Expanding the frontier of gold-catalyzed cyclizations and rational ligand design.

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EXPANDING THE FRONTIER OF GOLD-CATALYZED CYCLIZATIONS AND RATIONAL LIGAND DESIGN

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DEDICATION

This dissertation is dedicated to my respected father ‘Sh. Pawan Kumar Malhotra’,
mother ‘Smt. Kiran Malhotra’ and my grandparents.
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The focus of my dissertation work is to study the gold-catalyzed intramolecular and intermolecular cyclizations involving oxonium intermediates towards the application of synthetically interesting frameworks under ambient conditions and developing a rational approach for the effective catalyst design in gold catalysis. We explored the gold-catalyzed oxygen-transfer reactions of 2-alkynyl-1,5-diketones or 2-alkynyl-5-ketoesters to furnish five-membered rings bearing a quaternary carbon tethered to a carbonyl group. The detailed mechanistic investigation on the newly proposed intramolecular [4+2] cycloaddition mechanism was performed by means of isotopic experiments and quantum chemical calculations. The reactivity of alkynylenolate was investigated in the reactions of allenic ketones and vinyl ketones which led to versatile syntheses of 2-alkynyl-1,5-diketones, 4-alkynyl-3-hydroxycyclohexones and 4-alkynylcyclohexenones. We also investigated the gold-catalyzed annulations of 2-alkynyl benzaldehyde with acyclic or cyclic vinyl ethers under very mild conditions, and successfully developed synthetically interesting dihydronaphthalenes, acetal-tethered isochromenes and bicyclo[2.2.2]octane
derivatives often found in biologically active molecules and natural products. Although there have been numerous reviews and publications on new gold-catalyzed transformations, the development of new catalysts still relies on a hit-and-miss approach. Because the decay of the active cationic gold catalyst is the main reason for the high catalytic loading required for the majority of gold-catalyzed transformations, we developed a modular approach for effective catalyst design in gold catalysis. We discovered a new phosphine–based precatalyst that is broadly applicable and highly efficient—in the parts per million (ppm) range—at room temperature or slightly elevated temperatures (<50 °C). The ligand was preapared in one step from readily available starting materials.
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CHAPTER 1. INTRODUCTION

1.1 Background of gold catalysis

In the past two decades, homogeneous gold catalysis has proven to be a constructive tool for the synthesis of versatile organic frameworks. It has emerged as a hot research field and this is reflected by the exponential surge in the number of publications on gold-catalyzed transformations including cycloisomerizations, carbocyclizations, cycloadditions, and heteroatom addition to unsaturated C-C bonds to form myriad products of synthetic importance.\textsuperscript{1-17} For example, gold-catalyzed cyclizations provide an efficient way for the construction of wide range of heterocycles\textsuperscript{18} as well as carbocycles.\textsuperscript{19} Selected examples include cycloisomerization of propargyl ketones by Hashmi\textsuperscript{20}, cyclization of $\alpha$-hydroxy allenes by Krause\textsuperscript{21}, benzannulation of $o$-alkynylbenzaldehyde by Yamamoto\textsuperscript{22} and double cyclization of 1,5-enynes by Kozmin,\textsuperscript{23} as shown in Scheme 1.

Unlike other transition metal catalyzed reactions, most of the gold-catalyzed transformations occur at ambient conditions and can proceed well in the presence of air and moisture, making this chemistry greener and easier. The catalytic properties of both Au (III) and Au (I) complexes have been exploited in a plethora of organic transformations and many unique features are associated with its reactivity.
The unique reactivity of gold catalysts could be explained by the relativistic effect.\textsuperscript{24-26} As a result of the relativistic effect, the radius of the 6s orbital is contracted and 5d orbitals expand as displayed in Scheme 2. Therefore, the orbital contraction leaves the LUMO in a low-lying level of energy, which accounts for the higher reactivity observed.

Scheme 1: Selected examples of gold-catalyzed cyclizations.

Scheme 2: A: Schematic view of the molecular orbital energies for hypothetic Au compounds before and after relativistic considerations. B: Calculated relativistic contraction of 6s orbital.
From a mechanistic standpoint, the coordination of gold catalyst with substrates such as alkynes, alkenes, and allenes enhances their electrophilicity. Subsequently, a nucleophile attacks the activated C-C multiple bond either inter- or intramolecularly followed by electrodeauration to selectively form carbocycles or heterocycles as displayed in Scheme 3.

Scheme 3: General mechanism involved in gold catalysis.

1.2 Gold-catalyzed reactions involving gold-oxonium intermediates

Scheme 4: Oxonium intermediates involved in gold catalysis.

In general, when oxygen containing nucleophiles such as carbonyl compounds (aldehydes/ketones/esters) attack gold activated multiple bonds they generate an oxonium intermediate such as A. This oxonium intermediate A, being a highly energetic species, will undergo electron transfers/rearrangement/protodeauration to form corresponding products (Scheme 4). Similarly, when nucleophiles such as ethers/epoxides attack gold activated multiple bonds, an oxonium intermediate such as B is generated, which may
further undergo several rearrangements/transformations to furnish synthetically interesting products (Scheme 4).

1.2.1 Carbonyl compounds as nucleophiles

An early example of intramolecular cycloisomerization is the gold-catalyzed reaction of propargyl ketones 1-1 reported by Hashmi et al\textsuperscript{20} in 2000 (Scheme 5). The coordination of gold (III) activates the alkyne moiety which is followed by nucleophilic attack of the carbonyl oxygen to form gold oxonium intermediate 1-2A, which subsequently undergoes proton transfer/protodemetallation to afford furan substrates.

![Scheme 5: Cycloisomerization of propargyl ketone 1-1.](image)

In 2007, Yamamoto and coworkers reported the gold-catalyzed synthesis of substituted cyclic enones 1-10 from tethered alkynyl ketones 1-9, in good yields\textsuperscript{17} (Scheme 6). In this case, the gold activated alkyne is attacked by the carbonyl group to form an oxonium intermediate 1-9A, which subsequently undergoes electron transfer and ring opening to furnish cyclic enones. A year later, the same authors developed a gold-catalyzed cascade reaction towards the synthesis of polycyclic enones 1-11\textsuperscript{27}. In their tandem metathesis
and Nazarov reaction, the oxonium intermediate undergoes rearrangements followed by sequential Nazarov reaction to form polycyclic enones 1-11.

**Scheme 6:** Gold-catalyzed synthesis of substituted cyclic enones 1-10 polycyclic enones 1-11.

Manoharan and coworkers\(^2^8\) also reported a tandem heterocyclization/Nazarov reaction in 2011 that furnished substituted fused furan carbocycles 1-13 (Scheme 7). The oxonium intermediate 1-12A could be trapped using two equivalents of methanol that clearly revealed the heterocycle formation was triggered by a Nazarov reaction to form the corresponding fused furan carbocycles, using dichloromethane as solvent. The intermediate 1-12A undergoes Nazarov reaction to form intermediate 1-12B, which eventually form furan carbocycles. In the same year, Moran and coworkers\(^2^9\) reported a strategy for the synthesis of substituted furans by the cycloisomerization of \(\beta\)-alkynyl \(\beta\)-ketoesters 1-14 (Scheme 7). In this cycloisomerization, the intramolecular attack of the oxygen of a ketone on the activated alkyne formed the oxonium intermediate 1-15A, which underwent protodeauration and isomerization to yield substituted furans.
Scheme 7. Tandem heterocyclization and Nazarov reaction for fused furan carbocycles 1-13 and cycloisomerization of β-alkynyl β-ketoesters 1-14.

1.2.2 Ethers/epoxides as nucleophiles

In 2013, Hashmi et al.\textsuperscript{30} discovered a chemoselective one-pot synthesis of benzofuran 1-17 from alkynyl-7-oxabicyclo[4.1.0]heptan-2-ones 1-16 (Scheme 8). The carbonyl oxygen acts as nucleophile to the gold activated triple bond to generate the fused ring...
oxonium intermediate 1-17A, which subsequently undergoes 1,2-hydride shift followed by sequential rearrangements to give 1-17B which then eliminates methanol and water to yield substituted benzofurans.

Scheme 8. Chemoselective synthesis of benzofurans 1-17.

In 2004 Hashmi et al.\textsuperscript{31} reported a gold-catalyzed isomerization of alkynyloxiranes 1-18 to the corresponding furan derivates 1-19 (Scheme 9). In the mechanism, the gold catalyst activates the triple bond followed by nucleophilic attack of epoxide oxygen at the distal position of the activated alkyne to generate five membered oxonium intermediate 1-18B, which then undergoes deprotonation and proto-demetallation to yield substituted furans.
Scheme 9: Isomerization of alkynyloxiranes 1-18.

An efficient cycloisomerization of alkynyloxiranes 1-20 was developed by Liang et al.\textsuperscript{32} in 2007 to afford 2,5-disubstituted furans 1-21 (Scheme 10). The gold activated alkyne is attacked by an epoxide oxygen acting as nucleophile to form oxabicyclo oxonium ion intermediate 1-20A, which subsequently undergoes protonation to give 2,3-dihydrofuran, followed by reductive elimination to yield 2,5-disubstituted furans. Two years later, in 2009, Liang and coworkers\textsuperscript{33} reported a tandem cyclization/Friedel-Crafts reaction to furnish furan derivatives in good yields 1-23 (Scheme 10). Plausible mechanism for this reaction involves the nucleophilic attack of epoxide oxygen on the gold-coordinated alkynyl substrate, followed by protonation, reductive elimination and intermolecular Friedel-Crafts type reactions to generate substituted furans.
In 2011, Goualt and coworkers developed a gold-catalyzed intramolecular reaction of allyloxyphenylpropynone to afford chromones in moderate yields (Scheme 11). The gold activated alkyne moiety is attacked by a lone pair on oxygen to generate six-membered oxonium ion intermediate, which then undergoes substituent transfer via carbometallation to form substituted chromone derivatives.
Scheme 11: Intramolecular reaction of allyloxyphenylpropynone 1-24.

While probing the reactivity of the alkynylenolate (Scheme 12) we discovered the synthesis of 2-alkynyl-1,5-dicarbonyl derivatives 3-3 from the Michael addition of activated allenes to electron-deficient olefins, the detailed synthesis of which will be described in Chapter 3. Since two carbonyls and a carbon–carbon triple bond had been installed in the substrate, we envisioned that oxonium intermediate (Scheme 12) containing a quaternary propargylic carbon J could be generated from the 2-alkynyl-1,5-dicarbonyl 3-3 as a result, Path A would be blocked and an alternate Path B could provoke novel transformations of the oxonium intermediate to generate complex ring systems (Scheme 12). Gratifyingly, an intramolecular-oxygen-transferred reaction yielded highly substituted five-membered rings bearing a quaternary carbon tethered to a carbonyl group and the detailed scope and mechanistic details of this transformation will be discussed in Chapter 2.
Gold-catalyzed benzannulations has been well documented in the literature thanks to the work of Yamamoto and coworkers.\textsuperscript{22,36} In this reaction, 2-alkynyl benzaldehyde 1-5 reacts with an alkyne or aldehyde as cyclization partners to furnish naphthalene derivative 1-6 in an efficient manner (Scheme 13). From a mechanistic standpoint, the gold catalyst activated the triple bond of 1-5. This activation is followed by nucleophilic attack of carbonyl oxygen to generate oxonium intermediate 1-5A; its formation from a gold catalyst and 2-alkynyl benzaldehyde substrate is well-accepted. 1-5A underwent [4+2] cycloaddition to generate intermediate 1-5B, which subsequently rearranged to afford naphthalene substrate 1-6. However, in the presence of an aldehyde, intermediate 1-5A underwent reverse electron demand Diels Alder reaction with the enol form of aldehyde to generate intermediate 1-5C, which further rearranged to furnish naphthalene derivative 1-6. We posited that in the presence of a suitable gold catalyst, 2-alkynyl
benzaldehyde 1-5 would generate an oxonium intermediate, which could undergo reaction with a vinyl ether and yield synthetically interesting products; the details of the scope and mechanism of this reaction will be discussed in Chapter 4 (Scheme 13).

### 1.3 Ligand design in gold catalysis

In many palladium-catalyzed coupling reactions, such as the Suzuki reaction, the catalyst loading can be reduced to ppm levels\textsuperscript{37} but the common practice to use 5\% loading in gold catalysis often makes it impractical to use in large scale synthesis. Ligands play a major role in the tuning of reactivity of gold catalysis and hence they hold the key to improving turnover numbers, but a rational understanding of ligand effects in gold catalysis is lacking, despite the intensive effort of notable researchers. Professor Dean Toste (UC Berkley) correctly articulated the crux of the limitations on ligand effects in gold catalysis in his recent Chemical Reviews paper (2008, 3351-3378).\textsuperscript{38} In his conclusions, the author states “although a great deal of empirical information is now available … in homogeneous Au catalysis, the development of new catalysts and reactions continues to rely upon trial and error.” Rational design of suitable ligands to achieve better efficiency is almost non-existent in gold catalysis and needs careful attention. Although the catalytic cycle of gold (Scheme 16) is well known, a rational design of ligands to improve its efficiency has not been reported yet. The influence of ligands on reactivity is not clear at all. For example: Toste and co-workers reported on the gold-catalyzed hydroamination of allenes\textsuperscript{39} 1-27 and ring expansion of propargyl cyclopropanols.\textsuperscript{40} They determined that in these two reactions, electron deficient phosphine ligands (e.g. (p-CF\textsubscript{3}C\textsubscript{6}H\textsubscript{4})\textsubscript{3}P) accelerate the reaction whereas electron rich phosphine ligands slow down the reaction (Scheme 14a). However, in the majority of
gold-catalyzed reactions, electron deficient phosphine ligands like \((p\text{-CF}_3\text{C}_6\text{H}_4)_3\text{P}\) don’t work well; instead, electron rich ligands work better (Scheme 14b). These inconsistencies clearly underscore the complexity of gold catalysis. Moreover, the deactivation of gold is ubiquitous in gold catalysis, but how a ligand affects gold deactivation is unknown. The deactivation of gold catalyst further complicates the predictability of ligand performance in gold catalysis.

Scheme 14: Ligand effect in hydroamination of allenes 1-27 and cycloisomerization of propargyl amines 1-29.

There have been few reactions in the literature that achieved high turnover numbers (TONs) using gold catalysts. Notable examples include the \([(\text{NHC})\text{AuI}]\)-catalyzed hydration of alkyne, reported by Nolan and coworkers; the hydroamination of alkynes with a hyperhalogenated carba-closo-dodecaborate anionic ligand, reported by Lavallo and coworkers; and the ester assisted hydration of alkynes catalyzed by small gold clusters, reported by Corma and coworkers. In some exceptional cases, even higher turnovers can be achieved but at the cost of employing relatively high temperatures (e.g. 120 °C). More recently, in 2013, extremely high turnover numbers were achieved by Hashmi and coworkers in the intramolecular addition of diol to alkyne 1-31 using only 0.000001 mol% of N-Acyclic carbene (NAC)-based silsesquioxane-substituted
mononuclear homogeneous gold catalyst, shown in Scheme 15. The high turnover numbers could be attributed to the fact that these bulky silsesquioxane substituted NAC based ligands have a stabilizing effect on the catalyst.

Scheme 15: Intramolecular addition of diol to alkyne with highly active mononuclear gold catalyst.

We became interested in developing a rational protocol to design ligands for gold-catalyzed reactions. To achieve this goal we carried a structure–activity relationship (SAR) study between the structure of a ligand and its reactivity. We focused our study on phosphine ligands since phosphine ligands are the most versatile neutral 2e⁻ donor ligands available and their soft base character is compatible with gold, which is a soft Lewis acid. Moreover, ³¹P NMR spectroscopy is a helpful and readily available tool in understanding the effect of ligands in transition metal catalysis. This tool allowed different phosphine-based ligands to be screened in our laboratory.

Typical gold catalytic cycle: It is well accepted that most gold-catalyzed reactions go through three major stages (Scheme 16). In stage 1, a nucleophile attacks a [AuLₙ]⁺-activated alkyne (or alkene) A to form a trans-alkenyl gold complex intermediate B (or an alkyl gold complex in the case of alkenes). In stage 2, the resulting vinyl complex reacts with an electrophile (E⁺), usually a proton, to yield the final product via protodeauration, which also regenerates the cationic gold species (Scheme 16). Additionally, in almost all
gold-catalyzed reactions, decay or deactivation of the gold catalyst takes place via the reduction of cationic gold to gold(0) (stage 3).

Scheme 16: Typical gold catalytic cycle.

From a previous paper from our group on ligand effects and ligand design on homogeneous gold catalysis, we found that two scenarios were possible in gold-catalyzed reactions: in the first one (type I) the nucleophilic addition to alkyne/allene/alkene (stage 1) is the rate-determining step. Therefore, electron-deficient ligands ought to speed-up this stage. In type I gold-catalyzed reaction, electron poor ligands give faster reaction rates. In type II, the regeneration of cationic gold catalyst (e.g., protodeauration) is the rate-determining step (stage 2). Therefore, electron-rich ligands ought to facilitate this stage. In type II gold-catalyzed reactions, electron rich ligands increase the reaction rate. These electronic effects hold true when the decay of cationic gold is not significant. With this background knowledge, we planned to develop a broadly applicable, readily prepared cationic gold catalyst that is efficient at low loading levels and mild reaction temperatures.
To design such a gold catalyst we focused on the three major factors that account for the high loading in gold catalysis. These factors are: (i) the decay of the gold catalyst during the reaction, (ii) the formation of off-cycle gold species, and (iii) the mismatch of electronic effects within the gold ligand. We used the intermolecular hydroamination of phenyl acetylene with aniline as a model reaction for our study. As seen in Figure 1, a ligand like Ph₃P is not a good choice since the reaction is relatively slow (i.e. 20% conversion after 18 h). It was observed that the presence of a biphenyl group and introduction of two electron rich t-Bu groups (L₃, JohnPhos) produced an even faster rate and full conversion to product. We hypothesized that two sterically demanding biaryls on the phosphine ligand could surround the gold center further and discourage the formation of D (Figure 1). Thus, we designed ligand L₁ (featuring two electron-rich and sterically demanding ortho-biphenyl groups and one electron rich cyclohexyl group. We prepared L₁ in a single step from commercially available starting materials. The crystallographic structure of L₁-AuCl (Figure 1) demonstrated that the two ortho-biphenyl motifs were able to surround or embed the gold center. This L₁-AuCl was found to be highly efficient.
at extremely low loadings in C-C, C-O bond forming and cycloisomerization reactions at relatively low temperatures, the details of which will be described in Chapter 5.
1.4 Outline of the dissertation:

Chapter 1: Gold catalyzed intramolecular oxygen transfer reactions.

Chapter 2: Tandem Michael addition/aldol reaction of allenic ketones with vinyl ketones.

Chapter 3: Gold catalyzed cyclizations of 2-alkynyl benzaldehydes.

Chapter 4: Rational ligand design and broadly applicable ligand L1-AuCl.
CHAPTER 2. GOLD-CATALYZED INTRAMOLECULAR OXYGEN TRANSFER REACTIONS OF 2-ALKYNYL-1,5-DIKETONES OR 2-ALKYNYL-5-KETOESTERS

2.1 Background

During the past few years our group has been working towards the development of efficient and selective gold-catalyzed transformations to discover simple approaches for the synthesis of interesting organic compounds. A major breakthrough occurred in 2008 while investigating the reactivity of allenoates to afford γ-lactones; our group discovered the formation of stable organogold(I) complexes. This important discovery supported the postulated mechanism of gold catalysis at the time, providing the first experimental evidence to support the mechanism of Au-catalyzed reactions of carbon-carbon multiple bonds, including alkynes/allenes/alkenes.

Continuing our efforts to explore gold-catalyzed transformations, we became interested in exploring the reactivity of 2-alkynyl-1,5-dicarbonyl for the construction of α,β-unsaturated enones or similar compounds. This class of compounds has been at the forefront of synthetic organic chemistry since its inception, not only because these compounds are important building blocks in organic synthesis but also because the conjugated enone substructure in itself is a significant motif in natural products or...
biologically active compounds.\textsuperscript{47-53} Aldol condensations and Wittig-type reactions have been utilized for the construction of this moiety for decades.\textsuperscript{54-62} Recently though, an oxygen transfer from a carbonyl group to a carbon–carbon triple bond, also known as alkyne–carbonyl metathesis, has attracted the interest of synthetic chemists because this methodology could be an efficient, as well as atom-economical alternative to the Wittig reaction through the simultaneous formation of a new carbon–carbon double bond and carbonyl group.\textsuperscript{63-74} In this regard, many Lewis or Brønsted acid catalyzed intermolecular or intramolecular alkyne–carbonyl metathesis reactions have been extensively developed (Scheme 17, top).\textsuperscript{75-80} Notably, by using tethered alkynylketones as the substrates, Yamamoto and co-workers reported the gold- or TfOH-catalyzed oxygen-transfer reactions to give highly substituted cyclic enones as the products (Scheme 17, bottom).\textsuperscript{17,27,81}

\[
\begin{align*}
\text{Lewis acid or Brønsted acid} & \quad \text{ref. 75-78} \\
\text{Lewis acid: } & \text{In(O\text{TF})}_3, \text{GaCl}_3, \text{Yb(O\text{TF})}_3, \\
& \text{AgSbF}_6, \text{BF}_3(\text{OEt})_2, \text{SbF}_5 \\
\text{Bronsted acid: } & \text{HBF}_4, \text{TFA, TfOH} \\
\text{AuCl}_2/\text{AgSbF}_6 & \quad \text{or TfOH} \\
& \quad \text{ref. 17,27,81}
\end{align*}
\]

Scheme 17. Lewis or brønsted acid- and gold-catalyzed intermolecular or intramolecular alkyne-carbonyl metathesis.

A few years ago, we investigated the reactivity of alkynylenolates and other extended enolates,\textsuperscript{82-85} and found that 2-alkynyl-1,5-dicarbonyl derivatives could be conveniently obtained from the tetra-\textit{n}-butylammonium fluoride (TBAF) mediated Michael addition of activated allenes to electron-deficient olefins. The detailed synthesis will be discussed in
Chapter 3. Since two carbonyls and a carbon–carbon triple bond are installed in 2-1, we envisioned that an oxonium intermediate could arise from one of the carbonyls and the triple bond, and engender novel transformations. The chemistry of the oxonium ions formed from alkynylic aldehydes or ketones by mediation of transition metals, Lewis acids, Bronsted acids, or even electrophiles such as iodine, has attracted a lot of attention because these intermediates could undergo both inter- and intramolecular cycloadditions to carbon–carbon multiple bonds to give products of synthetic importance. Because of our continuous interest in gold catalysis, we subjected compound 2-1a to gold catalysis and found that the reaction, using AuCl as the catalyst, cleanly furnished cyclopentenyl ketone 2-2a, an intramolecular-oxygen-transferred product, in excellent yields after only 5 min at room temperature (Scheme 18). 

Scheme 18: Gold-catalyzed oxygen transfer reaction.

2.2 Results and discussion

Highly substituted five-membered rings bearing a quaternary carbon tethered to a carbonyl group are often found in natural products or biologically active compounds. Selected examples include Xestenone, Chloriolin-A, Spergulagenin-A and Saussureal (Scheme 19). Methods for the construction of these highly substituted carbocycles are rare in literature. Thus, we studied the scope of the gold-catalyzed intramolecular oxygen transfer reaction and developed a fast and efficient synthetic
method to construct this important substructure. Various substrates were subjected to this reaction; the results are summarized in Table 1.

Scheme 19: Selected examples of natural products having a carbonyl tethered quaternary carbon on a five-membered ring.

It was found that the reactions of 2-alkynyl-1,5-diketones 2-1 with either aromatic or aliphatic groups substituted at the R₁ position proceeded smoothly, and the corresponding products 2-2a–2-2i were isolated in excellent yields (Table 1, entries 1–9). The variation on R₄ from methyl to ethyl and phenyl did not have a deleterious effect on the reaction, and the corresponding products 2-2j–2-2m were obtained in very good yields (Table 1, entries 10–13). Also, replacing the phenyl group at the R₃ position with a methyl group did not diminish the efficiency of the reaction (Table 1, entry 14). To our surprise though, when the phenyl group at the R₃ position was replaced by an ethoxy group, that is, when 2-alkynyl-5-ketoesters were used, the reaction still proceeded as smoothly and efficiently as before, although longer reaction times were required. The only exception occurred with 2-1u, from which 2-2u was isolated in only 50% yield, along with unidentified
products (Table 1, entries 15–22). For the 2-alkynyl-5-ketoester substrate **2-1w** bearing an aliphatic group at the R₁ position, the reaction did not take place (Table 1, entry 23).

**Table 1: Gold-catalyzed intramolecular oxygen transfer reactions of 2-alkynyl-1,5-diketones or 2-alkynyl-5-ketoesters.**

<table>
<thead>
<tr>
<th>entry</th>
<th>R₁/R₂/R₃/R₄</th>
<th>yield/2-2[a]</th>
<th>entry</th>
<th>R₁/R₂/R₃/R₄</th>
<th>yield/2-2[a]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhMe/PhMe 2-1a</td>
<td>2-2a, 98</td>
<td>13</td>
<td>p-CIC₆H₄Me/Ph/Ph 2-1m</td>
<td>2-2m, 99</td>
</tr>
<tr>
<td>2</td>
<td>p-MeOCC₆H₄Me/Ph/PhMe 2-1b</td>
<td>2-2b, 99</td>
<td>14</td>
<td>PhMe/Me/Me 2-1n</td>
<td>2-2n, 92</td>
</tr>
<tr>
<td>3</td>
<td>p-CIC₆H₄Me/Ph/Me 2-1c</td>
<td>2-2c, 92</td>
<td>15</td>
<td>PhMe/Me/Me/Me 2-1o</td>
<td>2-2o, 88</td>
</tr>
<tr>
<td>4</td>
<td>n-C₆H₄Me/Me/Ph/Me 2-1d</td>
<td>2-2d, 99</td>
<td>16</td>
<td>p-MeOCC₆H₄Me/MeOEt/Me 2-1p</td>
<td>2-2p, 92</td>
</tr>
<tr>
<td>5</td>
<td>Ph/PhMe/Me/PhMe 2-1e</td>
<td>2-2e, 96</td>
<td>17</td>
<td>p-CIC₆H₄Me/MeOEt/Me 2-1q</td>
<td>2-2q, 90</td>
</tr>
<tr>
<td>6</td>
<td>t-BuMe/Me/Ph/Me 2-1f</td>
<td>2-2f, 95</td>
<td>18</td>
<td>PhMe/Me/Ph/Ph 2-1r</td>
<td>2-2r, 91</td>
</tr>
<tr>
<td>7</td>
<td>Me/Me/Ph/Me 2-1g</td>
<td>2-2g, 91</td>
<td>19</td>
<td>p-MeOCC₆H₄Me/MeOEt/Ph 2-1s</td>
<td>2-2s, 92</td>
</tr>
<tr>
<td>8</td>
<td>Bn/Me/PhMe 2-1h</td>
<td>2-2h, 94</td>
<td>20</td>
<td>p-CIC₆H₄Me/MeOEt/Ph 2-1t</td>
<td>2-2t, 92</td>
</tr>
<tr>
<td>9</td>
<td>CypCH₂Me/Me/PhMe 2-1i</td>
<td>2-2i, 99</td>
<td>21</td>
<td>Ph/BnOEt/Me 2-1u</td>
<td>2-2u, 50</td>
</tr>
<tr>
<td>10</td>
<td>PhMe/PhEt 2-1j</td>
<td>2-2j, 98</td>
<td>22</td>
<td>Ph/BnOEt/Ph 2-1v</td>
<td>2-2v, 90</td>
</tr>
<tr>
<td>11</td>
<td>PhMe/Ph/Ph 2-1k</td>
<td>2-2k, 93</td>
<td>23</td>
<td>n-C₆H₄Me/MeOEt/Me 2-1w</td>
<td>NR</td>
</tr>
<tr>
<td>12</td>
<td>p-MeOCC₆H₄Me/Me/Ph/Ph 2-1l</td>
<td>2-2l, 91</td>
<td></td>
<td>n-C₆H₄Me/MeOEt/Me 2-1w</td>
<td>Complex</td>
</tr>
</tbody>
</table>

[a] General Reaction Conditions: 2-Alkynyl-1,5-Diketone or 2-Alkynyl-5-ketoester **2-1** (0.3 mmol), CH₂Cl₂ (2.0 mL). For Alkynyl diketones, Reaction Time = 5 minutes; For Alkynyl ketoesters, Reaction Time = 30 minutes; [b] Isolated Yields; [c] Reaction was conducted in toluene at 80 °C. Cyp = Cyclopentanyl; NR = No Reaction.

