Many biologically active compounds contain multiple fused rings, and often the synthesis of these compounds can be quite complex. Efforts to produce these intricate molecular frameworks through cycloaddition reactions are advantageous, with the ability to produce fused ring structures in only one step. This document describes the work towards the synthesis of fused ring products through gold-catalyzed cycloadditions. The construction of various carbocycles was achieved through transannular, intermolecular, and intramolecular methods. Rapid assembly of the core structure of Cortistatin A, a potent antiangiogenesis natural product, was achieved through a transannular [4 + 3] cycloaddition from a macrocyclic precursor. Additionally, the [4 + 3] cycloaddition reaction was extended to the intermolecular variant using propargyl ester and diene precursors. Progress towards the application of intramolecular gold-catalyzed cycloadditions is also described. Where appropriate, investigation of the regioselectivity and stereochemistry of these reactions is analyzed, and mechanistic pathways are also investigated.
GOLD-CATALYZED CYCLOADDITIONS: AN APPROACH TOWARD COMPLEX MOLECULAR FRAMEWORKS VIA TRANSANNULAR, INTERMOLECULAR, AND INTRAMOLECULAR METHODS

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Introduction

The ability to access complex structures through cycloaddition is a powerful tool for organic chemists. The use of gold-catalyzed cycloaddition has received much attention in recent years. With the desire for increased atom economy and green chemistry at the forefront of today’s synthetic planning, gold has been found to have significant advantages. Its unique properties allow it to be used in low quantities in both heterogeneous and homogeneous catalysis and it has been shown to have high activity at ambient temperatures. Gold is beneficial due to its low toxicity and tolerance of both moisture and air, and can be used with alternative solvents for easy recycling. These benefits allow for reactions to be carried out quickly under mild conditions. In addition, gold is also more abundant than palladium, platinum, and rhodium and its byproducts are environmentally safe.1,2

Our group was initially inspired by Cortistatin A, a steroidal alkaloid first isolated from the marine sponge Corticium simplex. It is a potent inhibitor of angiogenesis, the process of forming new capillary blood vessels, and is responsible for the proliferation of tumor cells.3 Cortistatin A contains a center oxabicyclo [3.2.1] octene ring system. These fused seven-membered ring carbocycles appear in many naturally occurring products. Consequently, the development of new synthetic strategies to make these molecular frameworks is valuable. Though the Diels-Alder reaction (a [4 + 2] cycloaddition) has been extensively studied, its related [4 + 3] cycloaddition has been much less explored. Literature demonstrating the ability of gold to act as a catalyst in both intermolecular and intramolecular [4 + 2] and [4 + 3] cycloadditions have been reported.4-7 The complex molecular frameworks that can be accessed through these methods can be used as precursors in the synthesis of promising anti-tumor agents and naturally occurring products.

In this thesis, various ways to access bridged bicyclic and oxabicyclic systems through gold catalysis is discussed. Specifically, the ability of gold to activate propargyl esters towards attack from olefinic nucleophiles is investigated. In order to optimize and improve the results, various substrates, gold catalysts, and reaction conditions were attempted. Different variants of the gold-catalyzed cycloadditions including transannular, intermolecular, and intramolecular methods were examined. The mechanistic pathways that could be involved in these transformations were also explored.
Chapter 1.

Gold-Catalyzed Transannular [4 + 3] Cycloadditions: Progress Towards the Synthesis of the ABCD Carbon Framework of Cortistatin A

1.1 Introduction

Transannular cycloadditions are potent synthetic tools for the rapid assembly of multiple fused ring systems in a single step. A transannular cycloaddition involves a reaction between two nonbonding groups in a macrocycle. Although inter- and intramolecular [4 + 3] cycloadditions are well established transformations, there are drastically fewer reports of the transannular version of this reaction. In the last decade, an enormous number of intramolecular cycloisomerization reactions have appeared in the literature as opposed to only a single report of a transannular isomerization catalyzed by PtCl₂.

Cortistatin A is a steroidal alkaloid originally isolated from the marine sponge Corticium simplex. Studies have demonstrated that it is a powerful inhibitor of angiogenesis, which is responsible for the generation of new capillary blood vessels in tumor progression, rheumatoid arthritis, and psoriasis. Uncontrolled angiogenesis can lead to the spread of cancerous cells, so specific inhibitors of this process can be promising anti-tumor agents. Specifically, cortistatin A has been found to be a selective inhibitor of the proliferation of human umbilical vein endothelial cells, or HUVECs. When compared to other cortistatins, this target has the simplest functionality and the strongest growth inhibitory activity against HUVECs, and prevents cell proliferation without any cytotoxic effect.

Inspired by the core pentacyclic structure of cortistatin A (1), we reasoned that a transannular [4 + 3] cycloaddition reaction could produce four fused rings in one step (Scheme 1.1). In order for this transformation to be successful, several conditions must be met including an efficient synthesis of the macrocyclic precursor, and a high yield and diastereoselectivity of the key transannular [4 + 3] cycloaddition step.

![Scheme 1.1 Retrosynthetic Analysis of Cortistatin A.](image)

Initial attempts to form the pentacyclic system began with the synthesis of macrocyclic allenes as precursors. This was activated by an appropriate catalyst in a set of conditions to induce a transannular [4 + 3] cycloaddition reaction to form the oxabicyclo[3.2.1]octene ring system and concomitant formation of two peripheral six-membered rings. Initial attempts to form this structure were partially successful with a Pd(OAc)₂ catalyst, forming the desired product in low yields. Further investigation into intramolecular [4 + 3] cycloadditions led to the use of Pt and Au catalysts. The Mascarenas group were the first to report activation of an allene for an
intramolecular [4 + 3] cycloaddition. As a result, these methods were applied to the macrocyclic allenes.\textsuperscript{16} However in the best of conditions, a 1:1 mixture of the transannular [4 + 3] and [4 + 2] products were obtained when a Au(I) catalyst was employed.

With the goal achieving a higher yield of the [4 + 3] product and better control of the regioselectivity, a different starting material was utilized. The furan moiety is essential to forming the oxabicyclo[3.2.1]octene ring system, so a different functional group must be used in place of the allene three-carbon tether. The rearrangement of propargyl esters to form acetoxyallene intermediates and subsequent tandem reactions of these moieties have been extensively studied.\textsuperscript{17-28} However, there has been no report of the tandem-3,3-rearrangement followed by a transannular [4 + 3] cycloaddition reaction until now. This chapter investigates the transannular [4 + 3] cycloaddition using furan as the four-carbon component and propargyl acetates as the three-carbon component. Mechanistic implications and variation of the gold catalyst were investigated.

1.2 Results and Discussion

To begin the study of the tandem-3,3-rearrangement and gold-catalyzed [4 + 3] cycloaddition reactions, a macrocyclic propargyl acetate must be successfully obtained. To this end, a Nozaki-Hiyama-Kishi (NHK) reaction using CrCl\textsubscript{2} was envisioned to establish the propargylic alcohol precursor.\textsuperscript{29} The preparation of the macrocyclic precursor is shown in Scheme 1.2.

Known monosubstituted furan 3 was converted to the disubstituted furan 4 by alkylation of the lithiated furan with 1,4-dibromobutane. Alkynyation of the bromide with sodium acetylide provided 5 and subsequent removal of the tetrahydropyranyl ether protecting group followed by PCC oxidation of the resulting alcohol gave aldehyde 6. Several methods were carried out on this substrate to form a chiral propargyl alcohol, but none were successful in forming the macrocycle. As a result the NHK reaction, a known method to form propargyl alcohol macrocycles, was attempted.

After iodination of the terminal alkyne, the key macrocyclization step was carried out by slow addition of substrate 7 to a suspension of CrCl\textsubscript{2} and NiCl\textsubscript{2} in THF to yield macrocycle 8. The propargyl alcohol was acylated to provide the macrocyclic propargyl acetate precursor 9. It is noteworthy that the quality of the CrCl\textsubscript{2} reagent is crucial to the success of the macrocyclization. An old bottle of CrCl\textsubscript{2} gave consistently low yields of the macrocycle. A chromium (II) species is required for the reduction of nickel (II) to nickel (0), which is the active catalyst in this reaction. It is likely that our old bottle of chromium (II) chloride was oxidized to chromium (III). This would prevent the initial oxidative addition step with nickel because the nickel (0) species was never generated.
Scheme 1.2 Synthesis of the Macrocyclic Precursor

The resultant macrocycle 9 was screened with three different Au catalysts. It was first treated with 5 mol % Au\textsuperscript{I} catalyst 10 (Table 1.1) in the presence of 5 mol % AgSbF\textsubscript{6} co-catalyst. Gratifyingly, the reaction produced the desired transannular [4 + 3] cycloadduct 13 in 70 % yield as a single diastereomer (entry 1). Reaction with 5 mol % Au\textsuperscript{I} catalyst 12 in the presence of 5 mol % AgSbF\textsubscript{6} also generated cycloadduct 13, albeit in lower yield (entry 3). Interestingly, when macrocycle 9 was treated with Au\textsuperscript{III} catalyst 11, a mixture of tetracyclic products 13 and 14, both arising from a [4 +3] transannular cycloaddition, were isolated in a 1:3 ratio (entry 2).
Table 1.1 Tandem 3,3-rearrangement/transannular [4 + 3] cycloadditions.

\[
\begin{align*}
& \text{Entry} & \text{Catalyst} & \text{t [h]} & \text{13 [%]}^a & \text{14 [%]}^a \\
& 1 & \text{catalyst 10}^b & 6 & 70 & 0 \\
& 2 & \text{catalyst 11}^c & 48 & 21 & 64 \\
& 3 & \text{catalyst 12}^c & 3 & 56 & 0 \\
\end{align*}
\]

[a] Isolated yields. [b] With 5 % AgSbF₆. [c] One equivalent of NaHCO₃ was added.

The stereochemistry of cycloadduct 13 was established by preparing the crystal derivative of the compound (Scheme 1.3). Hydrogenation of 13 with Pd/C occurred selectively at the disubstituted olefin. The resulting vinyl acetate 15 underwent base-catalyzed hydrolysis to form ketone 16, followed by reaction with a hydrazine derivative to provide hydrazone 17. This product was easily crystallized by slow diffusion, which was carried out by the careful addition of methanol to a solution of 17 in methylene chloride. The crystal structure showed three fused six-membered rings in chair conformations with the bridgehead hydrogens being oriented syn to the bridging oxygen atom.
The stereochemistry of product 14 was assigned based on two-dimensional NMR spectroscopy analysis (Figure 1.1). Product 14 was used to generate the core pentacyclic ABCD ring structure of Cortistatin A, shown in Scheme 1.1. Attempts to eliminate the tertiary acetate with DBU were unsuccessful, so compound 14 was selectively hydrogenated using Wilkinson’s catalyst to provide 18 (Scheme 1.4). The acetate was successfully hydrolyzed to the tertiary alcohol, though the reaction was sluggish. Efforts to generate a better leaving group from the alcohol with tosylate and mesylate groups were also ineffective and resulted in only recovery of starting material. However, it was later discovered that the tertiary alcohol could be easily eliminated using Burgess reagent to provide the ABCD ring structure of Cortistatin A (figure 20). Complete hydrogenation of this compound using palladium on carbon provided the known compound 21 along with a small amount of diastereomers.30

Figure 1.1 NOE Correlation of Cycloadduct 14.
Scheme 1.4 Conversion of 14 to ABCD Ring Structure of Cortistatin A.

The proposed mechanism (Scheme 1.5) depicts a compact transition state for the transannular [4 + 3] cycloaddition reaction, due to the observed stereochemistry of products 13 and 14. The regiochemistry of the final products is determined by the original position of the acetoxy group. When similar reactions were employed with the macrocyclic allenes, no regioselectivity was observed and a mixture of [4 + 3] and [4 + 2] products were obtained.16 The propargyl ester 9 undergoes a 3,3-sigmatropic rearrangement to generate the acetoxy allene A. The allene functionality is further activated by gold to provide the Au-allyl cation B which undergoes a transannular [4 + 3] cycloaddition. The subsequent gold carbenoid species C, when in the presence of the cationic Au\textsuperscript{I} catalysts 10 or 12, undergoes a 1,2-acetate migration followed by deauration to form 13. However, when the Au\textsuperscript{III} catalyst is used (11), a 1,2-hydride shift becomes more competitive and a mixture of products 13 and 14 was observed. The process of the 1,2-hydride shift in the gold-catalyzed tandem 3,3-rearrangement/Nazarov reaction sequence has been studied and found to have a relatively high barrier.31 The results from the reactions with the propargyl acetates suggest there is only one pathway available. Although two products were formed, both result from a transannular [4 + 3] cycloaddition, in accordance with the fact that no other cycloadducts were observed. The full results of this study are now published.30

Scheme 1.5 Proposed Mechanism for Transannular [4 + 3] Cycloaddition
1.3 Conclusion

In summary, a highly regio- and diastereoselective transannular \([4 + 3]\) cycloaddition reaction has been discovered. In contrast to the several reports of intramolecular \([4 + 3]\) cycloadditions using allenes as a three-carbon component, our report uses a propargyl acetate precursor. By using macrocyclic propargyl esters with gold catalysts, this study was able to demonstrate that the propargyl acetate as three-carbon-components provide much better control of regioselectivity than simple allenes, as no \([4 + 2]\) products were observed in these reactions. This difference suggests that the gold carbenoid generated from propargyl esters are more suitable for undergoing \([4 + 3]\) cycloadditions than the corresponding gold carbenoids generated from allenes. This methodology provides easy access to the core structure of the biologically relevant natural product Cortistatin A.
1.4 Experimental Procedures

General Experimental Procedures

Unless otherwise stated, all reactions were carried out under an inert nitrogen atmosphere with dry solvents under anhydrous conditions. Dry tetrahydrofuran (THF) and toluene (PhCH₃) were distilled over sodium benzophenone, dichloromethane (CH₂Cl₂) and benzene (PhH) were distilled over calcium hydride. Reagents were purchased and used without further purification unless otherwise stated. Yields refer to chromatographically and spectroscopically (¹H NMR) homogeneous materials, unless otherwise stated. Reactions were monitored by thin layer chromatography (TLC) carried out on 0.25 mm Merck silica gel plates (60F-254) using UV light as the visualizing agent and an acidic mixture of anisaldehyde, phosphomolybdic acid, or ceric ammonium molybdate, or basic aqueous potassium permanganate (KMnO₄), and heat as developing agents. Merck silica gel (60, particle size 0.043–0.063 mm) was used for flash column chromatography. NMR spectra were recorded on Bruker Av-500, and Av-300 instruments and calibrated using residual undeuterated solvent as an internal reference (CHCl₃ @ 7.26 ppm ¹H NMR, 77.0 ppm ¹³C NMR). The following abbreviations (or combinations thereof) were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad. High resolution mass spectra (HRMS) were recorded at Ohio State University. IR spectra were recorded on a Perkin Elmer Spectrum 2000 FTIR spectrometer. Melting points were recorded on a Thomas-Hoover melting point apparatus.

2-(5-(5-(4-bromobutyl)furan-2-yl)pentyloxy)tetrahydro-2H-pyran (4)

![Chemical Structure](image)

Compound 3 (8.09 g, 33.9 mmol) was dissolved in dry THF (56.6 mL) under an atmosphere of nitrogen. The solution was cooled to 0 °C and BuLi (1.6 M in hexane, 27.6 mL, 44.1 mmol) was added dropwise at this temperature. The suspension stirred at this temperature for 2h and was then cooled to -78 °C. 1,4-dibromobutane (11.0 g, 50.9 mmol) was added in one portion by syringe. The reaction mixture stirred at this temperature 1 h. The reaction mixture was warmed to 0 °C and stirred 1h and then allowed to warm to rt overnight. The reaction was quenched by the careful addition of brine. The layers were separated and the aqueous layer was extracted with Et₂O. The combined organic layers were dried over MgSO₄ and concentrated. The residue was purified by silica gel chromatography (5-10-20% EtOAc:Hex) and provided 10.3 g (82%) of the bromide (4) as a yellow oil. ¹H NMR (500 MHz, CDCl₃): δ 1.40-1.93 (16H, m), 2.56-2.62 (4H, m), 3.36-3.43 (3H, m), 3.49-3.51 (1H, m), 3.72-3.76 (1H, m), 3.84-3.88 (1H, m), 4.57 (1H, s), 5.84-5.87 (2H, m). ¹³C NMR (125 MHz, CDCl₃): δ 19.7, 25.5, 25.8, 26.7, 27.1, 28.0, 29.5,
30.8, 32.2, 33.4, 62.4, 67.5, 98.9, 105.0, 105.4, 153.5, 154.7. LCMS m/z calcd for C_{18}H_{29}BrO_{3}Na 395.1, found 395.2 (M + Na).

