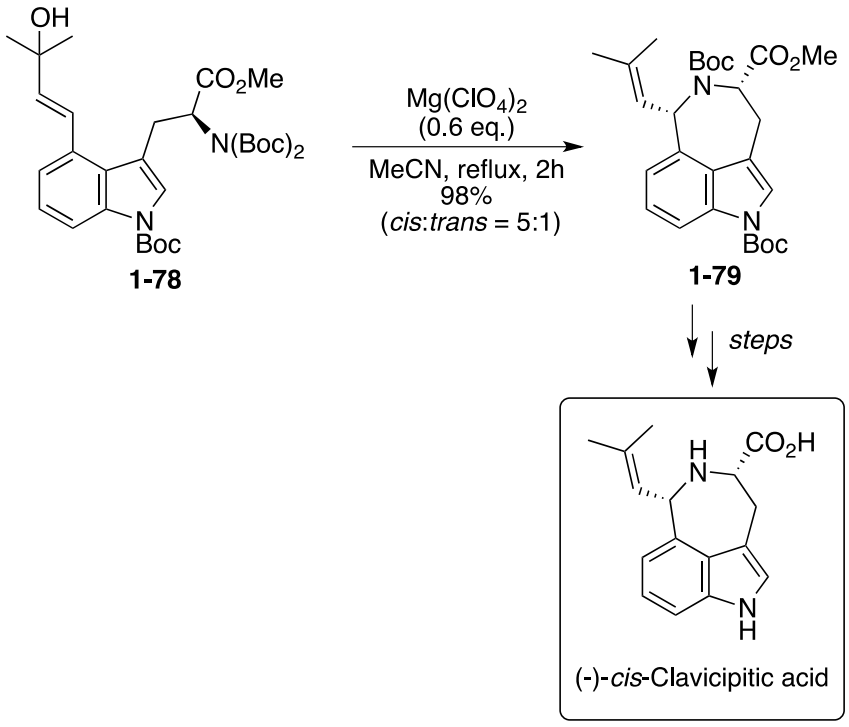


Figure 1-27. Magnesium-promoted formation of azepane **1-79** in the total synthesis of (-)-*cis*-Clavicipitic acid

In 2012, the conditions were optimized to allow for a process that is catalytic in magnesium.[39] Treating sulfonamides or carbamates **1-80** with 10 mol% of $Mg(ClO_4)_2$ at 80 °C in acetonitrile gave the desired tetrahydroisoquinolines **1-81** in reasonable yields

for secondary and tertiary allylic alcohols, as well as, primary allylic acetates (Figure 1-28). Piperidines and pyrrolidines could also be prepared, however substrates containing primary alcohols were shown to be sluggish even with a full equivalent of magnesium. After further optimization, this methodology was then applied to the total synthesis of a known fungal inhibitor demethoxyfumitremorgin C.

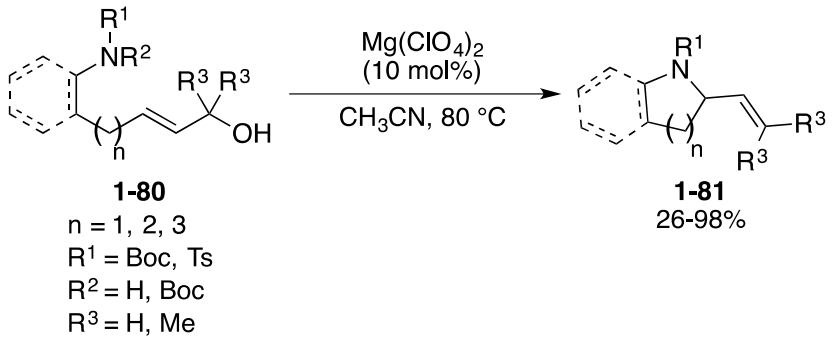


Figure 1-28. Formation of azacycles by magnesium-catalyzed dehydrative cyclization

Ionization using Gold Complexes

In 2009, Chan *et al.* described an efficient gold-catalyzed dehydrative cyclization to form 1,2-dihydroquinolines.[40] Under very mild conditions arylsulfonamides **1-82** were transformed into the desired dihydroquinolines **1-83** in relatively good yields (Figure 1-29).

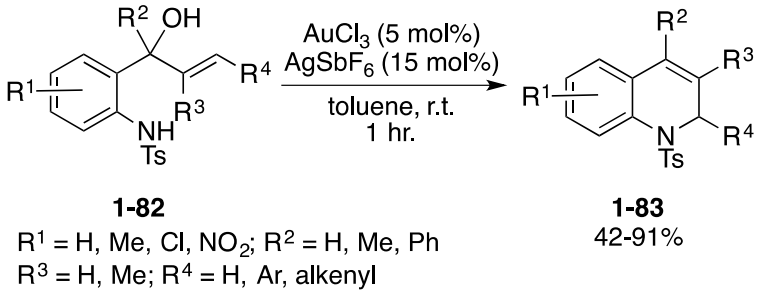


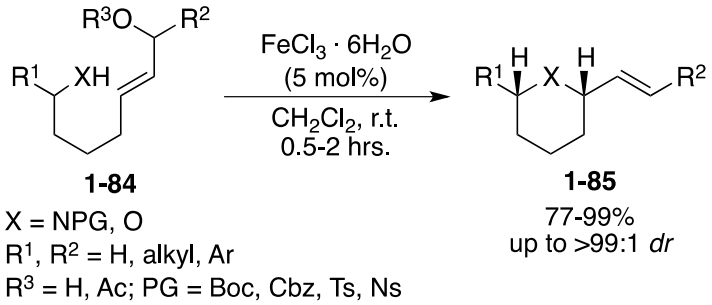
Figure 1-29. Gold-catalyzed formation of 1,2-dihydroquinolines

The authors speculate that the process proceeds via a cationic mechanism. Interestingly, this is in contrast to the gold-catalyzed synthesis of chromenes reported

by our group,[34c] which does not form a cationic intermediate in many cases. Furthermore, they were able to use this methodology for the racemic total synthesis of the tetrahydroquinoline alkaloid (±)-angustureine.

Ionization using Iron Complexes

Cossy and coworkers recently reported an attractive method for the diastereoselective formation of cis-piperidines and tetrahydropyrans.[41] This iron-catalyzed process provides the desired products **1-85** from allylic alcohols **1-84** in high yields and very high diastereoselective for the *cis*-products under mild conditions (Figure 1-30). Given the cationic nature of the reaction transposed allylic alcohols were also readily cyclized under the reaction conditions.



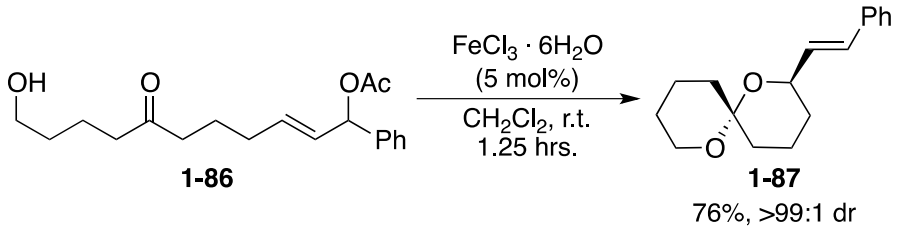


Figure 1-30. Iron-catalyzed formation of saturated heterocycles

Interestingly, this catalyst system can also be applied to the cyclization of ketoalcohol **1-86** to form the desired spiroketal **1-87** in a diastereomeric ratio of >99:1. The high stereoselectivity is believed to be a product of the epimerization/equilibration of the *trans*-**1-88** to the more stable *cis*-**1-88** through an allyl cation intermediate **1-89**

(Figure 1-31). Although the method demonstrates broad functional group tolerance and high diastereoselectivities, it does not provide access to enantiopure products.

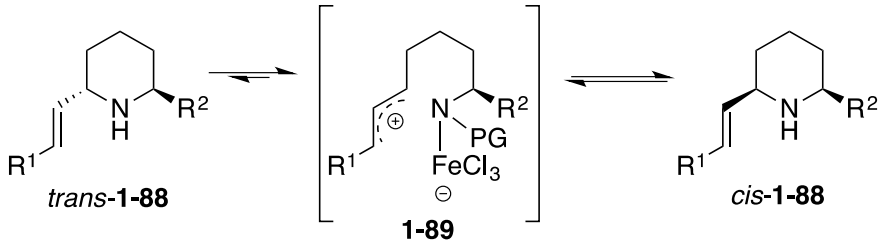
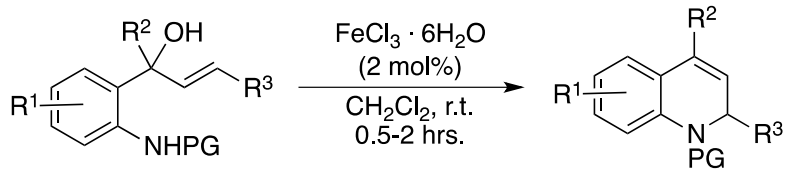


Figure 1-31. Rationale for high diastereoselectivity

Sun *et al*. later used this catalyst system for the formation of substituted dihydroquinolines and quinolines.[42] The process offers cyclizations of anilines **1-90** to form dihydroquinolines **1-91** with low catalysts loadings and good yields in most cases (Figure 1-32). When enantiopure allylic alcohols were used they exhibited no transfer of chirality, instead producing a racemic mixture of dihydroquinoline products. Treating the products **1-91** with sodium hydroxide in ethanol at reflux furnished the corresponding quinoline products allowing selective access to either azacycle.



1-90

R^1 = H, Cl
R^2 = H, Me, Ph
R^3 = H, Ar; PG = Ts, Ms, Bz

1-91
18-96%

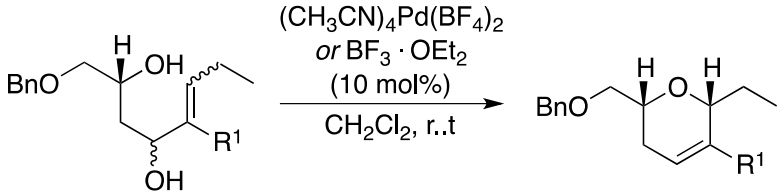
Figure 1-32. Iron-catalyzed formation of dihydroquinolines

Ionization using Palladium Complexes

During their studies of the total synthesis of jerangolid A, Hanessian and coworkers discovered a highly diastereoselective cyclization of monoallylic diols **1-92** to form 1,3-*cis*-dihydropyrans **1-93** with very high diastereoselectivity (Figure 1-33).[43] The

cyclizations are facile using either the cationic palladium complex $(CH_3CN)_4Pd(BF_4)_2$, or $BF_3 \cdot OEt_2$ with 10 mol% catalyst loadings.

Their systems gave selectively the *cis*-products, regardless of the stereochemical configuration of the alkene and/or the allylic alcohol. These results suggest that the cyclizations likely go through a cationic mechanism. Furthermore, the cycloetherification protocol was used to complete the first total synthesis of jerangolid A, which was completed in sixteen linear steps from an enantiopure glycidol.[43a]



1-92
R^1= H, CH_3

1-93
40-82%
up to >99:1 dr

Figure 1-33. Stereoselective formation of 1,3-*cis*-dihydropyrans

Miscellaneous Cases

The following section encompasses selected examples that would not necessarily fit in the previous sections, however, they demonstrate interesting cases for metal-catalyzed formation of saturated heterocycles from allylic systems.

Formation of Heterocycles via a Sequential Ruthenium enyne/Palladium Allylation Process

In 2006, Trost and coworkers demonstrated a sequential one-pot ruthenium enyne coupling followed by a palladium-catalyzed allylation to form nitrogen and oxygen heterocycles.[44] Allylic *p*-nitrophenyl ethers **1-97** generated after the ruthenium enyne coupling of **1-94** and **1-95** give the desired heterocycles **1-96** with moderate to good enantioselectivities (Figure 1-34). The process can also be used to form oxygen

heterocycles **1-99** from sequential coupling and cyclization with substrates **1-94** and **1-98**. Diastereoselective syntheses of piperidines, furans, and tetrahydropyrans were also possible through this methodology, generally providing excellent stereoselectivity with the use of chiral ligands. Interestingly, diastereomers that are generally thermodynamically disfavored can be obtained through this protocol.

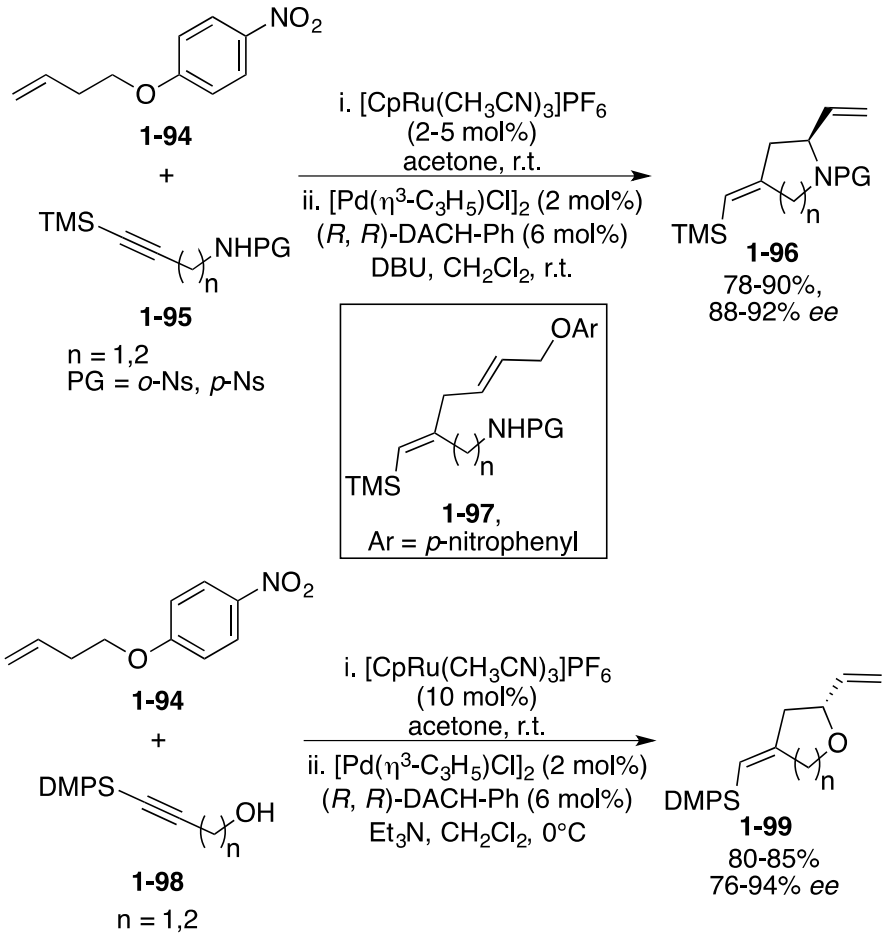


Figure 1-34. Sequential Ru/Pd catalysis to form N- and O-heterocycles

Additionally, the stereochemistry seems to be determined by the hard/soft nature of the incoming nucleophiles. For sulfonamides (soft) the initial π-allyl system formed is kinetically trapped, whereas, alcohols (hard) go through a slow trapping mechanism allowing for the equilibration/interconversion of the π-allyl diastereomers. Lastly, their

methods were applied to the synthesis of the B-ring of the chemotherapeutic natural product bryostatin.

Formation of Heterocycles via a Tandem Iridium-catalyzed Vinylation/Allylic Amination Reaction

A short time later, You and coworkers reported an efficient enantioselective iridium-catalyzed tandem allylic vinylation/amination method to form 2,3-dihydro-1H-benzo[*b*]azepines.[45] The reaction sequence starts with an allylic vinylation of **1-100** with **1-101** thereby creating a monoallylic carbonate intermediate that further undergoes intramolecular allylic amination to give the desired azepines **1-102** (Figure 1-35). In most cases yields were high, and enantioselectivities were consistently good.

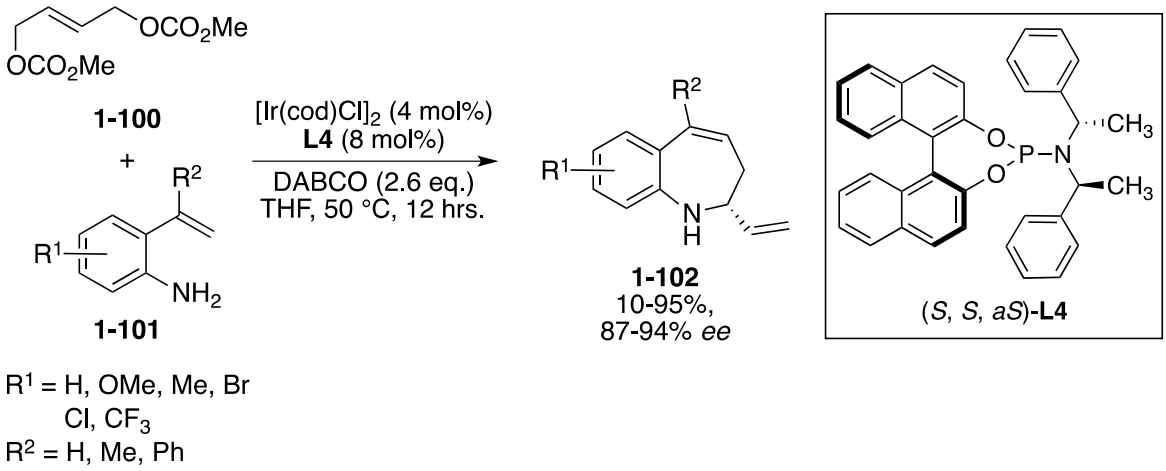


Figure 1-35. Enantioselective tandem iridium-catalyzed allylic vinylation/amination reaction to form azepines

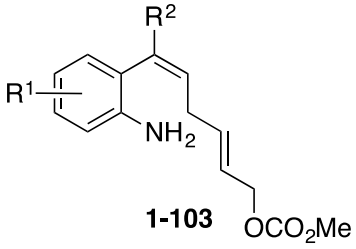


Figure 1-36. Allyl carbonate intermediate

Evidence for the proposed pathway was found through experiments that verified the monoallylic carbonate intermediates **1-103** could both be formed and cyclized under the optimized conditions (Figure 1-36). Moreover, it is interesting to note that this method is one of the few processes in this chapter that gives dependable enantioselective access to 7-membered nitrogen heterocycles.

Formation of Heterocycles via C-H Activation of Allylic Systems

Metal-catalyzed C-H functionalization has recently become a prominent strategy in the formation of complex structures.[46] The White group has developed various methodologies for the formation of saturated heterocycles via C-H activation of allylic systems, and has applied this approach to the syntheses of biologically relevant compounds.[47] While most of the heterocycles formed in their reports are intermediates toward 1,2- and 1,3-aminoalcohols or diols, this strategy can also be used to synthesize intricate heterocycles. For instance, during the total synthesis of 6-deoxyerythronolide B, and during studies determining the influence of a configurational bias during macrolactonization of erythromycin cores, an efficient macrolactonization was achieved using a palladium-catalyzed C-H oxidation (Figure 1-37).[47c,f] Treating compounds **1-104** and **1-106** gave the 14-membered macrolides **1-105** and **1-107**, respectively.

Even though Yamaguchi macrolactonizations were also performed, the C-H oxidation macrolactonization provides a complementary route without the need for oxidation at the C13 center (which can also be made through C-H activation). In most cases, diastereoselectivities were also higher for the C-H oxidation method when compared to the Yamaguchi protocol, albeit with lower yields.[47f] More importantly, this report demonstrates that there is no need for conformational elements that shape or

preorganize the desired macrolactonization, a philosophy that has been well accepted for over twenty years.[47f]

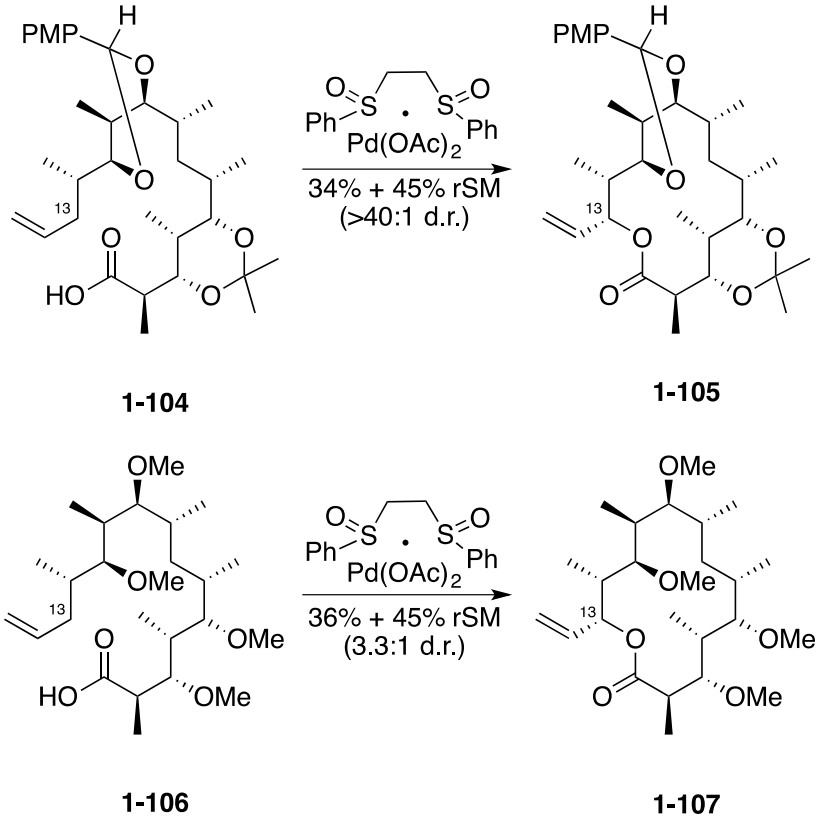


Figure 1-37. Macrolactonization via palladium-catalyzed C-H activation

Conclusion

The formation of heterocycles through metal-catalyzed allylic alkylation reactions is an important synthetic technique that is ever growing. From the reports discussed in this chapter it is easy to appreciate the role these reactions play in the syntheses of various natural products and biologically active compounds. In the past ten years numerous research groups have demonstrated the abundance of catalysts and reaction pathways that can be used to produce structurally unique heterocycles of all varieties. Given the fresh nature of this field there is a clear path for new discoveries.

CHAPTER 2
FORMATION OF AZACYCLES VIA GOLD-CATALYZED DEHYDRATIVE CYCLIZATIONS

Introduction

Recently, there has been an influx of publications focused on the metal-catalyzed formation of nitrogen and oxygen-heterocycles via allylic alkylation reactions,[48] due to their prevalence in natural products and biologically relevant compounds. In 2008, Aponick and coworkers reported the first intramolecular gold-catalyzed dehydrative cyclization of monoallylic diols **2-1** in the formation of tetrahydropyrans and furans **2-2** (Figure 2-1, A).[33] Since this report, many extensions have been reported by our group[34] as well as many others,[35] including an efficient process for the transfer of chirality for these diols (Figure 2-1, B).[34d] With low catalyst loadings, facile substrate syntheses, and water as the only by-product, these methods have become powerful tools for the synthesis of complex heterocycles.

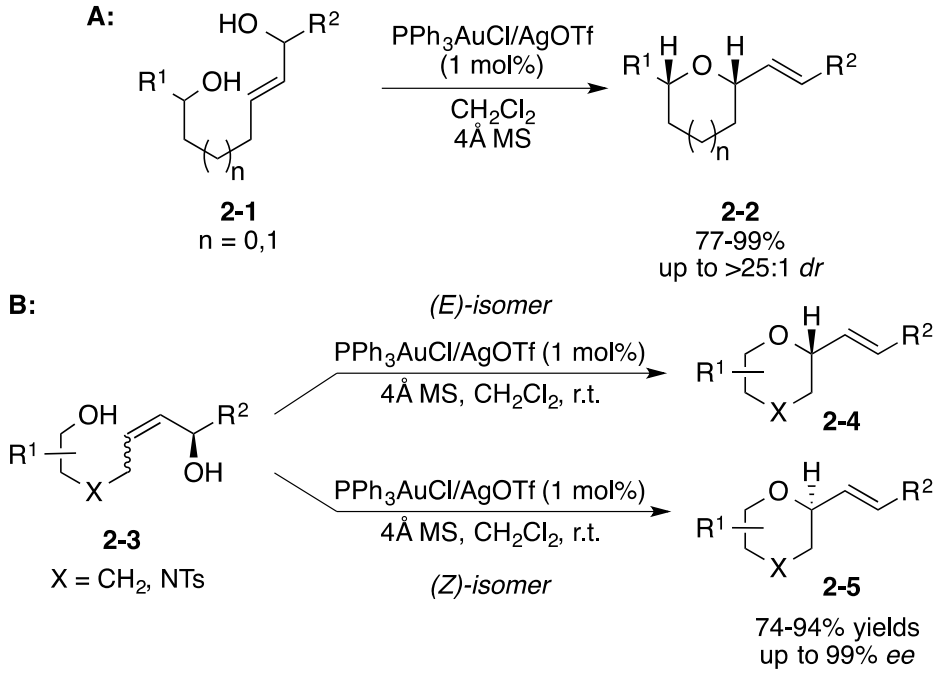


Figure 2-1. Gold-catalyzed dehydrative cyclizations to form tetrahydropyrans reported by Aponick *et al.*

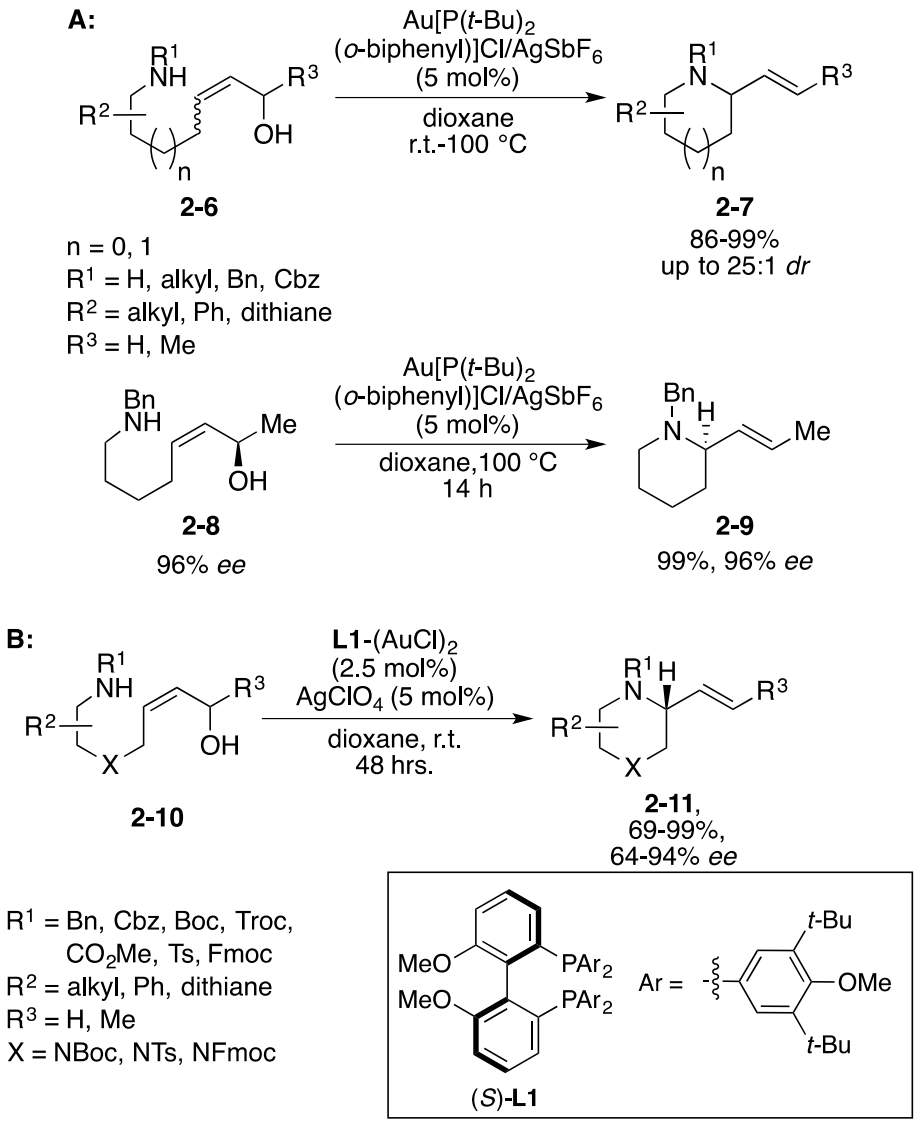


Figure 2-2. Gold-catalyzed dehydrative cyclizations to form azacycles reported by the Widenhoefer group

As a logical extension of the previously reported cyclization of monoallylic diols, we were interested in utilizing these dehydrative cyclization reactions for the formation of nitrogen heterocycles. During these studies, Widenhoefer and coworkers published two reports concerning the gold-catalyzed dehydrative cyclization of alkyl amines[35c] and carbamates[35d] (Figure 2-2, A and B), however, our efforts were focused on general

conditions that would not require excessive heating or the use of a chiral bis(gold) complex.

In their first report, Widenhoefer and coworkers demonstrated the first gold-catalyzed cyclization of alkyl amines **2-6** to form piperidines and pyrrolidines **2-7** (Figure 2-2, A).[35c] The scope was limited to basic alkyl amines, most of which required heating to 100 °C. Furthermore, many of the substrates shown incorporate geminal substituents that cause a Thorpe-Ingold (gem-dimethyl) effect; because of this effect the substrates have a higher propensity to undergo the desired cyclization. Their studies demonstrated that the benzyl amine **2-8** could undergo an efficient transfer of chirality to the product **2-9** at 100 °C in dioxane.

Later, in 2012, the same group reported a similar dehydrative cyclization using carbamates nucleophiles.[35d] The enantioselective cyclization of carbamates **2-10** to form azacycles **2-11** is relatively facile taking place at room temperature over 2 days; however, the method has some major drawbacks (Figure 2-2, B). Nearly all of the substrates include gem-dialkyl substituents to facilitate cyclization. Additionally, substitution at the allylic position gives rise to matched and mismatched cases with respect to the chiral gold complex. As a result of these matched/mismatched interactions, a mixture of *E*- and *Z*-olefins products **2-11** can be obtained when an allylic substituent is present, unless an enantioenriched allylic alcohol is used.

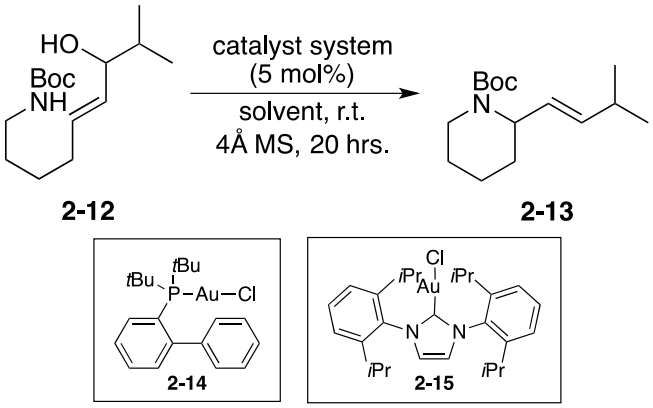
Given the drawbacks of the aforementioned systems we were still interested in finding gold-catalyzed conditions that would facilitate the cyclization for a broad range of substrates without the use of gem-dialkyl substituents, higher temperatures, and a chiral gold-complex.

Gold-Catalyzed Dehydrative Cyclizations of Carbamates

Initial Studies

Initial experiments demonstrated an inherent preference for sulfonamides to undergo cyclization more readily than carbamates **2-12**. Furthermore, it was previously demonstrated that *Z*-allylic alcohols cyclize more easily than the corresponding *E*-allylic alcohols.[34e] Given this difficulty, efforts were focused on finding optimized conditions that would enable the formation of piperidines **2-13** from carbamates **2-12** (Table 2-1).

Table 2-1. Optimization for the formation of piperidines

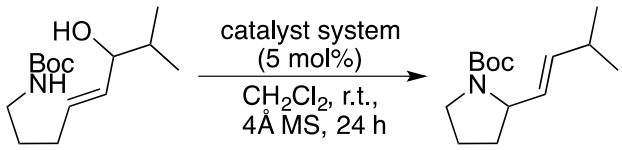


Entry	Gold salt	Silver salt	Solvent	Yield[a]
1	Ph_3PAuCl	AgOTf	CH_2Cl_2	<5[b]
2	AuCl	AgOTf	CH_2Cl_2	9
3	[(*o*-biphenyl)-di-*t*-butyl-P]AuCl (**2-14**)	AgOTf	CH_2Cl_2	<5[b]
4	$(Ph_3PAu)_3O^+BF_4^-$	-	CH_2Cl_2	N.R.
5	(IPr)AuCl (**2-15**)	$AgBF_4$	CH_2Cl_2	93
6	(IPr)AuCl (**2-15**)	$AgBF_4$	CH_2Cl_2	87[c]
7	(IPr)AuCl (**2-15**)	$AgBF_4$	THF	<5[b]
8	-	$AgBF_4$	CH_2Cl_2	N.R.

[a] Purified yields. [b] Conversion by ^{1}H NMR (300 MHz). [c] 4Å MS omitted.

To begin these studies, the complex generated *in situ* from Ph_3PAuCl and AgOTf was used, because this complex efficiently catalyzed the formation of tetrahydropyrans via dehydrative cyclizations of monoallylic diols.[33] Surprisingly, treatment of **2-12** under the optimized conditions for the formation of tetrahydropyrans resulted in little conversion to the desired product (Table 2-1, entry 1). Furthermore, little product formation was observed with the more Lewis acidic (Table 2-1, entry 2), and other gold-complexes that have been utilized in the activation of analogous allylic/propargylic systems (Table 2-1, entries 3-4). Gratifyingly, switching to a more electron donating carbene ligand (IPr, **2-15**) gave the product **2-13** in a 93% yield after 20 hours at room temperature in CH_2Cl_2 (Table 2-1, entry 5). Removing molecular sieves from the reaction had little effect on the cyclization giving the desired product in 87% (Table 2-1, entry 6). When **2-12** was treated with $AgBF_4$ no reaction occurred with only the silver salt, demonstrating that the cationic gold-complex is required for the desired reaction to occur (Table 2-1, entry 7).

Table 2-2. Optimization for the formation of pyrrolidines



2-16 **2-17**

entry	gold salt	silver salt	yield[a]
1	Ph_3PAuCl	AgOTf	62
2	(IPr)AuCl	$AgBF_4$	71
3	[(*o*-biphenyl)-di-*t*-butyl-P]AuCl	AgOTf	<5[b]

[a] Purified yields.[b] Conversion by ^1H NMR (300 MHz).

Interestingly, formation of pyrrolidine **2-17** from **2-16** can be done either with the previously reported conditions ($Ph_3PAuCl/AgOTf$) or using (IPr)AuCl as the gold salt (Table 2, entries 1-2). The combined results from the cyclization of piperidines and pyrrolidines, showed that the cyclizations were consistently more facile using the cationic gold-complex formed from (IPr)AuCl/$AgBF_4$. For this reason, these conditions were adopted as the optimized catalyst system for the formation of these azacycles.

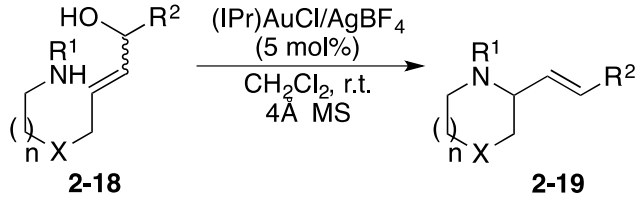
Substrate Scope and Limitations

With the optimum conditions established the substrate scope was then explored. Sulfonamides **2-18a** and **2-18b** were readily cyclized with catalyst loadings as low as 1 mol% at room temperature (Table 2-3, entries 1-3). This result demonstrated that the cyclizations of sulfonamides were much more facile than their carbamate analogues. When treated under the standard conditions *E*-allylic alcohol **2-18c** gave little conversion to the desired piperazine **2-19c.** Conversely, *Z*-allylic alcohol **2-18d** underwent smooth cyclization to give 89% of the product **2-19c** after 16 hours at room temperature (Table 2-3, entries 4-5). The method also allows easy access to morpholines such as **2-19d**, although the cyclization was again more facile when the *Z*-allylic alcohol isomer was used (Table 2-3, entries 6-8).

Lastly, it was found that even though carbamates and sulfonamides readily undergo cyclization, amides such as **2-20** were unable to produce any of the desired lactams **2-21** under various conditions (Table 2-4). Despite attempts to electronically tune the substrates to facilitate cyclization by varying the substituents on the nitrogen, and at the allylic position, the desired products were not observed with substrates **2-20(a-d)**, even while refluxing the reaction mixture (Table 2-4, entries 3 and 5). Interestingly, although terminal carbamates like that of **2-18** readily undergo the desired

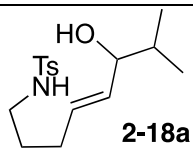
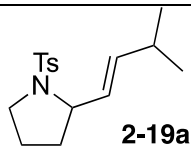
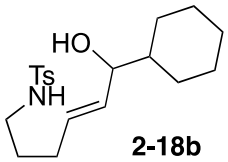
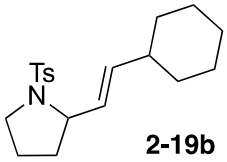
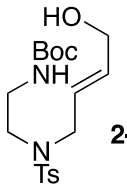
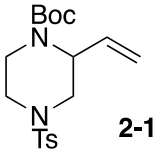
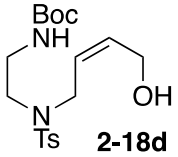
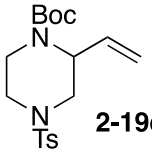
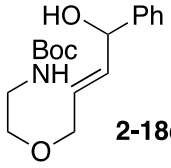
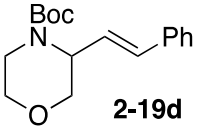
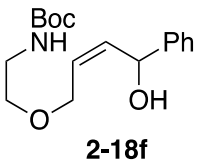
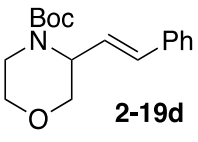
cyclization, internal carbamate **2-20d** did not cyclize under the optimized conditions (Compare Table 2-3 to Table 2-4 entry 5).