The traditional mechanism of the oxygen-transfer reaction invoked a [2+2] pathway (Scheme 20, top) for the inter-/intramolecular alkyne–carbonyl metathesis.¹⁷,²⁷,⁷⁵-⁸⁰,¹⁴² However, the fact that the oxygen-transfer reaction of 2-alkynyl-1,5-diketones or 2-alkynyl-5-ketoesters could be completed in minutes at room temperature, and with higher yields than previously reported oxygen transfer prompted us to propose an alternative [4+2] mechanism (Scheme 20, bottom). We envisioned that a five-membered ring furanium **C**⁸,²⁰,¹⁴³-¹⁵² would be much easier to form than the seven-membered ring oxonium **A**, this action is followed by a [4+2] cycloaddition of the furanium intermediate.
to the other carbonyl group to form the intermediate D, which finally yields the product after several electron transfer steps.

We designed an isotopic labeling experiment to elucidate if the well-accepted [2+2] mechanism, or our newly proposed [4+2] pathway was responsible for the gold-catalyzed intramolecular oxygen transfer of 2-alkynyl-1,5-diketones and 2-alkynyl-5-ketoesters (Scheme 20). We speculated that if an 18O atom could be incorporated into one of the carbonyl groups in the substrates, then the 13C NMR of the reaction product could be used to locate the 18O atom, and provide clues as to the more favorable mechanistic pathway. Hence, using alkynyldiketone 2-1b-18O (R1 = p-methoxyphenyl, R2 = phenyl) and alkynylketoester 2-1o-18O (R1 = phenyl, R2 = ethoxy) as the model substrates, we surmised that if the reaction followed a [2+2] route then the 18O would end up on the left carbonyl group in 2-2-18O-a (Scheme 20, top), whereas it would be incorporated on the benzoyl group or ester group in 2-2-18O-b if the reaction followed a [4+2] pathway (Scheme 20, bottom).

Substrate 2-1b-18O was synthesized from the 18O exchange of compound 2-1b with H218O under acidic conditions (Scheme 21). The 18O exchange occurred only on the methyl carbonyl group, as indicated by 13C NMR spectroscopy. A 0.05 ppm (5 Hz) upfield chemical shift was found on carbon 1 in the substrate, whereas no chemical shift change occurred on carbon 2. The 2-1b-18O substrate was subjected to the gold-catalyzed oxygen transfer reaction and the product 2-2b-18O was obtained in quantitative yield, without any 18O loss, as determined by its ESI mass spectrum. It was found that only carbon 4 in the product 2-2b-18O exhibited the 0.05 ppm (5 Hz) upfield chemical shift in its 13C NMR spectrum (Scheme 22).
Scheme 20: $^{18}$O isotopic labeling experiment for mechanistic studies.

\[ R_1 \text{Au} \quad \text{[2+2]} \quad R_1 \text{Au} \]
\[ 2-1-^{18}O \]
\[ \text{or} \]
\[ 2-2-^{18}O-a \]
\[ 1b: R^1 = p\text{-MeOC}_6\text{H}_4, R^2 = \text{Ph} \]
\[ 1a: R^1 = \text{Ph}, R^2 = \text{OEt} \]

Scheme 21: Synthesis of substrate 2-1b-$^{18}$O and its $^{13}$C NMR spectrum.

\[ p\text{-MeOC}_6\text{H}_4 \quad \text{Me} \quad \text{H}_2^{18}\text{O} \text{ (2 equiv)} \quad \text{PPTS (10 mol\%)} \quad p\text{-MeOC}_6\text{H}_4 \quad \text{Me} \]
\[ 2-1b \quad \text{Ph} \quad \text{2-1b-}^{18}\text{O} \]

\[ 38\% ^{18}\text{O}^a \]

\[ ^a \text{Determined by MS (ESI).} \]

Scheme 21: Synthesis of substrate 2-1b-$^{18}$O and its $^{13}$C NMR spectrum.
Scheme 22: $^{18}$O isotopic experiment of alkynyl diketone and its $^{13}$C NMR spectrum.

By utilizing the same prior methodology, substrate $2\mbox{-}1\mbox{o-}^{18}$O was also synthesized from the $^{18}$O exchange of compound $2\mbox{-}1\mbox{o}$ with H$_2^{18}$O under acidic conditions. Again, the $^{18}$O exchange happened only at the methyl carbonyl group, as indicated by $^{13}$C NMR spectroscopy. A 0.05 ppm (5 Hz) upfield chemical shift was found only on carbon 1 (Scheme 23). Substrate $2\mbox{-}1\mbox{o-}^{18}$O was subjected to the gold-catalyzed oxygen transfer reaction under the same conditions, and the corresponding product $2\mbox{-}2\mbox{o-}^{18}$O was isolated in good yield. By running its $^{13}$C NMR spectrum, it was found that only carbon 4 at the ester group in the product $2\mbox{-}2\mbox{o-}^{18}$O showed the 0.037 ppm (3.7 Hz) upfield chemical shift (Scheme 24). The absence of any detectable $^{18}$O incorporation at carbon 3 in both products ($2\mbox{-}2\mbox{b-}^{18}$O and $2\mbox{-}2\mbox{o-}^{18}$O) demonstrated that the [2+2] pathway is disfavored, and instead it is the newly proposed [4+2] pathway that accounted for the mechanism of the gold-catalyzed intramolecular oxygen transfer of 2-alkynyl-1,5-diketones and 2-alkynyl-5-ketoesters.

\[\text{Scheme 22: }\]

\[\text{By utilizing the same prior methodology, substrate } 2\mbox{-}1\mbox{o-}^{18}\text{O was also synthesized from the }^{18}\text{O exchange of compound } 2\mbox{-}1\mbox{o with } \text{H}_2^{18}\text{O under acidic conditions. Again, the }^{18}\text{O exchange happened only at the methyl carbonyl group, as indicated by }^{13}\text{C NMR spectroscopy. A 0.05 ppm (5 Hz) upfield chemical shift was found only on carbon 1 (Scheme 23). Substrate } 2\mbox{-}1\mbox{o-}^{18}\text{O was subjected to the gold-catalyzed oxygen transfer reaction under the same conditions, and the corresponding product } 2\mbox{-}2\mbox{o-}^{18}\text{O was isolated in good yield. By running its }^{13}\text{C NMR spectrum, it was found that only carbon 4 at the ester group in the product } 2\mbox{-}2\mbox{o-}^{18}\text{O showed the 0.037 ppm (3.7 Hz) upfield chemical shift (Scheme 24). The absence of any detectable }^{18}\text{O incorporation at carbon 3 in both products (2-2b-}^{18}\text{O and 2-2o-}^{18}\text{O) demonstrated that the [2+2] pathway is disfavored, and instead it is the newly proposed [4+2] pathway that accounted for the mechanism of the gold-catalyzed intramolecular oxygen transfer of 2-alkynyl-1,5-diketones and 2-alkynyl-5-ketoesters.} \]
Scheme 23: Synthesis of substrate 2-1o-\(^{18}\)O and its \(^{13}\)C NMR spectrum.

\[ \text{Ph} \equiv \text{C} \equiv \text{Me} \overset{\text{EtO}}{\overset{\text{O}}{\text{O}}} \text{H}_{2}\text{O} \text{(2 equiv)} \text{PPTS (10 mol%)} \text{CH}_3\text{CN, RT, 24 h} \]

2-1\text{o} \rightarrow 2-1\text{o-^{18}O}

\( \text{carbon 1} \quad \text{with } ^{16}\text{O} \quad 207.668 \quad 207.666 \quad \text{with } ^{18}\text{O} \quad \)

\( \text{carbon 2} \quad 172.892 \)

Scheme 24: \(^{18}\)O isotopic experiment of alkynylketoester and its \(^{13}\)C NMR spectrum.

\[ \text{Ph} \equiv \text{C} \equiv \text{Me} \overset{\text{EtO}}{\overset{\text{O}}{\text{O}}} \text{AuCl (5 mol%)} \text{CDCl}_3, \text{RT, 30 min} \]

2-1\text{o-^{18}O} \rightarrow 2-2\text{o-^{18}O}, 88\%

\( \text{carbon 3} \quad \text{with } ^{16}\text{O} \quad 196.473 \)

\( \text{carbon 4} \quad \text{with } ^{18}\text{O} \quad 178.263 \quad 176.226 \)

\(^a\) Isolated Yield.

Scheme 24: \(^{18}\)O isotopic experiment of alkynylketoester and its \(^{13}\)C NMR spectrum.
Alongside our experimental studies, we turned to quantum chemical calculations to seek further verification that the proposed [4+2] mechanism was the preferred pathway and to understand the origins of this selectivity. We also sought to clarify the mechanism of the competing [2+2] pathway, which had been invoked on a number of occasions to rationalize carbonyl-alkyne metathesis reactions. All calculations were performed with Gaussian 09.\textsuperscript{157} Stationary points were fully optimized with the B3LYP\textsuperscript{158-161} (hybrid GGA) and M06-2X\textsuperscript{162} (hybrid meta-GGA) density functionals, using a fine grid for numerical integration. Both functionals have been utilized extensively in computational studies of Au(I)-catalysis,\textsuperscript{25,163-169} although the M06-2X functional may be expected to describe non-bonding interactions with greater accuracy. For optimizations we used a combination of the Pople 6-31G(d) basis set for C, H, O and Cl and the LANL2DZ (Hay-Wadt) basis including an effective core potential for Au.\textsuperscript{170} Single point calculations were performed on these optimized structures with a larger (triple-ζ) 6-311+G(d,p) basis set on C, H, O and Cl. Where it was computationally tractable, we also performed optimizations at the “double-hybrid” density functional level of theory with the B2PLYP functional.\textsuperscript{171} This method replaces a fraction of the semi-local correlation energy by a non-local correlation energy expression that employs the Kohn-Sham orbitals in second order perturbation theory and delivers improved energetics over hybrid density functionals such as B3LYP. Geometries and energetics obtained at this level and from single point energy calculations at the SCS-MP2 level\textsuperscript{172} were also compared with the B3LYP and M06-2X results, to verify that the hybrid-GGA functionals gave geometries and energetics that agreed with these more demanding methods. Transition structures were confirmed by the presence of an imaginary harmonic vibrational frequency corresponding to a
displacement along the proposed reaction coordinate. NBO version 3.1 was used for the calculation of Wiberg bond order (BO) from the natural bond orbitals.\textsuperscript{173}

Competing [2+2] and [4+2] reaction coordinates were computed for a model substrate for which R1, R2, R3 and R4 are all methyl groups, allowing us to compare the performance of DFT at the hybrid-GGA level with more demanding B2PLYP and SCS-MP2 calculations. Experimentally, we demonstrated that similar substrates (Table 1, entry 7: R1,R2,R3=Me/R4=Ph and entry 14: R2,R3,R4=Me/R1=Ph) rearranged in 91-92% yield. We begin with a discussion of our newly proposed [4+2] pathway, for which the computed B2PLYP reaction coordinate is shown in Figure 2. The rate-limiting step in the rearrangement is the intramolecular nucleophilic addition to the Au-coordinated alkyne - the activation barrier for this step is computed to be a modest 8.8 kcal/mol, forming five-membered ring oxonium intermediate \textbf{B} (via 5-endo-dig \textbf{TS-1}). Once this cyclization has occurred to form \textbf{C} the remaining transformations that lead to the rearranged product are all computed to be relatively facile. \textbf{TS-2}, formally a [4+2] cycloaddition, involving the formation of two new C-C and C-O \sigma-bonds, lies only 4.4 kcal/mol above the starting complex \textit{2-1-Au}. The barriers for \textbf{TS-3}, the opening of acetal intermediate \textbf{C}, and \textbf{TS-4}, the opening of oxonium \textbf{D}, are very small indeed. At room temperature this process would be expected to occur readily, consistent with the 5 min reaction times observed experimentally.

B2PYLYP optimized transition structures (\textbf{TSs}) along the [4+2] pathway are also shown in Figure 2. Rate-limiting \textbf{TS-1} involves a 5-endo-dig cyclization, which is allowed according to Baldwin’s rules. Bond formation in \textbf{TS-5} can be seen to be highly asynchronous, with the forming C-O bond at 1.66 Å (Wiberg BO 0.60) and the C-C bond
at 2.67 Å (Wiberg BO 0.12), however, this process is concerted as no intermediate exists between B and C. All of the computational levels examined suggest the rate-limiting step in the [4+2] pathway is carbonyl-oxygen addition to the Au-coordinated alkyne, giving energetic profiles similar to that shown in Figure 2 and optimizations with either B2PLYP, B3LYP or M06-2X density functionals result in similar geometries. The computed B3LYP energetic profile was also computed for experimental substrate 2-1a to compare with our results for the model system used. These calculations were in good accord with those shown in Figure 2, again with the 5-endo addition as rate limiting step.

Figure 2: Above: B2PLYP/6-311+G(d,p)//B2PLYP/6-31G(d) (using LANL2DZ ECP on Au) Relative energy Profile computed for Both [2+2] and [4+2] pathways for a model substrate. R1,R2,R3,R4=Me, Au = AuCl. Below: B2PLYP/6-311+G(d,p)/B2PLYP/6-31G(d) computed stationary points for the model system. Energies relative to reactant 2-1-Au. Bond forming/breaking distances in Å.
Experimentally, we observed that alkynylketoesters underwent Au-catalyzed rearrangement more slowly than the alkynyldiketones. The computed [4+2] pathway for the rearrangement of a model alkynylketoester suggested that the overall energy change of reaction (-31.7 kcal/mol) is very close to that of the alkynyldiketone (-31.1 kcal/mol). However, the energetic barrier for 5-endo cyclization (i.e. TS-1') is 13.4 kcal/mol (c.f. a value of 8.8 kcal/mol for the diketone) suggests the initial alkyne addition is more difficult for the ester substrate. Interestingly the relative energy of TS-2' at 19.2 kcal/mol means that the [4+2] addition step is now more difficult than the cyclization step for the alkynylketoester. These values are consistent with the observations of the ester substrates reacting more slowly, although our proposed mechanism is still computed to be viable at room temperature. The transition structures for the rearrangement of the ketoester substrate are shown below in Figure 3.

![Figure 3: Proposed mechanism and B2PLYP/6-311+G(d,p)/B2PLYP/6-31G(d) computed stationary points for the oxetene pathway. Energies relative to reactant 2-1. Bond breaking distance in Å.](image)

We considered a number of alternative mechanisms that could constitute a competing [2+2] pathway so that we could safely discount these possibilities. These alternatives are discussed below. We have found that all of these mechanisms are disfavored relative to the [4+2] presented above, consistent with our $^{18}$O-labelled experiments. These computed [2+2] pathways, however, may well be important in Au-catalyzed transformations where
there is no possibility of a [4+2] pathway occurring. The Au- or Ag-catalyzed formal [2+2] addition of a carbonyl to an alkyne has been proposed to occur in a number of ways. Intra- and intermolecular reactions of aldehydes with alkynes catalyzed by Ag(I) have been proposed by Krische to proceed via an oxetene (or oxete) intermediate.77 Yamamoto has instead proposed that an Au-coordinated intermediate is more likely based on the formation of a γ,δ-enone byproduct in the carbocyclization of alkynyl ketones.17,27,142 DFT calculations suggest that intramolecular reactions of 1,n-enynes catalyzed by Au(I) proceed via the formation of a cyclopropanyl Au-carbene which then undergoes a 1,2-alkyl shift, fragmentation and elimination of Au.174,175 We investigated the viability of each of these pathways computationally.

First of all we considered the viability of the [2+2] oxetene mechanism, in which a four-membered ring is formed from addition of the carbonyl across the alkyne and is followed by an electrocyclic ring opening to give the enone product. The computed structure of the oxetene intermediate and of the ring-opening TS are shown below in Figure 4.

Figure 4: Proposed mechanism and B2PLYP/6-311+G(d,p)/B2PLYP/6-31G(d) computed stationary points for the oxetene pathway. Energies relative to reactant 2-1. Bond breaking distance in Å.
In accordance with Bredt’s rule oxetene E is highly strained due to the presence of a bridgehead C=C bond, lying 12.5 kcal/mol above the starting material. Therefore any TS or intermediate lying between 2-1 and E is necessarily higher in energy than TS-1 and so disfavored kinetically. Ring opening of E is possible in the absence of a coordinating metal (e.g. Au/Ag), via the 4π-electrocyclic TS-5, although this transformation would not be expected to occur readily at room temperature with a relative free energy of 14.0 kcal/mol. Therefore this pathway is disfavored relative to the [4+2] pathway.

We next considered the possibility of nucleophilic attack of the Au-coordinated alkyne from the carbonyl in a 7-endo-dig fashion, followed by a 4π electrocyclic ring closure which leads to the formation of an Au-coordinated bicyclic G, whose ring opening leads to the Au-coordinated enone product (Figure 5). This mechanism represents an Au-catalyzed form of the mechanism shown in Figure 4.

Figure 5: Proposed mechanism and B2PLYP/6-311+G(d,p)/B2PLYP/6-31G(d) computed stationary points for the 7-endo-dig pathway. Energies relative to reactant 2-1. Bond breaking distance in Å.

The initial attack of the Au-coordinated alkyne is disfavored relative to the 5-endo dig attack in the preferred [4+2] mechanism. Furthermore, as a consequence of the anti-
addition of the carbonyl and Au across the alkyne (*syn*-addition is impossible in this intramolecular case) and of the conrotatory fashion of the electrocyclic ring closing, the ring junction of G is necessarily *trans*-fused. This creates a significant degree of strain, such that ring-closing TS-7 lies 67.9 kcal/mol above the starting material and the relative energy of G is 22.4 kcal/mol. The final ring opening step to form the enone product via TS-8 lies uphill at 33.1 kcal/mol. Clearly this mechanism is highly unfavorable.

Based on previous experimental and computational studies of Au-catalyzed rearrangements of enynes,\textsuperscript{176} in which the formation of cyclopropyl Au-carbenes have been invoked, we also considered the possibility of the [2+2] mechanism proceeding via an epoxy Au-carbene as shown in Figure 6. In this mechanism we envisaged that an initial 6-*exo* cyclization via TS-9 to form H could then form epoxide I. Fragmentation of this epoxide could then lead to the formal [2+2] addition bicyclic J that upon ring-opening forms the enone product. Compared to the 5-*endo* cyclization TS-1 the cyclization via 6-*exo* TS-9 is disfavored, again highlighting the preference for the [4+2] mechanism. We were unable to locate a TS corresponding to the formation of an epoxy Au-carbene at the B2PLYP level of theory; I lies uphill at 23.0 kcal/mol suggesting that this process would be difficult at room temperature. Rearrangement to J, however, does result in the formation of a much more stable 5,4-bicyclic at -4.0 kcal/mol – being *cis*-fused this is much more stable than the corresponding *trans*-fused bicyclic G found in Figure 5. The final ring-opening step is relatively facile via TS-11. We have therefore considered three distinct mechanisms which could account for a [2+2] pathway. However, all three are clearly disfavored relative to the computed [4+2] mechanism, in support of our experimental observations. Of the [2+2] pathways considered, none is predicted to
occur readily at room temperature and a $4\pi$-electrocyclization step (TS-7) can be effectively discounted due to the large energetic barrier.

Figure 6: Proposed mechanism and B2PLYP/6-311+G(d,p)/B2PLYP/6-31G(d) computed stationary points for the 6-exo-dig pathway. Energies relative to reactant 1. Bond breaking distance in Å.

The [4+2] pathway is favored in large part due to the initial selectivity for alkyne addition via a 5-membered TS. To understand why 5-endo-dig attack is so dramatically preferred over 6-exo-dig or 7-endo-dig we computed the activation barrier for some model intramolecular and intermolecular additions of a carbonyl to an Au-coordinated alkyne (Figure 7). Notably, the intermolecular addition of acetone to AuCl-coordinated butyne occurs with an energy barrier of 19.3 kcal/mol, and the barriers of model 6-exo (20.4 kcal/mol) and 7-endo (19.9 kcal/mol) intramolecular reactions are very close to this value. In stark contrast the 5-exo mode of attack takes place with a much lower barrier of 9.5 kcal/mol. From this we can conclude that the preference for 5-exo cyclization comes about as TS-1 ($E_{act}$ 8.8 kcal/mol) is remarkably stable rather than any inherent instability of competing pathways proceeding via 6-exo or 7-endo transition states. Acceleration of this ring-closing due to the presence of a quaternary center (Thorpe-Ingold effect) in the five-
membered ring is only marginal, since replacing this carbon with methylene raises the barrier by just 0.7 kcal/mol. It seems that 5-exo attack benefits from an almost planar dihedral angle (0.8°) between the alkyne and attacking carbonyl not present in other modes of attack due to the constraints of the 6-membered (18°) or 7-membered ring (52°), and also in the intermolecular reaction (76°) due to steric demands absent in TS-1. Bond distances and Wiberg bond indices show the 5-exo TS to be earlier, which is a consequence of the increased stability of the cyclized 5-exo product.

![Image](image.png)

**Figure 7:** B2PLYP/6-311+G(d,p)/B2PLYP/6-31G(d) (hydrogen-deleted) transition structures for intramolecular and intermolecular cyclization of a ketone onto a Au-coordinated alkyne. Bond distances in Å with associated Wiberg bond indices italicized. Activation energies relative to Au-coordinated alkyne in kcal/mol.

### 2.3 Summary

In conclusion, we have developed a synthetic methodology to construct highly substituted cyclopentenyl ketones in very good yield by gold-catalyzed intramolecular alkyne-ketone metathesis of 2-alkynyl-1,5-diketones or 2-alkynyl-5-ketoesters under very mild conditions. The mechanistic investigations of this cycloisomerization using $^{18}$O isotopic labeling experiments and quantum chemical calculations revealed that the transformation appears to follow the intramolecular [4+2] cycloaddition of a gold-containing furanium
intermediate to a carbonyl group. To the best of our knowledge, this is the first example of [4+2] cycloaddition of an oxonium intermediate to a carbonyl group. The work described in this chapter was published in *Angew. Chem. Int. Ed.* 2010, 49, 9132-9135 and *Chem. Eur. J.* 2011, 17, 10690-10699.

### 2.4 Experimental

**General**

$^1$H and $^{13}$C NMR spectra were recorded at 500, 126 (or 400 and 101) MHz respectively, using CDCl$_3$ as a solvent. The chemical shifts are reported in $\delta$ (ppm) values relative to CHCl$_3$ ($\delta$ 7.26 ppm for $^1$H NMR and $\delta$ 77.0 ppm for $^{13}$C NMR), multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), h (hextet), m (multiplet) and br (broad). Coupling constants, $J$, are reported in Hertz. Coupling constants are reported in hertz (Hz). All air and/or moisture sensitive reactions were carried out under argon atmosphere. Solvents (tetrahydrofuran, ether, dichloromethane and DMF) were chemically dried using a commercial solvent purification system. All other reagents and solvents were employed without further purification. The products were purified using a Biotage flash$^+$ system or Chromatotron apparatus or a regular glass column. TLC was developed on Merck silica gel 60 F254 aluminum sheets. Elemental analysis was performed at Atlantic Microlabs Inc., Norcross, Georgia 30091. High resolution ESI-MS were obtained using a MS-FTICR-MS$^n$ system (LTQ FT, Thermo Electron Corp.) at the CREAM Mass Spectrometry Facility, University of Louisville, Kentucky.
General procedure for gold-catalyzed oxygen transfer of 2-alkynyl-1,5-diketones 2-1 to the corresponding cyclopentenylketones 2-2.

To a solution of 2-methyl-1-phenyl-2-(phenylethynyl)hexane-1,5-dione 2-1 (0.20 mmol) in dichloromethane (1.0 mL) was added AuCl (0.010 mmol). The mixture was stirred for 5 minutes at room temperature. The solvent was removed under reduced pressure and the residue was subjected to a flash column chromatography (eluent: ethyl acetate/n-hexane = 1/10) to give product 2-2 as a colorless oil.

Spectroscopic data of compounds (2-2a to 2-2j)

Compound 2-2a: a colorless oil; IR (neat) \( \tilde{\nu} \) 2968, 2930, 1673, 1645, 1596, 1446, 1283, 973 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 500 MHz) \( \delta \) 1.58 (3H, s), 1.70 (3H, s), 2.14-2.18 (1H, m), 2.48-2.53 (1H, m), 2.56-2.61 (1H, m), 2.76-2.78 (1H, m), 7.39-7.55 (6H, m), 7.48-7.84 (4H, t, \( J = 7.0 \) Hz); \(^{13}\)C NMR (CDCl\(_3\), 126 MHz) \( \delta \) 17.2, 24.5, 36.0, 38.5, 65.5, 128.1, 128.4, 128.5, 129.3, 131.4, 132.4, 137.3, 139.4, 140.8, 148.7, 196.5, 204.5. Anal. Calcd. For C\(_{21}\)H\(_{20}\)O\(_2\): C, 82.86; H, 6.62. Found: C, 82.68; H, 6.76.
Compound **2-2b**: a colorless oil; IR (neat) $\tilde{\nu}$ 2965, 2931, 1722, 1673, 1638, 1598, 1258, 1027 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 1.62 (3H, s), 1.66 (3H, s), 2.09-2.14 (1H, m), 2.45-2.55 (2H, m), 2.69-2.74 (1H, m), 3.88(3H, s), 6.93-6.95 (2H, d, $J = 9.0$ Hz), 7.36-7.39 (2H, t, $J = 7.5$ Hz), 7.43-7.46 (1H, t, $J = 7.4$ Hz), 7.79-7.81 (2H, d, $J = 9.0$ Hz), 7.84-7.86 (2H, d, $J = 9.0$ Hz); $^{13}$C NMR (CDCl$_3$, 126 MHz) $\delta$ 17.1, 22.5, 36.1, 38.2, 55.4, 65.4, 113.6, 128.0, 128.4, 131.2, 131.6, 132.1, 137.6, 140.7, 146.5, 163.2, 195.1, 204.4.

Compound **2-2c**: a colorless oil; IR (neat) $\tilde{\nu}$ 2969, 2931, 1671, 1645, 1586, 1446, 1342, 1089, 974 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 1.58 (3H, s), 1.72 (3H, s), 2.19-2.22 (1H, m), 2.47-2.61 (2H, m), 2.74-2.79 (1H, m), 7.38-7.49 (6H, m), 7.79-7.82 (4H, m); $^{13}$C NMR (CDCl$_3$, 126 MHz) $\delta$ 17.1, 24.6, 36.2, 38.3, 66.0, 128.1, 128.5, 128.6, 130.7, 131.7, 136.8, 137.7, 138.7, 140.3, 148.0, 195.4, 204.3. HRMS (ESI) Calcd. for C$_{21}$H$_{20}$ClO$_2$ (M+H$^+$) requires 339.1146, Found: 339.1152.

Compound **2-2d**: a colorless oil; IR (neat) $\tilde{\nu}$ 2955, 2870, 1730, 1677, 1447, 1261, 1176, 973 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 0.82-0.89 (3H, m), 1.09-1.28 (9H, m), 1.41-1.47...
(2H, m), 1.49 (3H, s), 1.85-1.89 (1H, m), 2.37-2.50 (3H, m), 2.64-2.71 (1H, m), 2.81-
2.86 (1H, m), 7.32-7.35 (2H, t, J = 7.5 Hz), 7.41-7.44 (1H, t, J = 7.5 Hz), 7.78-7.79 (2H,
d, J = 9.0 Hz); $^{13}$C NMR (CDCl$_3$, 126 MHz) δ 13.9, 17.4, 22.4, 23.7, 23.8, 28.7, 31.6,
35.4, 39.5, 42.5, 62.7, 128.3, 131.3, 132.4, 137.4, 144.4, 150.8, 199.7, 203.6.