2-(5-(5-(hex-5-ynyl)furan-2-yl)pentyloxy)tetrahydro-2H-pyran (5)

The bromide 4 (6.51 g, 17.4 mmol) was dissolved in dry DMF (17.4 mL) under an atmosphere of nitrogen. The solution was cooled to 0 °C and sodium acetylide (18 wt. % slurry in xylene/light mineral oil, 9.31 g, 34.9 mmol) was added dropwise over 20 min. The reaction mixture stirred at this temp 2.5 h and was allowed to warm to rt overnight. The reaction mixture was diluted with Et₂O, and slowly quenched with 1M HCl. The aqueous layer was extracted with Et₂O and the combined organic layers were washed with brine, dried over MgSO₄, and concentrated. The residue was purified via silica gel chromatography (5-10-20% EtOAc:Hex) and provided 3.88 g (70%) of the alkyne (5) as a pale yellow oil. \(^1\)H NMR (500 MHz, CDCl₃): δ 1.39-1.85 (18H, m), 1.94 (1H, t, J = 2.8 Hz), 2.19-2.23 (2H, m), 2.58 (4H, q, J = 7.7 Hz), 3.37-3.41 (1H, m), 3.47-3.51 (1H, m), 3.71-3.76 (1H, m), 3.84-3.88 (1H, m), 4.55-4.58 (1H, m), 5.81-5.86 (2H, m). \(^1^3\)C NMR (125 MHz, CDCl₃): δ 18.2, 19.7, 25.5, 25.8, 27.2, 27.5, 27.9, 28.0, 29.5, 30.8, 62.3, 67.5, 68.3, 84.3, 98.8, 105.0, 105.1, 153.9, 154.6. LCMS m/z calcd for C_{20}H_{30}O_{3}Na 341.2, found 341.2 (M + Na).

5-(5-(hex-5-ynyl)furan-2-yl)pentanal (6)

Compound 5 (4.07 g, 12.8 mmol) was dissolved in MeOH (213 mL) under an atmosphere of nitrogen. \(p\)-Toluenesulfonic acid (0.49 g, 2.56 mmol) was added in one portion. After stirring 1h at rt, the reaction mixture was concentrated then diluted with EtOAc and quenched with sat. NaHCO₃ (aq). The aqueous layer was extracted with EtOAc, dried over MgSO₄, and concentrated. The residue was purified by silica gel chromatography (20% EtOAc:Hex) to provide 2.88 g (96%) of the alcohol as a pale yellow oil. \(^1\)H NMR (500 MHz, CDCl₃): δ 1.40-
1.47 (4H, m), 1.57-1.79 (6H, m), 1.97 (1H, t, J = 2.5 Hz), 2.22-2.25 (2H, m), 2.61 (4H, q, J = 6.9 Hz), 3.67 (2H, t, J = 6.7 Hz), 5.87-5.89 (2H, m). $^{13}$C NMR (125 MHz, CDCl$_3$): δ 18.2, 25.3, 27.2, 27.5, 27.9, 28.0, 32.5, 62.9, 68.3, 84.3, 105.0, 105.2, 154.0, 154.4. LCMS m/z calcd for C$_{15}$H$_{22}$O$_2$Na 257.2, found 257.1 (M + Na).

To a suspension of PCC (5.51 g, 25.6 mmol), anhydrous sodium acetate (0.35 g, 2.56 mmol), and celite (1.56 g, 26.0 mmol) in dry methylene chloride (54 mL) was added a solution of the alcohol (2.85 g, 12.1 mmol) in CH$_2$Cl$_2$ (10 mL) dropwise by syringe. The reaction stirred 1h, then was diluted with Et$_2$O and filtered through a pad of silica. Filtrate was concentrated, then diluted again with Et$_2$O and filtered once more through silica to remove any excess PCC. The residue was purified by silica gel chromatography (5-10% EtOAc:Hex) to provide 1.97 g (70%) of aldehyde 6 as a colorless oil. $^1$H NMR (500 MHz, CDCl$_3$): δ 1.56-1.77 (8H, m), 1.94 (1H, t, J = 2.8 Hz), 2.20-2.23 (2H, m), 2.44-2.46 (2H, m), 2.58-2.61 (4H, m), 5.86 (2H, s). $^{13}$C NMR (125 MHz, CDCl$_3$): δ 18.2, 21.6, 27.2, 27.5, 27.6, 27.7, 27.9, 43.6, 68.3, 84.3, 105.2, 105.3, 153.7, 154.1 202.39. LCMS m/z calcd for C$_{15}$H$_{20}$O$_2$Na 255.1, found 255.1 (M + Na).

5-(5-(6-iodohex-5-ynyl)furan-2-yl)pentanal (7)

The terminal alkyne 6 (1.76 g, 7.57 mmol) was dissolved in anhydrous DMF (63.1 mL) under an atmosphere of nitrogen in the absence of light. To the solution was added N-iodosuccinimide (1.70 g, 7.57 mmol) and silver nitrate (0.257 g, 1.51 mmol) in one portion. The solution stirred in the dark at rt 2h, then was diluted with Et$_2$O and quenched with sat. NH$_4$Cl (aq). The aqueous layer was extracted with Et$_2$O and the organic layers were washed with H$_2$O and brine, dried over MgSO$_4$, and concentrated. The residue was purified by silica gel chromatography (5-10-20% EtOAc:Hex) to yield 1.81 g (67%) of 7 as a yellow oil. $^1$H NMR (500 MHz, CDCl$_3$): δ 1.53-1.59 (2H, m), 1.65-1.74 (6H, m), 2.38 (2H, t, J = 7.1 Hz), 2.44-2.47 (2H, m), 2.57-2.61 (4H, m), 5.86 (2H, m), 9.77 (1H, t, J = 1.8 Hz). $^{13}$C NMR (125 MHz, CDCl$_3$): δ 20.6, 21.6, 27.2, 27.5, 27.6, 27.8, 27.9, 43.6, 77.3, 94.4, 105.3, 105.4, 153.8, 154.1, 202.4. LCMS m/z calcd for C$_{15}$H$_{19}$IO$_2$ 358.0, found 359.1 (M + H).
16-oxabicyclo[11.2.1]hexadeca-1(15),13-dien-7-yn-6-ol (8)

\[
\begin{align*}
\text{NiCl}_2, \text{CrCl}_2 & \quad \text{THF} \\ 3 \text{Å MS} & \quad 86\%
\end{align*}
\]

Chromium (II) chloride (6.16 g, 50.1 mmol), nickel (II) chloride (0.389 g, 3.00 mmol), and 3Å molecular sieves (0.200 g) were charged to a flask under a nitrogen atmosphere. Contents were degassed three times, then THF (33.4 mL) was added and the slurry was deoxygenated by bubbling in nitrogen for 30 minutes. A solution of iodide 7 (1.79 g, 5.01 mmol) in THF (167 mL) was prepared in a nitrogen atmosphere, and this solution was also deoxygenated by bubbling in nitrogen for 30 min. The iodide solution was added dropwise over 15 h to the chromium slurry using a syringe pump. After 24 h, TLC indicated the starting material had fully reacted. The reaction was quenched with a 1M aqueous solution of ethylene diamine. The aqueous layer was extracted several times with a 1:1 Et₂O:EtOAc solution. The combined organic layers were washed with 1M HCl (aq) and brine. The organic phases were dried over MgSO₄, and concentrated. Residue was purified by silica gel chromatography (10-20% EtOAc:Hex) to yield 1.00 g (86%) of propargyl alcohol 8 a pale yellow solid. ¹H NMR (500 MHz, CDCl₃): \( \delta \) 1.25-1.48 (2H, m), 1.53-1.63 (2H, m), 1.64-1.73 (2H, m), 175-1.90 (2H, m), 2.10-2.23 (2H, m), 2.53-2.69 (4H, m), 4.38-4.40 (1H, m), 5.83 (1H, d, \( J = 2.8 \) Hz), 5.87 (1H, d \( J = 2.7 \) Hz). ¹³C NMR (125 MHz, CDCl₃): \( \delta \) 18.6, 23.7, 26.2, 26.9, 27.3, 27.6, 28.6, 37.6, 62.7, 81.0, 86.2, 105.5, 106.9, 152.9, 154.6. LCMS m/z calcd for C₁₅H₂₀O₂Na 255.1, found 255.1 (M + Na).

16-oxabicyclo[11.2.1]hexadeca-1(15),13-dien-7-yn-6-yl acetate (9)

\[
\begin{align*}
\text{AcCl, Py, DMAP} & \quad \text{CH}_2\text{Cl}_2, 0 \degree C \\ 99\%
\end{align*}
\]

Dimethylamino pyridine (0.010 g, 0.081 mmol) was dissolved in dry methylene chloride (12.4 mL) under an atmosphere of nitrogen. The solution was cooled to 0 °C, then propargyl alcohol 8
(0.375 g, 1.61 mmol) and pyridine (1.28 g, 16.1 mmol) were added. The mixture stirred at this temperature 15 min, then acetyl chloride (0.380 g, 4.84 mmol) was added dropwise by syringe. The reaction mixture stirred 1h at 0 °C, and was allowed to warm to rt. After 2h, the reaction was diluted with hexanes, vacuum filtered, and concentrated. The residue was purified through silica gel chromatography (10-20% EtOAc:Hex) to yield 0.437 g (99%) of acetate 9 as a colorless oil.  

\[ \text{H NMR (500 MHz, CDCl}_3\text{): } \delta 1.29-1.39 (2H, m), 1.42-1.51 (2H, m), 1.56-1.64 (1H, m), 1.65-1.74 (3H, m), 1.77-1.92 (2H, m), 2.05 (3H, s), 2.13-2.25 (2H, m), 2.54-2.70 (4H, m), 5.35-5.39 (1H, m), 5.84 (1H, d, J = 2.9 Hz), 5.88 (1H, d, J = 2.9 Hz). \]

\[ \text{13C NMR (125 MHz, CDCl}_3\text{): } \delta 18.6, 21.1, 23.5, 26.2, 26.7, 27.1, 27.5, 28.5, 34.4, 64.8, 77.3, 87.1, 105.5, 106.9, 152.9, 154.5, 170.0. \]

\[ \text{LCMS m/z calcd for C}_{17}\text{H}_{22}\text{O}_3\text{Na 297.1, found 297.1 (M + Na).} \]

**Typical Procedure for Au\(^{1}\)-catalyzed transannular [4 + 3] cycloadduct 13**

Gold(I) catalyst 10 (9 mg, 17 μmol) and silver hexafluoroantimonate (6 mg, 17 μmol) were charged to a flask under a nitrogen atmosphere, degassed three times, and purged with nitrogen for fifteen minutes before dry methylene chloride (1 mL) was added to the reaction flask. A solution of 9 in dry methylene chloride (1 mL) was added dropwise to the flask. After completion of reaction by TLC, the reaction was diluted with Et2O and filtered through a pad of silica and Celite. The ethereal layers were concentrated and the residue was purified via silica gel chromatography (10% EtOAc:Hex) to yield 35mg (70%) of a white solid.  

\[ \text{H NMR (500 MHz, CDCl}_3\text{): } \delta 0.96-1.06 (1H, m), 1.24-1.47 (4H, m), 1.51-1.61 (2H, m), 1.66-1.98 (8H, m), 2.10 (3H, s), 2.45-2.49 (1H, m), 2.71 (1H, d, J = 13.3 Hz), 5.97 (1H, d, J = 5.85 Hz), 6.78 (1H, d, J = 5.85 Hz). \]

\[ \text{13C NMR (125 MHz, CDCl}_3\text{): } \delta 20.3, 23.1, 23.4, 24.0, 24.2, 24.3, 25.9, 32.1, 34.9, 46.6, 83.6, 86.1, 129.2, 129.9, 139.5, 143.2, 168.7. \]

\[ \text{FTIR (neat): } 3079, 2940, 2932, 2865, 2853, 1748, 1671, 1444, 1370, 1210, 1178, 1160, 1143, 1120, 1054, 1040, 1018, 971, 944, 897, 887, 822, 755, 745 \text{ cm}^{-1}. \]

\[ \text{HRMS m/z calcd for C}_{17}\text{H}_{22}\text{O}_3\text{Na 297.1467, found 297.1461 (M + Na).} \]
Transannular Cycloaddition Product (14)

Dichloro(2-pyridinecarboxylato)gold 11 (9.4 mg, 24 μmol) and sodium bicarbonate (40 mg, 0.47 mmol) was added to a flask containing CH2Cl2 (3.7 ml) under a nitrogen atmosphere. Macrocycle 9 (0.13 g, 0.47 mmol) in CH2Cl2 (1.0 ml) was then added dropwise by syringe. After 2 d, TLC showed that no starting material was remaining and the reaction was diluted with ether and filtered through Celite. The solvent was evaporated and the residue was purified over silica gel (5-10% EtOAc/hexanes) which provided 83 mg (64%) of cycloadduct 14 and 27 mg (21%) of cycloadduct 13. Cycloadduct 14 1H NMR (500 MHz, CDCl3): δ 1.28-1.40 (3H, m), 1.58-1.69 (4H, m), 1.75-1.89 (5H, m), 1.98 (3H, s), 2.04-2.10 (2H, m), 2.24-2.30 (1H, m), 2.84-2.87 (1H, m), 5.64-5.65 (1H, d, J = 2.5Hz), 5.69-5.70 (1H, d, J = 6Hz), 6.70-6.71 (1H, d, J = 5Hz). 13C NMR (125 MHz, CDCl3): δ 21.3, 21.5, 22.2, 23.6, 24.8, 30.9, 31.1, 31.4, 32.2, 79.4, 85.5, 87.2, 119.2, 134.1, 142.3, 145.8, 170.1. HRMS calcd for C17H22O3Na 297.1467, found 297.1473 (M+Na).

Hydrogenated Compound 15

Compound 9 (0.096g, 0.349 mmol) and Pd/C (5 mg/0.1 mmol) was combined with EtOAc (14.0 mL) in an atmosphere of nitrogen and degassed. The solution was placed under a hydrogen atmosphere, and stirred 1.5 h at rt. Reaction was diluted with EtOAc, filtered through a celite plug, and concentrated. Residue was purified by silica gel chromatography to afford 92 mg (95 %) of the saturated vinyl acetate 15. 1H NMR (500 MHz, CDCl3): δ 1.10-1.36 (6H, m), 1.52-1.54 (2H, m), 1.60-1.89 (9H, m), 2.13 (3H, s), 2.21-2.23 (2H, m), 2.38-2.41 (1H, m), 2.67-2.69 (1H,m) 13CNMR (125MHz, CDCl3): δ 20.3, 23.8, 23.9, 24.0, 24.2, 25.0, 25.3, 31.0, 34.9, 37.1, 38.5, 47.6,81.2, 81.7, 126.3, 139.9, 168.7 LCMS m/z calcd for C17H24O3Na 299.2, found 299.2 (M + Na).
Preparation of Ketone 16

The vinyl acetate 15 (90 mg, 0.33 mmol) was dissolved in methanol (11 ml) and potassium carbonate (3 mg, 21 μmol) was then added. At 3 h, TLC indicated that the starting ester had fully reacted and the reaction mixture was diluted with ether and quenched with 1M HCl. The layers were separated and the aqueous phase was extracted with ether. The combined organic extracts were washed with brine and dried over MgSO4. The solution was concentrated and the residue was purified over silica gel (5-10% EtOAc/Hexane) to give 73 mg (94%) of ketone 16. 1H NMR (500 MHz, CDCl3): δ 1.15-1.29 (8H, m), 1.48-1.49 (2H, m), 1.74-1.93 (10H, m), 2.44-2.46 (2H, m). 13C NMR (125 MHz, CDCl3): δ 22.8, 23.8, 24.7, 31.2, 37.7, 57.9, 85.2, 209.3. FTIR (neat): 2972, 2918, 2856, 1704, 1454, 1365, 1314, 1261, 1167, 1076, 1058, 977, 970, 934, 875, 851, 800, 697 cm⁻¹. HRMS m/z calcd for C15H23O2 235.1698, found 235.1696 (M + Na).

Formation of Hydrazone 17

To a solution of ketone 16 (16 mg, 68 μmol) in methanol (3.4 ml) was added p-TsOH (1 mg, 3 μmol) followed by the 2,4-dinitrophenyl hydrazine (26 mg, 0.109 mmol). The reaction was heated to reflux and after 1h the reaction had completed as indicated by TLC. The reaction was cooled to rt and the solvent was removed by rotary evaporation. The residue was purified over silica gel and provided 22 mg (79%) of (17). A crystal of 17 was harvested and an X-ray structure of 17 was obtained. See next section for details. 1H NMR (500 MHz, CDCl3): δ 1.18-1.33 (m, 4H), 1.39-1.49 (1H, m), 1.51-1.60 (m, 2H), 1.78-1.84 (7H, m), 1.93-2.02 (3H, m), 2.05-2.08 (2H, m), 2.40-2.43 (1H, m), 2.72-2.77 (2H, m), 7.93 (1H, d, J = 9.60 Hz), 8.28 (1H, dd, J = 9.63, 2.60 Hz), 9.10 (1H, d, J = 2.55 Hz), 12.06 (1H, s). 13C NMR (125 MHz, CDCl3): δ 23.3, 23.9, 25.4, 26.0, 26.1, 28.1, 31.5, 32.8, 37.3, 37.7, 53.9, 54.1, 83.7, 84.4, 116.1, 123.5, 129.2, 129.9, 137.6, 146.2, 156.2. LCMS m/z calcd for C21H26N4O5Na 437.2, found 437.2 (M + Na).