Table 2-3. Substrate scope for the dehydrative cyclization of sulfonamides and carbamates



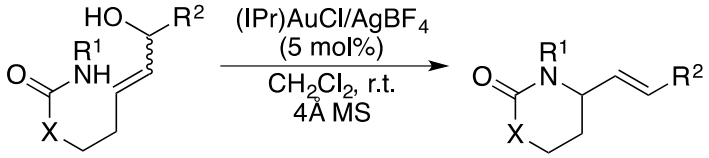
2-18 **2-19**

R^1 = Boc, Ts
R^2 = alkyl, aryl, H
X = O, NTs, CH_2
n = 0, 1

entry	substrate	mol (%)	time (h)	product	yield (%)[a]
1	 **2-18a**	1	20	 **2-19a**	71
2	 **2-18b**	2.5	6	 **2-19b**	88
3		5	1		92
4	 **2-18c**	5	16	 **2-19c**	<20[b]
5	 **2-18d**	5	16	 **2-19c**	89
6	 **2-18e**	5	24	 **2-19d**	30
7	 **2-18f**	5	7	 **2-19d**	51
8		5	24		81

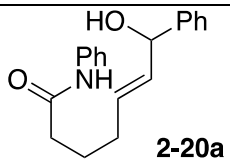
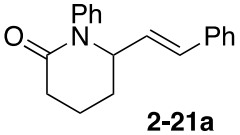
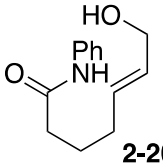
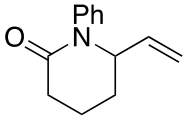
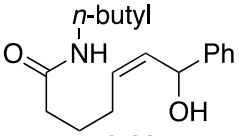
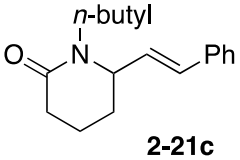
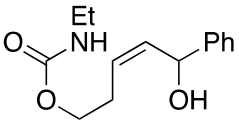
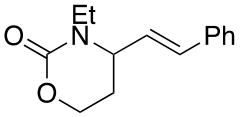
[a] Purified yields. [b] Conversion by ^{1}H NMR (300 MHz).

Table 2-4. Limitations of the method



2-20 **2-21**

R^1 = Ph, alkyl
R^2 = Ph, H
X = O, CH_2

entry	substrate	time (h)	product	yield (%)
1	 **2-20a**	24	 **2-21a**	–
2	 **2-20b**	24	 **2-21b**	–
3	 **2-20c**	24	 **2-21c**	–
4[a]		24		–
5[a]	 **2-20d**	24	 **2-21d**	–

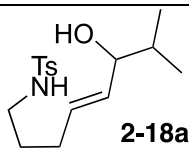
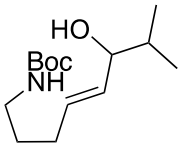
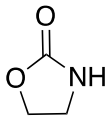
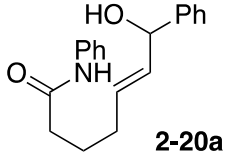
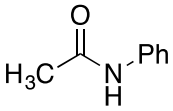
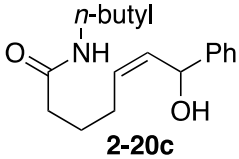
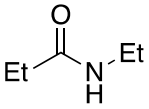
[a] Reaction run at reflux.

Various factors could cause the low reactivity observed by the amide substrates **2-20(a-c)**. One factor could be a general decrease in nucleophilicity for these amides with respect to other substrates that successfully undergo formal S_N2'-type cyclizations (which is unprecedented for amides). The second could be that these relatively unhindered amides may coordinate to the cationic gold-complex thereby shutting down the catalytic cycle, a type of coordination that could be minimized in the *tert*-

butylcarbamate substrates because of the increase in steric hindrance from the tertiary-butyl group.

Although the lower reactivity observed for these amides is not well understood, it should be noted that there seems to be a correlation between the pK_a of the substrates, and their ability to undergo the dehydrative cyclization. To estimate the pK_a's of the substrates, a comparison was made to analogous amides with known pK_a values (Table 2-5).

Table 2-5. pKa of analogous compounds in relation to the reactivity

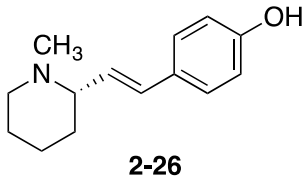
substrate	reaction conditions and yield	analogous compounds	pK_a of N-H for analogs (in DMSO)
 **2-18a**	1 mol%, r.t. 20 hrs. 71%	$TsNH_2$ **2-22**	16.3[49a]
 **2-16**	5 mol%, r.t. 24 hrs. 71%	 **2-23**	20.8[49b]
 **2-20a**	5 mol%, r.t. 24 hrs. No reaction	 **2-24**	21.5[49c]
 **2-20c**	5 mol%, reflux 24 hrs. No reaction	 **2-25**	26.5[49d]

As demonstrated in Table 2-5, the reactivity of the substrate increases with increasing acidity of the N-H bond. Furthermore, as the pK_a of the N-H bond approaches that of an alcohol, the reactivity of the amine substrate becomes more like that of a monoallylic diol for these cyclizations.[33,34] This relationship between acidity and

reactivity, may be due to the requisite hydrogen bonding interactions between the incoming nucleophile and the allylic alcohol that are needed to facilitate these dehydrative cyclizations (see Fig 1-22).[34f] The more acidic N-H bonds should have a higher tendency for hydrogen bonding, and thus a higher propensity to undergo dehydrative cyclizations.

Studies in the Transfer of Chirality for Carbamate Nucleophiles

A great deal of information was obtained through the studies of the optimization and scope of these cyclizations. Given the broad range of functionality that can be tolerated under the conditions, we set out to apply this method to the synthesis of a relatively simple natural product, *Caulophyllumine B* (**2-26**, Figure 2-3)**.**[50] The simplicity of the structure and the requisite stereocenter made it a great candidate for observing the transfer of chirality for the dehydrative cyclization of enantioenriched carbamates.



2-26

Figure 2-3. Caulophyllumine B

Retrosynthetically, **2-26** could easily come from the product of the gold-catalyzed cyclization of **2-27 (**Figure 2-4). Additionally, **2-27** could be easily made in a few simple steps starting from commercially available 5-hexyn-1-ol (**2-29**), allowing for short, direct stereoselective synthesis of **2-26**.

The synthesis first commenced with the production of the bis-carbamate **2-28** (Figure 2-5). Treating **2-28** under the standard Carreira asymmetric alkynylation conditions[51] with the pivaloyl protected 4-hydroxybenzaldehyde, gave the desired propargyl alcohol **2-30** in a reasonable yield with a good enantiomeric excess (92% ee).

Surprisingly, after reduction under Lindlar conditions and selective deprotection of one of the *t*-butoxycarbonyl (-Boc) groups with LiBr, a significant decrease in enantiomeric excess of the desired allylic alcohol **2-27** was observed

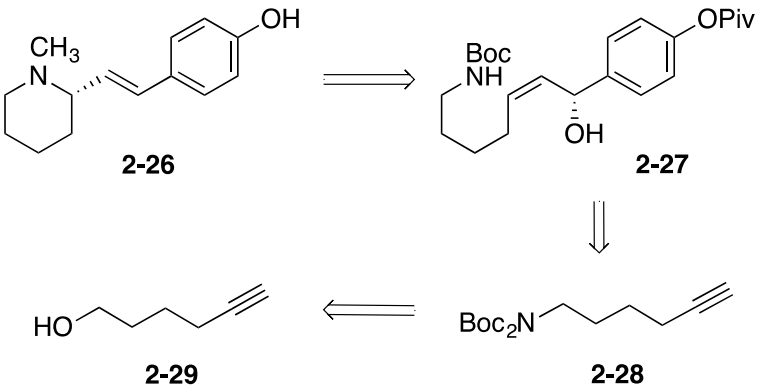


Figure 2-4. Retrosynthetic considerations for the synthesis of **2-26**

The racemization most likely occurred during the hydrogenation process, wherein the allylic alcohol could coordinate to the palladium and the electron donating oxygen in the *para*-position could help facilitate the inversion of the chiral center. Since the enantiomeric excess of **2-27** was already relatively low, our efforts were focused on finding a new substrate that would furnish higher ee before and, hopefully after the cyclization.

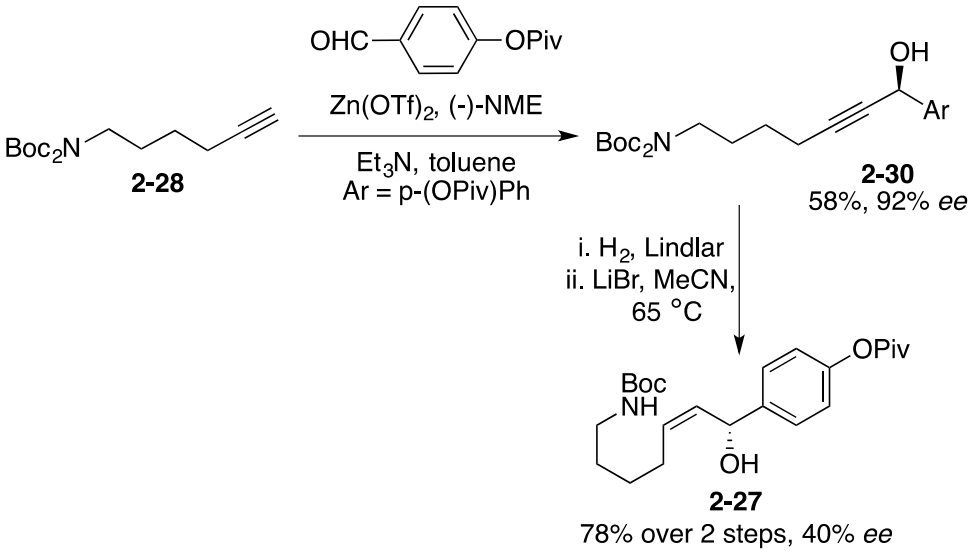


Figure 2-5. Synthesis of substrate **2-27**

To accomplish this goal a more deactivating (inductively withdrawing) 4-bromophenyl substituent was used, in hopes to circumvent the undesired racemization of the allylic alcohol and allow for a group that could be easily converted to the desired phenol. Again, treating alkyne **2-28** under the standard Carreira alkynylation conditions with 4-bromobenzaldehyde gave the desired propargyl alcohol **2-31** in a good yield with a 97% ee (Figure 2-6). Reduction of the alkyne, followed by partial deprotection of the bis-carbamate occurred with only minor racemization of the desired substrate **2-32**, allowing for an ideal demonstration of the previously reported transfer of chirality via a gold-catalyzed dehydrative cyclization.[34d,f] However, upon treatment of substrate **2-32** with the optimized conditions the product **2-33** was formed in only one hour in an unanticipated 30% ee. This result was somewhat puzzling and contrary to the high chirality transfer observed in the formation of tetrahydropyrans.[34d,f]

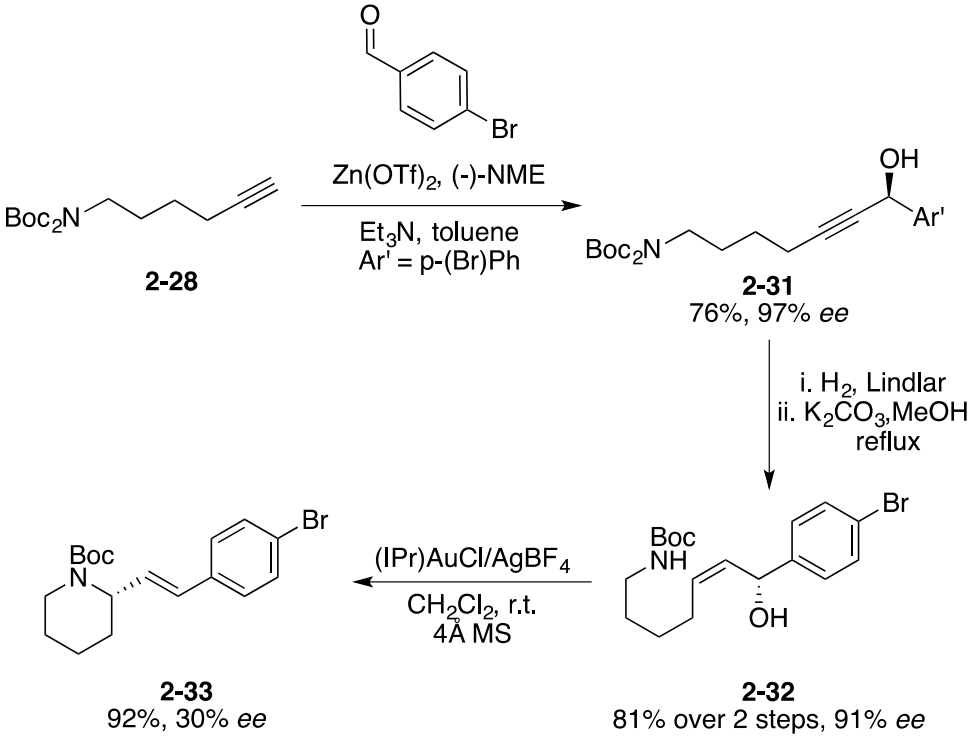


Figure 2-6. Synthesis of **2-33**

If these amine substrates followed a similar reaction pathway to their diol analogs, it would stand to reason that the substrate would undergo a similar mechanistic pathway and allow for a high transfer of chirality (Figure 2-7). The intermediate **2-34** can form a π-complex with the gold-catalyst, this intermediate can then undergo *anti*-addition of the carbamate to the π-complex to generate **2-35** (Figure 2-7). Loss of water and the cationic gold species (deauration) should give the enantioenriched product whose stereospecificity can be partially attributed to the hydrogen bonding interaction between the carbamate and the allylic alcohol, which acts as a stereochemical template throughout the mechanistic pathway.

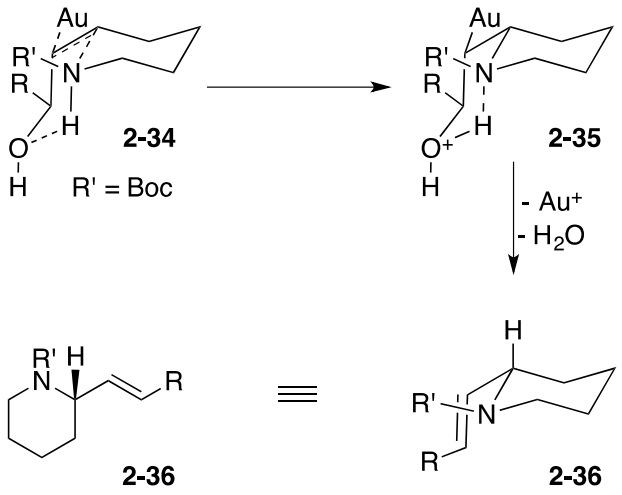


Figure 2-7. Mechanistic Pathways analogous to previous studies

A plausible explanation for the low enantiomeric excess found for **2-37** could be that the aromatic substituent brings about a competing pathway that causes the allylic system to undergo complete ionization, thereby giving a lower enantiomeric excess than would be expected. Additionally, when compared to their alcohol analogs, the carbamate nucleophiles may have a higher tendency for coordinating to the gold-

complex, which could also account for the longer reaction times observed for these azacyclizations.

With these interactions in mind, we envisioned two possible mechanistic pathways for the racemization of the enantioenriched allylic alcohol **2-32** (Figure 2-8). In pathway A, coordination of the alcohol to the gold-complex[52] **2-37** followed by ionization **2-38** creates an intermediate cation that is highly stabilized through resonance because it is both benzylic and allylic.

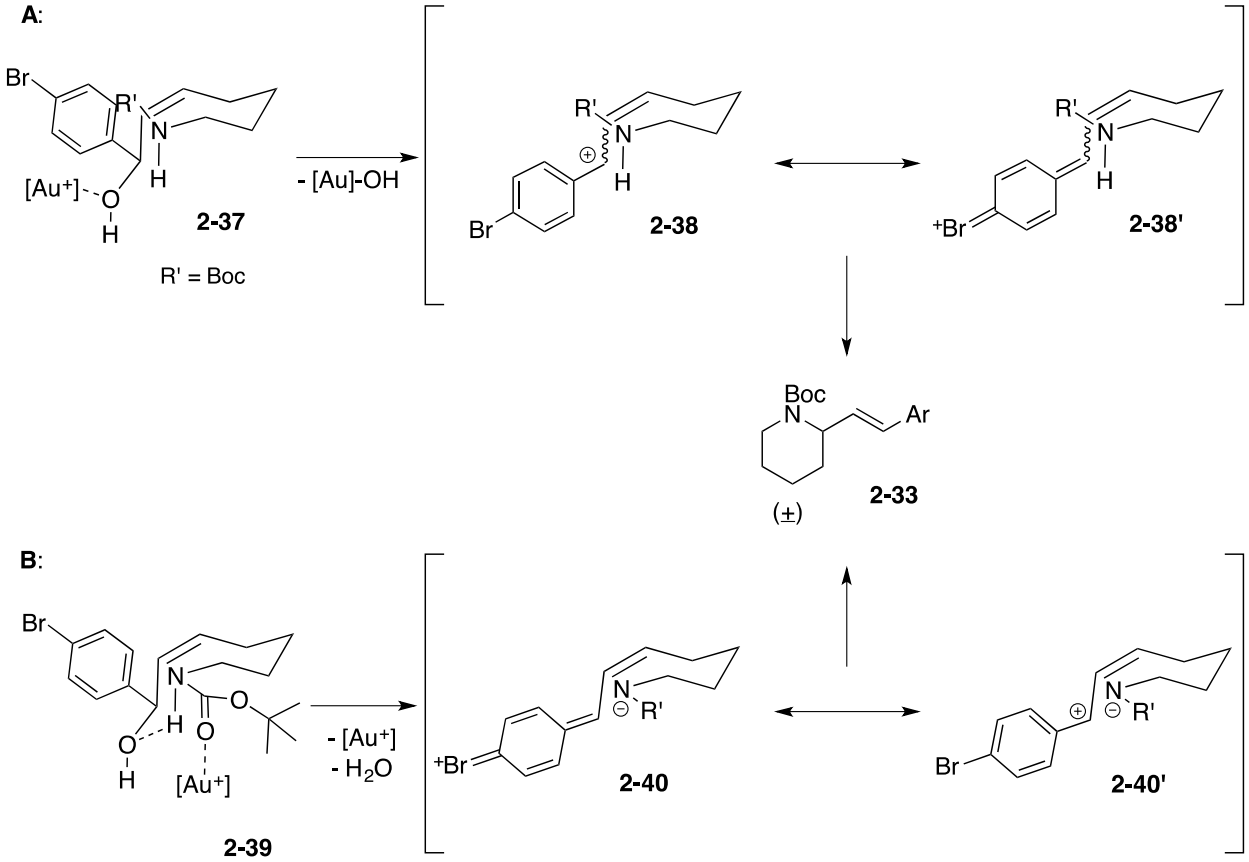


Figure 2-8. Possible ionization pathways. **A**: pathway A, **B**: pathway B.

In pathway B, coordination of the carbonyl oxygen in the carbamate to the gold-complex could sequester the catalyst creating a highly acidic proton on the nitrogen.

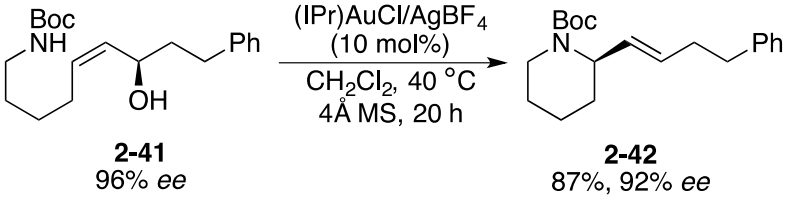
Protonation of the allylic alcohol in **2-39** would then create a hydronium ion that can easily be extruded as water creating a highly stabilized cationic system in **2-40**. After cyclization/rearomatization the product **2-33** would be formed as a racemic mixture. While coordination of the carbamate followed by deprotonation could be an equilibrium process occurring throughout any of the aforementioned azacyclizations, having an aromatic group in the allylic position should give a higher potential for cation formation, thereby creating the conjugated ionic system in **2-40**.

Although these possible competitive pathways have not been conclusively identified, they could account for the observed epimerization. Furthermore, if these pathways are in fact the main cyclization pathway for substrate **2-32** then there must be some memory of chirality[53] within the cyclization event since the product **2-33** is formed as a 65:35 mixture of enantiomers.

Given the aforementioned rationale for the observed epimerization, we were interested in learning more about the effect of having an aryl group in the allylic position and wanted to understand if it does in fact create a higher propensity for ionization of the allylic alcohol under these conditions. To test this theory, a similar cyclization precursor **2-41** with an alkyl substituent in the allylic position was prepared. This alkyl tether would create an allylic system that would be less susceptible toward ionization, hopefully resulting in a higher enatioselectivity after subsequent cyclization.

Gratifyingly, after treating carbamate **2-41** under gold-catalyzed conditions transfer of chirality was achieved with only small loss of enantiomeric excess to the product **2-42** (from 96% to 92% *ee*), albeit with somewhat more demanding conditions (Figure 2-9). Significantly, this result demonstrates the first gold-catalyzed transfer of

chirality using carbamates without the use of a chiral gold-complex,[54] and correlates well with the previously reported chiral transfer methodology for monoallylic diols.[34d]



2-41
96% *ee*

2-42
87%, 92% *ee*

Figure 2-9. Transfer of chirality from **2-41** to **2-42**

The studies on the gold-catalyzed dehydrative cyclization of carbamates have given invaluable insight into the potential mechanistic pathways that can occur for these reactions. The formation of azacycles under these conditions presents a mild and efficient route for the transfer of chirality without the need for a chiral metal-complex, and gives access to products with a broad range of functionality. These finding have since been accepted for publication,[55] and the methods are currently being applied to the synthesis and biological testing of various mefloquine analogs.

Synthesis of Mefloquine and Analogs

Historical and Biological Significance

Malaria is an infectious disease most-commonly found within tropical or subtropical regions of the globe that have high mosquito populations.[56] There are currently five known species of parasites that can be attributed to the cause of malaria in humans; however, the most deadly form is caused by the parasite *P. falciparum*.[56] These parasites are normally transferred to humans by an infected female mosquito, allowing for various avenues for preventative intervention measures in the spread of this devastating disease.[56]

All humans that travel or inhabit areas that are highly populated by these infected mosquitoes are at risk for contracting this treatable disease, especially in the sub-

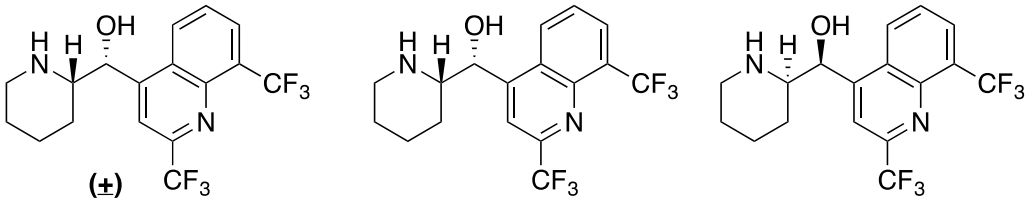
Saharan African regions.[57] It is estimated that in 2012 alone, the United States spent nearly $1.84 billion to finance and implement malaria control measures across the globe. In 2010, there were an estimated 219 million cases of malaria worldwide, as well as, 660,000 reported deaths.[56]

During the Vietnam War, the Walter Reed Army Institute of Research (WRAIR) began researching an antimalarial drug for the treatment and possible prevention of malaria.[58] Throughout their experiments, over 250,000 compounds were screened as potential candidates. From these screenings, mefloquine **2-43** (trade name Lariam) was discovered as a potent drug for the treatment of malaria, and was subsequently patented by the Hoffman-La Roche company. Lariam was then approved by the Food and Drug Administration (FDA) in 1989 and has since been marketed globally as an antimalarial drug.[58]

Mefloquine is one of several "priority" medications used in areas that carry the chloroquine-resistant *Plasmodium falciparum* (CRPF) strain of malaria, a strain that can be fatal in up to 4% of travelers who contract the disease.[57] It is defined as a suppressive chemoprophylactic because its mode of action involves targeting the parasites that have invaded the erythrocytes within the blood stream.[57] Although the drug suffers potential drawbacks, it is still one of the most prescribed antimalarial drugs worldwide because of its low cost, the ability to treat "at risk" individuals (pregnant women, children, etc.), and its once weekly dosage regimen. In fact, for pregnant women, no alternative antimalarial drug exists.[57]

The drug is sold as the *erythro*-isomer in its racemic form **2-43** and has gained much attention in recent years because of the long-term neurological side effects that

can develop before and after its use (Figure 2-10).[59] It is also speculated that (+)-mefloquine **2-44** is the active antimalarial drug whereas the (–)-mefloquine **2-45** enantiomer may cause the neurological problems associated with taking the commercial product.[60] For this reason, many researchers have focused on a stereoselective synthesis of (+)-**2-44**.[61]



2-43
(±)-Mefloquine (Lariam)
antimalarial drug

2-44
(+)-Mefloquine
potential for antimarial properties

2-45
(-)-Mefloquine
potential for psycholigcal side effects

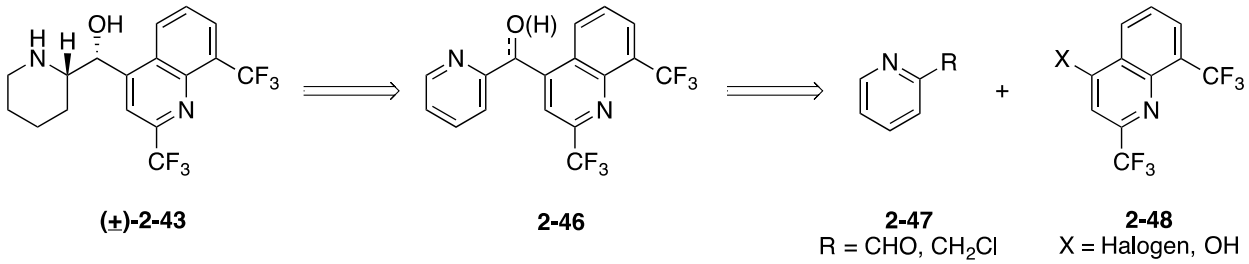
Figure 2-10. Mefloquine and its biological activity

Synthesis of Mefloquine and Its Derivatives

Given the recurrent use of this drug, its potential side effects, and a recent report that has unequivocally established the absolute configuration of (+)-**2-44**,[62] the need for a divergent asymmetric synthesis that could provide quick access to various analogs of this drug is critical. In the same respect, these analogs may increase the antimalarial properties while hopefully eradicating the potential psychotic side effects that can develop with its use. With this in mind, we set out to create a novel divergent asymmetric synthesis of (+)-mefloquine (**2-44**) and various enantioenriched analogs for the eventual biological testing against various malaria strains and psychotic effects.

Hoffman-La Roche gains rapid access to **2-43** by reduction of **2-46** which can be easily made by attachment of pyridine **2-47** to quinoline **2-48** (Figure 2-11).[63] While divergent and effective, this method generally only allows access to the racemic

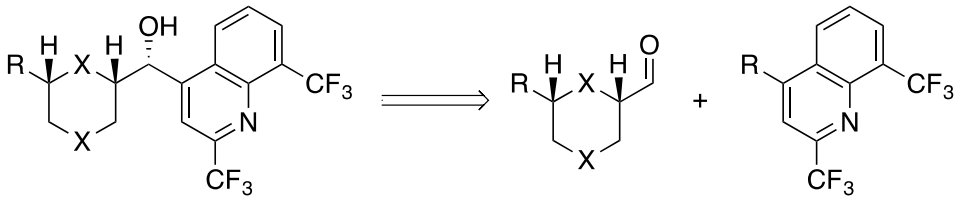
mixture. The use of pyridine **2-47** is also somewhat limiting as it gives little potential for certain analogs because of the lack of functional groups that can be incorporated into the pyridine ring.



(±)-2-43 **2-46** **2-47** R = CHO, CH_2Cl **2-48** X = Halogen, OH

Figure 2-11. Hoffman-La Roche's Approach to Lariam

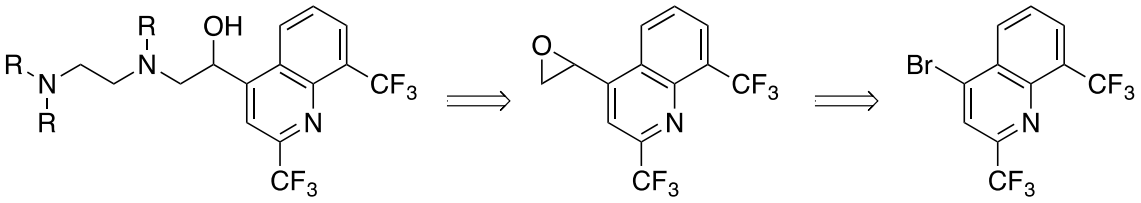
Our proposed retrosynthesis allows for a variety of mefloquine analogs **2-49** that have not been previously reported (Figure 2-12). Synthesis of unique analogs is of increasing importance due to the multitude of recent reports that have demonstrated the potential effectiveness of mefloquine and its derivatives against various diseases including: multiresistant tuberculosis,[64] multifocal leukoencephalopathy,[65] and vibrio cholera[66] to name a few. In addition to the potential health benefits, these analogs could also give further insight into the mechanism by which mefloquine functions in a biological setting.



2-49 **mefloquine derivatives** *potential for antimarial properties* X = NH, O R = aryl, alkyl **2-50** X = NH, O R = aryl, alkyl **2-51** R = Li, or Mg-halide

Figure 2-12. Proposed Retrosynthesis of Mefloquine Derivatives

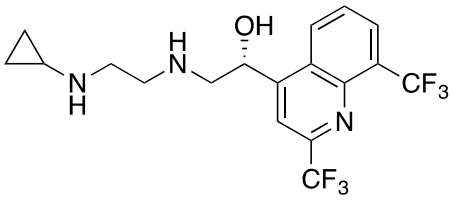
More recently, researchers at the Walter Reed Army Institute of Research screened various analogs that encompass diamine tethers like that in **2-52** (Figure 2-13).[67] These derivatives can be easily constructed through the epoxide opening of **2-53** using various diamines. During their studies, Milner and coworkers found a highly potent analog **2-54** (Figure 2-14, aka WR621308) that has a reduced accumulation in the central nervous system (CNS) in comparison to mefloquine.



2-52 **2-53** **2-48a**

Figure 2-13. Diamine Quinoline Methanols

In reference to **2-54**, the authors state: "…we identified a compound that is curative after single dose administration and has a longer half-life, lower partitioning into the CNS, and an improved cardiac safety index relative to mefloquine".[67] In addition to the aforementioned analogs of the parent mefloquine (Figure 2-12), it would be advantageous to construct analogs based on the structure of **2-52**.

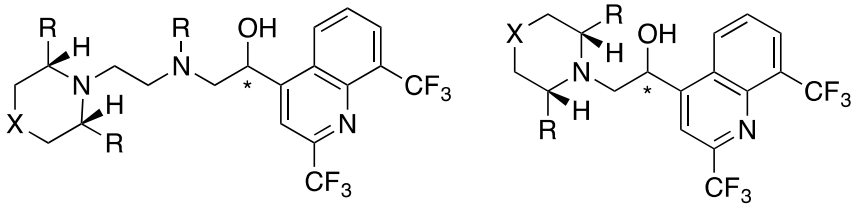


2-54
(WR621308)

Figure 2-14. Highly potent mefloquine analog **2-54**

With this in mind, we have also devised a plan to construct analogs with the general structures **2-55** and **2-56**. Enantioenriched azacycles can be easily synthesized

via the gold-catalyzed dehydrative cyclizations. These azacycles could then be easily tethered onto the epoxy-quinoline **2-53** via an epoxide ring opening, allowing rapid access to these analogs.



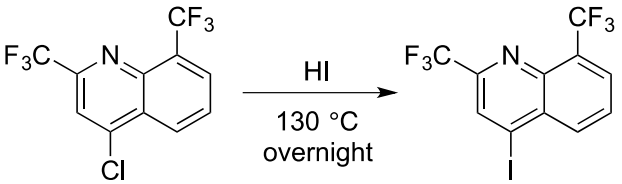
2-55
X = NH, O
R = aryl, alkyl

2-56
X = NH, O
R = aryl, alkyl

Figure 2-15. Potential Analogs of WR621308 (**2-54**)

Initial Experimentation

The initial studies for this project have focused on the design of an efficient asymmetric synthesis of mefloquine. Experimentation has thus far been concentrated on optimizing the addition of the metallated quinoline **2-51** to to an aldehyde. Isobutryaldehyde was chosen because its volatility would allow for easy purification, while its substitution pattern makes it a good model for the piperidine aldehyde **2-50**.



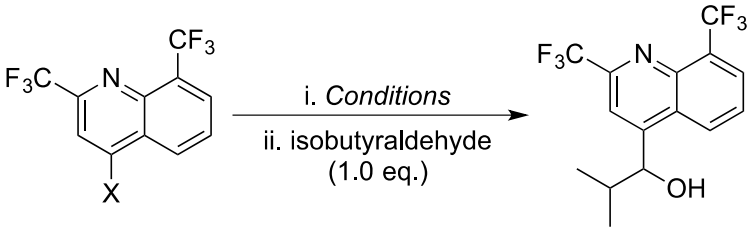
2-48b **2-48c**, 61%

Figure 2-16. Synthesis of **2-48c**

In order to generate the metallated **2-51** both the chloro- and iodo-analogs were synthesized to determine which halide would undergo a more facile metal-halogen exchange. Synthesis of the known 4-chloro-2,8-bis(trifluoromethyl)quinoline **2-48b** was easily achieved through literature procedures.[68] Additionally, the iodo quinoline **2-48c** was easily accessed by treating **2-48b** with hydroiodic acid (Figure 2-16).

With both halides in hand, studies of the lithium[69] and magensium[70] halogen-exchange reactions, followed by subsequent addition of these metallated quinolines to isobutyraldehyde were underway (Table 2-6). Unfortunately, under various conditions the metal-halogen exchange for the chloroquinoline **2-48b** was unsuccessful. Switching to the more inductively withdrawing iodoquinoline **2-48c** gave the desired product **2-58** in a 45% yield after lithiation with *n*-butyllithium (Table 2-6 entry 4). Furthermore, treatment of **2-48c** under Knochel conditions,[70] gave the desired product **2-58** in a 58% yield (Table 2-6 entries 5-6).

Table 2-6. Screening for the metal-halogen exchange of **2-48**



2-48b, X = chloro
2-48c, X = iodo

2-57

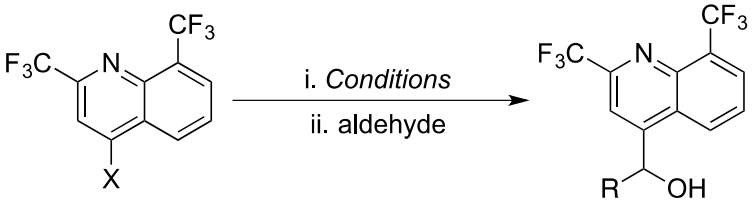
entry	halide	conditions	yield (%)[a]
1	**2-48b**	Mg^0, I_2	_
2	**2-48b**	*n*-BuLi	<10[b]
3	**2-48b**	*i*PrMgCl·LiCl	_
4	**2-48c**	*n*-BuLi	45
5	**2-48c**	*i*PrMgCl·LiCl	50[b]
6	**2-48c**	*i*PrMgCl	58

[a] Purified yields. [b] Conversion by ^{1}H NMR (300 MHz).

Although the yields for the additions of the metallated quinoline were rather low, when searching through the literature similar results have been shown for analogous reactions.[71] For instance, lithiation of the bromoquionoline **2-48a** gave poor results for

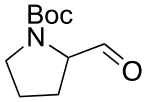
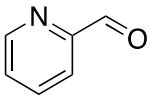
the addition to benzaldehyde and the pyrrolidine aldehyde **2-60** (Table 2-7, entries 1-2). Additionally, sulfoxide **2-48d** gave a 55% yield of the desired product after the sulfoxide-magnesium exchange with phenylmagnesium bromide and subsequent addition to the aldehyde **2-61** (Table 2-7, entry 3). These examples demonstrate some of the only reported reactions for addition of **2-48** to an aldehyde. The combined data (Table 2-6 and 2-7) demonstrate that lithiation of the halide gives dismal results, while exchange of the iodide or sulfoxide with magnesium can give moderate yields.

Table 2-7. Literature examples detailing the addition of **2-48** to aldehydes



2-48a, X = bromo
2-48d, X = S(O)-tolyl

2-58

entry	**2-48**	conditions	aldehyde	yield (%)[a]	reference
1	**a**	*n*-BuLi	benzaldehyde	36	71a
2	**a**	*n*-BuLi	 **2-59**	21	71a
3	**d**	PhMgBr	 **2-60**	55	71b

[a] Purified yields

As an alternateive to the direct addition of these metallated quinolines to an aldehyde, recent efforts have been focused on the addition of **2-48c** to the ozonide of **2-42**. This addition would be advantageous because it has been reported that the enantioenriched formyl-piperidine **2-62** can undergo epimerization.[72] Although, the addition of grignard reagent to ozonides has been well-known for quite some time,[73] its

use in synthetic chemistry is less common when compared to grignard addition to an aldehyde. Surprisingly, treatment of the *in situ* generated ozonide produced from the ozonlysis of **2-42**, produced the undesired product **2-62** in a 60% yield along with some residual formyl-piperidine **2-63**, and possibly a small amount of desired product (Figure 2-17).