Compound 2-2e: a colorless oil; IR (neat) $\bar{\nu}$ 2969, 2923, 1723, 1436, 1100, 746, 693 cm$^{-1}$;
$^1$H NMR (CDCl$_3$, 500 MHz) δ 0.89-0.91 (3H, d, J = 6.5 Hz), 0.95-0.97 (3H, d, J = 6.5
Hz), 1.46 (3H, s), 1.82-1.87 (1H, m), 2.15 (3H, s), 2.36-2.42 (1H, m), 2.64-2.69 (1H, m),
2.80-2.86 (1H, m), 2.91-2.96 (1H, m), 7.31-7.34 (2H, t, J = 7.5 Hz), 7.39-7.42 (1H, m),
7.76-7.77 (2H, d, J = 7.5 Hz); $^{13}$C NMR (CDCl$_3$, 126 MHz) δ 17.2, 18.3, 18.6, 23.8, 35.2,
38.2, 39.7, 62.8, 127.9, 128.3, 131.1, 137.5, 143.5, 150.6, 203.5, 203.7. HRMS (ESI)
Calcd. for C$_{18}$H$_{23}$O$_2$ (M+H$^+$) requires 271.1693, Found: 271.1696.

Compound 2-2f: a colorless oil; IR (neat) $\bar{\nu}$ 2971, 2933, 1716, 1673, 1447, 1263, 975,
712 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 500 MHz) δ 1.26 (9H, s), 1.51 (3H, s), 1.84 (3H, s), 1.96-
2.01 (1H, m), 2.28-2.34 (2H, m), 2.52-2.56 (1H, m), 7.34-7.37 (2H, t, J = 7.5 Hz), 7.42-
7.45 (1H, t, J = 7.5 Hz), 7.71-7.73 (2H, d, J = 7.5 Hz); $^{13}$C NMR (CDCl$_3$, 126 MHz) δ
17.4, 24.6, 27.6, 36.1, 37.7, 43.9, 66.7, 127.9, 128.3, 131.1, 137.9, 139.5, 141.4, 204.7,
Compound 2-2g: a white solid; IR (neat) $\tilde{\nu}$ 2970, 2931, 1674, 1652, 1430, 1262, 972, 710 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 1.46 (3H, s), 1.82-1.88 (1H, m), 2.14 (3H, s), 2.19 (3H, s), 2.33-2.41 (1H, m), 2.62-2.69 (1H, m), 2.78-2.87 (1H, m), 7.29-7.33 (2H, t, $J$ = 7.5 Hz), 7.38-7.42 (1H, t, $J$ = 7.2 Hz), 7.75-7.77 (2H, d, $J$ = 7.6 Hz); $^{13}$C NMR (CDCl$_3$, 101 MHz) $\delta$ 17.4, 23.7, 30.7, 35.4, 39.5, 62.6, 128.0, 128.3, 131.4, 137.3, 144.5, 152.4, 196.8, 203.6. Anal. Calcd. For C$_{21}$H$_{20}$O$_2$: C, 79.31; H, 7.49. Found: C, 79.43; H, 7.64.

Compound 2-2h: a colorless oil; IR (neat) $\tilde{\nu}$ 2952, 2868, 1676, 1652, 1446, 1263, 973, 707 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 1.53 (3H, s), 1.91-1.95 (1H, m), 2.19 (3H, s), 2.44-2.48 (1H, m), 2.67-2.73 (1H, m), 2.82-2.90 (1H, m), 3.86 (2H, s), 6.95-6.96 (2H, d, $J$ = 7.0 Hz), 7.10-7.27 (3H, m), 7.35-7.38 (2H, t, $J$ = 7.5 Hz), 7.45-7.48 (1H, t, $J$ = 7.5 Hz), 7.79-7.81 (2H, d, $J$ = 8.0 Hz); $^{13}$C NMR (CDCl$_3$, 126 MHz) $\delta$ 15.5, 21.9, 33.6, 37.5, 46.7, 61.1, 124.6, 126.0, 126.3, 126.4, 127.4, 129.3, 132.2, 135.4, 142.0, 149.6, 195.0, 201.6. HRMS (ESI) Calcd. for C$_{22}$H$_{23}$O$_2$ (M+H$^+$) requires 319.1693, Found: 319.1693.
Compound **2-2i**: a colorless oil; IR (neat) $\tilde{\nu}$ 2951, 2868, 1676, 1652, 1446, 1263, 973, 707 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 0.81-0.94 (2H, m), 1.42-1.51 (7H, m), 1.58-1.65 (2H, m), 1.81-1.86 (1H, m), 2.09-2.15 (4H, m), 2.36-2.42 (1H, m), 2.51-2.52(2H, d, $J = 7.0$ Hz), 2.64-2.70 (1H, m), 2.80-2.86 (1H, m), 7.31-7.33 (2H, dt, $J = 7.0$, 1.0 Hz), 7.38-7.42 (1H, dd, $J = 7.0$, 1.0 Hz), 7.77-7.78 (2H, d, $J = 8.5$ Hz), $^{13}$C NMR (CDCl$_3$, 126 MHz) $\delta$ 13.5, 19.7, 20.8, 28.2, 28.4, 31.3, 35.6, 44.7, 58.6, 123.9, 124.3, 127.2, 133.4, 140.6, 146.8, 195.1, 199.4. HRMS (ESI) Calcd. for C$_{21}$H$_{27}$O$_2$ (M+H$^+$) requires 311.2006, Found: 311.2008.

![2-2i](image)

Compound **2-2j**: a colorless oil; IR (neat) $\tilde{\nu}$ 2970, 2935, 1673, 1644, 1596, 1447, 1283, 1176, 976, 695 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 0.87-0.91 (3H, t, $J = 7.6$ Hz), 1.65 (3H, s), 1.91-1.97 (2H, m), 2.09-2.16 (1H, m), 2.41-2.48 (1H, m), 2.53-2.61 (1H, m), 2.68-2.75( 1H, m), 7.34-7.44 (5H, m), 7.50-7.54 (1H, m), 7.78-7.84 (4H, m); $^{13}$C NMR (CDCl$_3$, 101 MHz) $\delta$ 12.0, 23.9, 24.4, 34.8, 35.8, 65.5, 128.0, 128.3, 128.4, 129.1, 131.5, 132.4, 137.5, 139.5, 140.0, 152.9, 196.7, 204.4. HRMS (ESI) Calcd. for C$_{22}$H$_{22}$O$_2$Na (M+Na$^+$) requires 341.1512, Found: 341.1512.

![2-2j](image)

Compound **2-2k**: $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 7.90 (d, $J = 7.2$ Hz, 2H), 7.65 (d, $J = 7.6$ Hz, 2H), 7.44 (t, $J = 7.2$ Hz, 1H), 7.37 (t, $J = 7.6$ Hz, 2H), 7.24 (t, $J = 7.6$ Hz, 1H), 7.05-
7.13 (m, 7H), 3.22-3.29 (m, 1H), 3.00-3.09 (m, 1H), 2.64-2.72 (m, 1H), 2.22-2.28 (m, 1H), 1.73 (s, 3H). 13C NMR (CDCl₃, 100 MHz) δ 203.3, 196.5, 148.6, 141.2, 137.4, 137.3, 135.6, 132.1, 131.5, 129.5, 128.6, 128.4, 128.3, 128.1, 127.9, 127.7, 66.2, 36.4, 35.8, 24.3. HRMS m/z (ESI) calcd for C₂₆H₂₃O₂ (M+H⁺) 367.1693, found 367.1687; IR (neat) ν 1674, 1637, 1447, 1277, 1251, 968, 725, 693 cm⁻¹.

Compound 2-2l: ¹H NMR (CDCl₃, 400 MHz) δ 7.90 (d, J = 8.0 Hz, 2H), 7.67 (d, J = 8.0 Hz, 2H), 7.42 (t, J = 6.8 Hz, 1H), 7.35 (t, J = 6.8 Hz, 2H), 7.15 (brs, 2H), 7.09 (brs, 3H), 6.62 (d, J = 8.4 Hz, 2H), 3.70 (s, 3H), 3.02-3.29 (m, 1H), 2.95-3.01 (m, 1H), 2.61-2.69 (m, 1H), 2.17-2.23 (m, 1H), 1.66 (s, 3H). 13C NMR (CDCl₃, 100 MHz) δ 203.4, 195.1, 162.9, 146.7, 141.1, 137.7, 135.7, 131.8, 131.3, 130.1, 128.6, 128.3, 128.2, 128.1, 113.1, 65.9, 55.2, 36.1, 35.7, 24.2. HRMS m/z (ESI) calcd for C₂₇H₂₅O₃ (M+H⁺) 397.1798, found 397.1790, IR (neat) ν 1675, 1637, 1596, 1508, 1334, 1255, 1162, 763, 698 cm⁻¹.

Compound 2-2m: ¹H NMR (CDCl₃, 400 MHz) δ 7.88 (d, J = 8.0 Hz, 2H), 7.60 (d, J = 8.0 Hz, 2H), 7.46 (t, J = 7.2 Hz, 1H), 7.38 (t, J = 7.6 Hz, 2H), 7.10 (brs, 7H), 3.17-3.25 (m, 1H), 3.04-3.12 (m, 1H), 2.64-2.72 (m, 1H), 2.26-2.72 (m, 1H), 1.77 (s, 3H). 13C NMR (CDCl₃, 100 MHz) δ 203.4, 195.4, 148.5, 140.8, 138.3, 136.8, 135.8, 135.4, 131.7, 130.8, 128.7, 128.6, 128.3, 128.2, 128.1, 128.0, 66.8, 36.3, 36.0, 24.6. HRMS m/z (ESI) calcd
for C\textsubscript{26}H\textsubscript{22}O\textsubscript{2}Cl (M+H\textsuperscript{+}) 401.1303, found 401.1297. IR (neat) \( \tilde{\nu} \) 1674, 1637, 1576, 1275, 1251, 1089, 968, 747, 697 cm\textsuperscript{-1}.

![Compound 2-2n](image)

**Compound 2-2n:** \(^1\)H NMR (CDCl\textsubscript{3}, 400 MHz) \( \delta \) 7.75 (d, \( J = 7.6 \) Hz, 2H), 7.52 (t, \( J = 7.2 \) Hz, 1H), 7.42 (t, \( J = 7.6 \) Hz, 2H), 2.61-2.66 (m, 2H), 2.09-2.17 (m, 4H), 1.78-1.83 (m, 1H), 1.56 (s, 3H), 1.38 (s, 3H). \(^{13}\)C NMR (CDCl\textsubscript{3}, 100 MHz) \( \delta \) 210.7, 196.1, 150.1, 140.4, 139.2, 132.6, 129.0, 128.5, 64.8, 38.7, 34.9, 25.7, 22.0, 17.3. HRMS \( m/z \) (ESI) calcd for C\textsubscript{16}H\textsubscript{19}O\textsubscript{2} (M+H\textsuperscript{+}) 243.1380, found 243.1381. IR (neat) \( \tilde{\nu} \) 1706, 1640, 1447, 1346, 1281, 739, 696 cm\textsuperscript{-1}.

![Compound 2-2o](image)

**Compound 2-2o:** A colorless oil; \(^1\)H NMR (CDCl\textsubscript{3}, 400 MHz) \( \delta \) 1.02 (3H, t, \( J = 7.2 \) Hz), 1.46 (6H, s), 1.81 (1H, m), 2.27 (1H, m), 2.51 (2H, t, \( J = 7.2 \) Hz), 3.98 (2H, q, \( J = 7.2 \) Hz), 7.36 (2H, t, \( J = 7.6 \) Hz), 7.46 (1H, t, \( J = 6.8 \) Hz), 7.71 (2H, d, \( J = 7.6 \) Hz); \(^{13}\)C NMR (CDCl\textsubscript{3}, 126 MHz) 13.9, 17.1, 22.7, 36.5, 37.8, 58.7, 60.6, 128.3, 129.1, 132.4, 139.2, 139.4, 149.1, 176.2, 196.5. HRMS (ESI) Calcd. for C\textsubscript{17}H\textsubscript{20}NaO\textsubscript{3} (M+H\textsuperscript{+}) requires 295.1305, Found: 295.6667.
Compound 2-2p: A colorless oil; $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 1.00 (3H, t, $J = 7.0$ Hz), 1.44 (3H, s), 1.50 (3H, s), 1.79 (1H, m), 2.27 (1H, m), 2.48 (2H, m), 3.79 (3H, s), 3.96 (2H, q, $J = 7.2$ Hz), 6.84 (2H, d, $J = 8.8$ Hz), 7.73 (2H, d, $J = 8.8$ Hz); $^{13}$C NMR (CDCl$_3$, 100 MHz) 13.9, 16.9, 22.9, 36.5, 37.6, 55.4, 58.9, 60.6, 113.6, 131.6, 132.0, 139.0, 147.2, 163.2, 176.3, 195.3. HRMS (ESI) Calcd. for C$_{18}$H$_{22}$NaO$_4$ (M+H$^+$) requires 325.1410, Found: 325.5833.

![2-2p](image)

Compound 2-2q: A colorless oil; $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 1.02 (3H, m), 1.46 (6H, m), 1.81 (1H, m), 2.24 (1H, m), 2.49 (2H, t, $J = 6.8$ Hz), 3.97 (2H, m), 7.33 (2H, m), 7.68 (2H, m); $^{13}$C NMR (CDCl$_3$, 100 MHz) 14.0, 17.1, 22.7, 36.5, 37.8, 58.9, 60.7, 128.7, 130.5, 137.7, 138.8, 138.9, 149.3, 176.1, 195.2. HRMS (ESI) Calcd. for C$_{17}$H$_{19}$ClO$_3$ (M+H$^+$) requires 329.0915, Found: 329.7500.

![2-2q](image)

Compound 2-2r: $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 7.65 (d, $J = 8.0$ Hz, 2H), 7.26 (t, $J = 7.6$ Hz, 1H), 7.09-7.13 (m, 4H), 7.03-7.06 (m, 3H), 3.93-4.05 (m, 2H), 3.10-3.18 (m, 1H), 2.92-2.98 (m, 1H), 2.54-2.59 (m, 1H), 2.00-2.06 (m, 1H), 1.62 (s, 3H), 1.00 (t, $J = 7.2$ Hz, 3H). $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 197.0, 175.7, 148.7, 139.4, 137.3, 135.6, 132.3, 129.4, 128.2, 128.2, 127.9, 127.8, 60.8, 59.9, 36.4, 35.7, 23.1, 13.8. HRMS m/z (ESI)
calcd for C_{22}H_{23}O_{3} (M+H^+) 335.1642, found 335.1637. IR (neat) $\tilde{\nu}$ 1731, 1646, 1447, 1279, 1254, 1173, 1093, 696 cm$^{-1}$.

![Chemical Structure](image)

Compound 2-2s: $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 7.67 (d, $J = 8.8$ Hz, 2H), 7.14 (brs, 2H), 7.07 (brs, 3H), 6.64 (d, $J = 8.4$ Hz, 2H), 3.91-4.05 (m, 2H), 3.72 (s, 3H), 3.10-3.18 (m, 1H), 2.87-2.94 (m, 1H), 2.54-2.61 (m, 1H), 1.97-2.04 (m, 1H), 1.58 (s, 3H), 1.00 (t, $J = 7.2$ Hz, 3H). $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 195.7, 175.7, 163.0, 146.8, 139.2, 135.7, 131.8, 130.3, 128.2, 128.1, 127.9, 113.1, 60.8, 60.0, 55.3, 36.3, 35.4, 23.2, 13.8. HRMS m/z (ESI) calcd for C$_{23}$H$_{25}$O$_{4}$ (M+H$^+$) 365.1747, found 365.1741. IR (neat) $\tilde{\nu}$ 1729, 1637, 1597, 1507, 1256, 1162, 1093, 1027, 760, 697 cm$^{-1}$.

![Chemical Structure](image)

Compound 2-2t: $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 7.59 (d, $J = 7.6$ Hz, 2H), 7.08 (brs, 7H), 3.95-4.07 (m, 2H), 3.10-3.17 (m, 1H), 2.88-3.10 (m, 1H), 2.51-2.58 (m, 1H), 2.00-2.06 (m, 1H), 1.62 (s, 3H), 1.02 (t, $J = 6.8$ Hz, 3H). $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 195.7, 175.6, 149.2, 139.1, 138.5, 135.8, 135.4, 130.8, 128.6, 128.2, 128.1, 128.1, 60.8, 60.1, 36.5, 35.7, 23.2, 13.9. HRMS m/z (ESI) calcd for C$_{22}$H$_{22}$O$_{3}$Cl (M+H$^+$) 369.1252, found 369.1248. IR (neat) $\tilde{\nu}$ 1732, 1646, 1278, 1253, 1166, 1091, 860, 755, 697 cm$^{-1}$.
Compound 2-2u: $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 7.85 (d, $J = 7.5$ Hz, 2H), 7.55 (t, $J = 8.0$ Hz, 1H), 7.45 (t, $J = 8.0$ Hz, 2H), 7.25 (brs, 2H), 7.20 (brs, 3H), 4.00-4.08 (m, 2H), 3.64 (d, $J = 13.0$ Hz, 1H), 3.24 (d, $J = 13.0$ Hz, 1H), 2.18-2.27 (m, 1H), 2.11-2.16 (m, 2H), 1.36-1.40 (m, 4H), 1.04 (t, $J = 7.0$ Hz, 3H). $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 197.3, 175.7, 151.5, 139.3, 137.8, 135.7, 132.5, 130.6, 129.3, 128.3, 127.6, 126.2, 64.2, 60.8, 41.5, 37.7, 32.6, 16.8, 13.8. HRMS $m/z$ (ESI) calcd for C$_{23}$H$_{25}$O$_3$ (M+H$^+$) 349.1798, found 349.1799.

IR (neat) $\tilde{\nu}$ 1728, 1643, 1447, 1280, 1238, 1172, 1074, 703 cm$^{-1}$.

Compound 2-2v: $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 7.68 (d, $J = 7.2$ Hz, 2H), 7.38 (d, $J = 6.8$ Hz, 2H), 7.28 (t, $J = 7.6$ Hz, 1H), 7.13-7.25 (m, 6H), 7.01 (brs, 4H), 3.88-4.03 (m, 2H), 3.70 (d, $J = 13.6$ Hz, 1H), 3.33 (d, $J = 13.6$ Hz, 1H), 2.75-2.83 (m, 1H), 2.46-2.54 (m, 1H), 2.27-2.32 (m, 1H), 1.77-1.86 (m, 1H), 0.94 (t, $J = 6.8$ Hz, 3H). $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 197.8, 175.1, 151.1, 137.5, 136.2, 135.6, 132.2, 130.6, 129.5, 128.2, 128.0, 127.8, 127.5, 126.5, 65.3, 61.0, 42.3, 35.7, 32.7, 13.7. HRMS $m/z$ (ESI) calcd for C$_{28}$H$_{27}$O$_3$ (M+H$^+$) 411.1955, found 411.1949. IR (neat) $\tilde{\nu}$ 1727, 1642, 1447, 1278, 1247, 1175, 697 cm$^{-1}$.
$^{1}$H, $^{13}$C, $^{19}$F Spectra of compound 2-2a and 2-2o.
CHAPTER 3. TANDEM MICHAEL ADDITION/ALDOL REACTIONS OF ALLENIC KETONES

3.1 Background

In Chapter 2 the reactivity of 2-alkynyl-1,5-dicarbonyl compounds was explored. This work led to the construction of highly substituted five-membered rings bearing a quaternary carbon tethered to a carbonyl group. However, the synthesis of these versatile 2-alkynyl-1,5-dicarbonyl substrates is not trivial. A very practical method to synthesize these substrates was discovered while investigating the reactivity of alkynyl enolates and other extended enolates. Because of the importance of 2-alkynyl-1,5-dicarbonyl as substrates, it was decided to describe the extensive details of their reaction scope and our new synthesis of these molecules in this chapter. Since Michael additions and aldol reactions are common synthetic tools for the construction of complex organic molecules, their enolate chemistry continues to enrich the arsenal of organic synthetic chemistry. The reactivity of alkynyl enolates—an alkynyl-substituted enolate generated from allenoates or propargylic esters under basic conditions—makes them ideal nucleophiles in reactions such as aldol condensation, Michael addition, alkylation and halogenation (Scheme 25).

To probe the reactivity of alkynyl enolates, we speculated that the Michael addition of allenic ketones to vinyl ketones could yield 2-alkynyl 1,5-diketones, triggering an
intramolecular aldol reaction leading to the formation of hydroxycyclohexanones or cyclohexenones in tandem fashion.\textsuperscript{183-189} Gratifyingly, we observed the allenic ketones underwent tandem Michael addition/aldol reaction with alkyl vinyl ketones to form 2-alkynyl 1,5-diketones, 4-alkynyl-3-hydroxycyclohexanones and 4-alkynyl cyclohexenones. Although 1,5-diketones, hydroxycyclohexanones and cyclohexenones have often been employed in organic synthesis and found as substructures in bioactive molecules or natural products,\textsuperscript{190-196} the synthetically more interesting 2-alkynyl-substituted analogs have been rarely reported in the literature.\textsuperscript{197-199}

![Scheme 25: Reactivity of alkynylenolates generated from allenoates or propargylic esters.](image)

3.2 Results and discussion

To test this hypothesis, we first examined the reactivity of 2-methyl-1,4-diphenylbuta-2,3-dien-1-one 3-1a and methyl vinyl ketone 3-2a (MVK) as model substrates. We investigated the formation of the products 3-3a–3-5a as outlined in Table 2. As expected, 2-alkynyl 1,5-diketone 3-3a was obtained in good yield (73 %) when tetrabutyl
ammonium fluoride (TBAF) was used as the base (Table 2, entry 1).\textsuperscript{200-208} When potassium carbonate was employed as the base, only trace amounts of 3-3a was found and most of the starting material remained unreacted (Table 2, entry 2). Phase-transfer catalysis helped the reaction, as shown by the fact that 3-3a was obtained in moderate yield when tetrabutylammonium bromide (TBAB) was employed in the reaction (Table 2, entry 3).\textsuperscript{209-211} Also, under these weakly basic conditions, the tandem Michael addition/aldol condensation product 3-5a was isolated at higher temperature (Table 2, entry 4). When a strong base such as potassium hydroxide, lithium hydroxide, sodium hydroxide or cesium hydroxide was used in the reaction, compound 3-5a was obtained as the only product in most cases (Table 2, entries 5–9). Calcium hydroxide could not promote the reaction, possibly because of its poor solubility (Table 2, entry 10). Although potassium hydroxide could promote the reaction; due to its high hydrophilicity and lack of dispersion, it caused the reaction mixture to become dark quickly. We observed that when potassium carbonate was used as a co-promoter, the reaction became gentler and higher yield of product 3-5a was obtained (Table 2, entry 12). Product 3-5a was thought to arise from the dehydration of 3-4a, prompting us to postulate that the dehydration would not take place at low temperature. Indeed, 3-4a was isolated as the major product in good yield when the reaction was conducted at \(-40 \, ^\circ\text{C}\) (Table 2, entry 13). Other phase-transfer catalysts such as benzyltriethylammonium chloride (BnNEt\(_3\)Cl) and tetrabutylammonium hydrogen sulfate (Bu\(_4\)NHSO\(_4\)) were also investigated in the reaction, and similar results were obtained (Table 2, entries 14–15). The solvent effect was also studied and toluene was found to be the best solvent for the generation of product 3-5a (Table 2, entries 12 and 16–21).
<table>
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<th>Entry</th>
<th>Base</th>
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<th>Solvent</th>
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<th>yield(%)</th>
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<th>3-4a</th>
<th>3-5a</th>
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Table 2. Base-mediated reactions of allenic ketone 3-1a with methyl vinyl ketone.  

* 

55
Scheme 26: Control transformations between compounds 3-3a, 3-4a and 3-5a.

To demonstrate the transformations between 3-3a, 3-4a and 3-5a, we performed control reactions under the optimized conditions and the results are summarized in Scheme 26. It was found that 3-3a could transform into 3-4a under basic conditions at low temperature. Both compounds 3-3a and 3-4a could transform into 3-5a under the same conditions at room temperature. With the optimum conditions in hand, we proceeded to study the scope and limitations of these reactions. First, we investigated the TBAF-mediated Michael addition of allenic ketones 3-1 with vinyl ketones 3-2 to obtain 2-alkynyl 1,5-diketones 3-3 (Table 3). These reactions proceeded smoothly for both aromatic and aliphatic substrates, furnishing 3-3 in moderate to good yields. In next step, we carried out the tandem Michael addition/aldol reaction of allenic ketones 3-1 with vinyl ketones 3-2 at low temperature (–40 °C), with the corresponding products 3-4 obtained in moderate to good yields (Table 4). This reaction was slower under the utilized conditions, and prolonged reaction times were needed. Higher yields were obtained for aromatic substrates, which may be due to the higher stability of the aromatic system. Only one diastereoisomer of the product was obtained, even when ethyl vinyl ketone 3-2b was used as the Michael acceptor, as determined by the $^1$H and $^{13}$C NMR spectroscopy.
Table 3: TBAF-mediated Michael addition of allenic ketones 3-1 to vinyl ketones 3-2.[a]

![Chemical structure]

<table>
<thead>
<tr>
<th>Entry</th>
<th>R¹</th>
<th>R²</th>
<th>Yield(%)[b]</th>
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<td>CH₃ 3-2b</td>
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[a] General reaction conditions: allenic ketones 3-1 (0.4 mmol), vinyl ketones 3-2 (0.6 mmol), TBAF (0.2 equiv.), THF (2.0 mL). [b] Isolated yields.
Table 4. Tandem Michael addition/aldol reaction of allenic ketones 3-1 with vinyl ketones 3-2 at low temperature.[a]

![Chemical structures and reaction conditions](image)

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<th>R&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Yield(%)&lt;sup&gt;[b]&lt;/sup&gt;</th>
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<td>H (3-2a)</td>
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<td>p-CH&lt;sub&gt;3&lt;/sub&gt;OC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt; (3-1b)</td>
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[a] General reaction conditions: allenic ketones 3-1 (0.4 mmol), vinyl ketones 3-2 (0.6 mmol), KOH (2 equiv.), K<sub>2</sub>CO<sub>3</sub> (5 equiv.), TBAB (5 mol%), Toluene (2.0 mL). [b] Isolated yields.
3.2.1 Conformation analysis of transition states and NOESY effect of compound 3-4h

The configuration of substrate 3-4 was established by the conformational analysis of the transition states and was confirmed by NOESY studies of compounds 3-4h and 3-4i (Scheme 27 and Scheme 28). When methyl vinyl ketone (MVK) was used in the reaction, transition state TS-1 was kinetically more favorable than TS-2 because there is a 1,3-diaxial interaction between the methyl group and the axial proton in TS-2, whereas the interaction is diminished in TS-1, where the alkynyl moiety is axial. Thus, trans-3-4h was obtained as product through TS-1 instead of cis-3-4h through TS-2 and this configuration was also supported by NOESY experiment on the product. Moreover, when ethyl vinyl ketone (EVK) was used as the Michael acceptor in the reaction, the more favorable transition state was also the one in which the alkynyl group is axial and the

Scheme 27. Conformation analysis of transition states and NOESY effect of compound 3-4h.
methyl(b) group is equatorial. On the other hand, the Z-enolate in TS-3 is also less sterically hindered than the E-enolate in TS-4. Therefore, TS-3 is more favorable than TS-4, and cis,trans-3-4i was obtained from the reaction instead of trans,trans-3-4i. The configuration of 3-4i was also confirmed by its NOESY effect, where spatial proximity exists between the two axial protons, between the methyl(a) group and the hydroxy group, and between the proton(a) and the phenyl group.