Selective Hydrogenation of Transannular [4 + 3] Cycloadduct 14
Cycloadduct 14 (44 mg, 0.160 mmol) was dissolved in freshly distilled benzene (2 ml) and Wilkinson’s catalyst (30 mg, 32 μmol) was added under a nitrogen atmosphere. The nitrogen atmosphere was replaced with an atmosphere of hydrogen at 1 atm and the mixture was allowed to stir at rt for 19 h. The solvent was removed by rotary evaporation and the residue was purified over silica gel (2-5% EtOAc/hexanes) and provided 34 μg (77%) of 18. 1H NMR (500 MHz, CDCl3): δ 1.18-1.33 (3H, m), 1.46-1.48 (2H, m), 1.49-1.50 (1H, m), 1.52-1.55 (1H, m), 1.56-1.60 (1H, m), 1.62-1.65 (1H, m), 1.70-1.75 (1H, m), 1.76-1.89 (5H, m), 1.95-2.01 (2H, m), 2.02 (3H, s), 2.18-2.22 (1H, m), 2.34-2.42 (1H, m), 2.69-2.72 (1H, m) 5.87 (1H, d, J = 2.50 Hz). 13C NMR (125 MHz, CDCl3): δ 20.7, 22.2, 22.3, 24.0, 26.0, 31.4, 33.3, 33.4, 35.1, 36.0, 80.4, 83.7, 84.2, 119.6, 142.7, 170.3. LCMS m/z calcd for C17H24O3Na 299.2, found 299.1 (M + Na).

Hydrolysis of Acetate

The acetate 18 (21 mg, 76 μmol) was dissolved in methanol (2 mL) and potassium carbonate (0.3 mg, 2 μmol) was then added. At 4 d, TLC indicated that the starting ester had fully disappeared and the reaction mixture was diluted with ether and quenched with 1M HCl. The layers were separated and the aqueous phase was extracted with ether. The combined organic extracts were washed with brine and dried over MgSO4. The solution was concentrated and the residue was purified over silica gel (5-10% EtOAc/Hexane) to give 7 mg (39%) of ketone 19. 1H NMR (500 MHz, CDCl3): δ 1.25-1.31 (2H, m), 1.42-1.48 (3H, m), 1.49-1.61 (5H, m), 1.63-1.66 (1H, m), 1.70-1.74 (1H, m), 1.76-1.88 (4H, m), 1.90-1.96 (1H, m), 1.98-2.05 (2H, m), 2.17-2.21 (1H, m), 2.29-2.36 (1H, m), 4.97 (1H, d, J = 2.0 Hz). 13C NMR (125 MHz, CDCl3): δ 20.7, 22.4, 24.1, 26.1, 31.2, 32.7, 33.2, 35.2, 36.4, 36.5, 72.8, 81.5, 83.1, 124.9, 141.1. LCMS m/z calcd for C15H22O2Na 257.2, found 257.1 (M + Na).

X-ray Crystallography

Crystallization. In a typical procedure, the compound was dissolved in dichloromethane and placed in the long tube. The solution was carefully covered with methanol and sealed and let standing at room temperature. As the solvents diffused slowly, crystals were formed at the interface. Single crystal X-ray data were collected on a Smart6000 CCD diffractometer.
equipped with a low temperature device and a normal-focus sealed-tube X-ray source (Mo-Kα radiation, \( \lambda = 0.71073 \) Å, graphite monochromated) operating at 45 kV and 45 mA. Frames were collected with 0.3° intervals in \( \omega \) at 3 different \( \phi \) settings for 40 s (S2a) and 20 s (S2b) per frame such that more than a hemisphere of data was collected. Raw data collection was performed using SMART\(^1\); final unit cell determination, data reduction and corrections for Lorentz and polarization effects was performed using SAINT+.\(^2\) The structures were solved by direct methods and refined by full-matrix least-squares on \( F^2 \) with anisotropic displacement parameters for non-hydrogen atoms and isotropic atomic displacement factors for hydrogen atoms using SHELXTL 6.14.\(^3\)

**References:**


**Crystal Structure of 17**
Chapter 2.


2.1 Introduction

The ability to access multiple fused rings through a transannular [4 + 3] cycloaddition is certainly a novel reaction for an organic chemist. However, the preparation of a macrocyclic precursor, especially one that is highly functionalized, is tedious and not always trivial. It seems that the simplest and most accessible route to fused ring products would arise from the intermolecular variant of the [4 + 3] cycloaddition. The ability to prepare simple starting materials in high yield from only a few steps seems an attractive alternative to the transannular version of the reaction, and limits the time preparation to access the complex molecular structures. In addition, minor changes in the size of the macrocycle can lead to very different products, which limits the scope of the reaction depending on the desired target molecule.

Different versions of the intermolecular [4 + 3] reactions have been previously reported. The synthesis of azepines and benzonorcaradienes from propargyl ester precursors have been documented by the Toste group. Harmata and Huang reported the formation of [4 + 3] cycloadducts from 5-siloxydioxins and cyclopentadiene or furan. Both groups used gold-catalysis to achieve their desired transformation, but other transition metal catalysts have also been used. The Davies group utilized a Rh (II) catalyst to synthesize tropanes and (+)-frondosin B through a tandem cyclopropanation/Cope rearrangement process. Ohe and Uemura proposed the Ru-catalyzed cyclopropanation of propargyl acetates with unactivated dienes and subsequent thermal Cope rearrangement to form formal [4 + 3] cycloadducts.

We sought to expand our gold-catalyzed transannular [4 + 3] cycloaddition to the intermolecular version. To this end, we decided to employ reactions with propargyl acetates with unactivated dienes, as these were easily accessible, simple precursors to prepare. For this methodology to be successful, we would need to achieve a high yield of the [4 + 3] cycloadducts in mild reaction conditions. This chapter describes the gold-catalyzed intermolecular version of the [4 + 3] reaction. Cyclic dienes, such as cyclopentadiene and furan, and one example of an acyclic diene were investigated. Specific mechanistic considerations are also considered.

2.2 Results and Discussion

Propargyl esters are easily accessible synthetic precursors, and the well-studied 3,3-rearrangement to acetoxyallenes make them attractive candidates for the three-carbon component of [4 + 3] reactions. Propargyl esters 22a-e were prepared from 2-methyl-3-butyne-2-ol and the corresponding acyl chloride (see experimental section for details). The initial experiments were carried out with various propargyl esters 22a-e and cyclopentadiene using Au(III) catalyst PicAuCl₂ 11 (Table 2.1). Other Au(I) catalysts 10, 12, 26 and 27 were also screened for their catalytic activity (Figure 2.1).
In the presence of Au(III) catalyst PicAuCl$_2$ 11, the reaction of propargyl esters 22a-e and cyclopentadiene 23 underwent an intermolecular cyclopropanation reaction and a formal [4C + 3C] cycloaddition to afford products 24a-e and 25a-e, respectively. The yields for

**Table 2.1** [Au]-catalyzed Cyclopropanations/Intermolecular [4 + 3] Cycloadditions

<table>
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<th>Entry</th>
<th>[Au] cat.$^a$</th>
<th>mol %</th>
<th>R</th>
<th>Time (h)</th>
<th>%Yield</th>
<th>Ratio (24:25)</th>
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<td>11</td>
<td>5</td>
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<td>57</td>
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<tr>
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<td>11</td>
<td>5</td>
<td>$t$-Butyl (b)</td>
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<td>57</td>
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<tr>
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<td>11</td>
<td>5</td>
<td>Phenyl (c)</td>
<td>24</td>
<td>90</td>
<td>1:2.1</td>
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<tr>
<td>4</td>
<td>11</td>
<td>5</td>
<td>$p$-Tolyl (d)</td>
<td>24</td>
<td>92</td>
<td>1:2.1</td>
</tr>
<tr>
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<td>11</td>
<td>5</td>
<td>$p$-NO$_2$Ph (e)</td>
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<td>63</td>
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<td>$p$-Tolyl (d)</td>
<td>23</td>
<td>92</td>
<td>1:1.6</td>
</tr>
<tr>
<td>8$^b$</td>
<td>10</td>
<td>5</td>
<td>$p$-Tolyl (d)</td>
<td>3</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>9$^b$</td>
<td>26</td>
<td>5</td>
<td>$p$-Tolyl (d)</td>
<td>2</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>10$^b$</td>
<td>27</td>
<td>5</td>
<td>$p$-Tolyl (d)</td>
<td>0.25</td>
<td>n/a</td>
<td>n/a</td>
</tr>
</tbody>
</table>

[a] No silver co-catalyst was used for Au(III) catalyst 11.  [b] Complex mixtures.
these reactions were higher for the benzoate esters (entries 3 and 4) that did not contain an
electron withdrawing group. In the case of benzoate ester 22e which contained a nitro
substituent (entry 5), the yield was moderate (63%) and less of the desired [4 + 3] product was
obtained. It is also noteworthy that although the polarities of the two products 24a-d and 25a-d
were very similar, separation by silica gel chromatography to obtain pure samples was possible
with all the products except for 24e and 25e. The low yields of the two alkyl esters 22a and 22b
could be attributed to the volatility of the products (entries 1 and 2).

![Catalysts](image)

**Figure 2.1** Au(III) and Au(I) catalysts.

Though other Au (I) catalysts were ineffective for the desired transformations (entries 8-
10), we were delighted to discover that the Au(I) catalyst 12 with an N-heterocyclic carbene
(NHC) ligand was highly successful for this reaction. Using 5 mol % of catalyst 12, the reaction
was complete in just one hour (entry 6). Gratifyingly, the catalyst loading could be decreased to
just 1 mol % and with a longer reaction time, the transformation proceeded smoothly to give the
desired products in high yield (entry 7).

A report by Ohe and Uemura illustrates a very similar reaction using a rhodium catalyst, though
a higher reaction temperature and catalyst loading (2.5 mol %) is required, and low yields of the
[4 + 3] product were obtained. The reaction of 22a was studied in this report and assigned
end stereoisomer, based on the complete conversion of the vinyl cyclopropane to the [4 + 3]
cycloadduct in a thermal Cope rearrangement. The $^1$H NMR and $^{13}$C NMR spectra of our
compound were consistent with the data reported in this publication. As a result, our products
were also assigned endo stereoisomer. There was no evidence in our data of a vinyl
cyclopropane with exo stereoisomer.

The vinyl cyclopropanes 24a-e can be converted to their corresponding bicyclo[3.2.1]octa-2,6-
dienes 25a-e through a thermal Cope rearrangement by heating a solution of 24 in toluene at
reflux for 12h. The structure of the bicyclic products 25a-e was further confirmed by conversion
to the known ketone 28 by base-catalyzed ester hydrolysis (Scheme 2.1).
Scheme 2.1 Conversion of [4 + 3] Cycloadducts to Known Ketone 28.

It was reasonable to assume that substrates 24a-e could undergo a Cope rearrangement in situ to form bicycles 25a-e and that a longer reaction time could generate only the formal [4 + 3] product. However, refluxing the reaction in CH₂Cl₂ did not provide the [4 + 3] cycloadduct as a single product, and did not improve the ratios of the two products. In order to probe the mechanism of this reaction, substrate 24d was subjected to fresh Au(I) NHC catalyst 12 (see Table 1.1). No reaction occurred after the solution stirred overnight at room temperature. These results demonstrate that there are two competing mechanistic pathways which produce the products 24 and 25 (Scheme 2.2).

Scheme 2.2 Mechanistic Pathways of the Intermolecular Cycloadditions

Gold-catalyzed reactions of propargyl acetates have the possibility to react in two different ways. Often, the initial step of the reaction of these substrates is a 1,\(n\)-acyl shift (where \(n = 2\) or 3). Whether these substrates are more likely to undergo a 1,2- or a 1,3-acyl shift is a topic of much debate. It has been suggested that in fact these carbene and allene-type intermediates coexist in equilibrium with each other.\(^{10,39}\) This is consistent with the outcome of our reaction. The first mechanistic pathway involves a 1,2-acyl shift (top) to form a gold carbene which undergoes direct cyclopropanation with cyclopentadiene to form vinyl cyclopropanes 24. The second pathway (bottom) involves a 1,3-acyl shift, or 3,3-sigmatropic rearrangement, of the propargyl ester to generate an acetoxy allene. This species undergoes an intermolecular [4 + 3]...
Encouraged by the catalytic activity of Au(I) NHC catalyst 12, the study was expanded to different four-carbon components. The first study utilized furan as the diene substrate. In our initial studies, it seemed that the benzoate ester containing an electron donating group (Table 2.1, entry 4) provided the most favorable results. As a result, propargyl ester 22f, bearing a p-methoxy substituent, a slightly better electron donor than the tolyl ester, was synthesized and employed in the reaction with furan. In the presence of 1 mol % of 12, propargyl ester 22f was reacted with furan 29 (Scheme 2.3). Intriguingly, the activity of the gold catalyst 12 mirrors the reaction with the Ru catalyst40 and provides triene aldehyde 31f exclusively when CH2Cl2 was used as the solvent. However, when the same reaction was conducted in pentane, a significant amount of the formal [4 + 3] cycloadduct is obtained. The structure of 30f was verified by converting it to the known ketone 3241 (Scheme 2.3).

In order to expand the scope of the reaction to different substrates, a secondary propargyl ester was prepared. Propargyl ester 33 was reacted with cyclopentadiene in the presence of 5 mol % of catalyst 12 (Scheme 2.4). Interestingly, the reaction proceeded smoothly to provide 34 as the dominant product with a few minor impurities which were inseparable by column chromatography. To confirm the stereochemistry of 34, the ester was removed via base-catalyzed hydrolysis to provide 35a and 35b. Product 35a was identified as the major product and could be unambiguously identified as it had been previously prepared using the classical
oxyallyl cation addition to cyclopentadiene. Structure 35b was also isolated with a small amount of unidentified isomers.

![Scheme 2.4 Reactions of secondary propargyl ester 33.](image)

The reaction of the secondary propargyl ester 33 is drastically different from that of the tertiary propargyl esters 22a-e. The latter provided nearly a 1:1 mixture of cyclopropanation and [4 + 3] cycloadducts, while the former provided only the [4 + 3] cycloadduct with high diastereoselectivity. There was no evidence of the cyclopropanation products in the NMR data with this substrate. It is therefore likely that this substrate undergoes a direct [4 + 3] cycloaddition arising from formation of the acetoxy allene through the 3,3-rearrangement of the propargyl ester. This is evidence is supported by the mild reaction conditions utilized. In order to convert the cyclopropanation products of the tertiary propargyl esters to the [4 + 3] cycloadduct, high temperature is required. In contrast, the formation of the [4 + 3] cycloadduct 34 from the secondary propargyl ester was achieved at room temperature when the reaction was stirred overnight. It is also likely that the secondary propargyl ester bearing a phenyl substituent is prone to undergo a 3,3-rearrangement to form the acetoxy allene due to the increased stability of a benzylic allene. This would help to eliminate the possibility of the competing 1,2-acyl shift.

One final reaction was attempted to expand the scope of these intermolecular [4 + 3] reactions (Scheme 2.5). The secondary propargyl ester 33 was reacted with an acyclic diene, (Z)-buta-1,3-dienylbenzene 36. When the reaction stirred overnight with only 1 mol % [Au] catalyst 12 in the presence of AgSbF$_6$, 67% of a mixture of [4 + 3] cycloadduct 37a and vinylcyclopropane 37b were obtained in a 1.6:1 ratio. Regrettably, these products were inseparable by silica gel chromatography, so they were subjected to base-catalyzed hydrolysis to provide 38a and 38b. The identity of the structures was confirmed using 2D-COSY NMR experiments.
Intriguingly, there was no evidence of the other regioisomer that could arise in the [4 + 3] cycloaddition. This has further implications on the mechanism, suggesting that the [4 + 3] reaction occurs in a stepwise fashion for these substrates. If the cycloaddition were concerted, then it is likely a mixture of regioisomers would be obtained due to the steric hinderance of the two phenyl groups. However, these results suggest that the first step occurs at the least sterically hindered carbon, allowing for the formation of only one regioisomer.

The mechanism is shown below in Scheme 2.6. Gold-activation of the triple bond in 33 can initiate a 1,2-acyl shift to provide the gold carbene. Direct cyclopropanation with the terminal double bond of the acyclic diene gives vinyl cyclopropane 37a. However, this carbene can also be represented as a resonance structure with the vinyl carbocation. When this occurs, attack from the terminal double bond of the diene generates the second carbocation intermediate. This intermediate quickly undergoes a rearrangement to form the more stable benzylic cation. Subsequent deauration and trapping of the carbocation from the olefin moiety generates the intermolecular [4 + 3] cycloadduct 37a as a single regioisomer.
2.3 Conclusion

In conclusion, an improved intermolecular [4 + 3] cycloaddition has been discovered. The [4 + 3] cycloadducts are formed with higher yield and in milder conditions than previously reported with the Ru catalyst. The reaction with the Au catalysts proceeds exclusively to generate products with endo stereochemistry. The vinylcyclopropanes with exo stereochemistry were not detected as the subsequent thermal Cope rearrangement would not occur with these isomers. Additionally, we have demonstrated that there are two competing mechanistic pathways which generate the vinyl cyclopropanes and [4 + 3] cycloadducts, respectively. The vinyl cyclopropanes do not rearrange to the bicyclo[3.2.1]octa-2,6-dienes with fresh Au catalyst, eliminating the possibility of a stepwise cyclopropanation/Cope rearrangement sequence. The [4 + 3] products can be generated with furan as the four-carbon component to form the oxabicyclo[3.2.1]-octa-2,6-dienes when pentane is used as a solvent. The [4 + 3] cycloadduct can also be obtained exclusively when a secondary propargyl ester bearing a phenyl substituent is used. Lastly, it has been demonstrated that not only cyclic dienes, but acyclic dienes can also participate in this reaction. The reaction proceeds in a stepwise fashion to provide the [4 + 3] cycloadduct with exclusive regioselectivity, along with some of the vinyl cyclopropane product. This improved methodology leads to a much simpler way of generating seven-membered bridged rings from easily generated propargyl esters and unactivated dienes.
2.4 Experimental Procedures

General Experimental Procedures

Unless otherwise stated, all reactions were carried out under an inert nitrogen atmosphere with dry solvents under anhydrous conditions. Dry tetrahydrofuran (THF) and toluene (PhCH3) were distilled over sodium benzophenone, dichloromethane (CH2Cl2), dichloroethane (DCE), and pentane (C5H12) were distilled over calcium hydride. Reagents were purchased and used without further purification unless otherwise stated. Yields refer to chromatographically and spectroscopically (1H NMR) homogeneous materials, unless otherwise stated. Reactions were monitored by thin layer chromatography (TLC) carried out on 0.25 mm Merck silica gel plates (60F-254) using UV light as the visualizing agent and an acidic mixture of anisaldehyde, phosphomolybdic acid, or ceric ammonium molybdate, or basic aqueous potassium permangante (KMnO4), and heat as developing agents. Merck silica gel (60, particle size 0.043–0.063 mm) was used for flash column chromatography. NMR spectra were recorded on Bruker Av-500, and Av-300 instruments and calibrated using residual undeuterated solvent as an internal reference (CHCl3 @ 7.26 ppm 1H NMR, 77.0 ppm 13C NMR). The following abbreviations (or combinations thereof) were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad. IR spectra were recorded on a Perkin Elmer Spectrum 2000 FTIR spectrometer. Melting points were recorded on a Thomas-Hoover melting point apparatus.