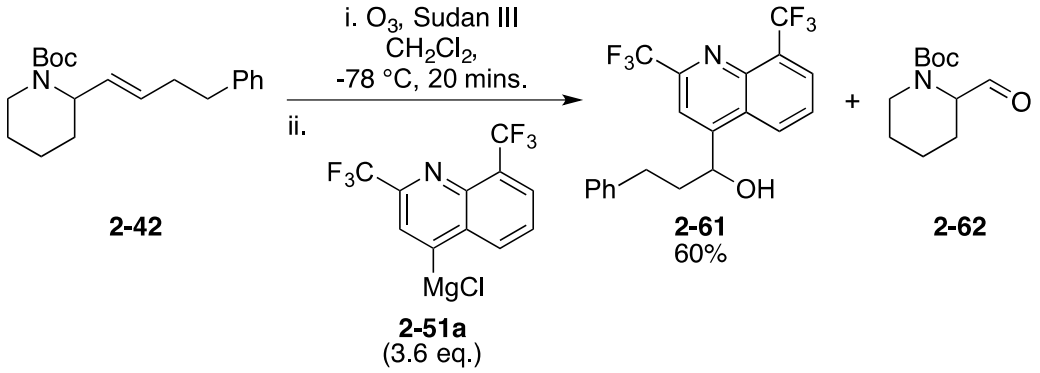


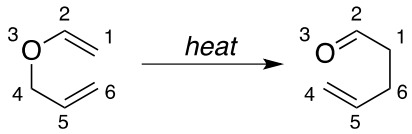
Figure 2-17. Treatment of ozonide with **2-51a**

Further experimentation for this project will focus on the optimization of the aforementioned processes in hopes to find a facile synthesis that efficiently stitches the quinoline and piperidine pieces together. These studies are currently underway and will be reported in due course.

CHAPTER 3
STUDIES IN THE TANDEM GOLD-CATALYZED HYDROALKOXYLATION/CLAISEN REARRANGEMENT

Introduction

The Claisen Rearrangement is a versatile synthetic transformation that enables the formation of two stereogenic centers and an γ,δ-unsaturated ketone **3-2** in one concerted step from an allyl vinyl ether **3-1** (Figure 3-1). This [3,3]-sigmatropic rearrangement was first discovered by Rainer Ludwig Claisen in 1912 and has since become one of the most well-known synthetic methods for the construction of carbon-carbon bonds.[74]



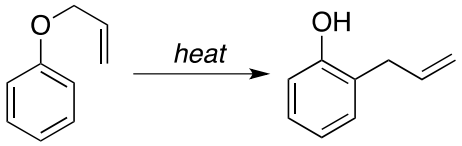
3-1 (*preformed*) **3-2**

Figure 3-1. General Claisen Rearrangement

In 1912, Claisen released a report that described the transformation of allyl phenyl ethers **3-3** to *ortho*-allylphenols **3-4** at high temperatures (Figure 3-2).[75] Since this initial account, many research groups have focused on the development of new variants of this sigmatropic process, especially in the field of catalysis. Some of the more well-known modifications are now considered classical methods, including: the Johnson(orthoester)-Claisen,[76] Eschenmoser-Claisen,[77] and the Ireland-Claisen[78] rearrangements (Figure 3-3).

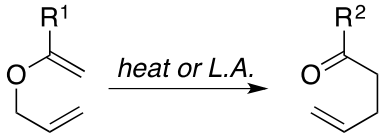
The carbonyl products formed in these reactions are highly functionalized and diverse synthons with various handles for further synthetic elaboration. As a

consequence of this utility, many groups have applied these methods in the construction of numerous natural products and biologically relevant building blocks.[79]



3-3 **3-4**

Figure 3-2. First Reported Claisen Rearrangement



3-5 **3-6**

R^1, R^2 = OR	*Johnson-Claisen*
R^1, R^2 = NMe_2	*Eschenmoser-Claisen*
R^1 = OTMS, R^2 = OH	*Ireland-Claisen*

Figure 3-3. Classical Variants of the Claisen Rearrangement

Mechanistically, it is well established that this [3,3]-rearrangement goes through a 6-membered chair transition state, like that of **3-7** (Figure 3-4). Although many transition state extremes (**3-8** – **3-11**) have been proposed, there is still no consensus for the precise transition state because it is highly dependent on the types of substituents.

The stereochemical outcome of the reaction is also dictated by the substituents in the allyl vinyl ether. In general, the chirality of the starting allyl vinyl ether is transferred to the ketone product after rearrangement (Figure 3-5).[74] In the case of the allyl vinyl ether **3-12** there are two major possible transition states **3-13** and **3-15**; however, **3-15** is disfavored because of the 1,3-diaxial interactions between substituents R^1 and X, thus the product **3-14** is formed rather than **3-16**. In substrates where no

satisfactory chair transition state exists the rearrangement can also take place through a boat-like transition state to alleviate many of the steric interactions.

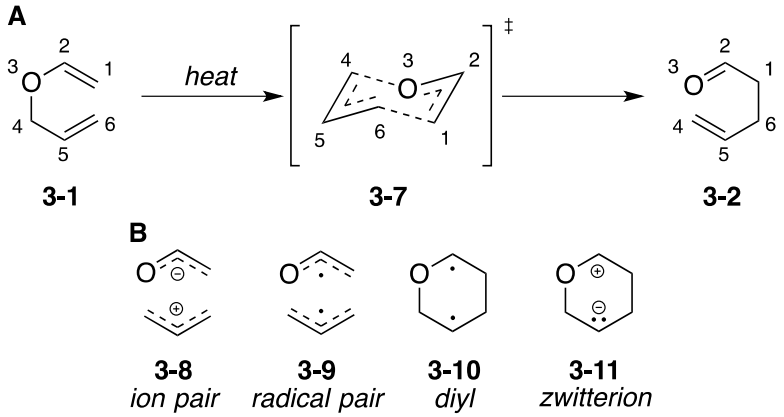


Figure 3-4. Possible Transition States of the Claisen Rearrangement; **A**: Chair-like transition state; **B**: Possible transition state extremes

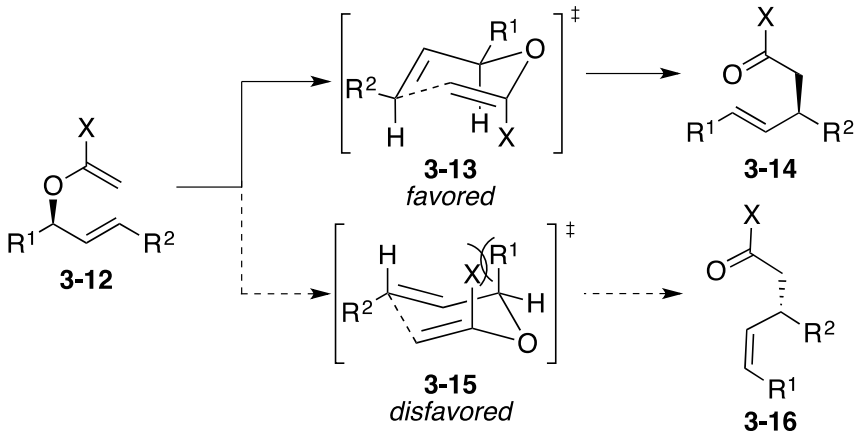


Figure 3-5. Stereochemical Considerations

Gold-catalyzed Claisen Rearrangements

Gold-catalysis has sparked a new wave of synthetic transformations, allowing for access to complex structures.[32] In 2004, Toste and coworkers reported the first gold-catalyzed formal-Claisen rearrangement, which details a stepwise [3,3]-rearrangement of propargyl vinyl ethers **3-17** to form allenols **3-18** with low catalyst loadings and high yields (Figure 3-6).[80] They were also able to demonstrate that the highest transfer of chirality from the starting material to the product was achieved using the cationic

oxonium gold-complex $[(PPh_3Au)_3O]BF_4$. In their best example, substrate **3-19** formed product **3-20** with high transfer of chirality and an extremely high diastereoselectivity.

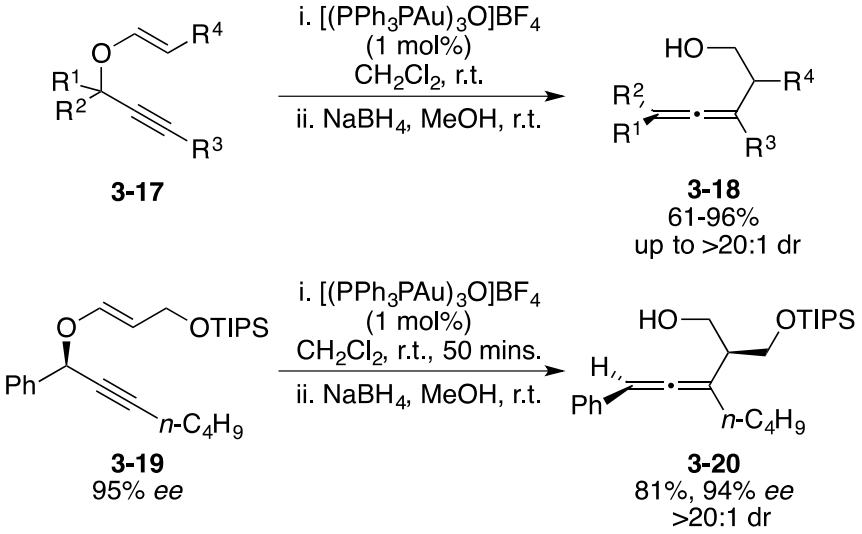


Figure 3-6. Gold-catalyzed propargyl Claisen rearrangement

Since this report many groups have published a variety of Claisen rearrangements catalyzed by gold-complexes.[81] In 2006, He *et al.* published a tandem gold-catalyzed Claisen rearrangement/hydroalkoxylation reaction for the synthesis of dihydrobenzofurans **3-23** from aryl allyl ethers **3-21** (Figure 3-7).[81c] The process is believed to go through a gold-catalyzed Claisen rearrangement to give intermediate **3-22**, followed by a gold-catalyzed hydroalkoxylation of the alkene. The authors state that the Claisen rearrangement is much faster when treated with a cationic gold(III)-complex, whereas the hydroalkoxylation step is much faster with a cationic gold(I)-complex. This is demonstrated in the formation of **3-26** from **3-24**, however, the experimental data does not detail these studies and the gold-complexes are not explicitly stated. For these reasons, it is hard to extrapolate any useful conclusions from their statements.

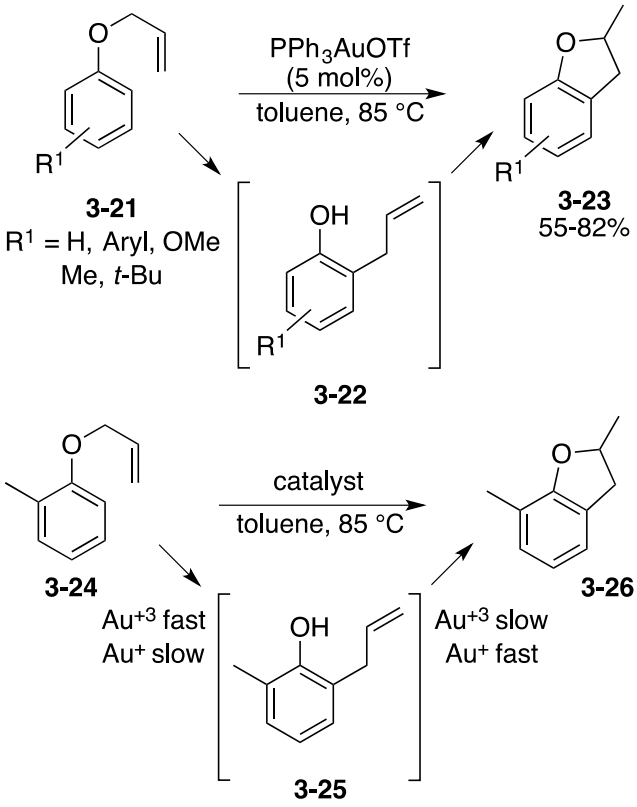


Figure 3-7. Gold-catalyzed tandem Claisen rearrangement/hydroalkoxylation reaction

A few years later, in 2010, Yeh and coworkers described the synthesis of spirocycles **3-29** from enynols **3-27** through a gold-catalyzed Claisen process followed by reduction of the subsequent alkene of **3-28** (Figure 3-8).[81f] The Claisen-type rearrangement from **3-27** to **3-28** was very facile, occurring in ≤20 minutes at room temperature with 5 mol% of a cationic gold-complex generated *in situ* from Ph_3PAuCl and AgOTf.

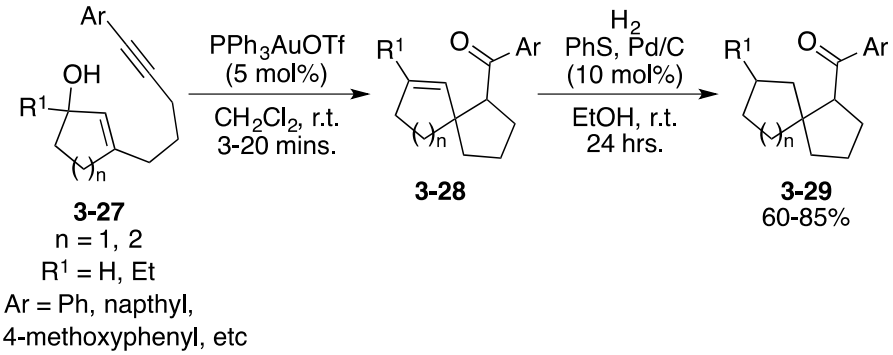


Figure 3-8. Spirocycles via gold-catalyzed Claisen-type rearrangement

The authors propose a mechanism that involves the activation of the alkyne in **3-30** with the cationic gold-complex to give intermediate **3-31** (Figure 3-9). After *anti*-addition of the alcohol to the alkyne to give the 9-membered oxonium ring **3-32**, a Claisen-type rearrangement occurs to give the bicyclic intermediate **3-33** followed by deauration and proton exchange to give the desired product **3-34**.

This highly efficient cycloisomerization allows access to complex bicyclic carbocycles, however, the synthesis of the requisite enynols **3-27** may impede the synthetic usefulness of this process. Furthermore, the alkyne substituents reported are always aromatic which severely limits the scope of this methodology.

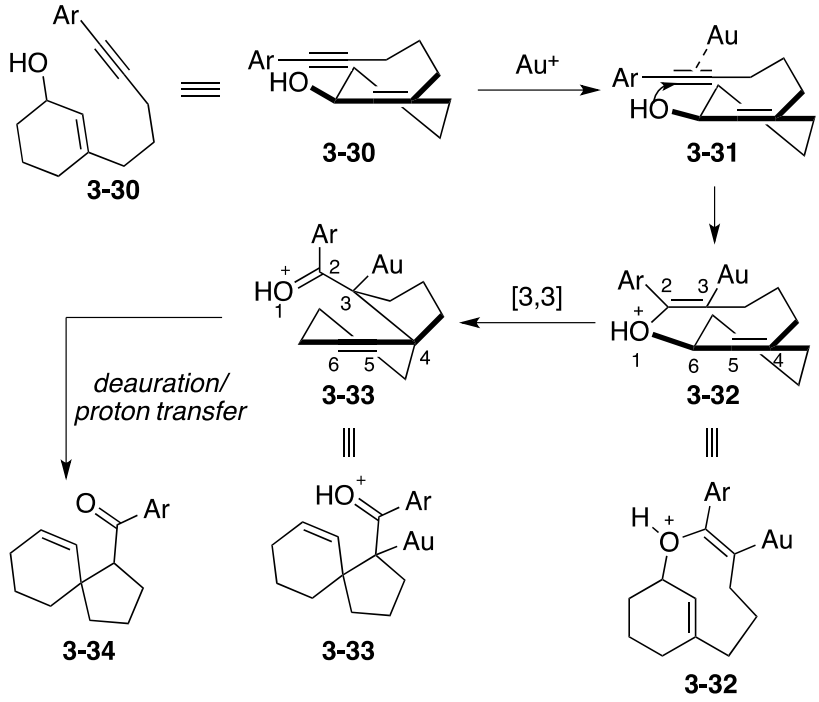


Figure 3-9. Proposed mechanism for the gold-catalyzed rearrangement of enynols

Gold-catalyzed Tandem Hydroalkoxylation/Claisen Rearrangement

In general, synthetic methodologies developed for the Claisen rearrangement involve preformed or highly activated substrates that have a high propensity to undergo the [3,3]-sigmatropic rearrangement (Figure 3-10). While surveying the literature we

noticed that, while these methodologies are well explored, processes for the formation of highly stereodefined acyclic allyl vinyl ethers are much less common, especially when *Z*-enol ethers that are not activated with additional functional groups are desired (where R^1 = H and R^2 = alkyl, aryl; **3-35**).[74, 82]

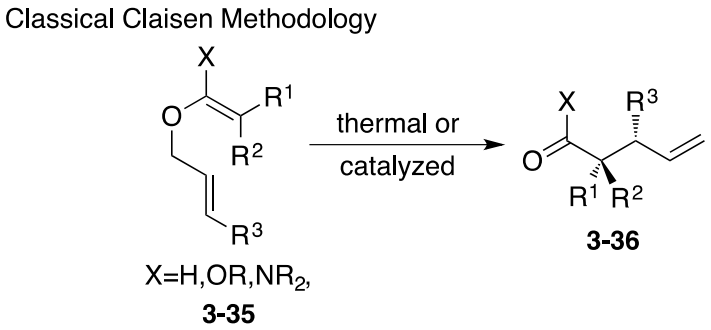


Figure 3-10. Classical Claisen Methodologies

Additionally, the synthesis and purification of the desired enol ether substrates has posed quite a challenge to the synthetic community. As a result of these challenges, many research groups have started focusing on tandem processes, which involve the formation of these enol ethers *in situ* followed by the sigmatropic rearrangement, in order to circumvent the problems associated with the stability of these compounds.[82e-g, 83]

In 2004, Buchwald and coworkers reported a tandem copper-catalyzed C-O coupling/Claisen rearrangement.[82f] During the reaction course an allylic alcohol **3-37** goes through a Cu(I)-catalyzed C-O coupling with a vinyl iodide **3-38** to form an allyl vinyl ether, which undergoes the rearrangement over 2 days at 120 °C to give the desired product **3-39** (Figure 3-11). The process occurs with reasonable yields and diastereoselectivity, however the formation of the requisite vinyl iodides can limit the

utility of the products. Moreover, the catalyst loadings, temperature and reaction times are quite high which may take away from the value of the reaction.

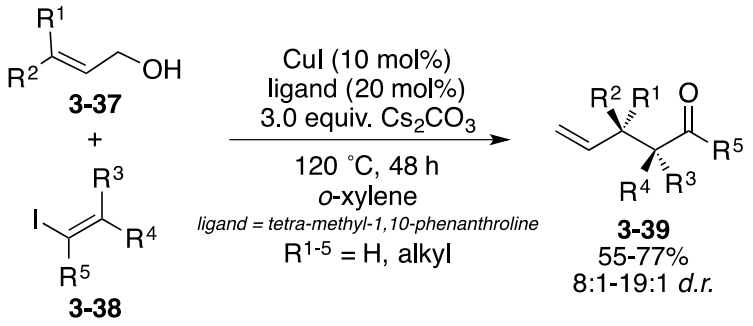


Figure 3-11. Cu-catalyzed C-O coupling/Claisen Rearrangement

In the same respect, Nelson and coworkers reported an attractive asymmetric iridium-catalyzed isomerization Claisen rearrangement (ICR) as an extension of their previously reported iridium methodologies.[83e,g] This elegant transformation converts diallyl ethers **3-41** into the desired Claisen products **3-42** with good yields and high stereoselectivity with low catalyst loadings (Figure 3-12). The isomerization of the terminal olefin is a good strategy to obtain the allyl vinyl ether, however, it limits the functionality of the products because only a methyl substituent on the α-carbon can be produced. In the same respect, the steric differentiation required for the selective iridium-catalyzed isomerization to occur results in the production of only aldehyde products only.

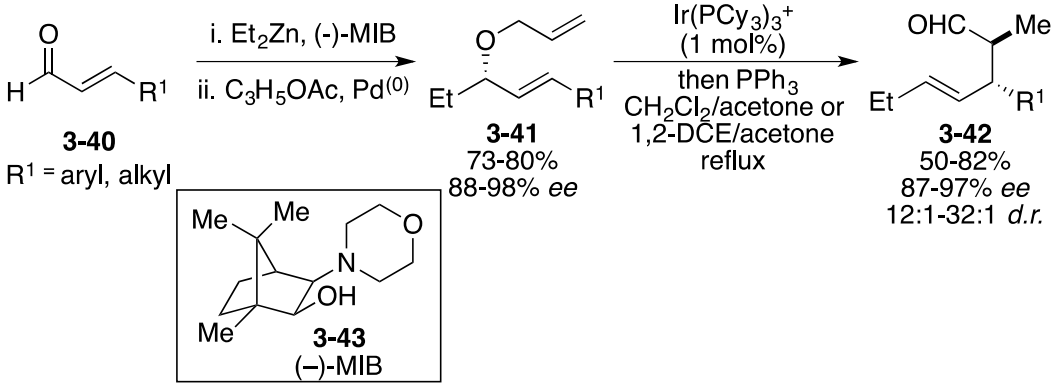


Figure 3-12. Iridium-catalyzed isomerization Claisen rearrangement (ICR)

Although the aforementioned tandem enol ether formation/Claisen rearrangement reactions are elegant, they have many drawbacks. In order to broaden the scope of these sequences we envisioned a tandem hydroalkoxylation/Claisen rearrangement process to give ketone products (Figure 3-13). This seemed like an attractive, atom-economic approach to help broaden the access to these diverse products. Additionally, a metal-catalyzed hydroalkoxylation would generate the enol ether in a stereodefined manner *in situ* based on the mechanism of alcohol addition.[84] Interestingly, while metal-catalyzed hydroalkoxylations of alkynes is well-known,[85] the tandem process we envisioned had never been reported.

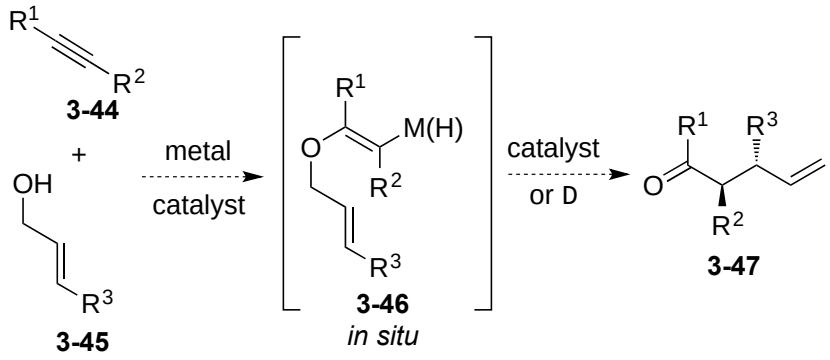


Figure 3-13. Proposed Hydroalkoxylation/Claisen rearrangement process

Results and Discussion

Preliminary studies utilized gold-complex **3-50** to test this tandem process, because this complex worked well during our studies of the intramolecular dehydrative alkoxylation of alkynes to form spiroketals.[34a] However, the inherent difficulties of the sequence became abundantly clear at the beginning of our studies. When alkyne **3-48** was treated with alcohol **3-49** in the presence of gold-complex **3-50**/AgOTf, a complex mixture of hydration (**3-52**, **3-53**) and self-condensation (**3-54)** products was formed, however, the desired product **3-51** was not observed (Figure 3-14). This result further

exemplified the challenges we would need to overcome in order to allow these allylic alcohols to serve as nucleophiles, since all of our previous methodologies have focused on the ability of propargyl and allylic alcohols to act as electrophiles under gold-catalyzed conditions.[34]

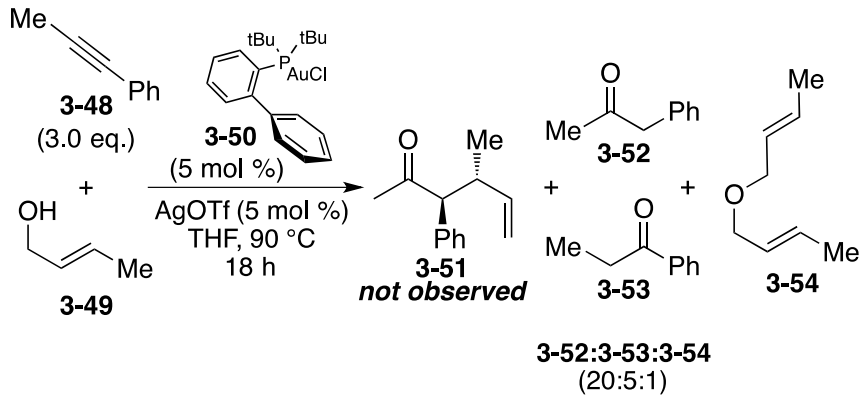


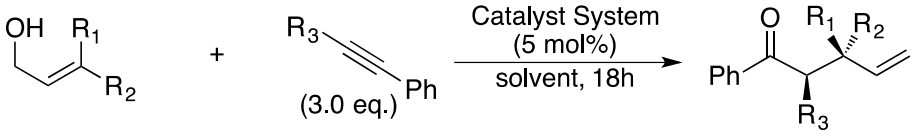
Figure 3-14. Inherent difficulties

Initially, we began our studies by testing various metal-complexes to see which, if any, could catalyze the tandem process. Crotyl alcohol was first employed (**3-49**) as the nucleophile, because it is a commercially available and inexpensive starting material. The volatility of the alcohol would also make purification much easier during these preliminary tests. In the same respect, alkyne **3-48** was readily available, had a high molecular weight, and could give preliminary insight into the regioselectivity of the reaction.

Unfortunately, when alcohol **3-49** was treated with various catalyst systems none of the desired product was obtained (Table 3-1 entries 1-4). Given the susceptibility of the allylic alcohol **3-49** to undergo intermolecular dehydrative S_N2' reactions, the nucleophile was replaced with a more hindered alcohol **3-55** in hopes to avoid these possible side reactions. Surprisingly, switching to the more hindered alcohol also did not produce any of the desired product, even under more harsh conditions (Table 3-1,

entries 5-6). Diphenylacetylene **3-56** was then used as the alkyne partner, in hopes to have a higher reactivity and alleviate any regioselectivity issues. The catalyst system and solvent were also switched to analogous conditions of a recent report that demonstrated an extremely high efficiency for the hydration of alkynes with water.[86]

Table 3-1. Preliminary Studies



3-49 (R^1 = H, R^2 = Me) **3-48** (R^3 = Me) **3-57** (R^1 = H; R^2, R^3 = Me)
3-55 (R^1, R^2 = Me) **3-56** (R^3 = Ph) **3-58** (R^1, R^2 = Me; R^3 = Ph)

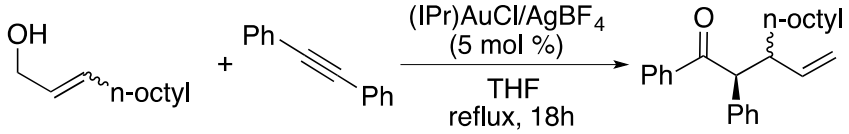
entry	alcohol	alkyne	catalyst system	solvent	temp (°C)	yield (%)[a]
1	**3-49**	**3-48**	**I**	THF	65	0[b]
2	**3-49**	**3-56**	AuCl	THF	65	0[b]
3	**3-49**	**3-56**	$PtCl_2$	THF	65	0[b]
4	**3-49**	**3-56**	$AuCl_3$/AgOTf[c]	THF	65	0[b]
5[d]	**3-55**	**3-48**	**I**	THF	90	0[b]
6	**3-55**	**3-48**	**I**	THF	65	0[b]
7	**3-55**	**3-56**	**II**	1,4-dioxane	100	25 (**3-58**)
8[d]	**3-55**	**3-56**	**II**	1,4-dioxane	120	34 (**3-58**)
9	**3-55**	**3-56**	**II**	THF	65	50 (**3-58**)

[a]Isolated yields. [b]A complex mixture of hydration and self-condensation products was observed. [c] $AuCl_3$ (5 mol%)/AgOTf (15 mol%). [d]Reaction run in sealed tube. **I**=(*o*-biphenyl-di-*tert*-butylphosphine)gold(I) chloride/ AgOTf; **II** = (IPr)AuCl/$AgBF_4$.

Gratifyingly, all of these changes were steps in the right direction, giving the desired product **3-58** in a 25% yield when **3-55** and **3-56** were treated with catalyst system **II** in 1,4-dioxane at 100 °C (Table 3-1, entry 7). Further increasing the

temperature of the reaction to 120 °C gave a slightly higher 34% yield of the product (Table 3-1, entry 8). Counterintuitively, the best yield was given when the reaction was run in refluxing tetrahydrofuran (65 °C), which is a much lower temperature than is normally required for these [3,3]-rearrangements.[74] Under these conditions the desired product **3-58** was produced in a 50% yield (Table 3-1, entry 9).

Table 3-2. Optimization Studies



3-59 = *E*
3-60 = *Z*

3-56
(3.0 eq.)

3-61 = *anti*
3-62 = *syn*

g	alcohol	additional conditions	yield (%)[a]	**3-61:3-62**[b]
1	**3-59**	–	73	5:1
2	**3-59**	(IMes)AuCl/$AgBF_4$	0	–
3	**3-59**	PPh_3AuNTf_2	0	–
4	**3-59**	$AgBF_4$ only	0	–
5	**3-59**	$HBF_4{\cdot}OEt_2$ only	0	–
6	**3-60**	–	0	–
7	**3-60**	Slow addition of **3-60**	33[c]	1:7
8	**3-60**	Slow addition of **3-60**, then 120°C for 6 hrs.	75	1:11

[a]Isolated yields. [b]Determined by ^{1}H NMR (500 MHz). [c]Enol ether adduct of **3-56** + **3-60** was also isolated in 37%, see supporting information.

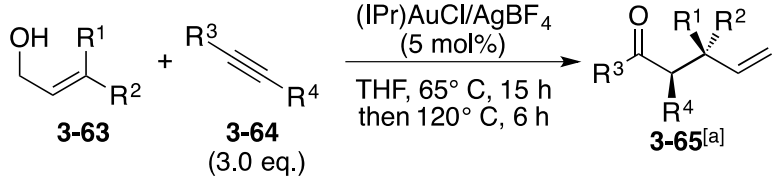
The preliminary studies demonstrated that cationic gold-complexes could catalyze the tandem process, however, we were still interested in optimizing the conditions to include the use of relatively unhindered allylic alcohols that have a higher propensity for S_N2' side reactions. Additionally, to quickly evaluate the progress of the reactions a less volatile alcohol was desired in order to monitor its conversion to the

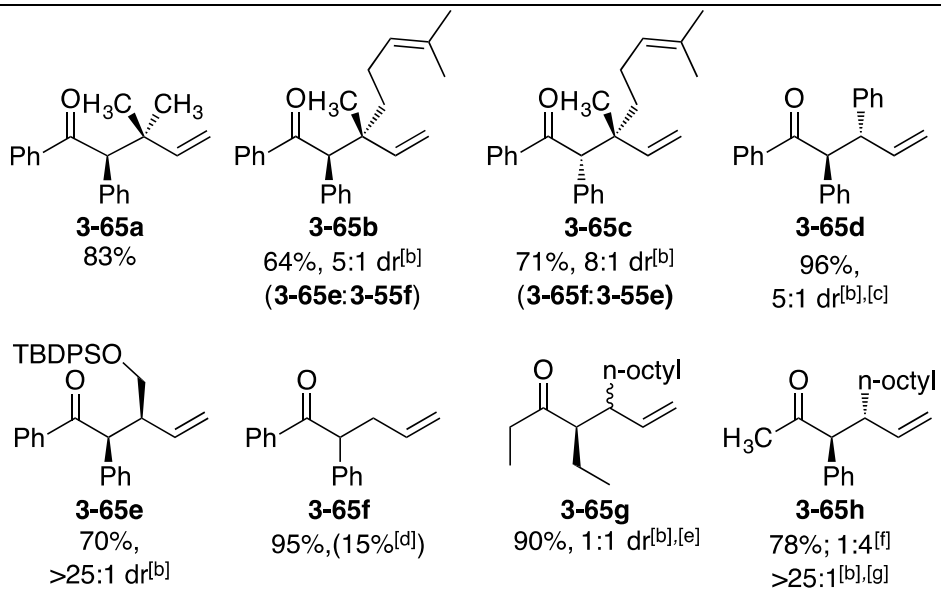
product by crude ^{1}H NMR. To satisfy all of these requirements, alcohols **3-59** and **3-60** were used for the optimization studies (Table 3-2).

We were delighted to find that treating the *E*-allylic alcohol **3-59** with the same conditions used in our preliminary studies (Table 3-1, entry 9) gave the product **3-61** in a 73% yield with a 5:1 diastereoselectivity (Table 3-2, entry 1). Several gold-complexes were then tested under the reaction conditions, and it was found that the process was selective for the original conditions (Table 3-2, entries 2-5). Treating the substrates with the cationic silver source or the protic acid that could be produced by the counter ion proved that the reaction was indeed catalyzed by the cationic gold-complex (Table 3-1, entries 4-5). Unfortunately, treating the *Z*-allylic alcohol **3-60** under the aforementioned conditions did not give any of the desired product **3-62** (Table 3-2, entry 6).

Since the *Z*-allylic alcohol **3-60** may have a higher predisposition toward self-condensation by an S_N2' reaction, the solution of the alcohol was then added slowly (over 12 hrs.) to the reaction mixture. Fortunately, slow addition of the alcohol provided the *syn*-product **3-62** in a 33% yield with a 7:1 dr (Table 3-2, entry 7), however, the mixture contained residual enol ether formed from the hydroalkoxylation of **3-56** with **3-60**. In hopes to fully convert the enol ether to the desired product, the slow addition was then followed by heating the solution at 120 °C in a sealed tube for six hours. Under these conditions the product **3-62** was formed in 75% yield with a 11:1 dr, which is higher than that of the *E*-allylic alcohol (compare Table 3-2 entries 1 and 8). Although higher temperatures are required, the conditions are still milder than most reported Claisen protocols, and these parameters were adopted as the optimized conditions.

Table 3-3. Selected Substrate Scope





[a] Isolated yields. [b] diastereoselectivity determined by ^{1}H NMR (500 MHz). [c] Slow addition of alcohol not required. [d] Yield obtained using conditions from Table 3-1, entry 9. [e] Substrates: **15**, 3-hexyne. [f] Ratio (arylketone:alkylketone) determined by ^{1}H NMR (500 MHz). [g] Only a single diastereomer of each regioisomer was observed.

With the optimum conditions established, the substrate scope of the reaction was then examined (Table 3-3). Hindered allylic alcohols with a lower susceptibility toward etherification cleanly produced the product in reasonable yields (Table 3-2, **3-65a-3-65c).** Furthermore, as demonstrated during the optimization process, *Z*-allylic alcohols give consistently higher diastereoselectivity in all cases when compared to the *E*-allylic alcohols (Table 3-2 entries 1,7 and Table 3-3 compare **3-65b** and **3-65c**). Under the optimized conditions the disubstituted olefin cinnamyl alcohol was efficiently converted to **3-65d** in a 96% yield with 5:1 dr, however when the more sterically hindered -

OTBDPS substituent was used the diastereoselectivity increased dramatically (**3-65e**, >25:1 dr).

Much to our delight, commercially available, unhindered allyl alcohol was also smoothly transformed to the product **3-65f** in a 95% yield under the optimized conditions. It was also found that the aliphatic alkyne 3-hexyne could easily undergo the desired tandem process to give the product **3-65g** with a high yield, albeit with a lower dr (1:1) than was found for the diphenylacetylene. Lastly, when 1-phenyl-1-propyne was used as the alkyne reaction partner with alcohol **3-59** the desired product **3-65h** was obtained in a 78% yield as a 1:4 mixture of regioisomers, where each regioisomer was obtained as a pure diastereomer.

The above studies demonstrated that various allylic alcohols, and aliphatic or aromatic acetylenes could form the desired product with a cationic gold-complex. Nevertheless, examining the factors that dictate the regioselectivity for the hydroalkoxylation could give further insight into the utilization of this methodology. Furthermore, if the reaction could preferentially form aryl ketones it would broaden the synthetic utility of the process, because electron rich aromatic ketones can be easily oxidized to the ester.[87] This would allow for a synthetic handle that could be easily removed if necessary.

From the outset of this project it was demonstrated that the regioselectivity would pose a significant problem when unsymmetrical alkynes were used (Figure 3-14). Allyl alcohol was used to further examine the regioselectivity in order to decrease the mixture of possible products caused by stereo- and regioselectivity issues. The commercial

availability and low boiling point also made it a great candidate for easy scalability and purification of the reactions.

Initial studies focused on tuning the sterics and electronics of the aromatic portion of the alkyne while leaving the aliphatic portion untouched (Figure 3-15). Additionally by careful tuning of the electronics and sterics of the aromatic ring, (Figure 3-15) the gold-complex would hopefully reside more toward the alkyl portion of the alkyne, thereby directing nucleophilic attack at the benzylic position.

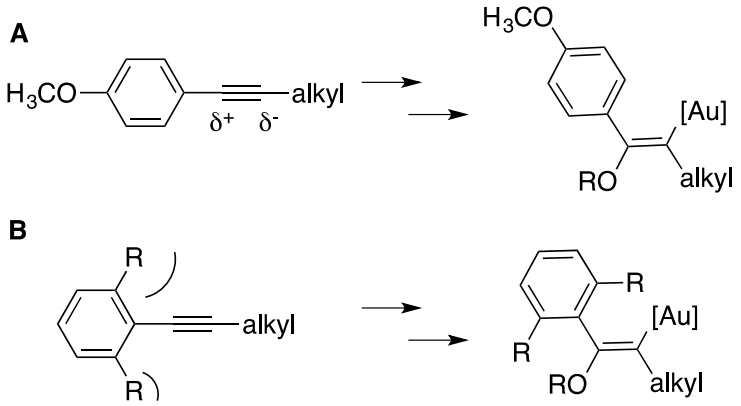
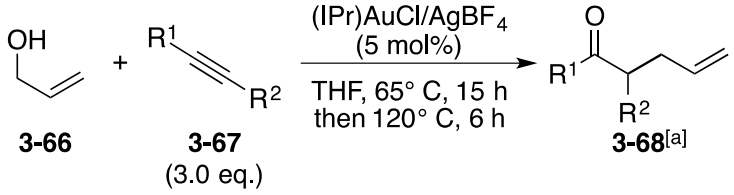


Figure 3-15. Tuning the regioselectivity. A: Electronic Tuning B: Steric Tuning

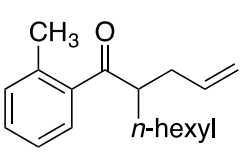
With this rationale in mind, studies of the regioselectivity were undertaken (Table 3-4). It was somewhat disappointing to find that placing a methyl group in the *ortho*-position of the ring gave the product **3-68a** with a 2:1 regioselectivity, while having an electron donating methoxy group in the *para*-position of the ring gave the exact same selectivity in the formation of **3-68b**. It was then assumed that these steric and electronic effects could be additive to give an even higher regioselectivity, however when a 2-methyl-4-methoxylphenyl substituent was used on the alkyne the product **3-68c** was formed with an even lower regioselectivity and yield than the previous alkynes.