![Scheme 28: Conformation analysis of transition states and NOESY effect of compound 3-4i.](image)

The tandem Michael addition/aldol condensation of allenic ketones 3-1 with vinyl ketones 3-2 at room temperature was also explored and the corresponding 4-alkynylcyclohexenones 3-5 were obtained as the products in moderate to good yields (Table 5). These reactions also proceeded smoothly and better results were obtained with aromatic substrates.
Table 5: Tandem Michael addition/aldol condensation of allenic ketones 3-1 with vinyl ketones 3-2 at room temperature.[a]

![Chemical Structure](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>R&lt;sub&gt;1&lt;/sub&gt;</th>
<th>R&lt;sub&gt;2&lt;/sub&gt;</th>
<th>Yield (%)</th>
<th>Isolated yields</th>
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<td>1</td>
<td>C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt; (3-1a)</td>
<td>H (3-2a)</td>
<td>3-5a, 71</td>
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<td>2</td>
<td>p-CH&lt;sub&gt;3&lt;/sub&gt;OC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt; (3-1b)</td>
<td>H (3-2a)</td>
<td>3-5b, 53</td>
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<td>3</td>
<td>p-ClC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt; (3-1c)</td>
<td>H (3-2a)</td>
<td>3-5c, 51</td>
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<tr>
<td>4</td>
<td>n-C&lt;sub&gt;9&lt;/sub&gt;H&lt;sub&gt;13&lt;/sub&gt; (3-1d)</td>
<td>H (3-2a)</td>
<td>3-5d, 47</td>
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<tr>
<td>5</td>
<td>i-Pr (3-1e)</td>
<td>H (3-2a)</td>
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<td>6</td>
<td>t-Bu (3-1f)</td>
<td>H (3-2a)</td>
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<td>7</td>
<td>CypCH&lt;sub&gt;2&lt;/sub&gt; (3-1h)</td>
<td>H (3-2a)</td>
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<td>8</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt; (3-1i)</td>
<td>H (3-2a)</td>
<td>3-5h, 49</td>
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<td>9</td>
<td>C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt; (3-1a)</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt; (3-2b)</td>
<td>3-5i, 59</td>
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<td>10</td>
<td>p-CH&lt;sub&gt;3&lt;/sub&gt;OC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt; (3-1b)</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt; (3-2b)</td>
<td>3-5j, 51</td>
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<td>12</td>
<td>n-C&lt;sub&gt;9&lt;/sub&gt;H&lt;sub&gt;13&lt;/sub&gt; (3-1d)</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt; (3-2b)</td>
<td>3-5l, 39</td>
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</tbody>
</table>

[a] General reaction conditions: allenic ketones 3-1 (0.4 mmol), vinyl ketones 3-2 (0.6 mmol), KOH (2 equiv.), K<sub>2</sub>CO<sub>3</sub> (5 equiv.), TBAB (5 mol%), Toluene (2.0 mL). [b] Isolated yields.

### 3.3 Summary

In this chapter the reactivity and scope of alkynylenate was investigated using allenic ketones and vinyl ketones as substrates and various alkynyl-substituted molecules were obtained. We developed a TBAF-mediated Michael addition reaction furnishing 2-alkynyl 1,5-diketones and these substrates were readily employed as starting material for the construction of α,β-unsaturated enones as described in Chapter 2. Moreover, under
stronger basic conditions, a tandem Michael addition/aldol reaction of the two starting materials was reported and 4-alkynyl-3-hydroxy-cyclohexanones were isolated at low temperature, whereas 4-alkynyl-cyclohexenones were obtained at room temperature. The conformational analysis of the reaction transition states provided a reasonable explanation for the formation of a single diastereoisomer of 3-4. The work described in this chapter was published in *Eur. J. Org. Chem.* 2010, 35, 6855-6862.

### 3.4 Experimental

#### General

$^1$H and $^{13}$C NMR spectra were recorded at 500, 126 (or 400 and 101) MHz respectively, using CDCl$_3$ as a solvent. The chemical shifts are reported in δ (ppm) values relative to CHCl$_3$ (δ 7.26 ppm for $^1$H NMR and δ 77.0 ppm for $^{13}$C NMR), multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), h (hextet), m (multiplet) and br (broad). Coupling constants, $J$, are reported in Hertz. Coupling constants are reported in hertz (Hz). All air and/or moisture sensitive reactions were carried out under argon atmosphere. Solvents (tetrahydrofuran, ether, dichloromethane and toluene) were chemically dried using a commercial solvent purification system. All other reagents and solvents were employed without further purification. The products were purified using a Biotage flash$^+$ system or Chromatotron apparatus or a regular glass column. TLC was developed on Merck silica gel 60 F254 aluminum sheets. Elemental analysis was performed at Atlantic Microlabs Inc., Norcross, Georgia 30091. High resolution ESI-MS were obtained using a MS-FTICR-MS$^\text{n}$ system (LTQ FT, Thermo
Electron Corp.) at the CREAM Mass Spectrometry Facility, University of Louisville, Kentucky.

**General procedure for the synthesis of 2-alkynyl 1,5-diketones 3-3:**

![Chemical reaction diagram]

To a solution of allenic ketone 3-1 (0.50 mmol) in THF (2.0 mL) was added methyl vinyl ketone (MVK) 3-2 (0.60 mmol) and TBAF (0.1 mL, 1 m in THF, 0.10 mmol). The mixture was stirred for 4 h at room temperature. The reaction mixture was quenched with water and extracted with diethyl ether. The solvent of the organic layer was removed under reduced pressure and the residue was subjected to a flash column chromatography (eluent: ethyl acetate/n-hexane = 1:10) to give product 3-3 as a colorless oil.

**General procedure for the synthesis of 4-alkynyl-3hydroxycyclohexanones 3-4:**

![Chemical reaction diagram]

To a solution of allenic ketone 3-1 (0.50 mmol) in toluene (2.0 mL) was added methyl vinyl ketone (MVK) 3-2 (0.60 mmol) and TBAB (5 mol %). The mixture was cooled to –40 °C followed by the addition of potassium carbonate (2.5 mmol) and potassium hydroxide (1 mmol). The mixture was stirred at –40 °C for 24 h. The reaction mixture
was quenched with water and extracted with diethyl ether. The solvent of the organic layer was removed under reduced pressure and the residue was subjected to a flash column chromatography (eluent: ethyl acetate/\(n\)-hexane = 1:10) to give product 3-4 as a colorless oil.

**General procedure for the synthesis of 4-alkynylcyclohexenones 3-5:**

![Chemical structure]

To a solution of allenic ketone 3-1 (0.50 mmol) in toluene (2.0 mL) was added methyl vinyl ketone (MVK) 3-2 (0.60 mmol), TBAB (5 mol-%), potassium carbonate (2.5 mmol) and potassium hydroxide (1 mmol). The mixture was stirred at room temperature for 4 h. The reaction mixture was quenched with water and extracted with diethyl ether. The solvent of the organic layer was removed under reduced pressure and the residue was subjected to a flash column chromatography (eluent: ethyl acetate/\(n\)-hexane = 1:10) to give product 3-5 as a colorless oil.

**Spectroscopic data of compounds 3-3.**

![Spectroscopic data]

**Data for 3-3a:** A colorless oil. IR (neat): \(\bar{\nu} = 2982, 1716, 1682, 1596, 1490, 1363, 1168, 965 \text{ cm}^{-1}\). \(^1\)H NMR (CDCl\(_3\), 500 MHz): \(\delta = 1.58 (s, 3 \text{ H}), 1.95–2.01 (m, 1 \text{ H}), 2.08 (s, 3\)
H), 2.34–2.43 (m, 1 H), 2.52–2.58 (m, 1 H), 2.63–2.69 (m, 1 H), 7.18–7.27 (m, 5 H), 7.35–7.38 (t, J = 7.5 Hz, 2 H), 7.45–7.48 (t, J = 7.5 Hz, 1 H), 8.23–8.25 (d, J = 8.0 Hz, 2 H) ppm. 13C NMR (CDCl3, 126 MHz): δ = 26.6, 30.0, 33.6, 39.7, 45.9, 86.7, 91.5, 122.8, 128.0, 128.3, 129.7, 131.3, 132.7, 135.3, 198.8, 208.0 ppm. C21H20O2 (304.14): calcd. C 82.86, H 6.62, found C 82.75, H 6.62.

**Data for 3-3b:** Colorless oil. IR (neat): ν = 2959, 2933, 1716, 1681, 1606, 1509, 1446, 1289, 1172, 1031, 966, 690 cm−1. 1H NMR (CDCl3, 500 MHz): δ = 1.65 (s, 3 H), 2.02–2.08 (m, 1 H), 2.17 (s, 3 H), 2.44–2.49 (m, 1 H), 2.61–2.66 (m, 1 H), 2.66–2.78 (m, 1 H), 3.79 (s, 3 H), 6.81–6.84 (m, 2 H), 7.27–7.30 (m, 2 H), 7.43–7.46 (m, 2 H), 7.52–7.55 (m, 1 H), 8.32–8.33 (m, 2 H) ppm. 13C NMR (CDCl3, 126 MHz): δ = 26.9, 30.3, 33.9, 40.0, 46.1, 55.5, 86.8, 90.2, 114.2, 115.2, 128.3, 130.0, 132.9, 133.0, 135.6, 159.8, 199.3, 208.3 ppm.

**Data for 3-3c:** A colorless oil. IR (neat): ν = 2932, 2870, 1717, 1683, 1489, 1239, 1090, 966, 715 cm−1. 1H NMR (CDCl3, 500 MHz): δ = 1.64 (s, 3 H), 2.01–2.09 (m, 1 H), 2.08 (s, 3 H), 2.42–2.49 (m, 1 H), 2.54–2.61 (m, 1 H), 2.67–2.71 (m, 1 H), 7.24–7.25 (d, J = 2.8 Hz, 4 H), 7.43–7.45 (t, J = 6.8 Hz, 2 H), 7.51–7.55 (t, J = 6.5 Hz, 1 H), 8.25–8.28 (d, J = 8.0 Hz, 2 H) ppm. 13C NMR (CDCl3, 126 MHz): δ = 26.5, 30.0, 33.6, 39.7, 45.9,
85.6, 92.5, 121.3, 128.1, 128.7, 129.6, 132.5, 132.8, 134.4, 135.2, 198.6, 207.9 ppm.

C_{21}H_{19}ClO_{2} (338.10): calcd. C 74.44, H 5.65, found C 74.36, H 5.68.

**Data for 3-3d:** Colorless oil. IR (neat): ν = 2931, 2858, 1717, 1681, 1441, 1240, 1176, 967, 714 cm⁻¹. \(^1^H\) NMR (CDCl₃, 500 MHz): δ = 0.86–0.89 (t, J = 7.0 Hz, 3 H), 1.26–1.47 (m, 9 H), 1.54 (s, 3 H), 1.91–1.95 (m, 1 H), 2.16–2.20 (m, 4 H), 2.31–2.37 (m, 1 H), 2.51–2.58 (m, 1 H), 2.65–2.72 (m, 1 H), 7.41–7.44 (t, J = 7.5 Hz, 2 H), 7.52–7.54 (t, J = 7.0 Hz, 1 H), 8.27–8.28 (d, J = 7.5 Hz, 2 H) ppm. \(^{13}\)C NMR (CDCl₃, 126 MHz): δ = 14.2, 19.1, 22.8, 27.1, 28.7, 30.2, 31.5, 34.0, 40.1, 45.6, 65.2, 82.4, 87.4, 128.1, 130.1, 132.7, 135.6, 200.1, 208.5 ppm.

**Data for 3-3e:** Colorless oil. IR (neat): ν = 2929, 2871, 1715, 1651, 1555, 1279, 1178, 965, 763, 694 cm⁻¹. \(^1^H\) NMR (CDCl₃, 500 MHz): δ = 1.11–1.12 (d, J = 7.0 Hz, 6 H), 1.52 (s, 3 H), 1.69–1.93 (m, 1 H), 2.16 (s, 3 H), 2.20–2.35 (m, 1 H), 2.51–2.56 (m, 2 H), 2.62–2.69 (m, 1 H), 7.34–7.43 (t, J = 8.0 Hz, 2 H), 7.50–7.51 (m, 1 H), 8.26–8.28 (dd, J = 7.5, 1.5 Hz, 2 H) ppm. \(^{13}\)C NMR (CDCl₃, 126 MHz): δ = 20.6, 22.7, 26.7, 29.9, 33.6, 39.7, 45.2, 81.5, 92.4, 127.7, 129.8, 132.4, 135.4, 199.6, 208.2 ppm. C_{18}H_{22}O_{2} (270.16): calcd. C 79.96, H 8.20, found C 79.69, H 8.20.
Data for 3-3f: Colorless oil. IR (neat): $\tilde{\nu} = 2967, 2931, 1717, 1683, 1596, 1456, 1172, 966, 715$ cm$^{-1}$. $^1$H NMR (CDCl$_3$, 500 MHz): $\delta = 1.16$ (s, 9 H), 1.51 (s, 3 H), 1.86–1.92 (m, 1 H), 2.15 (s, 3 H), 2.29–2.35 (m, 1 H), 2.47–2.55 (m, 1 H), 2.62–2.68 (m, 1 H), 7.39–7.42 (t, $J = 7.5$ Hz, 2 H), 7.49–7.52 (t, $J = 7.5$ Hz, 1 H), 8.26–8.27 (d, $J = 7.5$ Hz, 2 H) ppm. $^{13}$C NMR (CDCl$_3$, 126 MHz): $\delta = 26.8, 27.5, 29.9, 30.7, 33.6, 39.7, 45.1, 80.8, 95.2, 127.7, 129.8, 132.4, 135.4, 199.7, 208.2$ ppm. C$_{19}$H$_{24}$O$_2$ (284.17): calcd. C 80.24, H 8.51, found C 79.95, H 8.41.

Data for 3-3g: A colorless oil. IR (neat): $\tilde{\nu} = 2979, 2936, 1716, 1682, 1596, 1446, 1178, 966, 716$ cm$^{-1}$. $^1$H NMR (CDCl$_3$, 500 MHz): $\delta = 1.52–1.54$ (d, $J = 9.0$ Hz, 3 H), 1.82–1.83 (d, $J = 9.0$ Hz, 3 H), 1.88–2.15 (m, 1 H), 2.15–2.17 (d, $J = 8.5$ Hz, 3 H), 2.30–2.38 (m, 1 H), 2.51–2.59 (m, 1 H), 2.63–2.71 (m, 1 H), 7.40–7.43 (q, $J = 8.0$ Hz, 2 H), 7.50–7.53 (t, $J = 8.0$ Hz, 1 H), 8.24–8.27 (t, $J = 8.0$ Hz, 2 H) ppm. $^{13}$C NMR (CDCl$_3$, 126 MHz): $\delta = 3.7, 26.7, 29.9, 33.7, 39.8, 45.3, 81.2, 82.5, 127.9, 129.7, 132.5, 135.4, 199.5, 208.2$ ppm. C$_{16}$H$_{18}$O$_2$ (242.13): calcd. C 79.31, H 7.49, found C 78.85, H 7.59.
**Data for 3-3h:** A colorless oil. IR (neat): $\tilde{\nu} = 2982, 2938, 1714, 1682, 1597, 1449, 1243, 1175, 967, 702 \text{ cm}^{-1}$. $^1$H NMR (CDCl$_3$, 500 MHz): $\delta = 1.60$ (s, 3 H), 1.96–2.02 (m, 1 H), 2.14 (s, 3 H), 2.37–2.43 (m, 1 H), 2.54–2.61 (m, 1 H), 2.67–2.74 (m, 1 H), 3.63 (s, 2 H), 7.23–7.26 (m, 5 H), 7.37–7.40 (m, 2 H), 7.51–7.54 (m, 1 H), 8.24–8.26 (m, 2 H) ppm. $^{13}$C NMR (CDCl$_3$, 126 MHz): $\delta = 25.2$, 26.7, 29.9, 33.7, 39.7, 45.4, 84.3, 84.5, 126.5, 127.8, 127.9, 128.4, 129.7, 132.5, 135.3, 136.4, 199.3, 208.1 ppm. HRMS (ESI): Calcd. for C$_{22}$H$_{23}$O$_2$ [M+H$^+$] calcd. 319.1693, found 319.1694.

![Image](image-url)

**Data for 3-3i:** A colorless oil. IR (neat): $\tilde{\nu} = 2951, 2867, 1717, 1682, 1447, 1241, 1176, 965, 715 \text{ cm}^{-1}$. $^1$H NMR (CDCl$_3$, 500 MHz): $\delta = 1.16–1.22$ (m, 2 H), 1.47–1.58 (m, 7 H), 1.67–1.72 (m, 2 H), 1.74–2.01 (m, 2 H), 2.14 (s, 3 H), 2.17–2.19 (d, $J = 6.5$ Hz, 2 H), 2.31–2.36 (m, 1 H), 2.52–2.58 (m, 1 H), 2.64–2.71 (m, 1 H), 7.39–7.42 (t, $J = 7.5$ Hz, 2 H), 7.49–7.52 (t, $J = 7.5$ Hz, 1 H), 8.25–8.27 (d, $J = 7.5$ Hz, 2 H) ppm. $^{13}$C NMR (CDCl$_3$, 126 MHz): $\delta = 24.6$, 25.2, 26.8, 29.9, 31.9, 33.7, 38.9, 39.7, 45.3, 82.1, 86.6, 127.8, 129.7, 132.4, 135.3, 199.5, 208.1 ppm.

![Image](image-url)

**Data for 3-3j:** A colorless oil. IR (neat): $\tilde{\nu} = 2976, 2937, 1714, 1682, 1596, 1445, 1237, 1112, 972, 757, 691 \text{ cm}^{-1}$. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta = 1.01–1.04$ (t, $J = 7.6$ Hz, 3 H), 1.64 (s, 3 H), 2.02–2.09 (m, 1 H), 2.40–2.51 (m, 3 H), 2.54–2.62 (m, 1 H),
2.66–2.73 (m, 1 H), 7.24–7.33 (m, 5 H), 7.40–7.44 (t, \(J = 7.6\) Hz, 2 H), 7.50–7.54 (t, \(J = 7.2\) Hz, 1 H), 8.29–8.31 (d, \(J = 7.2\) Hz, 2 H) ppm. \(^{13}\)C NMR (CDCl\(_3\), 101 MHz): \(\delta = 7.8, 26.6, 33.7, 36.0, 38.3, 45.9, 86.7, 91.5, 122.8, 128.1, 128.3, 129.7, 131.3, 132.7, 135.3, 198.9, 210.6\) ppm. HRMS (ESI): Calcd. for C\(_{22}\)H\(_{22}\)O\(_2\)Na [M+Na\(^+\)] calcd. 341.1512, found 341.1513.

Data for 3-3k:

A colorless oil. IR (neat): \(\tilde{\nu} = 2975, 2936, 1714, 1683, 1606, 1510, 1457, 1249, 1109, 973, 716\) cm\(^{-1}\). \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta = 0.93–0.97\) (t, \(J = 7.2\) Hz, 3 H), 1.55 (s, 3 H), 1.92–1.99 (m, 1 H), 2.34–2.46 (m, 3 H), 2.46–2.54 (m, 1 H), 2.58–2.67 (m, 1 H), 3.694 (s, 3 H), 6.71–6.73 (d, \(J = 8.8\) Hz, 2 H), 7.17–7.20 (d, \(J = 8.8\) Hz, 2 H), 7.33–7.37 (t, \(J = 7.2\) Hz, 2 H), 7.42–7.46 (t, \(J = 7.2\) Hz, 1 H), 8.22–8.24 (d, \(J = 7.2\) Hz, 2 H) ppm. \(^{13}\)C NMR (CDCl\(_3\), 101 MHz): \(\delta = 7.8, 26.6, 33.7, 36.0, 38.4, 45.9, 55.2, 86.5, 90.0, 113.9, 114.9, 128.0, 129.7, 132.6, 132.7, 135.4, 159.6, 199.1, 210.7\) ppm. HRMS (ESI): Calcd. for C\(_{23}\)H\(_{24}\)O\(_3\)Na [M+Na\(^+\)] 371.1618, found 371.1624.

Data for 3-3l:

A colorless oil. IR (neat): \(\tilde{\nu} = 2976, 2836, 1715, 1684, 1490, 1237, 1091, 972, 715\) cm\(^{-1}\). \(^1\)H NMR (CDCl\(_3\), 500 MHz): \(\delta = 0.98–1.04\) (t, \(J = 7.6\) Hz, 3 H), 1.62 (s, 3 H), 2.00–2.07 (m, 1 H), 2.38–2.50 (m, 3 H), 2.53–2.57 (m, 1 H), 2.62–2.67 (m, 1 H), 7.22 (s, 4 H), 7.39–7.43 (t, \(J = 7.6\) Hz, 2 H), 7.49–7.53 (t, \(J = 7.2\) Hz, 1 H), 8.24–
8.25 (d, $J = 7.6$ Hz, 2 H) ppm. $^{13}$C NMR (CDCl$_3$, 126 MHz): δ = 7.8, 26.4, 33.6, 36.0, 38.3, 45.9, 85.5, 92.6, 121.3, 128.1, 128.6, 129.6, 132.5, 132.8, 134.3, 135.3, 198.6, 210.5 ppm. HRMS (ESI): Calcd. for C$_{22}$H$_{21}$ClO$_2$Na [M+Na$^+$] 375.1122, found 375.1126.

**Spectroscopic data of compounds 3-4**

![Diagram of 3-4a](image)

**Data for 3-4a:** A colorless oil. IR (neat): $\bar{\nu} = 3423, 2960, 2934, 1716, 1685, 1491, 1217, 1060, 758, 715$ cm$^{-1}$. $^1$H NMR (CDCl$_3$, 500 MHz): δ = 1.19 (s, 3 H), 2.04–2.10 (m, 1 H), 2.38–2.51 (m, 3 H), 2.55–2.56 (d, $J = 1.6$ Hz, 1 H), 2.94–3.02 (m, 1 H), 3.80–3.83 (d, $J = 14.0$ Hz, 1 H), 7.31–7.34 (m, 4 H), 7.36–7.41 (m, 4 H), 7.63–7.64 (d, $J = 7.5$ Hz, 2 H) ppm. $^{13}$C NMR (CDCl$_3$, 126 MHz): δ = 22.3, 35.9, 39.0, 41.3, 52.2, 80.3, 84.4, 93.2, 123.1, 126.5, 127.6, 128.2, 128.4, 131.4, 143.2, 210.6 ppm. HRMS (ESI): Calcd. for C$_{21}$H$_{20}$O$_2$Na [M+Na$^+$] 327.1356, found 327.1360.

![Diagram of 3-4b](image)

**Data for 3-4b:** A colorless oil. IR (neat): $\bar{\nu} = 3460, 2960, 2936, 1708, 1606, 1509, 1248, 1165, 1032, 732, 701$ cm$^{-1}$. $^1$H NMR (CDCl$_3$, 500 MHz): δ = 1.18 (s, 3 H), 1.65–1.66 (m, 1 H), 2.07–2.09 (m, 1 H), 2.39–2.50 (m, 3 H), 2.97–3.03 (m, 1 H), 3.83 (s, 3 H), 3.83–3.85 (d, $J = 11.0$ Hz, 1 H), 6.84–6.85 (d, $J = 9.0$ Hz, 2 H), 7.31–7.39 (m, 5 H), 7.62–7.63
(m, 2 H) ppm. $^{13}$C NMR (CDCl$_3$, 126 MHz): $\delta$ = 22.4, 36.0, 39.1, 41.2, 52.3, 55.3, 80.4, 84.3, 91.6, 114.0, 115.2, 126.5, 127.6, 132.8, 143.2, 159.5, 210.4 ppm. HRMS (ESI): Calcd. for C$_{22}$H$_{23}$O$_3$ [M+H$^+$] 335.1642, found 335.1646.

Data for 3-4c: A colorless oil. IR (neat): $\tilde{\nu}$ = 3428, 2958, 2934, 1707, 1489, 1091, 909, 828, 701 cm$^{-1}$. $^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ = 1.20 (s, 3 H), 2.06–2.09 (m, 1 H), 2.41–2.51 (m, 3 H), 2.60–2.66 (m, 1 H), 2.92–2.98 (m, 1 H), 3.77–3.81 (d, $J$ = 14.5 Hz, 1 H), 7.28–7.41 (m, 7 H), 7.61–7.63 (d, $J$ = 8.0 Hz, 2 H) ppm. $^{13}$C NMR (CDCl$_3$, 126 MHz): $\delta$ = 22.6, 36.2, 39.2, 41.6, 52.4, 80.4, 83.7, 94.5, 121.8, 126.7, 127.8, 127.9, 128.9, 132.9, 134.5, 143.3, 210.7 ppm. HRMS (ESI): Calcd. for C$_{21}$H$_{19}$ClO$_2$Na [M+Na$^+$] 361.0966, found 361.0968.

Data for 3-4d: A colorless oil. IR (neat): $\tilde{\nu}$ = 3433, 2955, 2929, 2858, 1715, 1447, 701 cm$^{-1}$. $^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ = 0.89–0.90 (m, 3 H), 1.07 (s, 3 H), 1.28–1.39 (m, 7 H), 1.50–1.54 (m, 2 H), 1.90–1.96 (m, 1 H), 2.20–2.27 (t, $J$ = 6.5 Hz, 2 H), 2.33–2.40 (m, 3 H), 2.89–2.93 (m, 1 H), 3.74–3.76 (d, $J$ = 14.0 Hz, 1 H), 7.27–7.35 (m, 3 H), 7.57–7.58 (d, $J$ = 7.0 Hz, 2 H) ppm. $^{13}$C NMR (CDCl$_3$, 126 MHz): $\delta$ = 14.3, 18.9, 22.8, 22.9, 28.9,
29.1, 31.5, 36.5, 39.2, 40.9, 52.5, 80.5, 83.8, 84.8, 126.8, 127.6, 127.7, 143.6, 211.2 ppm.

HRMS (ESI): Calcd. for C_{21}H_{28}O_{2}Na [M+Na\(^+\)] 335.1982, found 335.1985.

**Data for 3-4e:** A colorless oil. IR (neat): \(\tilde{\nu} = 3419, 2967, 2933, 1714, 1656, 1321, 967, 701 \text{ cm}^{-1}\). \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta = 1.03 (s, 3 \text{ H}), 1.15–1.17 (t, \text{J} = 6.4 \text{ Hz}, 6 \text{ H}), 1.87–1.93 (m, 1 \text{ H}), 2.07–2.11 (m, 1 \text{ H}), 2.29–2.39 (m, 3 \text{ H}), 2.51–2.59 (m, 1 \text{ H}), 2.51–2.85–2.93 (m, 1 \text{ H}), 3.72–3.75 (d, \text{J} = 14.0 \text{ Hz}, 1 \text{ H}), 7.24–7.34 (m, 3 \text{ H}), 7.54–7.56 (d, \text{J} = 7.2 \text{ Hz}, 2 \text{ H}) \text{ ppm}. \(^{13}\)C NMR (CDCl\(_3\), 101 MHz): \(\delta = 20.5, 22.5, 23.1, 23.2, 36.1, 38.9, 40.4, 52.2, 80.3, 82.9, 89.9, 126.5, 127.3, 127.4, 143.3, 210.8 \text{ ppm. HRMS (ESI): Calcd. for C}_{18}H_{22}O_{2}Na [M+Na\(^+\)] 293.1512, found 293.1516.}

**Data for 3-4f:** A colorless oil. IR (neat): \(\tilde{\nu} = 3386, 2963, 2929, 2866, 1703, 1636, 1360, 915, 701 \text{ cm}^{-1}\). \(^1\)H NMR (CDCl\(_3\), 500 MHz): \(\delta = 1.04 (s, 3 \text{ H}), 1.24 (s, 9 \text{ H}), 1.88–1.92 (m, 1 \text{ H}), 2.32–2.39 (m, 4 \text{ H}), 2.86–2.92 (m, 1 \text{ H}), 3.73–3.76 (d, \text{J} = 15.0 \text{ Hz}, 1 \text{ H}), 7.29–7.36 (m, 3 \text{ H}), 7.58–7.60 (d, \text{J} = 8.0 \text{ Hz}, 2 \text{ H}) \text{ ppm}. \(^{13}\)C NMR (CDCl\(_3\), 101 MHz): \(\delta = 22.5, 27.4, 30.4, 36.2, 38.9, 40.3, 52.2, 80.3, 82.2, 92.7, 126.6, 126.9, 127.3, 127.4, 143.3, 210.9 \text{ ppm. HRMS (ESI): Calcd. for C}_{19}H_{24}O_{2}Na [M+Na\(^+\)] 307.1669, found 307.1671.}
**Data for 3-4g:** A colorless oil. IR (neat): $\tilde{\nu} = 3446, 2951, 2867, 1707, 1447, 1373, 1053, 970, 701 \text{ cm}^{-1}$. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta = 1.06$ (s, 3 H), 1.54–1.62 (m, 5 H), 1.76–1.79 (m, 2 H), 1.90–1.96 (m, 1 H), 2.01–2.08 (m, 1 H), 2.14 (s, 1 H), 2.20–2.22 (d, $J = 6.0$ Hz, 2 H), 2.32–2.42 (m, 3 H), 2.87–2.96 (m, 1 H), 3.73–3.77 (d, $J = 14.4$ Hz, 1 H), 7.28–7.37 (m, 3 H), 7.56–7.58 (d, $J = 8.0$ Hz, 2 H) ppm. $^{13}$C NMR (CDCl$_3$, 101 MHz): $\delta = 22.6, 24.7, 31.5, 32.1, 36.3, 39.0, 39.2, 40.6, 47.6, 52.4, 80.3, 83.6, 84.0, 126.4, 127.0, 127.4, 127.5, 143.3, 210.7$ ppm. HRMS (ESI): Calcd. for C$_{21}$H$_{26}$O$_2$Na [M+Na$^+$] $333.1825$, found $333.1827$.