2-methylbut-3-yn-2-yl 4-methylbenzoate (22d)

\[
\text{OH} + \text{Cl} \xrightarrow{\text{DMAP, Pyridine, CH}_{2}\text{Cl}_2, \text{r.t. to reflux}} \text{O} \quad \text{22d}
\]

2-methyl-3-butyln-2-ol (200 mg, 2.4 mmol) was added to a solution of DMAP (15 mg, 0.119 mmol), pyridine (1.9 mL, 24.0 mmol) and CH2Cl2 (2.4 mL) under a nitrogen atmosphere. The mixture was stirred 15 min. at room temperature. The acid chloride (0.94 mL, 7.2 mmol) was added by syringe at the same temperature and the reaction was heated to reflux (45-50°C) and stirred overnight. The reaction was cooled to room temperature, diluted with Et2O, and quenched with 1N HCl. The aqueous layer was extracted with Et2O, and the combined organic extracts were washed with 10% aq. NaOH, and brine. The organic extracts were dried over MgSO4, filtered, concentrated, and purified via silica gel chromatography (5-10-20% EtOAc/hexanes) to yield 460 mg (95 %) of a colorless oil. 1H NMR (300 MHz, CDCl3): δ 1.81 (6H, s), 2.39 (3H, s), 2.57 (1H, s), 7.21 (2H, d, J = 8.1 Hz), 7.92 (2H, 8.1 Hz). 13C NMR (75
MHz, CDCl3): δ 21.6, 29.0, 71.9, 72.4, 84.8, 128.0, 128.9, 129.6, 143.4, 164.8. LCMS calcld for C\textsubscript{13}H\textsubscript{14}O\textsubscript{2}Na 225.1, found 225.0.

**1-phenylprop-2-ynyl 4-methylbenzoate (33)**

\[
\begin{align*}
\text{Ph} & \quad \text{O} \\
\text{CH}_2\text{CH}=\text{C} & \quad \text{O} \\
\text{H} & \quad \text{Cl} \\
\end{align*}
\]

1-phenylprop-2-yn-1-ol (250 mg, 1.9 mmol) was added to a solution of DMAP (12 mg, 0.095 mmol), pyridine (1.53 mL, 24.0 mmol) and CH\textsubscript{2}Cl\textsubscript{2} (3.8 mL) under a nitrogen atmosphere. The mixture was stirred 15 min. at 0 °C. The acid chloride (0.75 mL, 5.67 mmol) was added was added by syringe at the same temperature. After 2h and completion by TLC, the reaction was warmed to room temperature, diluted with Et\textsubscript{2}O, and quenched with 1N HCl. The aqueous layer was extracted with Et\textsubscript{2}O, and the combined organic extracts were washed with 10% aq. NaOH, and brine. The organic extracts were dried over MgSO\textsubscript{4}, filtered, concentrated, and purified via silica gel chromatography (5-10-20% EtOAc/hexanes) to yield 384 mg (81 %) of a colorless oil. \textsuperscript{1}HNMR (300 MHz, CDCl3): δ 2.39 (3H, s), 2.67-2.69 (1H, m), 6.69 (1H, d, J = 2.1 Hz), 7.22 (2H, d, J = 8.1 Hz), 7.36-7.42 (3H, m), 7.60-7.63 (2H, m), 7.96 (2H, d, J = 8.4 Hz). \textsuperscript{13}C NMR (75 MHz, CDCl3): δ 21.6, 65.6, 75.5, 80.4, 126.8, 127.6, 128.7, 129.0, 129.1, 129.9, 136.7, 144.0, 165.4. LCMS calcld for C\textsubscript{17}H\textsubscript{14}O\textsubscript{2}Na 273.1, found 273.1.

**Typical Procedure for Intermolecular Cyclopropanation/Formal [4C + 3C] Cycloaddition**

Dichloro(2-pyridinecarboxylato)gold 11 (12 μmol) was added to a flask containing CH\textsubscript{2}Cl\textsubscript{2} (0.6 mL) under a nitrogen atmosphere at room temperature. A solution of propargyl ester 22 (0.247 mmol) and cyclopentadiene (1.24 mmol) in CH\textsubscript{2}Cl\textsubscript{2} (0.6 mL) were added to the flask by syringe. The reaction was permitted to stir overnight and monitored by TLC. The reaction was diluted with EtOAc and filtered through a pad of silica and Celite. The filtrate was concentrated and purified via silica gel chromatography (1% EtOAc/hexanes).
**Vinylcyclopropane 24a.** A colorless oil (31 mg, 0.16 mmol, 23% yield). Data was consistent with previously reported values.37

**Formal [4C + 3C] Cycloadduct 25a.** A colorless oil (47 mg, 0.024 mmol, 34% yield). Data was consistent with previously reported values.37

**Vinylcyclopropane 24b.** A colorless oil (23 mg, 0.10 mmol, 17% yield). 1H NMR (500 MHz, CDCl3): δ 1.26 (9H, s), 1.51 (3H, s), 1.74 (3H, s), 1.82-1.86 (1H, m), 1.95-1.99 (1H, m), 2.12-2.16 (1H, m), 2.23-2.27 (1H, m), 2.48-2.53 (1H, m), 5.44-5.46 (1H, m), 5.66-5.68 (1H, m). 13C NMR (125 MHz, CDCl3): δ 17.1, 18.7, 22.5, 23.2, 27.3, 30.1, 32.9, 38.8, 122.9, 129.3, 129.7, 138.7, 176.8. LCMS calcd for C15H22O2Na 257.1, found 257.1.

**Vinylcyclopropane 24c.** A colorless oil (39 mg, 0.15 mmol, 29% yield). Data was consistent with previously reported values.37

**Formal [4C + 3C] Cycloadduct 25c.** A colorless oil (83 mg, 0.33 mmol, 61% yield). Data was consistent with previously reported values.37

**Vinylcyclopropane 24d.** A colorless oil (40 mg, 0.15 mmol, 30% yield). 1H NMR (500 MHz, CDCl3): δ 1.58 (3H, s), 1.80 (3H, s), 1.86-1.91 (1H, m), 2.08-2.11 (1H, m), 2.16-2.19 (1H, m), 2.28-2.31 (1H, m), 2.43 (3H, s), 2.50-2.55 (1H, m), 5.50-5.51 (1H, m), 5.65-5.67 (1H, m), 7.26 (2H, d, J = 6.95 Hz), 7.96 (2H, d, J = 8.05 Hz). 13C NMR (125 MHz, CDCl3): δ 17.4, 18.6, 21.7, 22.9, 23.5, 30.4, 33.11, 118.0, 123.3, 127.6, 129.1, 129.6, 129.9, 138.9, 143.6, 164.8. LCMS calcd for C18H20O2Na 291.1, found 291.1.

**Formal [4C + 3C] Cycloadduct 25d.** A colorless oil (83 mg, 0.31 mmol, 62% yield). 1H NMR (500 MHz, CDCl3): δ 1.00 (3H, s), 1.26 (3H, s), 1.90-1.94 (1H, m), 2.04-2.06 (1H, m), 2.41 (3H, s), 2.53 (1H, s), 2.85 (1H, s), 5.87-5.90 (2H, m), 6.41-6.42 (1H, m), 7.25 (2H, d, J = 8.20 Hz), 7.94 (2H, d, J = 8.05 Hz). 13C NMR (125 MHz, CDCl3): δ 21.7, 27.5, 38.4, 39.4, 40.3, 51.3, 120.1, 127.5, 129.1, 129.6, 131.2, 141.0, 143.8, 151.1, 165.3. LCMS calcd for C18H20O2Na 291.1, found 291.1.

**Vinylcyclopropane 24e.** A white solid (36 mg, 0.12 mmol, 28% yield). 1H NMR (500 MHz, CDCl3): δ 1.59 (3H, s), 1.82 (3H, s), 1.91-1.95 (1H, m), 2.09-2.12 (1H, m), 2.18-2.28 (2H, m), 2.53-2.58 (1H, m), 5.52-5.53 (1H, m), 5.62-5.64 (1H, m), 8.21-8.25 (2H, m), 8.28-8.33 (2H, m).

**Formal [4C + 3C] Cycloadduct 25e.** A white solid (45 mg, 0.15 mmol, 35% yield). 1H NMR (500 MHz, CDCl3): δ 1.01 (3H, s), 1.26 (3H, s), 1.90-1.94 (1H, m), 2.04-2.06 (1H, m), 2.57-2.58
(1H, m), 2.87-2.88 (1H, m), 5.90-5.95 (2H, m), 6.42-6.44 (1H, m), 8.21-8.25 (2H, m), 8.30-8.33 (2H, m). 13C NMR (125 MHz, CDCl3): δ 21.6, 27.5, 38.3, 39.1, 40.2, 51.3, 120.7, 123.6, 130.9, 131.3, 135.6, 141.0, 150.6, 151.2, 163.4.

(1S,5S)-2,2-dimethylbicyclo[3.2.1]oct-6-en-3-one (28)

A solution of 4M NaOH (aq.) (4.0 mL) was added to a mixture of 25 (0.72 mmol) in THF (16 mL) and MeOH (8 mL) under a nitrogen atmosphere at 0° C. The reaction stirred at this temperature 1 h, then was warmed to room temperature and stirred for 2 h. The solution was concentrated, then diluted with CH2Cl2 and quenched with 1N HCl. The aqueous layer was extracted with CH2Cl2, and the combined organic layers were washed with sat. NaHCO3 and brine. Organic extracts were dried over MgSO4, filtered, and concentrated. The residue was purified via column chromatography (5-10% EtOAc/hexanes) to give 62 mg (57%) of ketone as a colorless oil. Data was consistent with reported values.

Typical Procedure for Intermolecular Formal [4C + 3C] Cycloaddition with Furan

Chloro[1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene]gold(I) catalyst 12 (2 μmol) and AgSbF6 (5 μmol) were added to solvent (CH2Cl2 or pentane) (0.6 mL) under a nitrogen atmosphere at room temperature and this mixture was allowed to stir for 15 min. A solution of propargyl ester (0.247 mmol) and furan (1.24 mmol) in solvent (CH2Cl2 or pentane) (0.6 mL) were added to the flask by syringe. The reaction was permitted to stir 2 hours, or until completion as monitored by TLC. The reaction was diluted with EtOAc and filtered through a pad of silica and Celite. The filtrate was concentrated and purified via silica gel chromatography (1% EtOAc/hexanes).
**Formal [4C + 3C] Cycloadduct 30f.** A colorless oil (12 mg, 40 μmol, 18 % yield). ¹H NMR (500 MHz, CDCl₃): δ 0.93 (3H, s), 1.41 (3H, s), 3.87 (3H, s), 4.56 (1H, d, J = 2.00 Hz), 4.85-4.86 (1H, m), 6.04 (1H, d, J = 4.50 Hz) 6.07-6.09 (1H, m), 6.70-6.72 (1H, m), 6.94 (2H, d, J = 9.0 Hz), 8.00 (2H, d, J = 9.0 Hz). ¹³C NMR (125 MHz, CDCl₃): δ 18.2, 26.7, 39.6, 55.5, 75.9, 87.3, 113.8, 117.1, 122.1, 127.4, 131.9, 139.8, 150.2, 163.7. LCMS calcd for C₁₇H₁₈O₄Na 309.1, found 309.1.

**Triene Aldehyde 31f.** A yellow solid (34 mg, 0.12 mmol, 52 % yield, mixture of cis and trans isomers). Data is given for the major product, the trans isomer. ¹H NMR (300 MHz, CDCl₃): δ 1.78 (3H, s), 2.03 (3H, s), 3.90 (3H, s), 6.09 (1H, dd, J = 15.2, 8.1 Hz), 6.31 (1H, dd, J = 15.0, 11.4 Hz), 6.92-7.04 (3H, m), 7.18 (1H, dd, J = 15.2, 11.4 Hz), 8.15 (2H, d, J = 8.7 Hz), 9.54 (1H, d, J = 7.8 Hz).

**2,2-dimethyl-8-oxabicyclo[3.2.1]oct-6-en-3-one (32)**

The formal [4C + 3C] cycloadduct 31f (53 mg, 0.19 mmol) was dissolved in methanol (2 ml) and potassium carbonate (64 mg, 0.46 mmol) was then added. After stirring overnight, TLC indicated that the starting ester had disappeared and the reaction mixture was diluted with ether and quenched with 1M HCl. The layers were separated and the aqueous phase was extracted with ether. The combined organic extracts were washed with brine and dried over MgSO₄. The solution was concentrated and the residue was purified via column chromatography (10-20% EtOAc/hexanes) to give 12 mg (43%) of ketone. Data was consistent with reported values.³⁸

*(1R,4S,5S)-4-phenylbicyclo[3.2.1]octa-2,6-dien-3-yl 4-methylbenzoate (34)*

The same procedure used to prepare vinyl cyclopropanes 24a-e and the formal [4C + 3C] cycloaddition products 25a-e were used to prepare 34.
Formal [4C + 3C] Cycloadduct 34. A colorless oil (60mg, 0.19 mol, 95 % yield, with minor impurities). Data is given for the major product. $^1$HNMR (500 MHz, CDCl$_3$): $\delta$ 2.07-2.10 (1H, m), 2.18-2.19 (1H, m), 2.30 (3H, s), 2.95-2.96 (1H, m), 3.08-3.09 (1H, m), 4.19 (1H, d, J = 5 Hz), 5.38-5.39 (1H, m), 6.20-6.21 (1H, d, J = 7.5 Hz), 6.42-6.43 (1H, m), 7.07 (2H, d, J = 8 Hz), 7.11-7.14 (3H, m) 7.21 (2H, t, J = 7.3 Hz), 7.62 (2H, d, J = 8 Hz).

(1S,2S,5S)-2-phenylbicyclo[3.2.1]oct-6-en-3-one (35a) and (1S,2R,5S)-2-phenyl bicyclo[3.2.1]oct-6-en-3-one (35b)

Ketones 35a and 35b. The formal [4 + 3] cycloaddition product 34 (60 mg, 0.19 mmol) was dissolved in methanol (2 mL) and potassium carbonate (66 mg, 0.47 mmol) was then added. After stirring overnight, TLC indicated that the starting material had disappeared and the reaction mixture was diluted with Et$_2$O and quenched with 1M HCl. The layers were separated and the aqueous phase was extracted with Et$_2$O. The combined organic extracts were washed with brine and dried over MgSO$_4$. The solution was concentrated and the residue was purified via column chromatography (5-10% EtOAc/hexanes) to give 21 mg (55%) of ketones 35a and 35b. Data was consistent with reported values.42

6,7-diphenylcyclohepta-1,4-dienyl 4-methylbenzoate (37a) and 2-phenyl-1-(2-styrylcyclopropyl)vinyl 4-methylbenzoate (37b)
Formal [4C + 3C] Cycloadduct 37a and Vinyl Cyclopropane 37b. Chloro[1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene]gold(I) catalyst 12 (1.00 mg, 2 μmol) and AgSbF₆ (1.00 mg, 4 μmol) were added to CH₂Cl₂ (0.5 mL) under a nitrogen atmosphere at room temperature and this mixture was allowed to stir for 15 min. A solution of propargyl ester (50.0 mg, 0.200 mmol) and (Z)-buta-1,3-dienylbenzene 36 (31.0 mg, 0.240 mmol) in CH₂Cl₂ (0.5 mL) were added to the flask by syringe. The reaction was permitted to stir overnight, until completion as monitored by NMR. The reaction was diluted with EtOAc and filtered through a pad of silica and Celite. The filtrate was concentrated and purified via silica gel chromatography (2-5-10% EtOAc/hexanes) to yield 51.0 mg (67%) of a mixture of formal [4C + 3C] cycloadduct 37a and vinyl cyclopropane 37b in a 1.6:1 ratio.