Since tuning the electronics on the aromatic group did not produce as big of an effect as was expected, the aliphatic portion of the alkyne was then modified to determine what effect this would have on the system (Table 3-4). Surprisingly, by placing an inductively withdrawing methoxyether on the aliphatic chain provided the desired product **3-68d** with a 3:1 distribution of regioisomers. Furthermore, combining this inductive effect with an electron rich aryl substituent enabled the production of the desired aryl ketone **3-68e** with a 9:1 regioselectivity. Lastly, placing an electron withdrawing group on the aryl ring gave the α-arylation product **3-68f** with a high yield and regioselectivity.

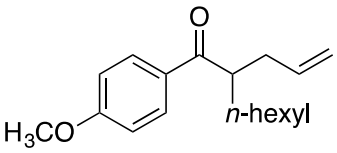
Table 3-4. Regioselectivity Studies



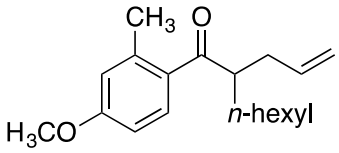
3-66 **3-67** (3.0 eq.) **3-68**[a]



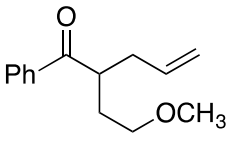
3-68a
64%; 2:1[b]



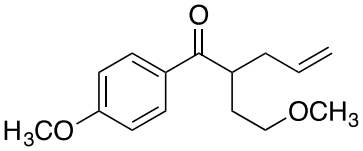
3-68b
70%; 2:1[b]



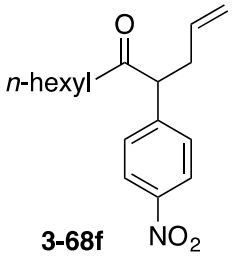
3-68c
46%; 1.5:1[b]



3-68d
79%; 3:1[b]



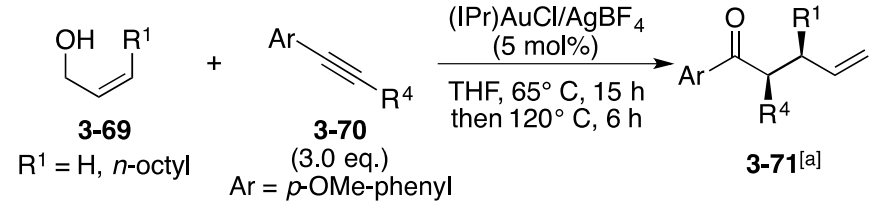
3-68e
87%; 9:1[b]



3-68f
99%; 1:8[b]

[a]Isolated yields. [b]Ratio (arylketone:alkylketone) determined by ^{1}H NMR (500 MHz). [g]Only a single diastereomer of each regioisomer was observed. Ar = *p*-OMe-phenyl.

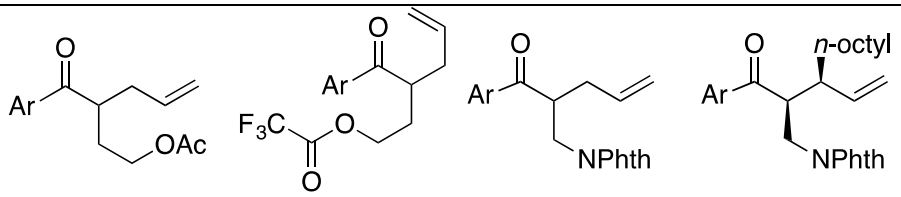
Table 3-5. Selected Substrate Scope II



3-69
R^1 = H, *n*-octyl

3-70
(3.0 eq.)
Ar = *p*-OMe-phenyl

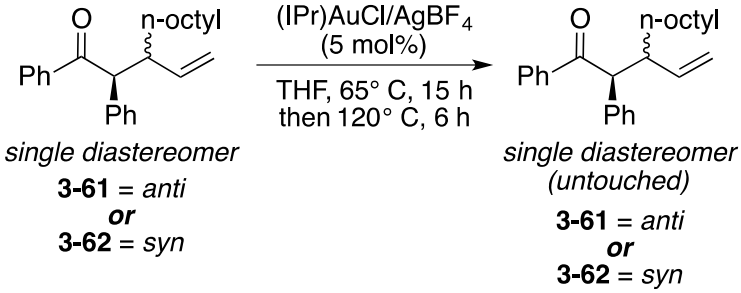
3-71[a]



3-71a	**3-71b**	**3-71c**	**3-71d**
65%; 8:1[b]	50%; >25:1[b]	72%; >25:1[b]	59%, >25:1[b] >25:1[c]

[a]Isolated yields. [b]Ratio (arylketone:alkylketone) determined by ^{1}H NMR (500 MHz). [c]diastereoselectivity determined by ^{1}H NMR (500 MHz).

Delighted with the resulting selectivities and functional group tolerance, a rationale for the observed difference in diastereoselectivities for *E*- and *Z*-allylic alcohols was investigated. The ketone products contain an alpha-hydrogen that could be epimerizing during the reaction course, or after filtration with potentially acidic silica gel. Control experiments were run to test this theory, and it was shown that pure diastereomers of **3-61** and **3-62** do not epimerize under the optimized conditions (Figure 3-16).



single diastereomer
3-61 = *anti*
or
3-62 = *syn*

single diastereomer
(untouched)
3-61 = *anti*
or
3-62 = *syn*

Figure 3-16. Epimerization experiments

Upon further inspection of the literature, it was found that only a few reports give selective access to the trisubstituted *Z*-enol ethers that are formed under our conditions. To deduce the possible mechanistic pathways, the observed diastereoselectivities were used to shed light on the probable transitions states. Since the chair transition states for most thermal Claisen rearrangements are generally lower in energy than the boat conformation, the *Z*-allylic alcohols will lead to *syn* products **3-72** and the *E*-allylic alcohols lead to *anti* products **3-73** (Figure 3-17).

Interestingly, when comparing the possible transition states ***chair*-1**/***boat*-1** vs. ***chair*-2**/***boat*-2**, one can see that the $\Delta\Delta G^{\pm}$ should be much higher for the **C1/B1** than the **C2/B2** transition states (Figure 3-17). This energy difference is due to the eclipsing interactions between the psuedoaxial R^2 and R^3 substituents of ***boat*-1**, which should be significantly higher in energy than the 1,3-diaxial interactions found in ***chair*-1**. Since this eclipsing interaction between the R^2 and R^3 substituents is absent in ***boat*-2** the energy barrier between **C2/B2** transition states is lower, thereby making the boat conformer a more accessible intermediate. This rationale correlates well with our empirical results, and may be the cause of the lower diastereoselectivity for products formed from *E*-allylic alcohols.

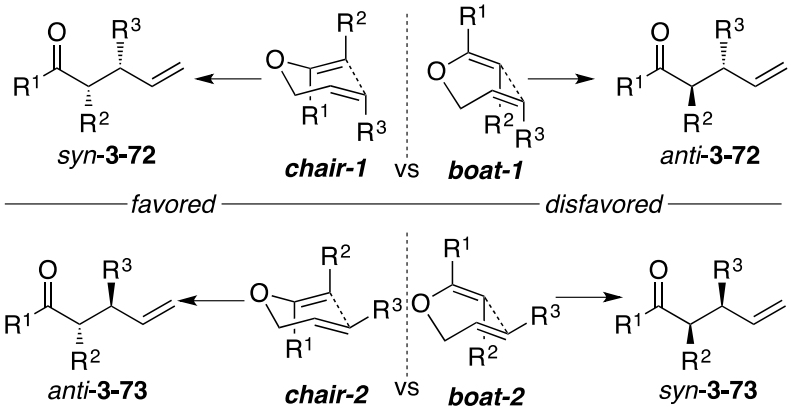
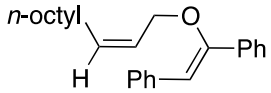
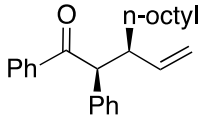
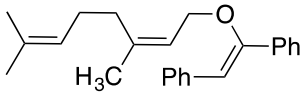
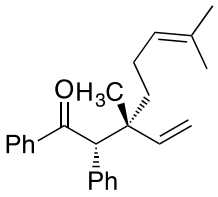
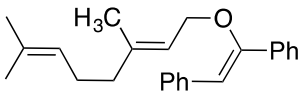
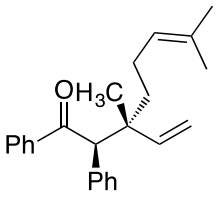


Figure 3-17. Possible transition states

Table 3-6. Effects of Gold-catalyst and heat on enol rearrangement

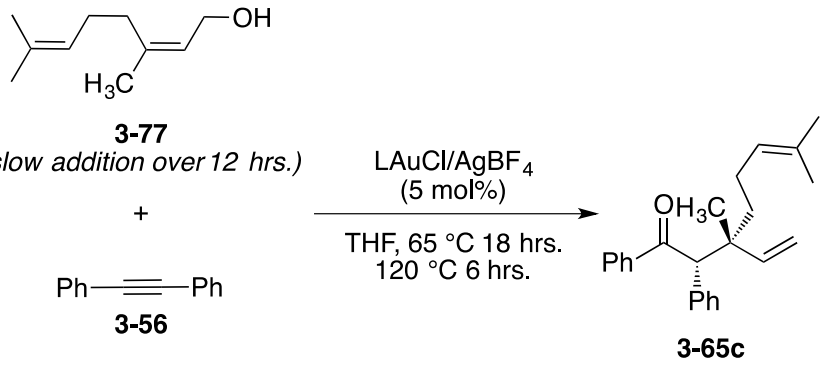
entry	enol	conditions[a]	product	conversion(%)[b]	dr[b]
1	 **3-74** (*Z*, *Z*)	A (heat)	 **3-62**	30	>25:1
2		B (Au)		40	>25:1
3	 **3-75** (*Z*, *Z*)	A (heat)	 **3-65c**	65	14:1
4		B (Au)		69	18:1
5		C (Au)		60	15:1
6	 **3-76** (*E*, *Z*)	A (heat)	 **3-65b**	65	9:1
7		B (Au)		60	10:1

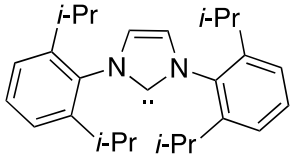
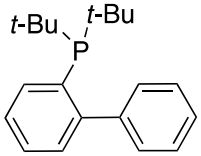
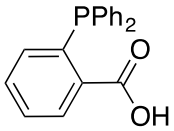
[a]Conditions A: THF 65C, 18 hrs; Conditions B: (IPr)AuCl/$AgBF_4$ (5 mol%), THF 65C, 18 hrs; Conditions C: Me_3PAuCl/$AgBF_4$ (5 mol%), THF 65C, 18 hrs. [b]Determined by ^1H NMR (500 MHz).

The aforementioned transition states are based on thermal rearrangement processes, however we cannot ignore the possibility that the process can be partially or completely gold-catalyzed. To investigate this, various enol ethers (**3-74**-**3-76**) were treated under thermal and gold-catalyzed conditions to observe their effects (Table 3-6). The results show that allyl vinyl ethers **3-75** and **3-76** are more readily converted to the product than **3-74**, most likely due to the higher steric encumbrance of the trisubstituted olefins. As previously found, the Z-allylic alcohols give a higher dr than the *E*-allylic alcohols, when treated with a gold-complex or thermal conditions (Table 3-6, compare entries 3-5 to 6-7). Interestingly, changing the ligand on the gold from IPr (1,3-Bis(2,6-diisopropylphenyl-imidazol-2-ylidene) to PMe_3 decreased the diastereoselectivity significantly (Table 3-6, entries 4-5). This decrease in diastereoselectivity with respect

to the ligand prompted a study on the effects the ligand on the gold-complex may have on the tandem process.

Table 3-7. Effects of Ligand of the Tandem Hydroalkoxylation/Claisen Rearrangement



entry	ligand (L)	diastereoselectivity[a]	yield (%)[b]
1	 **3-78**	8:1	71
2	 **3-79**	10:1	56
3	 **3-80**	–	–
4	Me_3P **3-81**	–	–

[a] Determined by ^{1}H NMR (500 MHz). [b] Isolated yields.

To monitor the change in diastereoselectivity the commercially available geraniol **3-77** was used because it gave a moderate dr for the reaction, which would make it a good candidate to observe any changes in the selectivity. From the ligands screened in

this process only the gold-complexes made from the NHC (IPr) ligand **3-78** and the phosphine ligand **3-79** were able to catalyze the tandem process under the optimized conditions (Table 3-7, entries 1-2). The phosphine ligand **3-79** gave a higher dr than the NHC ligand **3-78**, and this could be attributed to the rate of protodeauration.

Recently, Xu *et al.* discovered that the phosphine ligand **3-73** helps the gold-complex protodeaurate faster than the NHC ligand **3-72**.[88] A faster protodeauration would cause the complex to undergo faster decomplexation with the intermediate enol ether, and it is possible that this could create a transition state that leads to a higher selectivity. Lastly, it is interesting to note that the trimethylphosphine (**3-81**) gold-complex could not catalyze the tandem process, however the enol ether **3-75** underwent facile rearrangement with this complex at 65 °C (compare Table 3-6 entry 5 to Table 3-7 entry 4).

The combined data from the aforementioned tables does not conclusively demonstrate the role of the gold-complex in the reaction, because the thermal promoted and gold-catalyzed conditions give comparable results (Table 3-6). Additional experimentation at lower temperatures could give further insight into whether the complex is catalyzing both steps, or only the initial hydroalkoxylation step.

Although the following experiments have not given a decisive mechanistic pathway, valuable insight was gained into the possible pathways and the factors governing them. Collaborative computational studies are still ongoing, however initial studies have proven to be quite challenging since there are a very high number of possible transition states with the gold-complex involved. Our gold-catalyzed tandem hydroalkoxylation/Claisen rearrangement methods give a complimentary method to the

other valuable Claisen methodologies. The method allows access to highly functionally diverse synthons from very simple, and/or commercially available starting materials and many of these advances have since been described in our recent publication.[89]

Sequential Gold-catalyzed Enol Formation/Ru-catalyzed Allylation

Introduction

During the studies of the gold-catalyzed tandem hydroalkoxylation/Claisen rearrangement, we became interested in an intramolecular variant of the process. Conceivably, an enyne such as **3-82** could easily undergo a gold-catalyzed formation of the *Z*-enol ether **3-83** and subsequently form the [3,3]-rearrangement product **3-84** under thermal or Lewis-acid catalyzed conditions.

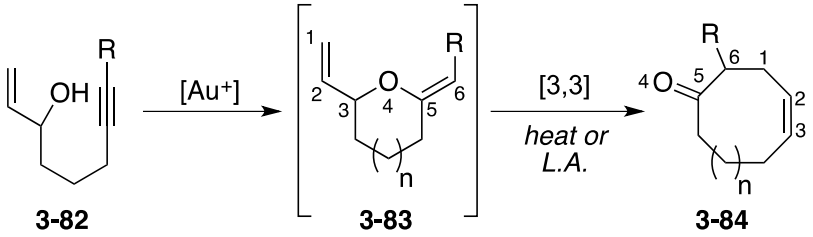


Figure 3-18. Gold-catalyzed intramolecular hydroalkoxylation/Claisen rearrangement

Although similar processes were recently reported by Rhee *et al.*[81d] as well as in collaborative studies between the Rhee and Kirsch research groups,[81e] the substrate scope is limited to terminal alkynes (Figure 3-19). Furthermore, their rearrangements are charge-accelerated by an oxonium ion intermediate, so the use of allylic alkyl or silyl ethers are required for the process to work. Consequently, the removal of these ethers is then required to obtain the desired ketone products.

Conditions that would not require the use of these allylic ethers could reduce the synthetic steps to the desired products. Furthermore, a process that would accommodate substituted alkynes would increase the scope of these reactions

immensely. For these reasons we began our studies of an intramolecular sequence that would be analogous to our intermolecular reactions.

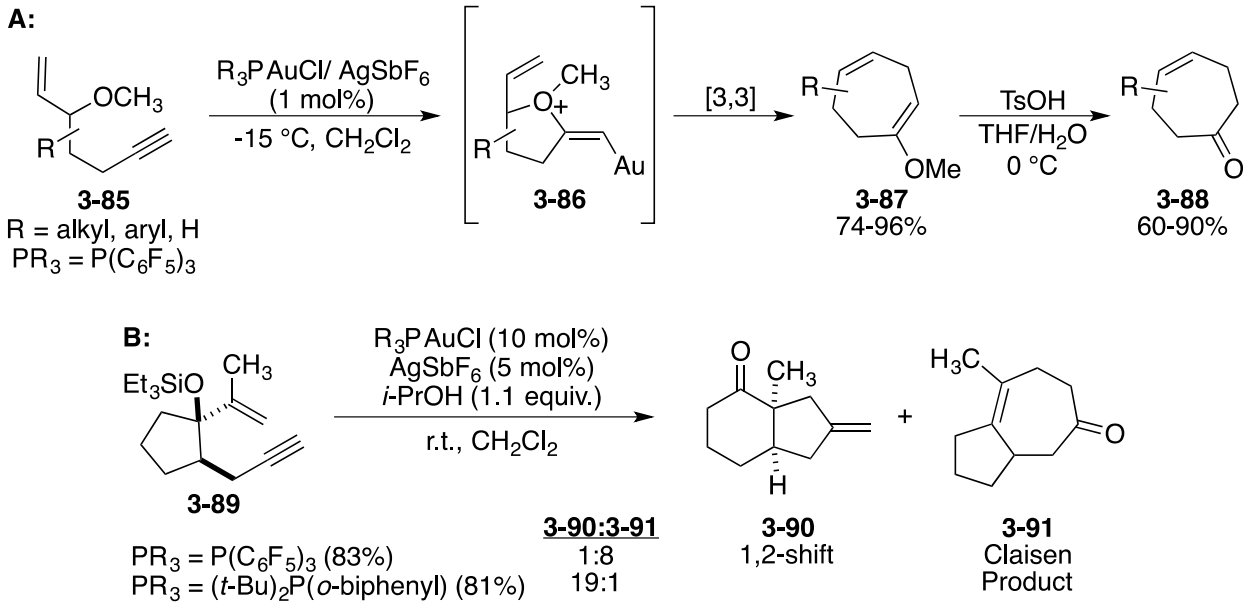


Figure 3-19. Selected gold-catalyzed intramolecular Claisen rearrangements. **A**: Work by Rhee *et al.*; **B**: Collaborative studies from the Rhee and Kirsch research groups.

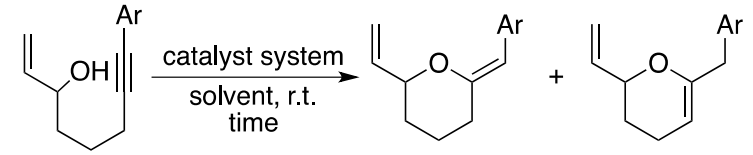
Results and Discussion

The studies began by finding the optimal conditions for the formation of the requisite allyl vinyl ether **3-93** (Table 3-8). During this analysis it was intriguing to find that the formation of **3-93** from **3-92** is highly dependent on the solvent in the reaction. For instance, when a non-coordinating solvent such as CH_2Cl_2 is used, the undesired internal vinyl ether **3-94** is formed selectively, regardless of the substrate or gold-complex used (Table 3-8, entries 1-3). Conversely, when a more coordinating solvent such as THF or 1,4-dioxane is used, selective formation of the desired exocyclic vinyl enol ether **3-93** is achieved (Table 3-8, entries 4-7).

The formation of product **3-94** was somewhat interesting because it was not the anticipated exocyclic enol ether product (Figure 3-20). During the catalytic cycle, the

gold-complex **3-95** coordinates to the alkyne in **3-92** to form **3-96**. After coordination, the alkyne undergoes selective *anti*-alkoxylation to form the oxonium **3-97**, which subsequently forms product **3-93** after protodeauration.

Table 3-8. Solvent effects on enol ether formations[a]



3-92 (a or b) **3-93 (a or b)** **3-94 (a or b)**

Ar = *p*-nitrophenyl, **a**
Ar = phenyl, **b**

entry	substrate	gold salt	silver salt	solvent	time (h)	**3-93:3-94**[b]
1	**3-92a**	PPh_3AuCl	AgOTf	CH_2Cl_2	1.5	1:2 (**a**)
2	**3-92b**	PPh_3AuCl	AgOTf	CH_2Cl_2	1	1:>25 (**b**)
3	**3-92b**	(IPr)AuCl	$AgBF_4$	CH_2Cl_2	1	1:5 (**b**)
4	**3-92a**	(*o*-biphenyl-di-*t*-butylphosphine)AuCl	AgOTf	THF	0.5	>25:1 (**a**)
5	**3-92a**	(IPr)AuCl	$AgBF_4$	THF	0.5	>25:1 (**a**)
6	**3-92b**	(IPr)AuCl	$AgBF_4$	THF	1.0	>25:1 (**b**)
7	**3-92b**	(IPr)AuCl	$AgBF_4$	1,4-dioxane	1.5	>25:1 (**b**)

[a] Conditions: Substrate (0.2 mmol), [Au] (5 mol%), [Ag] (5 mol%) [b] Determined by ^1H NMR (300 MHz).

A probable explanation for the formation of **3-94** is that the gold-complex recoordinates to the product **3-93** after decomplexation to form an intermediate like that of **3-98** (Figure 3-21). The oxonium ion can causes proton H_b to become more acidic, allowing for a facile proton exchange to give the undesired internal enol ether **3-94**. Of course, if this process occurs a possible equilibrium between the formation of **3-93** and **3-94** cannot be ruled out, since the reverse process could easily regenerate the exocyclic **3-93**. The formation of the oxonium **3-98** is most likely impeded by solvents that can provide further stabilization of the cationic gold-complex; this increase in

stabilization could decrease the acidity of the complex and inhibit the formation of the enol ether **3-94**.

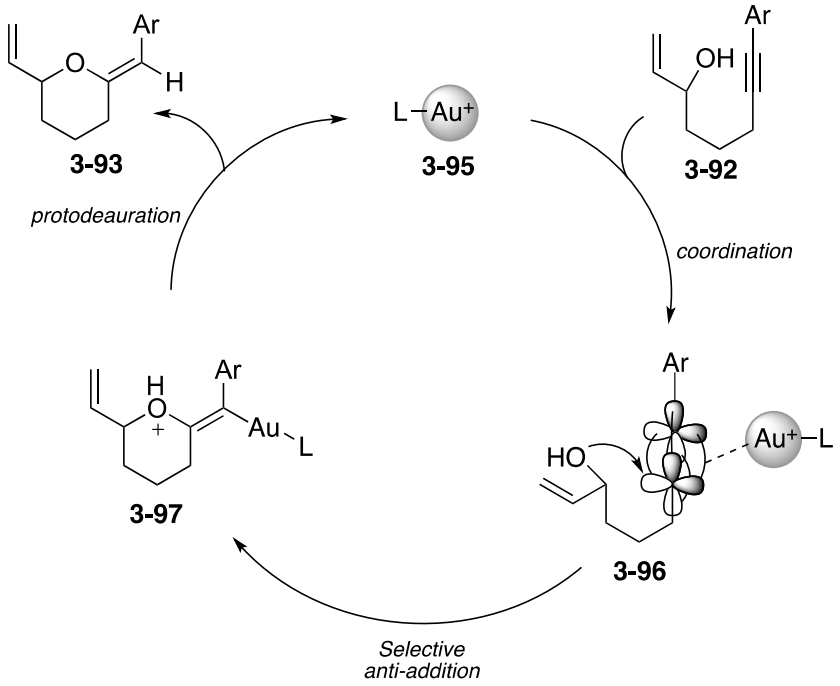


Figure 3-20. Proposed mechanism for the gold-catalyzed formation of **3-93**

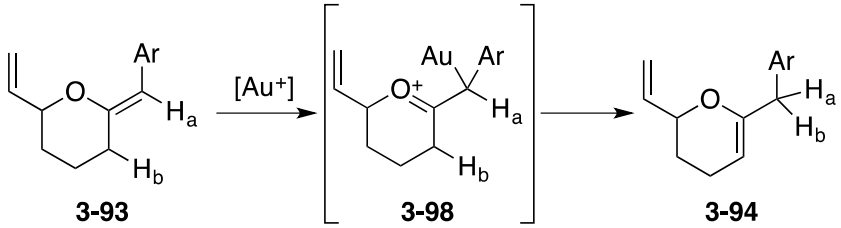


Figure 3-21. Proposed mechanism for the gold-catalyzed formation of **3-94**

After finding conditions that gave selective access to the desired enol ether **3-93**, a test reaction was run to determine if these allyl vinyl ethers could perform the [3,3]-rearrangement. Surprisingly, when **3-93a** was heated in refluxing toluene overnight the expected product **3-100** was formed in a dismal 23% yield, however, the [1,3]-rearrangement product **3-99** was formed as one diastereomer in a 51% yield (Figure 3-22). These results changed the direction of the project to finding conditions that would

give selectively the [1,3]-rearrangement products, because of the high utility of these 3-vinylcyclohexanones.

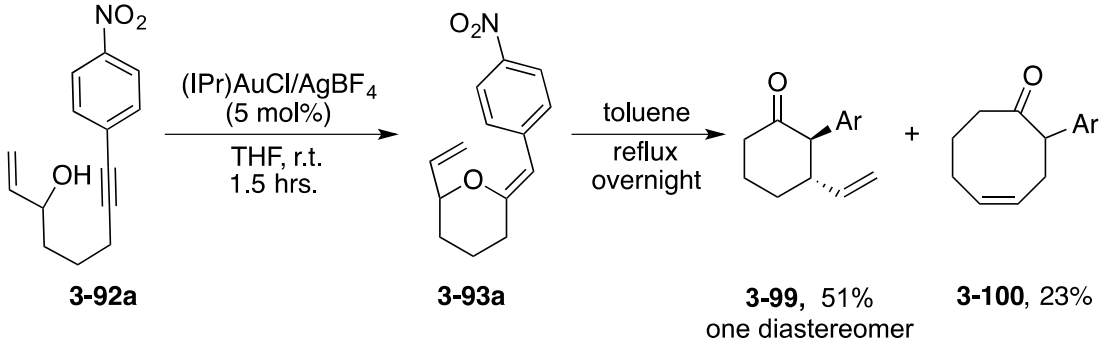


Figure 3-22. Formation of [1,3]-rearrangement product **3-99**

Metal-catalyzed formation of cyclic 3-vinylketones **3-102** via [1,3]-O to –C migrations have been well-known for quite some time, yet they are generally limited to allyl vinyl ethers like that of **3-101** that produce highly stabilized enolate intermediates.[90] Although, Trost and coworkers were the first to report this type of palladium-catalyzed isomerization,[90a] Tsuji published similar results shortly after.[90b] After their initial publication, Trost expanded the studies to give further insight into the mechanism of the reaction and the factors dictating the stereo- and regioselectivity of the rearrangement.[90c-e]

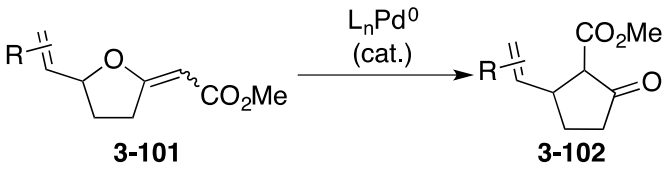


Figure 3-23. Palladium-catalyzed [1,3]-O to –C migrations via highly stabilized enolate intermediates

More recently, in 2010, Harrity and coworkers published the first and only case of these [1-3]-rearrangements with nonstabilized enolate intermediates (Figure 3-24).[91] Their method gave the *trans*-cyclohexanone products with good yields and high

selectivity. Nevertheless, high catalyst loadings and increased temperatures are required which poses a major drawback for this method. Additionally, requisite enol ethers **3-93** require a long synthetic route that produces a mixture of *E* and *Z*-vinyl ether products. Since the geometry of the vinyl ether has a great influence on the stereochemistry of the product, a process that could give selective access to either *E*- or *Z*-vinyl ether would be advantageous. Establishing a sequential gold-catalyzed enol formation/[1,3]-rearrangement process, and/or a tandem one-pot reaction sequence could provide a better synthetic route to these highly functionalized carbocycles.

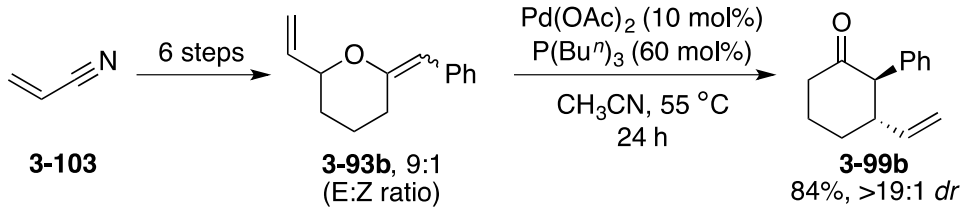


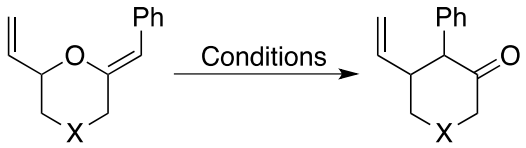
Figure 3-24. Comparable process by Harrity *et al.*

Inspired by the ruthenium-catalyzed allylic alkylation reactions reported by Kitamura and coworkers (Figure 1-12),[24-26] it was surmised that their cationic ruthenium-complex could help catalyze the [1,3]-rearrangement for substrates with a lower propensity for ionization. This could further expand the scope of these reactions and possibly lead to different selectivities, depending on the mechanistic pathway.

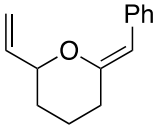
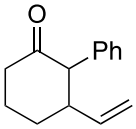
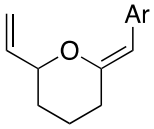
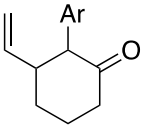
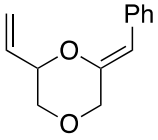
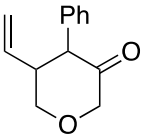
To test this theory, a catalyst screening was carried out to determine how the ruthenium-complex would compare to palladium for these isomerizations (Table 3-9). Gratifyingly, treatment of enol **3-93b** with the ruthenium-complex created *in situ* from $[CpRu(CH_3CN)_3]PF_6$ and quinaldic acid, gave the desired product **3-99b** in an 80% yield with a 2:1 dr in favor of the *cis*-substituted cyclohexanone. While treatment under palladium-catalyzed conditions also gave the desired product, heating was required and a lower selectivity and yield were observed (Table 3-9, entries 1-2). The electron rich

para-methoxyphenyl enol ether **3-93c** was also readily cyclized under the ruthenium conditions to give product **3-99c**, however with the palladium-complex the desired product was not formed in an appreciable amount (Table 3-9, entries 3-4).[92] This could be due to the fact that the electron rich system is more difficult to ionize, and requires a stronger Lewis acidic catalyst system.

Table 3-9. Comparison of Pd- and Ru-catalyzed alkylation reactions



3-93 **3-99**

entry	substrate	conditions[a]	time (h)	product	yield[b]	dr (cis:trans)[c]
1		**A**	18		80%	2:1
2	**3-93b**	**B**[d]	1.5	**3-99b**	61%	1:1
3		**A**	6		77%	2:1
4	**3-93c** Ar = 4-OMe-Ph	**B**	18	**3-99c**	<10%[c]	–
5		**A**	14		86%	10:1[e]
6	**3-93d**	**B**	20	**3-99d**	70%	1:10

[a] Conditions **A**: $[CpRu(CH_3CN)_3]PF_6$/Quinaldic Acid (5 mol%), THF, r.t.; Conditions **B**: $Pd(dppe)_2$ (5 mol%), CH_2Cl_2, r.t.; [b] Isolated yield from overall sequence (Au, then Pd or Ru).[c] Determined by ^1H NMR (500 MHz). [d] Reaction run at 40 °C.
[e] The product epimerized to the *trans*-isomer during purification.

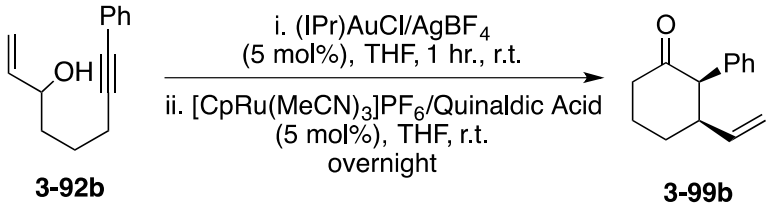
When the dioxane derivative **3-93d** was treated with the ruthenium-complex facile formation of the desired pyran product **3-99d** was observed with a 10:1 dr and

86% yield, again forming selectively the *cis*-product. Furthermore, treating **3-93d** with 5 mol% of $Pd(dppe)_2$ gave *trans*-**3-99c** with the same level of selectivity, albeit with a lower yield and longer reaction time (Table 3-9, entries 3-4).

These initial results demonstrated that the selectivity and yields were higher when the ruthenium-complex was used. Interestingly, these conditions produced the *cis*-products, which is contrary to the *trans*-products formed under palladium-catalyzed conditions. This suggests that the mechanistic pathway for the ruthenium-catalyzed rearrangements is somewhat different than that of the well-known palladium process. It is also noteworthy to realize that the conditions **A** and **B** gave access to the desired products with lower catalyst loadings and temperature than the previous report from Harrity and coworkers.[91] Furthermore, these conditions allow for simple access to highly functionalized pyrans, which are frequently found in natural products.[93]

Encouraged by the results of the initial screenings, further experimentation was run to find the optimized conditions for the [1,3]-rearrangement. Various modifications to the initial conditions (Table 3-9, entry 1, same as Table 3-10, entry 1) were made in order to determine if the diastereoselectivity or yield could be increased. Adding molecular sieves had little effect on the reaction outcome (Table 3-10, entry 2). Furthermore, changing the catalyst system or attempting one-pot process, resulted in poor yields (Table 3-10, entries 3-6). These results demonstrated that the best catalyst system for the rearrangements was the complex created *in situ* from $[CpRu(MeCN)_3]PF_6$ and quinaldic acid.

Table 3-10. Optimization of ruthenium-catalyzed allylation



3-92b **3-99b**

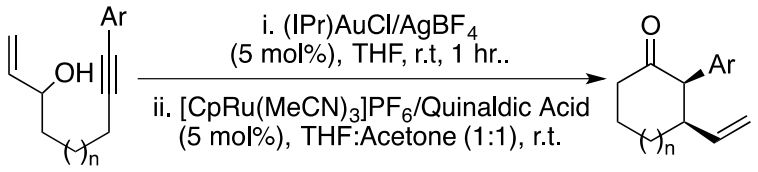
entry	modifications of conditions (ii)	yield[a]	dr[b]
1	–	80%	2:1
2	4Å MS added	75%	2:1
3	$[Cp^*Ru(MeCN)_3]PF_6$	–[c]	–
4	catalyst system was quinaldic acid (10 mol%), 4Å MS	–[c]	–
5	picolinic acid instead of quinaldic	30%	1:1
6	(i) transferred directly to (ii) without filtration	37%	2:1
7	solvent mixture $THF:CH_3CN$ (1:1)	–[c]	–
8	solvent mixture THF:acetone (1:1)	91%	2:1

[a] Isolated yields [b] Determined by ^1H NMR (500 MHz). [c] No desired product.

During these studies, an appreciable amount of solid precipitate would form during the ruthenium-catalyzed alkylation. Concerned that this was a result of a solubility issue with the active complex, a few solvent mixtures were screened in hopes to increase the yield of the reaction. When a mixture of acetonitrile and THF was used the reaction was completely shut down. Conversely, when a mixture of THF and acetone was used the product **3-99b** was formed in a 91% with a 2:1 diastereoselectivity (Table 3-10, entries 7-8). The highest yield and selectivity for

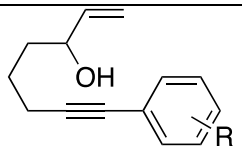
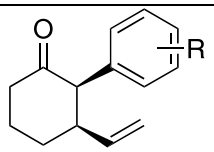
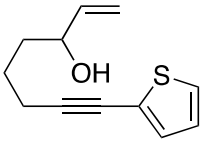
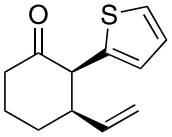
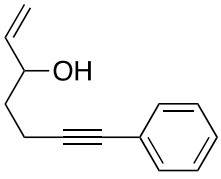
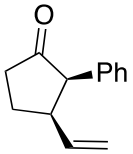
product **3-99b** was obtained under these conditions, which were consequently deemed the optimized reaction conditions.

Table 3-11. Selected substrate scope for the sequential enol formation/allylic alkylation reaction



3-92
n = 0, 1

3-99

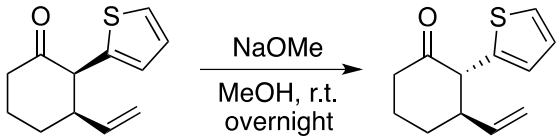
entry	substrate	time (h, Ru)	product	yield[a]	dr[b] (cis:trans)
					
1	R = H, **3-92b**	18	R = H, **3-99b**	91	2:1
2	R = *p*-NO_2, **3-92a**	4.5	R = *p*-NO_2, **3-99a**	98	2:1
3	R = *p*-OMe, **3-92c**	18	R = *p*-OMe, **3-99c**	90	2:1
4	 **3-92e**	3.5	 **3-99e**	92	1:1
5	 **3-92f**	4	 **3-99f**	–[c]	–

[a] Isolated yields [b] Determined by crude ^{1}H NMR on 500 MHz.[c] No desired product, enol left untouched.

