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Huey-San Melanie Siah

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Development of Au(I) Cycloadditions, Trifluoromethylation and Novel Au(I) Complexes

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Trondheim, May 2020

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My Australian and Norwegian families have been incredibly supportive through all the years despite not understanding much of what I work with. They mostly think I do reverse alchemy and turn gold into useless things, which I don't contest.

Most of all, I am thankful to Anders for everything he does on the home front. It goes without saying that this thesis would not have been possible without his unfailing support and patience. I look forward to coming home to you and our two wonderful children every day.

Melanie Siah

Trondheim, May 2020

Table of Contents

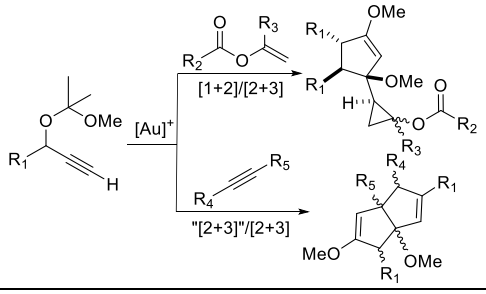
Acknowledgements i
Table of Contents iii
Graphical Abstract vi
Abstract vii
Publications and Contributions viii
Abbreviations x
Preface xii
1 Introduction 1
1.1 The inception of gold catalysis 1
1.2 Gold in homogeneous catalysis 3
1.3 Gold(I) catalysts 4
1.3.1 Gold(I) salts 4
1.3.2 Cationic gold(I) complexes 4
1.3.3 Ligand types 5
1.3.4 Chiral Gold(I) complexes 5
1.3.5 σ,π-Dual gold Au(I) complexes 7
1.3.6 Gold(I)-nitrone complexes 7
1.4 Gold(III) catalysts 7
1.5 Gold(I)-catalysed reactions 8
1.5.1 Gold(I)-catalysed transformations of alkynes 8
1.5.2 Propargyl substrates in gold catalysis 8
1.5.3 Electrophilic fluorine reagents in gold-catalysed reactions 12
2 Gold(I)-catalysed tandem cycloadditions of terminal propargyl acetals with C-C bonds 13
2.1 General introduction 13
2.2 Gold(I)-catalysed [1+2]/[2+3] tandem cycloadditions between propargyl acetals and vinyl esters 14
2.2.1 Initial studies 14
2.2.2 Proposed mechanism 15
2.2.3 Substrate scope 16
2.3 Gold(I)-catalysed "[2+3]"/[2+3] tandem cycloadditions between propargyl acetals and alkynes 18

2.3.1 Initial studies 18
2.3.2 Proposed mechanism 19
2.3.3 Substrate scope 20
2.3.4 NMR studies of tandem cyclisation product **4** 23
2.3.5 NOESY correlations of tandem cyclisation product **4** 24
2.3.6 NMR studies and NOESY correlations of regioisomer **6** 25
2.4 General remarks 26
3 Gold(I)-catalysed cycloadditions of non-terminal propargyl acetals with gold(I)-nitrone complexes 28
3.1 General introduction 28
3.2 Chiral gold(I)-nitrone complexes 28
3.3 Gold(I)-catalysed cycloadditions of non-terminal propargyl acetals 29
3.4 General remarks 31
4 Gold(I)-catalysed trifluoromethylation of terminal alkynes with Togni's reagent 33
4.1 General introduction 33
4.2 Initial studies 33
4.3 Optimisation studies and substrate scope 35
4.4 Proposed mechanism 36
4.4.1 Generation of the active catalytic dual gold species 37
4.4.2 LAu^+ fragment transfer to free alkyne and addition-elimination of Togni-H 38
4.5 General remarks 39
5 Novel σ,π-dual gold(I) complexes: preparation and catalytic activity 40
5.1 General introduction 40
5.2 Synthesis of JohnPhos dual gold(I) complexes 41
5.3 Synthesis of chiral bridged dual gold(I) complexes 42
5.4 Reactivity of JohnPhos dual gold(I) complexes in propargyl reactions 44
5.5 Reactivity of MeO-BIPHEP dual gold(I) complexes in propargyl reactions 45
5.6 General remarks 46
6 Catalytic studies of cyclometallated gold(III) complexes and a related MOF 48
6.1 General introduction 48
6.2 Synthesis of cyclometallated Au(III) complexes and UiO-67-[Au]Cl MOF 48
6.3 Reactivity of gold(III) catalysts in propargyl ester cyclopropanation 48
6.4 General remarks 50
7 Concluding Remarks 51

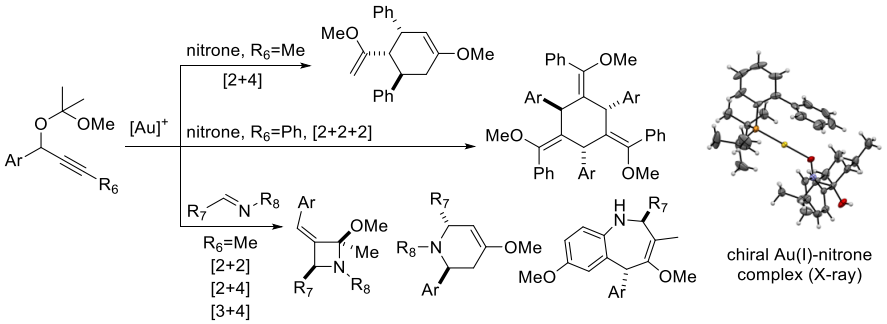
8 References 52
9 Appended Papers 69
PAPER I 71
PAPER II 105
PAPER III 133
PAPER IV 151
PAPER V 171
PAPER VI 203

Graphical Abstract

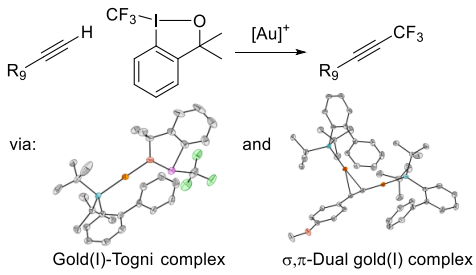
CHAPTER 2
GOLD(I)-CATALYSED REACTIONS OF TERMINAL PROPARGYL ACETALS



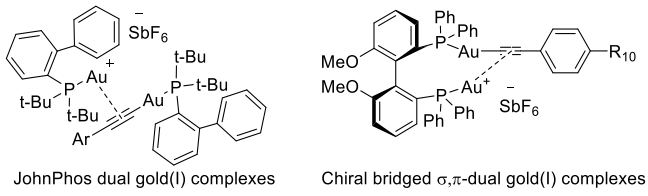
CHAPTER 3
GOLD(I)-CATALYSED REACTIONS OF NON-TERMINAL PROPARGYL ACETALS



CHAPTER 4
GOLD(I)-CATALYSED TRIFLUOROMETHYLATION OF TERMINAL ALKYNES



CHAPTER 5
σ,π-DUAL GOLD(I) COMPLEXES



CHAPTER 6
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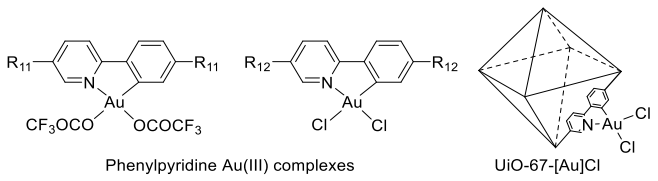


Abstract

The field of gold(I)-catalysed reactions in organic chemistry has been expanding rapidly in the last two decades. Gold catalyses a diverse range of transformations and is especially useful in the activation of triple bonds toward nucleophilic attack.

Gold(I)-catalysed reactions of highly reactive terminal propargyl acetals are a source of new chemistry due to novel electron-rich intermediates. Reactions between terminal propargyl acetals and vinyl esters underwent a unique [1+2]/[2+3] tandem cyclisation to give cyclopentene-cyclopropane tethered rings (yields up to 77%). Reactions of terminal propargyl acetals with alkynes produced novel fused bicyclic cyclopentene structures by a "[2+3]"/[2+3] tandem cyclisation (yields up to 60%).

Building on previous knowledge of gold(I)-nitrone chemistry, chiral nitrones were synthesised and their ability to tune gold(I) catalyst activity in reactions of non-terminal propargyl acetals was explored. NMR studies were conducted on chiral gold(I)-nitrone complexes. The crystal structure (X-ray) was obtained for one complex, which showed coordination of the chiral nitrone to gold(I) through the oxygen atom. The chemistry of non-terminal propargyl acetals was found to give a diverse range of cycloaddition products, involving several reactive intermediates. Interestingly, reaction of non-terminal propargyl acetals and imines gave heterocyclic products via gold(I)-catalysed [2+2], [2+4] and [3+4] cycloaddition reaction pathways.

Development of new methods for the introduction of trifluoromethyl groups is interesting; these groups can impart specific, pharmaceutically significant properties to compounds. Electrophilic trifluoromethyl reagents were combined with a gold(I) catalyst for the first time and a novel method of trifluoromethylation of terminal alkynes was developed (yields up to 46% with 12.5% active gold complex). Even more interesting was the discovery that the reaction pathway involved a gold(I)-Togni complex coordinated through the oxygen atom and a catalytically active dual gold(I) complex generated with the terminal alkyne substrate. Both these complexes were confirmed through X-ray crystallography and NMR studies.

Following the discovery that dual gold(I) complexes are catalytically active species, a series of JohnPhos dual gold(I) complexes was synthesised and their catalytic activity studied in known propargyl reactions. Furthermore, novel chiral bridged dual gold(I) complexes based on the (*R*)-MeO-BIPHEP ligand were generated. These chiral complexes were active in several propargyl reactions, and moderate enantioselectivity was observed by chiral HPLC (up to 52%).

The development of new and stable gold catalysts for use in organic tranformations continues to be of interest. Gold(III) complexes are rarely used in propargyl chemistry and the integration of ligated Au(III) complexes into metal-organic frameworks for use in heterogeneous chemistry has received little attention. A series of cyclometallated Au(III) complexes and the first phenylpyrimidine gold(III) MOF (synthesised by PhD candidate Volodymyr Levchenko, UiO) were shown to catalyse propargyl ester cyclopropanation (up to quantitative yields).

The work presented contributes to the understanding of propargyl substrates in gold(I)-catalysed reactions, explores the possibilities of gold(I)-catalysed trifluoromethylation and investigates the reactivity of dual gold(I) and gold(III) catalysts in the chemistry of propargyl substrates.

Publications and Contributions

Scientific Publications

Paper I
Gold(I)-Catalysed Tandem Cyclisation of Propargyl Acetals and Vinyl Esters
Siah, Huey-San Melanie; Kaur, Maya; Iqbal, Naseem; Fiksdahl, Anne*
European Journal of Organic Chemistry, 2014, Issue 8, 1727-1740.

Paper II
Gold(I)-catalysed tandem cyclization of propargyl acetals and alkynes
Siah, Huey-San Melanie; Hogsnes, Morten Christian; Iqbal, Naseem; Fiksdahl, Anne*
Tetrahedron, 2016, Volume 72, Issue 8, 1058-1068.

Paper III
Dual-gold(I)-generated trifluoromethylation of terminal alkynes with Togni's reagent
Siah, Huey-San Melanie; Fiksdahl, Anne*
Journal of Fluorine Chemistry, 2017, Volume 197, 24-33.

Paper IV
Development and catalytic activity of novel achiral and chiral σ,π-dual gold(I) complexes
Siah, Huey-San Melanie; Fiksdahl, Anne*
European Journal of Organic Chemistry, 2020, Issue 3, 367-377.

Paper V
Au(I)-catalysed cycloaddition pathways of non-terminal propargyl substrates
Siah, Huey-San Melanie; Jónsson, Helgi Freyr and Fiksdahl, Anne*
Synthetic Communications, *Manuscript accepted.*

Paper VI
Catalytic activity of cyclometallated gold(III) complexes and their related MOF
Levchenko, Volodymyr A.; Siah, Huey-San Melanie; Øien-Ødegaard, Sigurd; Fiksdahl, Anne and Tilset, Mats*
Molecular Catalysis, *Manuscript submitted.*

Conference Contributions

OKV28 – Organic Chemistry Winter Meeting 2013, Skeikampen, Norway
Poster: *Strategies to 9-Substituted-8-oxoadenines*
Huey-San Melanie Siah and Lise-Lotte Gundersen

7th International Gold Conference, Cardiff, Wales, 2015
Poster: *Propargyl Acetals; Versatile Substrates for a Diverse Range of Au(I)-Catalysed Cycloaddition Reactions*
Huey-San Melanie Siah, Sigvart Evjen and Anne Fiksdahl

OKV31 – Organic Chemistry Winter Meeting 2016, Skeikampen, Norway
Poster: *Studies of Au(I)-Catalysis in Trifluoromethylation*
Huey-San Melanie Siah and Anne Fiksdahl

4th Nordic Meeting on Organometallic Chemistry, 2016, Reykjavík, Iceland
Poster: *Studies of Au(I)-Catalysis in Trifluoromethylation*
Huey-San Melanie Siah and Anne Fiksdahl

OKV32 – Organic Chemistry Winter Meeting 2017, Skeikampen, Norway
Oral presentation: *Dual Gold(I)-generated Trifluoromethylation of Terminal Alkynes*
Huey-San Melanie Siah and Anne Fiksdahl

OKV34 – Organic Chemistry Winter Meeting 2019, Skeikampen, Norway
Poster: *σ,π-Dual gold complexes*
Huey-San Melanie Siah and Anne Fiksdahl

OKV35 – Organic Chemistry Winter Meeting 2020, Skeikampen, Norway
Poster: *Preparation and catalytic activity of novel σ,π-dual gold(I) acetylide complexes*
Huey-San Melanie Siah and Anne Fiksdahl

Abbreviations

Ac	Acetate
BAr^F_4	Tetrakis[3,5-bis(trifluoromethyl)phenyl]borate
Bz	Benzoyl
ccc	*cis-cis-cis*
cct	*cis-cis-trans*
CF_3	Trifluoromethyl
$^+CF_3$-reagent	Electrophilic trifluoromethylation reagent
conv.	Conversion
ctc	*cis-trans-cis*
ctt	*cis-trans-trans*
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DMSO	Dimethyl sulfoxide
DIPEA	*N*,*N*-Diisopropylethylamine (Hünig's base)
DGC	Dual gold complex
de	Diastereomeric excess
equiv.	Equivalent(s)
ee	Enantiomeric excess
GLC	Gas-liquid chromatography
h	hour(s)
HPLC	High-performance liquid chromatography
HRMS	High-resolution mass spectroscopy
JohnPhos	(2-Biphenyl)di-tert-butylphosphine
Me	Methyl
MOF	Metal-organic framework
MW	Microwave heating
NHC	*N*-Heterocyclic carbene

NMR	Nuclear magnetic resonance
NOESY	Nuclear Overhauser Effect Spectroscopy
NPs	Nanoparticles
OAc^F	$OCOCF_3$
IS	Internal standard
Pic	2-Picolinato
rx	Reaction
TDE	Thiodiglycol
THF	Tetrahydrofuran
THT	Tetrahydrothiophene
TLC	Thin-Layer Chromatography
tr	*trans*
ttc	*trans-trans-cis*

Preface

This doctoral thesis is written as a collection of articles and consists of four published scientific papers, one accepted manuscript and one submitted manuscript, which can be found in the appendices of this thesis. Based on work carried out by the Fiksdahl group,[1-6] the goals of this thesis were:

1) Investigation of novel gold(I)-catalysed reactions of propargyl acetal substrates;
2) Incorporation of trifluoromethyl groups into products from gold(I)-catalysed reactions using electrophilic trifluoromethylation reagents;
3) Development of chiral gold(I) catalysts for use in propargyl chemistry;
4) Catalytic studies of recyclable gold catalysts in propargyl chemistry.

Chapter 1 gives a theoretical framework and background to the doctoral work, including an introduction to gold complexes, discussion of relevant gold(I)-catalysed propargyl reactions and an overview of gold-catalysed reactions with electrophiles.

Chapter 2 addresses Papers I and II and explores the chemistry of new gold(I)-catalysed cycloadditions involving the transformation of terminal propargyl acetals into reactive intermediates and cyclisation with alkenes and alkynes to give novel complex compounds. This research builds on our earlier work on gold(I)-catalysed reactions of terminal propargyl acetals and vinyl derivatives.[2]

Chapter 3 covers the further exploration of the reactivity of gold(I)-nitrone complexes and the chemistry of non-terminal propargyl acetals (Paper V), work which is a continuation of our studies of gold(I)-nitrone catalysed cyclotrimerisations of 1,2-diaryl propargyl acetals.[5, 6]

Chapter 4 describes the work toward gold(I)-catalysed incorporation of the trifluoromethyl group into propargyl acetal chemistry, based on work in the group on incorporation of electrophilic fluorine into gold(I)-catalysed reactions of homopropargyl acetals.[4] A novel dual gold(I)-catalysed method of trifluoromethylation of terminal alkynes is presented (Paper III).

Chapter 5 discusses the development of chiral and dual gold(I)-based complexes for use in propargyl reactions, inspired by the discovery of a σ,π-dual gold(I) complex as the active catalytic species in Paper III. The main findings are published in Paper IV, which reports on the synthesis and catalytic activity of novel σ,π-dual gold(I) catalysts in reactions of propargyl substrates.

Chapter 6 presents the results from a study of the catalytic activity of homogeneous and heterogenous gold(III) complexes in propargyl reactions, from a collaboration with the Catalysis group at the University of Oslo (Paper VI).

The compound numbers in this thesis follows those used in the respective papers.

Contributions

Paper I: Maya Kaur carried out studies on the tandem cyclisation reaction, including synthesis and characterisation of 1 cyclopropanation and 7 tandem cyclisation products. Melanie Siah conducted catalyst screening and optimisation reactions on all aryl propargyl substrates and 1 alkyl propargyl substrate, and synthesised and characterised 8 tandem cyclisation products, 1 cyclopropanation product and 1 dimer. Naseem Iqbal contributed advice and initial scientific inspiration. The paper was written by Anne Fiksdahl and Melanie Siah.

Paper II: Morten Hogsnes carried out studies on the tandem cyclisation reaction and worked with 4 propargyl substrates and 1 alkyne. Melanie Siah was responsible for catalyst screening, optimisation reactions, assigning of stereochemistry for the 5 diastereoisomers, and has worked on all 8 propargyl substrates and 9 alkynes. The synthesis and characterisation of the products was a combined effort between Morten Hogsnes and Melanie Siah. Naseem Iqbal contributed with advice and initial scientific inspiration. The paper was written by Anne Fiksdahl and Melanie Siah.

Paper III: All experimental work was carried out by Melanie Siah, with advice from Anne Fiksdahl. The paper was written by Melanie Siah and Anne Fiksdahl.

Paper IV: All experimental work was carried out by Melanie Siah, with advice from Anne Fiksdahl. The paper was written by Melanie Siah and Anne Fiksdahl.

Paper V: Melanie Siah carried out synthesis and characterisation of the chiral nitrones, NMR coordination studies and worked on all test reactions. Helgi Freyr Jónsson was responsible for the initial work on both non-terminal propargyl acetals and synthesised one of the dimers. The paper was written by Melanie Siah and Anne Fiksdahl with input from Helgi Freyr Jónsson.

Paper VI: Melanie Siah and Volodymyr A. Levchenko collaborated on the experimental work within homogenous catalysis. Volodymyr A. Levchenko synthesised the catalysts and was responsible for the heterogeneous work. Sigurd Øien-Ødegaard carried out X-ray crystallography. The paper was written by Volodymyr A. Levchenko and Melanie Siah, with input from Sigurd Øien-Ødegaard, Mats Tilset and Anne Fiksdahl.

1 Introduction

1.1 The inception of gold catalysis

"Gold is forever. It is beautiful, useful, and never wears out. Small wonder that gold has been prized over all else, in all ages, as a store of value that will survive the travails of life and the ravages of time."

James Blakely, Eureka Mine discoverer

Gold, or *aurum* in Latin, is a fascinating metal that has many applications due to its chemical and physical properties.[7] This shiny, yellow metal has traditionally been believed to be of divine origin, while the ultimate goal of Western alchemy was to create the "Philosopher's Stone", imagined to be a tool that gave the wielder the ability to transmute base metals such as lead into much more valuable gold. Although alchemists were unsuccessful in their endeavours to create gold, they were skilled chemists, and other discoveries, such as the distillation of alcohol, occurred in an alchemist's laboratory.[7, 8]

Despite our failures to create gold, our ancient fascination with it has continued into the modern age. From the times of the earliest civilisations, gold has been valued for its exceptional metallurgic qualities, such as high malleability and ductility, and has been associated with images of power, such as deities, royalty and wealth. Gold has frequently been used in jewellery and artefacts, as currency, in medicine and dentistry, and even as an additive in food and drinks.[9]

Its qualities as an inert, non-toxic and non-irritating metal are well-known and, due to its lack of sensitivity to corrosion and oxidation, gold is a noble metal. However, this chemical inertness coupled with its reputation as being less affordable than other metals has resulted in gold being largely ignored in chemistry.[7]

Fortunately, for gold-orientated chemists, it is a relatively abundant metal and is mined on the scale of thousands of tons a year. Also, gold can be recycled from technical devices, although the amount of gold being recycled is affected by the price of gold and world economic conditions.[7, 10, 11] For use in organometallic chemistry, gold is commercially available in a range of oxidation states, with or without ligands. The abundance of gold means a more stable price compared to other metals, however, the identity of the ligand can have a significant effect on the price of the catalyst.[10]

The history of gold in catalysis can be traced to the early 19th century. From as early as 1823, it was discovered that macroscopic gold could catalyse the decomposition of ammonia.[12] Later, the ability of gold to catalyse the reaction of hydrogen and oxygen at room temperature and the hydrocracking of polyethylene was reported.[13, 14] Despite some early discoveries, interest in gold catalysis did not take off until the turn of the 21st Century. Some important contributions that have led to the "gold rush" of the last twenty years in the fields of heterogeneous and homogenous gold catalysis are presented here.

In 1973, Bond used chloroauric acid to impregnate silica and alumina to generate heterogeneous gold catalysts with activity towards hydrogenation of olefins.[15] Haruta and co-workers designed, in 1987, heterogeneous catalysts for the oxidation of carbon monoxide at low temperatures by co-precipitating gold with iron, cobalt or nickel oxides.[16]

In 1991, Fukuda and co-workers published a series of articles on transformations of organic molecules using an inorganic gold(III) salt. They reported the gold(III)-catalysed addition of water or methanol over triple bonds, an example of nucleophilic addition to an alkyne,[17] one of the iconic reactions associated with gold catalysis in organic synthesis.[10] The same group also carried out gold(III)-catalysed hydration studies on other substrates, including conversion of methyl propargyl esters into α,β-unsaturated ketones.[18] In addition, Fukuda reported that, while Pd(II) catalysts have been successful at catalysing intramolecular additions of amines to alkenes, the parallel reaction on alkynes is less successful. Gold (III) salts easily catalysed the intramolecular addition of amine to an alkyne, exemplifying gold's specific affinity for activation of triple bonds.[19]

Around the turn of the 21st Century, interest in the ability of gold to activate alkynes and allenes began to increase. In the early 2000s, Hashmi reported the ability of gold(III) chloride to catalyse cross cycloisomerisation/dimerisation of terminal allenyl ketones and α,β-unsaturated ketones, a transformation that failed with Pd(II).[20, 21] Gold(III) chloride could also selectively catalyse the formation of arenes from alkynes and furans.[22, 23]

In 1986, a cationic gold(I)-iron complex was reported by Ito and co-workers, consisting of a gold(I) centre and a ferrocenylphosphine ligand, that was capable of enantioselectively catalysing aldol reactions.[24] In 1998, Teles investigated the stability of cationic phosphane-gold(I) complexes that could catalyse the addition of alcohols to alkynes.[25] A range of factors were studied, including the identity of the ligand and the counterion. Interestingly, the phosphane ligands affording gold(I) complexes with the highest activity were also found to be the most destabilising for the complex.[25] This research revolutionised homogenous gold catalysis, as one disadvantage of using inorganic gold(III) salts in catalysis is their instability and relatively fast decomposition to metallic gold.[17]

In 2002, Mizushima expanded on Teles' work using cationic gold(I) complexes to catalyse the hydration of alkynes, commenting that the transformation was a valuable alternative to the Wacker oxidation and could be particularly interesting in the field of total synthesis.[26] In 2004 and 2005, the Toste and Echavarren groups published studies on the ability of cationic gold(I) complexes to catalyse cyclisations, rearrangements and ring expansions.[27-36]

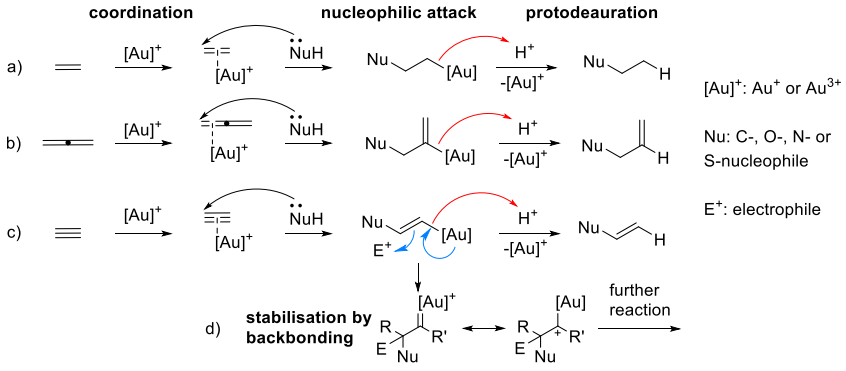
Gold-catalysed transformations, explored over the last few decades, have not only been solely for the sake of performing elegant chemistry. The use of gold catalysis in total synthesis has expanded parallel to methodological investigations, and many natural products have been synthesised using gold catalysis as part of the synthetic route.[37-39] As gold has the ability to generate structural complexity from simple starting materials, gold catalysis will likely become more widely used in natural product synthesis.[37, 38]

The field of gold catalysis has undergone explosive growth in the last 30 years and a growing number of research groups are interested in gold catalysis. A consideration of the number of publications in the field of gold catalysis (from 221 references in 2009 to 1464 references in 2019) reveals steady growth and shows that gold catalysis is a vital field in organic chemistry.[40, 41]

1.2 Gold in homogeneous catalysis

Gold exists in a wide range of forms and occurs in oxidation states from 1− to 5+. Oxidation states 0 and 1+/3+ are most commonly seen in literature for heterogeneous and homogeneous catalysis, respectively.[7, 42] Some examples of compounds with rarer oxidation states are caesium auride (1−),[43] gold sulphate (2+, containing Au_2^{4+} cations)[44] and gold hexafluorate (5+).[7, 45] At the time of writing, these rarer states seem to be more curiosities than they are useful tools for organic synthesis.[7]

Research on the catalytic properties of electrophilic gold(I) and gold(III) complexes has mainly been based on their soft Lewis acid properties and their ability to activate π-systems, such as alkenes, allenes and alkynes, for nucleophilic attack (Scheme 1.1a-c).[46] The gold centre coordinates to the multiple bond, forming a π-complex and withdrawing electron density, making the multiple bond more susceptible to nucleophilic attack. The catalytic cycle can be completed by protodeauration, where the gold centre is simply replaced by a proton (red arrows).[47] An alternative reaction pathway is based on the stabilising backbonding effect of gold, which can generate a gold-carbenoid intermediate that enables the incorporation of an electrophile (blue arrows) and further reaction (Scheme 1.1d).[48] Alkynes show greater reactivity in gold-catalysed nucleophilic additions than alkenes, possibly due to a lower LUMO in the Au–alkyne complex than for the LUMO of the analogous Au–alkene complex,[47] and are thus commonly used substrates in gold catalysis.



Scheme 1.1. General activation of multiple bonds by gold, nucleophilic attack and protodeauration.[46]

The superior ability of gold to act as a Lewis acid compared to other Group 11 metals has been explained by relativistic effects,[42] which become significant when the *4f* and *5d* orbitals are filled (as is the case for Pt, Au and Hg).[48] These effects result in a contraction of the valence 6*s* and *6p* orbitals and, therefore, a relatively low-lying lowest unoccupied molecular orbital (LUMO). The high electronegativity of Au (2.4) can also be explained by relativistic contraction of these orbitals.[48] However, the contraction of these orbitals also results in a shielding effect on the electrons of the *5d* orbitals that makes these electrons subject to a weaker attraction from the gold nucleus. In turn, this means the *5d* electrons are more loosely bound to the nucleus and can be delocalised, allowing gold to act as an electron-donor in order to stabilise carbocation intermediates.[7, 42]

Redox reactions in gold catalysis are rare, in contrast to other metal-catalysed transformations developed in the last century that are based on oxidative addition/reductive elimination processes. In fact, one of the limitations of gold catalysis is that Au(I) and Au(III) species can be irreversibly reduced *in situ* to nanoparticles or mirror gold/Au(I) species, respectively.[7]

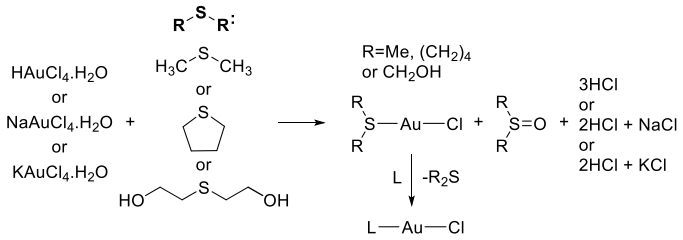
1.3 Gold(I) catalysts

Gold(I) species are linear with a maximum of two ligands. Both the ligands and counterion influence the catalytic properties of the gold complexes and the main groups of catalytically active gold(I) species are gold salts, cationic ligated gold complexes and chiral cationic gold complexes. In addition, dual gold(I) and gold(I)-nitrone complexes are important gold(I) species for this thesis.

1.3.1 Gold(I) salts

Gold(I) salts are gold(I) complexes with strongly bound anions (such as halogens). In the early years of homogeneous gold catalysis, inorganic gold(I) salts were often used as the catalytic species. Gold(I) chloride has been used in a limited number of catalytic reactions, mostly cyclisation reactions, and has been successful in reactions that fail with other transition metals.[7, 49-51] Other inorganic gold(I) halide salts (e.g. AuBr and AuI) have shown less catalytic activity than AuCl.[7]

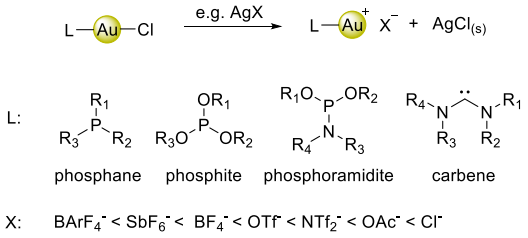
The presence of ligands on the gold(I) centre affects the stability and reactivity of gold(I) towards the various multiple bond substrates.[7, 10, 48, 52] The most common ligated gold(I) salts are of the type L-Au-Cl (Scheme 1.2), where L can be a phosphane, phosphite, phosphoramidite or carbene (Scheme 1.3).[7] These complexes can be generated by mixing the ligand with a derivative of AuCl that is soluble in organic solvents, for example, (Me_2S)AuCl, (THT)AuCl or (TDE)AuCl. These sources of AuCl can in turn be synthesised from inorganic gold(III) salts, $NaAuCl_4.nH_2O$, $KAuCl_4.nH_2O$ or $HAuCl_4.H_2O$, and the required thioester (Scheme 1.2).[7, 53] It is also possible to combine chloroauric acid with a phosphorous ligand in order to generate the gold(I) complex, but this method oxidises one equivalent of the ligand and is therefore wasteful.[54]



Scheme 1.2. General synthesis of thio gold(I) chloride complexes.