**Data for 3-4h:** A colorless oil. IR (neat): $\tilde{\nu} = 3372, 2974, 2936, 1715, 1558, 1338, 1069, 970, 766, 703 \text{ cm}^{-1}$. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta = 0.97$ (s, 3 H), 1.76 (s, 3 H), 1.81–1.85 (m, 1 H), 2.23–2.31 (m, 3 H), 2.41 (s, 1 H), 2.46–2.85 (m, 1 H), 3.63–3.66 (d, $J = 14.4$ Hz, 1 H), 7.18–7.29 (m, 3 H), 7.46–7.49 (d, $J = 8.0$ Hz, 2 H) ppm. $^{13}$C NMR (CDCl$_3$, 101 MHz): $\delta = 3.5, 22.5, 36.1, 39.0, 40.6, 52.2, 79.7, 80.2, 82.7, 126.5, 127.4, 127.5, 143.4, 211.1$ ppm. HRMS (ESI): Calcd. for C$_{16}$H$_{18}$O$_2$Na [M+Na$^+$] $265.1199$, found $265.1202$. 
**Data for 3-4i:** A colorless oil. IR (neat): $\bar{\nu} = 3501, 2976, 2937, 1711, 1489, 1262, 1099, 994, 757, 692 \text{ cm}^{-1}$. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta = 0.73–0.75 (d, J = 6.8 \text{ Hz}, 3 \text{ H}), 1.05 (s, 3 \text{ H}), 1.97–2.03 (m, 2 \text{ H}), 2.33–2.46 (m, 2 \text{ H}), 2.95–3.03 (td, J = 14, 6.0 \text{ Hz}, 1 \text{ H}), 3.67–3.73 (q, J = 6.8 \text{ Hz}, 1 \text{ H}), 7.17–7.35 (m, 7 \text{ H}), 7.45–7.55 (m, 2 \text{ H})$ ppm. $^{13}$C NMR (CDCl$_3$, 101 MHz): $\delta = 8.3, 23.0, 36.1, 39.1, 42.3, 50.2, 83.6, 84.7, 93.6, 123.2, 127.3, 128.1, 128.3, 131.4, 141.6, 211.2$ ppm. HRMS (ESI): Calcd. for C$_{22}$H$_{23}$O$_2$ $[\text{M}+\text{H}^+]$ 319.1693, found 319.1695.

**Data for 3-4j:** A colorless oil. IR (neat): $\bar{\nu} = 3502, 2972, 2936, 1715, 1653, 1606, 1457, 1247, 1031, 832, 737, 702 \text{ cm}^{-1}$. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta = 0.72–0.74 (d, J = 6.8 \text{ Hz}, 3 \text{ H}), 1.03 (s, 3 \text{ H}), 1.96–2.00 (m, 1 \text{ H}), 2.05 (s, 1 \text{ H}), 2.31–2.46 (m, 2 \text{ H}), 2.95–3.03 (td, J = 13.6, 6.4 \text{ Hz}, 1 \text{ H}), 3.67–3.71 (q, J = 6.8 \text{ Hz}, 1 \text{ H}), 3.74 (s, 3 \text{ H}), 6.77–6.79 (d, J = 8.4 \text{ Hz}, 2 \text{ H}), 7.18–7.30 (m, 5 \text{ H}), 7.49–7.55 (m, 2 \text{ H})$ ppm. $^{13}$C NMR (CDCl$_3$, 101 Hz): $\delta = 8.3, 23.1, 36.2, 39.2, 42.3, 50.1, 55.3, 83.7, 84.5, 92.0, 114.0, 115.3, 127.2, 132.8, 141.7, 159.5, 211.3$ ppm. HRMS (ESI): Calcd. for C$_{23}$H$_{25}$O$_3$ $[\text{M}+\text{H}^+]$ 349.1798, found 349.1801.
Data for 3-4k: A colorless oil. IR (neat): $\tilde{\nu} = 3488, 2932, 2858, 1711, 1652, 1456, 1340, 1159, 936, 701 \text{ cm}^{-1}$. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta = 0.70–0.72$ (d, $J = 7.2$ Hz, 3 H), 0.80–0.83 (t, $J = 7.2$ Hz, 3 H), 0.92 (d, 3 H), 1.15–1.35 (m, 7 H), 1.43–1.50 (m, 2 H), 1.82–1.87 (m, 2 H), 2.14–2.17 (t, $J = 7.2$ Hz, 3 H), 2.23–2.31 (td, $J = 13.2$, 4.0 Hz, 1 H), 2.35–2.40 (m, 1 H), 2.87–2.96 (td, $J = 13.6$, 6.4 Hz, 1 H), 3.61–3.66 (q, $J = 6.8$ Hz, 1 H), 7.19–7.28 (m, 3 H), 7.46 (br. s, 2 H) ppm. $^{13}$C NMR (CDCl$_3$, 101 MHz): $\delta = 8.3$, 14.0, 18.8, 22.5, 23.3, 28.6, 28.8, 31.3, 36.4, 39.1, 41.7, 50.0, 83.6, 83.9, 84.8, 125.9, 127.1, 127.9, 141.7, 211.6 ppm. HRMS (ESI): Calcd. for C$_{22}$H$_{31}$O$_2$ [M+H$^+$] 327.2319, found 327.2323.

Spectroscopic data of compounds 3-5.

Data for 3-5a: A colorless oil. IR (neat): $\tilde{\nu} = 3058, 2931, 1714, 1681, 1490, 1330, 1265, 1056, 756 \text{ cm}^{-1}$. $^1$H NMR (CDCl$_3$, 500 MHz): $\delta = 1.44$ (d, 3 H), 2.19–2.25 (m, 1 H), 2.38–2.42 (m, 1 H), 2.56–2.61 (m, 1 H), 2.99–3.06 (m, 1 H), 6.06 (s, 1 H), 7.32–7.33 (m, 3 H), 7.38–7.39 (m, 3 H), 7.43–7.45 (m, 2 H), 7.62–7.63 (m, 2 H) ppm. $^{13}$C NMR (CDCl$_3$, 126 MHz): $\delta = 28.1$, 35.2, 35.3, 38.9, 83.1, 91.6, 122.9, 127.4, 127.6, 128.2, 128.3, 128.8,
131.6, 138.7, 163.6, 198.8 ppm. HRMS (ESI): Calcd. for C_{21}H_{19}O [M+H^+] 287.1430, found 287.1434.

Data for 3-5b: A colorless oil. IR (neat): $\tilde{\nu} = 2930, 2837, 1673, 1606, 1456, 1248, 1172,$ $1032, 731$ cm$^{-1}$. $^1$H NMR (CDCl$_3$, 500 MHz): $\delta = 1.43$ (s, 3 H), 2.19–2.26 (m, 1 H), 2.38–2.42 (m, 1 H), 2.56–2.60 (m, 1 H), 3.01–3.09 (m, 1 H), 3.82 (s, 3 H), 6.06 (s, 1 H), 6.86–6.87 (d, $J = 9.0$ Hz, 2 H), 7.38–7.40 (m, 5 H), 7.63–7.64 (d, $J = 3.5$ Hz, 2 H) ppm. $^{13}$C NMR (CDCl$_3$, 126 MHz): $\delta = 28.4, 35.5, 35.6, 39.3, 55.6, 83.2, 90.3, 114.2, 115.3, 127.7, 127.8, 128.5, 129.1, 133.3, 139.1, 159.9, 164.4, 199.2$ ppm. HRMS (ESI): Calcd. for C$_{22}$H$_{21}$O$_2$ [M+H$^+$] 317.1536, found 317.1538.

Data for 3-5c: A colorless oil. IR (neat): $\tilde{\nu} = 2955, 2928, 1676, 1597, 1489, 1264, 1091, 828, 766, 701$ cm$^{-1}$. $^1$H NMR (CDCl$_3$, 500 MHz): $\delta = 1.45$ (s, 3 H), 2.21–2.27 (m, 1 H), 2.40–2.43 (m, 1 H), 2.58–2.61 (m, 1 H), 2.97–3.04 (m, 1 H), 6.07 (s, 1 H), 7.30–7.41 (m, 7 H), 7.60–7.61 (d, $J = 3.5$ Hz, 2 H) ppm. $^{13}$C NMR (CDCl$_3$, 126 MHz): $\delta = 28.3, 35.4, 35.6, 39.2, 82.3, 92.9, 121.6, 127.6, 128.0, 128.5, 128.9, 129.2, 133.1, 134.6, 138.9, 163.6, 198.9$ ppm. HRMS (ESI): Calcd. for C$_{21}$H$_{18}$ClO [M+H$^+$] 321.1041, found 321.1045.
Data for 3-5d: A colorless oil. IR (neat): $\tilde{\nu} = 2930, 2858, 1683, 1456, 1264, 701$ cm$^{-1}$. $^1$H NMR (CDCl$_3$, 500 MHz): $\delta = 0.87–0.89$ (t, $J = 7.0$ Hz, 3 H), 1.25–1.32 (m, 7 H), 1.35–1.42 (m, 2 H), 1.49–1.55 (m, 2 H), 2.06–2.13 (m, 1 H), 2.21–2.24 (m, 3 H), 2.47–2.52 (m, 1 H), 2.91–2.98 (m, 1 H), 5.97 (s, 1 H), 7.35–7.37 (m, 3 H), 7.56–7.58 (m, 2 H) ppm. $^{13}$C NMR (CDCl$_3$, 126 MHz): $\delta = 14.0, 18.7, 22.5, 28.4, 28.5, 28.7, 31.2, 34.7, 35.2, 39.3, 82.3, 83.4, 127.2, 127.4, 128.1, 128.7, 138.9, 164.4, 199.2$ ppm. HRMS (ESI): Calcd. for C$_{21}$H$_{27}$O [$M+H^+]$ 295.2056, found 295.2059.

Data for 3-5e: A colorless oil. IR (neat): $\tilde{\nu} = 2968, 2930, 2870, 1675, 1653, 1558, 1320, 1150, 701$ cm$^{-1}$. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta = 1.10$ (s, 6 H), 1.22 (s, 3 H), 1.98–2.05 (m, 1 H), 2.14–2.16 (m, 1 H), 2.40–2.45 (m, 1 H), 2.51–2.54 (m, 1 H), 2.83–2.90 (m, 1 H), 5.89 (s, 1 H), 7.29 (s, 3 H), 7.50 (s, 2 H) ppm. $^{13}$C NMR (CDCl$_3$, 101 MHz): $\delta = 20.6, 23.0, 28.3, 34.6, 35.2, 39.2, 81.5, 88.8, 127.2, 127.4, 128.1, 128.7, 138.9, 164.6, 199.3$ ppm. HRMS (ESI): Calcd. for C$_{18}$H$_{21}$O [$M+H^+]$ 253.1587, found 253.1589.
Data for 3-5f: A colorless oil. IR (neat): $\tilde{\nu}$ = 2967, 2929, 2867, 1677, 1599, 1270, 1150, 701 cm$^{-1}$. $^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ = 1.24 (s, 9 H), 1.29 (s, 3 H), 2.06–2.13 (td, $J$ = 13.0, 4.0 Hz, 1 H), 2.20–2.24 (dt, $J$ = 13.0, 4.5 Hz, 1 H), 2.48–2.53 (dt, $J$ = 16.5, 4.0 Hz, 1 H), 2.89–2.96 (m, 1 H), 5.97 (s, 1 H), 7.36–7.38 (t, $J$ = 3.5 Hz, 3 H), 7.57–7.59 (m, 2 H) ppm. $^{13}$C NMR (CDCl$_3$, 126 MHz): $\delta$ = 27.2, 30.7, 34.3, 34.9, 38.9, 80.5, 91.4, 126.8, 127.2, 127.7, 128.4, 138.7, 164.4, 198.9 ppm. HRMS (ESI): Calcd. for C$_{19}$H$_{23}$O [M+H$^+$] 289.1563, found 289.1566.

![Chemical Structure 3-5f](image)

Data for 3-5g: A colorless oil. IR (neat): $\tilde{\nu}$ = 2949, 2865, 1677, 1558, 1264, 1151, 766, 701 cm$^{-1}$. $^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ = 1.25–1.29 (m, 2 H), 1.31 (s, 3 H), 1.54–1.66 (m, 3 H), 1.76–1.82 (m, 2 H), 2.04–2.15 (m, 2 H), 2.23–2.27 (m, 3 H), 2.49–2.54 (m, 1 H), 2.94–3.05 (m, 1 H), 5.99 (s, 1 H), 7.37–7.38 (t, $J$ = 3.5 Hz, 3 H), 7.59–7.61 (m, 2 H) ppm. $^{13}$C NMR (CDCl$_3$, 126 MHz): $\delta$ = 24.6, 25.3, 28.4, 32.0, 34.7, 35.2, 39.1, 39.4, 82.3, 82.8, 127.2, 127.4, 128.1, 128.7, 138.9, 164.4, 199.2 ppm. HRMS (ESI): Calcd. for C$_{21}$H$_{25}$O [M+H$^+$] 293.1900, found 293.1906.

![Chemical Structure 3-5g](image)

Data for 3-5h: A colorless oil. IR (neat): $\tilde{\nu}$ = 2951, 2922, 1674, 1616, 1558, 1456, 1264, 1151, 766, 701 cm$^{-1}$. $^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ = 1.29 (s, 3 H), 1.89 (s, 3 H), 2.07–2.13 (m, 1 H), 2.22–2.26 (m, 1 H), 2.48–2.53 (m, 1 H), 2.93–2.99 (m, 1 H), 5.98 (s, 1 H),
7.37–7.39 (m, 3 H), 7.57–7.58 (m, 2 H) ppm. \(^{13}\text{C NMR}\) (CDCl\(_3\), 126 MHz): \(\delta = 3.6, 28.3, 34.6, 35.2, 39.2, 78.6, 81.3, 127.2, 127.4, 128.1, 128.7, 138.9, 164.2, 199.1\) ppm. HRMS (ESI): Calcd. for C\(_{16}H_{17}O\) [M+H\(^+\)] 225.1274, found 225.1278.

\[\text{3-5i}\]

Data for 3-5i: A colorless oil. IR (neat): \(\tilde{\nu} = 2928, 2864, 1675, 1597, 1443, 1306, 1013, 892, 756, 704\) cm\(^{-1}\). \(^1\text{H NMR}\) (CDCl\(_3\), 400 MHz): \(\delta = 1.18\) (s, 3 H), 1.48 (s, 3 H), 2.07–2.14 (td, \(J = 13.2, 4.0\) Hz, 1 H), 2.26–2.31 (dt, \(J = 12.8, 4.8\) Hz, 1 H), 2.52–2.58 (dt, \(J = 13.2, 4.4\) Hz, 1 H), 2.89–2.98 (m, 1 H), 7.16–7.32 (m, 10 H) ppm. \(^{13}\text{C NMR}\) (CDCl\(_3\), 101 MHz): \(\delta = 13.4, 28.3, 35.3, 36.8, 37.8, 82.7, 92.0, 123.2, 127.5, 127.7, 128.0, 128.3, 131.6, 132.1, 138.5, 158.2, 198.9\) ppm. HRMS (ESI): Calcd. for C\(_{22}H_{21}O\) [M+H\(^+\)] 301.1587, found 301.1590.

\[\text{3-5j}\]

Data for 3-5j: A colorless oil. IR (neat): \(\tilde{\nu} = 2961, 2929, 1674, 1606, 1456, 1291, 1172, 1032, 892, 731\) cm\(^{-1}\). \(^1\text{H NMR}\) (CDCl\(_3\), 400 MHz): \(\delta = 1.17\) (s, 3 H), 1.48 (s, 3 H), 2.06–2.14 (td, \(J = 13.2, 4.0\) Hz, 1 H), 2.25–2.31 (dt, \(J = 13.2, 4.8\) Hz, 1 H), 2.51–2.57 (dt, \(J = 16.8, 4.0\) Hz, 1 H), 2.90–2.99 (m, 1 H), 3.72 (s, 3 H), 6.76–6.74 (d, \(J = 8.4\) Hz, 2 H), 7.14–7.17 (m, 2 H), 7.24–7.27 (m, 3 H), 7.29–7.33 (t, \(J = 7.6\) Hz, 2 H) ppm. \(^{13}\text{C NMR}\)
(CDCl$_3$, 101 MHz): $\delta = 13.4$, 28.4, 35.4, 36.8, 37.8, 55.3, 82.5, 90.4, 113.9, 115.3, 127.5, 127.7, 128.0, 131.9, 132.9, 138.6, 158.4, 159.4, 199.1 ppm. HRMS (ESI): Calcd. for C$_{23}$H$_{22}$O$_2$Na [M+Na$^+$] 353.1512, found 353.1515.

Data for 3-5k: A colorless oil. IR (neat): $\tilde{\nu} = 2966, 2928, 1674, 1606, 1456, 1306, 1089, 1013, 828, 762 \text{ cm}^{-1}$. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta = 1.20$ (s, 3 H), 1.48 (s, 3 H), 2.08–2.16 (td, $J = 12.8$, 4.0 Hz, 1 H), 2.27–2.33 (dt, $J = 13.2$, 4.8 Hz, 1 H), 2.53–2.59 (td, $J = 17.2$, 4.4 Hz, 1 H), 2.87–2.96 (m, 1 H), 7.12–7.17 (m, 2 H), 7.18–7.23 (m, 4 H), 7.24–7.27 (m, 1 H), 7.30–7.34 (m, 2 H) ppm. $^{13}$C NMR (CDCl$_3$, 101 MHz): $\delta = 13.4$, 28.2, 35.2, 36.9, 37.7, 81.7, 93.1, 121.6, 127.6, 128.1, 128.6, 132.2, 132.8, 134.1, 138.4, 157.9, 198.8 ppm. HRMS (ESI): Calcd. for C$_{22}$H$_{20}$ClO [M+H$^+$] 335.1197, found 335.1200.

Data for 3-5l: A colorless oil. IR (neat): $\tilde{\nu} = 2929, 2858, 1676, 1617, 1456, 1306, 1098, 896, 766 \text{ cm}^{-1}$. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta = 0.79$–0.83 (t, $J = 6.8$ Hz, 3 H), 1.06 (s, 3 H), 1.20–1.32 (m, 6 H), 1.38–1.45 (m, 5 H), 1.97–2.05 (td, $J = 12.8$, 4.0 Hz, 1 H), 2.10–2.16 (m, 3 H), 2.46–2.52 (dt, $J = 16.8$, 4.0 Hz, 1 H), 2.84–2.93 (m, 1 H), 7.13 (br. s, 2 H), 7.22–7.32 (m, 3 H) ppm. $^{13}$C NMR (CDCl$_3$, 101 MHz): $\delta = 13.3$, 14.0, 18.7, 22.5, 28.5,
28.6, 28.8, 31.3, 35.4, 36.2, 38.2, 82.4, 82.8, 127.3, 127.6, 127.8, 131.4, 138.7, 159.1, 199.4 ppm. HRMS (ESI): Calcd. for C\textsubscript{22}H\textsubscript{29}O \([\text{M+H}]^+\) 309.2213, found 309.2216.

\(^1\text{H}, \ ^{13}\text{C}\) spectra of compounds 3-3a, 3-4h and 3-5h.
CHAPTER 4. GOLD-CATALYZED ANNULATIONS OF 2-ALKYNYL BENZALDEHYDES

4.1 Background

Gold-catalyzed transformations have been used extensively in the field of synthetic organic chemistry to rapidly and effectively construct interesting organic frameworks.\textsuperscript{1,20,149,213-218} The development of gold catalysts with improved catalytic activity and stability has also attracted interest.\textsuperscript{7,18,88,219-222} Selected recent notable examples include N,O-chelating gold(III) catalysts,\textsuperscript{2,3,223-225} N-heterocyclic carbene (NHC) or acyclic carbene gold catalysts,\textsuperscript{226-241} cationic gold acetonitrile complexes\textsuperscript{242-244} containing Buchwald-type phosphine ligands\textsuperscript{245-250} and cationic gold-triazole complexes.\textsuperscript{251-257} On the other hand, counteranions, such as super acid anions including the bis(trifluoromethanesulfonyl)imide (NTf\textsubscript{2}),\textsuperscript{258-262} phosphates,\textsuperscript{263-269} and even hydroxide,\textsuperscript{19,270,271} have been found to play a significant role in the catalytic activities of gold catalysts (Scheme 29).

Due to their easy activation by various transition-metal catalysts and Lewis acids, the readily available 2-alkynyl benzaldehyde 4-I has served as a versatile scaffold in a number of organic transformations\textsuperscript{107,272-278} amongst which gold-catalyzed annulations stand out.\textsuperscript{95,97,279-283} Notably, Yamamoto and co-workers reported a gold-catalyzed benzannulation of 2-alkynyl benzaldehyde with an alkyne thereby furnishing naphthalene
derivative 4-2 in a highly efficient manner. A formal Diels–Alder-type [4+2]-cycloaddition mechanism for this gold-catalyzed annulation was proposed, but a stepwise mechanism via intermediate B was also suggested and supported by the substituent effects. However, decarbonylation occurred to yield 4-3 as the main product when copper was used as catalyst.

Scheme 29: Selected examples of recently developed gold catalysts.

The group of Yamamoto extended their formal [4+2]-cycloaddition protocol to alkenes, obtaining dihydronaphthalene derivative 4-4, but in this case the copper catalyst exhibited better catalytic activity than gold. Carbocation intermediate B was called for to account for the observed regio- and stereoselectivities. However, when vinyl ether was employed in the annulation with 2-alkynyl benzaldehyde, the reaction yielded naphthalene 4-2, rather than dihydronaphthalene 4-4. This result has been ascribed to the elimination of alcohol. This outcome was corroborated by work reported by the Porco group. Aldehydes or acetals having α-protons have been effectively involved in this gold-catalyzed annulation, but these substrates served as an enol source instead of a carbonyl source, affording the naphthalene product 4-2, due to the elimination of a water molecule (Scheme 30).
Scheme 30: Yamamoto’s group pioneered the gold or copper-catalyzed annulation of 2-alkynyl benzaldehyde with alkyne, alkene, vinyl ether, or aldehyde. $R_4$ is H or alkyl in B.

In line with our continuing interest in gold catalysis and ligand effects, we posited that a gold catalyst containing a suitable ligand may help to stabilize the carbocation intermediate and veer the reaction toward new synthetic paths. Recently, we reported the gold-catalyzed intramolecular annulations of 2-(ynol)aryl aldehydes 4-10, in which different gold catalysts furnished benzochromanes 4-11 or benzobicyclo[4.3.1]acetals 4-12 (Scheme 31). Thus, we envisioned that the reaction of 2-alkynyl benzaldehyde with a vinyl ether might yield a synthetically interesting product if a suitable gold catalyst could be found. Interestingly, we found that by selecting Au-1 as the catalyst, 2-alkynyl benzaldehyde reacted with vinyl ether to form acetal-tethered dihydronaphthalene 4-5 and isochromene 4-6, rather than naphthalene 4-2. Furthermore, a symmetrical bicyclo[2.2.2]octane 4-7 was produced from the reaction of 2-alkynyl benzaldehyde with a cyclic vinyl ether. By using (IPr)Au as the catalyst, a homo-
dimerization of 2-alkynyl benzaldehyde took place, affording a set of separable diastereomers 4-9 (Scheme 31). These interesting cyclic products are potentially useful synthetic templates of biologically active molecules and natural products such as codeine,\textsuperscript{288} CJ-17493,\textsuperscript{289} psychorubrin,\textsuperscript{290} trioxifene,\textsuperscript{291} regalamine, robustamine,\textsuperscript{292} and the trypticene analogue TT13\textsuperscript{293,294} (Scheme 32). To the best of our knowledge, the synthesis of similar cyclic compounds is rare, and, normally, harsh reaction conditions are needed.\textsuperscript{295-302}

Scheme 31: New developments on gold-catalyzed annulations of 2-alkynyl benzaldehydes with vinyl ethers.
4.2 Results and discussion

Although for the most part the selection of gold catalysts relies on an empirical trial and
error approach, some patterns on ligand effect in gold catalysis have emerged
recently.41,284,285 For example, the cationic gold complex Au-1, developed by Echavarren
and co-workers, exhibited excellent stability and catalytic activity in the
cycloisomerization of enynes due to its bulky and electron-rich phosphine
ligand.176,215,303,304 Accordingly, we first employed Au-1 as the catalyst in the reaction of
2-phenylethynyl benzaldehyde with ethyl vinyl ether. To our delight, along with
Yamamoto’s naphthalene product 4-2a (which was obtained in low yield) we isolated the
acetal-tethered dihydronaphthalene derivative 4-5a as the major product, under mild
conditions (Table 6, entry 1). Other catalysts such as AuCl, AuCl3, triazole gold, and
(IPr)AuCl/AgOTf, as well as AgOTf failed to give any identifiable product. The fragility
of this reaction may be due to the instability of ethyl vinyl ether to acidic
conditions.^{305,306} Next, various 2-alkynyl benzaldehyde substrates with different substituents on the aromatic ring were prepared for use in this new gold-catalyzed annulation with vinyl ether, and the results are summarized in Table 6. All the reactions gave the desired dihydronaphthalene derivatives in moderate yields at, or below, room temperature. Mechanistically, the tethered acetal might have been generated from an oxonium intermediate reacting with an alkoxide anion.^{126} Thus, we wondered if the oxonium intermediate could be intramolecularly trapped by an adjacent phenolic hydroxyl group or if the desired product would be formed preferably in the presence of additional ethanol. To our satisfaction, when substrate 4-1f was employed in this reaction, the reaction intermediate was indeed trapped by the adjacent phenolic hydroxyl group, furnishing the structurally interesting tricyclic compound 4-5f as the main product (Table 6, entry 6).^{307} However, when two equivalents of ethanol were added to the reaction, a new acetal-tethered isochromene 4-6a was obtained in good yield, rather than the corresponding dihydronaphthalene derivative (Table 7, entry 1).
Table 6: Scope of the gold-catalyzed annulation of 2-alkynyl benzaldehyde with vinyl ether.\textsuperscript{a}

\[
\begin{align*}
\text{R}^1\text{CHO} + \text{R}^2\text{OEt} & \xrightarrow{\text{Au-1 (5 mol\%)} \atop \text{DCM, RT, 30 min}} \text{R}^1\text{CHO} \text{R}^2\text{OEt} \\
4-1 & \rightarrow 4-5
\end{align*}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product\textsuperscript{b}</th>
<th>Entry</th>
<th>Substrate</th>
<th>Product\textsuperscript{b}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(\text{4-1a})</td>
<td>(4-5a (52%))</td>
<td>4</td>
<td>(\text{4-1d})</td>
<td>(4-5d (51%)\textsuperscript{d})</td>
</tr>
<tr>
<td>2\textsuperscript{c}</td>
<td>(\text{4-1b})</td>
<td>(4-5b (67%))</td>
<td>5</td>
<td>(\text{4-1e})</td>
<td>(4-5e (53%)\textsuperscript{d})</td>
</tr>
<tr>
<td>3</td>
<td>(\text{4-1c})</td>
<td>(4-5c (56%))</td>
<td>6</td>
<td>(\text{4-1f})</td>
<td>(4-5f (41%))</td>
</tr>
</tbody>
</table>

\textsuperscript{a} General reaction conditions: 2-alkynyl benzaldehyde 4-1 (0.145 mmol), ethyl vinyl ether (0.72 mmol), \textit{Au-1} (5 mol\%), CH\textsubscript{2}Cl\textsubscript{2} (1.0 mL); \textsuperscript{b} isolated yields; \textsuperscript{c} reaction time: 15 min; \textsuperscript{d} ethyl vinyl ether (1.45 mmol) was used and the reaction was carried out at 0 °C.
Since isochromene derivatives are also attractive substrates in organic chemistry, we investigated the gold-catalyzed annihilation of 2-alkynyl benzaldehydes with vinyl ether in the presence of alcohol. The results are outlined in Table 7. All the desired products were obtained in good yields. It should be noted that, for substrate 4-1f, the intramolecular trapping was bypassed by an intermolecular quenching with ethanol (Table 7, entry 6),

Table 7: Gold-catalyzed annihilation of 2-alkynyl benzaldehyde with vinyl ether in the presence of alcohol.\(^a\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product(^b)</th>
<th>Entry</th>
<th>Substrate</th>
<th>Product(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4-1a</td>
<td>4-6a (86%)</td>
<td>5</td>
<td>4-1e</td>
<td>4-6e (51%)(^d)</td>
</tr>
<tr>
<td></td>
<td>4-1b</td>
<td>4-6b (82%)</td>
<td>6</td>
<td>4-1f</td>
<td>4-6f (56%)</td>
</tr>
<tr>
<td>2</td>
<td>4-1c</td>
<td>4-6c (71%)</td>
<td>7</td>
<td>4-1a</td>
<td>4-6g (89%)</td>
</tr>
<tr>
<td>3</td>
<td>4-1d</td>
<td>4-6d (54%)(^d)</td>
<td>8</td>
<td>4-1a</td>
<td>4-6h (81%)</td>
</tr>
</tbody>
</table>

\(^a\) General reaction conditions: 2-alkynyl benzaldehyde 4-1 (0.145 mmol), ethyl vinyl ether (0.72 mmol), alcohol (0.29 mmol), Au-1 (5 mol%), CH\(_2\)Cl\(_2\) (1.0 mL); \(^b\) isolated yields; \(^c\) reaction time: 10 min; \(^d\) reaction was carried out at 0 °C.
which could be explained by the fact that alkoxide is a stronger nucleophile than phenoxide. Other alcohols, such as methanol and isopropanol, were tested in this reaction, and similar products were obtained in good yields (Table 7, entries 7 and 8).