With the optimized conditions in hand, the focus was set on determining the scope and limitations of the sequential process. As previously demonstrated, the

phenyl substituted **3-92b** gave the desired product in a high yield and a 2:1 dr (Table 3-11, entry 1). Electron withdrawing and donating substituents on the aromatic ring also give the desired product in high yields (Table 3-11, entries 2-3). Interestingly, the nitro-substituted enol ether undergoes the alkylation reaction in only 4.5 hours, which is much faster than any other substrate. It is likely that this electron-withdrawing group gives the enol ether a higher susceptibility for ionization, thereby allowing for a faster rearrangement to occur.

Gratifyingly, other aromatic substituents can also be tolerated under these conditions. The thiophene substituted **3-92e** underwent smooth gold-catalyzed cyclization, followed by the ruthenium-catalyzed rearrangement to gave the desired product **3-99e** in a 92% yield as a 1:1 mixture of diastereomers (Table 3-11, entry 4). Furthermore, treating product **3-99e** with sodium methoxide in methanol at room temperature overnight, provided selectively the ***trans*-3-99e** in a 90% yield (Figure 3-25). Lastly, removing one methylene spacer from the chain (**3-92f**) resulted in an enol ether that was unable to rearrange with the optimized ruthenium conditions (Table 3-11, entry 5).



3-99e
1:1 dr

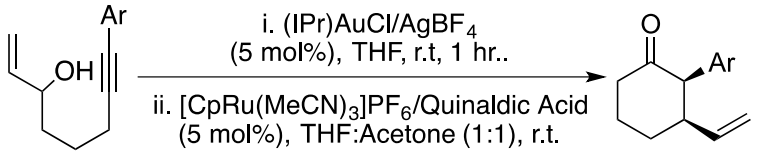
***trans*-3-99e**
90%, >25:1 *dr*

Figure 3-25. Diastereoselective access to *trans*-**3-99**

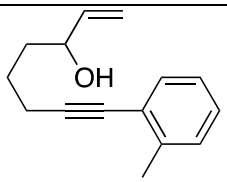
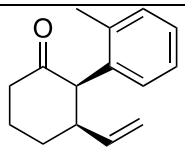
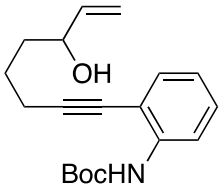
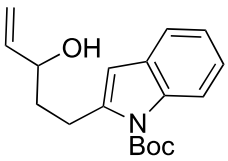
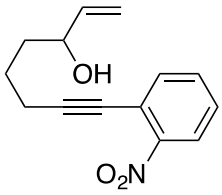
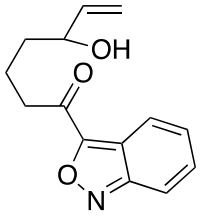
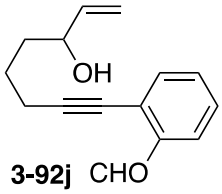
During these trials, a common trend was observed with *ortho*-substituted phenyl substrates in that they were unable to produce the desired product under our conditions. For instance, when an *ortho*-methyl group was placed in the phenyl ring **3-92g**, the enol

ether from the gold reaction was left untouched during the allylic alkylation reaction (Table 3-12, entry 1). Additionally, placing heteroatoms that are relatively non-nucleophilic in the *ortho*-position resulted in various heterocyclic byproducts during the gold reaction (Table 3-12, entries 2-4).

Table 3-12. Limitations of *ortho*-substituted aromatic substrates



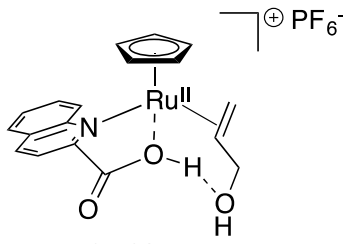
3-92 **3-99**

entry	substrate	time (h, Ru)	product	yield[a]
1	 **3-92g**	18	 **3-99g**	–[b]
2	 **3-92h**	–	 **3-104**	92%[c]
3	 **3-92i**	–	 **3-105**	50%[c]
4	 **3-92j**	–	–	35%[c,d]

[a] Isolated yields. [b] No desired product, enol left untouched. [c] Formed during gold-cyclization [d] Unidentifiable product.

While gold-catalyzed formation of indoles[94] and isoxazoles[95] is well-known with alkynyl anilines and nitrophenyls respectively, it was somewhat surprising that these cyclizations were much faster than the desired hydroalkoxylation of the alkyne. Of course, this is most likely due to the proximity of these *ortho*-substitutions to the alkyne.

Mechanistically, we envision that the bifunctional ruthenium-complex coordinates to the allyl vinyl ethers in a similar fashion to the proposed mechanism for allyl alcohols (Figure 3-26).[24] The authors suggest a type of synergy between the ruthenium-complex and the quinaldic acid ligand, wherein the nitrogen in the quinoline ring donates electron density to the ruthenium metal, making it more Lewis basic, while the carboxylic acid helps to ionize the allylic system via hydrogen bonding to the allylic alcohol.



3-106

Figure 3-26. Proposed coordination of the ruthenium-complex to allyl alcohols .

Analogous to their proposed mechanism, the current [1,3]-O to –C rearrangement could start with the coordination of the ruthenium-complex to ether **3-92** to form the intermediate **3-108** (Figure 3-27). Hydrogen bonding between the carboxylic acid ligand, and the enol ether helps to facilitate the oxidative addition of the complex to form **3-109**. The enolate formed in **3-109** can then attack the π-allyl system, followed by subsequent reductive elimination and decomplexation of the ruthenium-complex to form the desired carbocycle **3-99**, and the active catalyst **3-107**.

The preferential formation of *cis*-substituted products for the ruthenium rearrangement suggests that the mechanism of these [1,3]-rearrangements is different than the palladium-catalyzed sequence. Furthermore, the higher diastereoselectivity found in the formation of the ketopyran **3-99d** suggests that the dimethylene-ether may play a role in the mechanism of the reaction. Mechanistic studies are currently ongoing in our laboratory and will be reported in due course.

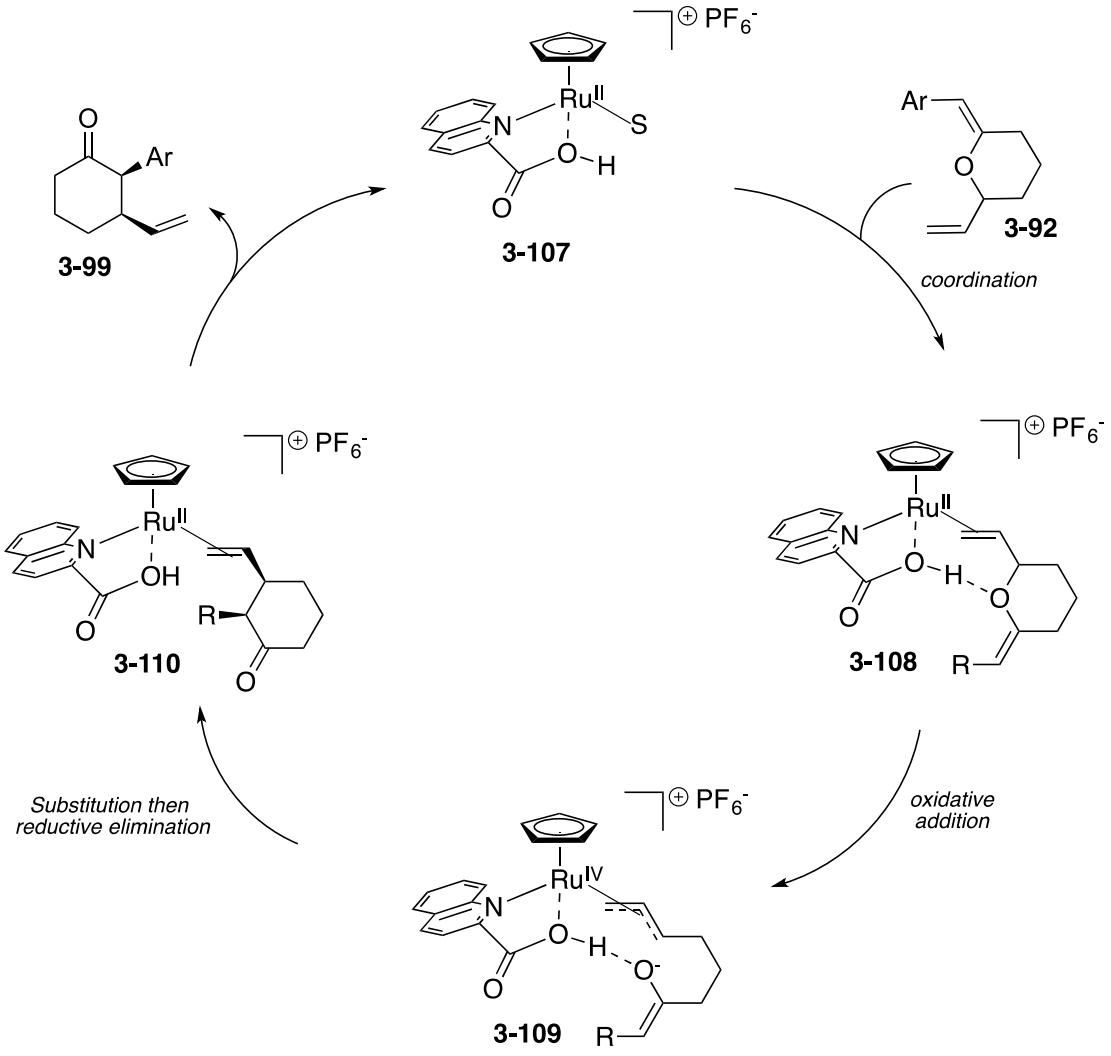


Figure 3-27. Proposed mechanism for the ruthenium-catalyzed [1,3]-rearrangement

The reported sequential enol formation/allylation process has a few minor drawbacks, however it allows simple access to highly functionalized cyclohexanones

and pyrans. The process is higher yielding than the previously reported palladium-catalyzed process, and provides a short synthetic route for these *cis*-cyclic ketones.

CHAPTER 4
EXPERIMENTAL SECTION

General Experimental Procedures

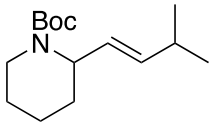
All reactions were carried out under an atmosphere of dry nitrogen unless otherwise specified. Anhydrous solvents were transferred via syringe to flame-dried glassware, which had been cooled under a stream of dry nitrogen. Anhydrous tetrahydrofuran (THF), dichloromethane (CH_2Cl_2), diethyl ether, benzene, and acetonitrile were dried using an mBraun solvent purification system. 5-hexyn-1-ol, 6-chloro-1-hexyne, and N-(5-hexynyl)phthalimide were graciously donated to us by Petra Research, Inc. Gold and silver catalysts were weighed in a glovebox under a dry argon atmosphere unless otherwise stated. All other reagents were ordered from Sigma-Aldrich and used without any further purification. Analytical thin layer chromatography (TLC) was performed using 250 μm Silica Gel 60Å pre-coated plates (Whatman Inc.). Flash column chromatography was performed using 230-400 Mesh 60Å Silica Gel (Whatman Inc.). The eluents employed are reported as volume:volume percentages. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded using Varian Unity Inova 500 MHz and Varian Mercury 300 MHz spectrometers. Chemical shift (δ) is reported in parts per million (ppm) downfield relative to tetramethylsilane (TMS, 0.0 ppm) or $CDCl_3$ (7.26 ppm). Coupling constants (*J*) are reported in Hz. Multiplicities are reported using the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad; Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were recorded using Varian Unity Mercury 300 and 500 spectrometers at 75 MHz, and 125 MHz respectively. Chemical shift is reported in ppm relative to the carbon resonance of $CDCl_3$ (77.23 ppm). Infrared spectra were obtained on a PerkinElmer Spectrum RX1

FTIR spectrometer at 1.0 cm^{-1} resolution and are reported in wavenumbers. Melting points were recorded on a MEL-TEMP® capillary melting point apparatus and are uncorrected. High performance liquid chromatography (HPLC) was performed on Shimadzu. Gas Chromatography analyses were obtained using a Hewlett Packard HP 5890 Series II - FID Detector. Specific Optical rotations were obtained on a JASCD P-2000 Series Polarimeter (wavelength = 589 nm). High resolution mass spectra (HRMS) were obtained by Mass Spectrometry Core Laboratory of University of Florida, and are reported as m/e (relative ratio). Accurate masses are reported for the molecular ion (M+) or a suitable fragment ion. All diastereoselectivities and regioselectivities for the reactions were observed in the spectrum of the crude reaction mixture on a Varian Unity Inova 500 MHz spectrometer or a Varian Mercury 300 MHz spectrometer.

Formation of Azacycles via Gold-Catalyzed Dehydrative Cyclizations

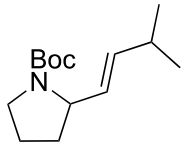
General Procedure: Although the catalyst systems varied in these experiments, the reactions conditions involve the same setup. An example procedure is as follows (Table 2-1, entry 5): A test tube with a septum on top, containing 1,3-bis(2,6-diisopropylphenyl-imidazol-2-ylidene)gold(I) chloride (6.2 mg, 0.01 mmol, 5 mol%), silver tetrafluoroborate (1.9 mg, 0.01 mmol, 5 mol%), 4Å MS (4-5 pellets, previously activated by flame drying under vacuum) and a stir bar, was taken from the glove box wrapped in aluminum foil and placed directly under dry nitrogen. A small portion of CH_2Cl_2 (0.2 mL) was added to the solid catalysts and the mixture was left to stir at room temperature for ten minutes, after which time a solution of the substrate in CH_2Cl_2 (0.8 mL) was added to the mixture all at once. The vessel was left to stir at room temperature. After TLC analysis had shown complete conversion the reaction mixture

was filtered through a short plug of silica with EtOAc, placed under vacuum to remove the solvents, and purified by flash column chromatography.



2-13

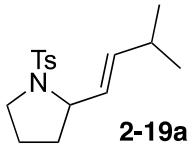
***E*)-*tert*-butyl-(7-hydroxy-8-methylnon-5-en-1-yl)carbamate** (**2-13):** The following compound was made under the optimized gold-catalyzed dehydrative cyclization conditions (Table 2-1, entry 5) with **2-12** (39.4 mg, 0.14 mmol), 1,3-bis(2,6-diisopropylphenyl-imidazol-2-ylidene)gold(I) chloride (4.7 mg, 0.008 mmol, 5 mol%), silver tetrafluoroborate (1.4 mg, 0.007 mmol, 5 mol%), 4Å MS (4 pellets), and 1.0 mL of CH_2Cl_2. Purified by flash column chromatography using a solvent gradient (0-5% EtOAc/hexanes) to yield the product as a clear oil (34.2 mg, 93%). R_f = 0.47 (10% EtOAc/hexanes). IR (neat) 2934, 2862, 1690, 1403, 1363, 1161 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.48-5.28 (m, 2H), 4.72-4.71 (m, 1H), 3.96-3.84 (m, 1H), 2.81 (td, *J* = 12.8, 3.0 Hz, 1H), 2.28 (dq, *J* = 13.1, 6.6 Hz, 1H), 1.73-1.29 (m, 13H), 0.98 (d, *J* = 6.8, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.7, 139.1, 125.1, 79.3, 52.2, 39.8, 31.2, 29.7, 28.7, 25.9, 22.8, 22.7, 19.7.



2-17

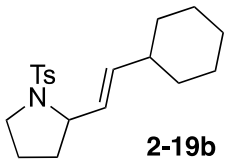
(*E*)-*tert*-butyl-(6-hydroxy-7-methyloct-4-en-1-yl)carbamate (2-17): The following compound was made under the optimized gold-catalyzed dehydrative cyclization conditions (Table 2-2, entry 2) with **2-16** (76.8 mg, 0.3 mmol), 1,3-bis(2,6-

diisopropylphenyl-imidazol-2-ylidene)gold(I) chloride (9.3 mg, 0.015 mmol, 5 mol%), silver tetrafluoroborate (2.9 mg, 0.015 mmol, 5 mol%), 4Å MS (5 pellets), and 1.5 mL of CH_2Cl_2. Purified by flash column chromatography using a solvent gradient (0-5% EtOAc/hexanes) to yield the product as a clear oil (50.6 mg, 71%). R_f = 0.70 (20% EtOAc/hexanes). IR (neat) 2958, 2870, 1693, 1390, 1363, 1164, 1115 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.46-5.36 (m, 1H), 5.29-5.20 (m, 1H), 4.16 (br s, 1H), 3.44-3.27 (m, 2H), 2.29-2.20 (m, 1H), 1.96 (br s, 1H), 1.87-1.73 (m, 2H), 1.67-160 (m, 1H), 1.42 (s, 10H), 0.96 (d, *J* = 6.7 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 154.8, 137.5, 127.7, 79.0, 58.8, 46.3, 32.7, 30.9, 29.9, 28.7, 28.6, 22.8.



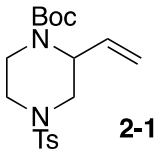
2-19a

(*E*)-2-(3-methylbut-1-en-1-yl)-1-tosylpyrrolidine (2-19a):[96] The following compound was made under the optimized gold-catalyzed dehydrative cyclization conditions (Table 2-3, entry 1) with **2-18a** (159.6 mg, 0.5 mmol), 1,3-bis(2,6-diisopropylphenyl-imidazol-2-ylidene)gold(I) chloride (3.1 mg, 0.005 mmol, 1 mol%), silver tetrafluoroborate (1.0 mg, 0.005 mmol, 1 mol%), 4Å MS (10 pellets), and 2.5 mL of CH_2Cl_2. Purified by flash column chromatography using a solvent gradient (20-50% EtOAc/hexanes) to yield the product as a pale yellow oil (106.8 mg, 71%). All data matched that of the previously reported data.[96]



2-19b

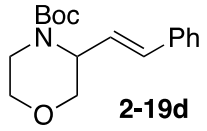
(*E*)-2-(2-cyclohexylvinyl)-1-tosylpyrrolidine (2-19b): The following compound was made under the optimized gold-catalyzed dehydrative cyclization conditions (Table 2-3, entry 2) with **2-18b** (72.8 mg, 0.21 mmol), 1,3-bis(2,6-diisopropylphenyl-imidazol-2-ylidene)gold(I) chloride (6.4 mg, 0.01 mmol, 5 mol%), silver tetrafluoroborate (2.0 mg, 0.01 mmol, 5 mol%), 4Å MS (5 pellets), and 1.5 mL of CH_2Cl_2. Purified by flash column chromatography with a 20% EtOAc/hexanes solution to yield the product as a clear oil (64.0 mg, 92%). R_f = 0.60 (20% EtOAc/hexanes). IR (neat) 3046, 2923, 2850, 1447, 1342, 1156 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.70 (d, *J* = 8.2 Hz, 2H), 7.28 (d, *J* = 8.1 Hz, 2H), 5.56 (ddd, *J* = 15.4, 6.4, 1.1 Hz, 1H), 5.27 (ddd, *J* = 15.4, 6.8, 1.4 Hz, 1H), 4.10 (td, *J* = 7.1, 3.9 Hz, 1H), 3.41 (ddd, *J* = 9.7, 7.3, 4.6 Hz, 1H), 3.29 (dt, *J* = 9.9, 7.1 Hz, 1H), 2.42 (s, 3H), 1.97-1.87 (m, 1H), 1.85-1.57 (m, 5H), 1.30-1.19 (m, 2H), 1.14 (qt, *J* = 12.6, 3.1 Hz, 1H), 1.08-0.96 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 143.2, 137.7, 136.0, 129.6, 127.8, 127.7, 61.9, 48.7, 40.2, 33.0, 32.8, 26.4, 26.2, 26.1, 24.0, 21.7.



2-19c

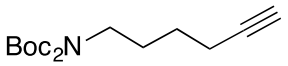
***tert*-butyl 4-tosyl-2-vinylpiperazine-1-carboxylate (2-19c):** The following compound was made under the optimized gold-catalyzed dehydrative cyclization conditions (Table 2-3, entry 5) with **2-18d** (150.3 mg, 0.39 mmol), 1,3-bis(2,6-diisopropylphenyl-imidazol-2-ylidene)gold(I) chloride (12.1 mg, 0.02 mmol, 5 mol%), silver tetrafluoroborate (3.8 mg, 0.02 mmol, 5 mol%), 4Å MS (10 pellets), and 2.0 mL of CH_2Cl_2. Purified by flash column chromatography using a solvent gradient (10-30% EtOAc/hexanes) with a 20% EtOAc/hexanes solution to yield the product as a white solid (127.2 mg, 89%). R_f = 0.80 (60% EtOAc/hexanes). IR (neat) 2976, 2930, 1702,

1455, 1415, 1342, 1159 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.69 (d, *J* = 8.2 Hz, 2H), 7.34-7.26 (m, 2H), 5.70-5.55 (m, 1H), 5.23-5.10 (m, 2H), 4.79-4.68 (m, 2H), 3.81 (s, 2H), 3.47 (s, 2H), 3.32-3.19 (m, 2H), 2.42 (s, 3H), 1.47 (s, 9H).^{13}C NMR (125 MHz, $CDCl_3$): δ 155.4, 154.9, 143.6, 136.8, 133.2, 130.0, 127.5, 119.6, 80.9, 51.9, 46.4, 45.8, 28.6, 21.8.



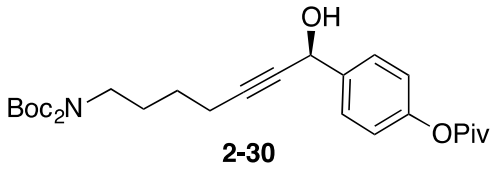
2-19d

(*E*)-*tert*-butyl 3-styrylmorpholine-4-carboxylate (2-19d): The following compound was made under the optimized gold-catalyzed dehydrative cyclization conditions (Table 2-3, entry 8) with **2-18f** (100.0 mg, 0.32 mmol), 1,3-bis(2,6-diisopropylphenyl-imidazol-2-ylidene)gold(I) chloride (10.0 mg, 0.016 mmol, 5 mol%), silver tetrafluoroborate (3.1 mg, 0.016 mmol, 5 mol%), 4Å MS (6 pellets), and 1.6 mL of CH_2Cl_2. Purified by flash column chromatography using a solvent gradient (10-30% EtOAc/hexanes) with a 20% EtOAc/hexanes solution to yield the product as an off white solid (75.0 mg, 81%). R_f = 0.85 (60% EtOAc/hexanes). IR (neat) 2975, 2922, 2857, 1699, 1683, 1394, 1168 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.43-7.26 (m, 5H), 5.96-5.90 (m, 1H), 5.87-5.81 (m, 1H), 5.23 (d, *J* = 6.1 Hz, 1H), 4.90 (s, 1H), 4.00 (dt, *J* = 5.0, 0.9 Hz, 2H), 3.48 (t, *J* = 5.2 Hz, 2H), 3.35-3.19 (m, 2H), 2.25 (s, 1H), 1.44 (s, 10H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.2, 142.9, 135.4, 128.8, 128.0, 127.6, 126.5, 79.6, 74.7, 71.1, 69.6, 40.7, 28.7.



2-28

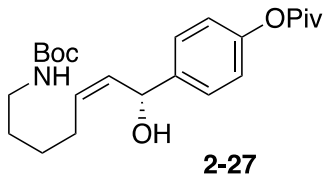
***N*,*N*-di-*tert*-butyloxycarbonyl-6-amino-1-hexyne** (**2-28):** To a flask containing di-(tert-butyl)-imidodicarbonate (3.1 g, 14.3 mmol, 1.2 eq.), a stir bar and DMF (25 mL) was added NaH (60% in mineral oil, 0.399g, 14.26 mmol, 1.4 eq.) portion wise at room temperature. The solution was placed at 60 °C for 1 hr., then allowed to cool back to room temperature. The reaction mixture was then added to a solution of hex-5-yn-1-yl 4-methylbenzenesulfonate[97] (3.0 g, 11.9 mmol, 1.0 eq.) in DMF (10 mL) at room temperature. After stirring overnight the reaction was placed at 0 °C and quenched with deionized water (100 mL) and extracted with CH_2Cl_2 (3x50mL). The organic phase was then dried over $MgSO_4$, filtered, and the solvents were evaporated in vacuum. Purified by flash column chromatography using a solvent gradient (5-10% EtOAc/hexanes) to yield the product as an off-white solid (1.41 g, 40%). R_f = 0.70 (20% EtOAc/hexanes). IR (neat) 2980, 2935, 1744, 1696, 1368, 1139, 1114 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 3.58 (t, *J* =6.9 Hz, 2H), 2.22 (dt, *J* = 7.6, 2.7 Hz, 2H), 1.94 (t, *J* = 2.6 Hz, 1H), 1.75-1.64 (m, 2H), 1.62-1.45 (m, 20H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.8, 84.3, 82.3, 68.7, 46.0, 28.4, 28.3, 25.9, 18.4. HRMS (APCI) Calcd for $C_{16}H_{28}NO_4$ $(M+H)^+$: 298.2013; found 298.2000.



2-30

(*S*)-4-7-(*N*,*N*-di-*tert*-butyloxycarbonyl)-1-hydroxyhept-2-yn-1-yl)phenyl pivalate(2-30): The following compound was made using conditions similar to the standard Carreira asymmetric alkynylation conditions.[51] To a solution of $Zn(OTf)_2$ (1.2 g, 3.3 mmol, 1.1 eq.) and (-)-N-methylephedrine (0.54 g, 3.0 mmol, 1.0 eq.) in toluene (10

mL) was added Et_3N (0.46 mL, 3.3 mmol, 1.1 eq.) and the solution as left to stir at room temperature for 2 hrs, at which point **2-28** (892.2 mg, 3.0 mmol, 1.0 eq.) in toluene (1 mL) as added to the mixture. The solution was left to stir for 20 mins. and a solution of 4-(pivaloyloxy)benzaldehyde[98] (618.7 mg, 3.0 mmol, 1.0 eq.) in toluene (1.0 mL) was added. The reaction mixture was left to stir at room temperature overnight, then quenched with NH_4Cl (30 mL) and extracted with CH_2Cl_2 (3x30mL). The organic phase was then dried over $MgSO_4$, filtered, and the solvents were evaporated in vacuum. Purified by flash column chromatography using a solvent gradient (10-25% EtOAc/hexanes) to yield the product as a clear pale yellow oil (876.1 mg, 58%). R_f = 0.64 (30% EtOAc/hexanes). IR (neat) 2980, 2935, 1744, 1696, 1368, 1139, 1114 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 3.58 (t, *J* =6.9 Hz, 2H), 2.22 (dt, *J* = 7.6, 2.7 Hz, 2H), 1.94 (t, *J* = 2.6 Hz, 1H), 1.75-1.64 (m, 2H), 1.62-1.45 (m, 20H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.8, 84.3, 82.3, 68.7, 46.0, 28.4, 28.3, 25.9, 18.4. HRMS (APCI) Calcd for $C_{16}H_{28}NO_4$ $(M+H)^+$: 298.2013; found 298.2000. IR (neat) 3478, 2978, 2935, 1749, 1694, 1368, 1138, 1116 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.47 (d, *J* = 8.4 Hz, 2H), 6.99 (d, *J* = 8.6 Hz, 2H), 5.37 (s, 1H), 3.54 (t, 2H), 2.25 (dt, *J* = 7.0, 2.0 Hz, 2H), 1.72-1.57 (m, 2H), 1.57-1.37 (m, 20H), 1.31 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.1, 152.9, 151.0, 138.9, 127.8, 121.6, 87.0, 82.4, 80.7, 77.43, 64.2, 46.0, 39.2, 28.2, 27.3, 25.7, 18.6. HRMS (ESI) Calcd for $C_{28}H_{41}NNaO_7$ $(M+Na)^+$: 526.2775; found 526.2792. The enantiomeric excess (92%) was determined by HPLC analysis (Chiralpak IB, 5% *i*-PrOH in hexanes, 1.0 mL/min, 254 nm), tr 7.7 (minor), 9.2 (major).

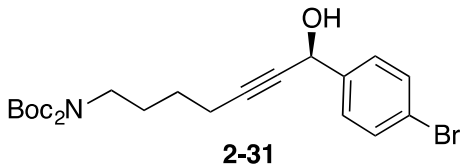


2-27

***(R*,*Z*)-4-(7-((*tert*-butoxycarbonyl)amino)-1-hydroxyhept-2-en-1-yl)phenyl pivalate (2-27)**: A two-necked flask containing **2-30** (503.6 mg, 1.0 mmol, 1.0 eq.), Lindlar's catalyst (100.0 mg, 20% by wt.), quinoline (100.0 mg, 20% by wt.), pentane:EtOAc (4.2 mL: 0.42 mL) and a stir bar was evacuated and backfilled with H_2 (g) The solution was stirred vigorously at room temperature under the H_2 (g) atmosphere. The reaction was monitored by obtaining ^{1}H NMRs from small aliquots of the reaction mixture. When the reaction was complete the mixture was filtered through a plug of cotton with EtOAc to remove the palladium, and the volatiles were removed under vacuum. The crude material was sufficient to use in the next step.

To a flask containing the crude alkene (from reduction of **11)**, acetonitrile (5 mL) and a stir bar, was added LiBr (260.5 mg, 3.0 mmol, 3.0 eq.) at room temperature. The reaction mixture was then placed at 65 °C and left to stir at this temperature overnight. The reaction mixture was cooled to room temperature, diluted with EtOAc (30 mL) and washed with 0.01M HCl (3x20mL). The organic phase was then dried over $MgSO_4$, filtered, and the solvents were evaporated in vacuum. Purified by flash column chromatography using a solvent gradient (5-40% EtOAc/hexanes) to yield the product as a clear pale yellow oil (315.9 mg, 78% over 2 steps). R_f = 0.15 (30% EtOAc/hexanes). $[\alpha]_D$ = -16.2 (*c* 1.00, CH_2Cl_2); IR (neat) 3355, 2931, 1709, 1691, 1681, 1514, 1278, 1172 cm^{-1}.^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38 (d, *J* = 0.5 Hz, 2H), 7.02 (d, *J* = 8.6 Hz, 2H), 5.71-5.45 (m, 3H), 4.66-4.49 (m, 1H), 3.25-2.98 (m, 1H), 2.57-2.45 (m,

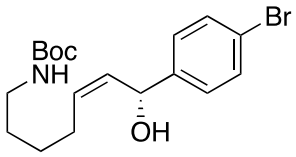
1H), 2.40-2.25 (m, 1H), 2.22-2.06 (m, 1H), 1.56-1.37 (m, 14H), 1.35 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.3, 156.3, 150.4, 141.3, 132.8, 131.6, 127.2, 121.6, 79.4, 69.1, 40.4, 39.2, 29.6, 28.6, 27.3, , 27.1, 26.4. HRMS (ESI) Calcd for $C_{23}H_{35}NNaO_5$ $(M+Na)^+$: 428.2407; found 428.2449. The enantiomeric excess (42%) was determined by HPLC analysis (Chiralpak IB, 10% *i*-PrOH in hexanes, 1.0 mL/min, 254 nm), tr 7.8 (minor), 8.5 (major).



2-31

(*S*)-7-*(N*,*N*-di-*tert*-butyloxycarbonyl)-1-(4-bromophenyl)hept-2-yn-1-ol (2-31): The following compound was made using conditions similar to the standard Carreira asymmetric alkynylation conditions.[51] To a solution of $Zn(OTf)_2$ (400.0 mg, 1.1 mmol, 1.1 eq.) and (-)-N-methylephedrine (180.0 mg, 1.0 mmol, 1.0 eq.) in toluene (4 mL) was added Et_3N (0.16 mL, 1.1 mmol, 1.1 eq.) and the solution as left to stir at room temperature for 2 hrs, at which point **2-28** (297.4 mg, 1.0 mmol, 1.0 eq.) in toluene (1 mL) as added to the mixture. The solution was left to stir for 20 mins. and a solution of 4-bromobenzaldehyde (182.0 mg, 1.0 mmol, 1.0 eq.) in toluene (1.0 mL) was added. The reaction mixture was left to stir at room temperature overnight, then quenched with NH_4Cl (10 mL) and extracted with CH_2Cl_2 (3x10mL). The organic phase was then dried over $MgSO_4$, filtered, and the solvents were evaporated in vacuum. Purified by flash column chromatography using a solvent gradient (10-25% EtOAc/hexanes) to yield the product as a colorless oil (366.6 mg, 76%). R_f = 0.32 (20% EtOAc/hexanes). IR (neat) 3464, 2979, 2931, 1729, 1691, 1366, 1134, 1112 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ

7.47-7.43 (m, 2H), 7.39-7.35 (m, 2H), 5.38-5.31 (m, 1H), 3.59-3.52 (m, 2H), 2.74-2.70 (m, 1H), 2.29-2.22 (m, 2H), 1.73-1.61 (m, 2H), 1.57-1.41 (m, 20H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.0, 140.5, 131.7, 128.5, 122.2, 87.3, 82.5, 80.5, 64.2, 46.0, 28.3, 28.1, 25.6, 18.6. HRMS (APCI) Calcd for $C_{23}H_{32}BrNNaO_5$ $(M+Na)^+$: 504.1379; found 504.1356. The enantiomeric excess (97%) was determined by HPLC analysis (Chiralpak IB, 5% *i*-PrOH in hexanes, 0.8 mL/min, 254 nm), tr 16.4 (major), 17.5 (minor).

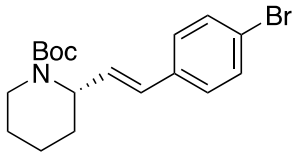


2-32

(*R*,*Z*)-*tert*-butyl (7-(4-bromophenyl)-7-hydroxyhept-5-en-1-yl)carbamate (2-32): A two-necked flask containing **12** (366.6 mg, 0.76 mmol, 1.0 eq.), Lindlar's catalyst (73.3 mg, 20% by wt.), quinoline (73.3 mg, 20% by wt.), MeOH (4 mL) and a stir bar was evacuated and backfilled with H_2 (g) The solution was stirred vigorously at room temperature under the H_2 (g) atmosphere. The reaction was monitored by obtaining ^{1}H NMRs from small aliquots of the reaction mixture. When the reaction was complete the mixture was filtered through a plug of cotton with EtOAc to remove the palladium, and the volatiles were removed under vacuum. The crude material was sufficient to use in the next step.

To a flask containing the crude alkene (from reduction of **11)**, MeOH (5 mL) and a stir bar, was added K_2CO_3 (525.2 mg, 3.8 mmol, 5.0 eq.) at room temperature. The reaction mixture was then placed at reflux and left to stir overnight. The reaction mixture was cooled to room temperature, and the excess K_2CO_3 was filtered off and the

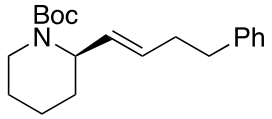
solution was placed under vacuum to remove the MeOH. The crude product was then diluted with EtOAc (30 mL) and washed with brine (2x10mL). The organic phase was then dried over $MgSO_4$, filtered, and the solvents were evaporated in vacuum. Purified by flash column chromatography using a solvent gradient (0-30% EtOAc/hexanes) to yield the product as a clear pale yellow oil (245.9 mg, 81% over 2 steps). $[\alpha]_D$ = -100.3 (*c* 1.00, CH_2Cl_2); R_f = 0.22 (20% EtOAc/hexanes). IR (neat) 3339, 2930, 1687, 1516, 1486, 1169 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.47-7.41 (m, 2H), 7.28-7.22 (m, 2H), 5.61-5.44 (m, 3H), 4.65-4.45 (m, 1H), 3.24-3.10 (m, 1H), 3.10-2.97 (m, 1H), 2.76 (s, 1H), 2.42-2.23 (m, 1H), 2.20-2.04 (m, 1H), 1.58-1.31 (m, 12H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.3, 142.9, 132.7, 131.8, 131.7, 127.9, 126.1, 121.3, 79.6, 68.9, 40.3, 29.5, 28.7, 27.0, 26.3. The enantiomeric excess (91%) was determined by HPLC analysis (Chiralpak IB, 5% *i*-PrOH in hexanes, 0.8 mL/min, 254 nm), tr 15.9 (major), 20.3 (minor).



2-33

(*S*,*E*)-*tert*-butyl 2-(4-bromostyryl)piperidine-1-carboxylate (2-33): The following compound was made under the optimized gold-catalyzed dehydrative cyclization conditions with **2-32** (20.0 mg, 0.05 mmol), 1,3-bis(2,6-diisopropylphenyl-imidazol-2-ylidene)gold(I) chloride (1.6 mg, 0.0026 mmol, 5 mol%), silver tetrafluoroborate (0.5 mg, 0.0026 mmol, 5 mol%), 4Å MS (2 pellets), and 1.0 mL of CH_2Cl_2. Purified by flash column chromatography using a solvent gradient (0-5% EtOAc/hexanes) to yield the product as a clear, colorless oil (16.8 mg, 92%). R_f = 0.56

(20% EtOAc/hexanes). R_f = 0.56 (20% EtOAc/hexanes). $[\alpha]_D$ = -8.5 (*c* 1.00, CH_2Cl_2); IR (neat) 2935, 2857, 1684, 1486, 1399, 1159 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.45 (d, *J* = 8.5 Hz, 2H), 7.24 (d, *J* = 8.4 Hz, 2H), 6.34 (dd, *J* = 16.2, 1.9 Hz, 1H), 6.20 (dd, *J* = 16.1, 4.8 Hz, 1H), 4.97 (s, 1H), 4.02 (d, *J* = 13.9 Hz, 2H), 2.91 (td, *J* = 13.0, 2.8 Hz, 1H), 1.88-1.74 (m, 2H), 1.72-1.61 (m, 2H), 1.61-1.37 (m, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.6, 136.2, 131.8, 129.9, 129.8, 128.0, 121.3, 79.8, 52.4, 40.2, 29.7, 28.7, 25.7, 19.9. The enantiomeric excess (30%) was determined by HPLC analysis (Chiralpak IB, 0.5% *i*-PrOH in hexanes, 0.8 mL/min, 254 nm), tr 18.1 (minor), 20.3 (major).