1.3.2 Cationic gold(I) complexes

Gold(I) complexes that have weakly coordinating anions are called cationic gold(I) complexes. Ligated gold(I) salts are often poor catalysts and therefore are commonly used as pre-catalysts. They are easily transformed into catalytically active cationic complexes by treatment with a silver salt, which forms insoluble AgCl that can be removed by filtration (Scheme 1.3). Potassium and sodium salts can also be used in the same manner. The identity of the counterion is important and affects the Lewis acidity and catalytic behaviour of the cationic gold(I) complex.[7, 55] The weakly coordinating anions are shown in order of increasing coordination strength to gold.[55-57]



Scheme 1.3. Anion exchange of ligated gold(I) salts (LAuCl) with silver salts (AgX), typical ligand types (L) and commonly used anions (X).

A few, less common, methods of generating active catalysts are also known. Teles used L-Au-Me complexes as pre-catalysts, which are protonated by an acid whose anion is non-coordinating to gold, to give the active cationic gold(I) species.[25] However, this method has not become popular due to challenges in generating the methyl gold(I) species and acidic reaction conditions that could conflict with the reactants and/or products.[7] A similar method starting from L-Au-OH in acidic conditions has also been employed with similar drawbacks.[58] L-Au-Cl pre-catalysts can also be activated using $BF_3.OEt_2$, which appears to generate weakly coordinating BF_3Cl^-.[25]

1.3.3 Ligand types

One very popular class of ligand in gold(I) catalysis is the phosphane ligands, containing alkyl or aryl groups. A range of this type of gold(I) complexes is available commercially or can be easily made in the laboratory.[7] Such ligands include trialkylphosphanes, triarylphosphanes and biphenyldialkylphosphines, the last of which is the most successful (Figure 1.1a).[32, 36, 59-63]

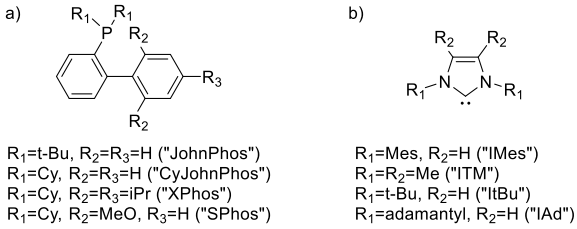


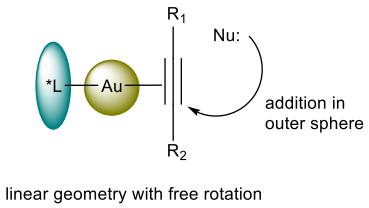
Figure 1.1 Common biphenyldialkylphosphane and NHC ligands used in gold(I) catalysis.

Another class of popular complexes are the two-electron donating *N*-heterocyclic carbenes ("NHCs", Figure 1.1b), which are part of a larger class of carbene-based ligands. NHCs have been employed in a range of synthetic transformations since their initial isolation in 1973. They have been described as excellent σ-donors[64] and can stabilise gold centres electronically and provide steric bulk. NHC-gold(I) complexes are usually less electrophilic than phosphane-gold(I) complexes, which can make NHC-gold(I) complexes more selective in catalytic transformations.[64]

1.3.4 Chiral Gold(I) complexes

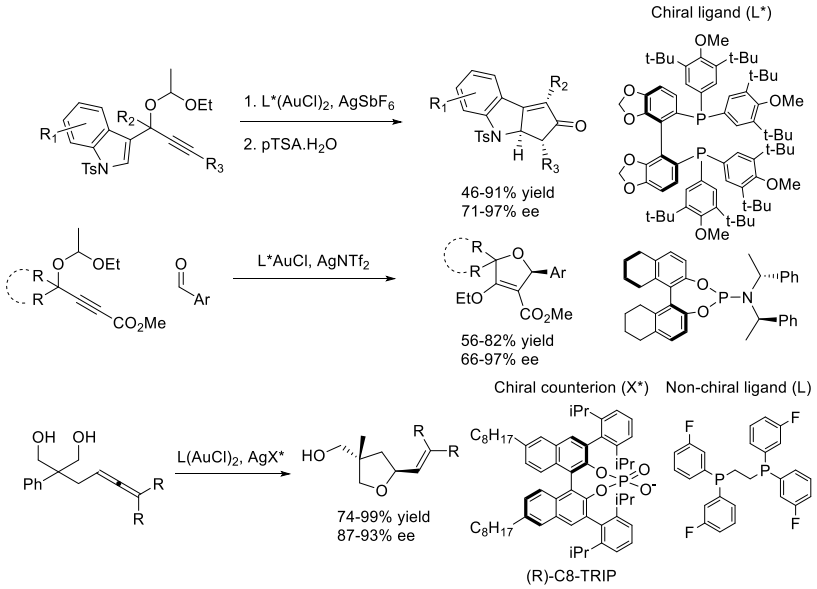
Asymmetric catalysis is somewhat of a holy grail for metal-catalysed transformations. In the field of gold catalysis, relatively little research has been carried out on development of chiral gold(I) catalysts, for several reasons. The first is that gold(I) takes a linear geometry and this formation places the chiral ligand on the opposite side of the gold centre from the substrate, limiting its effect on the enantioselectivity of the transformation. Secondly, the most common type of gold-catalysed

reaction – nucleophilic addition to a multiple bond – occurs by "outer-sphere pathways", which means the addition occurs outside the first coordination sphere of the gold centre, thus further distancing the transformation from the chiral ligand (Scheme 1.4).[65]



Scheme 1.4. Representation of the linear geometry of gold(I), with a chiral ligand, activating an alkyne substrate.

Despite these challenges, there has been some success in tuning the gold(I) catalyst, most often by using bulky chiral ligands, although bulky counterions are also reported to affect enantioselectivity.[65-67] A number of substrates has been investigated, including alkynes, allenes, alkenes and carbonyl compounds, and some selected reactions are shown below (Scheme 1.5).[68-71]

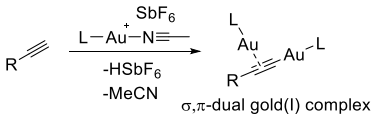


Scheme 1.5. Selected examples of reactions with enantioselective chiral ligands and counterions.

Chiral ligands or counterions to gold(I) with enantioselective effect must be large and bulky to affect the result of the reaction. The types of ligands used are based on the standard groups of ligands for gold – including phosphane, phoshoramidite and carbene ligands. However, forays into the development of new types of chiral gold(I) catalysts include gold(I) complexes based on helicenes,[72, 73] cyclodextrins,[74] phospholanes[75] and more. It is an exciting field under development and more research in this area is likely in the coming years.[65, 66]

1.3.5 σ,π-Dual gold Au(I) complexes

σ,π-Dual gold(I) acetylide complexes are an interesting group of complexes based on phosphane[76] or NHC ligands.[77] Synthesis can be carried out by mixing cationic gold(I) species with a terminal alkyne (Scheme 1.6).[78] Earlier, it was thought that these complexes were a "dead-end" in gold catalysis, but these complexes are now known to be the catalytically active species in a variety of organic transformations.[47, 55, 76, 79-82] Dual gold(I) catalysts can show different catalytic activity compared to monogold(I) complexes and give greater selectivity in reactions.[76, 80, 83]



Scheme 1.6. General method for synthesis of σ,π-dual gold complexes.

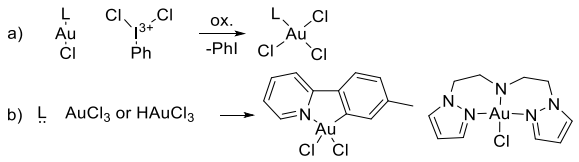
1.3.6 Gold(I)-nitrone complexes

In contrast to oxidising nitrones, nitrones that act in a non-oxidising manner are known to partake in gold(I)-catalysed reactions[84, 85] and also act as organocatalysts.[86, 87] Notably, chiral nitrones are capable of enantioselective organocatalysis.[88-90] Recently, the structures of several novel gold(I)-nitrone complexes were reported by the Fiksdahl group, with the nitrone unit bonding to the gold centre through the O-atom, forming a linear complex. Such complexes are reported to give unique reactivity in propargyl acetal chemistry by tuning the nature of the gold(I) catalyst.[5, 6]

1.4 Gold(III) catalysts

Gold(III) complexes have square planar geometry and can coordinate to a maximum of four ligands. The use of gold(III) species in organic catalysis has mostly been limited to ligand-free, less stable species, such as $AuCl_3$ or K/Na/H($AuCl_4$).[91, 92] The instability of the catalytically active inorganic Au(III) salts that were mainly studied initially led to a more rapid development in the field of gold(I) catalysis than gold(III). However, stable ligated Au(III) complexes were still studied for their biological activity, such as inhibition of DNA/RNA synthesis, and anti-angiogenic, antimicrobial, antifungal and anti-biofilm properties.[93-96]

Use of ligated Au(III) complexes in organic catalysis is growing, along with an interest in the design and synthesis of such complexes.[97-107] In particular, there have been some promising reports of enantioselective organic transformations with chiral Au(III) complexes.[106, 108-110] Ligated Au(III) complexes can be prepared by several routes, including oxidation of ligated Au(I) complexes (Scheme 1.7a)[111] or direct coordination of $AuCl_3$/$HAuCl_3$ to the ligand (Scheme 1.7b), sometimes with the addition of acid, base or silver salts.[97, 112-114] Using bi- and tridentate ligands, a large variety of stable cyclometallated gold(III) complexes can be synthesised.[92, 112, 115, 116]



Scheme 1.7. General routes for synthesis of Au(III) complexes and some examples of bis- and triscyclometalled complexes.[112, 115]

1.5 Gold(I)-catalysed reactions

1.5.1 Gold(I)-catalysed transformations of alkynes

Alkynes have a special affinity to gold(I), and alkyne moieties undergo a wide range of transformations. A common denominator for these transformations is the gold-catalysed activation of a triple bond followed by nucleophilic addition. Possible nucleophiles can be external or internal and can involve a wide range of O-, N- and C-nucleophiles.[10, 117, 118] Depending on the substrate and reactive partner, the result can be a simple addition over the triple bond[25, 26, 119, 120] or cyclisation or cycloisomerisation to give more complex products.[10, 27, 34, 121-129]

Gold(I)-catalysed transformations have proven to be useful in the synthesis of heterocycles through inter- or intramolecular addition of heteroatom nucleophiles to alkynes,[125, 130-144] intramolecular cyclisation of polyunsaturated substrates[145-147] (including enantioselective reactions[146, 148]), cyclisation via α-oxo gold carbenoids[69, 149-153] and cycloaddition reactions.[125, 154-159] Many heterocyclic compounds, such as furans, pyrroles, thiophenes and benzofurans, are important building blocks in drug design and material sciences, and can be used as key synthetic intermediates in a range of reactions.[125, 160] Due to the non-toxicity and stability of gold compared to other transition metals, the option of using gold in such syntheses is advantageous.

Since Trost discovered Pd(I)-catalysed cycloisomerisation reactions of 1,*n*-enynes,[161] these types of reactions have attracted a great deal of attention, especially due to interest in atom economy and green chemistry.[162] A large variety of transformations are possible, giving molecular complexity through annulations, tandem reactions and rearrangements. Gold-catalysed cycloisomerisations of 1,5- or 1,6-enynes[48, 163-166 146, 164, 167-171] tend to proceed under milder conditions (e.g. lower temperatures) than those required by other transition metals.[162, 163] Products can be carbocycles or heterocycles and an internal or external nucleophile can be involved, such as an alcohol or carbon nucleophile.[164, 165, 169-172] Cycloisomerisations of larger 1,*n*-enynes ($n>6$) are reported, but have not been studied as extensively.[169, 173]

The most common gold(I)-catalysed reactions utilise either intramolecular reactions or two components to control product formation. A few gold-catalysed multi-component reactions involve three components. One example is the reaction between aldehydes, terminal alkynes and secondary amines to give propargyl amines.[174-176] Other three-component reactions result in propargyl esters[177] or heterocycles.[178, 179]

Gold(I)-catalysed transformations can give high levels of molecular complexity from simple starting materials using simple mechanistic principles. Gold has displayed an ability to catalyse the formation of heteroatom-carbon and carbon-carbon bonds, rearrange molecular skeletons, and much more, making it a fascinating area of chemistry.

1.5.2 Propargyl substrates in gold catalysis

One important area of gold(I) catalysis is the transformation of propargyl substrates (Figure 1.2). Much attention has been given to gold-catalysed transformations of propargyl esters,[1, 30, 71, 180-208] but similar substrates, such as propargyl ethers[29, 209-218] have also been studied.[208] In recent years, the field of propargyl acetals[2, 3, 69, 84, 219] has been growing, mainly due to the work of the Fiksdahl group. Propargyl substrates are easily accessible from simple functional groups, such as aldehydes, ketones and alkynes. Reactions on these substrates are readily catalysed by gold(I) complexes and, due to

the stability of the catalysts toward oxygen and water, reactions can be carried out without inert atmosphere. Many of the reactions mentioned in Section 1.5.1 involve propargyl substrates.

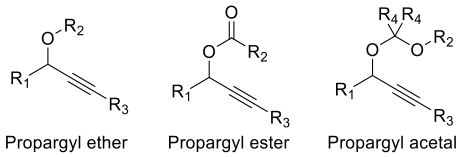
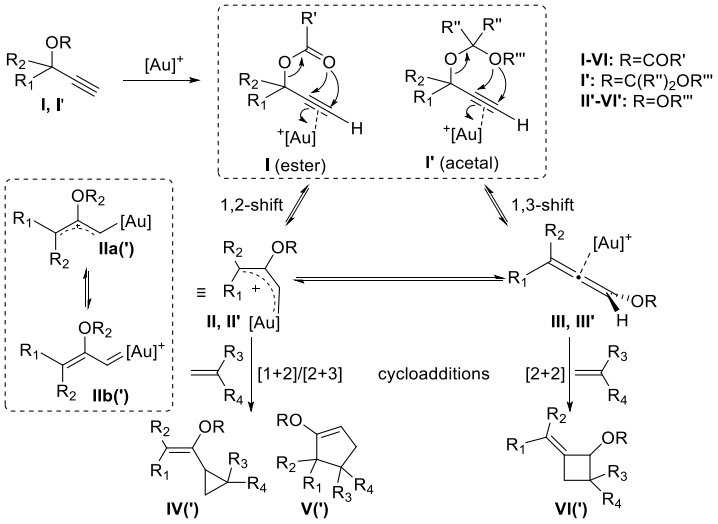


Figure 1.2. General structures of propargyl substrates.

The field of gold(I) catalysis with respect to transformations of propargyl esters and further reaction with appropriate reactants is vast.[1, 30, 71, 180-208, 220] Propargylic esters **I** (Scheme 1.8) undergo gold(I)-catalysed 1,2- and 1,3-acyloxy shifts by carbonyl O-atom attack on the alkyne moiety.[30, 31, 208, 221-224] The outcome of the reaction depends on the identity of the ligand, the substrates and the reaction conditions. Key gold(I) species **I**, **II** and **III** can exist in rapid equilibrium and each species can lead to competing pathways that give stable products.



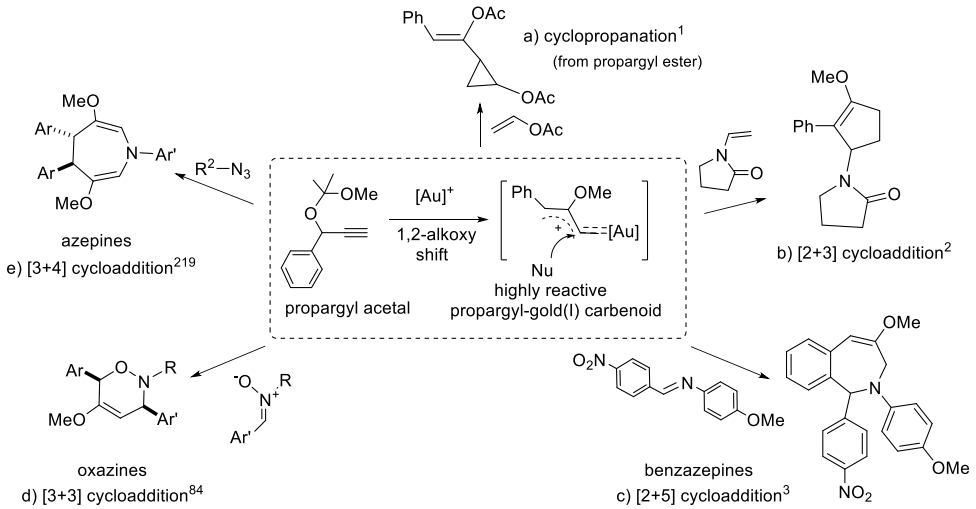
Scheme 1.8. Gold(I)-promoted activation of propargylic substrates and possible subsequent alkene cycloadditions.

Gold species **II**, from gold-catalysed 1,2-acyloxy migration of terminal propargyl esters **I**, can give vinylcyclopropyl products **IV** by a [1+2] cycloaddition with alkenes. Both intra-[225] and intermolecular[1, 30, 226] cyclopropanations are known and gold(I)-catalysed [1+2] cycloadditions have been used in natural product synthesis.[227-229] Investigations on the enantioselectivity of different catalysts in cyclopropanation reactions have also been reported.[30, 230] Alternatively, gold species **II** can give cyclopentenyl products **V** through [2+3] cycloadditions with alkenes,[1, 2] or can undergo nucleophilic attack by a range of nucleophiles (e.g. 1,3-dicarbonyl compounds,[231] dienes,[192] arenes,[231] or sulphur- or nitrogen-based nucleophiles).[200, 232]

Gold-catalysed 1,3-acyloxy migration of propargyl esters **I** gives gold-allene species **III**. This pathway is usually preferred when the substituent on the alkyne is an alkyl or aryl group, but is observed with terminal propargyl esters too.[224, 231, 233-235] The gold-allene complex is able to take

several resonance forms,[236, 237] that can lead to a variety of reaction mechanisms with different reacting partners, such as nucleophilic double bonds,[206, 238-241] aromatic and alkyl groups,[197, 231, 242] heteroatoms,[181, 243-245] carbon nucleophiles[231] and even electrophiles.[246-248] One example is the [2+2] cyclisation of allene **III** with a nucleophilic double bond, giving compound **VI**.[2]

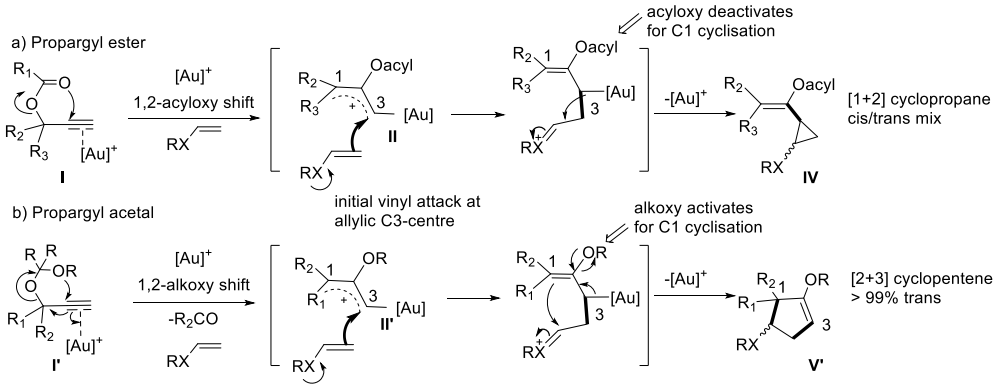
Propargyl acetals **I'** also undergo gold(I)-catalysed 1,2-alkoxy shifts (with cleavage of a ketone) to give gold species **II'**,[2, 221] which can be represented as the allylic-gold cation complex **IIa'** or the gold-stabilised allyl cation **IIb'**. These gold species are electrophilic and react in cyclisation reactions with a range of nucleophiles.[2, 3, 69, 84, 219, 221] Alternatively, propargyl acetals **I'** can undergo a gold(I)-catalysed 1,3-alkoxy shift to generate electron-rich alkoxy-allene species **III'**, which can react in [2+2] cyclisations with alkenes or form cyclotrimerisation products.[2, 5]



Scheme 1.9. Examples of gold(I)-catalysed reactions with terminal propargyl acetals reported by the Fiksdahl group.[1-3, 84, 219]

Research in the Fiksdahl group on the gold(I)-catalysed reaction between propargyl esters and vinyl derivatives showed that cyclopropanation is the favoured reaction pathway for propargyl ester substrates,[1] in accordance with previous literature[30] (Scheme 1.9a). In contrast, a later study found that gold(I)-catalysed reactions of propargyl acetals and vinyl derivatives gave cyclopentenylation products (Scheme 1.9b).[2]

The key reason for the difference in reactivity between propargyl esters and propargyl acetals is the presence of the electron-donating methoxy group on the gold-carbocation intermediate **II'**, which favours "C3-C1" cyclisation (Scheme 1.10b).[2] In comparison, the electron-withdrawing ester group on the gold-intermediate **II** generated from propargyl esters deactivates for C1 cyclisation, giving cyclopropanation instead (Scheme 1.10a).



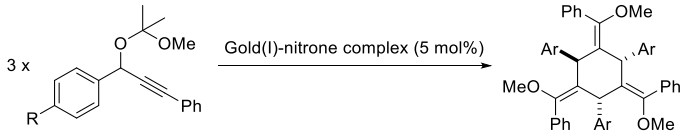
Scheme 1.10. Gold(I)-catalysed rearrangement of propargyl esters and acetals resulting in different reaction pathways.

In addition to giving different chemoselectivity from propargyl esters, it was reported that the propargyl acetals showed significantly higher reactivity, since the alkoxy group in the gold vinylic intermediate species **II'** (Scheme 1.10b) activates the species for reaction. Since propargyl acetals exhibit higher reactivity, different reaction pathways and different chemoselectivity, the propargyl acetal class of compounds is attractive for further research.

The Fiksdahl group also reported gold(I)-catalysed [2+5] cycloadditions of propargyl acetals with benzaldimine substrates (Scheme 1.9c).[3] The mechanism involved a gold(I)-catalysed 1,2-alkoxy shift to give a gold-carbocation intermediate, followed by nucleophilic benzaldimine *N*-attack at the C3 position, and finally a deauration step that promoted ring closure through an intramolecular Pictet–Spengler-type reaction with the aldiminium unit. These benzazepine derivatives are interesting as their framework is often observed in biologically active compounds.[249]

In 2016, Evjen investigated gold(I)-catalysed reactions of a range of terminal propargyl acetals with 1,3-dipolar compounds (nitrones and azides) giving novel compounds (Scheme 1.9c and d).[84, 219] The first study on the reaction of propargyl acetals and nitrones gave [3+3] cyclisation through O-nucleophilic C1-attack of the nitrone gold(I)-carbenoid **II'**, followed by ring closure. The second study with azides gave azepine products by generation of a *Z*-2-methoxy vinyl imine intermediate from the gold-carbenoid and azide (with cleavage of N_2), then subsequent [3+4] cycloaddition with a second gold-carbenoid unit.

Jónsson's research on the gold(I)-catalysed [2+2+2] cyclotrimerisation of 1,3-diarylpropargyl acetals (Scheme 1.11) arose from attempts to react non-terminal phenyl propargyl acetals with nitrones. However, the nitrone coordinated to the gold(I) complexes, tuning their catalytic activity and resulting in gold(I)-catalysed trimerisation through allenic intermediates **III'** generated by gold-catalysed 1,3-alkoxy rearrangements (Scheme 1.8),[5, 6]



Scheme 1.11. [2+2+2] Cyclotrimerisation of 1,3-diarylpropargyl acetals by gold(I)-nitrone complexes.

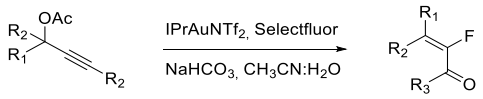
1.5.3 Electrophilic fluorine reagents in gold-catalysed reactions

There has been a steady increase in the number of bioactive organic compounds with one or more fluorine atoms and it is known that the incorporation of fluorine can impart beneficial chemical and medicinal properties to a compound.[250, 251] In the last decade, new discoveries in methods of introducing a fluorine atom or a trifluoromethyl group into an organic molecule have been reported.[252]

Several strategies to fluorinated compounds within gold-catalysis are known:[253]

- use of fluorinated building blocks,
- use of nucleophilic sources of fluorine,
- use of electrophilic sources of fluorine, and
- use of fluorine has an oxidative reagent.

Methods involving electrophilic sources of fluorine have dominated fluorination processes.[253] Gold(I)-catalysed reactions with incorporation of fluorine have been reported using Selectfluor,[254, 255] including work on propargyl acetate substrates (Scheme 1.12)[256, 257] and homopropargyl acetals.[4]



Scheme 1.12. Gold(I)-catalysed rearrangement and fluorination of propargyl acetates by de Haro.[256]

The application of gold catalysis to trifluoromethylation is virtually unexplored. There is one report of a gold(III) complex containing an aryl group and a trifluoromethyl group undergoing reductive elimination to a gold(I) species and forming a C_{aryl}-CF_3 bond, in a stoichiometric process.[258] Similarly, a difluoromethylated gold complex has been reported to undergo reductive elimination to give an aryl-CF_2H compound.[259] Catalytic processes for trifluoromethylation using gold have been elusive. Electrophilic trifluoromethylation reagents, such as those shown in Figure 1.3,[260-262] are applicable in many transformations and may find use in gold-catalysed chemistry.[261, 263]

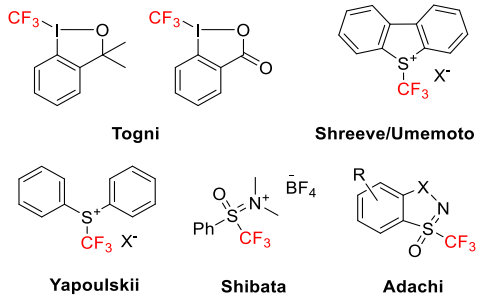
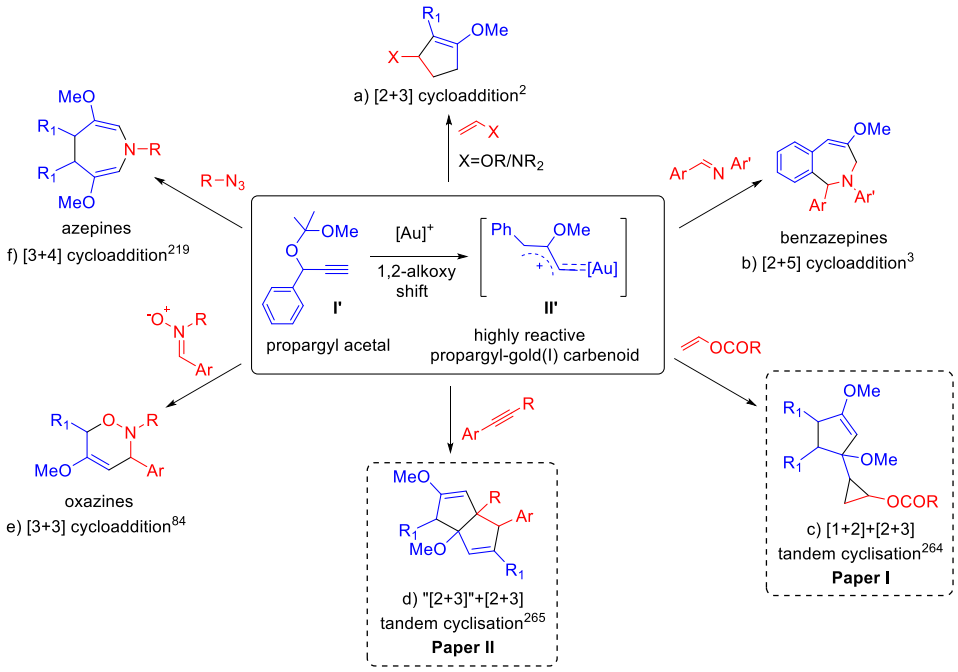


Figure 1.3. Some examples of electrophilic trifluoromethylation agents.

2 Gold(I)-catalysed tandem cycloadditions of terminal propargyl acetals with C-C bonds

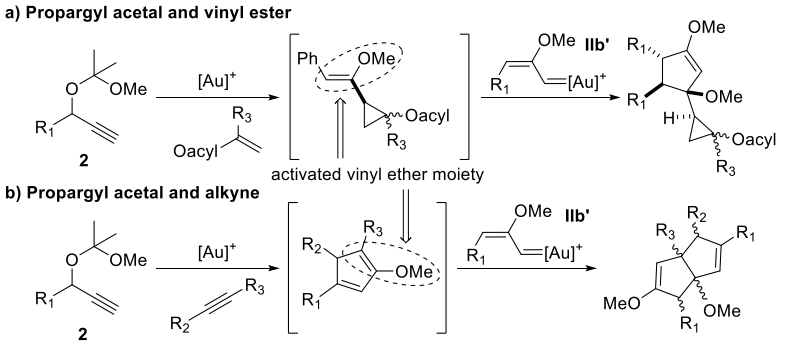
2.1 General introduction

An overview of gold(I)-catalysed cycloadditions with terminal propargyl acetals is shown in Scheme 2.1. Prior to the work presented in this chapter, the chemistry of propargyl acetals had received little attention, and studies on terminal propargyl acetals were non-existent apart from two reports in 2013 (Scheme 2.1a and b).[2, 3] In the work carried out by the current author (Papers I and II, Scheme 2.1c and d), terminal propargyl acetals react with alkenes and alkynes in the presence of a gold(I) catalyst to give cyclopropyl-cyclopentenyl and bicyclic pentalene compounds, respectively.[264, 265] Compound numbers used in this chapter follow those used in the respective paper.



Scheme 2.1. Overview of gold(I)-catalysed cycloadditions of terminal propargyl acetal with different reactants.[2, 3, 84, 219, 264, 265]

Gold(I)-catalysed reactions of terminal propargyl acetals with vinyl ethers and amides gave different reactivity when compared to analogous propargyl ester reactions (Scheme 1.10).[1, 2] Propargyl acetals were reported to have higher reactivity and follow a different reaction pathway, due to the electron-donating methoxy group that activates the gold(I)-intermediates. Based on these results, the differences between the reactivity of propargyl esters and acetals were explored by studying gold(I)-catalysed reactions between propargyl acetals and other reactive partners. Investigation of the reaction of propargyl acetals and vinyl acetates (Scheme 2.2a) allowed comparison with analogous propargyl ester reactions.[1] Gold(I)-catalysed propargyl acetal reactions with alkynes increased the scope of reactants in such reactions (Scheme 2.2b).



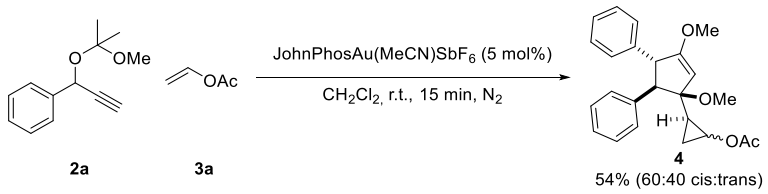
Scheme 2.2. Gold(I)-catalysed tandem cycloadditions of terminal propargyl acetals with a) vinyl esters and b) alkynes, respectively.