Ketones 38a and 38b. A mixture of the formal [4 + 3] cycloaddition product 37a and vinyl cyclopropane 37b (51.0 mg, 0.134 mmol) was dissolved in methanol (1.40 mL) and potassium carbonate (46.0 mg, 0.335 mmol) was then added. After stirring 1 hour, TLC indicated that the starting material had disappeared and the reaction mixture was diluted with Et₂O and quenched with sat. NH₄Cl. The layers were separated and the aqueous phase was extracted with Et₂O. The combined organic extracts were washed with brine and dried over MgSO₄. The solution was concentrated and the residue was purified via column chromatography (2-5-10% EtOAc/hexanes) to give 16 mg (46%) of ketone 38a and 12 mg (34%) of ketone 35b.

Ketone 38a. A white solid (16 mg, 61 μmol, 46% yield). ¹HNMR (500 MHz, CDCl₃): δ 2.48-2.53 (1H, m), 2.62-2.67 (1H, m), 2.82-2.87 (1H, m), 3.11-3.18 (1H, m), 4.11-4.14 (1H, m), 4.36 (1H, d, J = 11.50 Hz), 5.74-5.78 (1H, m), 5.82-5.87 (1H, m), 7.04-7.20 (10H, m). ¹³C NMR (125 MHz, CDCl₃): δ 24.5, 42.1, 49.2, 64.0, 126.6, 127.0, 128.1, 128.2, 128.3, 128.6, 128.7, 134.0, 127.2, 142.3, 209.9. LCMS calcd for C₁₉H₁₈ONa 285.1, found 285.1.

Ketone 38b. A colorless oil (12 mg, 46 μmol, 34% yield). ¹HNMR (500 MHz, CDCl₃): δ 1.01-1.04 (1H, m), 1.56-1.59 (1H, m), 2.06-2.09 (1H, m), 2.43-2.45 (1H, m), 3.83 (2H, s), 5.06 (1H, t, J = 10.50 Hz), 6.40 (1H, d, J = 11.50 Hz), 7.21-7.34 (10H, m). ¹³C NMR (125 MHz, CDCl₃): δ 19.4, 25.8, 30.2, 50.9, 126.9, 127.0, 128.3, 128.6, 128.7, 129.5, 130.3, 131.9, 134.1, 136.9. LCMS calcd for C₁₀H₁₈ONa 285.1, found 285.1.
Chapter 3.

Gold-Catalyzed Intramolecular Cyclopropanation Reactions.

B.W. Gung, L.N. Bailey, D.T., Craft, C.L., Barnes, K., Kirschbaum, *Manuscript Pending*
3.1 Introduction

Gold-catalyzed intramolecular cycloadditions have been widely studied in the literature.\textsuperscript{10,11} In particular, there are many examples of gold-catalyzed cyclopropanation reactions, probably due to the propensity of various catalysts to form gold carbene intermediates. Many of these reports involve intramolecular cyclopropanation reactions with propargyl esters and alkenes either using Pt\textsuperscript{45-47} or Au catalysts.\textsuperscript{48-52} Other reports demonstrate cyclopropanation reactions from enyne-precursors.\textsuperscript{53, 54} Of all the literature involving reactions with propargyl esters, the ester group is always outside the olefin and the alkyne moieties. There is only one report where the ester is between the two functionalities.\textsuperscript{50} Additionally, the products from all the reactions reported contain an \textit{endo}cyclic olefin in the final product. During our studies of gold catalyzed cycloadditions, we discovered a high-yielding cyclopropanation reaction which generated an \textit{exo}cyclic olefin. These vinyl cyclopropanes lend themselves to further reactions as the cyclopropane functionality is very reactive and can be used to create more complex molecules.\textsuperscript{52, 55, 56}

Throughout our studies in these gold-catalyzed processes, we have found particular success with N-heterocyclic carbene catalyst 12, Au(I)IPr.\textsuperscript{30, 44} We have been interested in performing enantioselective reactions, and this curiosity led us to investigate the use of chiral Au(I)-NHC complexes. Currently, only a few chiral Au-NHC complexes have been reported in the literature.\textsuperscript{57,58} The commercial availability of chiral biarylphosphines has allowed for enantioselective reactions with Au(I) chiral phosphine ligands to make significant progress,\textsuperscript{59-62} however, we have only had limited success with the Au(I) phosphine complexes.\textsuperscript{30} As a result, it is essential to find an effective chiral Au(I)-NHC complex to catalyze enantioselective inter- and intramolecular [4 + 3] cycloadditions.

This chapter discusses a newly discovered intramolecular cyclopropanation reaction with propargyl acetates and terminal olefins. The reaction is examined with the Au(I)IPr catalyst 12, and two new chiral Au(I)-NHC catalysts which were synthesized in our lab. The different reactivities and thermal stabilities of the catalysts are investigated, and two potential mechanistic pathways are proposed.

3.2 Results and Discussion

We have previously reported gold-catalyzed transannular and intermolecular [4 + 3] reactions.\textsuperscript{30, 44} We sought to expand this methodology to the intramolecular variant. To this end, we synthesized propargyl acetates 39 a-b and employed them in the Au-catalyzed [4 + 3] cycloaddition reaction (Scheme 3.1). Unfortunately, the intramolecular [4 + 3] cycloaddition reactions are not nearly as straightforward as the transannular and intermolecular variants. The propargyl esters, substituted with either a phenyl group (39a) or an alkyl group (39b), had quite
different reactivities in the reaction. The phenyl substituted propargyl ester generated the desired [4 + 3] cycloadduct 40a in 73% yield when Au(I)-NHC catalyst 12 was used. Conversely, when the alkyl substituted propargyl ester was used, a mixture of the [4 + 3] cycloadduct 40b and a formal [2 + 2] cycloadduct 41b were obtained in low yields.

\[
\begin{align*}
\text{Scheme 3.1 Intramolecular [4 + 3] Cycloadditions} \\
\text{In order to improve the selectivity and limit the number of possible reaction pathways, we decided to simplify the starting material by excluding the possible [4 + 3] pathway. Unexpectedly, rather than a formal [2 + 2] cycloaddition, we came across a high yielding cyclopropanation reaction using Au(I)IPr catalyst 12. The propargyl esters 42a-c were reacted with the Au(I) catalyst at room temperature to provide cyclopropanation products 43a-c in high yield (Scheme 3.2). These cyclopropanation substrates differ from other reports using gold catalysts in that the acetate is located between the terminal double bond and the alkyne, save for one account. However, the commonality between all the previous literature accounts is that they generate an endocyclic olefin where the double bond is part of the ring system. In our reaction, the olefin is exocyclic and allows for the potential for subsequent reactions to either expand the ring size or create a quaternary carbon center.}
\end{align*}
\]

\[
\begin{align*}
\text{Scheme 3.2 Intramolecular Cyclopropanations with Au(I)-NHC catalyst 12.}
\end{align*}
\]
The preparation of substrates 42a-c is shown in Scheme 3.3. The propargyl alcohols 44a-c were prepared using a known procedure from propargyl chloride and the corresponding aldehyde. Acylation of the alcohols 44a-c with acyl chloride in the presence of DMAP in pyridine/methylene chloride provide propargyl acetates 45a-c. These substrates were converted to their corresponding iodides by reaction with sodium iodide in acetone in the absence of light at room temperature. The known 2-allyl dimethyl malonate 47 was treated with NaH in THF to generate the anion, which reacted with iodides 46a-c to form the desired substrates 42a-c in good yields.

Scheme 3.3 Synthesis of Intramolecular Cyclopropanation Precursors

The chiral Au(I) catalysts 48 and 49 were prepared in our laboratory and characterized by x-ray crystallography. The list of Au(I)-catalysts examined in this study are shown in Figure 3.1. The reactivity of each of the two new chiral Au(I)-NHC catalysts were compared in the high-yielding cyclopropanation reaction. The reactivity of each catalyst was slightly different from that of catalyst 12. The results of these reactions are displayed in Table 3.1.

Figure 3.1 Au(I) NHC Catalysts
Table 3.1 Catalytic Activity of Au(I)-NHC Catalysts 48 and 49.

<table>
<thead>
<tr>
<th>Substrate</th>
<th>[Au] cat.</th>
<th>R</th>
<th>Time (h)</th>
<th>%Yield</th>
<th>Isomeric Ratio (Z:E)</th>
</tr>
</thead>
<tbody>
<tr>
<td>42a</td>
<td>12</td>
<td>Phenyl</td>
<td>2</td>
<td>90</td>
<td>1:0</td>
</tr>
<tr>
<td>42b</td>
<td>12</td>
<td>n-propyl</td>
<td>1</td>
<td>97</td>
<td>3:1</td>
</tr>
<tr>
<td>42c</td>
<td>12</td>
<td>i-propyl</td>
<td>1</td>
<td>94</td>
<td>2.4:1</td>
</tr>
<tr>
<td>42a</td>
<td>48</td>
<td>Phenyl</td>
<td>3</td>
<td>65 (50a)</td>
<td>N/A</td>
</tr>
<tr>
<td>42b</td>
<td>48</td>
<td>n-propyl</td>
<td>2</td>
<td>97</td>
<td>2:1</td>
</tr>
<tr>
<td>42c</td>
<td>48</td>
<td>i-propyl</td>
<td>2</td>
<td>95</td>
<td>1:1</td>
</tr>
<tr>
<td>42a</td>
<td>49</td>
<td>Phenyl</td>
<td>2</td>
<td>56 (50b)</td>
<td>3:1</td>
</tr>
<tr>
<td>42b</td>
<td>49</td>
<td>n-propyl</td>
<td>3</td>
<td>96</td>
<td>2:1</td>
</tr>
<tr>
<td>42c</td>
<td>49</td>
<td>i-propyl</td>
<td>1.5</td>
<td>94</td>
<td>1:1</td>
</tr>
</tbody>
</table>

[a] For [Au] catalyst 12, 5 mol % [Au] and AgSbF$_6$ were used. [b] All yields refer to product 43 except were indicated otherwise. [c] Product 50a was produced only with the combination of [Au] catalyst 48 and substrate 42a. [d] Product 50b was produced only with the combination of [Au] catalyst 49 and substrate 42a.

In most cases, the activity of the new chiral Au(I)-NHC catalysts 48 and 49 were comparable to that of Au(I)IPr catalyst 12, producing the same product in similar yield and isomeric ratios. However, in the case of substrate 42a, a clear difference could be seen. When saturated Au(I)-NHC catalyst 48 was reacted with phenyl-substituted 42a, only 50a was isolated. This product arises from a 3,3-rearrangement of the propargyl ester to generate the acetoxy allene. In the presence of benzimidazole catalyst 49, substrate 42a reacted to give the [2 + 2] cycloadduct 50b. These results suggest very different reactivity from Au(I)IPr 12. All the substrates 42a-c reacted with 12 generated the expected cyclopropanation products 43a-c.
In order to examine the stability of the chiral Au(I)-NHC catalysts, a variable temperature NMR experiment was performed. Equal molar amounts of each of the Au(I)-NHC catalysts and AgSbF₆ were dissolved in CDCl₃ and allowed to stir for 15 minutes. The mixture was filtered into an NMR tube to remove the solid AgCl and a VT-NMR experiment was executed. NMR spectra were taken at 30 minute intervals with increasing temperature, monitored at 5 degree increments up to 55 °C. A graph of the percentage of intact catalyst versus temperature was constructed and shown in Figure 3.2.

![Catalyst Stability Study](image)

**Figure 3.2 Catalyst Stabilty Study**

The graph above demonstrates the thermal stability of each of the Au(I)-NHC catalysts. Active catalyst 12 is the most stable, and no evidence of decay was detected even at 55 °C. Surprisingly, the saturated Au(I)-catalyst 48, although the least reactive of the three catalysts, was not the most unstable. After 30 minutes at room temperature, 80% of the intact catalyst remained. Even all the way up to 55 °C, there was still about 20% of the intact catalyst left in solution. The benzimidazole catalyst 49 appeared to be the least stable. The first NMR after 30 minutes at room temperature only displayed about 40% of the intact catalyst. At only 45 °C, there appeared to be no more of the active catalyst species remaining. Both of the chiral Au(I)-NHC catalysts appeared to decay nearly linearly with increasing temperature. Additionally, after the NMR tubes were removed, there appeared to be a significant amount of Au-mirroring on the
There are two possible mechanistic pathways that could account for the cyclopropanation products. The first mechanistic pathway (Scheme 3.4) involves the possibility of a 1,2-acetate migration (top) which occurs when catalyst 12 is used, or a 1,3-acetate migration, which can occur with both catalyst 48 and 49 (bottom). In the top pathway, the Au-catalyst activates the alkyne to initiate a 1,2-acetate shift forming the Au carbene. Subsequent cyclopropanation with the terminal olefin can occur readily from this species. However, then R= phenyl and either one of the chiral Au(I)-NHC catalysts 48 or 49 are used, a 1,3-acetate migration can occur. This generates the acetoxy allene 50a which was isolated when the saturated Au(I) catalyst 48 was used. When catalyst 49 is used, a concerted [2 + 2] reaction can occur directly from intermediate 50a to provide 50b. A stepwise [2 + 2] reaction is unlikely as a primary carbocation would be formed.

**Scheme 3.4** Mechanistic Pathway 1: 1,2- or 1,3-acyl shifts

This mechanism provides some information about the reactivity of the new Au(I)-NHC catalysts. In addition, these results are similar to those obtained in the intermolecular [4 + 3] reactions44 in that there seems to be competition between the allene-type intermediates, and Au-carbene intermediates.10, 39 According to this proposed mechanistic pathway, the Au(I)-NHC catalysts 48 and 49 are more able to promote a 1,3-acetate migration than the Au(I)IPr catalyst.
Additionally, catalyst 49 appears to have more activity than catalyst 48 in that the acetoxy allene 50a never underwent any subsequent reaction, even with longer reaction time and heating the reaction to reflux. It is also possible that the phenyl group is able to provide more stability for the formation the acetoxy allene, explaining the difference in reactivity with this particular substituent.

Scheme 3.5 Mechanistic Pathway 2: Enyne Cyclization

The second mechanistic pathway is also possible (Scheme 3.5). This involves an initial enyne-cyclization, where the acetate group does not participate in the initial carbene formation. However, the only way to account for the formation of 50a in this pathway is if an equilibrium exists between the initial gold activation in the enyne pathway and a 1,3-acyl migration when R=Ph and Au(I)-NHC catalyst 48 is used. Conversely, in the enyne pathway, Au(I) activation of the alkyne could initiate attack from the terminal olefin to provide a cyclohexyl carbocation intermediate. Consequent Au-carbene formation would initiate the trapping of the carbocation with the alkene, and a 1,2-acetate shift and deauration would provide products 43a-c when Au(I)IPr catalyst 12 is employed. To account for the formation of the [2 + 2] product, when R = phenyl, it is possible that the cyclopropane ring could undergo a ring opening with the Au carbene to provide the cyclobutyl carbocation intermediate. A subsequent 1,3-acetate shift and deauration would generate 50b.
This mechanistic pathway shown above is also quite plausible. Toste proposed a stepwise \([2 + 2]\) mechanism for his reactions with allene and he was able to verify this mechanism through trapping reactions of the carbocation.\(^{65}\) However, his substrates contained stabilized benzyl carbocations, so it seems less likely this pathway is occurring in our case.

Other groups have been able to demonstrate Au-catalyzed enyne reactions,\(^{53,54}\) and have examined the possibilities of a 1,2-shift, then cyclization or cyclization first, then 1,2-shift.\(^{47}\) Moreover, the Echavarren group has been able to demonstrate reactions of propargyl esters with olefins where the acetate group does not participate in the reaction.\(^{66}\) However, the vast majority of Au-catalyzed cyclopropanation reactions suggest a 1,2-migration of the acetate to form the Au-carbene. In light of our recent research in this area\(^{30,44}\) it seems more plausible that mechanistic pathway 1 (Scheme 3.4) is responsible for the formation of the products, though more experimentation needs to be done to fully exclude either pathway.