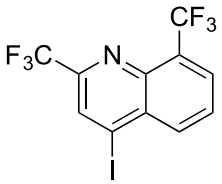


2-42

(*R*,*E*)-*tert*-butyl 2-(4-phenylbut-1-en-1-yl)piperidine-1-carboxylate (2-42): The following compound was made under the optimized gold-catalyzed dehydrative cyclization conditions with **2-41** (13.0 mg, 0.04 mmol), 1,3-bis(2,6-diisopropylphenyl-imidazol-2-ylidene)gold(I) chloride (2.4 mg, 0.004 mmol, 10 mol%), silver tetrafluoroborate (0.8 mg, 0.004 mmol, 10 mol%), 4Å MS (3 pellets), and 1.0 mL of CH_2Cl_2 at 40 °C. Purified by flash column chromatography using a solvent gradient (0-5% EtOAc/hexanes) to yield the product as a white solid (10.4 mg, 87%). R_f = 0.62 (20% EtOAc/hexanes). $[\alpha]_D$ = 30.1 (*c* = 0.70, CH_2Cl_2); IR (neat) 2931, 2857, 1687, 1407, 1363, 1159 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.29-7.25 (m, 2H), 7.20-7.15 (m, 3H), 5.48 (dtd, *J* = 15.1, 6.6, 1.7 Hz, 1H), 5.41-5.35 (m, 1H), 4.72 (s, 1H), 3.88 (d, *J* = 13.5 Hz, 1H), 2.78-2.66 (m, 3H), 2.39-2.33 (m, 2H), 1.66-1.61 (m, 2H), 1.58-1.50 (m, 3H),

1.45 (s, 9H), 1.42- 1.33 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.6, 142.0, 130.9, 129.4, 128.7, 128.5, 126.0, 79.4, 52.0, 39.8, 36.0, 34.5, 29.6, 28.7, 25.8, 19.6. The enantiomeric excess (92%) was determined by HPLC analysis (Chiralcel OJ-H, 1.0% *i*-PrOH in hexanes, 1.0 mL/min, 215 nm) tr 8.8 (major), 13.2 (minor).

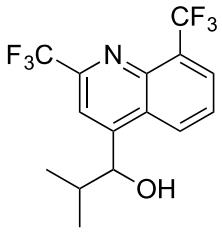
Synthesis of Mefloquine and Analogs



2-48c

4-iodo-2,8-bis(trifluoromethyl)quinoline (2-48c): To a flask containing 4-chloro-2,8-bis(trifluoromethyl)quinoline[68] (1.0 g, 3.3 mmol) and a stir bar was added hydroiodic acid (57% in water, 3 mL). The solution was placed in a 130 °C bath, and was left to stir at this temperature overnight. The solution was then taken out of the bath and cooled to room temperature and further in an ice bath. The mixture was diluted with water and chloroform, and the pH of the solution was raised to 14 using NaOH (3.0 M solution in water). The aqueous phase was extracted with $CHCl_3$ (3x30mL). The combined organic phases were then washed with water (2x30mL), sodium thiosulfate (sat. in water, 2x30mL), and brine respectively. The crude product was then purified by flash column chromatography using a solvent gradient (0-10% CH_2Cl_2/hexanes) to yield the product as a white solid (734.9 mg, 61%). R_f = 0.72 (40% CH_2Cl_2/hexanes). IR (neat) 2922, 2849, 1573, 1419, 1302, 1141, 1103 $cm^{-1.}$ ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.39 (s, 1H), 8.29 (d, *J* = 8.4 Hz, 1H), 8.20 (d, *J* = 7.4 Hz, 1H), 7.78 (t, *J* = 8.0 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.0 (q, *J* = 35.8 Hz), 143.2, 136.2, 131.6, 130.3 (q, *J* = 5.4 Hz), 129.5 (q, *J* = 2.2 Hz), 129.0, 128.6, 128.5, 123.3 (q, *J* =

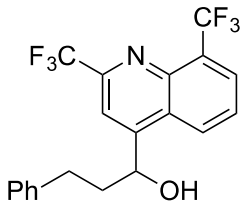
272.5 Hz), 120.3 (q, *J* = 275.0 Hz), 118.5, 113.4. ^{19}F NMR (282 MHz, $CDCl_3$): δ -59.9, -67.5.



2-57

1-(2,8-bis(trifluoromethyl)quinolin-4-yl)-2-methylpropan-1-ol (2-57): The following compound was made through various routes, and example procedure is given here. To a solution of 4-iodo-2,8-bis(trifluoromethyl)quinoline (90.6 mg, 0.23 mmol, 1.0 eq.) and THF (1.0 mL) was added *i*PrMgCl (2.0 M, 0.12 mL, 0.25 mmol, 1.1 eq.) at -40 °C. The solution was left to stir for 15 minutes until all of the iodide had disappeared by TLC. After this time isobutyraldehyde (previously distilled, 18 µL, 0.2 mmol, 1.0 eq.) was added (neat) to the mixture at -40 °C. The reaction was left to stir at the same temperature for 1.5 hrs., at which point phosphate buffer (2.0 mL) was added to the mixture. The solution was then diluted with water, extracted with EtOAc, dried over Na_2SO_4, filtered and evaporated to give the crude product. The crude product was then purified by flash column chromatography using a solvent gradient (0-20% EtOAc/hexanes) to yield the product **2-58** as a white solid (45.0 mg, 58%). R_f = 0.31 (25% EtOAc/hexanes). IR (neat) 3443, 3086, 2971, 2936, 2880, 1713, 1604, 1586, 1519, 1470, 1433, 1371, 1311, 1153 $cm^{-1.}$ ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.28 (d, *J* = 8.7 Hz, 1H), 8.15 (d, *J* = 6.9 Hz, 1H), 7.99 (s, 1H), 7.71 (t, *J* = 7.5 Hz, 1H), 5.30 (dd, *J* = 4.8 Hz, 1H), 2.12-2.20 (m, 1H), 1.05 (d, *J* = 6.9 Hz, 3H), 0.92 (d, *J* = 6.6 Hz, 3H). ^{13}C

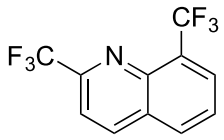
NMR (125 MHz, $CDCl_3$) δ 152.7, 148.2, 144.0, 128.9, 128.8, 127.8, 125.6, 121.9, 119.7, 115.4, 75.2, 35.0, 20.3, 16.4. ^{19}F NMR (282 MHz, $CDCl_3$): δ -60.3, -68.0.



2-61

1-(2,8-bis(trifluoromethyl)quinolin-4-yl)-3-phenylpropan-1-ol (2-61): A solution of **2-42** (31.5 mg, 0.1 mmol, 1.0 eq.) and Sudan III (1.0 mg used as an indicator) in CH_2Cl_2 (1.0 mL) was treated with ozone at -78 °C for 10 minutes. During this time a solution of 4-iodo-2,8-bis(trifluoromethyl)quinoline **2-48c** (142 mg, 0.36 mmol, 3.6 eq.) and THF (1.0 mL) was added *i*PrMgCl (2.0 M, 0.18 mL, 0.36 mmol, 3.6 eq.) at -78 °C. The solution was left to stir for 15 minutes until all of the iodide had disappeared by TLC. The solution of ozonide produced from ozonlysis of **2-42** was then flushed with Ar(g) for 10 mins., after this time the grignard was then added to the ozonide at -78 °C. The mixture was left ot stir at this temperature for 2 hrs. and the reaction was then quenched with deionized water (3 mL). The solution was then diluted with water, extracted with EtOAc, and dried over Na_2SO_4, filtered and evaporated to give the crude product, which was primarily composed of **2-61**, **2-62** and **4-1**. The crude product was then purified by flash column chromatography using a solvent gradient (0-20% EtOAc/hexanes) to yield the product as a clear oil (45.0 mg, 58%). R_f = 0.31 (25% EtOAc/hexanes). IR (neat) 3439, 3078, 3030, 2929, 2362, 1603, 1586, 1430, 1372, 1310, 1189, 1144, 1109, 770 $cm^{-1.}$ ^1H NMR (500 MHz, $CDCl_3$) δ 8.16 (d, *J* = 7.2 Hz, 1H), 8.08 (s, 1H), 7.95 (d, *J* = 8.6 Hz, 1H), 7.65 (t, *J* = 7.9 Hz, 1H), 7.39-7.34 (m, 2H),

7.31-7.26 (m, 3H), 5.47-5.42 (m, 1H), 2.95 (t, *J* = 7.3 Hz, 2H), 2.20-2.02 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.5, 140.8, 128.9, 128.8, 127.2, 126.7, 114.4, 69.3, 40.3, 32.3 ^{19}F NMR (282 MHz, $CDCl_3$): δ -60.4, -68.0.



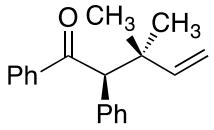
4-1

2,8-bis(trifluoromethyl)quinoline (4-1): The following compound was a common byproduct obtained from the halogen-exchange experiments. The following data was obtained: R_f = 0.40 (25% EtOAc/hexanes). IR (neat) 2919, 2847, 1585, 1326, 1290, 1190, 1145, 1098 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.43 (d, *J* = 8.4 Hz, 1H), 8.18 (d, *J* = 7.2 Hz, 1H), 8.11 (d, *J* = 8.1 Hz, 1H), 7.84 (d, *J* = 8.4 Hz, 1H), 7.73 (t, *J* = 8.1 Hz, 1H). ^{19}F NMR (282 MHz, $CDCl_3$): δ -60.4, -67.9.

Gold-catalyzed Tandem Hydroalkoxylation/Claisen Rearrangement

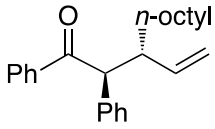
Optimized Conditions: A pressure tube (screw cap) containing a stir bar was taken from the oven and placed directly into a glovebox. To this vessel was added 1,3-bis(2,6-diisopropylphenyl-imidazol-2-ylidene)gold(I) chloride (6.2 mg, 0.01 mmol, 5 mol%), and silver tetrafluoroborate (1.9 mg, 0.01 mmol, 5 mol%). The vessel was capped with a septum and then taken out of the glovebox where it was immediately placed under dry nitrogen atmosphere. 0.5 mL of THF was added to the tube and the mixture was left to stir ~10 mins to activate the complex. After this time a solution of alkyne (0.6 mmol in 0.5 mL of THF) was transferred to the tube, and the vessel was then placed in a 65 °C oil bath. 1.0 mL of a 0.2 M soln. of an allylic alcohol (in THF) was then added slowly over 12 hrs. via syringe pump (~0.8 mL/hr). After the addition was

complete the solution was allowed to stir at this temperature for an additional 3 hrs. The tube is then sealed with a screwcap and placed in a 120 °C oil bath for 6 hrs. (Note: No problems occurred during this process, however, when sealed the reactions were placed behind a blast shield for added safety.) After cooling to room temperature the screwcap was removed and the solution was filtered over a plug of silica with EtOAc. The solution was then evaporated, the crude was characterized, and purified.



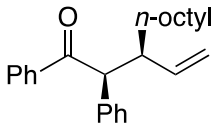
3-58

3,3-dimethyl-1,2-diphenylpent-4-en-1-one (3-58): The following compound was made through various conditions, a representative reaction is shown here. The optimized conditions were employed with prenyl alcohol (**3-55**) (1.0 mL of 0.2M soln., 0.2 mmol) diphenylacetylene (107 mg, 0.6 mmol, 3.0 eq.). Purified by flash column chromatography using a solvent gradient (0-20% CH_2Cl_2/hexanes) to yield the product as a clear colorless oil (43.5 mg, 83%). R_f = 0.66 (20% EtOAc/hexanes). IR (neat) 3086, 3055, 2966, 2924, 1684, 1540, 1507, 1457, 1447 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.87 (d, J = 7.5 Hz, 2H), 7.49-7.46 (m, 1H) 7.40-7.37 (m, 4H), 7.32-7.29 (m, 2H), 7.26-7.23 (m, 1H), 6.11 (dd, *J* = 17.5, 11.0, 1H), 4.95 (dd, *J* = 11.0, 1.0 Hz, 1H), 4.88 (dd, *J* = 17.5, 1.0 Hz, 1H), 4.59 (s, 1H), 1.17 (s, 3H), 1.14 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 200.2, 146.3, 138.7, 135.8, 132.7, 130.7, 128.7, 128.5, 128.3, 127.3, 112.2, 62.3, 50.0, 26.4, 24.9; HRMS (DART) Calcd for $C_{19}H_{21}O$ $(M+H)^+$ 265.1587, found 265.1593**.**



3-61

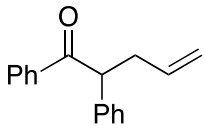
***anti*-1,2-diphenyl-3-vinylundecan-1-one (3-61):** The following compound was made with the optimized conditions with (*E*)-undec-2-en-1-ol[99] (**3-59**) (1.0 mL of 0.2M soln., 0.2 mmol) and diphenylacetylene (110.0 mg, 0.62 mmol, 3.0 eq.). Purified by flash column chromatography using a solvent gradient (0-20% CH_2Cl_2/hexanes) to yield the product as a white solid (50.2 mg, 72%; major diastereomer, 5:1 *dr*): mp = 66-68°C R_f = 0.36 (2% Et_2O/pentanes). IR (neat) 3064, 3022, 2926, 2854, 2361, 2334, 1683, 1267, 913 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.98 (d, *J* = 8.5 Hz, 2H), 7.51-7.46 (m, 1H), 7.42-7.38 (m, 2H), 7.29-7.22 (m, 4H), 7.17-7.13 (m, 1H), 5.38 (dt, *J* = 17.1, 10.3, Hz, 1H), 4.82 (dd, *J* = 10.3, 1.9 Hz, 1H), 4.76 (dd, *J* = 17.1, 1.9 Hz, 1H), 4.49 (d, *J* = 10.2 Hz, 1H), 3.06-2.98 (m, 1H), 1.43-1.51 (m, 1H), 1.22-1.28 (m, 15H), 0.85 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 200.1, 139.8, 139.1, 137.8. 133.1, 129.3, 128.8, 128.7, 128.7, 127.1, 116.7, 58.6, 47.8, 33.9, 32.1, 29.7, 29.7, 29.5, 27.6, 22.9, 14.3; HRMS (DART) Calcd for $C_{25}H_{33}O$ $(M+H)^+$ 349.2526, found 349.2547**.**



3-62

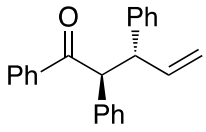
***syn*-1,2-diphenyl-3-vinylundecan-1-one (3-62):** The following compound was made through various methods. A representative method is shown. Following the optimized conditions with (*Z*)-undec-2-en-1-ol[100] (**3-60**) (1.0 mL of 0.2M soln., 0.2 mmol) and diphenylacetylene (107.0 mg, 0.6 mmol, 3.0 eq.). Purified by flash column chromatography using a solvent gradient (0-20% CH_2Cl_2/hexanes) to yield the product

as a white solid (52.3 mg, 75%; major diastereomer, 11:1 *dr*): mp = 74-76°C; R_f = 0.36 (40% CH_2Cl_2/hexanes). IR (neat) 3078, 3045, 2920, 2852, 1673, 1644, 1557, 1538, 1445 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.96-7.92 (m, 2H), 7.50-7.45 (m, 1H), 7.42-7.35 (m, 3H), 7.32 – 7.27 (m, 3H), 7.23-7.18 (m, 1H), 5.62 (dddd, *J* = 17.2, 10.1, 8.7, 0.9 Hz, 1H), 5.07 (ddd, *J* = 17.2, 1.6, 0.9, 1H), 4.99 (dd, *J* = 10.3, 1.6 Hz, 1H), 4.54 (d, *J* = 10.2 Hz, 1H), 3.07–2.98 (m, 1H),1.34-1.05 (m, 14H), 0.90-0.83 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 199.9, 140.6, 137.9, 137.7, 132.9, 129.3, 128.9, 128.7, 128.6, 127.3, 116.9, 58.3, 46.9, 32.0, 31.8, 29.7, 29.6, 29.4, 26.9, 22.8, 14.3; HRMS (DART) Calcd for $C_{25}H_{33}O$ $(M+H)^+$ 349.2526, found 349.2530.



3-65b

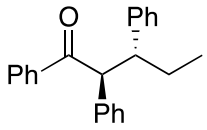
1,2-diphenylpent-4-en-1-one (3-65b):[101] The following compound was made with the optimized conditions with allyl alcohol (1.0 mL of 0.2M soln., 0.2 mmol) and diphenylacetylene (107.0 mg, 0.6 mmol, 3.0 eq.). Purified by flash column chromatography using a solvent gradient (0-20% CH_2Cl_2/hexanes) to yield the product as a clear colorless oil (45.0 mg, 95%), that satisfactorily matched all previously reported data.[101]



3-65c

***anti*-1,2,3-triphenylpent-4-en-1-one (3-65c):** The following compound was provided via Procedure A, with cinnamyl alcohol (40.0 mg, 0.3 mmol, 1.0 eq.), diphenylacetylene (160.0 mg, 0.9 mmol, 3.0 eq.), 1,3-bis(2,6-diisopropylphenyl-

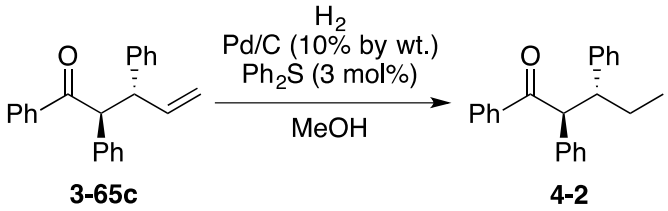
imidazol-2-ylidene)gold(I) chloride (9.3 mg, 0.015 mmol, 5 mol%), and silver tetrafluoroborate (3.0 mg, 0.015 mmol, 5 mol%) in 1.0 mL of THF. Purified by flash column chromatography using a solvent gradient (0-20% CH_2Cl_2/hexanes) to yield the product as a white solid (60 mg, 96%; major diastereomer; 5:1 *dr*). mp = 161-163 °C; R_f = 0.15 (15% EtOAc/hexanes). IR (neat) 3065, 3027, 1673, 1595, 1447, 1267, 910 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.98-7.95 (m, 2H), 7.51-7.46 (m, 1H), 7.42-7.37 (m, 2H), 7.31-7.29 (m, 4 H), 7.23-7.20 (m, 1H), 5.82 (ddd, *J* = 17.0, 10.2, 8.0 Hz, 1H), 5.10 (d, *J* = 11.5 Hz, 1H), 4.87 (ddd, *J* = 10.3, 1.6, 1.0 Hz, 1H) 4.75 (dt, *J* = 17.0, 1.6 Hz, 1H), 4.36 (dd, *J* = 11.5, 8.0 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 198.8, 142.6, 139.6, 137.5, 137.3, 132.9, 129.4, 129.0, 128.7, 128.6, 128.5, 128.2, 127.6, 126.6, 116.6, 58.6, 53.2; HRMS (DART) Calcd for $C_{23}H_{21}O$ $(M+H)^+$ 313.1587, found 313.1578.



4-2

***anti*-1,2,3-triphenylpentan-1-one (4-2):** The following compound was synthesized by the chemoselective reduction of *anti*-1,2,3-triphenylpent-4-en-1-one (**3-65c**) following a known procedure.[102] A flask containing a stir bar, *anti*-1,2,3-triphenylpent-4-en-1-one (**3-65c**, 60.0 mg, 0.19 mmol), Pd/C (6 mg, 10% by wt.), Ph_2S (1.0 mg, 3 mol%) and 2 mL of MeOH was evacuated and backfilled 3 times with H_2 gas via a three way valve attached to a hydrogen balloon. The solution was allowed to mix at room temperature for 24 hrs. The solution was filtered through a plug of celite with CH_2Cl_2 and the solvent was evaporated. Purified by flash column chromatography using a solvent gradient (0-20% CH_2Cl_2/hexanes) to yield the product as a white solid (60 mg, quantitative, one observable diastereomer) which matched the well known

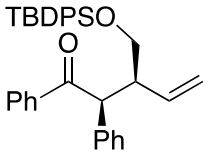
melting point of the *anti*(erythro) product.[103] mp = 169-170°C; R_f = 0.32 (40% CH_2Cl_2/hexanes). IR (neat) 3055, 3029, 2952, 2917, 2857, 1673, 1446, 1271 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.78-7.71 (m, 2H), 7.49-7.44 (m, 1H), 7.41-7.36 (m, 1H), 7.35-7.30 (m, 2H), 7.30-7.26 (m, 4H), 7.24-7.19 (m, 2H), 7.11-7.08 (m, 1H), 4.91 (d, *J* = 10.9 Hz, 1H), 3.46 (td, *J* = 10.7, 4.3 Hz, 1H), 1.48-1.36 (m, 2H), 0.60 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 199.6, 143.5, 138.1, 137.7, 132.7, 129.3, 129.2, 129.0, 128.5, 128.5, 128.5, 128.4, 128.4, 127.5, 126.34, 60.0, 50.5, 26.6, 11.9.; HRMS (DART) Calcd for $C_{23}H_{22}O$ $(M+H)^+$ 315.1743, found 315.1735.



3-65c **4-2**

Note[103]
mp of *anti* = 169-170 °C
mp of *syn* = 91-92 °C

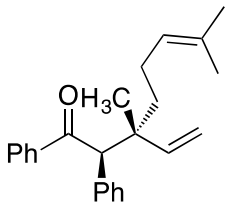
Figure 4-1. Confirmation of Stereochemistry via synthesis of *anti*-1,2,3-triphenylpentan-1-one (erythro)



3-65d

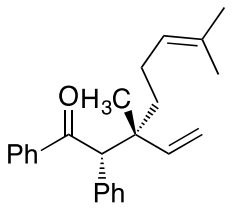
***syn*-3-(((*tert*-butyldiphenylsilyl)oxy)methyl)-1,2-diphenylpent-4-en-1-one (3-65d):** The following compound was with the optimized conditions optimized conditions with (*Z*)-4-(tert-butyldiphenylsilanyloxy)-but-2-ene-1-ol (1.0 mL of 0.2M soln., 0.2 mmol) and diphenylacetylene (107.0 mg, 0.6 mmol, 3.0 eq.). Purified by flash column chromatography using a solvent gradient (0-1% Et_2O/hexanes) to yield the product as a clear, colorless oil (70.0 mg, 70%; >25:1 *dr*): R_f = 0.62 (20% Et_2O/hexanes). IR (neat)

3071, 2958, 2857, 2822, 1683, 1447, 1109 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.05-7.94 (m, 2H), 7.61-7.55 (m, 2H), 7.53-7.17 (m, 14H), 6.03 (ddd, *J* = 17.2, 10.4, 8.2 Hz, 1H), 5.18-5.00 (m, 3H), 3.57 (dd, *J* = 10.0, 3.2 Hz, 1H), 3.48 (dd, *J* = 10.0, 4.1 Hz, 1H), 3.34-3.05 (m, 1H), 1.06 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 199.6, 164.6, 138.4, 137.2, 135.9, 135.7, 133.0, 129.8, 129.7, 129.5, 128.9, 128.8, 127.8, 127.7, 127.4, 117.5, 106.8, 64.8, 53.5, 49.2, 27.1, 19.6.



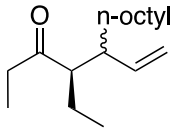
3-65e

***anti*-3,7-dimethyl-1,2-diphenyl-3-vinyloct-6-en-1-one (3-65e):** The following compound was made using the optimized conditions with geraniol (1.0 mL of 0.2M soln., 0.2 mmol) and diphenylacetylene (108.0 mg, 0.6 mmol, 3.0 eq.). Purified by flash column chromatography using a solvent gradient (0-20% CH_2Cl_2/hexanes) to yield the product as a clear colorless oil (42.5 mg, 64%; major diastereomer; 5:1 *dr*). R_f = 0.55 (40% CH_2Cl_2/hexanes). IR (neat) 3085, 3062, 3027, 2968, 2925, 1682, 1597, 1581, 1447, 1212, 1002, 915 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.90-7.87 (m, 2H), 7.47-7.43 (m, 1H), 7.38-7.34 (m, 4H), 7.28-7.25 (m, 2H), 7.23-7.21 (m, 1H), 5.97 (ddd, *J* = 17.5, 10.8, 0.9 Hz, 1H), 5.06 (dd, *J* = 10.8, 1.2 Hz, 1H), 5.04-4.99 (m, 1H), 4.81 (dd, *J* = 17.5, 1.2 Hz, 1H), 4.64 (s, 1H), 1.97-1.80 (m, 2H), 1.70-1.42 (12H), 1.20 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 200.1, 144.4, 138.8, 135.4, 132.7, 131.4, 130.9, 128.7, 128.5, 128.2, 127.3, 124.9, 113.8, 61.8, 44.3, 38.4, 25.8, 23.2, 20.3, 17.7; HRMS (DART) Calcd for $C_{24}H_{29}O$ $(M+H)^+$ 333.2213, found 333.2229.



3-65f

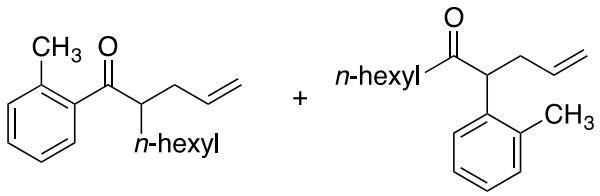
***syn*-3,7-dimethyl-1,2-diphenyl-3-vinyloct-6-en-1-one (3-65f):** The following compound was made with the optimized conditions with nerol (1.0 mL of 0.2M soln., 0.2 mmol) and diphenylacetylene (108.0 mg, 0.6 mmol, 3.0 eq.). Purified by flash column chromatography using a solvent gradient (0-20% CH_2Cl_2/hexanes) to yield the product as a clear colorless oil (47.2 mg, 71%; major diastereomer; 8:1 *dr*). R_f = 0.56 (40% CH_2Cl_2/hexanes). IR (neat) 3063, 3020, 2969, 2924, 1684, 1447, 1215 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.91-7.85 (m, 2H), 7.49-7.41 (m, 1H), 7.40-7.33 (m, 4H), 7.31- 7.17 (m, 3H), 6.17 (dd, *J* = 17.6, 10.9 Hz, 1H), 5.06 (dd, *J* = 10.9, 1.4 Hz, 1H), 5.03-4.96 (m, 1H), 4.82 (dd, *J* = 17.6, 1.4 Hz, 1H), 4.66 (s, 1H), 1.93-1.78 (m, 1H), 1.62 (s, 3H), 1.61-1.38 (m, 6H), 1.14 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 200.2, 144.3, 138.8, 135.5, 132.7, 131.5, 131.0, 128.6, 128.5, 128.2, 127.4, 124.8, 114.2, 62.12, 44.5, 39.7, 25.9, 23.1, 20.3, 17.8. HRMS (DART) Calcd for $C_{24}H_{29}O$ $(M+H)^+$ 333.2213, found 333.2207.



3-65g

4-ethyl-5-vinyltridecan-3-one (3-65g): The following compound was made with the optimized conditions with (*E*)-undec-2-en-1-ol[99] (**3-59**) (1.0 mL of 0.2M soln., 0.2 mmol) and 3-hexyne (70 μL, 0.6 mmol, 3.0 eq.). Purified by flash column chromatography using a solvent gradient (0-2% Et_2O/pentanes) to yield the product as a clear colorless oil (45.5 mg, 90%; 1:1 mixture of diastereomers). R_f = 0.95 (10%

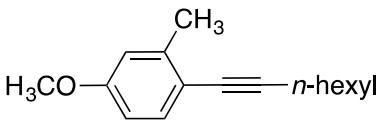
Et_2O/pentanes). IR (neat) 2985, 2935, 1742, 1373, 1241, 1047 cm^{-1}. ^1H NMR mixture of diastereomers (500 MHz, C_6D_6): δ 5.44-5.35 (m, 1H), 5.02 (dd, *J* = 10.5, 2.0 Hz, 2H), 4.98-4.93 (m, 1H), 2.45-2.37 (m, 3H), 2.30-3.26 (m, 1H), 1.57 (q, *J* = 7.0 Hz), 1.26-1.16 (m, 16 H), 1.02 (t, *J* = 7.5 Hz, 1H), 0.95 (d, *J* = 7.0 Hz, 2 H), 0.89-0.84 (m, 5H), 0.76 (t, *J* = 7.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 214.6, 140.3, 139.6, 116.7, 116.6, 58.2, 50.5, 46.8, 46.7, 44.2, 37.1, 33.1, 33.9, 32.0, 29.7, 29.7, 29.7, 29.5, 29.5, 27.5, 27.5, 23.2, 22.8, 17.2, 14.3, 14.2, 14.0, 12.1, 7.7, 1.2. HRMS (DART) Calcd for $C_{17}H_{33}O$ $(M+H)^+$ 253.2526, found 253.2527.



3-68a ***iso*-3-68a**

2-allyl-1-(*o*-tolyl)octan-1-one (3-68a) and **4-(*o*-tolyl)undec-1-en-5-one (3-68b):** The following products were obtained using the optimized conditions with allyl alcohol (1.0 mL of 0.2M soln., 0.2 mmol) and 1-methyl-2-(oct-1-yn-1-yl)benzene[102] (120.2 mg, 0.6 mmol, 3.0 eq.) Purified by flash column chromatography using a solvent gradient (0-20% CH_2Cl_2/hexanes) to yield the product as a clear colorless oil (33.0 mg, 64%; 2:1 mixture of regioisomers aryl:alkyl ketone). Analytical fractions of each were obtained; their characterization is as follows: ***Aryl Ketone* (3-68a)**: R_f = 0.45 (40% CH_2Cl_2/hexanes). IR (neat) 3066, 2954, 2928, 2856, 1686, 1458, 1210 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ7.56 (d, *J* = 7.3 Hz, 1H), 7.38-7.32 (m, 1H), 7.29-7.21 (m, 2H), 5.75 (ddt, *J* = 17.2, 10.1, 7.1 Hz, 1H), 5.08-4.95 (m, 2H), 3.31 (tt, *J* = 7.6, 5.8 Hz, 1H), 2.54-2.39 (m, 4H), 2.32-2.18 (m, 1H), 1.82-1.67 (m, 1H), 1.47 (dt, *J* = 14.8, 6.1 Hz, 1H), 1.36-

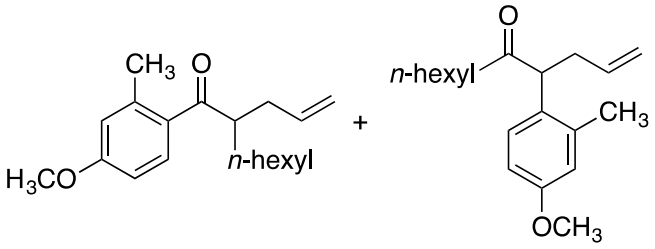
1.14 (m, 6H), 0.87-0.81 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): 208.1, 139.3, 138.2, 136.2, 132.0, 131.1, 128.2, 125.7, 116.9, 49.4, 36.3, 31.9, 31.8, 29.6, 27.5, 22.8, 21.1, 14.3. HRMS (DART) Calcd for $C_{17}H_{32}O$ $(M+H)^+$ 259.2056, found 259.2068. The following data was accrued from a fraction obtained as a mixture of products that is primarily the alkyl ketone. ***Alkyl Ketone* (*iso*-3-68b)**: R_f = 0.40 (40% CH_2Cl_2/hexanes). IR (neat) 3066, 2956, 2927, 2857, 1715, 1490, 1458, cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.27-7.22 (m, 1H), 7.21-7.13 (m, 2H), 7.07-7.03 (m, 1H), 5.67 (ddd, *J* = 17.1, 10.2, 6.9 Hz, 1H), 5.03-4.98 (m, 1H), 4.93 (ddd, *J* = 10.1, 2.1, 1.1 Hz, 1H), 3.96-3.91 (m, 1H), 2.87 (t, 1H), 2.82-2.74 (m, 1H), 2.40 (s, 4H), 2.35 (dtq, *J* = 14.2, 7.1, 1.2 Hz, 2H), 2.28-2.23 (m, 2H), 1.70 (h, *J* = 7.4 Hz, 1H), 1.53-1.41 (m, 2H), 1.37-1.08 (m, 11H), 0.83 (t, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): 210.2, 137.3, 136.3, 131.0, 127.4, 127.2, 125.8, 126.8, 116.6, 54.5, 42.0, 36.5, 31.7, 28.9, 23.9, 22.6, 20.3, 14.2. HRMS (DART) Calcd for $C_{18}H_{27}O$ $(M+H)^+$ 259.2056, found 259.2065.



4-3

4-methoxy-2-methyl-1-(oct-1-yn-1-yl)benzene (4-3): To a mixture of Et_3N (3.0 mL), PPh_3PdCl_2 (46.0 mg, 0.07 mmol, 5 mol%), CuI (25.0 mg, 0.13 mmol, 10 mol%), and 1-octyne (0.24 mL, 1.6 mmol, 1.2 eq.) at room temperature was added 2-methyl-4-methoxyiodobenzene (320.0 mg, 1.3 mmol, 1.0 eq.). The mixture was left to stir at room temperature overnight, then diluted with EtOAc and washed with sat. NH_4Cl (x2). The organic phase was washed with brine, dried over $NaSO_4$, and filtered. Purified by flash column chromatography using a solvent gradient (0-20% CH_2Cl_2/hexanes) to yield the product as a clear colorless oil (196.5 mg, 66%). R_f = 0.8 (30% EtOAc/hexanes). IR

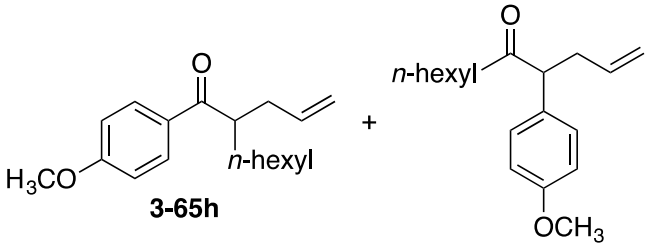
(neat) 2999, 2955, 2930, 2858, 1606, 1497, 1567, 1464, 1234 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.31 (d, *J* = 8.4 Hz, 1H), 6.74 (d, *J* = 2.7 Hz, 1H), 6.66 (dd, *J* = 8.4, 2.7 Hz, 1H), 3.79 (s, 3H), 2.46 (t, *J* = 6.9 Hz, 2H), 2.42 (s, 3H), 1.69-1.57 (m, 2H), 1.55 – 1.43 (m, 2H), 1.41-1.27 (m, 4H), 0.93 (t, *J* = 7.0 Hz 3H).^{13}C NMR (75 MHz, $CDCl_3$): δ 159.0, 141.7, 133.1, 116.4, 115.1, 111.2, 92.8, 79.3, 55.3, 31.6, 29.2, 28.8, 22.8, 21.2, 19.7, 14.3. HRMS (DART) Calcd for $C_{16}H_{23}O$ $(M+H)^+$ 231.1743, found 231.1745.



3-68c ***iso*-3-68c**

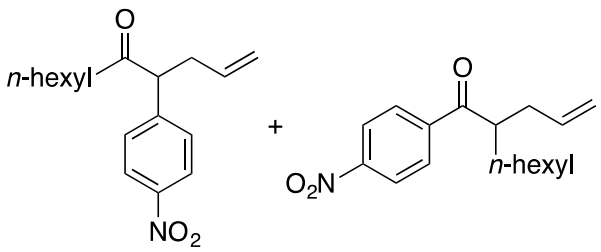
2-allyl-1-(4-methoxy-2-methylphenyl)octan-1-one (3-68c) and **4-(4-methoxy-2-methylphenyl)undec-1-en-5-one (*iso*-3-68c):** The following products were obtained using the optimized conditions with allyl alcohol (1.0 mL of 0.2M soln., 0.2 mmol) and 4-methoxy-2-methyl-1-(oct-1-yn-1-yl)benzene (**4-3**) (138.2 mg, 0.6 mmol, 3.0 eq.). Purified by flash column chromatography using a solvent gradient (0-20% EtOAc/hexanes) to yield the product as a clear orangeish oil, mixture of products (26.5 mg, 46%; 2:1 mixture of regioisomers aryl:alkyl ketone). An analytical fraction of the aryl ketone was obtained; the characterization is as follows: ***Aryl Ketone* (3-68c)**: R_f = 0.24 (40% CH_2Cl_2/hexanes). IR (neat) 3066, 2954, 2927, 2855, 1674, 1603, 1567, 1247, 1126 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.66-7.62 (m, 1H), 6.78-6.73 (m, 2H), 5.74 (ddt, *J* = 17.1, 10.2, 7.1 Hz, 1H), 5.02 (dd, *J* = 17.1, 1.1, 1H), 4.96 (dd, *J* = 10.2, 1.1 Hz, 1H), 3.84 (s, 3H), 3.33 (tt, *J* = 7.7, 5.8 Hz, 1H), 2.49 (s, 3H), 2.48-2.42 (m, 1H), 2.25-2.18 (m, 1H), 1.77-1.66 (m, 1H), 1.52-1.42 (m, 1H), 1.32-1.15 (m, 6H), 0.84 (t, *J* = 6.7, 3H). ^{13}C

NMR (125 MHz, $CDCl_3$): δ 206.2, 161.7, 141.9, 136.4, 131.6, 131.1, 117.6, 116.6, 110.7, 55.5, 48.5, 36.8, 32.3, 31.9, 29.7, 27.6, 22.8, 22.1, 14.3. HRMS (DART) Calcd for $C_{19}H_{29}O_2$ $(M+H)^+$ 289.2162, found 289.2166.