The reactive intermediates generated from propargyl acetal substrates **2** resemble familiar products from propargyl ester chemistry (cyclopropane **IV** and cyclopentene **V'**, Scheme 1.10). However, unique to intermediates formed from propargyl acetals, is the electron-donating nature of the vinyl substituent, which enables the intermediates to react further with another unit of the gold-carbenoid in tandem cyclisation reactions (Scheme 2.2).

2.2 Gold(I)-catalysed [1+2]/[2+3] tandem cycloadditions between propargyl acetals and vinyl esters

2.2.1 Initial studies

The reaction of terminal propargyl acetal **2a** and vinyl acetate (**3a**, 3 equiv.) in the presence of gold catalyst JohnPhosAu(MeCN)SbF_6 (5 mol%, JohnPhos=(2-biphenyl)di-tert-butylphosphine) gave [1+2]/[2+3] tandem cyclisation product **4**, as mixture of two diastereoisomers (Scheme 2.3). Product **4** was confirmed by ^{1}H NMR and HRMS to consist of two propargyl acetal units and one vinyl acetate unit, despite the latter being present in a three-fold excess. NMR analysis revealed the structure of the products to be a cyclopentene ring tethered to a cyclopropane ring. The reaction was thus a combination of the products reported by Sperger and Iqbal in earlier literature.[1, 2]



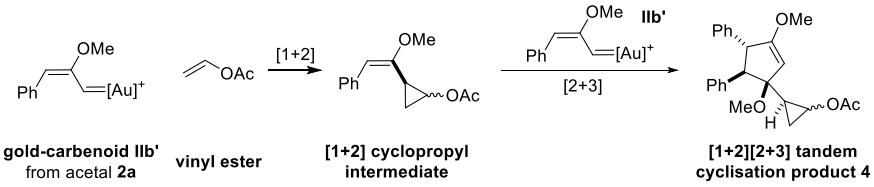
Scheme 2.3. Initial reaction conditions used to probe the gold(I)-catalysed reaction between propargyl acetal **2a** and vinyl acetate **3a**.

Reaction with other gold(I) complexes resulted in lower yields or hydrolysis of the acetal group. Gold(III) species gave partial or full hydrolysis, likely because Au(III) complexes are generally harder Lewis acids than gold(I) complexes and coordinate more readily to oxygen atoms,[7, 266] activating the propargylic position for hydrolysis. Variation of the solvent resulted in longer reaction times (MeCN) or solvent polymerisation (THF).

Acetonitrile as a solvent is in large excess and, since nitriles coordinate to gold(I) centres, may hinder the reaction by competitively binding to the metal centre. Reaction in THF gave product formation (TLC), but rapidly formed an insoluble gel-like substance. It is known that acids, including gold(III)-generated acids,[267] can catalyse the polymerisation of THF.[268] Alternatively, superacids can be generated by abstraction of the terminal proton of the propargyl substrate,[76, 269] and these acids can cause THF-polymerisation.

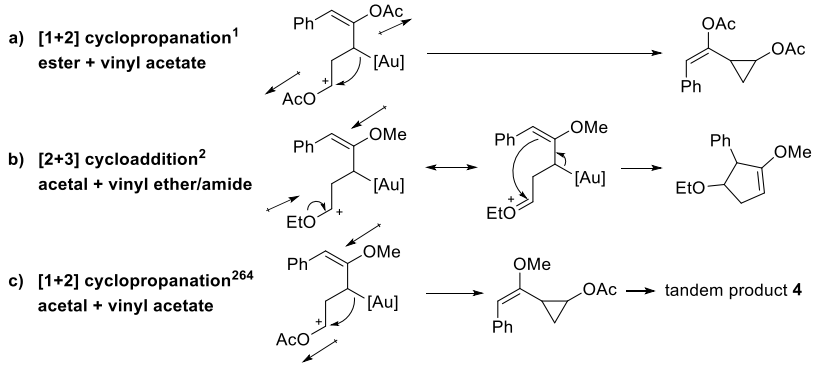
2.2.2 Proposed mechanism

Based on previous reports,[1, 2] a mechanism was proposed for the formation of the tandem cyclisation product **4** (Scheme 2.4). The propargyl acetal **2a** undergoes gold(I)-catalysed 1,2-methoxy migration to give gold-carbenoid **IIb'** (see Scheme 1.8), which reacts with the nucleophilic vinyl acetate in a [1+2] cycloaddition to give a cyclopropyl intermediate, analogous to the product from the gold(I)-catalysed reaction of propargyl esters and alkenes.[1] The cyclopropyl intermediate reacts with a second unit of gold-carbenoid **IIb'** in a [2+3] cycloaddition to give the [1+2]/[2+3] tandem cyclisation product **4**.



Scheme 2.4. Proposed mechanism for the formation of the gold-catalysed tandem cyclisation product.

Interestingly, the first step is not a [2+3] cycloaddition, as might have been expected from the gold(I)-catalysed reaction of propargyl acetals and vinyl amides/ethers (Scheme 1.10b). Several factors affect whether [1+2] or [2+3] cycloaddition is preferred, including the electronic properties of the vinylic and propargyl reagents.[1-3] Previous reactions of propargyl esters **I** and vinyl acetates[1] gave intermediates with electron-withdrawing groups both on the double bond and next to the positively charged carbon atom, resulting in cyclopropanation (Scheme 2.5a). Conversely, reactions of propargyl acetals **I'** and vinyl ethers/amides[2] formed intermediates with electron-donating groups on both the double bond and next to the positive charge (Scheme 2.5b) that could delocalise the positive charge and activate for C1-cyclisation, giving cyclopentenylation.



Scheme 2.5. Comparison of intermediates from gold(I)-catalysed reactions of propargyl acetals and alkenes.[1, 2, 264]

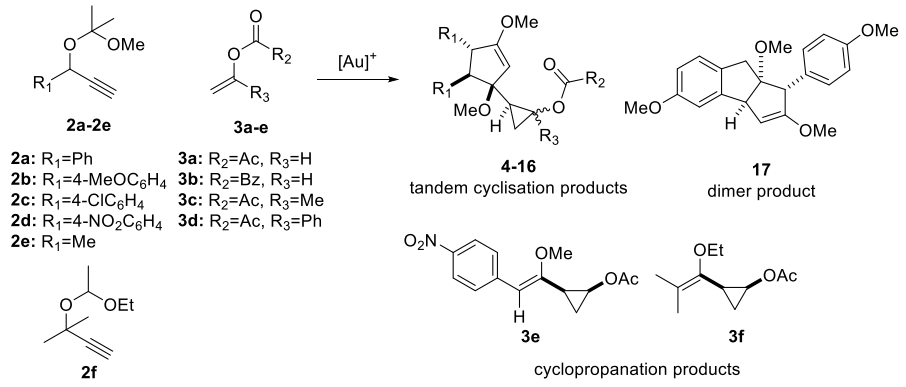
In contrast, the current [1+2]/[2+3] tandem cycloaddition reaction goes via an intermediate with an electron-donating group on the double bond and an electron-withdrawing group next to the positive charge (Scheme 2.5c). The electron-poor vinylic group is the dominating factor and favours attack from the C-Au bond rather than the vinyl ester moiety, resulting in cyclopropanation in the first step. The subsequent [2+3] cycloaddition (Scheme 2.4) is in accordance with previous reports of gold(I)-catalysed reactions of propargyl acetals and vinyl ethers.[2]

Notably, the cyclopentenyl rings of tandem cyclisation product **4**[264] and previous cyclopentenylation products[2] contain vinyl ether moieties. However, these compounds do not undergo further reaction with gold-carbenoid **II'** units. The reason for this is not known, but the electronic properties (e.g. lack of aryl substituent on the alkene) or conformation of the cyclic vinyl ether moieties could prevent further reaction.

2.2.3 Substrate scope

Further studies showed that aryl propargyl acetals **2a-d**, monosubstituted alkenes **3a-b** and low temperatures gave best yields of tandem cyclisation products **4-16** (Table 2.1, entries 1-6). Alkyl propargyl acetals **2e-f** (entries 7-8) and sterically hindered vinyl esters **3c-d** performed poorly and many by-products were formed, making purification challenging.

Table 2.1. Selected results of gold(I)-catalysed reactions of propargyl acetals and vinyl esters.[264]



Entry	Acetal	Alkene	T (°C)	Time (min)	Product	Yield [%]	Cis:trans
1	**2a**	**3a**	−78	15	**4**	69	50:50
2	**2b**	**3b**	−78	120	**7**	53[a]	67:33
3	**2c**	**3a**	−40	15	**9**	77	58:42
4	**2c**	**3e**	−40	30	**13**	77[b]	58:42
5	**2d**	**3a**	20	120	**14**	62	58:42
6	**2d**	**3a**	−40	15	**14**	58	68:32
					3e	40	100:0
7	**2e**	**3a**	−40 to 0	120	**15**	15	60:40
8	**2f**	**3a**	20	15	**3f**	5	100:0

a) at r.t., dimer **17** was isolated (2-4%); b) 1:1.1 propargyl acetal:vinyl ether.

Propargyl acetals with electron-poor aryl groups performed best (entries 1, 3 and 5), due to increased electrophilicity of the gold-carbenoid **II'** intermediate and polarisation of the double bond of the cyclopropane intermediate, activating the electrophile for the second cycloaddition reaction. At low temperatures, electron-poor propargyl acetal **2d** also gave significant amounts of

cyclopropanation product **3e** (Table 2.1, entry 6), which could be reacted with propargyl acetals **2c** or **2d** to give tandem product **14** or mixed tandem product **13** (Figure 2.1a) in good yields. Compound **3e** could be a useful synthetic intermediate, e.g. in gold(I)-catalysed reactions with other propargyl acetals to give mixed tandem cyclisation products or with propargyl esters to give dicyclopropyl products (Figure 2.1b).[2]

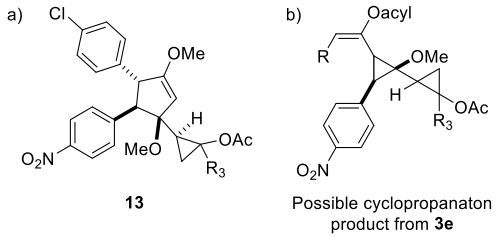
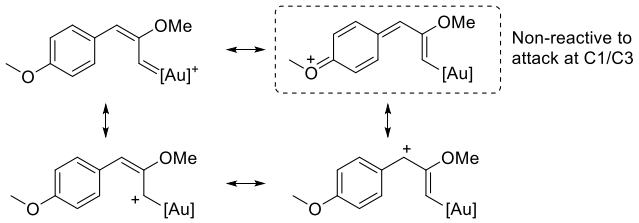


Figure 2.1. Mixed tandem cyclisation product **13** and possible cyclopropanation product from vinyl ether **3e**.

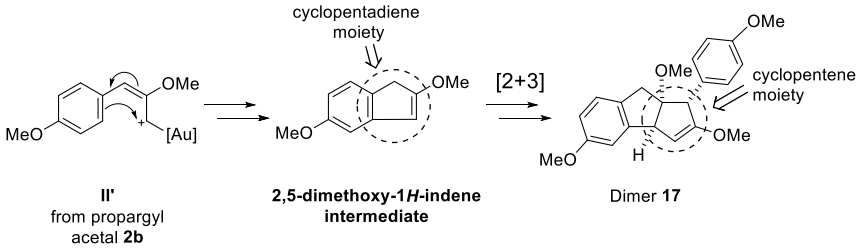
Conversely, the electron-rich methoxy group gave lower yields and longer reaction times (entry 2). The methoxy group increases electron-density on the gold-carbenoid **II'** and makes nucleophilic attack at either C1 or C3 less attractive (Scheme 2.6), affecting the efficacy of both steps of the tandem cyclisation reaction.



Scheme 2.6. Resonance forms of gold-carbenoid **II'** with a *para*-methoxy group on the aryl ring.

Dimer **17**, formed in reactions with propargyl acetal **2b** (entry 2, footnote a), was isolated in very low yields, probably due to instability in the purification process (e.g. during silica column chromatography). It is likely generated through a two-step mechanism (Scheme 2.7), via an intramolecular electrophilic aromatic substitution, followed by the same [2+3] cycloaddition proposed for the tandem cyclisation products (Scheme 2.4). The formation of trimers or polymerisation of the substrate is possible but was not observed.

The cyclic vinyl ether intermediate (generated in the formation of dimer **17**, Scheme 2.7) has an electron-donating aryl substituent on the alkene and a flatter geometry than dimer **17** or the cyclopentene moieties in our tandem cycloaddition products (Scheme 2.2). These factors promote [2+3] cyclisation with a second gold-carbenoid unit to give dimer **17**, but no further trimerisation or polymerisation.



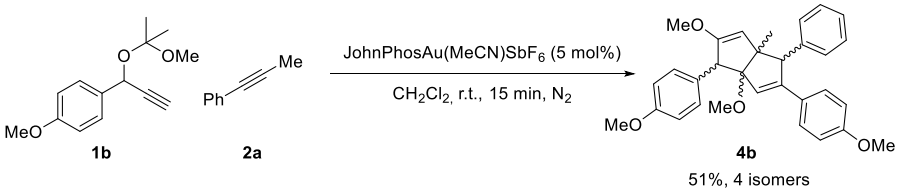
Scheme 2.7. Proposed mechanism for the generation of dimer **17**.

The gold-catalysed self-dimerisation of electron-rich acetals could be an interesting reaction to study in the future, although use of more appropriate purification methods is required, e.g. milder stationary phase during column chromatography, and deuterated dichloromethane when carrying out NMR analyses to avoid product decomposition. In addition, gold-catalysed reactions between 2,5-dimethoxy-*1H*-indene (generated in situ from electron-rich propargyl acetal **2b**, Scheme 2.7) and electron-poor propargyl acetals (e.g. compound **2c** or **d**) could give analogues of dimer **17**.

2.3 Gold(I)-catalysed "[2+3]"/[2+3] tandem cycloadditions between propargyl acetals and alkynes

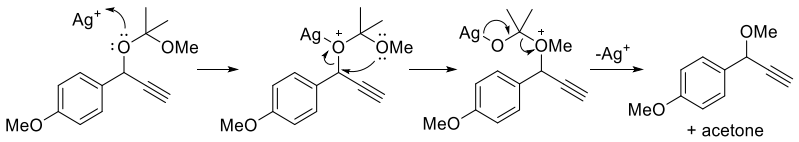
2.3.1 Initial studies

Reaction of terminal propargyl acetal **1b** and alkyne **2a** in the presence of gold(I) catalyst JohnPhosAu(MeCN)SbF_6 gave "[2+3]"/[2+3] tandem cyclisation product **4b**, as a mixture of four diastereoisomers (Scheme 2.8). Isolation of each diastereoisomer was challenging due to small differences in elution time during column chromatography and instability of the compounds during purification and in solution. However, the structures of the diastereoisomers were successfully elucidated (NMR/HRMS) and product **4** consisted of two units of propargyl acetal **1b** and one unit of alkyne **2a**. One major isomer was observed (44%, **4b-*cis-cis-cis***, relative stereochemistry for aryl-MeO, MeO-Me and Me-Ph, determined by NOESY).



Scheme 2.8. Initial reaction conditions used in the gold(I)-catalysed reaction of propargyl acetal **1b** and alkyne **2a**.

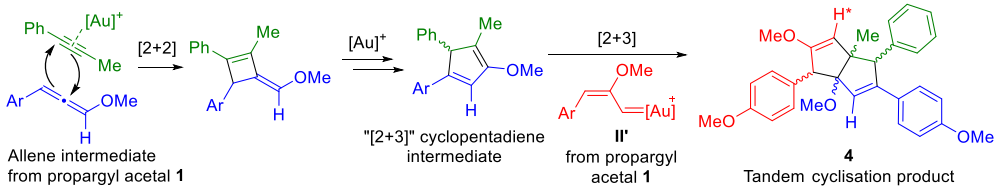
A range of gold(I) and gold(III) catalysts were screened and JohnPhosAu(MeCN)SbF_6 was the best catalyst for the reaction. In addition, silver salts were tested to understand possible side reactions that could arise from gold chloride activation by silver salt counterion exchange. Contamination of gold catalysts with excess silver salts can affect reaction outcomes, e.g. propargyl alcohols undergo Ag-catalysed nucleophilic substitution with methanol and other nucleophiles.[270] In the current case, silver salts rapidly (within 15 min) catalysed an intermolecular nucleophilic attack of the methoxy group to form a propargyl methyl ether (Scheme 2.9). This intramolecular transformation with propargyl acetals has not been reported previously, although gold(I)- and silver-catalysed decarboxylation of propargyl esters is known, with much longer reaction times.[271]



Scheme 2.9. Proposed silver-catalysed generation of 1-methoxy-4-(1-methoxyprop-2-yn-1-yl)benzene.

2.3.2 Proposed mechanism

The generation of the tandem cyclisation products in the current reaction involved a complicated mechanism (Scheme 2.10). One unit of propargyl acetal **1** undergoes a gold(I)-catalysed 1,2-shift to form gold(I)-carbenoid **II'**, while another unit undergoes a gold(I)-catalysed 1,3-shift to give an allene (see Scheme 1.8). The allene reacts with the gold(I)-activated alkyne in a [2+2] cycloaddition and the cyclobutene intermediate undergoes a gold-assisted rearrangement to form a cyclised "[2+3]" intermediate that reacts with gold-carbenoid **II'** in a [2+3] cycloaddition to give the fused bicyclic tandem cyclisation product **4**.



Scheme 2.10. Proposed mechanism for the gold(I)-catalysed tandem cycloaddition of two units of acetal **1** and one unit of alkyne.

The generation of electron-rich allenes from propargyl acetals by a gold-catalysed 1,3-alkoxy shift is a parallel to the gold-catalysed 1,3-rearrangement of propargyl esters to give electron-poor allenes.[201, 241] Allenes from propargyl acetals are rarer, although gold-allenic intermediates **III'** (Scheme 1.8) are reported by the Fiksdahl group from reactions with a terminal propargyl acetal[2] and several non-terminal propargyl acetals.[5, 272] These electron-rich allenes intermediates appear to be much more reactive and unstable than ester analogues and could not be isolated.

Since gold activation of the propargyl acetal generates both electrophilic gold-carbenoid species **II'** and a nucleophilic allene species, the outcome of the reaction depends on the nature of the reactive partners. When a nucleophile is present (e.g. vinyl acetate), the preferred reaction is [1+2] cyclisation with the gold-carbenoid. When an electrophile is present (e.g. a gold-activated alkyne), the preferred reaction is [2+2] cyclisation with the allene intermediate.

In the current reaction, the cyclopentadiene intermediate (Figure 2.2a) reacts in a [2+3] cyclisation reaction with gold-carbenoid **II'**, in contrast to cyclopentenyl products (e.g. [2+3] cycloaddition product, Figure 2.2c). One major difference is the cyclopentadiene's extended conjugation with the electron-donating aryl ring, which activates the vinyl ether bond (Figure 2.2a), similar to the indene intermediate for dimer **17** (Figure 2.2b).

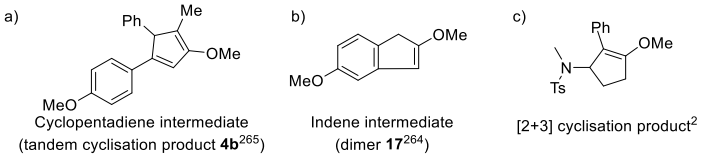
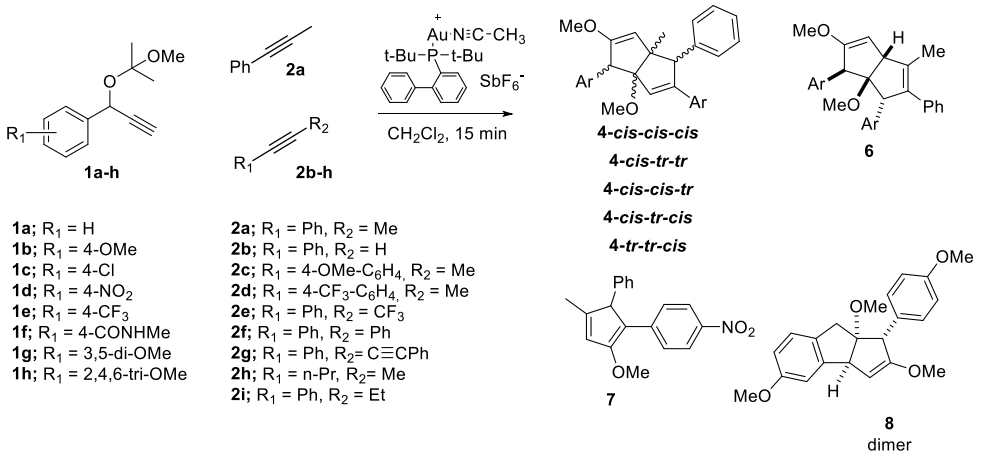


Figure 2.2. Structures of a) cyclopentadiene intermediate (from tandem cyclisation giving **4b**); b) indene intermediate (from formation of dimer **17**); and c) [2+3] cyclisation product.[2, 264, 265]

2.3.3 Substrate scope

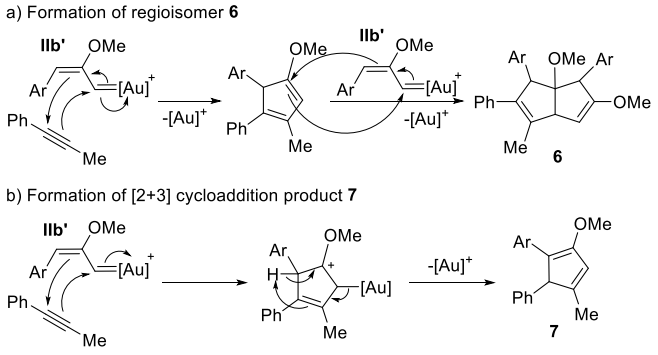
Variation of the aryl substituents of the propargyl acetals **1** and alkynes **2** (Table 2.2) gave a rich assortment of products – five diastereoisomers of **4**, two regioisomers **6**, one [2+3] cyclisation product **7** and dimer **8**. Theoretically, other diastereomers of products **4** and **6** exist and several possible products were detected (TLC), isolated in mixtures and observed (NMR). Unfortunately, some could not be identified due to amounts obtained and low purity. Product **6** is a regioisomer of compound **4**, from two successive [2+3] cycloadditions (Scheme 2.11a). Product **7** arises from a [2+3] cycloaddition (Scheme 2.11b) and product **8** is the dimer presented earlier (Scheme 2.7).

Table 2.2. Selected results of gold(I)-catalysed tandem cyclisation of propargyl acetal **1** in reaction with alkyne **2a**.



Entry	Acetal	Aryl substituents	Total yield 4 [%]	ccc	ctt	cct	ctc	ttc	Yield 6 [%]	Yield 7 [%]
1	**1a**	(4-H)	**60**	22	14	6	5	<5	**7**	-
2	**1b**	4-OMe	**51**	44	5	<1	<1	-	-	-
3	**1c**	4-Cl	**22**	(4)	12	6	4	-	**7**	-
4	**1e**	4-CF_3	**0**	-	-	-	-	-	**17**[a]	-
5	**1d**	4-NO_2	**0**	-	-	-	-	-	-	**15**
6	**1f**	4-CONHMe	**<30**	<24	<6	-	-	-	-	-
7	**1g**	3,5-diOMe	**17**	10	-	4	3	-	-	-
8	**1h**	1,3,5-triOMe	**0**	-	-	-	-	-	**11**	-

a) 2 isomers, only one was pure enough to be identified by NMR.

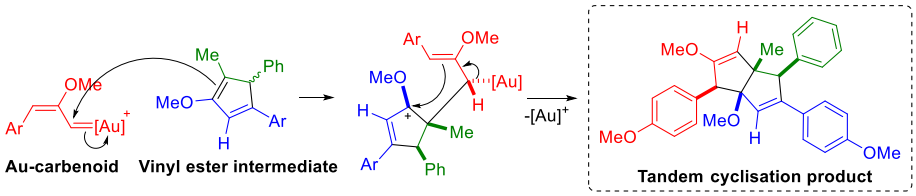


Scheme 2.11. Proposed mechanisms for the formation of a) regioisomers **6** and b) product **7**.

The chemoselectivity for product **4** or products **6**/**7** depends on whether the gold(I)-catalysed [2+2] allene-alkyne cycloaddition or [2+3] gold-carbenoid-alkyne cycloaddition is preferred in the initial step. Electron-rich acetal **1b**, favours the allenic pathway, resulting in more selective formation of "[2+3]"/[2+3] tandem cyclisation product **4**. As the electron-density of the aryl ring decreases (**1b**>**1a**>**1c**>**1e**, entries 1-4), the selectivity shifts toward product **6**, because electron-poor acetals generate allenes that are poor nucleophiles in the gold(I)-catalysed [2+2] cyclisation. On the other hand, these acetals generate electron-poor gold(I)-carbenoids **IIb'** that are good electrophiles in gold(I)-catalysed [2+3] cycloadditions with alkynes. Very electron-poor propargyl acetal **1d** undergoes a [2+3] cycloaddition (entry 5), but the cyclopentadiene product is too electron-poor for a further [2+3] reaction with a second gold(I)-carbenoid.

Steric hindrance also affects the outcome, with electron-rich diMeO-substituted acetal **1g** showing selectivity for compound **4**, but in lower yields than mono-substituted acetal **1b**, indicating that the [2+2] cyclisation step and formation of the cyclobutene ring may be difficult (entry 7). Electron-rich, highly sterically hindered triMeO-substituted acetal **1h** failed the [2+2] cyclisation step and formed only small amounts of product **6** (entry 8).

The reasons for the different distributions of product **4** are complex. It appears that steric considerations play a role. The proposed formation of the major product **4-*cis-cis-cis*** is shown in Scheme 2.12. Due to the bulk of the gold catalyst, the gold-carbenoid most likely approaches from the opposite face to the phenyl group on the vinyl ether intermediate. Subsequently, the methoxy group and the second aryl group also prefer to be trans to the gold complex for the same steric reasons, resulting in a *cis-cis-cis* confirmation.



Scheme 2.12. Proposed formation of the major diastereomer in the gold-catalysed "[2+2]"[2+3] tandem cyclisation reaction between propargyl acetals and alkynes.

However, steric hindrance alone does not explain the formation of the other diastereoisomers. For instance, the second most common diastereoisomer, **4-*cis-trans-trans*** starts with the gold-carbenoid approaching on the same side of the vinyl ester as the phenyl group, followed by the methoxy and aryl groups cyclising on the same side as the gold complex. This situation would appear to be sterically unfavourable and there are clearly other factors to consider.

Another important factor is the configuration of the fused bicyclic ring system (see examples in Figure 2.3). When the substituents on the bridging bond (OMe and Me) are *cis*, the rings take a "bent" conformation (ccc and cct). When the same substituents are trans, the rings take a "flat" conformation (ctt, ctc and ttc). The distances between the different functional groups and between the groups and the gold complex are consequently difficult to visualise.

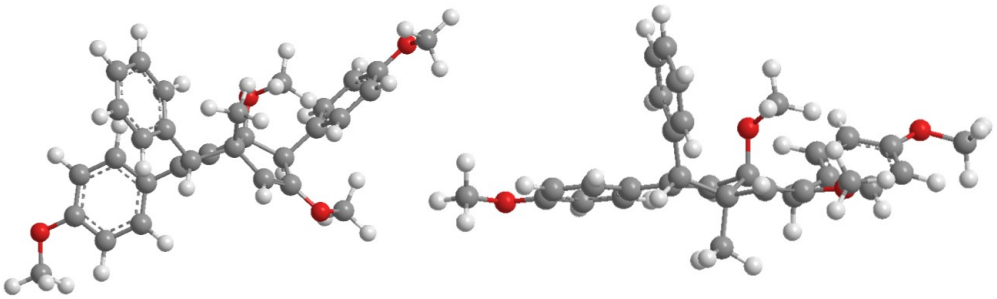


Figure 2.3. 3D models of **4b-*cis-cis-cis*** (left) and **4b-*cis-trans-trans*** (right) showing the "bent" and "flat" configurations, respectively.

From the results (Table 2.2, entries 1-3, 6 and 7), three trends are observable.

1) The gold-carbenoids prefer to approach the vinyl ether intermediate on the face opposite to the phenyl group (*cis* over the Ph-Me bond). The exception is propargyl acetal **1c** (entry 3) with the electron-withdrawing chlorine atom. This gold-carbenoid is more activated for nucleophilic attack and the difference in energy for attack on the two sides of the vinyl ether intermediate may be smaller than for the other gold-carbenoids.
2) The methoxy groups prefer to be *cis* to the methyl groups and thus further away from the gold-carbenoid. Once again, propargyl acetal **1c** is the exception, meaning other factors impact the result once more.
3) The aryl groups prefer to be *cis* to the methoxy group and further away from the gold centre.

Variation of the alkyne reagent was carried out using electron-rich propargyl acetal **1b** and alkynes **2a-i** (Table 2.2), but most of the alkynes were unsuitable for the desired tandem cyclisation reaction. Terminal alkyne **2b** resulted in a complex reaction mixture and although some products were isolated (14% of the major isomer), the purity was low, and many different compounds were observed by TLC. The terminal proton of phenylacetylene has the added complication of being able to generate a gold(I)-acetylide and corresponding dual gold(I)-complex that affects the nature of the catalytic species (see Chapter 5).[76, 77]

Alkynes **2d-g** are more electron-poor than alkyne **2a** and gave no product. Only full conversion to the parent alcohol and dimer **8** was observed. These results are in accordance with the proposed mechanism, as these alkynes are poorer nucleophiles than alkyne **2a**, and are less likely to undergo [2+2] cycloaddition and any vinyl ether intermediate would be deactivated for reaction in the [2+3] cycloaddition. These alkynes would also be unlikely to give the regioisomer **6** for the same reasons. In the absence of a suitable multiple bond partner, the acetal **1b** underwent self-dimerisation to compound **8**.

Non-aryl alkyne **2h** is a more electron-rich alkyne than alkyne **2a**. However, due to the lower polarisation of the triple bond, the reaction gave an extremely complex mixture of products where only impure compounds were observed and a variety of diastereoisomers and regiostereoisomers appeared to be produced. The products were also observed to be unstable and decompose even at low temperatures. It is possible that the alkyl chain does not stabilise some of the intermediates in

the same manner as the aryl ring. The presence of the aryl ring appears to be necessary both for the reaction to occur and to increase the stability of the products. Alkyne **2i** gave lower yield of the major product (32%) than alkyne **2a**, likely due to steric effects of the longer alkyl chain.

The most surprising result was obtained with alkyne **2c**, which gave good yields (52%), but poor stereoselectivity, giving three diastereoisomers **4-ccc, 4-cct** and **4-ttc** (15%, 19%, and 18%, respectively. The electron-rich nature of alkyne **2c** could assist both the cycloaddition steps, but the reason for the formation of these specific diastereoisomers is unknown. One explanation could be that the activation energy and energy of the transition states of these three isomers are lower when alkyne **2c** is used, compared to alkyne **2a**.