![Scheme 3.4](image)

**Scheme 3.4** Conversion of enol acetates to their corresponding ketones

The isolated cyclopropanation products were obtained as a mixture of E/Z isomers, where the dominant product was the Z-isomer. This assignment was based on the fact that the E-isomers showed a slightly more upfield shift of the vinyl proton due to the shielding from the acetate group. Regrettably, these products were inseparable by silica gel chromatography. In order to verify the identity of these compounds, the products were subjected to base-catalyzed hydrolysis to remove the ester group. This provided homogenous products 51a-e and allowed for clear identification by NMR spectroscopy (Scheme 3.6). Optical rotation for the ketones generated from the chiral Au(I)-NHC catalysts were taken, but the values were very low and barely registered on the polarimeter, so therefore negligible. To further demonstrate the utility of these vinyl cyclopropanes, bicyclic ketone 43b was converted to cyclohexane derivative 52 by the Samarium iodide ring opening reaction.\(^{52}\) To verify the structure of the \([2 + 2]\) derivative,
the product 50b was subjected to ozonolysis to generate the cyclobutyl ketone and benaldehyde products and unambiguously confirm its identity.67

3.3 Conclusion

In summary, a very high-yielding Au-catalyzed intramolecular cyclopropanation reaction has been discovered. The reaction generates an exocyclic double bond which is different from previous reports and can be used as a precursor to form various other products. The new chiral Au(I)-NHC catalysts 45 and 46 developed in our lab and used in this reaction demonstrate slightly different reactivity and thermal stability from that of the Au(I)IPr catalyst 12. Both catalysts can initiate the cyclopropanation reaction, but can also form different cycloaddition intermediates and products. The mechanistic pathway responsible for these transformations most likely involves a 1,2-acetate shift to give rise to the cyclopropanation products, and a 1,3-acetate migration which gives rise to the acetoxy allene and [2 + 2] cycloaddition product. Further studies to verify the mechanism could be performed with Au-carbene or carbocation trapping experiments. The investigation into more chiral Au(I)-NHC catalysts that might provide better enantioselectivity is ongoing in our laboratory. In addition, the full scope and limitations of the intramolecular [4 + 3] cycloadditions discussed briefly in this chapter will be reported in an upcoming publication.
3.4 Experimental Procedures

General Experimental Procedures

Unless otherwise stated, all reactions were carried out under an inert nitrogen atmosphere with dry solvents under anhydrous conditions. Dry tetrahydrofuran (THF) and toluene (PhCH₃) were distilled over sodium benzophenone, dichloromethane (CH₂Cl₂) and benzene (PhH) were distilled over calcium hydride. Reagents were purchased and used without further purification unless otherwise stated. Yields refer to chromatographically and spectroscopically (¹H NMR) homogeneous materials, unless otherwise stated. Reactions were monitored by thin layer chromatography (TLC) carried out on 0.25 mm Merck silica gel plates (60F-254) using UV light as the visualizing agent and an acidic mixture of anisaldehyde, phosphomolybdic acid, or ceric ammonium molybdate, or basic aqueous potassium permanganate (KMnO₄), and heat as developing agents. Merck silica gel (60, particle size 0.043–0.063 mm) was used for flash column chromatography. NMR spectra were recorded on Bruker Av-500, and Av-300 instruments and calibrated using residual undeuterated solvent as an internal reference (CHCl₃ @ 7.26 ppm ¹H NMR, 77.0 ppm ¹³C NMR). The following abbreviations (or combinations thereof) were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad. High resolution mass spectra (HRMS) were recorded at Ohio State University. IR spectra were recorded on a Perkin Elmer Spectrum 2000 FTIR spectrometer. Melting points were recorded on a Thomas-Hoover melting point apparatus.

Synthesis of Intramolecular Precursors.

![Reaction scheme]

A slurry of NaH (1.94 mmol) and THF (5.70 mL) was prepared under a nitrogen atmosphere and cooled to 0 °C. A solution of dimethyl 2-(penta-2,4-dienyl)malonate (1.77 mmol) in THF (1 mL) was added to the slurry dropwise. The reaction mixture stirred 1h at this temperature, then a solution of iodide (2.12 mmol) in THF (1 mL) was added dropwise to the reaction at 0 °C. The solution was permitted to warm to rt and stir overnight. The reaction was quenched with H₂O and the aqueous layer was extracted with Et₂O. The combined organic extracts were washed with brine, dried over MgSO₄, and concentrated. The residue was purified by silica gel chromatography (5-10-20% EtOAc/hexanes).
dimethyl 2-(4-acetoxy-4-phenylbut-2-ynyl)-2-(penta-2,4-dienyl)malonate (39a). An orange oil (4.07 g, 10.6 mmol, 84% yield). $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 2.10 (3H, s), 2.81 (2H, d, $J = 8.00$ Hz), 2.87 (2H, s), 3.70 (3H, s), 3.71 (3H, s), 5.03 (1H, d, $J = 10.0$ Hz), 5.11 (1H, d, $J = 16.5$ Hz), 5.44-5.50 (1H, m), 6.07-6.12 (1H, m), 6.22-6.30 (1H, m), 6.40 (1H, s), 7.35-7.40 (3H, m), 7.49 (2H, d, $J = 6.50$ Hz). $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 20.8, 23.6, 35.9, 52.5, 57.6, 65.8, 80.4, 82.8, 116.5, 127.2, 127.6, 128.5, 128.7, 135.7, 136.7, 137.5, 169.4, 170.1.

dimethyl 2-(4-acetoxyhept-2-ynyl)-2-(penta-2,4-dienyl)malonate (39b). A yellow oil (0.452 g, 1.29 mmol, 73 % yield). $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 0.94 (3H, t, $J = 7.00$ Hz), 1.40-1.48 (2H, m), 1.65-1.74 (2H, m), 2.06 (3H, s), 2.79-2.80 (4H, m), 3.73 (6H, s), 5.03 (1H, d, $J = 10.0$ Hz), 5.14 (1H, d, $J = 17.0$ Hz), 5.30 (1H, t, $J = 6.50$ Hz), 5.45-5.51 (1H, m), 6.11-6.17 (1H, m), 6.24-6.30 (1H, m). $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 13.4, 18.1, 20.8, 22.9, 35.4, 36.7, 52.5, 57.0, 63.8, 80.1, 80.9, 116.6, 126.9, 135.4, 136.3, 169.7, 169.9.


![Diagram of the reaction](image)

Typical Procedure

Gold (I)-NHC catalyst 12 (13 $\mu$mol) and AgSbF$_6$ (13 $\mu$mol) were dissolved in CH$_2$Cl$_2$ (0.6 mL) under a nitrogen atmosphere at room temperature and this mixture was allowed to stir for 15 min. A solution of diene-propargyl ester 39 (0.130 mmol) in CH$_2$Cl$_2$ (0.7 mL) was added to the flask by syringe. The solution was permitted to stir overnight at room temperature, until complete as monitored by NMR. The reaction was diluted with Et$_2$O and filtered through a pad of silica and Celite. The filtrate was concentrated and purified via silica gel chromatography (5-10-20% EtOAc/hexanes) to yield the [4 + 3] (40) and/or [2 + 2] (41) cycloadducts.

dimethyl 8-acetoxy-7-phenyl-3,3a,6,7-tetrahydroazulene-2,2(1H)-dicarboxylate (40a). A colorless oil (36.5 mg, 95 $\mu$mol, 73% yield). $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 1.08 (3H, s), 2.16-2.21 (1H, m), 2.28-2.33 (1H, m), 2.65-2.75 (2H, m), 2.81-2.85 (1H, m), 3.12 (1H, d, $J = 17.5$ Hz), 5.45-5.51 (1H, m), 6.11-6.17 (1H, m), 6.24-6.30 (1H, m). $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 13.4, 18.1, 20.8, 22.9, 35.4, 36.7, 52.5, 57.0, 63.8, 80.1, 80.9, 116.6, 126.9, 135.4, 136.3, 169.7, 169.9.

Yields of 40:41

R = Ph, 73:0
R = n-Pr, 18:24

46
Hz), 3.65-3.68 (1H, m), 3.74 (3H, s), 3.75-3.77 (1H, m), 3.78 (3H, s), 5.84-5.91 (2H, m), 7.19-7.23 (3H, m), 7.29 (2H, t, J = 7.50 Hz). $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 20.4, 33.2, 37.7, 37.8, 40.8, 45.4, 52.8, 52.9, 58.2, 126.6, 127.8, 128.4, 128.8, 130.3, 136.0, 142.8, 143.6, 168.1, 171.4, 171.8.

dimethyl 8-acetoxy-7-propyl-3,3a,6,7-tetrahydroazulene-2,2(1H)-dicarboxylate (40b). A colorless oil (9.0 mg, 26 $\mu$mol, 18% yield). $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 0.89 (3H, t, J = 7.0 Hz), 1.26-1.42 (4H, m), 1.58-1.61 (1H, m), 2.12 (3H, s), 2.15-2.20 (1H, m), 2.25-2.26 (1H, m), 2.43-2.47 (1H, m), 2.65-2.69 (1H, m), 2.76-2.80 (1H, m), 3.04 (1H, d, J = 17.0 Hz), 3.52-3.54 (1H, m), 3.72 (3H, s), 3.75 (3H, s), 5.59-5.62 (1H, m), 5.67-5.71 (1H, m). $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 14.2, 20.1, 20.7, 29.5, 33.8, 37.7, 38.4, 39.8, 41.3, 52.7, 52.8, 57.8, 127.7, 128.2, 131.2, 146.1, 168.5, 171.5, 171.8.

dimethyl 1-acetoxy-7-butylidene-6-vinylbicyclo[3.2.0]heptane-3,3-dicarboxylate (41b). A colorless oil (12.0 mg, 34 $\mu$mol, 24% yield). $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 0.86 (3H, t, J = 7.35 Hz), 1.26-1.39 (3H, m), 1.83-1.90 (2H, m), 2.02 (3H, s), 2.51-2.52 (1H, m), 2.69-2.74 (2H, m), 3.05-3.09 (2H, m), 3.70-3.75 (6H, m), 4.96-5.06 (2H, m), 5.85-5.98 (2H, m).

Synthesis of Intramolecular Precursors.

Alkylation

$$\text{CHCl}_3 + \text{HOCR} \xrightarrow{1. \text{MeLi, Et}_2\text{O, -20 °C}} \xrightarrow{2. \text{Aldehyde, -20 °C to rt}} \text{HO-CHCl}$$

44a-c

Typical Procedure

Propargyl chloride (1.00 mL, 13.4 mmol) was dissolved in dry Et$_2$O (6.7 mL) under an atmosphere of nitrogen. The solution was cooled to -20 °C and MeLi (1.6 M in Et$_2$O, 9.23 mL, 14.8 mmol) was added dropwise by syringe. The solution stirred at this temperature for 45 min., then the aldehyde (26.8 mmol) was added dropwise by syringe. The reaction mixture stirred at this temperature 1h, then was allowed to slowly warm to rt and stir overnight. The reaction was quenched with H$_2$O and the aqueous layer was extracted with Et$_2$O. The combined organic layers were washed with brine, dried over MgSO$_4$, and concentrated. The residue was purified by silica gel chromatography (20-30% EtOAc/hexanes).

4-chloro-1-phenylbut-2-yn-1-ol (44a). A colorless oil (13.4 g, 74.3 mmol, 79% yield). Data was consistent with previously reported values.\textsuperscript{68}
1-chlorohept-2-yn-4-ol (44b). A colorless oil (1.85 g, 12.6 mmol, 94% yield). $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 0.96 (3H, t, J = 7.25 Hz), 1.46-1.50 (2H, m), 1.67-1.73 (2H, m), 1.84-1.90 (1H, bm) 4.17 (2H, d, J = 1.50 Hz), 4.43-4.44 (1H, m). $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 13.6, 18.3, 30.4, 39.5, 62.1, 79.4, 87.6.

6-chloro-2-methylhex-4-yn-3-ol (44c). A colorless oil (2.14 g, 14.6 mmol, 54% yield). Data was consistent with previously reported values.\textsuperscript{69}

Acetylation

![Acetylation Diagram]

Typical Procedure

Alcohol 44 (6.82 mmol) was added to a solution of DMAP (0.34 mmol), pyridine (68.2 mmol) and CH$_2$Cl$_2$ (20.0 mL) under a nitrogen atmosphere. The mixture stirred 15 min. at 0°C. Acetyl chloride (13.6 mmol) was added by syringe at the same temperature and the reaction was allowed to warm to rt. After 1h, the reaction mixture was diluted with hexanes and filtered. The solvent was evaporated and the crude residue was purified by silica gel chromatography (5-10% EtOAc/hexanes).

4-chloro-1-phenylbut-2-ynyl acetate (45a). A colorless oil (12.2 g, 55.0 mmol, 74% yield). Data is consistent with reported values.\textsuperscript{70}

1-chlorohept-2-yn-4-yl acetate (45b). A colorless oil (1.07 g, 5.66 mmol, 83% yield). $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 0.95 (3H, t, J = 7.50 Hz), 1.44-1.49 (2H, m), 1.73-1.78 (2H, m), 2.08 (3H, s), 4.16 (2H, d, J = 1.50 Hz), 5.39-5.42 (1H, m). $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 13.5, 18.2, 20.9, 30.1, 36.5, 63.6, 80.0, 83.9, 169.9. LCMS m/z calcd for C$_9$H$_{13}$ClO$_2$Na 211.1, found 211.0.

6-chloro-2-methylhex-4-yn-3-yl acetate (45c). A colorless oil (2.19 g, 11.6 mmol, 80% yield). $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 1.00 (3H, d, J = 6.50 Hz), 1.02 (3H, d, J = 6.50 Hz), 1.98-2.04 (1H, m), 2.09 (3H, s), 4.17 (2H, d, J = 1.50 Hz), 5.24 (1H, d, J = 5.50 Hz). $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 17.4, 18.0, 20.8, 30.1, 32.2, 68.6, 80.6, 82.7, 169.9. LCMS m/z calcd for C$_9$H$_{13}$ClO$_2$Na 211.1, found 211.0.
Iodination

\[
\begin{align*}
\text{AcO} & \quad \text{Cl} \\
\text{R} & \quad \text{I} \\
45a-c & \quad \text{AcO} \\
\end{align*}
\]

Typical Procedure

Chloride 45 (5.30 mmol) was dissolved in acetone (20.4 mL) under an atmosphere of nitrogen in the absence of light. To the solution was added sodium iodide (10.6 mmol) in one portion. The solution stirred in the dark at rt overnight. The reaction mixture was concentrated, then diluted with Et₂O and quenched with H₂O. The aqueous layer was extracted with Et₂O and the organic layers were washed with brine, dried over MgSO₄, and concentrated. The residue was purified by silica gel chromatography (5-10-20% EtOAc/hexanes).

4-iodo-1-phenylbut-2-ynyl acetate (46a). A yellow oil (9.98 g, 31.8 mmol, 58% yield). ¹H NMR (500 MHz, CDCl₃): δ 2.09 (3H, s), 3.73 (2H, d, J = 2.00 Hz), 6.46 (1H, s), 7.37-7.38 (3H, m), 7.49-7.50 (2H, m). ¹³C NMR (125 MHz, CDCl₃): δ -19.7, 20.9, 65.5, 81.4, 84.1, 127.6, 128.6, 129.0, 136.5, 169.7. LCMS m/z calcd for C₁₂H₁₁IO₂Na 337.0, found 337.0.

1-iodohept-2-yn-4-yl acetate (46b). A yellow oil (1.28 g, 4.58 mmol, 86% yield). ¹H NMR (500 MHz, CDCl₃): δ 0.95 (3H, t, J = 7.25 Hz), 1.43-1.48 (2H, m), 1.71-1.76 (2H, m), 2.08 (3H, s), 3.71 (2H, d, J = 2.00 Hz), 5.37 (1H, t, J = 6.75 Hz). ¹³C NMR (125 MHz, CDCl₃): δ -19.4, 13.5, 18.1, 20.9, 36.5, 63.8, 82.1, 82.6, 169.8. LCMS m/z calcd for C₉H₁₃IO₂ 280.0, found 281.2 (M +H).

6-iodo-2-methylhex-4-yn-3-yl acetate (46c). A yellow oil (2.86 g, 10.2 mmol, 88% yield). ¹H NMR (500 MHz, CDCl₃): δ 0.99 (3H, d, J = 6.50 Hz), 1.02 (3H, d, J = 7.00 Hz), 2.01-2.10 (1H, m), 2.09 (3H, s), 3.72 (2H, d, J = 2.00 Hz), 5.20-5.21 (1H, m). ¹³C NMR (125 MHz, CDCl₃): δ -19.3, 17.3, 18.0, 20.8, 32.3, 68.7, 81.4, 82.6, 169.7. LCMS m/z calcd for C₉H₁₃IO₂ 280.0, found 281.2 (M +H).

Alkylation

\[
\begin{align*}
\text{AcO} & \quad \text{CO₂Me} \\
\text{R} & \quad \text{CO₂Me} \\
47 & \quad 46a-c \\
\end{align*}
\]

1. NaH, THF, 0 °C
2. AcO, 0 °C to reflux

42a-c
**Typical Procedure**

A slurry of NaH (1.92 mmol) and THF (5.6 mL) was prepared under a nitrogen atmosphere and cooled to 0 °C. A solution of dimethyl 2-allylmalonate 47 (1.74 mmol) in THF (1 mL) was added to the slurry dropwise. The reaction mixture stirred 1 h at this temperature, then a solution of iodide 46 (1.92 mmol) in THF (1 mL) was added dropwise to the reaction at 0 °C. The solution was permitted to warm to rt and stir overnight. The reaction was quenched with H2O and the aqueous layer was extracted with Et2O. The combined organic extracts were washed with brine, dried over MgSO4, and concentrated. The residue was purified by silica gel chromatography (5-10-20% EtOAc/hexanes).

**dimethyl 2-(4-acetoxy-4-phenylbut-2-ynyl)-2-allylmalonate (42a).** A yellow oil (0.31 g, 0.865 mmol, 75% yield). 1H NMR (500 MHz, CDCl3): δ 2.09 (3H, s), 2.79 (2H, d, J = 7.50 Hz), 2.88 (2H, s), 3.71 (6H, d, J = 4.00 Hz), 5.10-5.15 (2H, m), 5.57-5.64 (1H, m), 6.40 (1H, s), 7.34-7.39 (3H, m), 7.48 (2H, d, J = 7.50 Hz). 13C NMR (125 MHz, CDCl3): δ 21.1, 23.1, 36.8, 52.7, 57.0, 65.7, 80.1, 82.5, 119.9, 127.7, 128.6, 128.9, 131.7, 137.1, 169.7, 170.1. LCMS m/z calcd for C20H22O6Na 381.1, found 381.1.