2-allyl-1-(4-methoxyphenyl)octan-1-one (3-65h) and **4-(4-methoxyphenyl)undec-1-en-5-one (*iso*-3-65h):** The following mixture was made using the optimized conditions with allyl alcohol (1.0 mL of 0.2M soln., 0.2 mmol) and 1-(4-methoxyphenyl)-1-octyne[103] (129.8 mg, 0.6 mmol, 3.0 eq.) Purified by flash column chromatography using a solvent gradient (0-20% EtOAc/hexanes) to yield the inseparable mixture of products as a clear pale yellow oil (38.4 mg, 70%; 2:1 mixture of regioisomers aryl:alkyl ketone) R_f = 0.24 (40% CH_2Cl_2/hexanes). IR (neat) 3077, 2997, 2956, 2930, 1712, 1672, 1601, 1510, 1254, 1171, 1034 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.94 (d, *J* = 8.9 Hz, 2H, major), 7.12 (d, *J* = 8.7 Hz, 2H, minor), 6.94 (d, *J* = 8.9 Hz, 2H, major), 6.85 (d, *J* = 8.7 Hz, 2H, minor), (ddd, *J* = 17.5, 10.5, 7.0 Hz 1H, major), 5.65 (ddd, *J* = 17.1, 10.2, 6.9 Hz, 1H, minor), 5.01 (dddd, *J* = 17.5, 3.5, 2.0, 1.5 Hz 1H, major), 4.99 (dddd, *J* = 17.5, 3.5, 2.0, 1.5 Hz 1H, minor), 4.97-4.91 (m, 4H, major and minor), 3.87 (s, 3H, major), 3.79 (s, 3H, minor), 3.64 (t, *J* = 7.5 Hz, 1H, minor), 3.44 (tt, *J* = 7.6, 5.8 Hz, 1H, major), 2.79-2.72 (m, 1H, minor), 2.53- 2.45 (m, 1H, major), 2.43-2.36 (m, 1H, minor), 2.36-2.31 (m, 2H, minor), 2.28-2.21 (m, 1H, major), 1.80-1.70 (m, 1H, major), 1.56-1.41 (m, 2H, major and minor), 1.29-1.09 (m, 18 H,

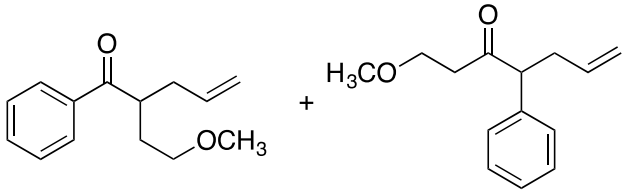
major and minor), 0.88-0.79 (m, 6H, major and minor). ^{13}C NMR (125 MHz, $CDCl_3$): 210.4, 202.5, 163.6, 136.3, 136.3, 130.8, 130.7, 129.5, 116.7, 116.6, 114.4, 114.0, 58.0, 55.7, 55.5, 45.7, 42.0, 36.8, 36.7, 32.4, 31.86, 31.71, 29.7, 28.9, 27.6, 23.9, 22.8, 22.7, 14.3, 14.2. HRMS (DART) Calcd for $C_{18}H_{27}O2$ $(M+H)^+$ 275.2006, found 275.1996.



3-65i ***iso*-3-65i**

4-(4-nitrophenyl)undec-1-en-5-one (3-65i) and **2-allyl-1-(4-nitrophenyl)octan-1-one (*iso*-3-65i):** The following products were obtained using the optimized conditions with allyl alcohol (1.0 mL of 0.2M soln., 0.2 mmol) and 1-(4-nitrophenyl)-1-octyne[106] (138.2 mg, 0.6 mmol, 3.0 eq.) Purified by flash column chromatography using a solvent gradient (0-20% CH_2Cl_2/hexanes) to yield the product as a clear pale yellow oil (57.9 mg 99%; 8:1 mixture of regioisomers alkyl:aryl ketone). Analytical fractions of each were obtained; their characterization is as follows: ***Alkyl Ketone* (3-65i)**: R_f = 0.27 (40% CH_2Cl_2/hexanes). IR (neat) 3079, 2956, 2930, 2858, 1716, 1606, 1521, 1346 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.18 (d, *J* = 8.7 Hz, 2H), 7.40 (d, *J* = 8.8 Hz, 2H), 5.61 (ddt, *J* = 17.1, 10.1, 6.9 Hz, 1H), 5.07-4.91 (m, 2H), 3.85 (t, *J* = 7.5 Hz, 1H), 2.81 (dtt, *J* = 14.2, 7.0, 1.3 Hz, 1H), 2.50-2.42 (m, 1H), 2.38 (dt, *J* = 7.1, 2.2 Hz, 2H), 1.57-1.41 (m, 2H), 1.28–1.09 (m, 8H), 0.82 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 208.7, 147.4, 146.0, 134.8, 129.4, 124.2, 117.8, 58.4, 42.9, 36.9, 31.7, 28.8, 23.7, 22.6, 14.2. HRMS (DART) Calcd for $C_{17}H_{24}NO_3$ $(M+H)^+$ 290.1751, found 290.1745***. Aryl Ketone (iso*-3-65i*)***: R_f = 0.29 (40% CH_2Cl_2/hexanes). IR (neat) 3075, 2929, 2857, 1689, 1526, 1346

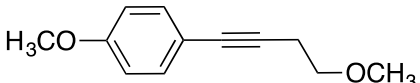
cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.32 (d, *J* = 8.9 Hz, 2H), 8.07 (d, *J* = 8.8 Hz, 2H), 5.72 (ddd, *J* = 17.1, 10.1, 7.1 Hz, 1H), 5.09-4.93 (m, 2H), 3.49 (tt, *J* = 7.5, 5.7 Hz, 1H), 2.58-2.45 (m, 1H), 2.34 – 2.22 (m, 1H), 1.85-1.67 (m, 2H), 1.33-1.11 (m, 8H), 0.91-0.78 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 202.6, 142.2, 135.4, 129.4, 124.2, 124.1, 117.4, 47.0, 36.4, 32.1, 31.8, 29.6, 27.5, 22.7, 14.2. HRMS (DART) Calcd for $C_{17}H_{24}O$ $(M+NH_4)^+$ 307.2016, found 307.2005.



3-65j ***iso*-3-65j**

2-(2-methoxyethyl)-1-phenylpent-4-en-1-one (3-65j) and **1-methoxy-4-phenylhept-6-en-3-one (*iso*-3-65j):** The following products were obtained using the optimized conditions with allyl alcohol (1.0 mL of 0.2M soln., 0.2 mmol) and 4-methoxy-1-phenyl-1-butyne.[107] Purified by flash column chromatography using a solvent gradient (0-20% EtOAc/hexanes) to yield the product as a clear colorless oil (34.5 mg, 79%; 3:1 mixture of regioisomers aryl:alkyl ketone). An analytical fraction of the aryl ketone was obtained; the characterization is as follows: ***Aryl Ketone* (3-65j)**: R_f = 0.65 (30% EtOAc/hexanes). IR (neat) 2928, 1671, 1601, 1508, 1396, 1247, 1171 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.00-7.95 (m, 2H), 7.59-7.53 (m, 1H), 7.49-7.45 (m, 2H), 5.73 (ddt, *J* = 17.1, 10.1, 7.0 Hz, 1H), 5.03 (dd, *J* = 17.0, 1.7 Hz, 1H), 4.97 (dd, *J* = 10.1, 1.7 Hz, 1H), 3.76-3.70 (m, 1H), 3.43-3.38 (m, 1H), 3.28 (ddd, *J* = 9.6, 7.6, 5.1 Hz, 1H), 3.22 (s, 3H), 2.55-2.47 (m, 1H), 2.31-2.23 (m, 1H), 2.07 (dddd, *J* = 13.9, 8.7, 6.2, 5.2 Hz, 1H), 1.81 (ddt, *J* = 14.0, 7.6, 5.3 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 203.9, 137.7, 135.6,

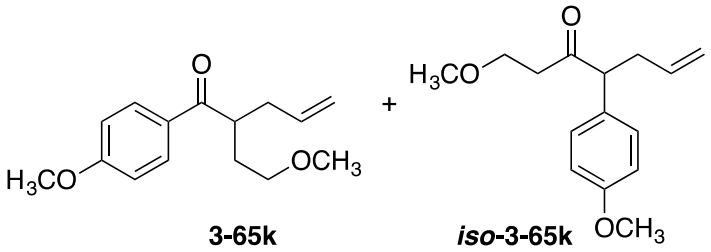
133.1, 128.8, 128.5, 117.2, 70.5, 58.7, 42.7, 37.0, 32.1. HRMS (DART) Calcd for $C_{14}H_{19}O_2$ $(M+H)^+$ 219.1380, found 219.1372. From a mixture of products the following NMR peaks were deduced as the alkyl ketone. ***Alkyl Ketone* (*iso*-3-65j)**: R_f = 0.65 (30% EtOAc/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34-7.30 (m, 2H), 7.22-7.18 (m, 2H), 5.68 -5.61 (ddd, *J* = 17.3, 10.1, 7.0 Hz, 1H), 5.05-4.92 (m, 2H), 3.59 (dt, *J* = 9.6, 6.6 Hz, 1H), 3.51 (dt, *J* = 9.6, 6.3 Hz, 1H), 3.25 (s, 3H), 2.81 (dtt, *J* = 14.3, 7.2, 1.3 Hz, 1H), 2.68-2.56 (m, 2H), 2.47-2.39 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 208.1, 138.3, 135.9, 129.1, 128.6, 127.6, 116.8, 67.7, 59.3, 58.9, 42.0, 36.3.



4-4

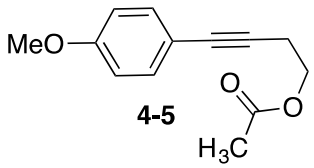
1-methoxy-4-(4-methoxybut-1-yn-1-yl)benzene (4-4): The following compound was made through a related procedure for facile methylation of alcohols.[107] To a flask containing a stir bar and a mixture of MeI (0.31 mL, 5.0 mmol, 2.0 eq.), NaH (60% in mineral oil, 200 mg, 5.0 mmol, 2.0 eq.) and 3.0 mL of THF at room temperature was slowly and carefully added 4-(4-methoxyphenyl)-but-3-yn-1-ol[101] (neat, 440.0 mg, 2.5 mmol, 1.0 eq.). Minor bubbling occurred and the solution was placed in a 40°C oil bath for 1 hr. After this point the solution was cooled to r.t. and slowly quenched with 10 mL of deionized water. The solution was taken up in ether and washed with $NaHCO_3$ and brine, dried over $NaSO_4$, and filtered. Purified by flash column chromatography using a solvent gradient (0-20% EtOAc/hexanes) to yield the product as a clear colorless oil (237.8 mg, 50%). R_f = 0.5 (20% EtOAc/hexanes). IR (neat) 3040, 2931, 2837, 1608, 1506, 1464, 1289, 1246, 1174, 1117 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34 (d, *J* = 8.8 Hz, 2H), 6.81 (d, *J* = 8.8 Hz, 2H), 3.79 (s, 3H), 3.58 (t, *J* = 7.0 Hz, 2H), 3.41 (s, 3H),

2.67 (t, *J* = 7.0 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.3, 133.1, 115.9, 113.9, 85.2, 81.3, 71.1, 58.8, 55.3, 20.8. HRMS (DART) Calcd for $C_{12}H_{15}O_2$ $(M+H)^+$ 191.1067, found 191.1073.



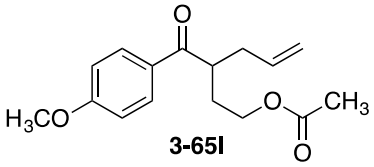
3-65k ***iso*-3-65k**

2-(2-methoxyethyl)-1-(4-methoxyphenyl)pent-4-en-1-one (3-65k) and **1-methoxy-4-(4-methoxyphenyl)hept-6-en-3-one (*iso*-3-65k):** The following products were obtained using the optimized conditions with allyl alcohol (1.0 mL of 0.2M soln., 0.2 mmol) and 1-methoxy-4-(4-methoxybut-1-yn-1-yl)benzene. Purified by flash column chromatography using a solvent gradient (0-20% EtOAc/hexanes) to yield the product as a white crystalline solid (43.2 mg, 87%; 9:1 mixture of regioisomers aryl:alkyl ketone). An analytical fraction of the aryl ketone **3-65k** was obtained; the characterization is as follows: R_f = 0.53 (50% Et_2O/hexanes). IR (neat) 3064, 2925, 2874, 2822, 1682, 1447, 1117 cm^{-1}. ^{1}H NMR (500 MHz, C_6D_6): δ 8.06 (d, *J* = 8.9 Hz, 2H), 6.68-6.63 (d, *J* = 8.8 Hz 2H), 5.76 (ddd, *J* = 17.0, 10.2, 7.0 Hz, 1H), 5.02 (ddt, *J* = 17.0, 2.0, 1.5 Hz, 1H), 4.92 (ddt, *J* = 10.2, 2.0, 1.5 Hz, 1H), 3.74 (dddd, *J* = 8.6, 7.5, 6.1, 5.1 Hz, 1H), 3.24-3.12 (m, 5H), 2.99 (s, 3H), 2.63-2.55 (m, 1H), 2.27-2.19 (m, 1H), 2.20-2.12 (m, 1H), 1.78 (ddt, *J* = 14.0, 7.8, 5.2 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 202.3, 163.7, 135.8, 130.8, 130.7, 117.0, 113.9, 70.5, 58.7, 55.7, 42.2, 37.1, 32.3. HRMS (DART) Calcd for $C_{15}H_{21}O_3$ $(M+H)^+$ 249.1485, found 249.1489.



4-5

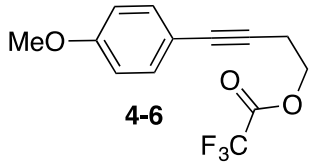
4-(4-methoxyphenyl)but-3-yn-1-yl acetate (4-5): The following compound was made via acetylation of the known alcohol 4-(4-methoxyphenyl)-but-3-yn-1-ol[108]. The procedure is as follows: To a solution of 4-(4-methoxyphenyl)-but-3-yn-1-ol[108] (358.0 mg, 2 mmol, 1.0 eq.), DMAP (12.0 mg, 0.1 mmol, 5 mol%) and pyridine (10 mL) submerged in an ice bath, was added acetic anhydride (0.4 mL, 4.2 mmol, 2.0 eq.). The solution was stirred for 2 hours then quenched with $NaHCO_3$ (10 mL), and diluted with EtOAc (30 mL). The organic phase was then washed with $CuSO_4$ (3x10mL). The organic phase was then dried over $NaSO_4$, and filtered. Purified by flash column chromatography using a solvent gradient (0-20% EtOAc/hexanes) to yield the product as a clear colorless oil (100.0 mg, 23%). R_f = 0.44 (20% EtOAc/hexanes). IR (neat) 2960, 2838, 1737, 1606, 1509, 1442, 1234 $cm^{-1.}$ ^1H NMR (300 MHz, $CDCl_3$): δ 7.33 (d, *J* = 8.9 Hz, 2H), 6.81 (d, *J* = 8.9 Hz, 2H), 4.24 (t, *J* = 7.0 Hz, 2H), 3.79 (s, 3H), 2.73 (t, *J* = 7.0 Hz, 2H), 2.09 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0, 159.4, 133.1, 115.6, 114.0, 84.0, 81.9, 62.7, 55.4, 21.1, 20.1.



3-65l

3-(4-methoxybenzoyl)hex-5-en-1-yl acetate (3-65l): The following product was obtained using the optimized conditions with allyl alcohol (1.0 mL of 0.15 M soln., 0.15 mmol) and 4-(4-methoxyphenyl)but-3-yn-1-yl acetate **4-5** (100 mg, 0.45 mmol, 3.0 eq.). Purified by flash column chromatography on florisil using a solvent gradient (0-20%

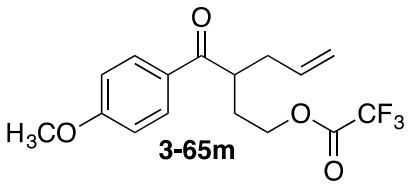
EtOAc/hexanes) to yield the product as a clear oil (36.0 mg, 65% as an 8:1 mixture of regioisomers aryl:alkyl ketone). Data for the major isomer reported: R_f = 0.45 (20% EtOAc/hexanes). IR (neat) 3077, 2936, 2842, 1735, 1670, 1598, 1510, 1365, 1234, 1169, 1029 $cm^{-1.}$ ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.94 (d, *J* = 8.8 Hz, 2H), 6.94 (d, *J* = 8.9 Hz, 2H), 5.72 (ddt, *J* = 17.0, 10.1, 7.1 Hz, 1H), 5.07-5.02 (m, 1H), 5.01 -4.98 (m, 1H), 4.09 (dt, *J* = 11.3, 6.4 Hz, 1H), 4.01 (dt, *J* = 11.2, 6.5 Hz, 1H), 3.87 (s, 3H), 3.58 (dtd, *J* = 8.7, 6.7, 5.0 Hz, 1H), 2.53-2.45 (m, 1H), 2.30-2.22 (m, 1H), 2.21-2.11 (m, 1H), 1.93 (s, 3H), 1.86 (dtd, *J* = 11.4, 6.4, 4.8 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 201.2, 171.1, 163.8, 135.3, 130.8, 130.1, 129.6, 117.4, 114.6, 114.1, 62.89, 55.70, 42.45, 37.19, 30.70, 21.04.



4-6

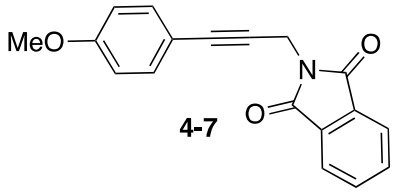
4-(4-methoxyphenyl)but-3-yn-1-yl 2,2,2-trifluoroacetate (4-6): To a solution of 4-(4-methoxyphenyl)-but-3-yn-1-ol[108] (358.0 mg, 2 mmol, 1.0 eq.), DMAP (12.0 mg, 0.1 mmol, 5 mol%) and pyridine (10 mL) submerged in an ice bath, was added acetic anhydride (0.4 mL, 4.2 mmol, 2.0 eq.). The solution was stirred for 2 hours then quenched with $NaHCO_3$ (10 mL), and diluted with EtOAc (30 mL). The organic phase was then washed with $CuSO_4$ (3x10mL). The organic phase was then dried over $NaSO_4$, and filtered. Purified by flash column chromatography using a solvent gradient (0-20% EtOAc/hexanes) to yield the product as a clear colorless oil (100.0 mg, 23%). R_f = 0.61 (20% EtOAc/hexanes). IR (neat) 2970, 2841, 1785, 1607, 1509, 1447, 1142 $cm^{-1.}$ ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33 (d, *J* = 8.6 Hz, 2H), 6.83 (d, *J* = 8.9 Hz, 1H), 4.52 (t, *J* = 6.9 Hz, 2H), 3.80 (s, 3H), 2.86 (t, *J* = 6.9 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$)

δ159.7, 133.2, 116.6, 115.2, 114.1, 82.9, 82.1, 65.8, 55.4, 19.8.^{19}F NMR (282 MHz, $CDCl_3$): δ75.39.



3-65m

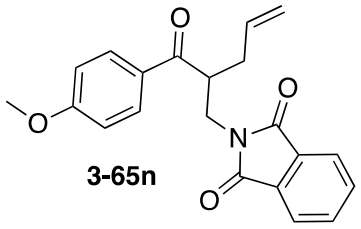
3-(4-methoxybenzoyl)hex-5-en-1-yl 2,2,2-trifluoroacetate (3-65m): The following product was obtained using the optimized conditions with allyl alcohol (1.0 mL of 0.16 M soln., 0.16 mmol) and 4-(4-methoxyphenyl)but-3-yn-1-yl 2,2,2-trifluoroacetate **4-6** (130 mg, 0.48 mmol, 3.0 eq.). Purified by flash column chromatography on florisil using a solvent gradient (0-50% EtOAc/hexanes) to yield the product as a clear oil (26.0 mg, 50%; >25:1 mixture of regioisomers aryl:alkyl ketone). R_f = 0.35 (20% EtOAc/hexanes). IR (neat) 2984, 1736, 1673, 1601, 1237, 1044 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.04-7.93 (m, 2H), 6.97-6.92 (m, 2H), 5.74 (ddt, *J* = 17.1, 10.1, 7.1 Hz, 1H), 5.07-4.96 (m, 2H), 3.87 (s, 3H), 3.82-3.57 (m, 3H), 2.52 (dt, *J* = 14.0, 6.9 Hz, 1H), 2.27 (dt, *J* = 14.1, 7.1 Hz, 1H), 2.10-2.00 (m, 1H), 1.85-1.74 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ202.5, 163.8, 135.7, 130.9, 130.3, 124.5, 117.1, 114.6, 60.92, 55.70, 42.35, 37.04, 34.56, 29.05. ^{19}F NMR (282 MHz, $CDCl_3$): δ84.08.



4-7

2-(3-(4-methoxyphenyl)prop-2-yn-1-yl)isoindoline-1,3-dione (4-7): The following compound was made via sonogashira coupling between N-propargylphthalimide[109] and 4-iodoanisole, the reaction is as follows: To a flask

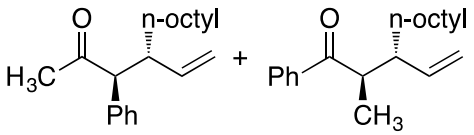
containing N-propargylphthalimide (500 mg, 2.7 mmol, 1.0 eq.), 4-iodoanisole (631 mg, 2.7 mmol, 1.0 eq.), PPh_3PdCl_2 (37.0 mg, 0.05 mmol, 2 mol%), CuI (20.0 mg, 4 mol%) and CH_3CN (12 mL) under a N_2 atmosphere, was added Et_3N (1.3 mL) at room temperature. The solution was stirred for 2 hours at room temperature then the volatiles were evaporated and the solid residue was triturated with EtOAc to give an light brown solid that was used without further purification (668.0 mg, 85%). R_f = 0.71 (CH_2Cl_2). IR (neat) 2971, 2943, 1768, 1715, 1604, 1508, 1390, 1252 $cm^{-1.}$ ^1H NMR (500 MHz, $CDCl_3$): δ 7.89 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.73 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.35 (d, *J* = 8.8 Hz, 2H), 6.79 (d, *J* = 8.8 Hz, 2H), 4.66 (s, 2H), 3.78 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.40, 165.61, 165.55, 159.95, 134.43, 134.33, 133.62, 132.35, 123.73, 114.62, 114.03, 110.22, 83.09, 81.45, 55.47, 28.16.



3-65n

2-(2-(4-methoxybenzoyl)pent-4-en-1-yl)isoindoline-1,3-dione (3-65n) The following product was obtained using the optimized conditions with allyl alcohol (1.0 mL of 0.12M soln., 0.12 mmol) and 2-(3-(4-methoxyphenyl)prop-2-yn-1-yl)isoindoline-1,3-dione **4-7** (107 mg, 0.6 mmol, 3.0 eq.). Purified by flash column chromatography using a solvent gradient (20-100% CH_2Cl_2/hexanes) to yield the product as a clear oil (31.3 mg, 72%; >25:1 mixture of regioisomers aryl:alkyl ketone). R_f = 0.41 (40% EtOAc/hexanes). IR (neat) 3076, 2935, 2842, 1711, 1671, 1598, 1511, 1172 $cm^{-1.1}H$ NMR (500 MHz, $CDCl_3$): δ 8.03-7.98 (m, 2H), 7.85-7.81 (m, 2H), 7.74-7.69 (m, 2H), 6.94-6.89 (m, 2H), 5.75 (ddt, *J* = 17.1, 10.2, 6.9 Hz, 1H), 5.05 (d, *J* = 17.3 Hz, 1H), 4.96 (d, *J* = 10.1 Hz,

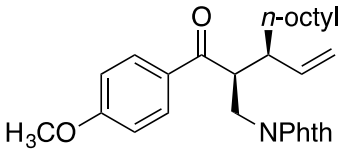
1H), 4.15 (p, *J* = 6.8 Hz, 1H), 4.03 (dd, *J* = 13.5, 6.5 Hz, 1H), 3.94-3.87 (m, 1H), 3.85 (s, 3H), 2.64 (dt, *J* = 14.3, 7.0 Hz, 1H), 2.34 (dt, *J* = 14.0, 6.6 Hz, 1H).[13]C NMR (125 MHz, $CDCl_3$): δ 199.2, 168.5, 163.9, 134.8, 134.2, 132.1, 131.0, 129.9, 123.5, 117.4, 114.1, 55.67, 44.09, 39.93, 34.68.



3-65o ***iso*-3-65o**

***anti*-3-phenyl-4-vinyldodecan-2-one (3-65o)** and ***anti*-2-methyl-1-phenyl-3-vinylundecan-1-one (*iso*-3-65o)** The following compounds were made with the optimized conditions with (*E*)-undec-2-en-1-ol[99] (1.0 mL of 0.2M soln., 0.2 mmol) and 1-phenyl-1-propyne (70 mg, 0.6 mmol, 3.0 eq.). Purified by flash column chromatography using a solvent gradient (0-20% CH_2Cl_2/hexanes) to yield the mixture of products as a clear colorless oil (45.0 mg, 78%; 4:1 mixture of regioisomers alkyl:aryl ketone; only one observable diastereomer for each regioisomer). Analytical fractions of each were obtained; their characterization is as follows: ***Alkyl Ketone* (3-65o)**: R_f = 0.40 (40% CH_2Cl_2/hexanes). 2926, 2856, 1715, 1455, 1354, 1151 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32-7.22 (m, 2H), 7.22 -7.14 (m, 3H), 5.26 (ddd, *J* = 16.9, 10.4, 9.3 Hz, 1H), 4.82 -4.72 (m, 2H), 3.59 (d, *J* = 10.2 Hz, 1H), 2.92-2.79 (m, 1H), 2.10 (s, 3H), 1.49-1.14 (m, 12H), 0.84 (t, *J* = 6.2 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 208.3, 139.5, 137.5, 129.4, 128.7, 127.4, 116.7, 64.8, 46.1, 33.6, 32.1, 30.5, 29.8, 29.8, 29.5, 27.4, 22.9, 14.3. HRMS (DART) Calcd for $C_{17}H_{32}O$ $(M+H)^+$ 287.2369, found 287.2362. ***Aryl Ketone* (*iso*-3-65o)**: R_f = 0.42 (40% CH_2Cl_2/hexanes). IR (neat) 3067, 2927, 2855, 1684, 1458, 1355, 1214 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.97-7.92 (m, 2H), 7.60-

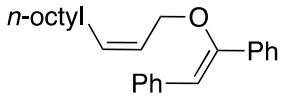
7.53 (m, 1H), 7.51-7.44 (m, 2H), 5.51 (ddd, 17.0, 10.3, 9.6 1H), 5.07 (dd, *J* = 10.3, 2.0 Hz, 1H), 4.95 (ddd, *J* = 17.0, 2.0, 0.7 Hz, 1H), 3.42 (q, *J* = 7.0 Hz, 1H), 2.52-2.39 (m, 1H), 1.33-1.15 (m, 14H), 1.11 (d, *J* = 6.9 Hz, 3H), 0.86 (t, *J* = 6.5 Hz 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 204.6, 139.6, 137.6, 133.0, 128.8, 128.4, 116.9, 47.3, 44.7, 33.4, 32.1, 29.7, 29.5, 27.7, 22.9, 15.2, 14.3. HRMS (DART) Calcd for $C_{20}H_{31}O$ $(M+H)^+$ 287.2369, found 287.2359.



3-65p

***syn*-2-(4-methoxybenzoyl)-3-vinylundecyl)isoindoline-1,3-dione (3-65p)** The following products were obtained using the optimized conditions with (*Z*)-undec-2-en-1-ol[100] **(3-60)** (1.0 mL of 0.2M soln., 0.2 mmol) and **4-7** (180 mg, 0.6 mmol, 3.0 eq.). Purified by flash column chromatography using a solvent gradient (20-100% CH_2Cl_2/hexanes) to yield the product as a clear oil (56.0 mg, 59%, >25:1 *dr;* >25:1 mixture of regioisomers aryl:alkyl ketone). R_f = 0.2 (80% CH_2Cl_2/hexanes). IR (neat) 3075, 2925, 2854, 1773, 1712, 1671, 1598, 1393, 1170 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): 7.90-7.82 (m, 2H), 7.75 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.64 (dd, *J* = 5.5, 3.0 Hz, 2H), 6.83 (d, *J* = 8.9 Hz, 2H), 5.71 (ddd, *J* = 17.1, 10.2, 9.0 Hz, 1H), 5.17-4.74 (m, 2H), 4.28-4.05 (m, 2H), 3.87-3.75 (m, 4H), 2.50-2.36 (m, 1H), 1.55-1.44 (m, 1H), 1.36-1.02 (m, 10H), 0.86 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 199.8, 168.4, 163.6, 138.9, 134.0, 132.1, 131.2, 130.8, 123.4, 117.0, 113.9, 55.6, 47.6, 45.8, 38.6, 32.0, 31.3, 29.7, 29.6, 29.5, 27.5, 22.9, 14.3.

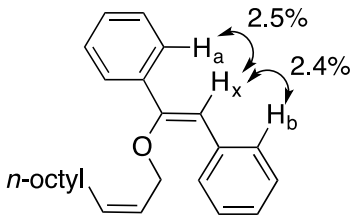
Epimerization experiments (Figure 3-16): Single diastereomers of ketones **3-61** and **3-62** were obtained by careful separation via column chromatography. An example of these experiments is as follows: A pressure tube (screw cap) containing a stir bar was taken from the oven and placed directly into a glovebox. To this vessel was added 1,3-bis(2,6-diisopropylphenyl-imidazol-2-ylidene)gold(I) chloride (6.2 mg, 0.01 mmol, 5 mol%), and silver tetrafluoroborate (1.9 mg, 0.01 mmol, 5 mol%). The vessel was capped with a septum and then taken out of the glovebox where it was immediately placed under a dry nitrogen atmosphere. 0.5 mL of THF was added to the tube and the mixture was left to stir ~10 mins to activate the complex. After this time a solution of ketone **3-61** or **3-62** (0.2 mmol in 0.5 mL of THF) was transferred to the tube, and the vessel was then placed in a 65 °C oil bath and left to stir for 15 hrs. The tube was then sealed with a screwcap and placed in a 120 °C oil bath for 6 hrs (behind a safety shield). After cooling to room temperature the screwcap was removed and the solution was filtered over a plug of silica with EtOAc. The solution was then evaporated, and the crude was characterized by 1H NMR (500 MHz) which showed exclusively the unaltered isomers **3-61** and **3-62** respectively.



3-74

((*Z*)-1-((*Z*)-undec-2-en-1-yloxy)ethene-1,2-diyl)dibenzene enol (3-74; adduct of **3-56** + **3-60)**: The following enol was obtained using the conditions discussed in Table 2, Entry 4. A pressure tube (screw cap) containing a stir bar was taken from the oven and placed directly into a glovebox. To this vessel was added 1,3-bis(2,6-diisopropylphenyl-imidazol-2-ylidene)gold(I) chloride (6.2 mg, 0.01 mmol, 5 mol%), and

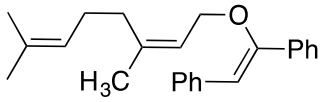
silver tetrafluoroborate (1.9 mg, 0.01 mmol, 5 mol%). The vessel was capped with a septum and then taken out of the glovebox where it was immediately placed under dry nitrogen atmosphere. 0.5 mL of THF was added to the tube and the mixture was left to stir ~10 mins to activate the complex. After this time a solution of alkyne (107.0 mg, 0.6 mmol, 3.0 eq. in 0.5 mL of THF) was transferred to the tube, and the vessel was then placed in a 65 °C oil bath. (*Z*)-undec-2-en-1-ol[100] (**3-60**) (1.0 mL of 0.2M soln., 0.2 mmol)) was then added slowly over 12 hrs. via syringe pump (~0.8 mL/hr). After the addition was complete the solution was allowed to stir at this temperature for an additional 6 hrs. After cooling the to room temperature the solution was filtered over a plug of silica with CH_2Cl_2. The solution was then evaporated, and the mixture was purified by flash column chromatography using a solvent gradient (0-20% CH_2Cl_2/hexanes) to give the desired product **3-62** (23.0 mg, 33%), and **3-74** (25.8 mg, 37%) as a clear, colorless oil. Characterization of the enol **3-74** is as follows: R_f = 0.70 (40% CH_2Cl_2/hexanes). IR (neat) 3057, 3022, 2925, 2855, 1634, 1600, 1492, 1448, 1199, 1058, 1026, 914 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.77 (d, *J* = 7.5 Hz, 2H), 7.60 (d, *J* = 7.0 Hz, 2H), 7.42 (t, *J* = 7.0 Hz, 2H), 7.34-7.37 (m, 3H), 7.22 (t, *J* = 7.5 Hz, 1H) 6.14 (s, 1H), 5.69-5.74 (m, 1H), 5.57-5.63 (m, 1H), 4.38 (d, *J* = 6.5 Hz, 2H), 1.95 – 1.88 (m, 1H), 1.31-1.18 (m, 14H), 0.86 (t, *J* = 7.0, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.3, 137.0, 136.3, 134.7, 128.9, 128.6, 128.5, 128.4, 126.8, 126.7, 125.0, 113.7, 66.2, 32.0, 29.7, 29.6, 29.5, 29.4, 27.7, 22.8, 14.3; HRMS (DART) Calcd for $C_{25}H_{33}O$ $(M+H)^+$ 349.2526, found 349.2523.



3-74

Figure 4-2. Confirmation of Enol geometry via NOE experiment

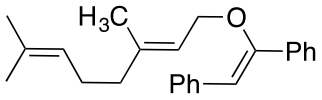
The *Z-enol-configuration* of **3-74** is established based on NOE DIFF experiments. The NOEs between vinyl-H (s = 6.14 ppm) and *ortho*-hydrogens (□ = 7.77 (**H_a**), 7.60 (**H_b**) ppm) of the phenyl groups of **3-74** is clearly seen allowing for the elucidation of the *Z*-enol configuration.



3-75

((*Z*)-1-(((*Z*)-3,7-dimethylocta-2,6-dien-1-yl)oxy)ethene-1,2-diyl)dibenzene (3-75): A test tube containing a stir bar was taken from the oven and placed directly into a glovebox. To this vessel was added 1,3-bis(2,6-diisopropylphenyl-imidazol-2-ylidene)gold(I) chloride (12.4 mg, 0.02 mmol, 5 mol%), and silver tetrafluoroborate (4.0 mg, 0.02 mmol, 5 mol%). The vessel was capped with a septum and then taken out of the glovebox where it was immediately placed under dry nitrogen atmosphere. 1.0 mL of THF was added to the tube and the mixture was left to stir ~10 mins to activate the complex. After this time a solution of diphenylacetylene (107.0 mg, 0.6 mmol, 3.0 eq. in 1.0 mL of THF) was transferred to the tube, and the vessel was then placed in a 65 °C oil bath. A solution of nerol (1.0 mL of 0.4M soln., 0.4 mmol) was then added slowly over 12 hrs. via syringe pump (~0.8 mL/hr). After the addition was complete the solution was allowed to stir at this temperature for an additional 3 hrs. After cooling the

to room temperature the solution was filtered over a plug of silica with CH_2Cl_2. The solution was then evaporated, and the mixture was purified by flash column chromatography using a solvent gradient (0-4% CH_2Cl_2/hexanes) to give the desired enol **3-75** as a clear, colorless oil (45.0 mg, 34%). R_f = 0.25 (20% CH_2Cl_2/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.81-7.76 (m, 2H), 7.62-7.58 (m, 2H), 7.44-7.40 (m, 2H), 7.39-7.34 (m, 3H), 7.25-7.21 (m, 1H), 6.14 (s, 1H), 5.55 (td, *J* = 7.2, 1.7 Hz, 1H), 5.02 (ddq, *J* = 6.9, 5.3, 1.6 Hz, 1H), 4.32 (dd, *J* = 6.8, 1.3 Hz, 2H), 2.06-1.96 (m, 4H), 1.78 (s, 3H), 1.65 (s, 3H), 1.55 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.5, 141.3, 137.2, 136.4, 128.9, 128.6, 128.5, 128.4, 126.8, 126.7, 123.9, 121.2, 113.6, 67.0, 32.4, 26.8, 25.8, 23.7, 17.8.



3-76

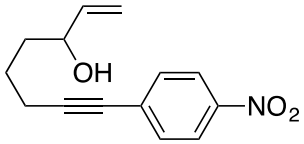
((*Z*)-1-(((*E*)-3,7-dimethylocta-2,6-dien-1-yl)oxy)ethene-1,2-diyl)dibenzene (3-76): A test tube containing a stir bar was taken from the oven and placed directly into a glovebox. To this vessel was added 1,3-bis(2,6-diisopropylphenyl-imidazol-2-ylidene)gold(I) chloride (12.4 mg, 0.02 mmol, 5 mol%), and silver tetrafluoroborate (4.0 mg, 0.02 mmol, 5 mol%). The vessel was capped with a septum and then taken out of the glovebox where it was immediately placed under dry nitrogen atmosphere. 1.0 mL of THF was added to the tube and the mixture was left to stir ~10 mins to activate the complex. After this time a solution of diphenylacetylene (107.0 mg, 0.6 mmol, 3.0 eq. in 1.0 mL of THF) was transferred to the tube, and the vessel was then placed in a 65 °C oil bath. A solution of geraniol (1.0 mL of 0.4M soln., 0.4 mmol) was then added slowly over 12 hrs. via syringe pump (~0.8 mL/hr). After the addition was complete the

solution was allowed to stir at this temperature for an additional 3 hrs. After cooling the to room temperature the solution was filtered over a plug of silica with CH_2Cl_2. The solution was then evaporated, and the mixture was purified by flash column chromatography using a solvent gradient (0-4% CH_2Cl_2/hexanes) to give the desired enol **3-75** as a clear, colorless oil (33.0 mg, 25%). R_f = 0.22 (20% CH_2Cl_2/hexanes) ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.78-7.73 (m, 2H), 7.60-7.55 (m, 2H), 7.43-7.29 (m, 5H), 7.22-7.16 (m, 1H), 6.10 (s, 1H), 5.54-5.45 (m, 1H), 5.12-5.04 (m, 1H), 4.35-4.28 (m, 2H), 2.12-1.98 (m, 4H), 1.67 (s, 3H), 1.59 (s, 3H), 1.52 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.4, 141.4, 137.2, 136.4, 131.9, 128.9, 128.6, 128.5, 128.4, 126.9, 126.6, 124.1, 120.2, 113.7, 67.2, 39.8, 26.6, 25.9, 17.9, 16.6.