In this study, our focus was on generating "[2+3]"/[2+3] tandem cyclisation products **4**, resulting in the selection of electron-rich propargyl acetal **1b** for use during alkyne variation. A future study could involve alkyne variation with electron-poor acetals **1e** and **1d** with the aim of forming analogues of [2+3][2+3] tandem cyclisation product **6** or [2+3] cyclisation product **7**, respectively.

2.3.4 NMR studies of tandem cyclisation product 4

Each isolated isomer gave a characteristic ^{1}H NMR spectrum, especially for the benzylic protons (H_a and H_b), vinylic protons (H_c and H_d), methoxy groups (=$COCH_3$ and -$COCH_3$) and methyl group (CH_3, where present from alkyne) (see Figure 2.4).

Large variations between stereoisomers (Δδ up to 1 ppm) were observed for benzylic proton H_a and vinylic proton H_d. Significant differences were also seen for the methyl group on the bridging carbon, ranging from 0.48 ppm to 1.75 ppm. The methoxy groups, on the other hand, were less affected by the conformation of the isomers. Table 2.3 summarises the important ^{1}H NMR shifts for the obtained diastereoisomers of **4**.

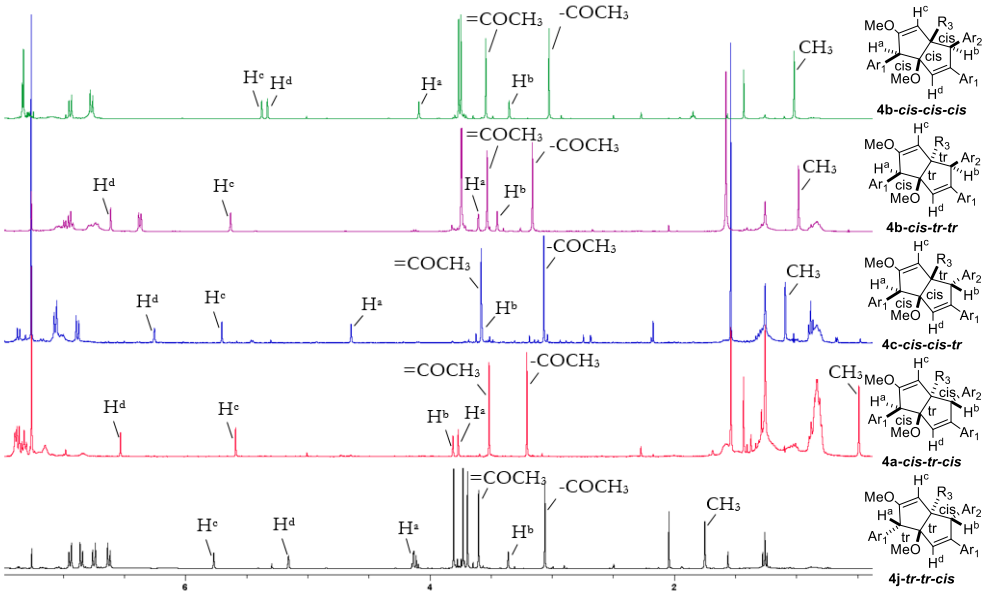


Figure 2.4. Representative ^{1}H NMR spectra for diastereoisomers of compound **4**.

Table 2.3. ^{1}H NMR shift ranges for key protons, methoxy and methyl groups for the diasteroisomers of **4**. The difference in the highest and lowest shift for each of the proton shifts (Δδ) is given in brackets.

Entry	Stereochemistry (compounds)	^{1}H NMR shift ranges (δ (Δδ) ppm)						
		H_a	H_b	H_c	H_d	$=COCH_3$	$-COCH_3$	CH_3
1	***cis-cis-cis*** (**4a**, **4b**, **4f**, **4g**, **4i**, **4j**, **4k**)	4.02-4.15 (0.13)	3.32-3.59 (0.27)	5.25-5.54 (0.29)	5.32-5.47 (0.15)	3.52-3.56 (0.04)	2.90-3.11 (0.21)	1.01-1.05* (0.04)
2	***cis-tr-tr*** (**4a-c**, **4f**)	3.60-3.66 (0.06)	3.16-3.47 (0.31)	5.63-5.66 (0.03)	6.38-6.64 (0.26)	3.51-3.53 (0.02)	3.14-3.16 (0.02)	0.98-0.99 (0.01)
3	***cis-cis-tr*** (**4a-c**, **4i**)	4.53-4.70 (0.17)	3.53-3.60 (0.07)	5.68-5.72 (0.04)	6.20-6.25 (0.05)	3.57-3.59 (0.02)	3.07-3.08 (0.01)	1.05-1.09 (0.04)
4	***cis-trans-cis*** (**4a-c**)	3.69-3.77 (0.08)	3.71-3.81 (0.10)	5.56-5.59 (0.03)	6.50-6.53 (0.03)	3.51-3.52 (0.01)	3.18-3.21 (0.03)	0.48-0.49 (0.01)
5	***tr-tr-cis*** (**4j**)	4.13	3.36	5.76	5.16	3.60	3.03	1.75

* Compound **4k** excluded as it contained an ethyl group instead of methyl group on the bridging carbon.

Interestingly, the chemical shifts are quite similar for each diastereoisomer, even with quite different substituents on the aryl rings. The difference in the highest and lowest shift for each peak (Δδ) is only between 0.01 ppm and 0.31 ppm, which is notable, considering that the substituents on the aryl ring varied from the weakly electron-withdrawing chlorine group to the strongly electron-donating dimethoxy groups.

The dramatic differences in shift between isomers could be mainly due to the position of the protons relative to the aryl rings. The effect of magnetic anisotropy on the chemical shift is positive or negative, and can be quite profound, depending on the position of the proton in the ring's field.[273, 274] In any case, the distinct proton shift patterns for each diastereomer enabled easy identification of the specific diastereoisomers from each reaction and allowed for fast identification of new isomers when they occurred.

2.3.5 NOESY correlations of tandem cyclisation product 4

One of the most challenging parts of this study was the assignment of the relative stereocentres for each diastereomer. The structures of the products were elucidated from NMR spectroscopy (COSY, HSQC/HMBC and NOESY). The proposed designations are based on a comparative study of the NOESY correlations observed and models of the diastereoisomeric structures. Due to the small size of the rings and the conformation of each isomer, a range of correlations was observed, even across *trans* bonds and across the fused-ring structure.

An example of each of the diastereomers and the observed NOESY correlations used to assign the relative stereochemistry of the main groups are given in Figure 2.5. The absence or presence of correlations was sometimes surprising and, in some cases, inconsistent between isomers. One of the surprising absences was between the methyl and methoxy groups on the bridge of the structure. In none of the diastereomers was this correlation present, possibly because these two groups can orient themselves relatively far apart.

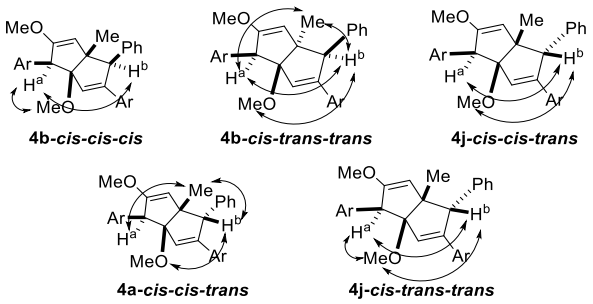


Figure 2.5. NOE correlations relevant to the assignment of the stereochemistry of the isolated diastereoisomers.

The stereochemistries are based on structural comparison of the 8 possible conformations with the observed NOESY signals between H_a and H_b and the methyl and methoxy groups. Due to some uncertainty in the interpretation of these correlations, it is emphasised that the assignments are only proposed stereochemistries. Crystal structures (X-ray) of the stereoisomers would have assisted in the identification of the stereochemistries, but X-ray quality crystals were not obtained.

2.3.6 NMR studies and NOESY correlations of regioisomer 6

Two diastereoisomers of compound **6** were identified and their stereochemistry is proposed using NMR spectroscopy techniques. The three analogues isolated (**6a**, **6c** and **6h**) are shown in Figure 2.6, along with the relevant NOESY correlations and suggested stereochemistry. The correlations for these compounds were challenging to discern, especially due to the close shifts of H_b and H_c for compounds **6c** and **6h**, and the suggested structures are subject to some uncertainty. The chemical shifts of the important signals in the ^{1}H NMR spectra are presented in Table 2.4.

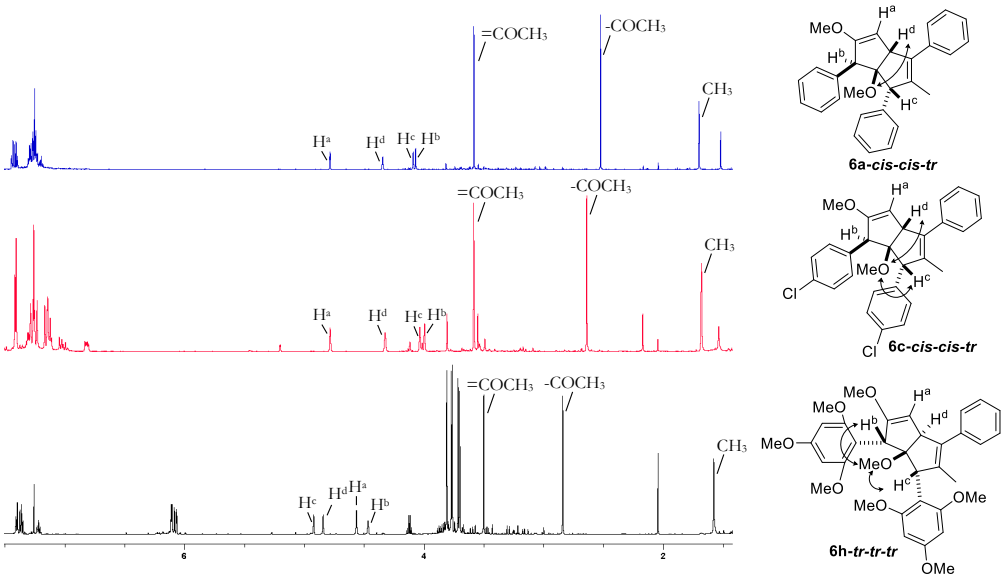


Figure 2.6. ^{1}H NMR of regioisomers **6a**, **6c** and **6h**.

Table 2.4. Chemical shifts for selected protons for compounds **6a, 6c** and **6h**.

Entry	Compound	H_a	H_b	H_c	H_d	$=COCH_3$	$-COCH_3$	CH_3
1	**6a**	4.78	4.07	4.09	4.34	3.58	2.52	1.70
2	**6c**	4.78	3.99	4.03	4.32	3.58	2.64	1.68
3	**6h**	4.56	4.46	4.92	4.84	3.50	2.84	1.58

The four CH peaks of the product **6** analogues have significantly lower chemical shifts than those of the major product **4** and all CH shifts are lower than 5 ppm. In addition, the shifts of the methyl groups were consistently much higher, corresponding better to the chemical shift of an allylic methyl than a methyl group connected to an sp^3-carbon.

In Paper II, regioisomer **6** is given with a *cis-cis-tr* configuration, but considering the similarity of the NMR data for **6a** and **6c** and significantly different data for compound **6h** (^{1}H NMR and NOESY, Figure 2.6 and Table 2.4), an alternative *tr-tr-tr* stereochemistry for compound **6h** is suggested. Another possibility is that the three methoxy groups on the aryl groups affect the chemical shifts of the CH-protons. However, given that the substituents on the aryl rings of compounds **4** did not affect the patterns of the characteristic peaks strongly, this seems unlikely.

2.4 General remarks

In this Chapter, two novel gold(I)-catalysed tandem cycloaddition reactions involving terminal propargyl acetals have been presented that are useful contributions to the field of gold catalysis. Both investigations resulted in products consisting of two units of acetal and one unit of reactant (vinyl ester or alkyne). The compounds are unique and structural elucidation was challenging. Interesting mechanistic considerations were encountered that are not fully understood. Especially for the second study of acetals and alkynes, computational calculations would have been useful to understand the mechanisms and transition states for the different regio- and stereoisomers and presents an opportunity for further work.

Some compounds with similar bicyclic systems to those synthesised in the tandem cyclisations are reported. One interesting natural product incorporating the cyclopropane-cyclopentene ring system, Halimediatrial, is isolated from *Halimeda* algae and has shown antimicrobial activity (Figure 2.7).[275-277] The cyclopropane-cyclopentene tandem cyclisation products presented in Section 2.2 could be interesting for biological studies.

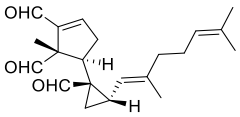
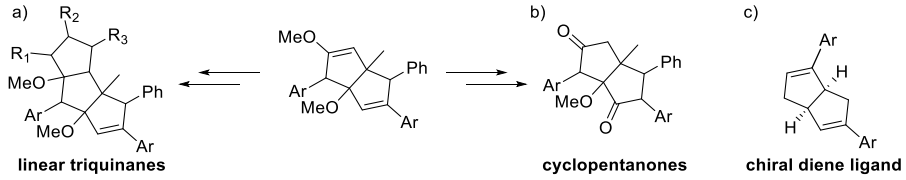


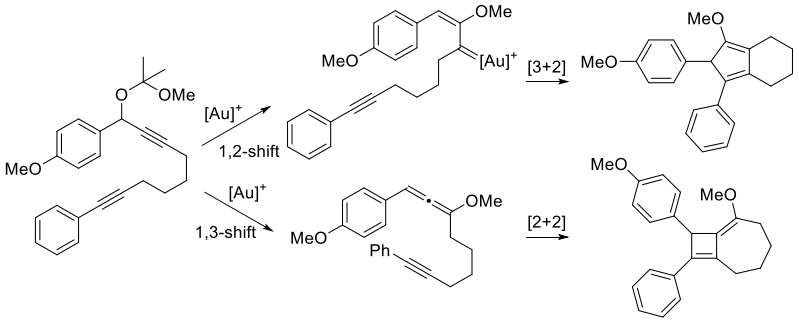
Figure 2.7. Structure of the biologically active natural product, Halimediatrial.

The novel fused compounds generated in this study could be precursors for potentially biologically active products, such as polycyclopentanoid natural products, such as linear triquinanes (Scheme 2.13a).[278, 279] Another group of compounds that could be synthesised using tandem cyclisation pathways are annulated cyclopentanones, which are attractive structural units for polycyclic cyclopentanoids (Scheme 2.13b).[280] It is possible that the compounds generated in this study are biologically active and could be tested for such activity. Futhermore, the "bent" fused compounds (**4-ccc**, **4-cct**, **6-cct**, Section 2.3) resemble known chiral diene ligands (Scheme 2.13c) and, if synthesised enantioselectively, could create good chiral environments for enantioselective reactions when bound to a metal.[281, 282]



Scheme 2.13. Linear triquinanes and cyclopentadienones that could be generated from compound **4**.

Further work in this area could include studying the acetal-alkyne reactions with a higher level of control, for example, by tethering a propargyl acetal to an alkyne. Allenes are known to undergo intermolecular gold(I)-catalysed [2+2] cycloadditions with alkenes, giving cyclobutane derivatives,[283, 284] and intramolecular gold(I)-catalysed [2+2] cycloadditions with alkynes, giving gold-cyclobutene derivatives that can be subjected to nucleophilic attack.[285, 286] In the absence of an appropriate nucleophile, a cyclobutene ring could be formed from the proposed gold(I)-cyclobutane intermediate to give the four-membered ring proposed in the current mechanism. Alternatively, a [2+3] mechanism could be possible, giving a cyclopentadiene ring. Examples of a possible substrate and products are shown in Scheme 2.14. The length of the alkane chain between the acetal and the alkyne could be varied to investigate the effect on product formation.

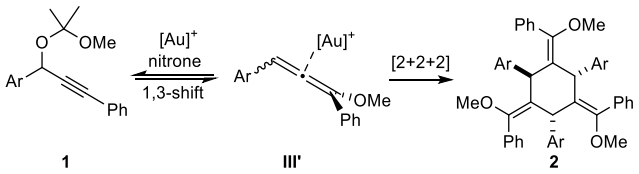


Scheme 2.14. Potential pathways for gold(I)-catalysed rearrangement and intramolecular cyclisations of propargyl acetals with tethered alkynes.

3 Gold(I)-catalysed cycloadditions of non-terminal propargyl acetals with gold(I)-nitrone complexes

3.1 General introduction

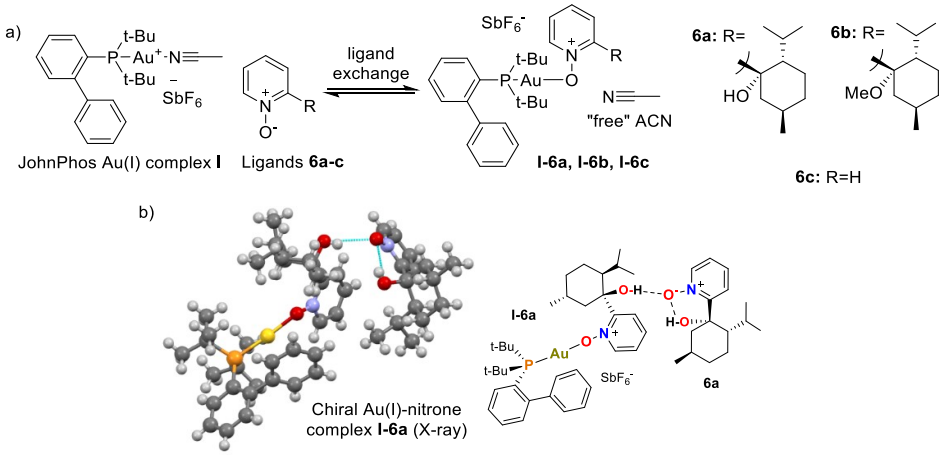
Nitrones are reported to act as oxidants[149-151] or substrates in gold-catalysed reactions,[69, 84, 85, 287] and also have uses as chiral organocatalysts.[86-90] The Fiksdahl group has reported the use of nitrones as essential additives that tune gold(I) catalyst activity for the chemoselective cyclotrimerisation of non-terminal propargyl acetals (Scheme 3.1).[5, 6] Building on this work, chiral nitrones were synthesised and tested for their ability to tune gold(I) catalyst activity in reactions with non-terminal propargyl acetals. Additional studies of reactions of non-terminal propargyl acetals gave gold(I)-catalysed cycloadditions, furnishing carbocycles and *N*-heterocycles (Paper V).



Scheme 3.1. Gold(I)-nitrone-catalysed cyclotrimerisation of non-terminal propargyl acetal **1** to trimer **2**.[5]

3.2 Chiral gold(I)-nitrone complexes

Chiral nitrones **6a** and **6b** were synthesised and, prior to use in reactions, chiral gold(I)-nitrone complexes **I-6a**, **I-6b** and **I-6c** were generated in situ by MeCN-ligand exchange (Scheme 3.2a). NMR coordination studies were carried out with mixtures of JohnPhosAu(MeCN)SbF_6 **I** and nitrone **6a** or **6b** in $CDCl_3$. From these studies, nitrone **6b** was observed to coordinate more strongly to the gold centre than nitrone **6a**, likely due to intramolecular hydrogen-bonding in **6a**.



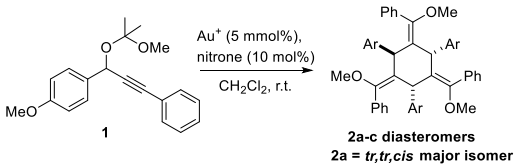
Scheme 3.2. a) In situ generation of gold(I)-nitrone complexes **I-6a,b,c**; b) Crystal structure (X-ray) of Au(I)-nitrone complex **I-6a**.

Both chiral nitrones coordinated poorer to the gold centre in solution than the achiral nitrones used in previous studies (e.g. pyridine *N*-oxide **6c**), likely for steric reasons.[5, 6] Complete ligand exchange was carried out with nitrone-OH **6a** by using a large excess of nitrone and the crystal structure of gold(I)-nitrone complex **I-6a** was obtained (Scheme 3.2b), showing a linear nitrone-O-Au(I)-P coordination mode, in accordance with earlier results.[6] In addition, intra- and intermolecular hydrogen-bonds were observed between the N-O and -OH groups (Scheme 3.2b), supporting the hypothesis that the coordination of nitrone-OH **6a** is hindered by intramolecular hydrogen-bonding.

3.3 Gold(I)-catalysed cycloadditions of non-terminal propargyl acetals

In situ-generated chiral gold(I)-nitrone complexes **I-6a** and **I-6b** showed catalytic activity in the known gold(I)-catalysed [2+2+2] cyclotrimerisation reaction with diaryl propargyl acetal **1** (Table 3.1).[5] MeO-derived complex **I-6b** (entry 3) gave higher yields than complexes **I-6a** and **I-6c** (entries 2 and 4), likely because nitrone **6b** coordinates stronger to the gold centre than nitrones **6a** and **6c**, and a stronger deactivation is required for appropriate tuning of the catalyst. Higher selectivity for the major stereoisomer **2a** was observed for complex **I-6a** compared to **I-6b** and **I-6c**, due to a combination of the steric bulk of the chiral nitrones and coordination strength to the gold catalyst.

Table 3.1. Gold(I)-catalysed [2+2+2] cyclotrimerisation of propargyl acetal **1** to trimer **2**.

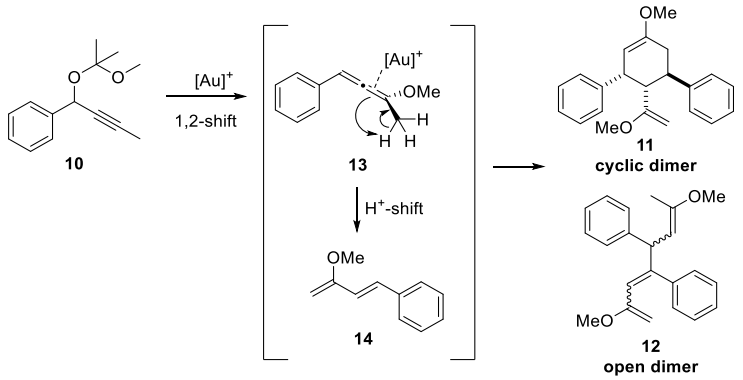


Entry	Au(I) complex	Time	Yield	**2a**[b]**:2b:2c**
1	**I**	2-24 h	-[5]	-
2	**I-6a**	18 h	40%	55:25:20
3	**I-6b**	18 h	73%	45:35:20
4	**I-6c**[6]	18 h	66%	45:25:30

a) complex product mixture; b) **2a** = *trans,trans,cis*; main product.

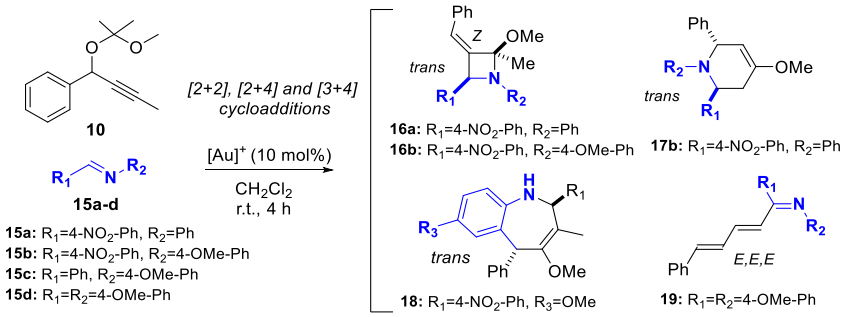
Methyl aryl propargyl acetal **10** underwent a gold(I)-catalysed 1,3-shift, in the presence of complex **I** or **I-6c**, giving allene **13** that transformed into 1,3-diene **14** through an unusual gold(I)-assisted rearrangement (Scheme 3.3). Gold-catalysed rearrangements of alkyl-substituted allenes to 1,3-dienes are limited and cationic gold(I) complexes (e.g. JohnPhosAuSbF$_6$) are reported to cause decomposition of the allene substrates,[288] so the current gold(I)-catalysed transformation of propargyl acetals to 1,3-dienes could lead to the development of new reaction pathways.

With gold(I)-nitrone complex **I-6c**, the cyclic dimer **11** may be formed from one unit of allene **13** and one unit of diene **14** in a Diels-Alder-like reaction. In contrast, open dimer **12** may be generated from two units of diene **14** with gold(I) complex **I**. Both products **11** and **12** were selectively formed according to crude ^{1}H NMR but the compounds are unstable and the low yields (25-30%) are due to loss during purification.



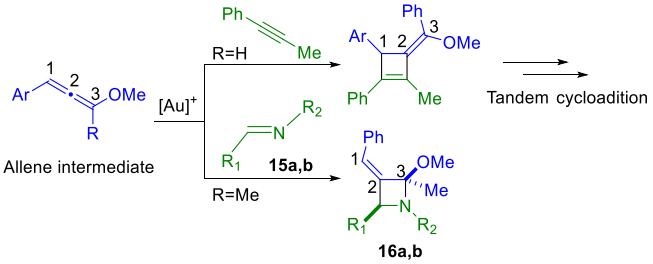
Scheme 3.3. Gold(I)-catalysed formation of intermediates allene **13** and diene **14** from propargyl acetal **10** and dimeric products **11** and **12**.

Since methyl aryl propargyl acetal **10** formed diene **14** in the presence of gold(I) complexes and diene **14** is known to undergo hetero-Diels-Alder reactions with imines,[289] the cycloaddition reactions of propargyl acetal **10** and imines **15a-d** were investigated (Scheme 3.4). Depending on the electronic properties of the imine, cycloaddition products **16-18** and acyclic compound **19** were formed (18-33%).



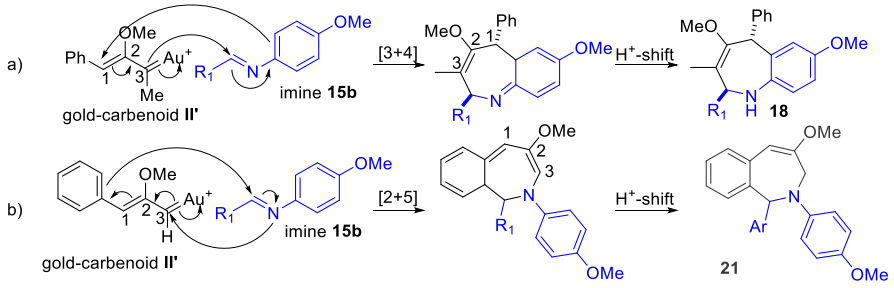
Scheme 3.4. Gold(I)-catalysed cycloaddition reactions of alkyl aryl propargyl acetal **10** with imines **15a-d**.

The [2+2] cycloaddition product **16**, generated via allene intermediate **13**, is similar to the cyclobutene intermediate formed in the gold(I)-catalysed "[2+3]"/[2+3] tandem cycloaddition of terminal propargyl acetals and alkynes (Scheme 3.5).[265] However, in the tandem cyclisation reaction, the C1-C2 double bond reacts with the alkyne, whereas the C2-C3 double bond reacts in the current [2+2] imine cyclisation. This inversion of the reaction pathway is likely due to the electron-rich aryl ring of the propargyl acetal substrate in the tandem cycloaddition reaction.



Scheme 3.5. Gold(I)-catalysed [2+2] cycloadditions of allenes with alkynes and imines.

The [3+4] cycloaddition product **18**, formed from gold-carbenoid **II'**, structurally resembles product **21**, generated from gold(I)-catalysed [2+5] cycloadditions of terminal propargyl acetals and imines (Scheme 3.6).[3] With non-terminal propargyl acetals (Scheme 3.6a), the imine aryl ring is incorporated into the seven-membered ring. Conversely, with terminal propargyl acetals (Scheme 3.6b), the acetal aryl ring is incorporated into the seven-membered ring. The difference is likely a combination of steric hindrance and electron-density at C3. Interestingly, the [2+3] cyclisation product is not observed in either case, possibly due to steric factors from the three aryl groups that would be on adjacent carbons in the hypothetical five-membered products.



Scheme 3.6. a) Gold(I)-catalysed [3+4] cycloaddition of non-terminal propargyl acetals and imines; and b) gold(I)-catalysed [2+5] cycloaddition of terminal propargyl acetals and imines.

3.4 General remarks

Two novel chiral JohnPhos-based gold(I)-nitrone complexes **I-6a** and **I-6b** were synthesised and the crystal structure (X-ray) of complex **I-6a** was obtained. ^{1}H NMR studies of the new complexes expanded on our earlier work on gold(I)-nitrones[5, 6] and showed that several factors affect the coordination strength of the nitrone to the Au centre, e.g. the steric bulk of the nitrone and internal H-bonding. The chiral gold(I)-nitrones **6a** and **6b** were successful in tuning the gold(I) catalyst activity of complex **I** and chiral gold(I)-nitrone complexes **I-6a** and **I-6b** catalysed our previously reported [2+2+2] cyclotrimerisation reaction of non-terminal propargyl acetal **1**.[5]

Non-terminal propargyl acetal **10** followed a novel dimerisation reaction pathway in the presence of a gold(I) catalyst, involving in situ generated allene **13** and diene **14** intermediates. Gold(I)-nitrone complex **I-6c** gave cyclic dimer **11** by a Diels-Alder-like [2+4] cycloaddition, while gold(I) complex **I** formed an open dimer **12**. These results demonstrate the ability of nitrones to tune the catalytic properties of gold(I) complexes for chemoselective product formation. Further investigation of gold(I)-catalysed reactions of non-terminal propargyl acetal **10** and imines resulted

in the discovery of [2+2], [2+4] and [3+4] cycloaddition reaction pathways to give products formed from allene, 1,3-diene and gold(I)-carbenoid intermediates.

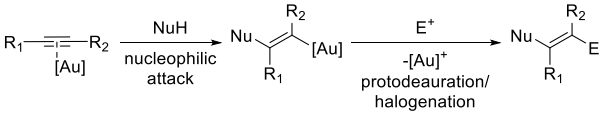
This study exemplifies the ability of non-terminal propargyl acetal substrates to form reactive intermediates in the presence of gold(I) catalysts. Generally, for both propargyl esters and acetals, the selectivity of the 1,2-shift compared to the 1,3-shift is governed by the group on the triple bond. The 1,2-shift is preferred for terminal propargyl substrates and the 1,3-shift is preferred for non-terminal substrates (see Section 1.5.2). To the best of our knowledge, gold-catalysed reactions of propargyl esters and heteroatom-containing double bonds have not been investigated. A study of gold-catalysed reactions of propargyl esters and imines would allow comparison of the reactivity of propargyl esters and acetals with C=N bonds.

Further work based on the current study could be screening of other gold(I)-catalysed reactions using our novel chiral gold(I)-nitrone complexes **I-6a** and **I-6b**. Specifically, it would be advantageous to choose reactions that give products with fewer chiral centres, with a focus on enantioselectivity. The gold(I)-nitrone-catalysed dimerisation reaction giving cyclic dimer **11** should be repeated with improved purification methods and variation of the aryl substituents of propargyl substrate **10**. In addition, the chiral nitrones **6a** and **6b** could be tested in this reaction. The work on gold(I)-catalysed cycloadditions with imines can be expanded by variation of the acetal, both with different substituents on the aryl group and other groups on the triple bond (e.g. CF_3 or other electron-withdrawing groups). Furthermore, the effect of tuning the gold(I) catalyst with achiral or chiral nitrones (e.g. **6a-c**) could give different reactivity.