**dimethyl 2-(4-acetoxyhept-2-ynyl)-2-allylmalonate (42b).** A colorless oil (0.50 g, 1.54 mmol, 88% yield). 1H NMR (300 MHz, CDCl3): δ 0.94 (3H, t, J = 7.35 Hz), 1.39-1.47 (2H, m), 1.65-1.73 (2H, m), 2.06 (3H, s), 2.77 (2H, d, J = 7.20 Hz), 2.82 (2H, d, J = 1.80 Hz), 3.74 (6H, s), 5.11-5.19 (2H, m), 5.28-5.33 (1H, m), 5.55-5.66 (1H, m). 13C NMR (125 MHz, CDCl3): δ 13.6, 18.3, 21.0, 23.0, 36.7, 36.9, 52.7, 57.0, 64.0, 80.3, 81.0, 119.8, 131.7, 170.0, 170.1. LCMS m/z calcd for C17H24O6Na 347.1, found 347.2.

**dimethyl 2-(4-acetoxy-5-methylhex-2-ynyl)-2-allylmalonate (42c).** A colorless oil (0.71 g, 2.19 mmol, 94% yield). 1H NMR (300 MHz, CDCl3): δ 0.95-1.00 (6H, m), 1.89-2.00 (1H, m), 2.08 (3H, m), 2.79 (2H, d, J = 8.10 Hz), 2.84 (2H, d, J = 2.40 Hz), 3.73 (6H, s), 5.11-5.19 (3H, m), 5.55-5.61 (1H, m). 13C NMR (75 MHz, CDCl3): δ 17.3, 18.1, 20.9, 23.0, 32.2, 36.7, 52.7, 57.0, 69.1, 79.5, 80.8, 119.8, 131.7, 170.0, 170.1. LCMS m/z calcd for C17H24O6Na 347.1, found 347.2.

**Intramolecular Cyclopropanation/Hydrolysis**

![Chemical structure of 42a-c, 43a-c, and 51a-c.](image-url)
Typical Procedure

Gold (I) catalyst (8 μmol) and AgSbF₆ (8 μmol) were dissolved in CH₂Cl₂ (0.8 mL) under a nitrogen atmosphere at room temperature and this mixture was allowed to stir for 15 min. A solution of propargyl ester 42 (0.154 mmol) in CH₂Cl₂ (0.7 mL) was added to the flask by syringe. The solution was permitted to stir 1-3 hr until complete by TLC. The reaction was diluted with Et₂O and filtered through a pad of silica and Celite. The filtrate was concentrated and purified via silica gel chromatography (10-20% EtOAc/hexanes) to yield cyclopropanes 43 as a mixture of E/Z isomers.

dimethyl 1-(1-acetoxy-3-methylbut-1-enyl)bicyclo[3.1.0]hexane-3,3-dicarboxylate (43c). ¹H NMR (500 MHz, CDCl₃).

<table>
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<th>Assignment of Chemical Shifts for Isomers of Vinylecyclopropanes 43c</th>
<th>(Z)-isomer, δ</th>
<th>(E)-isomer, δ</th>
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<tr>
<td>0.47 (1H, t, J = 5.00 Hz)</td>
<td>0.40 (1H, t, J = 5.00 Hz)</td>
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<td>0.81-0.84 (2H, m) (overlapping signals)</td>
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<td>1.01 (6H, d, J = 6.50 Hz)</td>
<td>1.52-1.54 (2H, m) (overlapping signals)</td>
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<tr>
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<tr>
<td>2.48-2.72 (8H, m) (overlapping signals)</td>
<td>2.27-2.33 (1H, m)</td>
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<tr>
<td>2.83 (1H, d, J = 14.00 Hz)</td>
<td>3.72 (3H, s)</td>
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<tr>
<td>3.70 (3H, s)</td>
<td>3.73 (3H, s)</td>
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</tr>
<tr>
<td>4.99 (1H, d, J = 10.50 Hz)</td>
<td>4.94 (1H, d, J = 9.50 Hz)</td>
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</tbody>
</table>

The (Z)-isomer was assigned on the basis of the shift of the vinyl proton. The (E)-isomer should have a more upfield shift on the basis that it experiences more shielding from the acetate moiety. The (Z)-isomer was assigned as the major isomer for vinyl cyclopropanes 43a and 43b in analogy with the cyclopropane chemical shifts at 0.47 and 0.40 ppm for the (Z)- and (E)-isomers, respectively.

The cyclopropane 43 (0.146 mmol) was dissolved in MeOH (2 mL) under an atmosphere of nitrogen and potassium carbonate (3 μmol) was added. The mixture was allowed to stir 1h at rt or until completion by TLC. The reaction mixture was diluted with Et₂O and quenched with 1M HCl. The aqueous layer was extracted with Et₂O, and the combined organic layers were washed with sat. NaHCO₃, and brine, dried over MgSO₄, and concentrated. The residue was purified via silica gel chromatography (10-20% EtOAc/hexanes).
dimethyl 1-(2-phenylacetyl)bicyclo[3.1.0]hexane-3,3-dicarboxylate (51a). A colorless oil (23 mg, 0.073 mmol, 58% yield). $^1$H NMR (500 MHz, CDCl$_3$): δ 0.80 (1H, t, J = 5.50 Hz), 1.52-1.54 (1H, m), 2.07-2.08 (1H, m), 2.54-2.55 (2H, m), 2.71 (1H, d, J = 14.5 Hz), 3.01 (1H, d, J = 14.0 Hz), 3.69 (2H, s), 3.71 (3H, s), 3.73 (3H, s), 7.16-7.17 (2H, d, J = 7.50 Hz), 7.24-7.26 (1H, m), 7.31 (2H, t, J = 7.50 Hz). $^{13}$C NMR (125 MHz, CDCl$_3$): δ 21.4, 30.6, 35.3, 35.8, 40.2, 45.3, 53.0, 53.1, 60.0, 126.8, 128.5, 129.3, 134.1, 171.6, 172.7, 205.8. LCMS m/z calcd for C$_{18}$H$_{20}$O$_5$Na 339.1, found 339.0.

dimethyl 1-pentanoylbicyclo[3.1.0]hexane-3,3-dicarboxylate (51b). A colorless oil (37 mg, 0.131 mmol, 76% yield). $^1$H NMR (500 MHz, CDCl$_3$): δ 0.75 (1H, t, J = 5.50 Hz), 0.90 (3H, t, J = 7.25 Hz), 1.26-1.33 (2H, m), 1.42-1.45 (1H, m), 1.51-1.57 (2H, m), 1.98-2.02 (1H, m), 2.27-2.40 (2H, m), 2.56 (2H, d, J = 3.00 Hz), 2.72 (1H, d, J = 14.0 Hz), 2.94 (1H, d, J = 14.0 Hz), 3.72 (3H, s), 3.74 (3H, s). $^{13}$C NMR (125 MHz, CDCl$_3$): δ 13.9, 20.9, 22.3, 26.0, 29.9, 35.3, 35.6, 38.0, 40.0, 53.0, 53.1, 59.9, 171.7, 172.8, 208.7. LCMS m/z calcd for C$_{15}$H$_{22}$O$_5$Na 305.1, found 305.1.

dimethyl 1-(3-methylbutanoyl)bicyclo[3.1.0]hexane-3,3-dicarboxylate (51c). $^1$H NMR (300 MHz, CDCl$_3$): δ 0.75-0.78 (1H, t, J = 5.5 Hz), 0.90 (6H, m), 1.26 (1H, m), 1.41-1.47 (1H, m), 2.0 (1H, m), 2.14-2.23 (2H, m), 2.21-2.23 (2H, d, J = 4.8 Hz), 2.56-2.57 (1H, d, J = 3.0 Hz), 2.70-2.75 (1H, d, J = 14.1 Hz), 2.93 (1H, J = 14.1 Hz), 3.73 (3H, s), 3.75 (3H, s). $^{13}$C NMR (75 MHz, CDCl$_3$): δ 20.7, 22.5, 24.4, 29.6, 35.3, 35.7, 40.3, 52.9, 53.0, 60.0, 171.6, 172.7, 208.1. LCMS m/z calcd for C$_{15}$H$_{22}$O$_5$Na 305.1, found 305.0.

![Chemical structure](image)

dimethyl 2-(2-acetoxy-4-phenylbuta-2,3-dienyl)-2-allylmalonate (50a). The same procedure used to prepare cyclopropanes 43a-c was used to prepare allene 50a. A colorless oil (33 mg, 92 µmol, 65% yield). $^1$H NMR (500 MHz, CDCl$_3$): δ 2.10 (3H, s), 2.80 (2H, d, J = 7.50 Hz), 3.01-3.04 (2H, m), 3.67 (3H, s), 3.68 (3H, s), 5.04-5.10 (2H, m), 5.56-5.68 (1H, m), 6.58 (1H, s), 7.26-7.44 (5H, m). $^{13}$C NMR (75 MHz, CDCl$_3$): δ 20.9, 35.2, 36.6, 52.5, 56.6, 104.5, 119.4, 121.1, 128.1, 128.3, 128.6, 132.0, 133.1, 167.8, 170.6, 197.8. LCMS m/z calcd for C$_{20}$H$_{22}$O$_6$Na 381.1, found 381.1.
Radical-Mediated Ring Opening

\[
\begin{align*}
\text{dimethyl 3-pentanoylcyclohexane-1,1-dicarboxylate (52)}
\end{align*}
\]

To a solution of SmI₂ (0.1M in THF, 6.20 mL, 0.620 mmol) was added HMPT (0.154 mL, 0.885 mmol) under a nitrogen atmosphere at room temperature. After 10 minutes of stirring, the blue solution had turned a deep violet color. Then a solution of cyclopropane \(43b\) (0.050 g, 0.177 mmol) in \(t\)-BuOH (0.084 mL) and THF (1.77 mL) was added to the violet solution. After 15 minutes of stirring, a TLC showed the disappearance of starting material. The reaction mixture was quenched with 1M HCl and the layers were separated. The aqueous layer was extracted with Et₂O and the combined organic extracts were washed with sat. NaHCO₃ and brine, dried over MgSO₄, and concentrated. The residue was purified via silica gel chromatography to yield 23 mg (46%) of ketone \(52\) as a colorless oil. \(^1\)H NMR (500 MHz, CDCl₃): \(\delta\) 0.90 (3H, t, \(J = 7.25\) Hz), 1.23-1.37 (4H, m), 1.52-1.58 (2H, m), 1.63-1.70 (2H, m), 1.80-1.84 (2H, m), 2.33-2.36 (1H, m), 2.44-2.47 (3H, m), 2.59-2.62 (1H, m), 3.71 (3H, s), 3.77 (3H, s). \(^1^3\)C NMR (125 MHz, CDCl₃): \(\delta\) 13.9, 22.2, 22.4, 25.8, 27.5, 30.7, 32.5, 40.8, 46.5, 52.6, 52.7, 54.7, 171.4, 172.3, 212.7. LCMS m/z calcd for C₁₅H₂₄O₅Na 307.2, found 307.1.

Catalyst Stability Study

A solution of Au(I)-NHC catalyst (8 \(\mu\)mol) and AgSbF₆ (8 \(\mu\)mol) was prepared in CDCl₃ under a nitrogen atmosphere and stirred at room temperature 15 min. The purple solution was filtered into an NMR tube for VT-NMR experiments. NMR spectra were taken every 30 minutes as the temperature increased from room temperature to 55 °C at approximately 5 degree increments (22-30-35-40-45-50-55 °C). The percentage of intact catalyst was recorded by integration of the chiral protons for catalysts \(48\) and \(49\) and the tertiary protons for catalyst \(12\).
Conclusion

In summary, three different versions of gold-catalyzed cycloadditions have been examined. The transannular \([4 + 3]\) cycloaddition has been shown to proceed in good yield with high diastereoselectivity to form four fused rings in a single step. This oxabicyclo[3.2.1]octene ring system bearing two pendant cyclohexane rings has been converted to form the core structure of Cortistatin A, a potent angiogenesis inhibitor. This methodology can be utilized to prepare complex natural products, which would otherwise take a multitude of steps to synthesize. In addition, intermolecular \([4 + 3]\) cycloadditions to form seven-membered rings from simple precursors have been explored. The transformations occur under mild reaction conditions with very low catalyst loading. This is one of the few reports in the literature that occur with unactivated diene systems. In this study we were able to unambiguously determine that there are two competing mechanistic pathways occurring to form the vinyl cyclopropanes and the bicyclo[3.2.1]octa-2,6-dienes, in contrast to other reports which involve the tandem Cope rearrangement to form the \([4 + 3]\) cycloadducts. Lastly, we also reported a new gold-catalyzed cyclopropanation reaction. Our substrates form products which have exocyclic double bonds, and these vinylcyclopropanes lend themselves open to further reactions and functionalizations. The report of two new chiral Au(I) catalysts and their catalytic activities have also been examined in this study. The different products formed with each one of these catalysts suggest a mechanism with an acetate migration, then cyclization process.

From these studies it is evident that gold has a unique ability to activate multiple bonds towards cyclization, though the mechanistic pathways might not always be as straightforward as hypothesized. These methods can be applied to the synthesis of natural products to increase atom economy and reduce the number of steps it takes to make complex molecular frameworks. Though the amount of research in gold catalysis has grown by leaps and bounds over the past decade, it seems there is still more work to do. With the advent of new gold catalysts being synthesized and the clever design of unique substrates for these reactions, it seems gold catalysis with be a high topic of interest for several more years to come.
Chapter 4

References

67. The reaction to confirm the structure of the [2 + 2] product was performed by D.T. Craft and will be listed along with the results from Chapter 3 in an upcoming publication.
Chapter 5.

Spectroscopic Data
Display Report

Analysis Info
Analysis Name: h2b-320.d
Method: NOVAKS:M
Sample Name: h2b-32
Comment: Diluted 1/20 in MEOH

Acquisition Info
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Operator: Administrator
Instrument: Esquire-LC_00137

Acquisition Parameters
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- Mass Range Mode: Std/Normal
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- Ion Polarity: Positive
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- Scan End: 500.00 m/z
- Scan Type: Scan
- Trap Drive: 35.4 V
- Auto MS/MS: Off

Chemical Structure

[M+Na]⁺

Thermal Chemistry

Br

THPO

Mass spectrum with peaks at 395.2, 315.2, 281.1, 293.2, 347.2, 413.3, 499.3 m/z
### Display Report

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- **Sample Name**: inh2-30
- **Comment**: Diluted 1/20 in MeOH
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![Mass Spectrum Image]

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**Bruker Daltonics DataAnalysis 3.0**

**printed**: 01/21/09 10:39:46

**Page 1 of 1**
Display Report

Analysis Info
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Method: NOVAKS.M
Sample Name: IMDb2-39
Comment: Diluted 1/20 in MEDH

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Operator: Administrator
Instrument: Esquire-LC_00137

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- Auto MS/MS: Off

Graphical representation of mass spectra with peaks at 359.1, 373.1, 239.1, 171.0, 197.1, 213.1, 185.0, 341.0, and 488.3 m/z.
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- **Comment:** diluted 1/10 in MeOH

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<tr>
<td>Scan Begin</td>
<td>50.00 m/z</td>
</tr>
<tr>
<td>Scan End</td>
<td>500.00 m/z</td>
</tr>
<tr>
<td>Trap Drive</td>
<td>33.1</td>
</tr>
<tr>
<td>Auto MS/MS</td>
<td>Off</td>
</tr>
</tbody>
</table>

### Bruker Daltonics DataAnalysis 3.0

- **Printed:** 12/03/08 15:15:05
- **Page:** 1 of 1

---

![Chemical Structure Image](image-url)

- **Peak 1:** 259.1
- **Peak 2:** 118.1
- **Peak 3:** 100.1
- **Peak 4:** 215.1
- **Peak 5:** 301.2
- **Peak 6:** 319.2
- **Peak 7:** 338.4
- **Peak 8:** 360.4
- **Peak 9:** 408.3
- **Peak 10:** 427.1

---

76
### Display Report

**Analysis Info**
- Analysis Name: Inb2-420.d
- Method: NOVAK'S.M
- Sample Name: Inb2-42
- Comment: Diluted 1/20 in MEOH
- Acquisition Date: 01/06/09 12:19:11
- Operator: Administrator
- Instrument: Esquire-LC_00137

**Acquisition Parameter**
- Ion Source Type: ESI
- Ion Polarity: Positive
- Mass Range Mode: SIS/Normal
- Scan Begin: 50.00 m/z
- Scan End: 500.00 m/z
- Capillary Exit: 355.0 Volt
- Sheath 1: 22.0 Volt
- Accumulation Time: 137 μs
- Averages: 20 Spectra
- Auto MS/MS: Off

---

![Mass Spectrogram](image)

**[M+Na]^+**

![Chemical Structure]

---

**Note:**
- Carry over

---

**Bruker Daltonics DataAnalysis 3.0**
- printed: 01/06/09 12:24:20
- Page 1 of 1

---

79
Observed M+Na 297.1461
Calc M+Na 297.1467
LNB-45
0.8 ppm
Obs M+H 235.1696
Calc M+H 235.1698

LNB-225
### Display Report

**Analysis Info**
- Analysis Name: ln2-750.d
- Method: XQ Default.ms
- Sample Name: ln2-75
- Comment: Diluted 1/20 in MEOH.
- Acquisition Date: 03/23/09 12:16:33
- Operator: Administrator
- Instrument: Esquire-LC_00137

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<td>Ion Source Type</td>
<td>ESI</td>
</tr>
<tr>
<td>Mass Range Mode</td>
<td>Std/ Normal</td>
</tr>
<tr>
<td>Capillary Exit</td>
<td>120.0 Volt</td>
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<td>Accumulation Time</td>
<td>3684 μs</td>
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<td>Ion Polarity</td>
<td>Positive</td>
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<td>Scan Begin</td>
<td>50.00 m/z</td>
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<tr>
<td>Scan End</td>
<td>700.00 m/z</td>
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<tr>
<td>Alternating Ion Polarity</td>
<td>n/a</td>
</tr>
<tr>
<td>Trap Drive</td>
<td>42.6</td>
</tr>
<tr>
<td>Auto MS/MS</td>
<td>Off</td>
</tr>
<tr>
<td>Averages</td>
<td>20 Spectra</td>
</tr>
</tbody>
</table>

---

**Diagram**

![Diagram of molecular structure with peaks at m/z values: 185.0, 118.0, 291.0, 257.1, 279.1, 299.2, 360.4, 411.3, 489.3, 537.3, 581.4, 625.4]
Display Report

Analysis Info
Analysis Name: Inb2-574.d
Method: XQ Default.ms
Sample Name: Inb2-57
Comment: Diluted 1/20 in MEOH.