Sequential Gold-catalyzed Enol Formation/Ru-catalyzed Allylation to form Functionalized Cyclohexanones and Tetrahydropyrans

Optimized conditions: A flask containing a stir bar was taken from the oven and placed directly into a glovebox. To this vessel was added 1,3-bis(2,6-diisopropylphenyl-imidazol-2-ylidene)gold(I) chloride (6.2 mg, 0.01 mmol, 5 mol%), and silver tetrafluoroborate (1.9 mg, 0.01 mmol, 5 mol%). The vessel was capped with a septum and then taken out of the glovebox where it was immediately placed under dry nitrogen atmosphere. 0.5 mL of THF was added to the tube and the mixture was left to stir ~10 mins to activate the complex. After this time a solution of alkyne (0.2 mmol in 0.5 mL of THF) was transferred to the active gold-complex at r.t. During this time 0.3 mL of acetone (previously distilled and degassed via freeze-pump-thaw) was added to a mixture of $[CpRu(MeCN)_3]PF_6$ (4.4 mg, 0.01 mmol, 5 mol%) and quinaldic acid (1.7 mg, 0.01 mmol, 5 mol%). The ruthenium solution was left to stir at r.t. for 30 mins. to form the active complex. After the gold reaction shows full conversion by TLC the solution

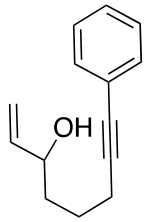
was filtered over a plug of florisil with EtOAc. The crude reaction was then evaporated, and the crude enol was then transferred to a solution of the active ruthenium complex with 0.3 mL of acetone (previously distilled and deoxygenated via freeze-pump-thaw) and 0.6 mL of THF (distilled over Na, benzophenone). The ruthenium solution is left to stir at r.t. until TLC shows full conversion of enol ether to the product. The crude mixture is then filtered over a plug of florisil with EtOAc, evaporated and purified via flash column chromatography.



3-92a

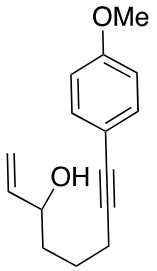
8-(4-nitrophenyl)oct-1-en-7-yn-3-ol (3-92a): A flask containing bis(triphenylphosphine)palladium(II) dichloride (37.1 mg, 0.05 mmol, 1.5 mol%) and copper (I) iodide (17.6 mg, 3 mol%), and 1-iodo-4-nitrobenzene (279.1 mg, 1.1 mmol, 1.1 eq.) was evacuated and backfilled three times with dry nitrogen. The solids were dissolved in 5.0 mL of CH_3CN and oct-1-en-7-yn-3-ol[110] (134.0 mg, 1.07, 1.0 eq) was added neat to the flask. Et_3N (0.5 mL, 3.6 mmol, 3.6 eq.) was added portionwise to the solution at room temperature. The solution was left to stir at room temperature for 1 hour after which time the solvents were removed under vacuum. Purified by flash chromatography using a solvent gradient (15-35% EtOAc/hexanes) to yield the product as a clear, slightly yellow oil (221.4 mg, 84%). R_f = 0.40 (30% EtOAc/hexanes). IR (neat) 3404, 3079, 2935, 2226, 1593, 1514, 1339, 852, 734 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 8.16 (m, 2H), 7.51 (m, 2H), 5.90 (ddd, J = 6.0, 10.2, 16.8 Hz, 1H), 5.13-5.29

(m, 2H), 4.18 (m, 1H), 2.50 (m, 2H) 1.66-1.79 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.0, 143.8, 137.7, 128.2, 123.8, 116.3, 79.1, 30.0, 30.0, 21.0.



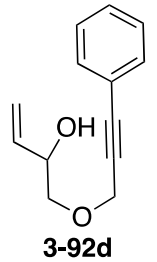
3-92b

8-phenyloct-1-en-7-yn-3-ol (3-92b): The following compound was made under standard sonogashira coupling conditions with oct-1-en-7-yn-3-ol[110] (250.0 mg, 2.0 mmol, 1.0 eq.) and iodobenzene (0.33 mL, 2.9 mmol, 1.4 eq.) PPh_3PdCl_2 (14.0 mg, 0.05 mmol, 1 mol%), CuI (7.6 mg, 0.04 mmol, 2 mol%) and CH_3CN (5 mL) under a N_2 atmosphere, was added Et_3N (0.5 mL) at room temperature. The solution was stirred overnight at room temperature then the volatiles were evaporated and the solid residue was purified by flash chromatography using a solvent gradient (0-20% EtOAc/hexanes) to yield the product as a clear, colorless oil (501.0 mg, 83%). R_f = 0.40 (20% EtOAc/hexanes). IR (neat) 3369, 3080, 2933, 2869, 1598, 1490, 1442, 1429, 1330 cm^{-1}. ^{1}H NMR (300 MHz, CDCl3): δ 7.37-7.40 (m, 2H), 7.25-7.30 (m, 3H), 5.90 (m, 1H), 5.25 (dt, J = 1.5, 17.1 Hz, 1H), 5.13 (dd, J = 1.2, 10.5 Hz, 1H), 4.17 (m, 1H), 2.46 (m, 2H), 1.66-1.75 (m, 4H). ^{13}C NMR (75 MHz, CDCl3): δ 141.2, 131.7, 128.4, 127.7, 124.1, 115.1, 90.0, 81.2, 73.0, 36.3, 24.8, 19.5; HRMS (ESI) Calcd for $C_{20}H_{31}O$ $(M+H)^+$ 201.1274, found 210.1277.



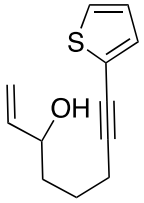
3-92c

8-(4-methoxyphenyl)oct-1-en-7-yn-3-ol (3-92c): The following compound was made under standard sonogashira coupling conditions with oct-1-en-7-yn-3-ol[110] (250.0 mg, 2.0 mmol, 1.0 eq.) and iodobenzene (0.33 mL, 2.9 mmol, 1.4 eq.) PPh_3PdCl_2 (14.0 mg, 0.05 mmol, 1 mol%), CuI (7.6 mg, 0.04 mmol, 2 mol%) and CH_3CN (5 mL) under a N_2 atmosphere, was added Et_3N (0.5 mL) at room temperature. The solution was stirred overnight at room temperature then the volatiles were evaporated and the solid residue was purified by flash chromatography using a solvent gradient (0-20% EtOAc/hexanes) to yield the product as a clear, colorless oil (228.0 mg, 90%). R_f = 0.40 (20% EtOAc/hexanes). IR (neat): 3377, 2935, 2886, 2838, 1607, 1509, 1246, 1033 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.32 (d, *J* = 8.8 Hz, 2H), 6.81 (d, *J* = 8.8 Hz, 2H), 5.89 (ddd, *J* = 17.3, 10.4, 6.2 Hz, 1H), 5.24 (dt, *J* = 17.2, 1.4 Hz, 1H), 5.12 (dt, *J* = 10.4, 1.3 Hz, 1H), 4.17 (qt, *J* = 6.0, 1.3 Hz, 1H), 3.79 (s, 3H), 2.46-2.40 (m, 2H), 1.76-1.61 (m, 4H).^{13}C NMR (125 MHz, $CDCl_3$): δ 159.2, 141.2, 133.1, 116.3, 115.0, 114.0, 88.4, 80.9, 73.0, 55.4, 36.3, 24.9, 19.5.



3-92d

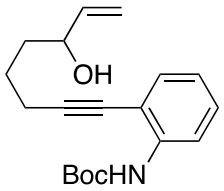
1-((3-phenylprop-2-yn-1-yl)oxy)but-3-en-2-ol (3-92d): The following compound was made under standard sonogashira coupling conditions with 1-(prop-2-yn-1-yloxy)but-3-en-2-ol[110] (252.0 mg, 2.0 mmol, 1.0 eq.) and iodobenzene (0.33 mL, 2.9 mmol, 1.4 eq.) PPh_3PdCl_2 (14.0 mg, 0.05 mmol, 1 mol%), CuI (7.6 mg, 0.04 mmol, 2 mol%) and CH_3CN (5 mL) under a N_2 atmosphere, was added Et_3N (0.5 mL) at room temperature. The solution was stirred overnight at room temperature then the volatiles were evaporated and the solid residue was purified by flash chromatography using a solvent gradient (0-20% EtOAc/hexanes) to yield the product as a clear, colorless oil (501.0 mg, 83%). R_f = 0.61 (30% EtOAc/hexanes). IR (neat) 3405, 3062, 2911, 2224, 1599, 1490, 1070 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.49-7.41 (m, 2H), 7.35-7.28 (m, 3H), 5.87 (dddd, *J* = 17.3, 10.6, 5.6, 0.6 Hz, 1H), 5.39 (dtd, *J* = 17.3, 1.5, 0.6 Hz, 1H), 5.22 (dtd, *J* = 10.6, 1.5, 0.6 Hz, 1H), 4.44 (dd, *J* = 2.4, 0.6 Hz, 2H), 4.42-4.36 (m, 1H), 3.70 (ddd, *J* = 9.6, 3.3, 0.6 Hz, 1H), 3.50 (ddd, *J* = 9.6, 7.8, 0.6 Hz, 1H), 2.47 (br s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 136.6, 132.0, 128.7, 128.5, 122.6, 116.8, 86.9, 84.8, 74.0, 71.6, 59.5.



3-92e

8-(thiophen-2-yl)oct-1-en-7-yn-3-ol (3-92e): The following compound was made under standard sonogashira coupling conditions with oct-1-en-7-yn-3-ol[110] (206.4 mg, 1.6 mmol, 1.0 eq.) and 2-iodothiophene (0.19 mL, 1.8 mmol, 1.1 eq.) PPh_3PdCl_2 (17.7 mg, 0.02 mmol, 1.5 mol%), CuI (10.0 mg, 0.05 mmol, 3 mol%) and CH_3CN (5 mL) under a N_2 atmosphere, was added Et_3N (0.5 mL) at room temperature. The solution

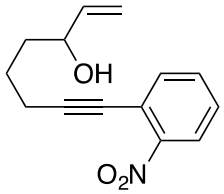
was stirred overnight at room temperature then the volatiles were evaporated and the solid residue was purified by flash chromatography using a solvent gradient (0-15% EtOAc/hexanes) to yield the product as a clear, colorless oil (297.0 mg, 87%). R_f = 0.40 (20% EtOAc/hexanes). IR (neat) 3334, 3076, 2931, 2865, 2226, 1643, 1518, 1427, 1190, 989, 922 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.16 (dd, *J* = 5.2, 1.1 Hz, 1H), 7.11 (dd, *J* = 3.6, 1.1 Hz, 1H), 6.93 (dd, *J* = 5.2, 3.6 Hz, 1H), 5.88 (ddd, *J* = 16.9, 10.4, 6.2 Hz, 1H), 5.24 (dt, *J* = 17.2, 1.4 Hz, 1H), 5.13 (dt, *J* = 10.4, 1.3 Hz, 1H), 4.15 (d, *J* = 5.9 Hz, 1H), 2.46 (td, *J* = 6.6, 3.3 Hz, 2H), 1.80-1.61 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 141.2, 131.2, 126.9, 126.1, 124.2, 115.1, 94.1, 74.3, 73.0, 36.2, 24.6, 19.8.



3-92h

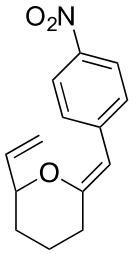
***tert*-butyl (2-(6-hydroxyoct-7-en-1-yn-1-yl)phenyl)carbamate** (**3-92h**): The following compound was made under standard sonogashira coupling conditions with oct-1-en-7-yn-3-ol[110] (100.0 mg, 0.81 mmol, 1.0 eq.) and *N*-Boc-2-iodoaniline (299 mg, 0.93 mmol, 1.1 eq.) PPh_3PdCl_2 (7.0 mg, 0.01 mmol, 1 mol%), CuI(3.0 mg, 0.02 mmol, 2 mol%) and CH_3CN (5 mL) under a N_2 atmosphere, was added Et_3N (0.5 mL) at room temperature. The solution was stirred overnight at room temperature then the volatiles were evaporated and the solid residue was purified by flash column chromatography using a solvent gradient (0-40% EtOAc/hexanes) to yield the product as a viscous oil (135 mg, 50%). R_f = 0.71 (CH_2Cl_2). IR (neat) 2971, 2943,1768, 1715, 1604, 1508, 1390, 1252 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 8.09 (d, *J* = 8.4 Hz, 1H), 7.36 -7.18 (m, 2H), 6.92 (td, *J* = 7.6, 1.2 Hz, 1H), 5.90 (ddd, *J* = 17.3, 10.4, 6.1 Hz, 1H), 5.26 (dt, *J* = 17.2,

1.4 Hz, 1H), 5.13 (dt, *J* = 10.4, 1.4 Hz, 1H), 4.19 (d, *J* = 5.8 Hz, 1H), 2.59-2.50 (m, 2H), 1.82-1.65 (m, 4H), 1.54 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ152.7, 141.2, 139.6, 131.8, 129.0, 122.2, 117.6, 115.1, 112.0, 97.1, 81.0, 76.6, 72.9, 36.2, 28.5, 24.7, 19.7.



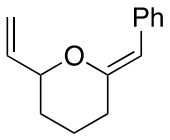
3-92i

8-(2-nitrophenyl)oct-1-en-7-yn-3-ol (3-92i): The following compound was made under standard sonogashira coupling conditions with oct-1-en-7-yn-3-ol[110] (100.0 mg, 0.81 mmol, 1.0 eq.), 1-bromo-2-nitrobenzene (202.0 mg, 1.0 mmol, 1.0 eq.), PPh_3PdCl_2 (40.0 mg, 0.05 mmol, 5 mol%), CuI (18.0 mg, 0.09 mmol, 9 mol%) and Et_3N (2.0 mL) under a N_2 atmosphere at room temperature. The solution was stirred overnight at room temperature then the volatiles were evaporated and the solid residue was purified by flash column chromatography using a solvent gradient (30% EtOAc/hexanes) to yield the product as a viscous oil (96.4 mg, 40%). R_f = 0.31 (30% EtOAc/hexanes). IR 3379, 3078, 2937, 2865, 2228, 1608, 1567, 1520, 1341, 743. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.96 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.59-7.47 (m, 2H), 7.39 (ddd, *J* = 8.7, 7.2, 1.8 Hz, 1H), 5.90 (ddd, *J* = 17.1, 10.4, 6.1 Hz, 1H), 5.25 (dt, *J* = 17.2, 1.4 Hz, 1H), 5.12 (dt, *J* = 10.4, 1.4 Hz, 1H), 4.30-4.11 (m, 1H), 2.63-2.47 (m, 2H), 1.91-1.64 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 141.2, 134.9, 132.7, 128.1, 124.6, 119.4, 115.0, 99.0, 82.1, 76.5, 72.9, 36.1, 24.3, 19.9.



3-93a

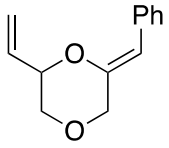
(*Z*)-2-(4-nitrobenzylidene)-6-vinyltetrahydro-2*H*-pyran (3-93a): A test tube with septum containing a stir bar, 1,3-bis(2,6-diisopropylphenyl-imidazol-2-ylidene)gold(I) chloride (6.4 mg, 0.01 mmol, 5 mol%), and silver tetrafluoroborate (2.0 mg, 0.01 mmol, 5 mol%) was taken from the glove box and placed directly under dry nitrogen. A small portion of THF (0.3 mL) was added and the mixture was left to stir at room temperature for 5 minutes after which time a solution of the allylic alcohol **3-92a** (49.0 mg, 0.2 mmol) in THF (0.7 mL) was added to the catalyst mixture all at once at room temperature. The reaction was left to stir at this temperature for 1.5 h and filtered through a short plug of silica with CH_2Cl_2, then placed under vacuum to remove the solvents. The crude product was verified by NMR data. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.12 (m, 2H), 7.71(m, 2H), 5.98 (ddd, *J* = 5.4, 10.8, 17.4, 1H), 5.43 (s, 1H), 5.38 (dt, *J* = 1.2, 17.4 Hz, 1H), 5.25 (dt, *J* = 1.2, 10.8 Hz, 1H), 4.45 (m, 1H), 2.41 (m, 2H), 1.62-1.97 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.0, 143.8, 137.7, 128.2, 123.8, 116.3, 79.1, 30.0, 30.0, 21.0.



3-93b

(*Z*)-2-benzylidene-6-vinyltetrahydro-2*H*-pyran (3-93b).[84] A test tube with septum containing a stir bar, 1,3-bis(2,6-diisopropylphenyl-imidazol-2-ylidene)gold(I)

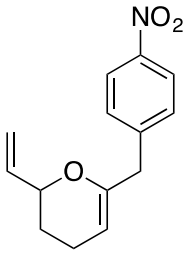
chloride (6.4 mg, 0.01 mmol, 5 mol%), and silver tetrafluoroborate (2.0 mg, 0.01 mmol, 5 mol%) was taken from the glove box and placed directly under dry nitrogen. A small portion of THF (0.3 mL) was added and the mixture was left to stir at room temperature for 5 minutes after which time a solution of the allylic alcohol **3-92b** (40.0 mg, 0.2 mmol) in THF (0.7 mL) was added to the catalyst mixture all at once at room temperature. The reaction was left to stir at this temperature for 30 minutes and filtered through a short plug of silica with CH_2Cl_2, then placed under vacuum to remove the solvents. The crude product was verified by NMR data. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.59 (m, 2H), 7.23-7.28 (m, 2H), 7.11 (m, 1H), 5.98 (ddd, *J* = 5.4, 11.1, 17.4 Hz, 1H), 5.39 (s, 1H – enol proton), 5.38 (dt, *J* = 1.2, 17.4 Hz, 1H), 5.21 (dt, *J* = 1.2, 11.1 Hz, 1H), 4.31 (m, 1H), 2.34 (m, 2H), 1.84-1.92 (m, 2H), 1.61-1.74 (m, 2H). The products' *Z*-vinyl ether geometry can be confirmed by comparison to the known *E*,*Z*-vinyl ether mixture.[84] Note that the *E*-enol is much farther upfield at 6.05 ppm, and no trace of this stereoisomer was found.



3-93d

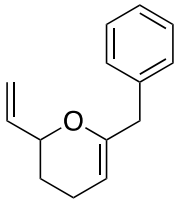
(*Z*)-2-benzylidene-6-vinyl-1,4-dioxane (3-93d): A test tube with septum containing a stir bar, triphenylphosphine-gold(I) chloride (5.1 mg, 0.01 mmol, 5 mol%), and silver trifluoromethanesulfonate (2.5 mg, 0.01 mmol, 5 mol%) was taken from the glove box and placed directly under dry nitrogen. A small portion of THF (0.3 mL) was added and the mixture was left to stir at room temperature for 5 minutes after which time a solution of the allylic alcohol **3-92d** (40.4 mg, 0.2 mmol) in THF (0.7 mL) was added to the catalyst all at once at room temperature. The reaction was left to stir at this

temperature for 1.5 h and filtered through a short plug of silica with CH_2Cl_2, then placed under vacuum to remove the solvents. The crude product was verified by NMR data as **11**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.66-7.62 (m, 1H), 7.34-7.30 (m, 2H), 7.22-7.18 (m, 1H), 5.96-5.89 (m, 1H), 5.55-5.50 (m, 1H), 5.50 (s, 1H), 5.36 (ddt, *J* = 10.7, 2.4, 1.3 Hz, 1H), 4.60-4.55 (m, 1H), 4.23 (s, 2H), 3.95 (ddd, *J* = 11.8, 3.2, 1.6 Hz, 1H), 3.65-3.60 (m, 1H).



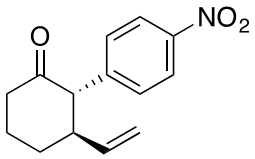
3-94a

6-(4-nitrobenzyl)-2-vinyl-3,4-dihydro-2*H*-pyran (3-94a): A test tube with septum containing a stir bar, triphenylphosphine-gold(I) chloride (5.1 mg, 0.01 mmol, 5 mol%), and silver trifluoromethanesulfonate (2.5 mg, 0.01 mmol, 5 mol%) was taken from the glove box and placed directly under dry nitrogen. A small portion of CH_2Cl_2 (0.3 mL) was added and the mixture was left to stir at room temperature for 5 minutes after which time a solution of the allylic alcohol **3-92a** (49.0 mg, 0.2 mmol) in CH_2Cl_2 (0.7 mL) was added to the catalyst all at once at room temperature. The reaction was left to stir at this temperature for 1.5 h and filtered through a short plug of silica with CH_2Cl_2, then placed under vacuum to remove the solvents. The crude product was verified by NMR data predominately **3-94a:** ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.12 (m, 2H), 7.43 (m, 2H), 5.85 (ddd, *J* = 5.4, 10.8, 17.1 Hz, 1H), 5.38 (dt, *J* = 1.2, 17.1 Hz, 1H), 5.25 (dt, *J* = 1.2, 10.8 Hz, 1H), 4.58 (t, *J* = 3.6 Hz, 1H), 4.31 (m, 1H), 3.42 (s, 2H) 1.97-2.14 (m, 2H), 1.83-1.92 (m, 1H), 1.52-1.67 (m, 1H).



3-94b

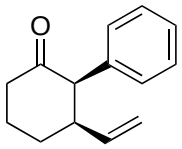
6-benzyl-2-vinyl-3,4-dihydro-2*H*-pyran (3-94b): A test tube with septum containing a stir bar, triphenylphosphine-gold(I) chloride (5.1 mg, 0.01 mmol, 5 mol%), and silver trifluoromethanesulfonate (2.5 mg, 0.01 mmol, 5 mol%) was taken from the glove box and placed directly under dry nitrogen. A small portion of CH_2Cl_2 (0.3 mL) was added and the mixture was left to stir at room temperature for 5 minutes after which time a solution of the allylic alcohol **3-92b** (40.0 mg, 0.2 mmol) in CH_2Cl_2 (0.7 mL) was added to the catalyst all at once at room temperature. The reaction was left to stir at this temperature for 1 h and filtered through a short plug of silica with CH_2Cl_2, then placed under vacuum to remove the solvents. The crude product was verified by NMR data predominately **3-94b:** ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.05-7.39 (m, 7H), 5.90 (ddd, *J* = 5.4, 10.8, 17.1 1H), 5.21 (dt, *J* = 1.2, 17.1 Hz, 1H), 5.12 (dt, *J* = 1.2, 10.8 Hz, 1H), 4.46 (t, *J* = 3.9 Hz, 1H), 4.33 (m, 1H), 3.32 (s, 2H), 1.53-2.08 (m, 4H).



3-99a

***trans*-2-(4-nitrophenyl)-3-vinylcyclohexan-1-one (3-99a):** A test tube containing a stir bar was placed under dry nitrogen with a septum on top. To this vessel was added crude **3-93a (**49.0 mg, 0.2 mmol) in 1.0 mL of toluene. The solution was heated a reflux overnight and the resulting mixture was purified by flash

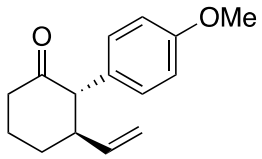
chromatography with a gradient (2-5% EtOAc/hexanes) affording products **3-99a** (25.0 mg, 51% as a white solid) and **3-100** (10.2 mg, R_f = 0.37 (30% EtOAc/hexanes). IR (neat) 3080, 2939, 2867, 1712, 1518, 1346 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 8.18 (d, *J* = 8.8 Hz, 1H), 7.22 (d, *J* = 8.7 Hz, 1H), 5.48 (ddd, *J* = 16.8, 10.6, 7.9 Hz, 1H), 4.85-4.77 (m, 2H), 3.55 (dd, *J* = 12.1, 1.0 Hz, 1H), 2.72 (tdd, *J* = 11.5, 7.9, 3.6 Hz, 1H), 2.62-2.56 (m, 1H), 2.55-2.47 (m, 1H), 2.23 (ddd, *J* = 12.5, 5.9, 2.9 Hz, 1H), 2.12-2.06 (m, 1H), 1.94-1.76 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 208.0, 145.0, 139.4, 130.7, 123.6, 116.2, 62.7, 50.3, 41.9, 32.2, 25.9. Assignment of relative stereochemistry was accomplished by 2D-COSY (500 MHz, $CDCl_3$).



3-99b

2-phenyl-3-vinylcyclohexanone (3-99b):[91] The following compound was formed during the gold-catalyzed cyclization using the optimized conditions using **3-92b** (46.0 mg, 0.22 mmol). Purified by flash chromatography (2% EtOAc/hexanes) to give the product as a clear, colorless oil (43.2 mg, 94% as a mixture of diastereomers (2:1 cis:trans before purification)). IR (neat) 2929, 1710, 1681, 1597, 1448, 1218, 920 cm^{-1}. ***cis*-diastereomer**: ^1H NMR (300 MHz, $CDCl_3$): δ 7.38-7.22 (m, 5H), 5.82 (ddd, J = 1.8, 10.8, 16.8 Hz, 1H),5.03 (dt, J = 1.8, 10.8 Hz, 1H), 4.93 (dt, J = 1.8, 16.8 Hz, 1H), 3.88 (d, J = 4.8 Hz, 1H *cis* H-H), 3.02 (m,1H), 2.54 (m, 2H) 2.14-1.95 (m, 1H). ***trans*-diastereomer**: ^1H NMR (300 MHz,$CDCl_3$): δ 7.29-7.21 (m, 3H), 7.05 (m, 2H), 5.53 (ddd, J = 7.5, 10.5, 17.4 Hz, 1H) 4.87-4.80 (m, 2H), 3.39 (d, J = 11.7 Hz, 1H *trans* H-H), 2.74

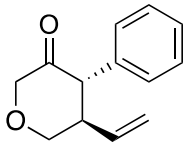
(m, 1H), 2.41-2.59 (m, 2H), 1.71-2.22 (m, 4H). The data for the *trans*-diastereomer satisfactorily matched that of the known compound.[91]



3-99c

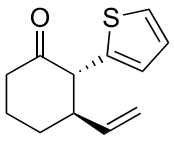
***trans*-2-(4-methoxyphenyl)-3-vinylcyclohexan-1-one (3-99c)**: 8-(4-methoxyphenyl)oct-1-en-7-yn-3-ol **3-92c** (58.2 mg, 0.25 mmol) was treated with the optimized conditions to give the diastereomeric mixture of 2-(4-methoxyphenyl)-3-vinylcyclohexan-1-one (52.0 mg, 90% as a 2:1 mixture of diastereomers (cis:trans)). An analytical fraction of the *cis*-2-(4-methoxyphenyl)-3-vinylcyclohexan-1-one was obtained to give the following data: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.19-7.15 (m, 2H), 6.84-6.82 (m, 2H), 5.90-5.74 (m, 1H), 5.04 (ddt, *J* = 10.4, 1.7, 0.8 Hz, 1H), 4.98-4.89 (m, 1H), 3.86-3.83 (m, 1H), 3.78 (s, 3H), 3.04-2.94 (m, 1H), 2.59-2.53 (m, 1H), 2.51-2.44 (m, 2H), 2.16-2.06 (m, 2H), 2.03-1.93 (m, 2H). For characterization the diastereomeric mixture of 2-(4-methoxyphenyl)-3-vinylcyclohexan-1-one was then treated with NaOMe (25% in MeOH, 50 □L) in 1.0 mL of MeOH. R_f = 0.48 (20% EtOAc/hexanes). Extracted with EtOAc, dried over sodium sulfate, filtered, and evaporated to give the crude product. Purified by flash column chromatography using a solvent gradient (0-5% EtOAc/hexanes) to yield the *trans*-product as a clear colorless oil (15.0 mg, 40%). R_f = 0.48 (20% EtOAc/hexanes). IR (neat) 3076, 2934, 2864, 1713, 1514, 1248 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.97 (d, *J* = 8.7 Hz, 1H), 6.86 (d, *J* = 8.7 Hz, 1H), 5.58-5.50 (m, 1H), 4.89-4.80 (m, 2H), 3.79 (s, 3H), 3.36 (d, 1H), 2.74-2.64 (m, 1H), 2.56 (ddd, *J* = 4.4, 3.0, 1.7 Hz, 1H), 2.54 (td, *J* = 3.0, 1.5 Hz, 1H), 2.46 (tdd, *J* = 13.6, 6.0, 1.1 Hz, 1H),

2.21-2.15 (m, 1H), 2.09-2.03 (m, 1H), 1.91-1.73 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 209.8, 158.6, 140.6, 130.6, 129.3, 115.1, 113.9, 62.2, 55.4, 49.7, 42.1, 32.2, 26.0.



3-99d

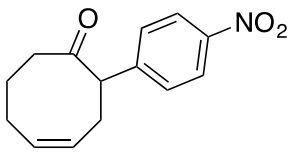
***trans*-4-phenyl-5-vinyldihydro-2*H*-pyran-3(4*H*)-one (3-99d)**: 1-((3-phenylprop-2-yn-1-yl)oxy)but-3-en-2-ol **3-92d** (40.4 mg, 0.20 mmol) was treated with the optimized conditions to give the diastereomeric mixture of predominately the *cis*-4-phenyl-5-vinyldihydro-2*H*-pyran-3(4*H*)-one (10:1 dr; cis:trans). During purification using flash column chromatography with silica gel the mixture epimerized to give predominately the *trans*-isomer of **3-99d**. Assignment of relative stereochemistry was accomplished by 2D-COSY (500 MHz, $CDCl_3$). R_f = 0.48 (25% EtOAc/hexanes). IR (neat) 3062, 2927, 1719, 1679, 1597, 1449, 1123, 1016, 753 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36-7.32 (m, 2H), 7.30-7.27 (m, 1H), 7.11-7.08 (m, 2H), 5.54 (ddd, *J* = 17.2, 10.5, 7.8 Hz, 1H), 4.99 (dt, *J* = 10.5, 1.0 Hz, 1H), 4.94 (dt, *J* = 17.2, 1.1 Hz, 1H), 4.23 (dd, *J* = 15.7, 1.0 Hz, 1H), 4.16-4.12 (m, 1H), 4.10 (dd, *J* = 15.8, 0.7 Hz, 1H), 3.76 (dd, *J* = 11.8, 10.1 Hz, 1H), 3.53 (d, *J* = 11.4 Hz, 1H), 3.17-3.09 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 205.9, 135.9, 135.3, 129.6, 128.7, 127.6, 118.2, 74.9, 71.2, 60.2, 48.0.



***trans*-3-99e**

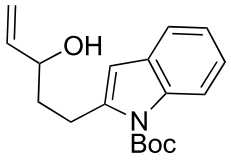
***trans*-2-(thiophen-2-yl)-3-vinylcyclohexan-1-one (3-99e)**: 8-(thiophen-2-yl)oct-1-en-7-yn-3-ol **3-92e** (40.0 mg, 0.2 mmol) was treated with the optimized conditions to

give the diastereomeric mixture of 2-(thiophen-2-yl)-3-vinylcyclohexan-1-one (37.4 mg, 92% as a 2:1 mixture of diastereomers (cis:trans)). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.24 (ddd, *J* = 5.1, 1.2, 0.6 Hz, 1H), 7.22 (s, 1H), 6.98-6.93 (m, 4H), 6.77 (ddt, *J* = 3.5, 1.2, 0.6 Hz, 1H), 5.78-5.56 (m, 2H), 5.07-4.88 (m, 5H), 4.17 (dd, *J* = 5.1, 0.9 Hz, 1H), 3.77 (d, *J* = 11.0 Hz, 1H), 3.09-2.98 (m, 2H), 2.73-2.59 (m, 3H), 2.58-2.54 (m, 1H), 2.51-2.38 (m, 3H), 2.22-2.01 (m, 7H), 1.97-1.85 (m, 2H), 1.85-1.67 (m, 2H). For characterization the diastereomeric mixture of 2-(thiophen-2-yl)-3-vinylcyclohexan-1-one (37.0 mg, 0.18 mmol) with NaOMe (25% in MeOH, 50 □L) in 1.0 mL of MeOH. The solution was left to stir overnight then quenched with 5.0 mL of NH_4Cl (sat. in water) at 0 °C. Extracted with EtOAc, dried over sodium sulfate, filtered, and evaporated to give the crude product. Purified by flash column chromatography using a solvent gradient (0-5% EtOAc/hexanes) to yield the product as a clear colorless oil (33.3 mg, 90%). R_f = 0.36 (15% EtOAc/hexanes). IR (neat): 3076, 2934, 2864, 1713, 1613, 1514, 1248 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.24 (ddd, *J* = 5.1, 1.2, 0.5 Hz, 1H), 6.96 (dd, *J* = 5.1, 3.5 Hz, 1H), 6.77 (ddd, *J* = 3.5, 1.2, 0.6 Hz, 1H), 5.63 (ddd, *J* = 17.1, 10.4, 7.5 Hz, 1H), 4.97-4.89 (m, 2H), 3.77 (d, *J* = 11.1 Hz, 1H), 2.73-2.64 (m, 1H), 2.58 (dddd, *J* = 13.7, 4.4, 3.7, 1.7 Hz, 1H), 2.45 (dddd, *J* = 13.7, 12.7, 5.9, 1.1 Hz, 1H), 2.16 (dddd, *J* = 12.7, 6.9, 5.8, 3.7 Hz, 1H), 2.11-2.03 (m, 1H), 1.90-1.71 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 208.2, 140.1, 139.6, 126.6, 126.5, 124.9, 115.6, 57.5, 50.9, 41.6, 31.9, 25.7.



3-100

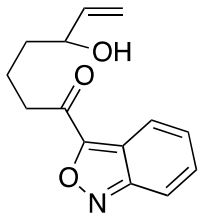
(*Z*)-2-(4-nitrophenyl)cyclooct-4-en-1-one (3-100): A test tube containing a stir bar was placed under dry nitrogen with a septum on top. To this vessel was added crude **3-93a** (49.0 mg, 0.2 mmol) in 1.0 mL of toluene. The solution was heated a reflux overnight and the resulting mixture was purified by flash chromatography with a gradient (2-5% EtOAc/hexanes) affording products **3-99a** (25.0 mg, 51% as a white solid) and **3-100** (10.2 mg, 23% as a clear colorless oil) respectively. The following was data obtained for compound **3-100**: IR (neat) 3079, 2939, 2867, 1712, 1600, 1518, 1346, 1170 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.21 (d, *J* = 8.8 Hz, 2H), 7.47 (d, *J* = 9.0 Hz, 2H), 5.92-5.76 (m, 2H), 3.92 (dd, *J* = 11.3, 4.1 Hz, 1H), 3.01 (ddd, *J* = 13.0, 11.2, 8.1 Hz, 1H), 2.65-2.46 (m, 2H), 2.38-2.18 (m, 3H), 1.86-1.76 (m, 1H), 1.70-1.58 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 189.2, 157.8, 145.1, 132.7, 129.0, 128.3, 124.0, 62.1, 39.4, 27.7, 26.8, 25.3.



3-104

***tert*-butyl 2-(3-hydroxypent-4-en-1-yl)-1*H*-indole-1-carboxylate (3-104):** The following compound was formed during the gold-catalyzed cyclization using the optimized conditions using **3-92h** (68.0 mg, 0.2 mmol). Purified by flash column chromatography using a solvent gradient (0-20% EtOAc/hexanes) to yield the product as a off white solid (60.0 mg, 92%). R_f = 0.66 (20% EtOAc/hexanes). IR (neat) 3386, 3071, 3056, 2978, 2933, 2872, 1731, 1455, 1370, 1329, 1158 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.11-8.04 (m, 1H), 7.46- 7.41 (m, 1H), 7.24-7.15 (m, 2H), 6.36 (apq, *J* = 0.9 Hz, 1H), 5.88 (ddd, *J* = 17.2, 10.4, 6.1 Hz, 1H), 5.24 (dt, *J* = 17.2, 1.4 Hz, 1H), 5.11 (dt,

J = 10.4, 1.3 Hz, 1H), 4.22-4.14 (m, 1H), 3.11-2.95 (m, 2H), 1.87-1.74 (m, 3H), 1.62-1.72 (m, 12H).^{13}C NMR (125 MHz, $CDCl_3$): δ150.8, 142.2, 141.3, 136.8, 129.5, 123.4, 122.8,119.9, 115.8, 114.9, 107.5, 84.0, 73.0, 36.8, 30.0, 28.5, 25.0.



3-105

1-(benzo[*c*]isoxazol-3-yl)-5-hydroxyhept-6-en-1-one (3-105): The following compound was formed during the gold-catalyzed cyclization using the optimized conditions using **3-92i** (68.0 mg, 0.2 mmol). Purified by flash column chromatography using a solvent gradient (0-20% EtOAc/hexanes) to yield the product as a off white solid (60.0 mg, 92%). IR (neat) 3426, 3072, 2925, 2365, 2337, 1683, 1558 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ8.09-8.01 (m, 1H), 7.77-7.70 (m, 1H), 7.46-7.37 (m, 1H), 7.32-7.22 (m, 1H), 5.97-5.82 (m, 1H), 5.26 (dt, *J* = 17.2, 1.3 Hz, 1H), 5.14 (dt, *J* = 10.4, 1.3 Hz, 1H), 4.26-4.15 (m, 1H), 3.24 (t, *J* = 7.2 Hz, 2H), 2.03-1.81 (m, *J* = 6.4 Hz, 2H), 1.74-1.52 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ190.2, 159.8, 157.7, 141.0, 131.5, 128.7, 121.4, 119.4, 116.1, 115.2, 73.0, 40.0, 36.4, 19.5.

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BIOGRAPHICAL SKETCH

John Michael Ketcham was born in Ocala, Florida on July 23rd, 1984 to the proud parents of Huey L. Ketcham and Vicki J. Ketcham. The youngest of three sons, he has spent most of his life in the central Florida area enjoying the outdoors. After graduating from Forest High School in 2002, he attended the University of Central Florida (UCF) where he studied Organic Chemistry under the direction of Professor Seth Elsheimer. During his time at UCF, a collaboration between Professor Clovis A. Linkous at the Florida Solar Energy Center (FSEC) and Prof. Elsheimer led him to study the synthesis of a superacid-substituted PEEK (polyether ether ketone) monomer for eventual use in proton exchange membranes (PEMs).

In 2007, John received his bachelor of science in Chemistry from UCF and moved to the University of Florida to pursue a doctoral degree in Organic Chemistry. Since moving to UF, he has been working under the supervision of Professor Aaron Aponick in the field of gold-catalysis. During his doctoral pursuit, his projects were focused on the utilization of allylic alcohols as both electrophiles and nucleophiles in gold-catalyzed reactions. After obtaining his doctoral degree. in the summer of 2013, he started a postdoctoral position at the University of Texas at Austin working under the direction of Professor Michael J. Krische.