4 Gold(I)-catalysed trifluoromethylation of terminal alkynes with Togni's reagent

4.1 General introduction

The combination of gold catalysis and electrophilic trifluoromethylation reagents ("$^{+}CF_3$-reagents") has potential uses in organic synthesis for incorporation of trifluoromethyl groups by gold-catalysed reactions, e.g. using propargyl substrates. Gold-activated alkynes undergo nucleophilic attack and protodeauration to give substituted alkenes (Scheme 4.1, $E^{+}=H^{+}$). Incorporation of electrophilic fluorine and other halogens in gold-catalysed reactions using Selectfluor/NXS is reported, including by our group with homopropargyl acetal substrates,[4, 254, 290, 291] and it was envisioned that introduction of a trifluoromethyl (CF_3) group was similarly possible by using $^{+}CF_3$-reagents.

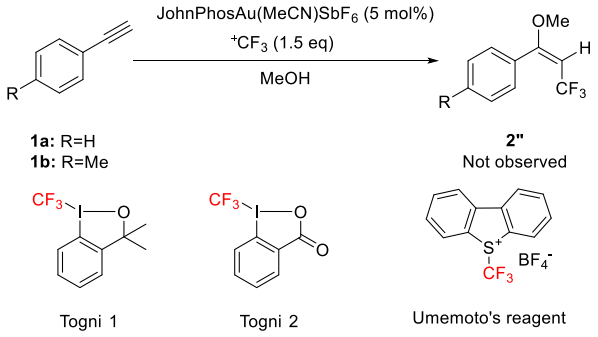


Scheme 4.1. General scheme for the overall gold-catalysed addition of a nucleophile over an alkyne and deauration with an external electrophile (E^{+}).

The properties of $^{+}CF_3$-reagents vary greatly, and the hypervalent iodine Togni reagents and Umemoto's reagent were chosen for the current study due to their relative stability and reactivity (Scheme 4.2).[261, 263] Attempts toward gold-catalysed CF_3-incorporation were made by adding $^{+}CF_3$-reagents to propargyl and homopropargyl reactions, with no success.[4, 264] Studies on simpler terminal aryl alkynes resulted in the discovery of novel gold(I)-Togni and σ,π-dual gold complexes, and a new method of trifluoromethylation of terminal alkynes, resulting in Paper III.[292]

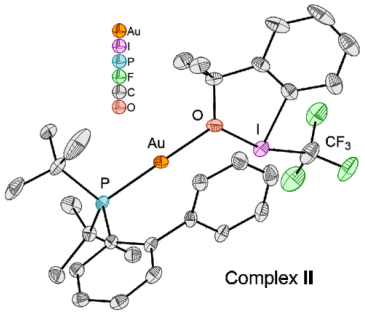
4.2 Initial studies

The gold(I)-catalysed preparation of vinyl-CF_3 products, such as compound **2"**, using conditions based on a literature method for the gold-catalysed fluorination of alkynes (Scheme 4.2)[254, 290] gave addition of methanol over the triple bond without incorporation of the CF_3 group. However, the presence of Togni 1 slowed the reaction rate significantly, compared to reaction with no electrophile.



Scheme 4.2. Test reaction for the trifluoromethylation of terminal alkynes.

^{1}H and ^{19}F NMR studies of 1:1 mixtures of the gold(I) catalyst and Togni 1 showed a displacement of the MeCN ligand and coordination of Togni 1. Similar NMR observations were recorded for Togni 2, which bonds more weakly to the gold centre. No interaction was observed in the case of Umemoto's reagent. Single crystal X-ray spectroscopy revealed the unique structure of the gold-Togni complex **II** (Figure 4.1), which shows the O-atom in the Togni molecule coordinating to the gold centre with a linear coordination mode between the P-Au-O atoms.



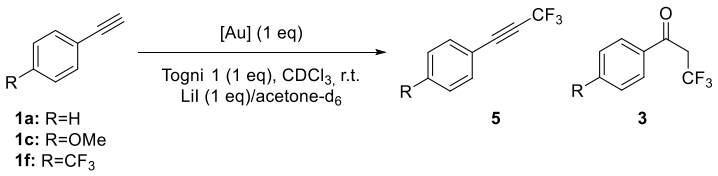
Compound	I-O bond length	I-CF_3 bond length	^{19}F NMR (CF_3)
Togni 1[293]	2.118 Å	2.267 Å	−40.1 ppm
Protonated Togni 1[293]	2.440 Å	2.214 Å	−20 ppm
Complex II	2.281 Å	2.219 Å	−31.2 ppm

Figure 4.1 Crystal structure (X-ray) of gold(I)-Togni complex **II** (counterion ($^{-}SbF_6$) excluded for clarity) and selected bond lengths and ^{19}F NMR shift values (CF_3) for Togni 1, protonated Togni 1 and complex **II**.

Prior to the current study, there were no reports describing the interaction of Togni 1 with a metal centre, although Togni 2 is known to coordinate to zinc centres,[294] which makes the discovery of this gold(I)-Togni 1 complex extraordinary. Coordination through the oxygen atom is also unusual as oxygen donor ligands in gold complexes are usually anionic and form hydroxo, oxo, or alkoxo complexes.[295] More recently, complexes of Togni 1 coordinated to $TiCl_4$, $ZrCl_4$, and $HfCl_4$ have been published.[296]

Comparison of the crystal structures and ^{19}F NMR shifts of Togni 1, the gold-Togni 1 complex, and protonated Togni (Figure 4.1), showed that the Togni unit was activated by the gold centre (entry 3), although not to the same extent as by $BAr^{F}{}_4$-superacid (entry 2). The I-O bond lengths increase while the I-CF_3 bond lengths decrease, as expected for activation at the oxygen position.

With the knowledge in hand that gold was activating Togni 1, stoichiometric amounts of gold catalyst and Togni 1 were combined and mixed with alkynes **1a**, **1c** and **1f** and a non-protic nucleophile (LiI in acetone-d_6) (Scheme 4.3). These reactions were followed by ^{1}H and ^{19}F NMR.



Scheme 4.3. Test reaction with stoichiometric amounts of gold catalyst, Togni reagent and aprotic nucleophile.

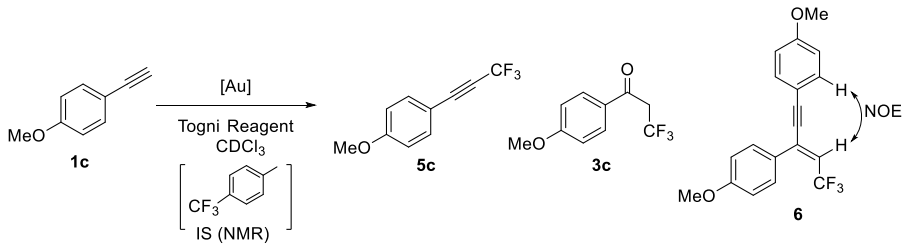
The reactions with LiI gave no incorporation of the iodine nucleophile, but fluorinated compounds **5** and **3** were observed in the reactions with alkynes **1a** and **1c**.[297, 298] Recent literature reports the regioselective gold-catalysed hydration of trifluoromethylated alkynes, supporting the hypothesis that alkyne **5** forms first before transformation into ketone **3**.[298] The addition of an inorganic base or water to the reaction with alkyne **1c** (to assist with the removal of the terminal proton) gave only

slightly lower yields of fluorinated products. Although the trifluoromethylation of terminal alkynes is known using copper catalysts,[299] this is the first time gold catalysis and $^{+}CF_3$-reagents have successfully been combined.

4.3 Optimisation studies and substrate scope

^{1}H and ^{19}F NMR studies towards optimisation of the trifluoromethylation reaction were carried out with alkyne **1c**, using an internal standard (4-trifluoromethyltoluene) (Table 4.1). The factors that affected the yield and reaction rate were the amounts of gold(I) catalyst, alkyne and Togni 1, and temperature. Addition of acids or organic bases gave no positive effect and counterions other than $^{-}SbF_6$ gave lower yields. A selection of the results is presented in Table 4.1; yields are based on the amount of the limiting reagent (bold font).

Table 4.1. Selected results from optimisation studies of trifluoromethylation of alkyne **1c**.

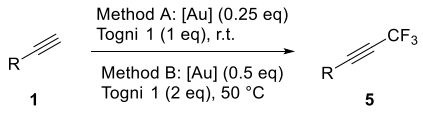


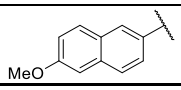
Entry	Amounts of reactants (equiv.)			Conditions		Yield [%]			
	Au	Togni	Alkyne	T (°C)	Time (h)	5	6	3	Total
1	1	1	**1**	r.t.	16	16	1	1	18
2	0.5	1	**1**	r.t.	16	29	3	0	32
3	0.5	2	**1**	50	2	32	3	3	38
4	0.25	**1**	1	r.t.	4	36	5	1	42
5	0.25	**1**	2.5	r.t.	24	25	17	3	46

Three trifluoromethylated products were obtained – alkyne **5c**, alkyne-alkene **6** and ketone **3c** (Table 4.1). Alkyne-alkene-CF_3 **6** is formed by gold-catalysed addition of a second alkyne over the triple-bond of alkyne **5**, which is reported in literature.[300] The highest yields of product **5c** were obtained with a mixture of 0.5:2:1 [Au]:alkyne **1c**:Togni 1 at r.t. (entry 3) or 0.25:1:1 [Au]:alkyne **1c**:Togni 1 at r.t. (entry 4). Higher total yields of trifluoromethylated products **3c**, **5c** and **6** were observed with an excess of alkyne (entry 5), with a decrease in chemoselectivity.

A substrate study, using these two sets of conditions, showed that the yields of trifluoromethylated products were highly dependent on the electronic nature of the terminal alkyne (Table 4.2) Electron-rich alkynes with *para*-methoxy groups performed best (entries 1-4). Alkynes without strongly electron-donating groups or electron-withdrawing groups gave poor results (entries 5-7). 2-Ethynyl-6-methoxynaphthalene (entries 10-11) performed poorer than 1-ethynyl-4-methoxybenzene (entries 1-2), but gave better results with Method B than Method A.

Table 4.2. Alkyne substrate variation in gold(I)-catalysed trifluoromethylation of terminal alkynes.



Entry	R	Method	Time	Yield
1	4-$CH_3OC_6H_4$	A	16 h	30%
2		B	2 h	32%
3	2-CH_3-4-$CH_3OC_6H_4$	A	48 h	32%
4		B	2 h	23%
5	4-$CF_3C_6H_4$	A	24 h	0%
6	Ph	A	24 h	1%
7	4-$CH_3C_6H_4$	A	24 h	3%
8	2-$CH_3OC_6H_4$	A	48 h	8%
9		B	2 h	7%
10		A	24 h	7%
11		B	2 h	18%

4.4 Proposed mechanism

Figure 4.2 shows how reaction progression was monitored and interpreted, using a reaction with 0.25:1:2.5 [Au]:Togni 1:**1c**. The generation of gold(I)-Togni complex **II** (step i, −31.2 ppm, ^{19}F), dual gold(I) complex **III** (step ii, 3.90 ppm, ^{1}H), a corresponding amount of Togni-H (−34.1 ppm, ^{19}F) and products **5c**, **6** and **3e** (step v, OMe region, ^{1}H) are clearly observed. The steps involved in the proposed mechanism (Scheme 4.4) are based on NMR studies, characterisation of gold complexes **II** and **III** (NMR, HRMS, X-ray), and previous literature in the field of dual gold catalysis.[76, 77, 80, 301]

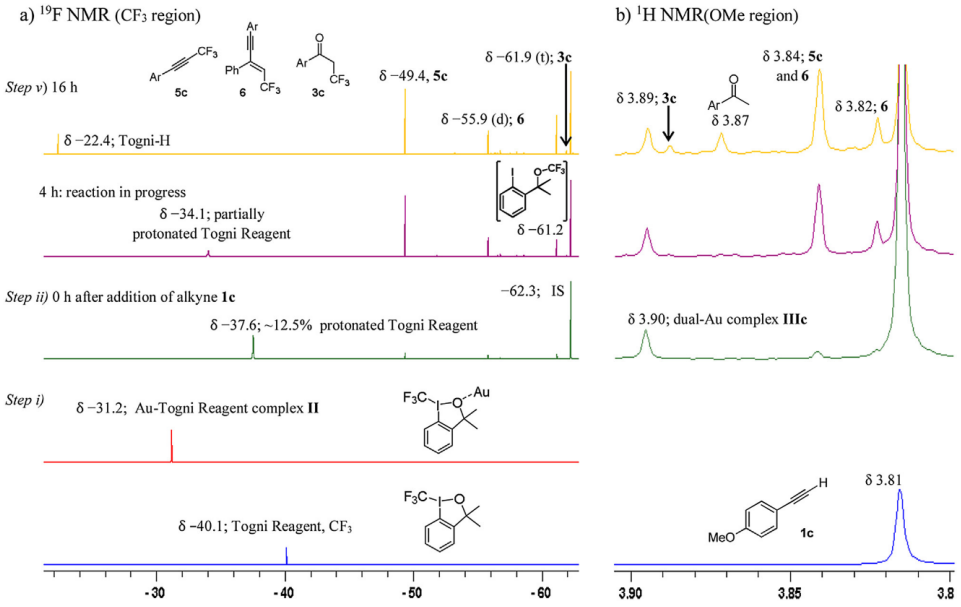
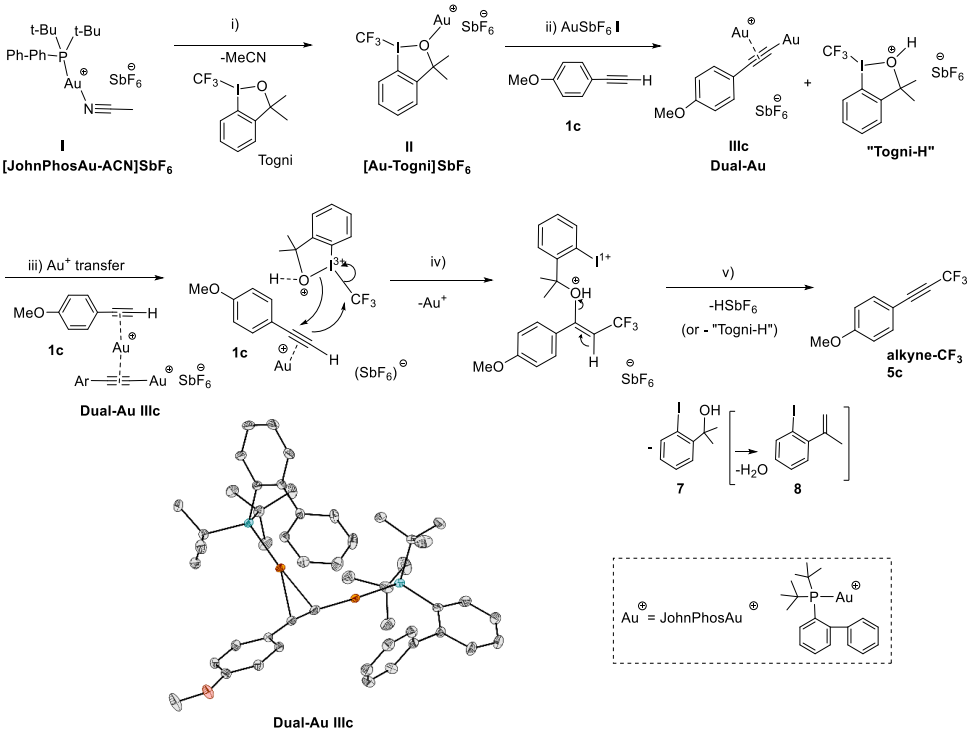


Figure 4.2. Selected ^{1}H and ^{19}F NMR spectra, following the progress of the trifluoromethylation of **1c** by observing the CF_3 and MeO signals from the gold complexes **II** and **III**, and products **5c**, **6** and **3c**.



Scheme 4.4. Proposed mechanism for Au(I)-promoted trifluoromethylation of alkyne **1c** and crystal structure (X-ray) of σ,π-dual gold complex **IIIc**.

4.4.1 Generation of the active catalytic dual gold species

Gold(I)-Togni 1 complex **II** is generated from gold catalyst **I** and Togni 1 (Scheme 4.4, step i) and is stable in solution at r.t. for several days. Addition of alkyne **1c** results in generation of dual gold(I) complex **III** and a corresponding amount of protonated Togni reagent ("Togni-H", step ii). Dual gold complex **III** was isolated, purified by flash chromatography and recrystallised. ^{1}H NMR analysis and HRMS showed that the complex consisted of two units of gold complex **I** and one unit of alkyne **1c**. Single crystal X-ray crystallography confirmed the structure of the σ,π-dual gold(I) complex.

The formation of dual gold(I) complexes has been described in literature,[77] including a description of superacid generation from the combination of the freed terminal proton and counterion from the gold catalyst.[76] DFT calculations carried out in the group of Hashmi explained the preferential generation of the dual gold complex rather than further gold-acetylide complexes, even in a large excess of alkyne, reporting that the gold-acetylide complex is more attractive to a second unit of gold catalyst than a free terminal alkyne.[301]

Dual gold complex **III** is stable in solution but decomposes in the presence of the generated superacid $HSbF_6$ if no base or other compound is available to absorb the acidic proton. Combination of solutions of only gold catalyst **I** and alkyne generated a dark purple solution immediately (Figure 4.3), which indicated formation of gold nanoparticles.[78, 302]

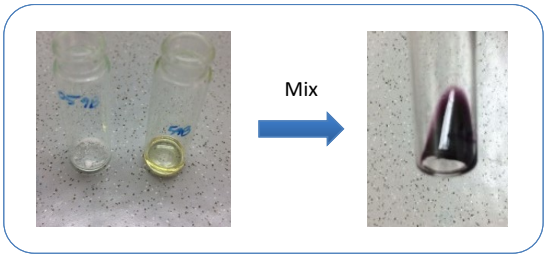
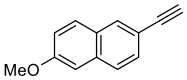


Figure 4.3. Combination of gold complex **I** in CH_2Cl_2 (colourless, far left) and 1-ethynyl-4-methoxybenzene in CH_2Cl_2 (pale yellow, second from left) gave a dark purple solution immediately (right).

The amount of Togni-H in the reaction can be estimated from the chemical shift of the trifluoromethyl peak (^{19}F NMR).[263] For example, a shift of approximately −37.6 ppm (Figure 4.2, step ii) indicates 12.5% protonation, corresponding to the amount of acid released from the generation of dual gold complex **III** from 25% gold catalyst **I**. The protonation of Togni 1 by the superacid is important because it prevents decomposition of the dual gold catalyst while simultaneously becoming activated for the trifluoromethylation reaction. As the Togni reagent is consumed, the superacid is regenerated and can cause decomposition of the catalyst.

In substrate testing experiments (Table 4.2), changes in the ^{1}H and ^{19}F NMR spectra were in agreement with the proposed mechanism (i.e. generation of dual gold complexes, release of the corresponding amount of acid and protonation of Togni 1, Table 4.3). The groups on the substituted aryl alkynes experienced a deshielding effect when incorporated into the dual gold complexes (entries 2-7) and the signal of the Togni-CF_3 group shifted for all substrates (ca. −37.5 ppm), corresponding to 12.5% Togni-H.

Table 4.3. ^{1}H and ^{19}F NMR data for the reaction mixtures with different substrates.

Entry	Substrate	Alkyne group observed	Original shift	New shift	Togni-CF_3 shift
1	PhC≡CH	-	-	-	−37.8 ppm
2	4-MeC_6H_4C≡CH	Me	2.35 ppm	2.45 ppm	−37.9 ppm
3	4-$MeOC_6H_4C$≡CH	MeO	3.81 ppm	3.90 ppm	−37.7 ppm
4	2-$MeOC_6H_4C$≡CH	MeO	3.91 ppm	3.95 ppm	−37.9 ppm
5	2-Me-4-$MeOC_6H_4C$≡CH	Me MeO	2.43 ppm 3.80 ppm	2.47 ppm 3.88 ppm	−37.6 ppm
6	4-$CF_3C_6H_4C$≡CH	CF_3	−62.92 ppm	−62.88 ppm	−37.8 ppm
7		MeO	3.92 ppm	3.97 ppm	−37.8 ppm

4.4.2 LAu^+ fragment transfer to free alkyne and addition-elimination of Togni-H

The generation of the dual gold complex **III** and Togni-H is followed by a transfer of the π-bonded gold fragment to a free alkyne (Scheme 4.4, step iii), then an addition-elimination of Togni-H to give the trifluoromethylated alkyne product **5c** (Scheme 4.4, steps iv and v). The dual gold complex is proposed to be the stable "resting state" of the gold catalyst that delivers a gold fragment to the reaction. This proposal is supported by DFT calculations of a gold-catalysed intramolecular reaction with a terminal alkyne.[301] Most of the reactions catalysed by dual gold complexes involve intramolecular gold fragment transfers.[79, 80] The current study reports a rare case of intermolecular transfer of a gold fragment to a free alkyne, activating it for reaction.

4.5 General remarks

The aim of this investigation was to use gold(I) catalysts and electrophilic CF_3-reagents to incorporate trifluoromethyl groups into organic molecules. Using terminal aryl alkynes as substrates, it was found that sub-stoichiometric amounts of gold(I) catalyst (25%) generated moderate yields of trifluoromethylated products (up to 46%), indicating a gold-catalysed process. Novel interactions between the gold(I) catalyst and Togni's reagent were studied and the structure of the gold(I)-Togni complex **II** was confirmed (NMR/X-ray). The proposed reaction pathway also included the generation of a σ,π-dual gold(I) complex **III**. These mechanistic discoveries provided insight into the gold(I) species that are involved in reactions with terminal alkynes.

Incorporation of the alkyne substrate into the σ,π-dual gold(I) complex had two implications:

1) The identity of the catalyst is affected by the alkyne, meaning that a variation of the alkyne substrate is also a variation of the catalyst. Pre-generation of a σ,π-dual gold complex from one alkyne and subsequent addition of the alkyne substrate would allow for independent variation of the substrate and the catalyst.
2) The generation of the active gold(I) species **III** consumes some of the substrate and incorporates two units of the gold complex **I**, which means that the catalyst loading is 50% lower and yields are higher (when alkyne **1** is the limiting reagent) than reported.

Thus, compared to the reported results (Paper III), the highest yields of trifluoromethylated products are, in fact, higher and the actual catalyst loading is lower (51% yield, 15% catalyst loading, entry 4). For easier interpretation of results, the dual gold(I) complex **III** could have been pre-generated or isolated before use in reactions. Based on this work, novel JohnPhos-based and chiral bridged σ,π-dual gold(I) complexes were synthesised and tested in propargyl reactions (Chapter 5).

Table 4.4. Adjusted reagent amounts and yields, considering that alkyne is used in the generation of the dual gold(I) complex and that each dual gold(I) complex contains two units of gold(I) catalyst **I**.

Entry	Amounts of reactants (equiv.)					Conditions			Yield [%]	
	Au	Dual Au	Togni	Alkyne	Alkyne, adjusted	T (°C)	Time (h)	Actual catalyst loading	Total	Total, adjusted
1	1	0.5	1	1	**0.5**	r.t.	16	100%	18	36
2	0.5	0.25	1	1	**0.75**	r.t.	16	33%	32	43
3	0.5	0.25	2	1	**0.75**	50	2	33%	38	51
4	0.25	0.125	1	1	**0.825**	r.t.	4	15%	42	51
5	0.25	0.125	**1**	2.5	2.06	r.t.	24	12.5%	46	46

Further work on this trifluoromethylation method could include use of other electrophilic $^{+}CF_3$-reagents. The cation-donating abilities of a range of $^{+}CF_3$-reagents are reported and can be used to evaluate possible candidates.[303] Alternatively, exploration of the combination of gold(I) catalysts and other hypervalent iodine reagents (such those shown in Figure 4.4) could result in development of useful synthetic tools.[304]

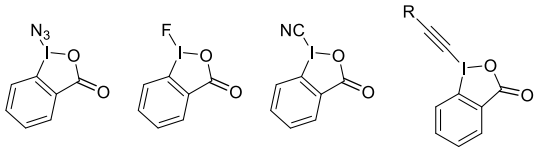


Figure 4.4. Hypervalent iodine reagents that could be used in gold(I)-catalysed reactions.

5 Novel σ,π-dual gold(I) complexes: preparation and catalytic activity

5.1 General introduction

The findings published in Paper IV[272] will be discussed in this chapter. σ,π-Dual gold(I) complexes ("DGCs") are catalytically active in several organic transformations,[76, 79, 80, 305] and are known to give different catalytic activity or regioselectivity, compared to monogold(I) complexes.[76, 80, 82, 83] DGCs with NHC ligands have received much attention and one of the most used NHC-DGCs (Hashmi, Figure 5.1)[80] has propyne as the alkyne unit, which is released in the initial transfer of the gold fragments.[80, 306-310] DGCs with phosphane ligands or aryl acetylide moieties are much less investigated,[76] and our previous discovery of complex **Ib** (Figure 5.1) as the active species in the gold(I)-catalysed trifluoromethylation of terminal alkynes[292] inspired us to carry out further work with JohnPhos-based DGCs.

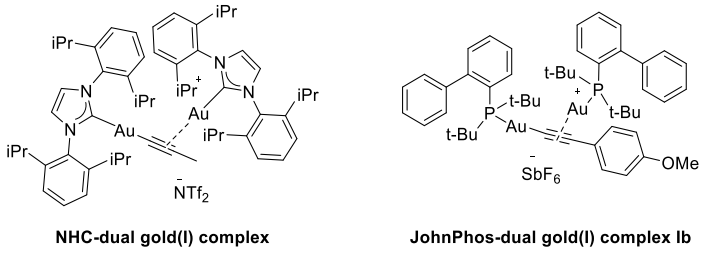
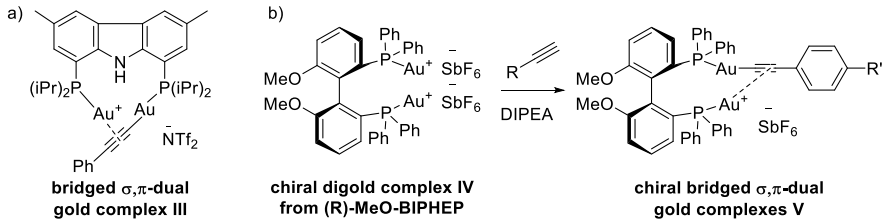


Figure 5.1. σ,π-Dual gold(I) catalysts reported by Hashmi[80] and Siah.[292]

To expand the scope and application of dual gold(I) complexes, studies were carried out with a range of JohnPhos-based DGCs in gold(I)-catalysed propargyl reactions developed by the Fiksdahl group.[1-3, 264] In addition, many of the gold(I)-catalysed cycloaddition reactions give rise to products with stereogenic centres.[1, 2, 126, 127, 264, 265, 311] Thus, it was decided to develop new chiral gold(I) complexes for enantioselective gold(I)-catalysed propargyl reactions.

Diphosphane digold(I) complexes, such as complex **IV** (Scheme 5.1b), are known to give enantioselectivity in a range of gold-catalysed transformations.[30, 68, 69, 230, 312-315] The bridged dual gold(I) complex **III** is the only reported example of a bridged diphosphane dual gold(I) complex (Scheme 5.1a), but its catalytic properties are unknown.[316]



Scheme 5.1. Structures of dual gold(I) complex **III**,[316] chiral digold(I) complex **IV**[30] and chiral dual gold(I) complexes **V**.

Generation of novel bridged dual gold(I) complexes, derived from chiral diphosphane ligands, is possible by treating complex **IV** and similar chiral digold(I) complexes with alkyne in the presence of base (Scheme 5.1b). These bridged complexes have the potential to display different catalytic activity and enantioselectivity than the parent digold(I) complex.

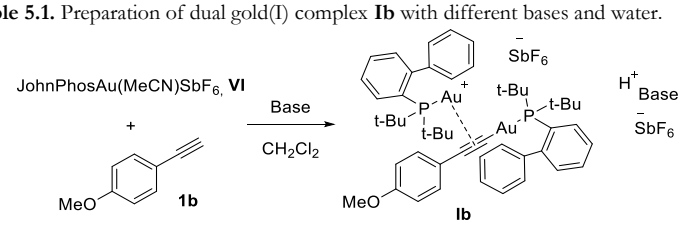
Based on this knowledge, there were two main goals of this study:

1) Synthesis of novel JohnPhos-based DGCs with achiral and chiral alkynes and testing of their catalytic activity and enantioselectivity (where relevant) in propargyl reactions; and
2) Synthesis of novel chiral bridged diphosphane DGCs with achiral alkynes and testing of their catalytic activity and enantioselectivity in propargyl reactions.

5.2 Synthesis of JohnPhos dual gold(I) complexes

The original method of synthesising DGCs, published in Paper III, involved mixing equal amounts of JohnPhosAu(MeCN)SbF_6 complex **VI** (Table 5.1) with alkyne **1b** in dichloromethane in the presence of inorganic base K_2CO_3 (entry 1).[292] As noted in the experimental section of Paper III, nanoparticles were formed immediately, likely because the base was insoluble and the free, generated superacid caused rapid decomposition of the DGC. A screening study was carried out, switching to organic bases (DBU and DIPEA) or a 2-phase system with water to facilitate removal of the acid generated from formation of the DGC (Table 5.1).

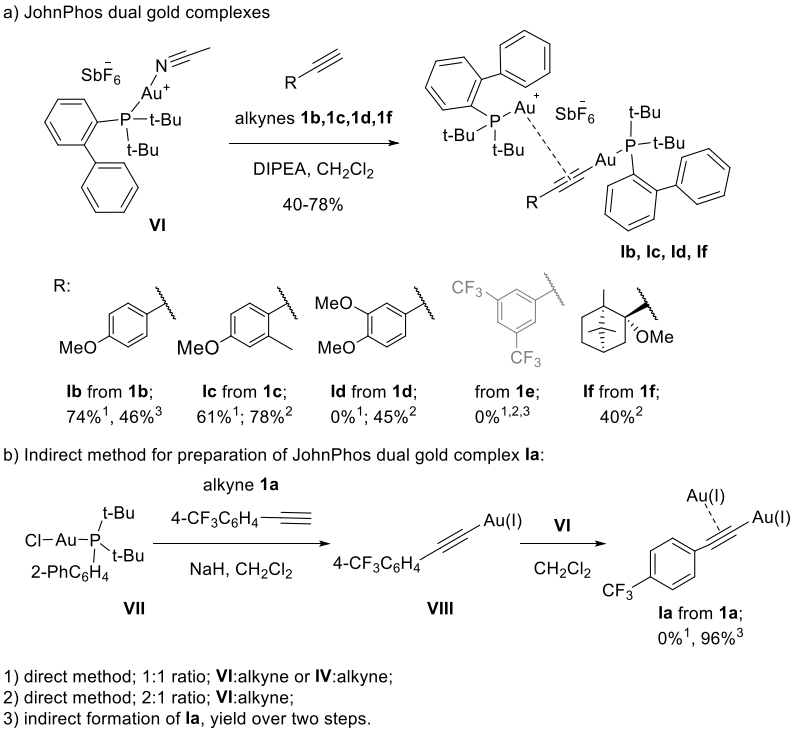
Table 5.1. Preparation of dual gold(I) complex **Ib** with different bases and water.