Plausible mechanisms for the formation of these new products have been proposed, as outlined in Scheme 33. The generation of intermediate A from a gold catalyst and 2-alkynyl benzaldehyde substrate is well-accepted, whereas the subsequent annulation with vinyl ether to form C is not clear. It could be either a concerted step, as in a Diels–Alder-type reaction, or in stepwise fashion, beginning with the formation of B. According to previous literature reports, the existence of B is supported by substituent effects and regio- and stereoselectivities. In our case, the formation of acetal-tethered isochromene 4-6 in the presence of alcohol also implies the generation of intermediate B. However, intermediate A was not trapped by alcohol before the formation of B, demonstrating the different catalytic activity of the gold catalyst. Once intermediate C was formed, it could transform into D, which reacted with another molecule of vinyl ether, generating intermediate E. Gold and ethoxide elimination and quenching of the oxonium ion with ethoxide took place in E, affording 4-5 as the product and re-generating the gold catalyst. A competitive elimination in D also occurred, furnishing naphthalene 4-2 as the product. With the selection of an appropriate gold catalyst, the elimination could be controlled.
Scheme 33: Proposed mechanisms for the gold-catalyzed annulations of 2-alkynyl benzaldehyde with vinyl ether.

Because gold alkoxide elimination took place at the stage of intermediate E, we envisioned that this elimination might have been prevented if a cyclic vinyl ether was chosen as the annulation partner. Thus, the readily available 2,3-dihydrofuran was employed in the reaction, and as expected, the gold alkoxide elimination was successfully prevented. Instead, a new bicyclo[2.2.2]octane derivative 4-7 was produced, in which two molecules of cyclic vinyl ether were involved. Catalyst Au-\textsuperscript{214} showed the best catalytic activity and therefore it was selected for subsequent reactions.
Table 8: Gold-catalyzed annulation of 2-alkynyl benzaldehyde with cyclic vinyl ether.\textsuperscript{a}

\[
\begin{array}{c c c c}
\text{R}_1^1&\text{R}_2\text{CHO} & + & \text{Au-2 (5 mol\%)} \\
\text{4-1} & \text{4-7} & & \text{DCM, RT, 30 min} \\
\end{array}
\]

<table>
<thead>
<tr>
<th>Reactant</th>
<th>Product\textsuperscript{b}</th>
<th>Reactant</th>
<th>Product\textsuperscript{b}</th>
</tr>
</thead>
<tbody>
<tr>
<td>\text{Ph} \text{CHO} &amp; \text{4-7a (51%)} &amp; \text{MeO} \text{CHO} &amp; \text{4-7f, 27}</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4-1a   &amp; 4-7b (32%) &amp; 4-1f &amp; 4-7g (65%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>\text{F} \text{CHO} &amp; &amp; \text{OMe} \text{Alpha} &amp;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4-1b   &amp; 4-7c (52%) &amp; 4-1g &amp; 4-7h (45%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>\text{Ph} \text{CHO} &amp; &amp; \text{OMe} \text{Alpha} &amp;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4-1c   &amp; 4-7d (41%) &amp; 4-1h &amp; 4-7i (45%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>\text{Ph} \text{CHO} &amp; &amp; \text{Ph} \text{CHO} &amp;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4-1d   &amp; 4-7e (69%) &amp; 4-1a &amp; 4-7j (37%)\textsuperscript{c}</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>\text{Ph} \text{CHO} &amp; &amp; \text{Ph} \text{CHO} &amp;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4-1e   &amp; &amp; &amp;</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\textsuperscript{a} General reaction conditions: 2-alkynyl benzaldehyde 4-1 (0.145 mmol), 2,3-dihydrofuran (0.72 mmol), \text{Au-2} (5 mol\%), CH\textsubscript{2}Cl\textsubscript{2} (1.0 mL); \textsuperscript{b} isolated yields in \%; \textsuperscript{c} 3,4-dihydro-2H-pyrane was used as cyclic vinyl ether.
Various substrates, having different substituents on the aromatic rings, were employed in this new gold-catalyzed annulation with 2,3-dihydrofuran, and the corresponding products 4-7a–i were isolated (Table 8). 3,4-Dihydro-2H-pyran was also employed as the cyclic vinyl ether due to its easy availability, and the corresponding product 4-7j was obtained in moderate yield.

The structure of product 4-7a was determined by using ¹H, ¹³C, DEPT, gCOSY, HMQC, and HMBC NMR spectroscopy as well as HRMS, and finally confirmed by using X-ray crystallography (the ORTEP-3 diagram of 4-7a is shown in Figure 8).

![ORTEP-3 diagram of bicyclo[2.2.2]octane derivative 4-7a, showing 40% probability ellipsoids. H atoms are shown as small spheres of arbitrary radii. Selected bond lengths [Å] and angles [°]: O1-C2, 1.4285(17); O1-C3, 1.4380(18); O2-C9, 1.4419(18); O2-C10, 1.4338(16); O3-C17, 1.2100(18); O2-C10-C1, 111.15(11); O1-C2-C3, 111.78(11); C2-C1-C10, 104.06(11).](image)

A plausible mechanism for the formation of the bicyclo[2.2.2]octane derivative is outlined in Scheme 34. After intermediate A is generated, a formal [4+2] cycloaddition to 2,3-dihydrofuran could take place either via a concerted or stepwise fashion to yield intermediate G. Intermediate G could transform itself into H, which then reacts with a second molecule of 2,3-dihydrofuran, generating I, before finally furnishing product 4-
and regenerating the gold catalyst. However, an alternative possibility could also be taken into account. Elimination of gold catalyst from H could generate tetrahydro naphthofuran derivative 4-8, which would then undergo an inverse-electron-demand Diels–Alder reaction with the second molecule of 2,3-dihydrofuran, furnishing the final product 4-7.36

Scheme 34: Proposed mechanism for the gold-catalyzed annulation of 2-alkynyl benzaldehyde with cyclic vinyl ether.

During our investigations on these gold-catalyzed annihilations, homo-dimerization of 2-alkynyl benzaldehyde was observed when (IPr)AuCl/AgOTf was employed as the catalyst in the absence of vinyl ether (Scheme 35).16 A set of separable diastereoisomers 4-9a and 4-9b was obtained in good yield, in a 3:5 ratio. The formation of this dimer has been ascribed to a gold-catalyzed hydrolysis of the 2-alkynyl benzaldehyde substrate, generating ketone 4-10, which then serves as a nucleophile for
attacking the electrophilic intermediate A. The structure of the dimer was also confirmed by X-ray crystallography. The ORTEP-3 diagram of the anti-isomer 4-9b is shown in Figure 9.

Scheme 35: Gold-catalyzed homo-dimerization of 2-alkynyl benzaldehyde and the proposed mechanism.

Figure 9: ORTEP-3 diagram of product 9b, showing one diastereoisomer of the racemic mixture at 40% probability ellipsoids. H atoms are shown as small spheres of arbitrary radii. Selected bond lengths [Å] and angles [°]: O1-C7, 1.3795(15); O1-C15, 1.4447(15); O2-C17, 1.2157(15); O3-C30, 1.2117(16); C15-C16, 1.5531(17); C7-O1-C15, 114.70(9); O1-C7-C8, 121.07(11); O1-C15-C16, 106.72(9).
4.3 Conclusions

We have investigated the gold-catalyzed annulations of 2-alkynyl benzaldehyde with acyclic or cyclic vinyl ethers under very mild conditions, and found a number of synthetically interesting transformations. With the selection of an appropriate gold catalyst, the reactions of various 2-alkynyl benzaldehydes with acyclic vinyl ethers afforded dihydronaphthalene derivatives as the products, whereas acetal-tethered isochromenes were obtained when the reaction was conducted in the presence of alcohol. Interestingly, a new bicyclo[2.2.2]octane derivative was isolated from the reaction of 2-alkynyl benzaldehyde with cyclic vinyl ether. The various mechanisms of formation of these reactions have been discussed. We also found that 2-alkynyl benzaldehyde undergoes dimerization under gold catalysis in the absence of vinyl ether. The work described in this chapter was published in Chem. Eur. J. 2013, 19, 4043-4050.

4.4 Experimental

General

$^1$H, $^{13}$C and $^{19}$F NMR spectra were recorded at 500, 126 and 470 (or 400, 101 and 376) MHz, respectively, by using CDCl$_3$ as a solvent. The chemical shifts are reported in $\delta$ (ppm) values ($^1$H and $^{13}$C NMR relative to CHCl$_3$, $\delta = 7.26$ ppm for $^1$H NMR and $\delta = 77.0$ ppm for $^{13}$C NMR and CFCl$_3$ ($\delta = 0$ ppm for $^{19}$F NMR), multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), h (hextet), m (multiplet) and br (broad). Coupling constants, $J$, are reported in Hertz (Hz). Solvents (tetrahydrofuran, ether, dichloromethane and DMF) were dried using a commercial solvent purification system. All other reagents and solvents were employed without further purification. The
products were purified using a commercial flash chromatography system or a regular glass column. TLC was developed on silica gel 60 F254 aluminum sheets. High resolution ESI-MS were obtained using a MS-FTICR-MS\textsuperscript{3} system (LTQ FT, Thermo Electron Corp.) at the CREAM Mass Spectrometry Facility, University of Louisville, Kentucky.

**General procedure for the formation of dihydronaphthalenes (4-5):**

\[
\begin{align*}
\text{R}^1 & \quad \text{R}^2 \\
\begin{array}{c}
\text{4-1} \\
\text{4-2a}
\end{array} \\
& \quad \text{Au-1 (5 mol\%)} \\
& \quad \text{DCM, RT, 30 min} \\
& \quad \text{4-5}
\end{align*}
\]

\text{Au-1 (0.0072 mmol) was added to a solution of 2-alkynylbenzaldehyde 4-1 (0.145 mmol), ethyl vinyl ether 4-2a (0.72 mmol) in DCM (1.0 mL). The mixture was stirred for 30 min at room temperature. The reaction mixture was quenched with water and extracted with DCM. The solvent in the organic layer was removed under reduced pressure and the residue was subjected to flash column chromatography (eluent: ethyl acetate/n-hexane = 1/10) to give product 4-5 as a colorless oil.}

**Spectroscopic data of compounds 4-5**
Data for **4-5a**: colorless oil; $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 1.13-1.16 (3H, t, $J = 7.2$ Hz), 1.23-1.26 (3H, t, $J = 7.2$ Hz), 1.84-1.88 (1H, m), 1.93-2.0 (1H, m), 2.42-2.49 (1H, m), 2.68-2.74 (1H, m), 3.01-3.06 (1H, m), 3.39-3.59 (3H, m), 3.63-3.71 (1H, m), 4.44-4.47 (1H, t, $J = 6.4$ Hz), 6.39-6.42 (1H, dd, $J = 6.4$, 3.2 Hz), 7.12-7.17 (1H, m), 7.19-7.20 (2H, m), 7.27-7.30 (1H, d, $J = 8.0$ Hz), 7.40-7.44 (2H, t, $J = 7.8$ Hz), 7.52-7.56 (1H, t, $J = 7.4$ Hz), 7.83-7.85 (2H, d, $J = 7.2$ Hz); $^{13}$C NMR (CDCl$_3$, 101 MHz) $\delta$ 15.3, 15.4, 29.0, 33.3, 37.3, 60.8, 61.0, 101.1, 126.3, 126.8, 127.8, 127.9, 128.3, 129.8, 131.1, 132.8, 135.2, 138.0, 138.3, 138.8, 196.7. HRMS (ESI) Calcd. for C$_{23}$H$_{26}$NaO$_3$ (M+Na$^+$) requires 373.1774, Found: 373.1775.

![Structural diagram of 4-5a](image)

Data for **4-5b**: a colorless oil; $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 1.07-1.11 (3H, t, $J = 7.2$ Hz), 1.17-1.21 (3H, t, $J = 7.2$ Hz), 1.75-1.93 (2H, m), 2.38-2.44 (1H, m), 2.62-2.69 (1H, m), 2.96-3.01 (1H, m), 3.33-3.64 (4H, m), 4.38-4.41 (1H, t, $J = 5.8$ Hz), 6.31-6.34 (1H, dd, $J = 6.4$, 3.2 Hz), 7.01-7.06 (2H, t, $J = 8.6$ Hz), 7.08-7.12 (1H, m), 7.14-7.15 (2H, m), 7.17-7.19 (1H, m), 7.81-7.84 (2H, m); $^{13}$C NMR (CDCl$_3$, 101 MHz) $\delta$ 15.3, 15.4, 28.9, 33.3, 37.3, 60.9, 61.0, 101.1, 115.5 (d, $J = 22.7$ Hz), 126.2, 126.9, 127.8, 131.0, 132.4, 134.2, 134.8, 138.3, 138.8, 165.6 (d, $J = 255.8$ Hz), 195.2; $^{19}$F NMR (CDCl$_3$, 376 MHz) $\delta$ -105.43 - -105.40 (m). HRMS (ESI) Calcd. for C$_{23}$H$_{25}$FNaO$_3$ (M+Na$^+$) requires 391.1680, Found: 391.1678.
Data for 4-5c: colorless oil; $^1$H NMR (CDCl$_3$, 400 MHz) δ 1.07-1.11 (3H, t, $J = 7.2$ Hz), 1.18-1.21 (3H, t, $J = 7.0$ Hz), 1.75-1.82 (1H, m), 1.88-1.95 (1H, m), 2.33 (3H, s), 2.36-2.42 (1H, m), 2.63-2.69 (1H, m), 2.96-3.00 (1H, m), 3.34-3.55 (3H, m), 3.58-3.66 (1H, m), 4.38-4.41 (1H, t, $J = 5.8$ Hz), 6.32-6.34 (1H, dd, $J = 6.0$, 2.8 Hz), 7.08-7.15 (3H, m), 7.21-7.26 (2H, m), 7.29-7.31 (1H, d, $J = 7.6$ Hz), 7.54-7.56 (1H, d, $J = 7.2$ Hz), 7.63 (1H, s); $^{13}$C NMR (CDCl$_3$, 101 MHz) δ 15.3, 15.4, 29.0, 30.0, 33.3, 37.3, 60.8, 60.9, 101.1, 126.9, 127.2, 127.8, 127.9, 128.2, 130.2, 131.2, 133.6, 134.9, 138.1, 138.2, 138.5, 138.8, 197.0. HRMS (ESI) Calcd. for C$_{24}$H$_{28}$NaO$_3$ (M+Na$^+$) requires 387.1931, Found: 387.1927.

Data for 4-5d: colorless oil; $^1$H NMR (CDCl$_3$, 400 MHz) δ 1.08-1.12 (3H, t, $J = 7.2$ Hz), 1.17-1.20 (3H, t, $J = 6.8$ Hz), 1.72-1.87 (2H, m), 2.35-2.40 (1H, m), 2.57-2.65 (1H, m), 2.85-2.91 (1H, m), 3.34-3.65 (4H, m), 4.37-4.40 (1H, t, $J = 6.0$ Hz), 5.84 (2H, s), 6.25-6.27 (1H, dd, $J = 6.0$, 3.0 Hz), 6.65 (1H, s), 6.82 (1H, s), 7.35-7.39 (2H, t, $J = 7.4$ Hz), 7.47-7.50 (1H, t, $J = 7.4$ Hz), 7.76-7.78 (2H, d, $J = 8$ Hz); $^{13}$C NMR (CDCl$_3$, 101 MHz) δ 15.36, 15.4, 29.0, 33.6, 37.2, 60.7, 61.1, 101.0, 101.1, 107.1, 108.5, 124.8, 128.3, 129.8,
132.7, 133.4, 134.0, 137.9, 138.1, 146.2, 146.8, 196.7. HRMS (ESI) Calcd. for C_{24}H_{26}NaO_{5} (M+Na^+) requires 417.1672, Found: 417.1671.

Data for 4-5e: colorless oil; $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 1.09-1.12 (3H, t, $J = 7.2$ Hz), 1.18-1.21 (3H, t, $J = 7.2$ Hz), 1.72-1.89 (2H, m), 2.34-2.42 (1H, m), 2.59-2.67 (1H, m), 2.88-2.94 (1H, m), 3.37-3.56 (3H, m), 3.60-3.65 (1H, m), 3.68 (3H, s), 3.83 (3H, s), 4.37-4.40 (1H, t, $J = 6.0$ Hz), 6.30-6.32 (1H, dd, $J = 6.0, 3.0$ Hz), 6.68 (1H, s), 6.95 (1H, s), 7.36-7.40 (2H, t, $J = 7.6$ Hz), 7.47-7.51 (1H, m), 7.76-7.78 (2H, d, $J = 8$ Hz); $^{13}$C NMR (CDCl$_3$, 101 MHz) $\delta$ 15.38, 15.44, 29.1, 33.2, 37.4, 55.8, 55.9, 61.0, 61.2, 101.3, 109.9, 111.1, 123.6, 128.3, 129.8, 131.8, 132.7, 134.9, 137.5, 147.3, 148.4, 196.9. HRMS (ESI) Calcd. for C$_{25}$H$_{30}$NaO$_{5}$ (M+Na$^+$) requires 433.1985, Found: 433.1991.

Data for 4-5f: semi solid; $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 1.23-1.27 (3H, t, $J = 7.2$ Hz), 1.76-1.84 (1H, q, $J = 10.8$ Hz), 2.10-2.25 (2H, m), 2.39-2.47 (1H, m), 3.07-3.14 (1H, m), 3.64-3.68 (1H, m), 3.77 (3H, s), 4.08-4.13 (1H, m), 5.15-5.16 (1H, d, $J = 7.6$ Hz), 6.27-6.29 (1H, dd, $J = 7.0, 2.8$ Hz), 6.60-6.62 (1H, d, $J = 8.4$ Hz), 6.74-6.76 (1H, d, $J = 8.4$ Hz), 7.35-7.38 (2H, t, $J = 7.6$ Hz), 7.47-7.50 (1H, t, $J = 7.6$ Hz), 7.78-7.80 (2H, d, $J = 7.2$ Hz); $^{13}$C NMR (CDCl$_3$, 101 MHz) $\delta$ 15.2, 29.6, 29.9, 34.2, 55.9, 64.8, 100.0, 109.9, 118.4,
120.7, 124.4, 128.3, 129.9, 132.8, 133.1, 137.9, 138.8, 141.5, 148.3, 196.9. HRMS (ESI) Calcd. for C_{22}H_{22}NaO_{4} (M+Na^+) requires 373.1410, Found: 373.1414.

**General procedure for the formation of isochromenes (4-6):**

![Chemical Reaction Diagram](Image)

Au-I (0.0072 mmol) was added to a solution of 2-alkynylbenzaldehyde 1 (0.145 mmol, ethyl vinyl ether (0.72 mmol) and ethanol (0.28 mmol) in DCM (1.0 mL). The mixture was stirred for 30 min at room temperature. The reaction mixture was quenched with water and extracted with DCM. The solvent in the organic layer was removed under reduced pressure and the residue was subjected to flash column chromatography (eluent: ethyl acetate/n-hexane = 1/10) to give product 4-6 as a colorless oil.

Data for 4-6a: colorless oil; $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 1.21-1.24 (3H, t, $J = 7.6$ Hz), 1.27-1.31 (3H, t, $J = 7.2$ Hz), 2.09-2.16 (1H, m), 2.42-2.49 (1H, m), 3.51-3.59 (1H, m), 3.61-3.71 (2H, m), 3.76-3.84 (1H, m), 4.90-4.93 (1H, dd, $J = 7.6$, 3.8 Hz), 5.50-5.53 (1H, dd, $J = 9.6$, 4.0 Hz), 6.47 (1H, s), 7.09-7.13 (2H, t, $J = 8.0$ Hz), 7.18-7.27 (2H, m), 7.34-7.43 (3H, m), 7.76-7.78 (2H, m); $^{13}$C NMR (CDCl$_3$, 101 MHz) $\delta$ 15.39, 15.41, 37.9, 60.9, 62.2, 75.0, 99.9, 100.6, 123.7, 124.0, 124.9, 126.6, 128.0, 128.4, 128.7, 130.9, 131.0,
134.6, 151.3. HRMS (ESI) Calcd. for C$_{21}$H$_{24}$NaO$_3$ (M+Na$^+$) requires 347.1618, Found: 347.1622.

![Diagram of 4-6b]

Data for 4-6b: colorless oil; $^1$H NMR (CDCl$_3$, 400 MHz) δ 1.10-1.13 (3H, t, $J$ = 7.0 Hz), 1.15-1.19 (3H, t, $J$ = 7.0 Hz), 1.97-2.04 (1H, m), 2.29-2.35 (1H, m), 3.40-3.60 (3H, m), 3.63-3.71 (1H, m), 4.75-4.78 (1H, dd, $J$ = 7.6, 3.8 Hz), 5.36-5.40 (1H, dd, $J$ = 9.4, 4.2 Hz), 6.28 (1H, s), 6.96-7.01 (4H, m), 7.07-7.11 (1H, m), 7.13-7.17 (1H, m), 7.61-7.64 (2H, m); $^{13}$C NMR (CDCl$_3$, 101 MHz) δ 15.3, 15.4, 37.8, 60.8, 62.1, 75.0, 99.8, 100.2, 115.3 (d, $J$ = 21.7 Hz), 123.7, 123.9, 126.7, 126.8, 128.1, 130.7, 150.4, 163.1 (d, $J$ = 247.1 Hz); $^{19}$F NMR (CDCl$_3$, 376 MHz) δ -112.50 - -112.43 (m). HRMS (ESI) Calcd. for C$_{21}$H$_{23}$FNaO$_3$ (M+Na$^+$) requires 365.1523, Found: 365.1523.

![Diagram of 4-6c]

Data for 4-6c: colorless oil; $^1$H NMR (CDCl$_3$, 400 MHz) δ 1.10-1.14 (3H, t, $J$ = 6.8 Hz), 1.16-1.20 (3H, t, $J$ = 7.2 Hz), 1.97-2.04 (1H, m), 2.31 (3H, s), 2.33-2.37 (1H, m), 3.40-3.48 (1H, m), 3.52-3.60 (2H, m), 3.65-3.73 (1H, m), 4.78-4.81 (1H, dd, $J$ = 7.6, 3.8 Hz), 5.37-5.40 (1H, dd, $J$ = 9.2, 4.0 Hz), 6.35 (1H, s), 6.98-7.02 (2H, t, $J$ = 8.0 Hz), 7.07-7.10 (2H, t, $J$ = 7.6 Hz), 7.13-7.21 (2H, m), 7.45-7.47 (2H, d, $J$ = 8.0 Hz); $^{13}$C NMR (CDCl$_3$, 101 MHz) δ 15.36, 15.38, 21.5, 37.8, 60.8, 62.2, 74.9, 99.8, 100.5, 122.1, 123.7, 123.9,
HRMS (ESI) Calcd. for C_{22}H_{26}NaO_{3} (M+Na^+) requires 361.1774, Found: 361.1777.

Data for 4-6d: colorless oil; \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta\) 1.10-1.13 (3H, t, \(J = 7.2\) Hz), 1.16-1.20 (3H, t, \(J = 7.2\) Hz), 1.90-1.97 (1H, m), 2.26-2.33 (1H, m), 3.39-3.47 (1H, m), 3.50-3.59 (2H, m), 3.65-3.72 (1H, m), 4.75-4.78 (1H, dd, \(J = 7.8, 4.0\) Hz), 5.28-5.31 (1H, dd, \(J = 9.2, 4.0\) Hz), 5.86 (2H, s), 6.27 (1H, s), 6.53-6.54 (2H, d, \(J = 4.8\) Hz), 7.22-7.26 (1H, m), 7.28-7.32 (2H, t, \(J = 7.6\) Hz), 7.62-7.63 (2H, d, \(J = 7.2\) Hz); \(^{13}\)C NMR (CDCl\(_3\), 101 MHz) \(\delta\) 15.3, 15.4, 37.8, 60.8, 62.3, 74.8, 99.8, 100.7, 100.9, 104.8, 104.9, 124.6, 125.2, 128.3, 128.5, 134.5, 146.3, 147.2, 149.7. HRMS (ESI) Calcd. For C_{22}H_{24}NaO_{5} (M+Na^+) requires 391.1516, Found: 391.1519.

Data for 4-6e: colorless oil; \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta\) 1.10-1.14 (3H, t, \(J = 7.2\) Hz), 1.18-1.22 (3H, t, \(J = 7.2\) Hz), 1.93-1.99 (1H, m), 2.28-2.35 (1H, m), 3.40-3.47 (1H, m), 3.55-3.60 (2H, m), 3.70-3.74 (1H, m), 3.81 (3H, s), 3.83 (3H, s), 4.78-4.81 (1H, dd, \(J = 8, 3.8\) Hz), 5.34-5.37 (1H, dd, \(J = 10.0, 4.0\) Hz), 6.31 (1H, s), 6.56-6.59 (2H, d, \(J = 13.6\) Hz), 7.24-7.28 (1H, t, \(J = 7.2\) Hz), 7.30-7.32 (2H, t, \(J = 6.8\) Hz), 7.63-7.65 (2H, d, \(J = 7.6\) Hz); \(^{13}\)C NMR (CDCl\(_3\), 101 MHz) \(\delta\) 15.36, 15.39, 38.1, 56.0, 56.2, 60.9, 62.6, 74.7, 100.0,
100.3, 107.6, 123.3, 123.8, 124.5, 128.3, 128.4, 134.7, 148.0, 148.7, 149.6. HRMS (ESI) Calcd. for $C_{23}H_{28}NaO_5$ (M+Na$^+$) requires 407.1829, Found: 407.1828.