Acquisition Date: 03/12/09 12:36:09
Operator: Administrator
Instrument: Esquire-LC_00137

Acquisition Parameter
- Ion Source Type: ESI
- Mass Range Mode: Std/Normal
- Capillary Exit: 8.1 Volt
- Accumulation Time: 568.0 µs
- Ion Polarity: Positive
- Scan Begin: 50.00 m/z
- Scan End: 500.00 m/z
- Alternating Ion Polarity: n/a
- Shim 1: 20.0 Volt
- Trap Drive: 29.6
- Averages: 20 Spectra
- Auto MS/MS: Off

Bruker Daltonics DataAnalysis 3.0
printed: 03/12/09 12:39:16
## Display Report

**Analysis Info**
- **Analysis Name**: lb2-1120.d
- **Method**: MFRLM
- **Sample Name**: inb2-112
- **Comment**: Diluted 1/20 in MeOH
- **Acquisition Date**: 06/18/09 12:54:59
- **Operator**: Administrator
- **Instrument**: Esquire-LC_00137

## Acquisition Parameter

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<tr>
<td>Mass Range Mode</td>
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<tr>
<td>Capillary Exit</td>
<td>89.7 Volt</td>
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<td>Accumulation Time</td>
<td>1208 µs</td>
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<td>Ions Polarity</td>
<td>Positive</td>
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<td>Scan Begin</td>
<td>50.00 m/z</td>
</tr>
<tr>
<td>Skim 1</td>
<td>21.2 Volt</td>
</tr>
<tr>
<td>Averages</td>
<td>20 Spectra</td>
</tr>
<tr>
<td>Alternating Ion Polarity</td>
<td>n/a</td>
</tr>
<tr>
<td>Scan End</td>
<td>500.00 m/z</td>
</tr>
<tr>
<td>Trap Drive</td>
<td>30.7</td>
</tr>
<tr>
<td>Auto MS/MS</td>
<td>Off</td>
</tr>
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</table>

---

**Chemical Structure**

```
\[ \text{[M+Na]}^+ \]
```

**Mass Spectrum**

- M/z values: 83.0, 100.1, 158.9, 204.1, 249.1, 316.3, 360.4, 413.3, 427.0

---

**Bruker Daltonics Data Analysis 3.0**
- **Printed**: 06/18/09 13:02:01
- **Page**: 1 of 1
3-Z-anidry tolly derivative
# Display Report

## Analysis Info
- **Analysis Name**: tolph000.d
- **Method**: NOVAKS.M
- **Sample Name**: hlb-olph
- **Comment**: Diluted 1/10 in MEOH
- **Acquisition Date**: 03/25/10 09:20:40
- **Operator**: Administrator
- **Instrument**: Esquire-LC_00137

## Acquisition Parameter
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<th>Value</th>
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<tbody>
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<td>ESI</td>
</tr>
<tr>
<td>Mass Range Mode</td>
<td>Std/Normal</td>
</tr>
<tr>
<td>Capillary Exit</td>
<td>87.4 Volt</td>
</tr>
<tr>
<td>Accumulation Time</td>
<td>828 µs</td>
</tr>
<tr>
<td>Ion Polarity</td>
<td>Positive</td>
</tr>
<tr>
<td>Scan Begin</td>
<td>50.00 m/z</td>
</tr>
<tr>
<td>Skim 1</td>
<td>19.4 Volt</td>
</tr>
<tr>
<td>Averages</td>
<td>20 Spectra</td>
</tr>
<tr>
<td>Trap Drive</td>
<td>30.7</td>
</tr>
<tr>
<td>Auto MS/MS</td>
<td>Off</td>
</tr>
<tr>
<td>Alternating Ion Polarity</td>
<td>n/a</td>
</tr>
<tr>
<td>Scan End</td>
<td>500.00 m/z</td>
</tr>
</tbody>
</table>

![Mass Spectrogram](image-url)

---

**Bruker Daltonics DataAnalysis 3.0**  
printed: 03/25/10 09:30:22  
Page 1 of 1
Display Report

Analysis Info
- Analysis Name: lb3-23A0.d
- Method: PTH-HMMS.M
- Sample Name: Inb3-23A
- Comment: Diluted 1:20 in MEOH
- Acquistion Date: 10/29/09 10:03:41
- Operator: Administrator
- Instrument: Esquire-LC_00137

Acquisition Parameter
- Ion Source Type: ESI
- Mass Range Mode: Std/Normal
- Capillary Ext: 96.0 Volt
- Accumulation Time: 226 μs
- Ion Polarity: Positive
- Scan Begin: 50.00 m/z
- Slit 1 Volt: 20.1 Volt
- Scan End: 500.00 m/z
- Trap Drive: 30.7
- Alternating Ion Polarity: n/a
- 20 Spectra

Chemical Structure:

\[ [M+Na]^+ \]

m/z 291.1

357.2

Bruker Daltonics DataAnalysis 3.0 printed: 10/29/09 10:12:25 Page 1 of 1

121
**Analysis Info**

<table>
<thead>
<tr>
<th>Analysis Name</th>
<th>b3-4200.d</th>
<th>Acquisition Date</th>
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<tbody>
<tr>
<td>Method</td>
<td>PTSH/MSMS.M</td>
<td>Operator</td>
<td>Administrator</td>
</tr>
<tr>
<td>Sample Name</td>
<td>Inb3-42</td>
<td>Instrument</td>
<td>Esquire-LC_00137</td>
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<tr>
<td>Comment</td>
<td>Diluted 1/20 in MEOH</td>
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**Acquisition Parameter**

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<th>Ion Source Type</th>
<th>ESI</th>
<th>Ion Polarity</th>
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<th>n/a</th>
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<tbody>
<tr>
<td>Mass Range Mode</td>
<td>Std/Normal</td>
<td>Scan Begin</td>
<td>50.00 m/z</td>
<td>Scan End</td>
<td>500.00 m/z</td>
</tr>
<tr>
<td>Capillary Exit</td>
<td>100.6 Volt</td>
<td>Skim 1</td>
<td>29.5 Volt</td>
<td>Trap Drive</td>
<td>33.1</td>
</tr>
<tr>
<td>Accumulation Time</td>
<td>201 µs</td>
<td>Averages</td>
<td>20 Spectra</td>
<td>Auto MSMS</td>
<td>Off</td>
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![MS Spectrogram](image)

---

**Bruker Daltonics DataAnalysis 3.0**

Printed: 12/15/09 10:38:28
Display Report

Analysis Info
Analysis Name: lc3-64A0.d
Method: XQ.Default.ms
Sample Name: mb3-64A
Comment: Diluted 1/20 in MEOH

Acquisition Info
Acquisition Date: 04/21/10 14:20:22
Operator: Administrator
Instrument: Esquire-LC_00137

Acquisition Parameter
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<td>Mass Range Mode</td>
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<tr>
<td>Capillary Ext</td>
<td>84.9 Volt</td>
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<td>Accumulation Time</td>
<td>731 μs</td>
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<td>Ion Polarity</td>
<td>Positive</td>
</tr>
<tr>
<td>Scan Begin</td>
<td>50.00 m/z</td>
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<tr>
<td>Scan End</td>
<td>500.00 m/z</td>
</tr>
<tr>
<td>Skim 1</td>
<td>17.4 Volt</td>
</tr>
<tr>
<td>Averages</td>
<td>20 Spectra</td>
</tr>
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<td>Alternating Ion Polarity</td>
<td>n/a</td>
</tr>
<tr>
<td>Trap Drive</td>
<td>33.1</td>
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Note: Compound too stable to do MSMS

Bruker Daltonics DataAnalysis 3.0 printed: 04/21/10 14:27:41 Page 1 of 1
Display Report

Analysis Info
Analysis Name: Ib3-1079.d
Method: NOVAKSM
Sample Name: Ib3-107
Comment: Diluted 1/100 in CHCl3 + 5uL ACN + 20uL of sample

Acquisition Info
Ion Source Type: ESI
Mass Range Mode: Std/Normal
Capillary Exit: 83.6 Volt
Accumulation Time: 91234 µs

Acquisition Parameter
Ion Polarity: Positive
Scan Begin: 150.00 m/z
Scan End: 500.00 m/z
Trap Drive: 29.6
Auto MS/MS: Off

Intensity x10^4

2.0+
1.5+
1.0+
0.5+

AcO

[Na^+]

Mass 192.1 211.0 232.1 281.2 306.1 339.1 481.3

m/z
PhenyI-Iodide
Display Report

Analysis Info
Analysis Name: InbPh-11.d
Method: NOVAKS.M
Sample Name: InbPh-1
Comment: Diluted 1:20 in MEOH

Acquisition Date: 03/29/10 10:20:16
Operator: Administrator
Instrument: Esquire-LC_00137

Acquisition Parameter
Ion Source Type: ESI
Mass Range Mode: 50.00 m/z
Capillary Exit: 82.2 Volt
Accumulation Time: 1757 µs
Scan Begin: 50.00 m/z
Scan End: 500.00 m/z
Slit 1: 15.2 Volt
Averages: 20 Spectra
Trap Drive: 30.7
Alternating Ion Polarity: n/a
Auto MS/MS: Off

Intensity x10^5

Bruker Daltonics DataAnalysis 3.0  printed: 03/29/10 10:29:30  Page 1 of 1
## Display Report

**Analysis Info**
- **Analysis Name**: lb3-8900.d
- **Method**: XQ Default.ms
- **Sample Name**: mb3-99
- **Comment**: Diluted 1/20 in MEOH
- **Acquisition Date**: 03/03/10 09:49:05
- **Operator**: Administrator
- **Instrument**: Esquire-LC_00137

### Acquisition Parameter

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<tr>
<td>Capillary Exit</td>
<td>50.5 Volt</td>
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<tr>
<td>Accumulation Time</td>
<td>273 µs</td>
</tr>
<tr>
<td>Ion Polarity</td>
<td>Positive</td>
</tr>
<tr>
<td>Scan Begin</td>
<td>24.1 Volt</td>
</tr>
<tr>
<td>Alternating Ion Polarity</td>
<td>n/a</td>
</tr>
<tr>
<td>Scan End</td>
<td>500.00 m/z</td>
</tr>
<tr>
<td>Trap Drive</td>
<td>33.1</td>
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<tr>
<td>Auto MS/MS</td>
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![Graphical Representation](image-url)
# Display Report

**Analysis Info**
- **Analysis Name**: lb3-1110.d
- **Method**: NOVAKS.M
- **Sample Name**: lb3-111
- **Comment**: Diluted 1/20 in MeOH

**Acquisition Date**: 03/29/10 11:50:22
- **Operator**: Administrator
- **Instrument**: Esquire-LC_00137

### Acquisition Parameter

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<td>600.00 m/z</td>
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<tr>
<td>Capillary Ext</td>
<td>93.9 Volt</td>
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<td>Sliim 1</td>
<td>24.5 Volt</td>
</tr>
<tr>
<td>Trap Drive</td>
<td>35.4</td>
</tr>
<tr>
<td>Accumulation Time</td>
<td>314 μs</td>
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<tr>
<td>Averages</td>
<td>20 Spectra</td>
</tr>
<tr>
<td>Auto MS/MS</td>
<td>Off</td>
</tr>
</tbody>
</table>

---

**Diagram**

![Diagram of chemical structure](image)

**Intens. x10^7**

- 1.50
- 1.25
- 1.00
- 0.75
- 0.50
- 0.25

**m/z**

- 0.00
- 100
- 200
- 300
- 400
- 500

---

**Bruker Daltonics DataAnalysis 3.0**

**printed**: 03/29/10 11:57:21
Display Report

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<tr>
<td>Scan End</td>
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<tr>
<td>Trap Drive</td>
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<td>Auto MS/MS</td>
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![Graph with chemical structure]

Bruker Daltonics DataAnalysis 3.0 printed: 03/29/10 13:09:33 Page 1 of 1

176
## Display Report

### Analysis Info
- **Analysis Name**: lb3-8000.d
- **Method**: NOVAKS.M
- **Sample Name**: lb3-80
- **Comment**: Diluted 1/20 in MEOH
- **Acquisition Date**: 02/18/10 12:08:51
- **Operator**: Administrator
- **Instrument**: Esquire-LC_00137

### Acquisition Parameter
- **Ion Source Type**: ESI
- **Mass Range Mode**: Std/Normal
- **Capillary Exit**: 105.0 Volt
- **Accumulation Time**: 180 μs
- **Ion Polarity**: Positive
- **Scan Begin**: 50.00 m/z
- **Scan End**: 500.00 m/z
- **Skim 1**: 32.7 Volt
- **Trap Drive**: 35.4
- **Averages**: 20 Spectra
- **Auto MS/MS**: Off
- **Alternating Ion Polarity**: n/a

---

![Mass Spectrogram](image1)

- **M+**: 381.1
- **M+ + Na+**: 399.2
- **M+ + K+**: 409.1

---

**Brook Daltionics DataAnalysis 3.0**

**printed**: 02/18/10 12:14:51

Page 1 of 1
Display Report

Analysis Info
Analysis Name: lb2-1540.d
Method: XQ Default.ms
Sample Name: lb2-154
Comment: Diluted 1/10 in MEOH

Acquisition Info
Acquisition Date: 04/01/10 10:15:25
Operator: Administrator
Instrument: Esquire-LC_00137

Acquisition Parameter
Ion Source Type: ESI
Mass Range Mode: Scan
Scan Begin: 50.00 m/z
Scan End: 500.00 m/z
Capillary Exit: 87.4 Volt
Slit 1: 19.4 Volt
Alternating Ion Polarity: n/a
Auto MS/MS: Off

Intensity x10^5

\[
\left[ \text{M} + \text{Na} \right]^+ \quad 339.0
\]

Bruker Daltonics DataAnalysis 3.0
printed: 04/01/10 10:28:31 Page 1 of 1

Couldn’t do MS/MS
### Display Report

#### Analysis Info
- **Analysis Name**: lb2-1460.d
- **Method**: ESI
- **Sample Name**: lb2-146
- **Comment**: Diluted 1/20 in MeOH
- **Acquisition Date**: 08/06/09 16:44:41
- **Operator**: Administrator
- **Instrument**: Esquire-LC_00137

#### Acquisition Parameter

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<tr>
<td>Mass Range Mode</td>
<td>Std/Normal</td>
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<tr>
<td>Capillary Exit Voltage</td>
<td>99.8 Volt</td>
</tr>
<tr>
<td>Accumulation Time</td>
<td>95 μs</td>
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<td>Ion Polarity</td>
<td>Positive</td>
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<tr>
<td>Scan Begin</td>
<td>150.00 m/z</td>
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<tr>
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<td>700.00 m/z</td>
</tr>
<tr>
<td>Alternating Ion Polarity</td>
<td>n/a</td>
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<tr>
<td>Trap Drive</td>
<td>35.4</td>
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<tr>
<td>Auto MS/MS</td>
<td>Off</td>
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<tr>
<td>Averages</td>
<td>8 Spectra</td>
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</tbody>
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**Diagram**: 347.1 [M+Na]

Bruker Daltonics DataAnalysis 3.0  printed: 08/06/09 16:49:04  Page 1 of 1
Display Report

Analysis Info
Analysis Name: it3-1020.d  
Method: NOVAKS.M  
Sample Name: itb3-102  
Comment: Diluted 1/25 in MEOH + 10% CHCl3

Acquisition Date: 03/29/10 15:16:25  
Operator: Administrator  
Instrument: Esquire-LC_00137

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<tr>
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<td>500.00 m/z</td>
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<tr>
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</tr>
<tr>
<td>Trap Drive</td>
<td>35.4</td>
</tr>
<tr>
<td>Auto MS/MS</td>
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![Graph with molecular structure and peaks at m/z 288.3, 305.1, 347.5, 389.3]
Display Report

Analysis Info
Analysis Name: Ib3-118.d
Method: XQ Default.ms
Sample Name: Ib3-118
Comment: Diluted 1/20 in MeOH

Acquisition Date: 04/12/10 12:47:16
Operator: Administrator
Instrument: Esquire-LC_00137

Acquisition Parameter
Ion Source Type: ESI
Mass Range Mode: Scan Normal
Capillary Exit: 40.8 Volt
Accumulation Time: 1225 μs

Ion Polarity: Positive
Scan Begin: 50.00 m/z
Scan End: 500.00 m/z
Sim 1: 22.1 Volt
Averages: 20 Spectra

Alternating Ion Polarity: n/a
Trap Drive: 33.1
Auto MS/MS: Off

Chemical structure image

Bruker Daltonics DataAnalysis 3.0
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