Entry	Alkyne	Base	Equiv. base	Purification method	Result
1	0.93 equiv.	K_2CO_3	1.2	Recrystallisation or pipette flash	Nanoparticle formation
2	1.1 equiv.	DBU	1.5	Recrystallisation	Au-DBU complex
3	1.1 equiv.	(H_2O-phase)	91	Phase separation then recrystallisation	**Ib**, 90%
4	1.2 equiv.	DIPEA	1.4	Recrystallisation or pipette flash	**Ib** and amine salt
5	1.2 equiv.	DIPEA	1.0	Aqueous wash then recrystallisation	**Ib**, 74%

DBU, DIPEA and water absorbed the superacid efficiently and no nanoparticle formation was observed (Table 5.1, entries 2-5), but use of DBU also resulted in coordination of the base to the gold center (entry 2). Use of water gave a high yield of DGC **1b** (90%, entry 3) after recrystallisation and the complex was pure according to NMR analysis. Use of DIPEA gave a mixture of target dual gold(I) complex **Ib** and the corresponding amine salt after recrystallisation or a pipette flash (entry 4) but gave pure complex **Ib** after aqueous washing and recrystallisation (74%, entry 5). Although water appeared to give a higher yield, it was difficult to judge the purity of the complex (NMR) and if any of the generated acid remained. Therefore, DIPEA was chosen for further synthesis of DGCs.

Dual gold(I) complexes **Ib**, **Ic**, **Id** and **If** were synthesised from monogold(I) complex **VI** in moderate to high yields (40-78%, Scheme 5.2a). The NMR data for the isolated dual gold(I) complex **Ic** was in accordance with the NMR data obtained during the trifluoromethylation reactions with alkyne **1c**,[292] confirming that dual gold(I) complexes were generated *in situ* in those reactions (Table 4.3, entry 5). With electron-poor alkyne **1a**, an indirect method was used with formation of gold-acetylide **VIII**[292] and subsequent coordination of complex **VI** to give complex **Ia** in high yield (96%, Scheme 5.2b).



Scheme 5.2. a) Synthesis of JohnPhos dual gold(I) complexes; b) Indirect method for synthesis of complex **Ia**.

5.3 Synthesis of chiral bridged dual gold(I) complexes

Chiral dual gold(I) complexes with a chiral bridging diphosphane ligand and an achiral alkyne have the potential to give enantioselectivity as the two gold centres are in closer proximity than in the parent chiral digold(I) complexes. For this study, formation of chiral bridged dual gold(I) complexes was attempted with several chiral diphosphane ligands (Figure 5.2).

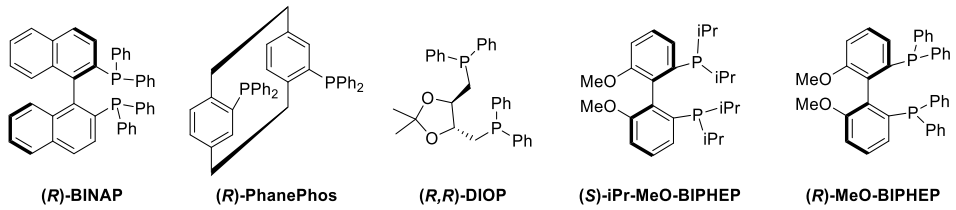
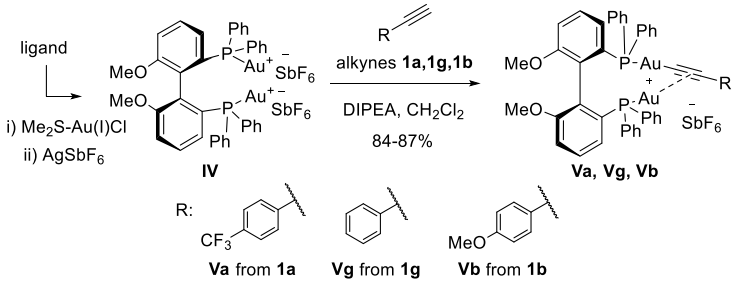


Figure 5.2. Chiral diphosphane ligands tested in the work towards chiral bridged diphosphane DGCs.

A direct method of generation was used for this study (Method 2, Section 5.2). The ligands were mixed with $(Me_2S)AuCl$ (2 equiv.) in CD_2Cl_2, then $AgSbF_6$ was added (2 equiv.) and finally a mixture of alkyne **1b** and DIPEA was added (shown for (*R*)-MeO-BIPHEP in Scheme 5.3). The steps were followed by NMR analysis (^1H and ^{31}P) and HRMS was carried out on the isolated material. For all ligands, the first two steps to the formation of the digold complex were successful, but the outcome in the final, dual gold(I)-forming step and isolation of the complexes varied. The formation of bridged dual gold(I) complex **Vb** from (*R*)-MeO-BIPHEP (Scheme 5.3) was successful and complex **Vb** was isolated in excellent yield (85%Scheme 5.3). Analogous complexes **Va** and **Vg** with alkynes **1a** and **1g** were also obtained (87% and 84%, respectively).



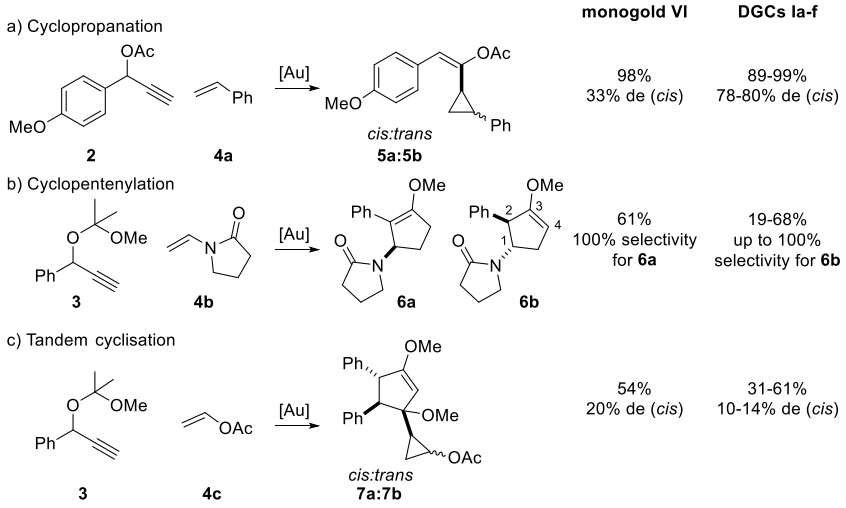
Scheme 5.3. Synthesis of (*R*)-MeO-BIPHEP dual gold complexes **V**.

For (*R*)-BINAP, the dual gold(I) complex was formed in solution, but was unstable and partially decomposed during isolation. HRMS indicated formation of the desired DGC and a second complex comprising one ligand, three gold atoms and two acetylide units. (*R*)-PhanePhos appeared to form a stable DGC complex with the correct mass (HRMS), but the ^{31}P NMR signal was broad indicating a dynamic equilibrium between different configurations of the complex. The geometry of the ligand may hinder the second gold atom forming a stable complex with the gold-acetylide moiety. More electron-rich ligands, (*R,R*)-DIOP and (*S*)-iPr-BIPHEP, generated at least four complexes in solution that precipitated together (^{31}P NMR). HRMS indicated the formation of the desired DGCs but gave much stronger peaks for other complexes, including LAu^+ and L_2Au^+ complexes, indicating that the DGC may not be the most favourable configuration for these ligands.

From these studies, it is shown that the identity of the ligand and its electronic nature and geometry affect the formation of a stable and isolatable dual gold complex. For example, ligands that are either less electron-rich ((*R*)-BINAP) or more electron-rich ((*S*)-iPr-BIPHEP) than (*R*)-MeO-BIPHEP fail to give stable complexes. The (*R*)-PhanePhos has a special geometry and one of the phenyl rings in the "window" can rotate, placing the second gold on the other side of the window to the gold-acetylide, this could explain the broad NMR signals. Further NMR studies at higher and lower temperatures could have given information about the structure of the PhanePhos DGC. In addition, the electronic nature of the substituent on the aryl alkyne also affects the stability of the final complex, with more electron-rich alkynes **1b** and **1g** giving more stable MeO-BIPHEP-based complexes than alkyne **1a**. It is possible that stable complexes with the other diphosphane ligands could be formed with less electron-rich alkyne **1a** and could be worth studying in the future.

5.4 Reactivity of JohnPhos dual gold(I) complexes in propargyl reactions

The catalytic activity of the synthesised JohnPhos-based dual gold(I) complexes **Ia-f** was tested in three propargyl reactions developed by our group and compared to monogold(I) JohnPhosAu(MeCN)SbF_6 complex **VI** (Scheme 5.4).[2, 97, 264] Generally, dual gold(I) complexes **Ia-f** were active in the test reactions and one or more of the DGCs gave better yields than that obtained with monogold complex **VI**. The DGCs were also more stereoselective in the cyclopropanation reaction and more regioselective in the cyclopentenylation reaction than complex **VI**. Chiral dual gold(I) complex **If** failed to give enantioselectivity, likely because the chiral unit is too far away from the propargyl substrate in the stereo-determining step.



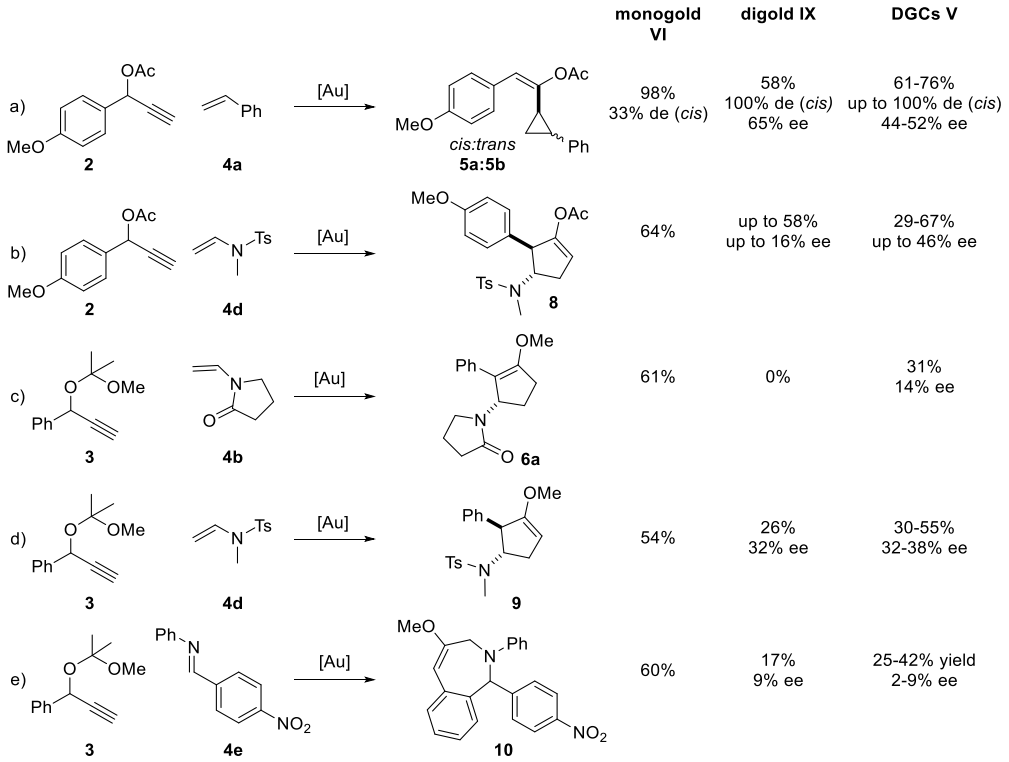
Scheme 5.4. Gold(I)-catalysed propargyl reactions with complex **VI** and DGCs **Ia-f**.

The opposite preference of the dual gold(I) complexes **1a-f** for the *cis* isomer (cyclopropanation, Scheme 5.4a) or regioisomer **6b** (cyclopentenylation, Scheme 5.4b) can be explained by the transfer of the gold fragment to the gold-acetylide and regeneration of the DGC in the deauration step. In the cyclopropanation reaction, the configuration of the intermediate favours the approach of the gold-acetylide and coordination of the departing gold fragment opposite to the bulky phenyl group, giving the *cis* isomer. Similarly, for the cyclopentenylation reaction, deauration from the intermediate with the gold fragment attached at C4 favours the approach of the gold-acetylide, giving regioisomer **6b**.

There were no clear trends for the overall catalytic activities of the dual gold(I) catalysts based on the substituents on the alkynes, as the overall activity of the complexes is governed by two opposing factors. First, the transfer of the π-bonded gold fragment from the gold-acetylide to the propargyl substrate, which would be favoured by an electron-poor alkyne. This transfer also requires an energy barrier to be crossed and explains the longer reaction times or higher temperatures required by the DGCs compared to monogold complex **VI**. Second, the deauration step to regenerate the DGC and reconnect the gold fragment to the gold-acetylide unit would be favoured by electron-rich alkynes.

5.5 Reactivity of MeO-BIPHEP dual gold(I) complexes in propargyl reactions

The catalytic activity of the novel chiral bridged MeO-BIPHEP DGCs **V** (Scheme 5.3) was tested in reactions with terminal propargyl esters and acetals (Scheme 5.5) and compared to the activity of monogold(I) complex **VI** and digold(I) MeO-BIPHEP complex **IV** (Scheme 5.5).



Scheme 5.5. Gold(I)-catalysed propargyl reactions with monogold(I) complex **IV**, digold(I) complex **VI** and dual gold(I) complexes **Va**, **Vb** and **Vg**.

In the presence of digold(I) complex **IV** and dual gold(I) complexes **V**, the cyclopropanation reaction of propargyl acetal **2** and alkene **4a** (Scheme 5.5a) gave good yields of cyclopropyl products **5** (58% and 61-76%, respectively) and substantial enantioselectivity for the *cis* isomer (65% ee and 44-52% ee, respectively). A possible explanation for the lower enantioselectivity obtained with dual gold(I) complexes **V** than digold complex **IV** is a proposed *gem*-digold intermediate, which is possible only for digold complex **IV** and brings the two gold centres close to the substrates (Figure 5.3a).

Digold and dual gold complexes **IV** and **V** required longer reaction times for full conversion of the propargyl substrate, as observed for the same reaction with JohnPhos-based DGCs **I**. Reaction times increased with increasing electron-density of the acetylide unit, indicating that the rate-limiting step is disconnection and transfer of the π-bound gold unit to the substrate. Digold and dual gold complexes **IV** and **V** preferred the *cis* isomer (up to 100% selectivity), likely for the same reason discussed for DGCs **I**.

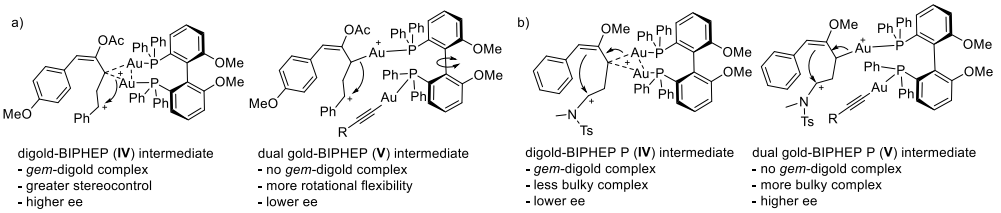


Figure 5.3. Possible gold-intermediates with digold(I) complex **IV** and dual gold(I) complexes **V** in the deauration step of the a) cyclopropanation reaction (Scheme 5.5a) and b) cyclopentylation reactions (Scheme 5.5b-d, illustrated with d).

The cyclopentenylation reaction with propargyl ester **2** and vinyl amide **4d** selectively gave compound **8** with all gold(I) catalysts **IV-VI** in fair to excellent yields (29-67%, Scheme 5.5b). Moderate enantioselectivities were observed with DGCs **V** (up to 46% ee), which significantly were much higher than digold complex **IV** (up to 16% ee). The formation of a larger ring in the step when the stereocenters are determined means that the proposed *gem*-digold intermediate has less impact on the outcome of the reaction, compared to the bulkier DGCs **V** (Figure 5.3b).

Similarly, the cyclopentenylation reaction with propargyl acetal **3** and vinyl amide **4d** (Scheme 5.5d) gave moderate yields of compound **9** in the presence of gold(I) catalysts **IV-VI**. Digold complex **IV** gave the lowest yield (26%), while DGCs **V** gave better yields (33-55%), comparable to that obtained from monogold complex **VI** (54%). The increase in yield followed the increase in the electron-density of the acetylide substituent in the DGCs **V** and indicated that the disconnection of the gold unit from the substrate and regeneration of the DGC is the rate determining step in this reaction. Dual gold(I) complexes **V** also gave equal or higher enantioselectivity (32-28% ee) compared to digold complex **IV**, for the same reasons as the cyclopentenylation reaction of propargyl ester **2** and vinyl amide **4d** (Scheme 5.5b).

Interestingly, with monogold complex **VI,** the cyclopentenylation reactions between propargyl ester **2** and vinyl amide **4d** or propargyl acetal **3** and vinyl amide **4d** gave cyclopentyl compounds **8** and **9** (Scheme 5.5b and d). Compounds **8** and **9** have the opposite regioselectivity of cyclopentyl product **6a**, which is preferred in the cyclopentenylation reaction between propargyl acetal **3** and vinyl amide **4b** (Scheme 5.5c). These results indicate that the identity of the amide affects the regioselectivity of the product, even with the smaller monogold complex **VI**. In previous work on these reactions, the regioselectivity difference was suggested to arise from the more electron-withdrawing character of the pyrrolidinone group,[2] but the results here indicate that the size of the group may also be a factor.

5.6 General remarks

In this work, two types of novel σ,π-dual gold(I) complexes have been synthesised and their catalytic activity tested in several propargyl ester and acetal reactions. First, JohnPhos dual gold(I) complexes **I** with different alkyne substituents were synthesised. Most of the alkynes chosen were aryl alkynes, with a range of electronic and steric properties, and one chiral alkyne was used to evaluate the enantioselectivity of the resulting dual gold(I) complex. In the cyclopropanation reaction, DGCs **I** gave excellent yields and higher *cis* selectivity than the reference monogold complex **VI**. A wider spread of yields was observed with cyclopentenylation and tandem cyclisation reactions, but in both cases, three of the five DGCs **I** gave higher yields than the monogold

complex **VI**. A preference for regioisomer **6b** was observed for DGCs **I**, but a review of current and previous results in this area indicates that the result may be affected by both the size of the catalyst and the amide involved in the reaction. Unfortunately, no enantioselectivity was observed with chiral DGC **If**, although the complex performed better than monogold complex **VI** in all reactions.

Second, chiral bridged MeO-BIPHEP dual gold(I) complexes **V** have been synthesised with three aryl alkynes with different electronic properties. Initial studies included attempts to synthesise DGCs with other chiral bidentate diphosphane ligands, but this proved to be challenging as other ligands were either unstable or formed an inseparable mixture of gold complexes. Both digold complex **IV** and DGCs **V** gave good yields in the cyclopropanation reaction and significant enantioselectivity was obtained (up to 65% ee), although the digold complex gave higher enantioselectivity than the DGCs. Three cyclopentenylation reactions were tested with varied outcomes and the best results were obtained with vinyl amide **4d**. Good yields were achieved with DGCs **V** compared to monogold **VI** and the yields and enantioselectivity with DGCs **V** (up to 67% yield and 46% ee) were higher than with digold complex **IV** (up to 58% yield and 32% ee).

More studies on chiral bridged dual gold(I) complexes could include different combinations of other chiral diphosphane ligands and alkynes, with focus on ascertaining which ligand and alkyne properties affect the enantioselectivity. In addition, chiral bridged DGCs with chiral alkynes (such as alkyne **1f**) could be more enantioselective than those with achiral alkynes.

Dual gold(I) complexes with NHC ligands are known in literature and have different properties compared to phosphane-based DGCs.[77, 78] Chiral bridged dual gold(I) complexes with hybrid phosphane-NHC ligands[317] or bidentate chiral NHC ligands[318] may represent interesting new structures with novel catalytic activity (Figure 5.4).

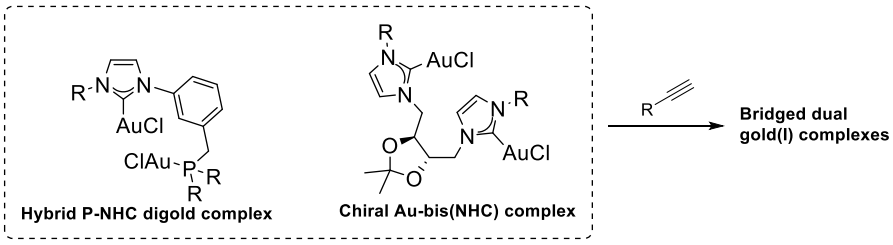


Figure 5.4. Examples of hybrid phosphane-NHC digold(I) and chiral bis-NHC-Au(I) complexes that could be transformed into bridged dual gold(I) complexes.

The current investigation presents the first example of chiral bridged dual gold(I) complexes and shows that the reactivity of both chiral and achiral DGCs is different from monogold(I) and digold(I) complexes. The reactions chosen here are restricted to a limited number of known propargyl reactions. Research into the catalytic activity of our chiral bridged dual gold(I) complexes in other gold(I)-catalysed reactions would provide more information on the scope of application of the complexes.

6 Catalytic studies of cyclometallated gold(III) complexes and a related MOF

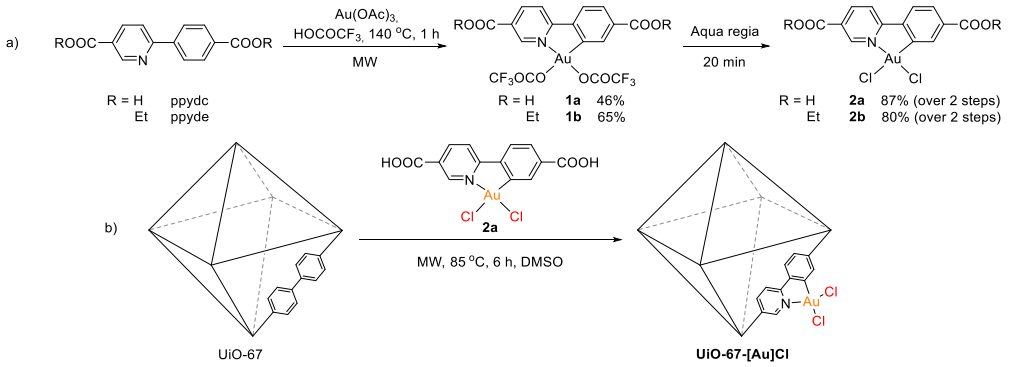
6.1 General introduction

In collaboration with PhD Candidate Volodymyr Levchenko at the University of Oslo, the catalytic activity and recyclability of novel cyclometallated gold(III) complexes and a metal-organic framework (MOF) was studied in a gold-catalysed propargyl test reaction (Paper VI, Appendix VI). The gold(III) catalysts were developed at UiO and the catalytic testing was performed both at NTNU and UiO.

MOFs are a class of crystalline, porous materials that are promising platforms for the immobilisation of molecular catalysts.[319, 320] Cationic gold(III) centres can be incorporated into MOFs with gold-functionalised linkers to generate heterogenous gold(III) catalysts with potential uses in organic transformations.[321-323] The novel gold(III)-functionalised MOF presented here is the first based on gold(III)-phenylpyridine dicarboxylic acids as a linker unit in UiO-67.

6.2 Synthesis of cyclometallated Au(III) complexes and UiO-67-[Au]Cl MOF

Cyclometallation of ppydc and ppyde with $Au(OAc)_3$ in $HOAc^F$ gave bistrifluoroacetate gold(III) complexes **1**, and substitution of the OAc^F groups with chloride ions using *aqua regia* gave gold(III) complexes **2** (Scheme 6.1a). Post-synthetic linker exchange[324] was employed to substitute biphenyl linkers in UiO-67 with the gold(III) phenylpyridine complex **2a**, to give the novel MOF **UiO-67-[Au]Cl** structure with 16% incorporation of Au(III)-functionalised linkers (Scheme 6.1b).

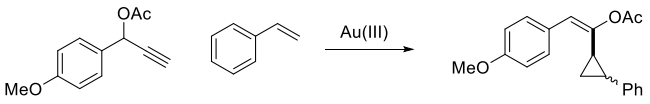


Scheme 6.1. a) Synthesis of cyclometallated Au(III) complexes **1** and **2**; b) Post synthetic linker exchange reaction with **UiO-67** and gold(III) complex **2a**.

6.3 Reactivity of gold(III) catalysts in propargyl ester cyclopropanation

Based on previous experience in the Fiksdahl group,[97] the gold-catalysed cyclopropanation reaction between propargyl ester **3** and alkene **4** (Table 6.1) was chosen for investigation of the catalytic activity of complexes **1-2** and MOF **UiO-67-[Au]Cl**. ^{1}H NMR studies were carried out and the conversion of substrate **3** to cyclopropanation product **5** was calculated following a literature method (Table 6.1).[97]

Table 6.1. ^{1}H NMR studies of the gold-catalysed cyclopropanation reaction of propargyl ester **3** and alkene **4**.[a]



3 **4** **5**

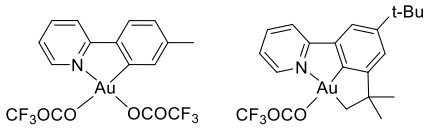
Entry	Catalyst	Conversion [%] of **3** to **5** (1 h)	*cis:tr* (1 h)	Conversion [%] of **3** to **5** (24 h) (isolated yield)	*cis:tr* (24 h)
1	**1a**	0	-	0	-
2	**2a**	17	32:68	45	23:77
3	**1b**[b]	33	22:78	77 (80)	22:78
4	**2b**	43	10:90	97 (>99)	16:84
5	**UiO-67-[Au]Cl**	48	20:80	56	14:86
6	**UiO-67-[Au]Cl**[c]	49	20:80	80	18:82

a) Reaction conditions: 5 mg propargyl ester **3**, 4 equiv. alkene **4**, 10 mol% gold(III) catalyst and 0.6 mL CD_2Cl_2), monitored for 24 h; b) Dark precipitate observed after 4 h; c) 10 mg propargyl ester **3**, with stirring.

Complexes **1b** and **2** gave conversion of propargyl ester **3** to only product **5** (up to 97%, entries 2-4), while complex **1a** showed no catalytic ability (entry 1). There were challenges with the solubility of the complexes in CD_2Cl_2, which may explain the poorer performance of dicarboxylic acid-functionalised complexes **1a** and **2a** compared to their diester-functionalised analogues **1b** and **2b**.

The stability of the complexes during the reaction was another reason for poorer catalytic performance. Bistrifluoroacetate complex **1b** was a less stable and efficient catalyst than the analogous dichloride complex **2b** and complex **1b** showed signs of decomposition after 4 h (entries 3-4). Bistrifluoroacetate complexes are reported to be prone to decomposition via protolytic cleavage of the Au-C_{Ar} bond, which is one explanation for their lower stability.[325]

Preliminary results from a cyclopropanation study of complexes **MSH-1** and **MSH-2** (Figure 6.1, synthesised by Dr. Marte Holmsen) provided further proof of the lower stability of bistrifluoroacetate gold complexes. During the reaction, bistrifluoroacetate complex **MSH-1** decomposed rapidly while pincer complex **MSH-2** was stable, in accordance with findings in previous literature.[325] Complex **MSH-2** was less catalytically active under these conditions, but given the stability of **MSH-2**, further investigation into the catalytic abilities of Au(III) pincer complexes should be carried out in the future.



MSH-1
5 mol% [Au], 24 h
23% conversion

MSH-2
5 mol% [Au], 24 h
7% conversion

Figure 6.1. Initial test results of gold(III) complexes **MSH-1**[115, 326] and **MSH-2**[325] in gold-catalysed cyclopropanation (Table 6.1) (unpublished results, presented with permission from Dr. Marte Holmsen and Professor Mats Tilset).

Gold(III)-catalysed cyclopropanation with MOF **UiO-67-[Au]Cl** at 5 mg scale in an NMR tube gave low conversion (entry 5) and decomposition to gold nanoparticles. Repeating the experiment at a 10 mg scale, with stirring, increased the conversion with no observable decomposition

(entry 6). Additional experiments indicated that the gold(III)-functionalised MOF was unstable during the reaction, leaking catalytically active gold species into the solution. **UiO-67-[Au]Cl** was thus degraded during the reaction and could not be recovered.

However, complex **2b** was stable and recoverable by precipitation with pentane (up to 93%), from both the NMR scale and larger scale reactions. The recovered complex was recyclable and showed high catalytic activity. Complex **2b** was also recyclable *in situ* for three cycles with the same activity.

6.4 General remarks

Substituted phenylpyrimidine gold(III) complexes **1b**, **2**, **MSH-1** and **MSH-2**, and Au(III)-functionalised MOF **UiO-67-[Au]Cl** showed catalytic activity in the gold-catalysed cyclopropanation test reaction. The recoverability and recyclability of Au(III) complex **2b** was a positive finding in this study. Reports of other recyclable Au(III) complexes are limited and such studies have focused on recyclability of the complexes in solution.[94, 175]

Further work could include studies of the catalytic ability and recoverability of the stable complexes **2b** and **MSH-2** in other gold-catalysed reactions (e.g. with propargyl acetals). The development of chiral gold(III)-pincer complexes based on the structure of **MSH-2** is another possible avenue of investigation.

Studies of the chemical stability of MOF **UiO-67-[Au]Cl** under different conditions and solvents could provide information on application scope of the MOF in organic reactions. Alternatively, development of new types of Au(III)-functionalised MOFs could be an interesting area of research – e.g. Au(III)-NHC-embedded MOFs or Au(III)-pincer MOFs.

7 Concluding Remarks

The core goal of the work presented in this thesis was to contribute to the growing field of gold catalysis within organic chemistry.

Gold(I)-catalysed cycloadditions of terminal propargyl acetals with alkenes and alkynes gave a better understanding of the chemistry of propargyl acetals the presence of gold(I). These reactions gave highly functionalised bicyclic compounds through tandem cycloaddition pathways. An intermediate with an activated vinyl alkoxy moiety is the key prerequisite, and driving force, for the novel tandem reactions. Such intermediates are unique to gold(I)-catalysed reactions of propargyl acetals, and result in new reaction pathways that differ from those reported in similar gold-catalysed propargyl ester reactions.

The investigation of non-terminal propargyl acetals demonstrated their versatility in gold(I)-catalysed cycloaddition reactions, which gave a range of *N*-heterocyclic products with different imine substrates. Additionally, the potential of gold(I)-nitrone systems to undergo complexation into catalytically active gold(I)-nitrone species and to selectively catalyse cyclotrimerisation or dimerisation of non-terminal propargyl acetals was shown. Thus, this study contributed to better knowledge of the reactivity of non-terminal propargyl acetals, as well as to new understanding of gold(I)-nitrone chemistry.

The detailed study of gold(I)-catalysed trifluoromethylation of terminal alkynes with Togni's reagent represents a valuable contribution to gold-fluorine chemistry. Notably, the compatibility and interaction of gold(I) catalysts with electrophilic trifluoromethylation reagents is demonstrated for the first time. Moderate yields of alkyne-CF_3 products in the presence of sub-stoichiometric amounts of gold catalyst indicated that gold(I) promotes the reaction in a catalytic manner. A σ,π-dual gold(I)-acetylide complex was isolated and was shown to be the active catalytic species in the reactions, adding to the complex picture of gold(I) catalysis.