![Image of 4-6f](image)

Data for 4-6f: colorless oil; $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 1.13-1.16 (3H, t, $J = 7.0$ Hz), 1.27-1.30 (3H, t, $J = 7.0$ Hz), 1.94-1.99 (1H, m), 2.32-2.38 (1H, m), 3.47-3.51 (1H, m), 3.60-3.67 (2H, m), 3.76-3.80 (1H, m), 3.89 (3H, s), 4.89-4.91 (1H, dd, $J = 7.8, 3.8$ Hz), 5.80 (1H, s), 5.89-5.92 (1H, dd, $J = 9.5, 4.0$ Hz), 6.37 (1H, s), 6.62-6.64 (1H, d, $J = 8.0$ Hz), 6.74-6.76 (1H, d, $J = 8.5$ Hz), 7.29-7.32 (1H, t, $J = 7.5$ Hz), 7.36-7.39 (2H, t, $J = 7.5$ Hz), 7.72-7.74 (2H, d, $J = 8.0$ Hz); $^{13}$C NMR (CDCl$_3$, 126 MHz) $\delta$ 15.2, 15.4, 36.9, 56.1, 60.76, 60.82, 70.1, 99.3, 99.8, 109.8, 115.6, 117.6, 124.2, 124.5, 128.3, 135.0, 140.3, 145.9, 148.6. HRMS (ESI) Calcd. for $C_{22}H_{26}NaO_5$ (M+Na$^+$) requires 393.1672, Found: 393.1683.

![Image of 4-6g](image)

Data for 4-6g: colorless oil; $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 1.20-1.23 (3H, t, $J = 7.0$ Hz), 2.07-2.14 (1H, m), 2.40-2.47 (1H, m), 3.45 (3H, s), 3.50-3.56 (1H, m), 3.62-3.69 (1H, m), 4.83-4.86 (1H, dd, $J = 8.0, 4.0$ Hz), 5.47-5.50 (1H, dd, $J = 10.0, 4.2$ Hz), 6.46 (1H, s), 7.06-7.12 (2H, m), 7.16-7.26 (2H, m), 7.33-7.42 (3H, m), 7.75-7.77 (2H, d, $J = 8.0$ Hz); $^{13}$C NMR (CDCl$_3$, 101 MHz) $\delta$ 15.3, 37.4, 53.5, 61.1, 74.9, 100.6, 100.7, 123.7, 124.0,
124.9, 126.7, 128.1, 128.4, 128.8, 130.88, 130.91, 134.6, 151.3. HRMS (ESI) Calcd. for C_{20}H_{22}NaO_3 (M+Na^+) requires 333.1461, Found: 333.1470.

Data for 4-6h: colorless oil; ^1^H NMR (CDCl_3, 400 MHz) δ 1.17-1.21 (3H, t, J = 7.0 Hz), 1.24-1.29 (6H, m), 2.00-2.07 (1H, m), 2.41-2.49 (1H, m), 3.50-3.63 (2H, m), 3.96-4.02 (1H, m), 4.96-4.99 (1H, dd, J = 8.0, 3.2 Hz), 5.47-5.51 (1H, dd, J = 10.4, 3.8 Hz), 6.46 (1H, s), 7.09-7.11 (2H, m), 7.16-7.26 (2H, m), 7.32-7.41 (3H, m), 7.74-7.76 (2H, d, J = 7.2 Hz); ^1^C NMR (CDCl_3, 101 MHz) δ 15.4, 22.3, 23.4, 38.5, 59.6, 69.4, 75.0, 98.2, 100.5, 123.7, 124.0, 124.8, 126.6, 128.0, 128.3, 128.7, 130.8, 131.0, 134.6, 151.1. HRMS (ESI) Calcd. for C_{22}H_{26}NaO_3 (M+Na^+) requires 361.1774, Found: 361.1776.

**General procedure for the formation of bicyclo[2.2.2]octanes (4-7):**

Au-2 (0.0072 mmol) was added to a solution of 2-alkynylnaldehyde 4-1 (0.145 mmol), 2,3-dihydrofuran (0.72 mmol) in DCM (1.0 mL). The mixture was stirred for 30 min at room temperature. The reaction mixture was quenched with water and extracted with DCM. The solvent in the organic layer was removed under reduced pressure and the
residue was subjected to a flash column chromatography (eluent: ethyl acetate/n-hexane = 1/10) to give product 4-7.

Data for 4-7a: white solid; mp. 188.2-193.0 °C; $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 1.13-1.21 (2H, m), 1.81-1.89 (2H, m), 2.54-2.61 (2H, m), 2.91-2.97 (3H, m), 3.29-3.35 (2H, q, $J = 7.2$ Hz), 4.48-4.50 (2H, d, $J = 8.4$ Hz), 7.05-7.18 (3H, m), 7.30-7.34 (2H, t, $J = 7.6$ Hz), 7.38-7.41 (1H, t, $J = 6.8$ Hz), 7.58-7.59 (1H, d, $J = 7.2$ Hz), 7.83-7.85 (2H, d, $J = 8.4$ Hz); $^{13}$C NMR (CDCl$_3$, 101 MHz) $\delta$ 30.3, 43.8, 44.2, 62.2, 68.5, 81.0, 126.4, 126.8, 127.3, 127.6, 129.0, 129.6, 130.8, 134.9, 137.8, 140.3, 204.0. HRMS (ESI) Calcd. for C$_{23}$H$_{23}$O$_3$ (M+H$^+$) requires 347.1642, Found: 347.1642.

Data for 4-7b: white solid; mp. 185.0-188.0 °C; $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 1.14-1.21 (2H, m), 1.84-1.90 (2H, m), 2.58-2.63 (2H, m), 2.94-3.0 (3H, m), 3.30-3.34 (2H, q, $J = 7.6$ Hz), 4.49-4.51 (2H, d, $J = 8.5$ Hz), 6.96-7.0 (2H, t, $J = 8.8$ Hz), 7.06-7.09 (2H, t, $J = 8.2$ Hz), 7.15-7.19 (1H, m), 7.29-7.31 (1H, d, $J = 7.5$ Hz), 7.97-8.0 (2H, m); $^{13}$C NMR (CDCl$_3$, 101 MHz) $\delta$ 30.3, 43.9, 44.1, 62.5, 68.4, 81.2, 114.5 (d, $J = 21.9$ Hz), 126.5, 126.6, 127.5, 129.7, 132.7, 135.0, 135.9, 137.8, 164.7 (d, $J = 253.5$ Hz), 201.5; $^{19}$F NMR
(CDCl₃, 470 MHz) δ -108.08 - -108.02 (m), HRMS (ESI) Calcd. for C₂₃H₂₁FNaO₃
(M⁺Na⁺) requires 387.1367, Found: 387.1371.

Data for 4-7c: white solid; mp. 179.2-184.8 °C; ¹H NMR (CDCl₃, 400 MHz) δ 1.15-1.21
(2H, m), 1.82-1.91 (2H, m), 2.31 (3H, s), 2.56-2.61 (2H, m), 2.89-2.94 (2H, m), 2.96-
2.98 (1H, m), 3.30-3.35 (2H, q, J = 7.6 Hz), 4.49-4.51 (2H, d, J = 8.4 Hz), 7.05-7.07 (1H,
m), 7.12-7.15 (2H, m), 7.18-7.21 (2H, m), 7.59 (1H, s), 7.64-7.66 (2H, m); ¹³C NMR
(CDCl₃, 101 MHz) δ 21.4, 30.3, 43.8, 62.0, 68.5, 80.9, 125.8, 126.3, 126.8, 127.2,
127.4, 129.1, 129.5, 131.4, 134.9, 137.5, 137.7, 140.5, 204.4. HRMS (ESI) Calcd. for

Data for 4-7d: semi solid; ¹H NMR (CDCl₃, 400 MHz) δ 1.18-1.26 (2H, m), 1.80-1.89
(2H, m), 2.48-2.54 (2H, m), 2.88-2.90 (1H, m), 3.02-3.08 (2H, m), 3.33-3.38 (2H, q, J =
7.8 Hz), 4.41-4.43 (2H, d, J = 8.8 Hz), 5.84 (2H, s), 6.59 (1H, s), 7.31-7.35 (3H, m),
7.38-7.42 (1H, m), 7.76-7.77 (2H, d, J = 7.2 Hz); ¹³C NMR (CDCl₃, 101 MHz) δ 30.3,
43.8, 44.3, 62.0, 68.6, 80.7, 100.6, 107.9, 110.9, 127.6, 127.8, 128.3, 128.4, 130.4, 130.5,
HRMS (ESI) Calcd. for C_{24}H_{22}NaO_{5} (M+Na^+) requires 413.1359, Found: 413.1365.

Data for 4-7e: yellow oil; \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta\) 1.16-1.24 (2H, m), 1.81-1.91 (2H, m), 2.54-2.57 (2H, q, \(J = 7.8\) Hz), 2.90-3.02 (3H, m), 3.32-3.38 (2H, q, \(J = 7.8\) Hz), 3.54 (3H, s), 3.83 (3H, s), 4.48-4.50 (2H, d, \(J = 8.4\) Hz), 6.60 (1H, s), 7.17 (1H, s), 7.30-7.35 (2H, m), 7.38-7.40 (1H, m), 7.84-7.86 (2H, d, \(J = 7.2\) Hz); \(^1^3\)C NMR (CDCl\(_3\), 101 MHz) \(\delta\) 30.3, 43.9, 55.4, 55.9, 61.9, 68.6, 81.2, 110.4, 113.5, 126.6, 127.7, 128.9, 130.7, 147.4, 204.7. HRMS (ESI) Calcd. for C_{25}H_{26}NaO_{5} (M+Na^+) requires 429.1672, Found: 429.1678.

Data for 4-7f: yellow oil; \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta\) 1.24-1.31 (2H, m), 1.92-1.99 (2H, m), 2.62-2.68 (2H, m), 3.12-3.16 (2H, m), 3.40-3.45 (2H, q, \(J = 7.8\) Hz), 3.67-3.68 (1H, m), 3.88 (3H, s), 4.52-4.54 (2H, d, \(J = 8.5\) Hz), 5.57 (1H, s), 6.69-6.70 (1H, d, \(J = 8.5\) Hz), 7.19-7.20 (1H, d, \(J = 8.5\) Hz), 7.38-7.41 (2H, t, \(J = 7.5\) Hz), 7.46-7.49 (1H, t, \(J = 7.2\) Hz), 7.90-7.92 (2H, d, \(J = 7.5\) Hz); \(^1^3\)C NMR (CDCl\(_3\), 101 MHz) \(\delta\) 30.3, 36.0, 43.4, 55.7, 61.7, 68.6, 80.9, 108.3, 121.1, 127.6, 128.8, 130.6, 140.5, 142.5, 144.7, 204.3. HRMS (ESI) Calcd. for C_{24}H_{24}NaO_{5} (M+Na^+) requires 415.1516, Found: 415.1518.
Data for 4-7g: white solid; mp. 185.2-187.6 °C; $^1$H NMR (CDCl$_3$, 400 MHz) δ 1.21-1.28 (2H, m), 1.85-1.94 (2H, m), 2.43 (3H, s), 2.57-2.63 (2H, m), 2.94-3.01 (3H, m), 3.34-3.40 (2H, q, $J = 7.6$ Hz), 4.52-4.54 (2H, d, $J = 8.8$ Hz), 7.11-7.13 (1H, m), 7.19-7.30 (5H, m), 7.76-7.78 (1H, d, $J = 7.6$ Hz), 7.97-7.99 (1H, t, $J = 7.6$ Hz); $^{13}$C NMR (CDCl$_3$, 101 MHz) δ 19.5, 30.4, 43.9, 44.3, 62.2, 68.4, 80.5, 124.7, 125.9, 126.3, 127.3, 128.7, 129.0, 131.0, 134.7, 136.2, 137.6, 140.8, 207.1. HRMS (ESI) Calcd. for C$_{24}$H$_{24}$NaO$_3$ (M+Na$^+$) requires 383.1618, Found: 383.1625.

Data for 4-7h: white solid; mp. 149.8-152.5 °C; $^1$H NMR (CDCl$_3$, 400 MHz) δ 1.13-1.21 (2H, m), 1.82-1.91 (2H, m), 2.57-2.64 (2H, m), 2.93-3.0 (3H, m), 3.28-3.34 (2H, q, $J = 7.6$ Hz), 3.78 (3H, s), 4.52-4.54 (2H, d, $J = 8.8$ Hz), 6.78-6.80 (2H, d, $J = 8.8$ Hz), 7.02-7.09 (2H, m), 7.13-7.18 (1H, m), 7.24-7.26 (1H, d, $J = 8.0$ Hz), 8.00-8.02 (2H, t, $J = 8.8$ Hz); $^{13}$C NMR (CDCl$_3$, 101 MHz) δ 30.3, 43.9, 44.2, 55.3, 62.5, 68.3, 81.4, 112.5, 126.34, 126.36, 127.4, 130.1, 132.2, 133.2, 135.6, 137.9, 162.4, 200.5. HRMS (ESI) Calcd. for C$_{24}$H$_{24}$NaO$_4$ (M+Na$^+$) requires 399.1567, Found: 399.1602.
Data for 4-7i: semi solid; $^1$H NMR (CDCl$_3$, 400 MHz) δ 1.14-1.24 (2H, m), 1.80-1.87 (2H, m), 2.18 (3H, s), 2.52-2.58 (2H, m), 2.92-3.0 (3H, m), 3.30-3.35 (2H, q, $J$ = 7.6 Hz), 4.46-4.48 (2H, d, $J$ = 9.2 Hz), 6.95 (2H, s), 7.31-7.35 (2H, t, $J$ = 7.6 Hz), 7.39-7.42 (1H, t, $J$ = 7.2 Hz), 7.49 (1H, s), 7.81-7.83 (2H, d, $J$ = 7.2 Hz); $^{13}$C NMR (CDCl$_3$, 101 MHz) δ 21.7, 30.3, 43.7, 43.9, 62.0, 68.5, 80.7, 127.02, 127.04, 127.6, 128.7, 130.3, 130.6, 134.4, 134.5, 136.3, 140.4, 204.3. HRMS (ESI) Calcd. for C$_{24}$H$_{24}$NaO$_3$ (M+Na$^+$) requires 383.1618, Found: 383.1619.

Data for 4-7j: white solid; mp. 188.0-194.0 °C; $^1$H NMR (CDCl$_3$, 400 MHz) δ 0.66-0.77 (2H, m), 1.23-1.29 (2H, m), 1.31-1.41 (2H, m), 1.53-1.63 (2H, m), 1.87-1.94 (2H, m), 2.54 (1H, s), 3.30-3.35 (2H, m), 3.62-3.69 (2H, m), 4.01-4.03 (2H, d, $J$ = 8.8 Hz), 7.02-7.04 (1H, d, $J$ = 6.8 Hz), 7.13-7.23 (2H, m), 7.31-7.39 (3H, m), 7.44-7.45 (2H, d, $J$ = 6.4 Hz), 8.18-8.20 (1H, d, $J$ = 7.2 Hz); $^{13}$C NMR (CDCl$_3$, 101 MHz) δ 20.4, 21.6, 40.6, 45.7, 60.5, 63.0, 75.5, 125.9, 126.56, 126.65, 126.7, 127.9, 128.6, 129.4, 133.9, 139.0, 141.5, 206.3. HRMS (ESI) Calcd. for C$_{25}$H$_{26}$NaO$_3$ (M+Na$^+$) requires 397.1774, Found: 397.1779.
General procedure for the formation of dimer (4-9):

(IPr)AuCl (0.0072 mmol) and AgOTf (10.0072 mmol) were added to a solution of 2-alkynylbenzaldehyde 4-1a (30 mg, 0.145 mmol) in toluene (1.0 mL). The mixture was stirred for 3 h at room temperature. The reaction mixture was quenched with water and extracted with DCM. The solvent in the organic layer was removed under reduced pressure and the residue was subjected to flash column chromatography (eluent: ethyl acetate/n-hexane = 1/10) to give product 4-9a (syn, 10.1 mg, 32%) as yellow liquid and 4-9b (anti, 16.3 mg, 52%) as a white solid.

Data for 4-9a (Syn diastereomer): yellow liquid; \(^1\)H NMR (CDCl\textsubscript{3}, 400 MHz) \(\delta\) 6.28-6.31 (1H, d, \(J = 9.6\) Hz), 6.60 (1H, s), 6.99-7.08 (4H, m), 7.12-7.27 (8H, m), 7.36-7.50 (3H, m), 7.60-7.64 (1H, t, \(J = 7.4\) Hz), 7.85-7.87 (2H, d, \(J = 8.4\) Hz), 7.99-8.01 (1H, d, \(J = 7.6\) Hz), 9.64 (1H, s); \(^{13}\)C NMR (CDCl\textsubscript{3}, 101 MHz) \(\delta\) 49.1, 79.8, 101.0, 124.4, 124.5, 126.0, 126.5, 127.6, 127.9, 128.36, 128.4, 128.6, 128.7, 129.6, 129.8, 130.4, 133.2, 133.5, 133.8, 134.7, 135.1, 136.9, 150.7, 192.9, 198.5. HRMS (ESI) Calcd. for C\textsubscript{30}H\textsubscript{22}NaO\textsubscript{3} (M+Na\textsuperscript{+}) requires 453.1461, Found: 453.1465.
Data for **4-9b** (Anti diastereomer): white solid; mp. 129.8-132.3 °C; $^1$H NMR (CDCl$_3$, 400 MHz) δ 5.92-5.94 (1H, d, $J = 7.6$ Hz), 6.17-6.20 (1H, d, $J = 9.6$ Hz), 6.58 (1H, s), 6.65-6.68 (1H, t, $J = 7.4$ Hz), 7.03-7.11 (3H, m), 7.18-7.19 (3H, m), 7.24-7.28 (2H, t, $J = 7.2$ Hz), 7.35-7.39 (2H, t, $J = 7.6$ Hz), 7.46-7.55 (4H, m), 7.77-7.80 (1H, d, $J = 8.0$ Hz), 7.98-8.00 (2H, d, $J = 8.0$ Hz), 9.57 (1H, s); $^{13}$C NMR (CDCl$_3$, 101 MHz) δ 46.1, 79.9, 100.5, 123.8, 125.1, 125.2, 125.4, 127.0, 128.0, 128.1, 128.2, 128.57, 128.66, 128.68, 129.3, 131.3, 133.2, 133.6, 134.0, 134.5, 135.5, 136.9, 150.7, 191.9, 198.2. HRMS (ESI) Calcd. for C$_{30}$H$_{22}$NaO$_3$ (M+Na$^+$) requires 453.1461, Found: 453.1464.
$^1$H, $^{13}$C and $^{19}$F spectra of compound 4-5a, 4-6a, 4-7a and 4-9.
CHAPTER 5. RATIONAL LIGAND DESIGN FOR GOLD CATALYSIS

5.1 Background

Gold catalysis is a landmark addition to the field of organic synthesis.\textsuperscript{9,10,12,315-317} Cationic gold species are regarded as the most powerful catalysts for the electrophilic activation of C-C unsaturated compounds (alkynes/allenes/alkenes) toward a variety of nucleophiles.\textsuperscript{318-322} However, high turnover numbers (or low catalyst loadings) have been achieved only for a narrow set of gold-catalyzed reactions.\textsuperscript{323,324} Notable examples include the [(NHC)Au\textsuperscript{I}]-catalyzed alkyne hydration, reported by Nolan and coworkers;\textsuperscript{325} the [(NHC)Au\textsuperscript{I}]-catalyzed intramolecular addition of diol to alkyne, reported by Hashmi and coworkers;\textsuperscript{45} the hydroamination of alkynes with a hyperhalogenated carba-closo-dodecaborate anionic ligand, reported by Lavallo and coworkers;\textsuperscript{43} and the ester assisted hydration of alkynes catalyzed by small gold clusters, reported by Corma and coworkers.\textsuperscript{326} In some exceptional cases, even higher turnovers can be achieved but at the cost of employing relatively high temperatures (e.g. 120 °C).\textsuperscript{325}

Despite these impressive numbers, for most gold-catalyzed reactions, it is still common to see 1-5% catalyst loadings. Considering that gold is a precious metal and homogeneous catalysts are difficult to recycle, a 5% loading is often not practical in large-scale synthesis. And more often than not, high temperatures are needed to achieve
high turnover numbers,\textsuperscript{325} which is not suitable for the synthesis of complex target molecules.

Our goal is to develop an ‘ideal’ gold catalyst that meets the following criteria: i) High turnover (or low gold catalyst loading) under mild conditions such as room temperature, or slightly elevated temperatures ($\leq 50^\circ$C). ii) Applicable for a large group of gold-catalyzed reactions with predictable behavior. iii) Easily obtainable (commercially available or easily prepared in the laboratory).

5.2 Results and discussions

A simplified gold catalytic cycle is shown in Scheme 36. First, a cationic gold complex ($\text{Au}^+$) acts as Lewis acids to activate C-C multiple bonds to form a $\pi$-complex $\text{Au-S}$. Interaction of $\text{Au-S}$ with a nucleophile (Nu) eventually will give a gold $\sigma$-complex ($\text{Au-S-Nu}$) (stage 1). The next stage is the regeneration of cationic gold (e.g. protodeauration), which gives the product $P$ (stage 2). In addition, decay of cationic gold(I) complexes also takes place, leading to the formation of an inactive species like Au(0), L$_2$Au$^+$ (stage 3). Recently, Widenhoefer and coworkers reported the formation of reversible off-cycle gold species\textsuperscript{327} (e.g. bis-Au-vinyl species, stage 3).
Scheme 36. Type I and Type II gold-catalyzed reactions.

Based on our most recent study, we can classify gold-catalyzed reactions based on their turnover limiting stage. According to Widenhoefer’s recent report, the complexation of cationic gold with $S$ is a fast process, so this step is unlikely to be rate-determining. Therefore, we can classify most homogeneous gold-catalyzed reactions into two categories: type I, when formation of the gold-$\sigma$-complex (stage 1 in Scheme 36) is the turnover limiting step; and type II, when the regeneration of cationic gold catalyst (e.g. protodeauration) from gold-$\sigma$-complex (stage 2) is the turnover limiting stage.

Most gold-catalyzed reactions actually are type II. This usually occurs when the nucleophile is relatively reactive and the substrate is an alkyne. The turnover limiting stage of a type II reaction is the regeneration of a cationic gold catalyst. Because this process involves the generation of cationic gold, an electron rich ligand capable of supplying electron density to the gold metal center should facilitate this process. And because protodeauration is the most common path for cationic gold regeneration, we used the protodeauration of a preformed gold complex as our model for the evaluation of ligand effects (Table 9).
For approximation purposes, the electron richness of a phosphine ligand was quantified using Tolman’s parameter, $\Sigma \chi_i$ ($i = 1$ to $3$). $\Sigma \chi_i$ corresponds to the combined effect of three groups attached to a phosphine center. A smaller number signifies higher electron density on the phosphine ligand. From Table 9 we can observe that the rates of protodeauration directly correlate to $\Sigma \chi_i$ for ligands with similar structural motifs (e.g. para-substituted phenyl groups) (Table 9, entries 1–4). When we switched the methyl substituent from the para position to the ortho position (Table 9, entry 5), the rate of protodeauration decreased even though the electron density of the ligands in entries 2 and 5 should have been similar. This discrepancy could be explained by an increase in steric hindrance. But when we replaced one phenyl ring in Ph₃P with an o-biphenyl group (Table 9, entry 6), the rate of protodeauration increased significantly, even though the electronic density was similar to that in entry 3.

Table 9: Ligand effects in the protodeauration of vinyl gold complex 1.

<table>
<thead>
<tr>
<th>ligand</th>
<th>$\Sigma \chi_i$</th>
<th>rel. rate</th>
<th>ligand</th>
<th>$\Sigma \chi_i$</th>
<th>rel. rate</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>10.5</td>
<td>4.7</td>
<td>5</td>
<td>10.8</td>
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<td>2</td>
<td>10.8</td>
<td>2.2</td>
<td>6</td>
<td>12.9</td>
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<tr>
<td>3</td>
<td>12.9</td>
<td>1.0</td>
<td>7</td>
<td>4.3</td>
<td>31</td>
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<tr>
<td>4</td>
<td>15</td>
<td>0.16</td>
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</tbody>
</table>
The increased steric hindrance should have reduced the rate of protodeauration, at least in theory. The combined effects of an \( o \)-biphenyl group and two electron donating groups (\( t \)-Bu) led to a very fast protodeauration (Table 9, entry 7).

The detailed mechanism for the \textit{ortho}-aromatic ring substitution-enhanced protodeauration is not yet clear. Our hypothesis is that during protodeauration—the process that generates the cationic gold center—the \textit{ortho}-phenyl ring may funnel small amounts of electronic density to the gold and therefore reduce the energy of the transition state (Figure 10a). Two notable findings are worth remarking: Widenhoefer and coworkers reported the formation of reversible off-cycle bis-Au-vinyl species,\textsuperscript{332-337} which are very resistant towards protodeauration; and Buchwald and coworkers’ development of phosphine ligands with an \( o \)-biphenyl dialkylphosphine backbone (e.g., JohnPhos, XPhos), widely used in transition metal catalysis.\textsuperscript{338-342} With the above findings as preamble, we hypothesized that two sterically demanding biaryls on the phosphine ligand could surround the gold center further and discourage the formation of bis-Au-vinyl species (Figure 10b).

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure10.png}
\caption{\textit{o}-Biphenyl group enhanced protodeauration.}
\end{figure}

In order to achieve a fast turnover in a type II gold-catalyzed reaction, we proposed the following guidelines for ligand design: i) create an electron rich phosphine center; ii) use \textit{ortho}-substitution to reduce catalyst deactivation and discourage the formation of off-
cycle bis-Au-vinyl species; iii) incorporate the o-biphenyl motif on a phosphine ligand to reduce the deactivation of cationic gold.\textsuperscript{328} According to Tolman’s phosphine ligand electronic effects study,\textsuperscript{331} the strongest electron donating groups in a phosphine ligand are substituted alkyl groups (e.g. $t$-Bu, Cy-). Hence, we will use these groups to create an electron rich phosphorus center. And because, in principle, we can introduce up to two o-biphenyl motifs (or other ortho-substituted structures) on a phosphine ligand, we can define two categories of ligands (Figure 11). Category 1 corresponds to mono-biphenyl ligands (mainly Buchwald-type ligands, many of which are commercially available). Category 2 corresponds to bis-biphenyl ligands, which can be made from commercial available materials in one-step.\textsuperscript{343}

Figure 11. Two categories of phosphine ligands.

In the literature, electron rich ligands such as N-heterocyclic carbene-based ligands (e.g. Nolan and Hashmi’s NHC ligands, Figure 12) have been used to achieve high turnover numbers.\textsuperscript{344,345} They all have a steric handle near the gold center. The success of these NHC ligands may be due to their electron rich nature and their steric handles. For our study though, we selected phosphine-based ligands because of their relatively easy synthesis and the ease by which we could manipulate their electron density and steric effects.
Thus, we designed ligand $L_1$ (Figure 13) featuring two electron-rich and sterically demanding *ortho*-biphenyl groups and one electron rich cyclohexyl group. We prepared $L_1$ in a single step from commercially available starting materials\textsuperscript{343} (shown in experimental section). The crystallographic structure of $L_1$-AuCl (Figure 13)\textsuperscript{346} demonstrated that the two *ortho*-biphenyl motifs were able to surround or embed the gold center.