Synthesis and catalytic testing of JohnPhos- and (*R*)-MeO-BIPHEP-based dual gold(I) complexes in propargyl reactions demonstrated that dual gold(I) complexes have different catalytic potential than the parent monogold(I) or digold(I) complexes. Chiral dual gold(I) complexes exhibited comparable catalytic activity and similar or higher enantioselectivity than the corresponding digold(I) species in selected propargyl reactions. The catalytic activity of bridged dual gold(I) complexes had not previously been studied, and this investigation gave new understanding of the synthesis, properties and catalytic potential of such complexes, including enantioselective chiral bridged dual gold(I) species.

Finally, studies on the catalytic activity of cyclometallated gold(III) complexes and a gold(III)-functionalised MOF in a propargyl reaction gave moderate to excellent conversions to the expected product. The recoverability and recyclability of one of the gold(III) catalysts demonstrated the potential use of stable, cyclometallated gold(III) complexes in other reactions.

8 References

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9 Appended Papers

Paper I

Paper II

Paper III

Paper IV

Paper V

Paper VI

PAPER I

Gold(I)-Catalysed Tandem Cyclisation of Propargyl Acetals and Vinyl Esters

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Gold(I)-Catalysed Tandem Cyclisation of Propargyl Acetals and Vinyl Esters

Huey-San Melanie Siah,[a] Maya Kaur,[a] Naseem Iqbal,[a] and Anne Fiksdahl*[a]

Keywords: Alkynes / Gold / Homogeneous catalysis / Tandem reactions / Vinylic compounds / Cyclization

The results of our previous comparative study of chemoselective gold(I)-catalysed alkene cycloadditions of propargyl substrates demonstrated that propargyl acetals react by different cyclisation pathways from the corresponding esters, and that they also have significantly higher reactivities. To increase understanding of the chemistry of propargyl acetals and to explore the possibilities of generating new compounds through gold(I)-catalysed reactions, a range of reactions of propargyl acetals with vinyl esters have been carried out. A new type of cyclopropyl–cyclopentenyl products, (1,3-dimethoxy-4,5-diphenylcyclopent-2-en-1-yl)-cyclopropyl ester derivatives, was obtained. A plausible mechanism, including sequential [1+2] and [2+3] cycloadditions, is proposed for these highly regio- and stereoselective gold(I)-catalysed reactions. The cyclopentenylation took place stereoselectively, whereas *cis*/*trans* mixtures of diastereoisomers were formed in the cyclopropanation step, with the selectivity being controlled by the bulkier vinylic substituent. The tandem reaction allows the construction of polysubstituted and highly functionalised bicyclic compounds.

Introduction

Gold(I) complexes are known to be efficient catalysts for the activation of C–C multiple bonds towards nucleophilic attack.[1–4] Propargylic esters and acetals have been shown to undergo triple-bond activation, followed by, respectively, 1,2-acyloxy and 1,5-alkoxy migrations. Subsequent nucleophilic attack generates a variety of complex small molecules with one or more chiral centres.[5–7] The structures of the products depend on the nature of both the propargyl moiety and the nucleophile.

The Fiksdahl group has previously reported a comparative study of the reactivity of chemoselective gold(I)-catalysed cycloadditions of propargyl esters and acetals with vinyl derivatives (Scheme 1a and b), and has shown how the regioselectivity of the cycloadditions is controlled by the electronic nature of the substrates.[8,9] Such propargyl derivatives are known to undergo gold(I)-catalysed migration–fragmentations to give gold carbenoid intermediates (**I**, **II**), which can be trapped with different reagents, typically alkenes, to give adducts **I′** and **II′**. We have studied such reactions with olefins directly connected to a heteroatom.

Cyclopropanation by a [1+2] cycloaddition reaction pathway is typical for the reactions of terminal *propargyl esters* with vinyl esters or amides (Scheme 1a, product **III**).[8] Changing from propargylic esters to acetals, the reaction pathway switches. The gold(I)-catalysed cyclisation reactions of *propargyl acetals* with vinyl amides or vinyl ethers are characterised by two important features. Firstly, in contrast to the usual olefin cyclopropanation that normally takes place with propargyl esters, an atypical cyclopentenylation by a [2+3] cycloaddition mechanism is the favoured reaction pathway for the corresponding acetals,[9] leading to *trans*-configured cyclopentenyl products (Scheme 1b, product **IV**). This reaction proceeds by a "C-3–C-1" reaction sequence, due to the presence of an alkoxy group in adduct **II′**, which activates it for C-1 cyclisation. Secondly, propargyl acetals show a significantly higher reactivity than the corresponding esters,[9,10] which is consistent with the assumption that the alkoxy substituent may activate the intermediate gold–propargyl-acetal complex **II**. Our recent studies have shown that propargyl acetals also undergo a gold-catalysed [2+5] cycloaddition with benzaldimines to give benz[*c*]azepine products (Scheme 1c, compound **V**).[10]

However, by replacing the vinyl amides or vinyl ethers (Scheme 1, b) with vinyl esters, the reaction outcome was altered. Propargyl acetals and vinyl esters were found to undergo a gold(I)-catalysed tandem cyclisation reaction involving two propargyl–gold units **II**, generated from propargyl acetals, to give rise to cyclopropyl–cyclopentenyl products **VI** (Scheme 1, d).

We wanted to further investigate the ability of the highly reactive gold(I) vinylcarbenoid complexes **II** to promote chemoselective cyclisations, and we chose to study the po-

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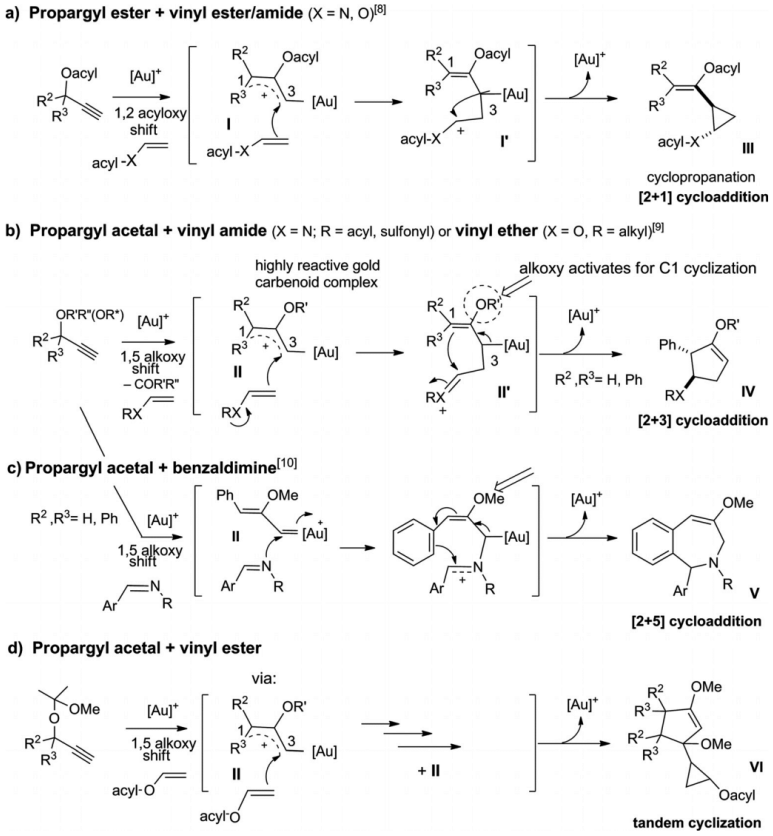


Scheme 1. Gold(I)-catalysed cycloaddition reactions of propargyl substrates.[8–10]

tential for propargyl acetals to give tandem products with vinyl esters by a double cycloaddition process. In this paper, we report the results of our studies on the new gold(I)-catalysed tandem reaction.

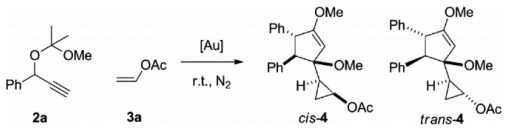
Results and Discussion

Introductory studies into the reaction of propargyl acetal **2a** and vinyl acetate (**3a**; 3 equiv. based on the propargyl substrate) in the presence of a gold(I) catalyst were carried out under reaction conditions previously used for propargyl acetal cycloadditions.[9] Structural studies (NMR spectroscopy) showed that the tandem cyclisation product could be identified as 2-(1,3-dimethoxy-4,5-diphenylcyclopent-2-enyl)cyclopropyl acetate, formed as a mixture of diastereomers (*cis*-/*trans*-**4a**).

Optimisation Studies

Optimisation studies showed that substrates **2a** and **3a** readily gave a 54% yield of products **4** after 15 min in the presence of [Au{P(*t*Bu)$_2$(*o*-biphenyl)CH$_3$CN}]SbF$_6$ (5 mol-%) in dichloromethane (Table 1, entry 1). These reaction conditions were used in further studies, as they gave the highest reactivity towards tandem cyclisation. The use of acetonitrile as a solvent resulted in a lower yield, and required a longer reaction time (48%, 60 min; Table 1, entry 2). Tetrahydrofuran seemed to undergo polymerisation, so it was deemed to be an unsuitable solvent for these reactions (Table 1, entry 3). A similar gold(I) catalytic complex lacking the acetonitrile ligand gave lower yields (31%; Table 1, entry 4). As previously observed,[9] no reaction took place when [Au{P(*t*Bu)$_2$(*o*-biphenyl)}]Cl was used, and it was important to generate the active gold(I) species by exchange of the chloride counterion with SbF_6^- (Table 1,

Table 1. Optimisation studies of gold(I)-catalysed tandem cyclisation reactions.[a]



2a 3a cis-4 trans-4

Entry	Gold catalyst	Solvent (time)	Yield [%] (*cis*/*trans*)
1	{Au[P(*t*Bu)$_2$(*o*-biphenyl)CH$_3$CN]}SbF$_6$	CH_2Cl_2 (15 min)	54 (60:40)
2	{Au[P(*t*Bu)$_2$(*o*-biphenyl)CH$_3$CN]}SbF$_6$	CH_3CN (60 min)	48 (60:40)
3	{Au[P(*t*Bu)$_2$(*o*-biphenyl)CH$_3$CN]}SbF$_6$	THF (60 min)	n.d.[b]
4	{Au[P(*t*Bu)$_2$(*o*-biphenyl)]}Cl + $AgSbF_6$	CH_2Cl_2 (15 min)	31 (65:35)
5	{Au[P(*t*Bu)$_2$(*o*-biphenyl)]}Cl	CH_2Cl_2 (19 h)	n.d.
6	Au(PPh_3)Cl + $AgSbF_6$	CH_2Cl_2 (15 min)	n.d.[c]
7	$AuCl_3$	CH_2Cl_2 (15 min)	n.d.[c]
8	$PicAuCl_2$	CH_2Cl_2 (19 h)	**1a**/**2a**; 3:2[c]

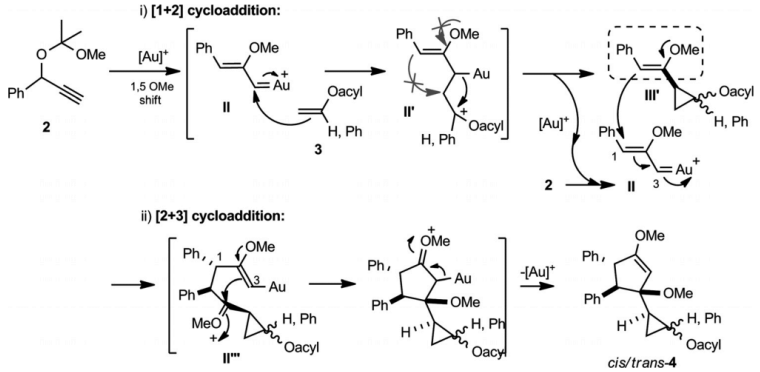
[a] The reactions were performed with **2a** (1 equiv.) and **3a** (3 equiv.) in solvent (approx. *c* = 90 mM) together with 5 mol-% gold catalyst at room temp. [b] Target molecules not detected (n.d.); polymerisation of THF at room temp.; no conversion at –78 °C. [c] Target molecules not detected (n.d.); hydrolysis into 1-phenylprop-2-yn-1-ol **1a** was observed by GC.

entry 5). A triphenylphosphane-based gold(I) catalyst (Table 1, entry 6) and gold(III) salts (Table 1, entries 7 and 8) resulted in full or partial hydrolysis into to the propargyl alcohol.

Proposed Mechanism

Based on our previous studies of regioselective cycloadditions of propargyl substrates,[8,9] the formation of tandem product **4** is proposed to take place by a two-step reaction. The general mechanism is shown for propargyl acetal **2** and vinyl ester **3** in Scheme 2.

Propargyl acetal **2** and vinyl ester **3** undergo an initial gold(I)-catalysed [1+2] cycloaddition reaction to give the cyclopropanation product (i.e., **III′**) by nucleophilic attack of the vinyl species on the gold carbenoid intermediate (i.e., **II**). The observed cyclopropyl products correspond to products formed in reactions of propargyl esters with vinyl esters or sulfonamides (Scheme 1, a).[8] The results of our previous studies indicate that propargyl acetals may be expected to undergo [2+3] cycloadditions with vinylic substrates (Scheme 1, b).[9] Nevertheless, we have also seen that the electronic nature of the vinylic reactants connected to a heteroatom may affect the reactivity and alter the reaction pathway and the outcome of propargyl cycloaddition reactions.[8–10] The unexpected cyclopropanation reaction that was found to be the favoured pathway for the reaction of propargyl acetals and vinyl esters may be a result of the presence of the electron-withdrawing ester moiety in adduct **II′** (Scheme 2). This is in contrast to the situation with vinylic compounds attached to an electron-releasing nitrogen or oxygen atom, which would enable stabilisation of an ammonium or oxonium cation intermediate **II′** (Scheme 1, b). Hence, electron-deficient vinylic compounds such as vinyl



Scheme 2. Proposed mechanism for gold(I)-catalysed tandem cyclisation reaction of propargyl acetals and vinyl esters.

esters may reduce the electron-releasing effect of the vinylic alkoxy group[9] in adduct **II′**. This would then decrease the tendency for the alkoxy group to promote a C-1 cyclisation that would result in pentaannulation. This electronic effect appears to make it more favourable for intermediate adduct **II′** to undergo cyclopropyl ring formation.

In contrast to the cyclopropyl products **III** previously obtained from propargyl esters (Scheme 1, a), product **III′** contains an activated vinyl ether moiety. Thus, intermediate **III′** may give rise to the new tandem reaction pathway by a subsequent cycloaddition reaction with gold carbenoid intermediates **II**, generated from a second unit of propargyl acetal **2**. However, in contrast to the "C-3–C-1" reaction sequence previously reported for the [2+3] cycloadditions of monosubstituted vinylic reactants (Scheme 1, b),[9] the opposite regioselectivity (i.e., a "C-1–C-3" reaction order) was observed, since the vinyl nucleophile (i.e., **III′**) attacks at the electrophilic allylic C-1 position of the second gold carbenoid complex (i.e., **II**) to give adduct **II′′′**. This change in regioselectivity may be due to the bulk of the 3-substituted vinyl ether **III′**. A similar "C-1–C-3" reaction order has been reported for [2+3] cycloaddition reactions of nonterminal propargyl acetals connected to an electron-withdrawing group, with aldehydes.[4]

The fact that a cyclopropyl intermediate **III′** (i.e., **3e**) was actually isolated from the reaction of the deactivated *p*-nitrophenylpropargyl acetal **2d** (see below; Table 2, entry 12) supports the proposed tandem mechanism.

Despite the formation of five stereogenic centres in product **4**, only one pair of *cis*/*trans* cyclopropyl diastereomers could be observed (Table 1), as the cyclopentenyl ring was formed in a diastereoselective 4,5-*trans* (Ph–Ph)/1,5-*cis* (OMe-Ph) /it>/*trans*-cyclopropanation[8] and stereoselective pentaannulation[9] reactions.

The overall outcome of the reaction is therefore the formation of tandem products *cis*/*trans*-**4** by two sequential cycloaddition reactions, involving two units of propargyl acetal **2** and one unit of vinyl ester **3**.

Reactivity

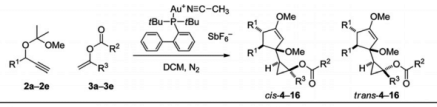
The tandem transformation was further studied by modifying the substrates and the reaction conditions. The results from the reactions of propargyl acetals **2a**–**2e** with vinylic esters **3a**–**3d** in the presence of {Au[P(*t*Bu)$_2$(*o*-biphenyl)CH$_3$CN]}SbF$_6$ in CH$_2$Cl$_2$ are presented in Table 2. The propargyl acetals gave the expected tandem cyclisation products (i.e., **4**–**16**), but the yields varied depending on the substituents on the propargyl acetal and the vinylic reactant. Additionally, the stability of the tandem products at room temperature appeared to vary, which could account for a reduction in the isolated yields. Temperature optimisation (room temp. to –78 °C) was carried out for each reaction, as complex mixtures of products were most often obtained at room temperature. The optimised reactions reached completion quickly (15–20 min), and moderate to high yields (39–77%; Table 2, entries 1, 2, 4, 5, 7, and 8) were generally obtained at –40 to –78 °C. This clearly demonstrates the ability of these highly reactive substrates to undergo tandem reactions. The corresponding tandem reactions with vinylsulfonamides were not as promising. With vinyltosylate (vinyl-OTs), propargyl substrates **2a** and **2c** gave two major products (as judged by TLC), but these were unstable, and they decomposed during work-up. Only low yields (up to 15%) of the unstable *cis* tandem products were obtained.

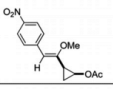
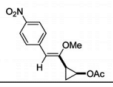
Aromatic propargyl acetals (**2a**–**2d**, up to 77% yields, Table 2, entries 1, 2, 5, 7, 8, 9, and 11) generally performed better than alkyl propargyl acetal **2e** (up to 15% yield, Table 2, entries 14 and 15). This demonstrates that benzylic stabilisation of the cationic gold intermediate is beneficial, but that it is not a requirement for the tandem cycloaddition. Bulky dimethyl propargyl substrate **2f** (Table 2, entry 16) failed to undergo the tandem cyclisation with vinyl acetate (**3a**), and only a minor compound (approx. 5%), which, by NMR spectroscopy, seemed to be cyclopropyl intermediate **3f**, was obtained. The difference in reactivity observed between dimethylpropargyl acetal **2f** and monomethyl substrate **2e** (Table 2, entry 14) may be explained by steric effects. Tandem cyclisations were also disfavoured by increasing the bulk of the vinyl ester substrates, as the reactivity dropped and the yields were reduced when further substituents were introduced onto the vinyl moiety (Me/**3c**; Ph/**3d**; Table 2, entries 3, 6, 9, and 10).

The presence of a *para* substituent on the aromatic propargyl acetals affected the reactivity and the outcome of the tandem reactions. Unsubstituted phenyl propargyl acetal **2a** gave good yields of the respective tandem products **4** and **5** (65–69%; Table 2, entries 1 and 2) in reactions with vinyl acetate (**3a**) and vinyl benzoate (**3b**) at –78 °C. Test reactions with the bulkier, but analogous ethyl acetal, PhCH(CCH)OCHMe(OEt), and vinyl benzoate (**3b**) indicated a slower reaction, but similar yields of the corresponding tandem product seemed to be formed.

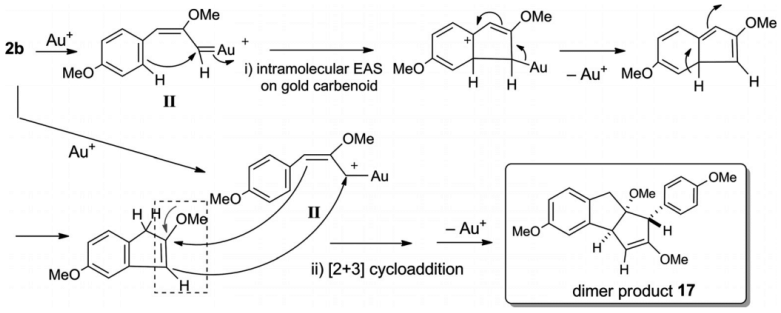
The presence of an electron-donating group in the propargyl substrate, such as the methoxy functionality in **2b**, would make it less electrophilic, and so make the nucleophilic attack of the vinyl species on the gold carbenoid intermediates **II** in both steps of the tandem cyclisation less favourable (Scheme 2). Consistent with this hypothesis, we observed decreased yields of tandem products **6** and **7** (39–49%; Table 2, entries 4 and 5) from *p*-OMe-phenylpropargyl acetal **2b** and vinyl esters **3a** and **3b**. Furthermore, a propargyl acetal dimer **17** was formed in the reactions carried out at room temperature (Table 2, entries 4 and 5; footnote [h]). Significant amounts of the dimer were formed (GLC, TLC), but it was unstable both during flash chromatography and in deuterated solvents. Attempts to prepare larger amounts of dimer **17** by separate dimerisation of propargyl acetal **2b** resulted in the formation of only small amounts of **17** (< 5%), which could be used for characterisation and structural elucidation. A possible tandem dimerisation reaction pathway, based on an intramolecular electrophilic aromatic substitution promoted by the

Table 2. Gold(I)-catalysed tandem cyclisation reactions of propargyl acetals and vinyl esters.[a]



Entry	Acetal		Alkene		Product	T [°C]	t [min]	Ratio *cis*/*trans*	Yield [%]
1		**2a**		**3a**	**4**	20	15	60:40	54
						0	15	62:38	45
						–40	15	50:50	54
						–78	**15**	**50:50**	**69**[b]
2		**2a**		**3b**	**5**	20	25	–	0
						0	25	31:69	29
						–30	25	63:27	38
						–40	25	45:55	62
						–78	**20**	**48:52**	**65**
3		**2a**		**3d**	_[c]	–40 to 0	45	17:83	<18[c]
4		**2b**		**3a**	**6**	20	15	85:15	29[b,h]
						–40	**30**	**87:13**	**39**[b]
						–78	120	83:17	36[b]
5		**2b**		**3b**	**7**	20	15	67:33	45[c,h]
						–40	**30**	**67:33**	**49**[b]
						–78	120	67:33	53[b]
6		**2b**		**3d**	**8**	–40 to 0	45	25:75	19[b,c]
7		**2c**		**3a**	**9**	20	9	73:27	56
						–40	**15**	**58:42**	**77**
						–78	30	57:43	46
8		**2c**		**3b**	**10**	20	18	64:36	44
						–40	**15**	**54:46**	**72**[b]
						–78	120	48:52	61
9		**2c**		**3c**	**11**	**20**	**15**	**75:25**	**<53**[b,c]
10		**2c**		**3d**	**12**	–40 to 0	45	44:55	17[c]
11		**2c**		**3e**	**13**	**–40**	**30**	**58:42**	**77**[d]
12		**2d**		**3a**	**14** + **3e**	**20**	**120**	**58:42**	**14** (62)[b,e]
						–40	15	68:32 100:0	**14** (58)[a] **3e** (20)
						–40	15	44:56 100:0	**14** (43) **3e** (40)[f]
						–78	15	100:0	**14** (0) **3e** (16)
13		**2d**		**3e**	**14**	–40 to r.t.	**120**	**52:48**	**65**[a]
14		**2e**		**3a**	**15**	20	15	67:33	<15[c]
						0	15	78:22	14
						–40 to 0	120	60:40	15[b]
15		**2e**		**3b**	**16**	0–20	30	100:0	5
16		**2f**		**3a**	 **3f**	20	15	100:0	5

[a] The reactions were performed with propargyl acetals **2a**–**2d** (1 equiv.) and vinyl esters **3a**–**3d** (3 equiv.) in CH_2Cl_2 ($c \approx 90$ mM) together with gold catalyst (5 mol-%). [b] Isolated as a mixture, which was separated later for full characterisation of the diastereomers, or as a combination of pure products and mixtures. [c] Purification and characterisation was not possible for all or some of the products; *cis*/*trans* ratio was calculated from the ^{1}H NMR spectrum of the crude product mixture based on a comparison of chemical shift values of similar products. [d] A 10% excess of acetal **2c** relative to intermediate **3e** was used; see the Exp. Sect. for details. [e] Ratio of acetal **2d**/alkene **3a** = 2:1; see the Exp. Sect. for details. [f] Ratio of acetal **2d**/alkene **3a** = 1:10; see the Exp. Sect. for details. [g] The preparation of product **14** could alternatively be carried out separately from acetal **2d** and intermediate **3e** (10% excess); see the Exp. Sect. for details. [h] Dimer **17** (2–4%) was isolated.



Scheme 3. Possible mechanism for tandem dimerisation of *p*-methoxyphenylpropargyl acetal **2b** (EAS = electrophilic aromatic substitution).

p-OMe substituent of the phenyl group, followed by [2+3] cycloaddition activated by the vinyl ether moiety of the intermediate, is shown in Scheme 3. The final [2+3] cycloaddition took place in a stereoselective manner, as shown by the relative stereochemistry (NOESY NMR spectra) of dimer **17**, which is consistent with previous observations.[9] The *cis* relationship of the OMe and Ph substituents on the pentenyl ring of dimer **17**, which is established in the final [2+3] cycloaddition, is also consistent with the corresponding 1,5-*cis* OMe/Ph configuration of tandem products **4**–**14**. The lower yields of tandem products **6** and **7** seem to be caused by the competing formation of dimer **17**, indicating that the nucleophilicity of vinyl esters **3a** and **3b** is insufficient to favour attack on the less electrophilic gold intermediate **II** (Scheme 2) and lead to the formation of tandem compounds **6** and **7** as the major products.

An electron-withdrawing chloride substituent (as in **2c**) should increase the electrophilicity of gold intermediate **II**. The higher yields obtained of the corresponding tandem products **9** and **10** (77–72%; Table 2, entries 7 and 8) demonstrate that an electron-withdrawing group on the phenyl ring does tend to favour the tandem cycloaddition reaction pathway. The electron-withdrawing chloride substituent allows an easier nucleophilic attack on the gold(I) carbenoid complex **II** by vinyl esters **3a** and **3b**, as well as by vinyl ether intermediates **III′** in both the cycloaddition steps (Scheme 2).

We thought that an electron-withdrawing *p*-nitro substituent could assist in activating the gold intermediate in the same way, and so allow easy nucleophilic attack of the vinyl species. On the other hand, the second [2+3] cycloaddition step might be hampered, since the cyclopropyl vinyl ether intermediate **III′** (Scheme 2) would be deactivated by the *p*-nitrophenyl moiety, and its nucleophilicity would be strongly decreased. The most successful reaction conditions discussed above were tested for the reactions of nitro derivative **2d** and vinyl acetate (**3a**). Both tandem product **14** (58%) and intermediate **3e** (20%) were produced at –40 °C (Table 2, entry 12, line 2). At –78 °C, the reaction failed to give any of the tandem product, and only intermediate **3e** (16%, Table 2, entry line 4) could be isolated. Addition of further amounts of **2d** (**2d**/**3a** = 2:1; standard ratio = 1:3) to a reaction carried out at room temperature resulted in the consumption of intermediate **3e**, but only a slight increase in the yields of tandem product **14** was observed (62%, Table 2, entry 12, line 1). By using a large excess of the vinyl reactant (**2d**/**3a** = 1:10, –40 °C, Table 2, entry 12, line 3), a 40% yield of intermediate **3e** was isolated, which could be used in a separate new reaction with acetal **2d** (Table 2, entry 13) or with a different propargyl reactant in the second step of the tandem reaction. Thus, the reaction of intermediate **3e** with *p*-Cl-phenyl propargyl acetal **2c** (10 mol-% excess of **2c**) gave a high yield of mixed *p*-NO_2/*p*-Cl tandem product **13** (76%; Table 2, entry 11). This demonstrates how the different effects of the electron-withdrawing nitro group, i.e., activating for nucleophilic attack but deactivating for the second step in the tandem cyclisation, can be used strategically to lead to a selective cyclopropanation, and so provide the possibility of introducing two different *para* phenyl substituents in mixed tandem products.

Tandem products **4**–**16** were formed as mixtures of two diastereomers (Table 1) in the *cis*/*trans*-cyclopropanation[8] and stereoselective pentaannulation[9] reactions. Due to challenging chromatographic separations, the isolation of each diastereomer was sometimes demanding. A slight preference for the formation of the *cis* isomer was observed, as had previously been seen for the cyclopropylations of propargyl substrates,[8] and consistent with the assumption that the cyclopropanation is controlled by the bulkier vinylic substituent.[5] However, varying the vinyl ester (OAc, OBz) gave no significant difference in the isomeric ratios of the products. In general, diastereomeric ratios were fairly low (*dr* approx. 20–50), being lower when reactivity and yields were higher. The only reaction that gave a significantly higher diastereoselectivity was the reaction between deactivated methoxypropargyl substrate **2b** and vinyl acetate (**3a**). The tandem product (i.e., **6**; up to 39%) was formed with a consistent diastereoselectivity (*dr* approx. 70; Table 2, entry 4) over all temperatures.

Conclusions

To contribute to a better understanding of the chemistry of propargyl acetals in the presence of gold(I), we have studied chemoselective gold(I)-catalysed cycloadditions of propargyl acetals **2a**–**2e** and vinyl esters **3a**–**3e**. We have found that that such substrates follow a new tandem cyclisation pathway.

Although the propargyl acetals were expected to undergo a gold(I)-catalysed [2+3] cycloaddition with vinyl substrates,[9] the propargyl acetals and vinyl acetates studied here were found to undergo an initial [1+2] cycloaddition reaction to give *cis*-/*trans*-cyclopropanation intermediates **III** by nucleophilic attack of the vinyl species at propargyl-generated gold(I) carbenoid intermediates **II**. This different chemoselectivity may be explained by the relatively electron-poor nature of the vinyl acetates, and this demonstrates how varying the electronic nature of the vinylic reactant can change the outcome of gold(I)-catalysed alkene–propargyl cycloadditions.

With its activated vinyl ether moiety, intermediate **III** may undergo a subsequent [2+3] cycloaddition with gold carbenoid intermediates **II**, in which an additional pentenyl ring is stereoselectively formed by a "C-1–C-3" cyclisation pathway. The standard "C-3–C-1" would be the expected reaction order,[9] and the observed "C-1–C-3"regioselectivity may be explained by the bulk of vinyl intermediate **III**.

The overall outcome of the reactions was therefore the formation of *cis*/*trans*-cyclopropyl–cyclopentenyl tandem products **4**–**16** by two sequential cycloaddition reactions, involving two units of propargyl acetals **2a**–**2e** and one unit of vinyl esters **3a**–**3e**. The highest tandem reactivity was observed for propargyl substrates with a moderately electron-withdrawing group (Cl) or with no substituent at the *para* position of the phenyl moiety. Strongly electron-withdrawing groups, or electron-donating groups, such as nitro and methoxy groups, hamper selective parts of the tandem process, resulting in a lower overall tandem reactivity.

The vinylic alkoxy group in cyclopropane intermediate **III**, which activates it for the final cycloaddition with a second unit of gold(I) carbenoid intermediate **II**, is the key prerequisite of this tandem reaction, which enables the construction of polysubstituted and highly functionalised bicyclic compounds.