A comparison between our new ligand $L_1$ and other benchmark ligands is shown in Table 10. We chose the carbene-based gold catalyst $L_4$ as a yardstick because of its proven efficiency towards gold-catalyzed reactions and the progress of these reactions was monitored by NMR experiment array. The details have been described in the experimental section. $L_1$ was the most reactive ligand (Table 10). A ligand with three $o$-
biphenyl motifs (L14) was less effective, probably because of its lower electronic density. The importance of the ligand electronic density on the rate of hydroamination became apparent when we kept the o-biphenyl motif unchanged and modulated the electron densities of the two remaining groups connected to phosphorus (L5 to L8). In this subset, electron richer ligands produced faster reaction rates. Substituting the o-biphenyl group with ferrocene decreased the reaction rate significantly (Table 10, L8 and L9). The merits of L1 were further assessed in other gold-catalyzed intermolecular and intramolecular reactions with C, N, or O nucleophiles so as to determine the reaction conditions needed to achieve the highest possible turnover for each of the reactions tested.

**Table 10. Relative rates of hydroamination for various ligands.**

We revisited the hydroamination reaction because it is a representative example of a C-N bond forming reaction where nitrogen is the nucleophile. Tanaka and coworkers reported an efficient gold-catalyzed intermolecular hydroamination of alkynes using the precatalyst PPh3AuCH3 in the presence of H3PW12O40 acting as acidic promoter.347 Using
an acidic promoter is appropriate in hydroamination because protodeauration is the rate limiting step.\textsuperscript{328} Shi and coworkers reported an even higher turnover using a Ph$_3$PAuOTf/benzotriazole/H$_3$PW$_{12}$O$_{40}$ system (Scheme 37-a).\textsuperscript{348} When we used Tanaka’s acidic promoter with our L1-AuCl precatalyst and the alkali salt of the bulky counterion CTf$_3^-$, we found that the catalytic loading could be reduced to 0.0025\% (25 ppm) and the reaction reached an impressive TON of 31200. To the best of our knowledge, no other catalyst system has matched this prowess at such low temperature (50°C). Our catalyst system also worked equally well in relatively larger scales (10 mmol).

We chose the gold-catalyzed intermolecular addition of N-hydroxyl benzotriazole 5-4 to an alkyne as our model system for O-H addition.\textsuperscript{349} We were able to reduce the catalytic loading to 0.1\% (Scheme 37-b). This result is a significant improvement over the original literature report (Scheme 37-b), which needed 5\% catalyst loading.

We also tested the intramolecular version of X-H addition to alkyne which is, in general, more efficient than the intermolecular version. For example, in the gold-catalyzed cyclization of homopropargylic diols,\textsuperscript{350,351} we observed that L1-AuCl needed only 20 ppm to yield 92\% of product 5-7 after 24h at room temperature (Scheme 37-c). This result was significantly better than the 2\% catalyst loading cited in the literature.\textsuperscript{350,351} L1-AuCl was also efficient in the intramolecular cyclization of 4-pentynoic acid 5-8 (Scheme 37-d), as demonstrated by the TON of 9900 achieved at room temperature. This result was far better than the available literature report (Scheme 37-d).\textsuperscript{352,353}
Since C-C bond formation is the most important class of reactions in synthesis, we studied several gold-catalyzed C-H additions to alkynes. We evaluated the Conia-ene reaction of β-ketoester 5-10 first\(^{354}\) (Scheme 38-a). Again, L1-AuCl worked very well in this reaction: it needed only 0.004% (40 ppm) catalyst loading at room temperature to
furnish the product in 95% yield. The use of an acidic promoter enhanced the reactivity, just as in the case in the hydroamination reaction described earlier.

Scheme 38. C-H additions to alkynes (C-C bond formations).

L1-AuCl also worked well in the intermolecular version of the Conia-ene reaction (Scheme 38-b); very good to excellent yields could be achieved in this reaction using low catalyst loadings in the presence of a co-catalyst–Ga(OTf)₃.³⁵⁵-³⁵⁷ L1-AuCl also
performed efficiently in the synthesis of α-pyrone (Scheme 38-c). We obtained the pyrone product 5-15 in 95% yield at 50°C using a catalyst load of only 0.05% (500 ppm) whereas the corresponding reaction cited in the literature needed a 5% loading. We reduced the catalyst loading to 0.02% (200 ppm) and still managed to obtain a respectable 80% yield (Scheme 38c). To broaden the applicability of our gold catalyst L1-AuCl, we chose another example of a C-H addition to an alkyne, namely the hydroarylation of 5-16 (Scheme 38-d). The product, 2H-chromene 5-17, was obtained in 95% yield at room temperature using a catalyst loading of 0.05% (500 ppm).

Scheme 39. Enyne and allenone cycloisomerization.

Enyne cycloisomerization is a class of reactions where gold catalysis has proved its might. Using 1,6- enyne 5-18 as model substrate, we found that our gold catalyst needed only a loading of 0.02% (200 ppm) to drive the enyne cycloisomerization to completion, furnishing 5-19 in almost quantitative yield (Scheme 39-a). In contrast, a similar reaction reported in the literature needed a 2% catalyst loading. We also investigated the cycloisomerization of allenone 5-20, first reported by Hashmi and
coworkers and later refined by Che and coworkers (Scheme 39-b). Using 0.01% (100 ppm) of our catalyst L1-AuCl, we obtained the desired furan 5-21 in quantitative yield after 7 h at room temperature. This result corresponded to a TON of 10,000.

### 5.3 Conclusions

In summary, we have developed a highly efficient and broadly applicable cationic gold catalyst system that is highly efficient at extremely low loadings and relatively low temperatures. The optimal catalyst (L1AuCl) is now available from Aldrich under the name BisPhePhos XD gold(I) chloride (catalog no. L511846). This new gold catalyst gives high turnover numbers (or low gold catalyst loading) that are in the ppm range, at room temperature or slightly elevated temperatures (≤ 50°C). These results should help to turn gold catalysis into the tool of choice for larger-scale synthesis. The work described in this chapter is in press *Angew. Chem. Int. Ed.* **2014**, 53, 4456-4459.

### 5.4 Experimental

#### General

$^1$H and $^{13}$C NMR spectra were recorded at 500 MHz and 126 MHz (or 400 MHz and 101 MHz) respectively, using CDCl$_3$ as a solvent. The chemical shifts are reported in δ (ppm) values ($^1$H and $^{13}$C NMR relative to CHCl$_3$, δ 7.26 ppm for $^1$H NMR and δ 77.0 ppm for $^{13}$C NMR and CFCl$_3$ (δ 0 ppm for $^{19}$F NMR), multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), h (hextet), m (multiplet) and br (broad). Coupling constants ($J$), are reported in Hertz (Hz). All reagents and solvents were employed without further purification. The products were purified using a commercial
flash chromatography system or a regular glass column. TLC was developed on silica gel 60 F254 aluminum sheets. KCTf₅ was purchased from Synquest Labs. All other chemicals like metal catalysts and ligands were purchased from Aldrich, Alfa Aesar or Strem.

**General procedure for the synthesis of Ligand L1**

Under argon, diethyl ether (140 mL) was added to a reaction flask followed by the addition of 2-bromo-2’,6’-diisopropoxy-1,1’-biphenyl (11.08 mL, 38.8 mmol). The flask was cooled in an ice bath, n-butyllithium (20 mL, 2.5 M, 50 mmol) was added slowly and the reaction mixture was stirred for 30 minutes at 0°C. Dichlorophosphane (3.0 mL, 19.4 mmol) was added to the reaction mixture slowly and the mixture was warmed to room temperature and left stirring at room temperature for 48 h. The reaction was quenched with water and was extracted by diethyl ether (2x100 mL). The combined organic layer was dried on sodium sulphate. The solvent was evaporated to yield a viscous oil which was further purified by column chromatography using hexane:ethyl acetate (100:1) solvent system to yield semisolid which was recrystallized/triturated with methanol to yield a white solid 3.9 gram (30%).
Synthesis of gold complexes (L-AuCl)

All gold complexes (L-AuCl) were synthesized using a slightly modified version of a literature method. These complexes were prepared via either one of the following general procedures:

Method 1: Sodium tetrachloroaurate(III) dihydrate (1 mmol) was dissolved in water, and the orange solution was cooled in ice. To this solution, 2,2’-thiodiethanol (3 mmol) was slowly added (ca. 10 min) with stirring. After stirring at 0°C for another 30 min, a solution of the phosphine ligand (1 mmol) in EtOH (if the ligand could not be dissolved, more EtOH was used) was added dropwise to yield a white solid. The solid was filtered off, washed with water followed by EtOH, and ultimately dried in vacuum.

Method 2: In a vial Chloro(dimethylsulfide)gold(I) (1 mmol) was dissolved in dichloromethane and cooled in an ice bath. A solution of phosphine ligand (1 mmol) in dichloromethane was added dropwise, and the resulting solution was allowed to warm to room temperature and stirred at room temperature for 3 h. After TLC indicated complete consumption of the starting material, the reaction solution was concentrated to dryness under reduced pressure, and the gold complex product was further dried under high vacuum.

General procedures for model reactions

Preparation of stock solutions

Because our gold precatalyst and silver activators were used at very low loading, we prepared the corresponding stock solutions.
Preparation of cationic gold (L-AuCl) stock solution.
Stock solution of L-AuCl (0.01 M) was prepared by dissolving L-AuCl (0.02 mmol) in CDCl₃ (2 mL). The solution was kept in the freezer (-20°C) until it was needed.

Preparation of stock solutions of silver activators (AgOTf and AgSbF₆).
Stock solutions of silver triflate and silver hexafluoroantimonate (0.01 M) were prepared by weighing AgOTf or AgSbF₆ (0.02 mmol) in a glass vial and dissolved it in deuterated acetone (2 mL). The solution was kept in the freezer (-20°C) until it was needed.

Preparation of cationic gold (L-Au⁺X⁻) stock solution.
Standard stock solutions of cationic gold catalyst were prepared by weighing the L-AuCl complex (0.02 mmol) in a vial and adding the corresponding deuterated solvent (usually CDCl₃) (2 mL), followed by 1.2 equiv. of silver activator. The vial was sonicated for 5-10 min at 5-10 °C, then it was centrifuged and the clear solution was transferred to a clean glass vial with a screw cap. The solution was kept in freezer (-20°C) until it was needed.

General procedure for the formation of imine (5-2)
AgOTf stock solution (60 μL, 0.01M, 0.0125 mol%) was introduced into a reaction vial and the solvent in the stock solution was evaporated under vacuum. Then a mixture of aniline (5 mmol) and phenylacetylene (6 mmol) containing H₃PW₁₂O₄ (5.0 mg, 0.03 mol%) and KCTf₃ (6.0 mg, 0.26 mol%) was added to the vial. The stock solution of L₁-AuCl in CDCl₃ (12.5 μL, 0.01M, 0.0025 mol%) was added to the reaction mixture and the reaction was heated at 50 °C. An aliquot (ca. 3 μL) from reaction mixture was dissolved in CDCl₃ (0.5 mL) and was analyzed by ¹H-NMR to monitor the progress of the reaction.
General procedure for larger scale (10 mmol) synthesis of imine (5-2)

To a mixture of aniline (10 mmol) and phenylacetylene (12 mmol), H$_3$PW$_{12}$O$_4$ (10 mg, 0.03 mol%) and KCTf$_3$ (12 mg, 0.26 mol%) were added to the vial. The stock solution of L1-AuCl in CDCl$_3$ (25 μL, 0.01M, 0.0025 mol%) was added to the reaction mixture and the reaction was heated at 50 °C. An aliquot (ca. 3 μL) from the reaction mixture was dissolved in CDCl$_3$ (0.5 mL) and was analyzed by $^1$H-NMR to monitor the progress of the reaction.

General procedure for synthesis of 5-5 via addition of benzotriazole 5-4 to alkyne.

AgOTf stock solution (100 μL, 0.01M) was introduced into a reaction vial and the solvent in the stock solution was evaporated under vacuum. Then 1-octyne (118 μL, 0.8 mmol), benzotriazole 5-4 (27.02 mg, 0.2 mmol), and deuterated chloroform (0.5 mL) were added followed by the addition of stock solution of L1-AuCl (20 μL 0.01M, 0.1 mol%). The reaction was sonicated for a minute and stirred at room temperature; the progress of the reaction was monitored by NMR.

General procedure for the cyclization of homopropargylic diols (5-6)

To a solution of homopropargylic diol 5-6 (22.64 μL, 0.1 mmol) in CDCl$_3$ (0.48 mL) inside a NMR tube, KCTf$_3$ (1.0 mg, 2 mol%) was added. The NMR tube was sonicated for 1-2 minute and the stock solution of AgSbF$_6$ (0.01 M, 0.01 mol%) was added and the solution was sonicated, followed by the addition of stock solution of L1-AuCl (2 μL, 0.001M, 0.002 mol%). The resulting mixture was further sonicated for 15-20 minutes at rt and the progress of reaction was monitored by $^1$H NMR.
General procedure for the intramolecular cyclization of 4-pentynoic acid (5-8)

To a solution of 4-pentynoic acid 5-8 (19.62 mg, 0.2 mmol) in CDCl₃ (0.48 mL), KCTf₃ (1.0 mg, 2 mol%) was added. The NMR tube was sonicated for 1-2 minute and the stock solution of AgOTf (0.01 M, 0.06 mol%) was added and the solution was sonicated; this was followed by the addition of stock solution of L1-AuCl (2 μL, 0.01M, 0.01 mol%). The solution was further sonicated for 15-20 minutes at rt and the progress of reaction was monitored by ¹H NMR. (Note: commercially available reactant contained hydrolyzed product as impurity).

General procedure for the Conia-ene reaction of β-ketoester (5-10)

To a solution of β-ketoester 5-10 (9.81 μL, 0.05 mmol) in CDCl₃ (0.48 mL), and stock solution of AgOTf (0.01 mol%), HOTf (0.01 mol%) was added and the solution was sonicated, followed by the addition of stock solution of L1-AuCl (2 μL, 0.001M, 0.004 mol%). The solution was further sonicated for 15-20 minutes at rt and the progress of reaction was monitored by ¹H NMR.

General procedure for the Nakamura reaction of 1,3-diketone (5-12)

To a vial containing acetyl acetone 5-12 (103.2 μL, 1.0 mmol), phenyl acetylene (219.6 μL, 2.0 mmol), Ga(OTf)₃ (26 mg, 5 mol%), L1-AuCl (50 μL (0.01M), 0.05 mol%) was added and the reaction was heated to 45°C and the progress of the reaction was monitored by ¹H NMR.

General procedure for the cyclization of propiolate (5-14)

To a solution of propiolate 5-14 (12.8 μL, 0.05 mmol) in CDCl₃ (0.48 mL), a stock solution of AgSbF₆ (0.1 mol%) was added and the solution was sonicated; the addition of
stock solution of \textbf{L1-AuCl} (10 μL, 0.001M, 0.02 mol\%) followed. The resulting mixture was sonicated for 15 minutes, heated to 50 °C and the progress of the reaction was monitored by \textsuperscript{1}H NMR.

**General procedure for the hydroarylation of alkynes (5-16)**
A stock solution of AgSbF\textsubscript{6} (0.25 mol\%) was added to a NMR tube and the solvent was evaporated under vacuum. CDCl\textsubscript{3} (0.48 mL) was added into the tube followed by the addition of \textbf{5-16} (23.48 μL, 0.2 mmol). Finally, the stock solution of \textbf{L1-AuCl} (10 μL, 0.01M, 0.05 mol\%) was added. The solution was sonicated for 10 minutes at rt and the progress of the reaction was monitored by \textsuperscript{1}H NMR.

**General procedure for the enyn cycloisomerization of 1,6- enyne (5-18)**
To a solution of 1,6- enyne \textbf{5-18} (42.04 μL, 0.2 mmol) in CDCl\textsubscript{3} (0.48 mL), a stock solution of AgSbF\textsubscript{6} (0.1 mol\%) was added followed by the addition of stock solution of \textbf{L1-AuCl} (4.0 μL, 0.01M, 0.02 mol\%). The solution was sonicated for 15-20 minutes at rt and the progress of the reaction was monitored by \textsuperscript{1}H NMR.

**General procedure for the cycloisomerization of allenone (5-20)**
To a solution of allenone \textbf{5-20} (23.4 mg, 0.1 mmol) in CDCl\textsubscript{3} (0.48 mL), KCTf\textsubscript{3} (1.0 mg, 2 mol\%) was added. The NMR tube was sonicated for 1-2 minute before a stock solution of AgOTf (0.05 mol\%) was added, the solution was sonicated again; this was followed by the addition of stock solution of \textbf{L1-AuCl} (1.0 μL, 0.01M, 0.01 mol\%). The solution was then sonicated for 15-20 minutes at rt and the progress of reaction was monitored by \textsuperscript{1}H NMR.
Monitoring of reactions using *in situ* NMR spectroscopy

When $^1$H NMR was used to monitor the progress of a reaction, a solution of tetramethylsilane in CDCl$_3$ (sealed in a capillary tube) was used as external standard for NMR integration. In some cases, 1,3,5-tri-tert-butylbenzene (internal standard) was used. The reactions were monitored with $^1$H NMR (single pulse or 1 scan for fast reactions, 8 scans for slow reactions). Some NMR measurements were conducted using a NMR experiment array (a series of spectra measured at predetermined time intervals over a period of time by adjusting the pre-acquisition delay). NMR experiment array gives better precision for both concentration (*via* integration) and reaction time, because each measurement is conducted at almost identical shimming and temperature conditions.

**Spectroscopic data of ligand L1 and L1AuCl:**

**L1**: white solid; $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 0.60-0.85 (6H, m), 0.98-1.0 (6H, d, $J$ = 6.0 Hz), 1.02-1.03 (6H, d, $J$ = 6.0 Hz), 1.13-1.15 (6H, d, $J$ = 6.0 Hz), 1.19-1.21 (6H, d, $J$ = 6.0 Hz), 1.28-1.48 (5H, m), 4.24-4.31 (2H, m), 4.40-4.49 (2H, m), 6.39-6.41 (2H, d, $J$ = 8.8 Hz), 6.47-6.49 (2H, d, $J$ = 8.0 Hz), 7.05-7.14 (6H, m), 7.19-7.23 (2H, m), 7.41-7.43 (2H, m); $^{13}$C NMR (CDCl$_3$, 101 MHz) $\delta$ 21.8, 22.0, 22.4, 26.3, 27.7 (d, $J$ = 9.6 Hz), 29.4 (d, $J$ = 9.5 Hz), 35.1 (d, $J$ = 19.7 Hz), 69.2, 69.7, 104.4, 105.0, 122.2, 124.9, 126.2, 127.7, 131.4, 135.5, 139.5 (d, $J$ = 23.5 Hz), 140.8 (d, $J$ = 25.1 Hz), 156.2, 156.4; $^{31}$P NMR (CDCl$_3$, 161 MHz) $\delta$ 5.43. HRMS (ESI) Calcd. for C$_{42}$H$_{54}$O$_4$P (M+H)$^+$ 653.3760, found 653.3755.

**L1-AuCl**: White solid; $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 0.66-0.76 (m, 2H), 0.82-0.90 (m, 1H), 0.94-1.04 (m, 2H), 1.05-1.07 (d, $J$ = 6 Hz, 6H), 1.12-1.13 (d, $J$ = 6 Hz, 6H), 1.16-1.17 (d, $J$ = 6.4 Hz, 6H), 1.19-1.21 (d, $J$ = 6 Hz, 6H), 1.36-1.45 (m, 3H), 1.60-1.66 (m,
2H), 1.82-1.91 (m, 1H), 4.41-4.53 (m, 4H), 6.56-6.58 (d, J = 8.4 Hz, 4H), 6.99-7.03 (m, 2H), 7.14-7.18 (m, 2H), 7.29-7.34 (m, 4H), 7.51-7.56 (m, 2H); ¹³C NMR (CDCl₃, 101 MHz) δ 21.9 (d, J = 4.1 Hz), 22.5 (d, J = 15.1 Hz), 25.7, 26.9 (d, J = 15.2 Hz), 31.2, 36.5 (d, J = 33.4 Hz), 69.9, 70.4, 105.8, 106.4, 121.0, 125.8 (d, J = 10.1 Hz), 129.3, 129.4, 131.6, 132.1, 132.6 (d, J = 8.6 Hz), 136.3 (d, J = 10.7 Hz), 140.7 (d, J = 11.2 Hz), 156.3, 156.7; ³¹P NMR (CDCl₃, 161 MHz) δ 38.19. HRMS (ESI) Calcd. for C₄₂H₅₃AuClNaO₄P (M+Na)⁺ 907.2933, found 907.2926.
$^{1}H$, $^{13}C$ and $^{19}F$ spectra of ligand L1 and array experiment.
Monitoring of hydroamination of 5-1

\[
\text{5-1} + \text{PhNH}_2 \xrightarrow{\text{L7-AuCl/AgOTf (1%)}} \text{rt, CDCl}_3 \xrightarrow{} \text{5-2}
\]
CONCLUSION

During the course of this work, we studied the gold-catalyzed intramolecular or intermolecular cyclizations involving oxonium intermediates and developed the gold-catalyzed oxygen-transfer reactions of 2-alkynyl-1,5-diketones or 2-alkynyl-5-ketoesters to furnish five-membered rings bearing a quaternary carbon tethered to a carbonyl group. Various aromatic or aliphatic groups substituted 2-alkynyl-1,5-diketones or 2-alkynyl-5-ketoesters underwent cyclization in good yields under very mild conditions. The detailed mechanistic investigation of this cycloisomerization was performed on the proposed intramolecular [4+2] cycloaddition mechanism by means of $^{18}$O isotopic labeling experiments and quantum chemical calculations. Both experimental and computational results corroborated the intramolecular [4+2] cycloaddition of a gold-containing furanium intermediate to a carbonyl group. Furthermore, the reactivity of alkynylenolate was investigated in the reactions of allenic ketones and vinyl ketones which lead towards the versatile synthesis of 2-alkynyl-1,5-diketones, 4-alkynyl-3-hydroxycyclohexones and 4-alkynylylcyclohexenones analogs in moderate to good yields. While exploring the gold-catalyzed annulations of 2-alkynyl benzaldehyde with acyclic or cyclic vinyl ethers, an approach for the synthesis of acetal-tethered dihydronaphthalene, isochromenes and bicyclo[2.2.2]octane derivatives under mild conditions was developed and these derivatives are often found in biologically active molecules and natural products.
In order to combat the decay of the active cationic gold catalyst, which accounts for the high catalytic loading in these transformations, a modular approach has been developed for the effective catalyst design in gold catalysis to address the limitation of high catalyst loading. A highly efficient and broadly applicable cationic gold catalyst system has been successfully designed and developed and it works at extremely low catalytic loadings and relatively low temperatures. This new gold catalyst displayed high turnover numbers using mild reaction conditions, that is, room temperature or slightly elevated temperatures ($\leq 50^\circ$C) which would be highly desirable for the successful application of gold catalysis towards practical synthesis. This catalyst is now commercialized by Aldrich Chemicals under the name BisPhePhos XD gold(I) chloride (catalog no. L511846). In order to gain further insight into the ligand effects in gold catalysis, the quantum chemical model could be a useful tool to predict the electronics, which can guide in designing more efficient catalytic systems. In the future, we will focus our attention on exploring the application of ligand L1 in other metal catalysis such as palladium catalyzed Suzuki coupling, aminations and fluorinations.
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(346) Cambridge Crystallographic Data Centre (CCDC) depository # 973355.


(359) The use of AgOTf is less effective in our catalytic system.


APPENDIX-1

LIST OF ABBREVIATIONS

DCM: Dichloromethane
DMSO: Dimethyl sulfoxide
THF: Tetrahydrofuran
ESI-MS: Electrospray Ionization mass spectrometry
EtOAc: Ethyl Acetate
GC: Gas Liquid Chromatography
h: Hour
HOMO: Highest occupied molecular orbital
HRMS: High resolution mass spectroscopy
Hz: Hertz
$^{18}$O: 18 Oxygen
IR: Infrared
LDA: Lithium diisopropylamide
LUMO: Lowest unoccupied molecular orbital
M: Molar
mg: milligram
min: minute
mL: milliliter
mmol: millimole
m/z: mass to charge ratio
NMR: Nuclear magnetic resonance spectroscopy

\( \alpha \): alpha
\( \beta \): beta
\( \gamma \): gamma
\( \delta \): delta
\( \zeta \): zeta
\( o \): ortho
\( m \): meta
\( p \): para
\( tert \): tertiary

ppm: Parts per million

L: Ligand

PTSA: \( p \)-Toluene sulfonic acid

RT: Room temperature

MVK: Methyl vinyl ketone

AgOTf: Silver triflate

AgSbF\(_6\): Silver hexafluoroantimonate

TBAF: Tetra-\( n \)-butylammonium fluoride

TBAB: tetrabutylammonium bromide

TfOH: Trifluoromethanesulfonic acid

TLC: Thin layer chromatography

NHC: N-Heterocyclic carbene

NTf\(_2\): bis(trifluoromethanesulfonyl)imide

Nu: Nucleophile

Cy: Cyclohexyl

TON: Turnover number

TOF: Turnover frequency
APPENDIX-2

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- Maintained electronic laboratory notebook (eLNB) in accordance with company code while working at GSK.
- Proficient in using research database softwares such as SciFinder and Reaxys.
- Trained and mentored undergraduate and new graduate students.
- Presenting theoretical topics and scientific research at group meetings, chemistry department, regional and national meetings.
- Personal skills include collaboration, organization, good verbal and written communication skills.

**AWARDS AND ACHIEVEMENTS**
- Awarded University of Louisville Sponsored Research Award in Spring 2014.
- Travel award from IMD-3 (Institute of Molecular Diversity and Drug Design) to present talk in 245<sup>th</sup> ACS (American Chemical Society) National meeting held in New Orleans, Louisiana in Fall 2013.
- Prestigious IMD-3 (Institute of Molecular Diversity and Drug Design) Graduate Research Fellowship award in Fall 2011-2012.
- Received Graduate Fellowship from Department of Chemistry, University of Louisville in Fall 2009-2010.
- University of Louisville Graduate Student Association Travel Award for attending 42<sup>nd</sup> ACS Regional Meeting, held at Indianapolis, Indiana in June 2010.
- Bronze Recognition Award by GlaxoSmithKline for “Synthesis of key compounds for S1P1 program. In particular developing SAR around simplified C ring Analogues”’ in Aug. 2008.
- In conjunction with Bronze Award as part of the GSK R&D (Research and Development) Recognition Program, received a cash reward in the amount of £150.
- Awarded **Junior Research Fellowship** with CSIR (Council of Scientific and Industrial Research) ranking in “CSIR-UGC” National Eligibility Test (NET) conducted by UGC (University Grants Commission) & CSIR, a funding agency of Government of India in 2007.
- **Lectureship (NET)** ranking in Chemical Sciences conducted by CSIR-UGC, India in 2006.
- Awarded the prestigious “**University Rank Holder**” MHRD (Ministry of Human Resource Development)-UGC Post graduate Merit Scholarship (2005-2007).
- Ranked 2nd in Panjab University, Chemistry department, India in 2005.
- Indira Gandhi Scholarship for Post graduate studies (2005-2007).
- Ranked 2nd in Panjab University, Chemistry department, India in 2007.

**RESEARCH PUBLICATIONS**


**PRESENTATIONS/POSTERS**

Meeting, Indianapolis, Indiana on 10th September, 2013-Poster Presentation (ORGN-383).
7. Deepika Malhotra “Use of new technologies for the synthesis and purification of drug molecules” at UKIERI and GSK meet held at Foreign & Commonwealth office held at London, United Kingdom on 21st February, 2008-Poster Presentation.
8. Deepika Malhotra and Tej Vir Singh “Alternatives of CFC’s” at 1st Chandigarh Science Congress held at Panjab University, Chandigarh, India-Poster Presentation.

**PROFESSIONAL MEMBERSHIPS:**
American Chemical Society (ACS)
Division of Organic Chemistry.