Experimental Section

General Methods: All reactions were performed under a nitrogen atmosphere. Commercial grade reagents were used as received. 1-Phenylvinyl acetate was synthesised following a literature procedure.[11] Dry solvents were collected from a solvent-purification system. All reactions were monitored by GC and by thin-layer chromatography (TLC) using silica gel 60 F254 plates (0.25 mm thickness). Flash chromatography was carried out using silica gel 60 (0.040–0.063 mm). High-Throughput Flash Purification (HPFP) was carried out using pre-packed cartridges. ^{1}H and ^{13}C NMR spectra were recorded using 300 or 400 MHz spectrometers. Chemical shifts are reported in ppm (δ) downfield from tetramethylsilane, which was used as an internal standard. Coupling constants (J) are reported in Hertz (Hz). The assignments of the chemical shifts were determined using COSY, HMQC, HMBC, and NOESY experiments. Melting points (m.p.) were determined using a Stuart apparatus. Accurate mass determination in either positive or negative mode was performed with a "Synapt G2-S" Q-TOF instrument from Waters. Samples were ionised with an ASAP probe, and no chromatographic separation was used before the mass analysis. IR spectra were obtained using a Smart Endurance reflection cell.

Preparation of the Propargyl Acetals: Propargyl acetals were synthesised following a modified procedure starting from the appropriate aldehyde or propargyl alcohol (compounds **1**).[4,12] Propargyl acetal **2f** was synthesised following a literature procedure.[9]

{1-[(2-Methoxypropan-2-yl)oxy]prop-2-yn-1-yl}benzene (2a): A mixture of 1-phenylprop-2-yn-1-ol (213.5 mg, 1.615 mmol) and 2-methoxypropene (10.0 mL, 104 mmol) was cooled to 0 °C, then pyridinium *p*-toluenesulfonate (catalytic amount) was added. The cooling bath was removed, and the mixture was stirred at room temperature for 4 h. The mixture was diluted with CH_2Cl_2 (20 mL), washed with water (3× 20 mL), dried with anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (1:50 EtOAc/pentane) to give **2a** (266.0 mg, 81%) as a colourless oil. R_f = 0.78 (1:10 EtOAc/pentane). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.51–7.47 (m, 2 H, H_{arom}), 7.38–7.7.26 (m, 3 H, H_{arom}), 5.42 (d, J = 2.2 Hz, 1 H, CHC≡), 3.18 (s, 3 H, OCH_3), 2.53 (d, J = 2.3 Hz, 1 H, C≡CH), 1.54 (s, 3 H, CCH_3) 1.33 (s, 3 H, CCH_3) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 140.3 (1 C, C_{arom}), 128.5 (2 C, CH_{arom}), 128.0 (1 C, CH_{arom}), 126.9 (2 C, CH_{arom}), 101.9 (1 C, O*C*OCH$_3$), 84.5 (1 C, CH*C*≡), 73.7 (1 C, ≡CH), 62.6 (1 C, *C*HC≡) 49.5 (1 C, OCH_3), 25.4 (1 C, C*C*H$_3$), 24.9 (1 C, C*C*H$_3$) ppm. ^{1}H and ^{13}C NMR spectroscopic data are consistent with literature data.[9]

1-(4-Methoxyphenyl)prop-2-yn-1-ol (1b): A solution of ethynylmagnesium bromide (0.50 M in THF; 19.0 mL, 9.5 mmol) was cooled to –20 °C. A solution of 4-methoxybenzaldehyde (1.0336 g, 7.5916 mmol) in dry THF (1.5 mL) was added, and the flask was washed out with further THF (0.5 mL), which was added to the reaction mixture. The cooling bath was removed, and the reaction mixture was stirred at room temperature for 1 h. The reaction was quenched by the addition of saturated aqueous ammonium chloride (10 mL), and the mixture was extracted with Et_2O (2× 20 mL). The combined organic layers were dried with Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (1:3 EtOAc/pentane) to give **1b** (1.113 g, 90%) as a pale yellow oil. R_f = 0.31 (1:3 EtOAc/pentane). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.51–7.46 (m, 2 H, H_{arom}), 6.93–6.90 (m, 2 H, H_{arom}), 5.43 (dd, J = 6.2, 2.1 Hz, CHC≡), 3.82 (s, 3 H, OCH_3), 2.66 (d, J = 2.2 Hz, ≡CH), 2.10 (d, 6.2 Hz, OH) ppm. ^{1}H NMR spectroscopic data are consistent with literature data.[13]

1-Methoxy-4-{1-[(2-methoxypropan-2-yl)oxy]prop-2-yn-1-yl}benzene (2b): A mixture of **1b** (1.113 g, 6.862 mmol) and 2-methoxypropene (25.0 mL, 261 mmol) was cooled to 0 °C, then pyridinium *p*-toluenesulfonate (catalytic amount) was added. The cooling bath was removed, and the mixture was stirred at room temperature for 90 min. The mixture was diluted with dichloromethane (100 mL), washed with water (3× 100 mL), dried with anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (gradient 1:50 to 1:20 EtOAc/pentane) to give **2b** (1.217 g, 76%) as a colourless oil. R_f = 0.57 (1:5 EtOAc/pentane). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42 (d, J = 8.7 Hz, 2 H, H_{arom}), 6.89 (d, J = 8.8 Hz, 2 H, H_{arom}), 5.37 (d, J = 2.2 Hz, 1

H, C*H*C≡), 3.80 (s, 3 H, PhOCH_3), 3.18 (s, 3 H, COCH_3), 2.54 (d, *J* = 2.2 Hz, 1 H, C≡C*H*) 1.53 (s, 3 H, CCH_3), 1.33 (s, 3 H, CCH_3) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 159.4 (1 C, C_{arom}), 132.5 (1 C, C_{arom}), 128.3 (2 C, CH_{arom}), 113.9 (2 C, CH_{arom}), 101.8 (1 C, O*C*OCH$_3$), 84.7 (1 C, CH*C*≡), 73.5 (1 C, ≡*C*H), 62.2 (1 C, *C*HC≡) 55.3 (1 C, PhO*C*H$_3$), 49.5 (1 C, O*C*H$_3$), 25.4 (1 C, C*C*H$_3$), 25.0 (1 C, C*C*H$_3$) ppm. IR (thin film): ṽ = 3286, 2991, 1463, 1209, 968, 826, 637 cm^{-1}. HRMS (EI): calcd. for $C_{14}H_{18}O_3$ 234.1250; found 234.1250.

1-(4-Chlorophenyl)prop-2-yn-1-ol (1c): A solution of ethynylmagnesium bromide (0.50 M in THF; 18 mL, 9.0 mmol) was cooled to –20 °C. A solution of 4-chlorobenzaldehyde (1.0105 g, 7.19 mmol) in THF (2.5 mL) was added, and the flask washed out with more THF (0.5 mL), which was then added to the reaction mixture. The cooling bath was removed, and the reaction mixture was stirred at room temperature for 5 min. The reaction was quenched by the addition of saturated aqueous ammonium chloride (10 mL), and the mixture was extracted with Et_2O (2× 20 mL). The combined organic extracts were dried with Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (gradient 1:10–1:3 EtOAc/pentane) to give **1c** (1.078 g, 90%) as a pale yellow oil. R_f = 0.47 (1:3 EtOAc/pentane). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.51–7.48 (m, 2 H, H_{arom}), 7.38–7.35 (m, 2 H, H_{arom}), 5.45 (dd, *J* = 6.1, 2.1 Hz, CHC≡), 2.68 (d, *J* = 2.2 Hz, ≡CH), 2.21 (d, *J* = 6.1 Hz, OH) ppm. ^{1}H NMR spectroscopic data are consistent with literature data.[14]

1-Chloro-4-{1-[(2-methoxypropan-2-yl)oxy]prop-2-yn-1-yl}benzene (2c): A mixture of **1c** (1.078 g, 6.47 mmol) and 2-methoxypropene (20.0 mL, 209 mmol) was cooled to 0 °C, then pyridinium *p*-toluenesulfonate (catalytic amount) was added. The cooling bath was removed, and the mixture was stirred at room temperature for 2 h. The mixture was diluted with dichloromethane (100 mL), washed with water (3× 100 mL), dried with anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (1:30 EtOAc/pentane) to give **2c** (1.3234 g, 86%) as a colourless oil. R_f = 0.28 (1:30 EtOAc/pentane). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.43 (d, *J* = 8.4 Hz, 2 H, H_{arom}), 7.33 (d, *J* = 8.5 Hz, 2 H, CH_{arom}), 5.39 (d, *J* = 2.2 Hz, 1 H, CHC≡), 3.17 (s, 3 H, OCH$_3$), 2.54 (d, *J* = 2.2 Hz, 1 H, C≡CH), 1.53 (s, 3 H, CCH$_3$), 1.32 (s, 3 H, CCH$_3$) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 138.9 (1 C, C_{arom}), 133.8 (1 C, C_{arom}), 128.7 (2 C, CH_{arom}), 128.2 (2 C, CH_{arom}), 102.0 (1 C, O*C*OCH$_3$), 84.0 (1 C, CH*C*≡), 74.0 (1 C, ≡CH), 61.9 (1 C, *C*HC≡), 49.5 (1 C, OCH$_3$), 25.4, (1 C, C*C*H$_3$), 24.9 (1 C, C*C*H$_3$) ppm. IR (thin film): ṽ = 3296, 1210, 1146, 1092, 842, 633 cm^{-1}. HRMS (EI): calcd. for $C_{12}H_{11}OCl$ [M – CH_4O]$^+$ 206.0493; found 206.0490.

1-(4-Nitrophenyl)prop-2-yn-1-ol (1d): A solution of ethynylmagnesium bromide (0.50 M in THF; 16 mL, 8.0 mmol) was cooled to –20 °C. A solution of 4-nitrobenzaldehyde (1.0296 g, 6.8135 mmol) in THF (10 mL) was added, and the flask was washed out with THF (a total of 5 mL), which was then added to the reaction mixture. The cooling bath was removed, and the reaction mixture was stirred at room temperature for 30 min. The reaction was quenched by the addition of saturated aqueous ammonium chloride (10 mL), and the mixture was diluted with Et_2O (50 mL), water (25 mL), and EtOAc (50 mL). The phases were separated, and the aqueous phase was extracted with EtOAc (50 mL). The combined organic extracts were dried with Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (1:4 EtOAc/pentane) to give **1d** (1.1091 g, 92%) as a pale yellow oil. R_f = 0.17 (1:4 EtOAc/pentane). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.27–8.23 (m, 2 H, H_{arom}), 7.75–7.73 (m, 2 H, H_{arom}), 5.58 (dd, *J* = 5.9, 2.2 Hz, CHC≡), 2.74 (d, *J* = 2.2 Hz, ≡CH), 2.43 (d, *J* = 5.8 Hz, OH) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 147.9 (1 C, C_{arom}), 146.6 (1 C, C_{arom}), 127.3 (2 C, CH_{arom}), 123.8 (2 C, CH_{arom}), 82.3 (1 C, C≡), 76.0 (1 C, ≡CH), 63.3 (1 C, C-OH) ppm. ^{1}H and ^{13}C NMR spectroscopic data are consistent with literature data.[15]

1-{1-[(2-Methoxypropan-2-yl)oxy]prop-2-yn-1-yl}-4-nitrobenzene (2d): A mixture of **1d** (1.1091 g, 6.26 mmol) and 2-methoxypropene (20.0 mL, 209 mmol) was cooled to 0 °C, then pyridinium *p*-toluenesulfonate (catalytic amount) was added. The cooling bath was removed, and the mixture was stirred at room temperature for 1 h. The mixture was diluted with dichloromethane (100 mL), washed with water (3× 100 mL), dried with anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (1:50 EtOAc/pentane) to give **2d** (1.335 g, 86%) as a colourless oil. R_f = 0.10 (1:50 EtOAc/pentane). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.24–8.22 (m, 2 H, H_{arom}), 7.69 (m, 2 H, CH_{arom}), 5.52 (d, *J* = 2.2 Hz, 1 H, CHC≡), 3.18 (s, 3 H, OCH$_3$), 2.58 (d, *J* = 2.3 Hz, 1 H, C≡CH), 1.56 (s, 3 H, CCH$_3$), 1.34 (s, 3 H, CCH$_3$) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 147.6 (1 C, C_{arom}-NO_2), 147.3 (1 C, C_{arom}), 127.5 (2 C, CH_{arom}), 123.8 (2 C, CH_{arom}), 102.2 (1 C, O*C*OCH$_3$), 83.1 (1 C, CH*C*≡), 74.7 (1 C, ≡CH), 61.6 (1 C, *C*HC≡), 49.6 (1 C, OCH$_3$), 25.3, (1 C, C*C*H$_3$), 24.8 (1 C, C*C*H$_3$) ppm. IR (thin film): ṽ = 3257, 2992, 2940, 2857, 1517, 1343, 1211, 1186, 1145, 1030, 852, 701 cm^{-1}. HRMS (EI): calcd. for [M – CH_3O]$^+$ 218.0817; found 218.0815.

3-[(2-Methoxypropan-2-yl)oxy]but-1-yne (2e): A mixture of 3-butyn-2-ol (513.0 mg, 7.319 mmol) and 2-methoxypropene (10.0 mL, 104 mmol) was cooled to 0 °C, then pyridinium *p*-toluenesulfonate (catalytic amount) was added. The cooling bath was removed, and the mixture was stirred at room temperature for 1 h. The mixture was diluted with diethyl ether (25 mL), washed with water (3× 25 mL), dried with anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (1:20 Et_2O/pentane) to give **2e** (668.6 mg, 64%) as a colourless oil. R_f = 0.58 (1:20 Et_2O/pentane). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.49 (dq, *J* = 6.7, 2.0 Hz, 1 H, CHC≡), 3.24 (s, 3 H, OCH$_3$), 2.36 (d, *J* = 2.0 Hz, 1 H, ≡CH), 1.45 (s, 3 H, CCH$_3$), 1.43 (d, *J* = 6.7 Hz, 3 H, CH$_3$CC≡), 1.36 (s, 3 H, CCH$_3$) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 101.1 (1 C, O*C*OCH$_3$), 86.1 (1 C, CH*C*≡), 71.3 (1 C, ≡CH), 56.3 (1 C, *C*HC≡), 49.1 (1 C, OCH$_3$), 25.4 (1 C, MeOC*C*H$_3$), 24.6 (1 C, MeOC*C*H$_3$), 23.4 (1 C, CH*C*H$_3$) ppm. ^{1}H and ^{13}C NMR spectroscopic data are consistent with literature data.[9]

Tandem Cyclisation Reactions

General Procedure: The gold catalyst ({Au[P(*t*Bu)$_2$(*o*-biphenyl)-CH$_3$CN]}SbF_6, 5 mol-%) was dissolved in dry CH_2Cl_2 (1.5 mL), and the solution was stirred under a nitrogen atmosphere at the required temperature. The appropriate propargyl acetal (compounds **1a**–**1d**) and vinyl ester or alkene (3 equiv.) were dissolved in dry CH_2Cl_2 (1.0 mL), and this solution was added to the solution of the gold catalyst. The flask was washed out with further dry CH_2Cl_2 (2× 0.5 mL), and this was added to the mixture. When the acetal had been consumed, the reaction was quenched with NEt_3 (5 drops), the mixture was filtered through Celite™, and the filtrate was concentrated in vacuo. The residue was purified by flash chromatography using an appropriate eluent system to give the desired tandem products.

***cis-/trans*-2-(1,3-Dimethoxy-4,5-diphenylcyclopent-2-en-1-yl)cyclopropyl Acetate (*cis-/trans*-4):** Compounds ***cis*-4** and ***trans*-4** were synthesised following the general procedure, using gold catalyst (13.0 mg, 16.8 μmol), compound **2a** (73.5 mg, 360 μmol), and vinyl acetate (85.1 mg, 989 μmol), at –78 °C for 15 min. The products

were purified using an eluent system of 1:20 EtOAc/pentane to give a 1:1 mixture of compounds ***cis*-4** and ***trans*-4** (47.2 mg, 69%) as a yellow oil.

Data for ***cis*-4**: R_f = 0.36 (1:10 EtOAc/pentane). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.26 (m, 10 H, H_{arom}), 4.85 (dd, J = 2.3, 1.5 Hz, 1 H, C=CH), 4.44 (s, 1 H, C=C*H*CH), 4.06 (d, J = 1.2 Hz, 1 H, C=CHC*H*), 4.00 (dt, J = 7.1, 4.2 Hz, 1 H, C*H*OAc), 3.70 (s, 3 H, C=COCH_3), 3.04 (s, 3 H, C=CHCOCH_3), 2.09 (s, 3 H, COOCH_3), 0.91 (ddd, J = 8.2, 6.6, 4.2 Hz, 1 H, AcOCHCH_2), 0.81 (dt, J = 10.2, 6.8 Hz, 1 H, AcOCHCH_2), 0.39 (ddd, J = 10.2, 8.2, 7.2 Hz, 1 H, AcOCHC*H*) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 171.2 (1 C, OC=O), 159.7 (1 C, C=*C*OCH$_3$), 141.2 (1 C, C_{arom}CHCHC=), 137.6 (1 C, C_{arom}CHC=), 129.7 (2 C, *o*-CH_{arom}), 129.4 (2 C, *o*-CH_{arom}), 128.0 (2 C, *m*-CH_{arom}), 127.8 (2 C, *m*-CH_{arom}), 126.9 (1 C, *p*-CH_{arom}), 126.4 (1 C, *p*-CH_{arom}), 99.7 (1 C, C=*C*H), 86.8 (1 C, C=CH*C*OCH$_3$), 60.3 (1 C, C=CHCH), 56.7 (=CO*C*H$_3$), 53.2 (1 C, *C*HOAc), 53.1 (1 C, C=CH*C*H), 51.8 (1 C, C=CHCO*C*H$_3$), 21.7 (1 C, OOC*C*H$_3$), 21.2 (1 C, *C*HCHOAc), 9.2 (1 C, *C*H$_2$CHOAc) ppm. IR (thin film): $\tilde{\nu}$ = 3034, 2940, 2826, 1742, 1228, 701 cm^{-1}. HRMS (EI): calcd. for $C_{24}H_{26}O_4$ [M]$^+$ 378.1831; found 378.1828.

Data for ***trans*-4**: R_f = 0.32 (1:10 EtOAc/pentane). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39–7.37 (m, 2 H, H_{arom}), 7.32–7.20 (m, 8 H, H_{arom}), 4.66 (t, J = 2.0 Hz, 1 H, C=CH), 4.46 (dt, J = 7.4, 4.0 Hz, 1 H, C*H*OAc), 4.17 (br. s, 1 H, C=C*H*CH), 4.01 (br. s, 1 H, C=CHC*H*), 3.60 (s, 3 H, C=COCH_3), 2.47 (s, 3 H, C=CHCOCH_3), 2.10 (s, 3 H, COOCH_3), 1.47–1.36 (m, 2 H, AcOCHCH_2 and AcOCHC*H*), 1.17–1.11 (m, 1 H, AcOCHCH_2) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 171.6 (1 C, C=O), 159.1 (1 C, *C*=CH), 141.3 (1 C, C=CHCC_{arom}), 137.8 (1 C, C=CHC_{arom}), 130.9 (2 C, C=CHCHC*C*H$_{arom}$), 129.8 (2 C, C=CHC*C*H$_{arom}$), 127.7 (2 C, *m*-CH_{arom}), 127.4 (2 C, *m*-CH_{arom}), 126.6 (1 C, *p*-CH_{arom}), 126.2 (1 C, *p*-CH_{arom}), 97.5 (1 C, C=CH), 84.9 (1 C, CH$_3$O*C*H), 58.0 (1 C, Ph*C*H), 57.3 (1 C, Ph*C*H), 56.5 (1 C, *C*H$_3$OC=), 52.3 (1 C, *C*H$_3$OCH), 51.9 (1 C, AcO*C*H), 24.5 (1 C, AcOCH*C*H), 20.8 (1 C, OCO*C*H$_3$), 9.2 (1 C, CH$_2$) ppm. IR (thin film): $\tilde{\nu}$ = 3023, 2935, 2826, 1745, 1227, 1035, 701 cm^{-1}. HRMS (EI): calcd. for $C_{23}H_{23}O_3$ [M – CH$_3$O]$^+$ 347.1647; found 347.1647.

***cis*-/*trans*-2-(1,3-Dimethoxy-4,5-diphenylcyclopent-2-en-1-yl)cyclopropyl Benzoate (*cis*-/*trans*-5):** Compounds ***cis*-5** and ***trans*-5** were synthesised following the general procedure, using gold catalyst (13.2 mg, 16.8 μmol), compound **2a** (68.2 mg, 334 μmol), and vinyl benzoate (152.0 mg, 1.03 mmol), at –78 °C for 20 min. The products were purified using an eluent system of 1:1 CH_2Cl_2/pentane then CH_2Cl_2 to give ***cis*-5** (25.7 mg, 34%) as a colourless solid and ***trans*-5** (23.0 mg, 31%) as a yellow oil.

Data for ***cis*-5**: R_f = 0.57 (CH_2Cl_2), m.p. 154–158 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.04 (dd, J = 8.3, 1.3 Hz, 2 H, $CH_{o\text{-}OBz}$), 7.59 (t, J = 7.4 Hz, 1 H, $CH_{p\text{-}OBz}$), 7.46 (t, J = 7.7 Hz, 2 H, $CH_{m\text{-}OBz}$), 7.23–7.35 (m, 10 H, CH_{arom}), 4.99 (dd, J = 2.2, 1.3 Hz, 1 H, C=CH), 4.40 (s, 1 H, C=C*H*CH), 4.17 (s, 1 H, C=CHC*H*), 4.08 (dt, J = 7.1, 4.2 Hz, CHOBz), 3.73 (s, 3 H, C=COCH_3), 3.16 (s, 3 H, C=CHCOCH_3), 1.11 (ddd, J = 8.1, 6.4, 4.2 Hz, 1 H, CH$_2$), 0.97 (dt, J = 10.1, 6.7 Hz, 1 H, CH$_2$) 0.58 (ddd, J = 10.1 8.2, 7.1 Hz, 1 H, BzOCHC*H*) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 167.2 (1 C, C=O), 160.2 (1 C, C=*C*OCH$_3$), 140.6 (1 C, C_{arom}CHCHC=), 137.7 (1 C, C_{arom}CHC=), 133.1 (1 C, $CH_{p\text{-}OBz}$), 130.3 (1 C, $C_{arom\text{-}OBz}$), 129.6 (2 C, $CH_{o\text{-}OBz}$), 129.5 (1 C, CH_{arom}), 129.1 (2 C, CH_{arom}), 128.4 (2 C, $CH_{m\text{-}OBz}$), 128.1 (2 C, CH_{arom}), 127.7 (2 C, CH_{arom}), 127.0 (1 C, C_{arom}), 126.4 (2 C, CH_{arom}), 99.3 (1 C, C=*C*H), 86.2 (1 C, C=CH*C*OCH$_3$), 59.8 (1 C, C=*C*HCH), 56.8 (=CO*C*H$_3$), 54.5 (1 C, C=CH*C*H), 53.5 (1 C, *C*HOBz), 52.0 (1 C, C=CHCO*C*H$_3$), 22.9 (1 C, *C*HCHOBz), 9.1 (1 C, CH$_2$) ppm. IR (neat): $\tilde{\nu}$ = 2927, 1722, 1644, 1452, 1272, 709 cm^{-1}. HRMS (EI): calcd. for $C_{29}H_{28}O_4$ [M]$^+$ 440.1982; found 440.1979.

Data for ***trans*-5**: R_f = 0.64 (CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.03 (d, J = 7.2 Hz, 2 H, $CH_{o\text{-}OBz}$), 7.56 (t, J = 7.4 Hz, 1 H, $CH_{p\text{-}OBz}$), 7.45–7.40 (m, 2 H, $CH_{m\text{-}OBz}$), 7.34–7.23 (m, 10 H, CH_{arom}), 4.70 (dt, J = 7.0, 4.6 Hz, 1 H, CHOBz), 4.55 (t, J = 1.9 Hz, 1 H, C=C*H*), 4.34 (s, 1 H, C=C*H*), 4.09 (s, 1 H, C=CHC*H*), 3.23 (s, 3 H, C=COCH_3), 2.46 (s, 3 H, C=CHCOCH_3), 1.63 (m, 1 H, BzOCHCH_2), 1.59 (m, 1 H, BzOCHC*H*), 1.28 (m, 1 H, BzOCHCH_2) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 167.3 (1 C, O*C*=O), 158.8 (1 C, C=*C*OCH$_3$), 141.4 (1 C, C_{arom}CHC=), 137.9 (1 C, C_{arom}CHCHC=), 133.2, (1 C, $CH_{p\text{-}OBz}$), 130.7 (2 C, CH_{arom}), 130.0 (1 C, OCO$C_{arom\text{-}OBz}$), 129.6 (2 C, $CH_{o\text{-}OBz}$), 129.6 (1 C, CH_{arom}), 128.4 (2 C, $CH_{m\text{-}OBz}$), 127.8 (2 C, CH_{arom}), 127.4 (2 C, CH_{arom}), 126.6 (2 C, CH_{arom}), 126.2 (1 C, CH_{arom}), 97.6 (1 C, C=*C*H), 84.9 (1 C, C=CH*C*OCH$_3$), 59.3 (1 C, C=CHCH), 56.5 (1 C, C=CH*C*H), 56.2 (1 C, C=CO*C*H$_3$), 52.4 (1 C, CH*C*OCH$_3$), 51.9 (1 C, *C*HOBz), 24.8 (1 C, *C*HCHOBz), 9.8 (1 C, *C*H$_2$) ppm. IR (thin film): $\tilde{\nu}$ = 3012, 2930, 1714, 1662, 1267, 716, 696 cm^{-1}. HRMS (EI): calcd. for $C_{29}H_{28}O_4$ [M]$^+$ 440.1982; found 440.1982.

***cis*-/*trans*-2-[1,3-Dimethoxy-4,5-bis(4-methoxyphenyl)cyclopent-2-en-1-yl]cyclopropyl Acetate (*cis*-/*trans*-6):** Compounds ***cis*-6** and ***trans*-6** were synthesised following the general procedure, using gold catalyst (13.3 mg, 17.2 μmol), compound **2b** (80.7 mg, 344 μmol), and vinyl acetate (89.6 mg, 1.04 mmol), at –40 °C for 30 min. The products were purified using an eluent system of 1:3 Et_2O/pentane to give a 87:13 mixture of compounds ***cis*-6** and ***trans*-6** (29.3 mg, 39%).

Data for ***cis*-6**: R_f = 0.19 (1% THF/CH_2Cl_2). Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.25–7.23 (m, 2 H, C=CHCCH_{arom}), 7.18–7.16 (m, 2 H, C=CHCCHCCH_{arom}), 6.87–6.85 (m, 2 H, C=CHCCHCH_{arom}), 6.85–6.84 (m, 2 H, C=CHCCHCCH-CH_{arom}), 4.80–4.79 (m, 1 H, C=CH), 4.37 (br. s, 1 H, C=C*H*), 4.05–4.00 (m, 1 H, C*H*OAc), 3.99 (br. s, C=CHC*H*), 3.80 (s, 3 H, C*H*$_3$O-PhCHC=), 3.78 (s, 3 H, C*H*$_3$O-PhCHCCH=), 3.68 (s, 3 H, C=COCH_3), 3.04 (s, 3 H, C=CHCOC*H*$_3$), 2.10 (s, 3 H, OCOCH_3), 0.92–0.87 (m, 1 H, CH$_2$), 0.85–0.79 (m, 1 H, CH$_2$), 0.42–0.36 (m, 1 H, C*H*CHOAc) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 171.1 (1 C, OC=O), 159.6 (1 C, C=*C*OCH$_3$), 158.5 (1 C, MeO-C_{arom}), 158.1 (1 C, MeO-C_{arom}), 133.1 (1 C, C=CHCCH*C*$_{arom}$), 130.5 (2 C, C=CHCCHC*C*H$_{arom}$), 130.2 (2 C, C=CHC*C*H$_{arom}$), 129.4 (1 C, C=CH*C*$_{arom}$), 113.4 (2 C, C=CHCCHCCH*C*H$_{arom}$), 113.1 (2 C, C=CHCCH*C*H$_{arom}$), 99.7 (1 C, C=CH), 86.6 (1 C, C=CH*C*H), 59.5 (1 C, C=CH), 56.6 (1 C, C=CO*C*H$_3$), 55.1 (1 C, *C*H$_3$OPh), 55.1 (1 C, *C*H$_3$OPh), 53.2 (1 C, *C*HOAc), 51.9 (1 C, C=CH*C*H), 51.8 (1 C, C=CHCO*C*H$_3$), 21.5 (1 C, *C*HCHOAc), 21.2 (1 C, OCO*C*H$_3$), 9.1 (1 C, CH$_2$) ppm. IR (thin film): $\tilde{\nu}$ = 2934, 1742, 1609, 1509, 1463, 1227, 1175, 830, 729 cm^{-1}. HRMS (EI): calcd. for $C_{26}H_{30}O_6$ [M]$^+$ 438.2042; found 438.2038.

Data for ***trans*-6**: R_f = 0.15 (1% THF/CH_2Cl_2). Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.29–7.26 (m, 2 H, C=CHCCH_{arom}), 7.22–7.19 (m, 2 H, C=CHCCHCCH_{arom}), 6.86–6.85 (m, 2 H, C=CHCCHCH_{arom}), 6.83–6.82 (m, 2 H, C=CHCCH-CCHCH_{arom}), 4.61–4.60 (m, 1 H, C=CH), 4.47–4.41 (m, 1 H, C*H*OAc), 4.08 (br. s, 1 H, C=C*H*), 3.95 (br. s, C=CHC*H*), 3.80 (s, 3 H, C*H*$_3$O-Ph), 3.79 (s, 3 H, C*H*$_3$O-Ph), 3.59 (s, 3 H, C=COCH$_3$), 2.52 (s, 3 H, C=CHCOC*H*$_3$), 2.10 (s, 3 H, OCOCH$_3$), 1.41–1.31 (m, 1 H, CH$_2$), 1.41–1.31 (m, 1 H, C*H*CHOAc), 1.16–1.09 (m, 1 H, CH$_2$) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 171.6 (1 C, OC=O), 159.1 (1 C, C=*C*OCH$_3$), 158.3 (1 C, MeO-C_{arom}), 158.1 (1 C, MeO-C_{arom}), 133.5 (1 C, C=CHCCH*C*$_{arom}$), 131.5 (2 C,

C=CHCCHCCH$_{arom}$), 130.6 (2 C, C=CHCCH$_{arom}$), 129.9 (1 C, C=CHC$_{arom}$), 113.2 (2 C, MeO-CCH$_{arom}$), 112.9 (2 C, MeO-CCH$_{arom}$), 97.4 (1 C, C=CH), 84.6 (1 C, C=CHCH), 57.0 (1 C, C=CH), 56.6 (1 C, C=COCH$_3$), 56.5 (1 C, C=CHCH), 55.2 (1 C, CH$_3$OPh), 55.1 (1 C, CH$_3$OPh), 52.4 (1 C, C=CHCOCH$_3$), 51.9 (1 C, CHOAc), 24.3 (1 C, CHCHOAc), 20.8 (1 C, OCOCH$_3$), 9.2 (1 C, CH$_2$) ppm. IR (thin film): $\tilde{\nu}$ = 2930, 2826, 1743, 1609, 1511, 1246, 1177, 1034 cm^{-1}. HRMS (EI): calcd. for $C_{26}H_{30}O_6$ [M]$^+$ 438.2042; found 438.2044.

***cis-/trans*-2-[1,3-Dimethoxy-4,5-bis(4-methoxyphenyl)cyclopent-2-en-1-yl]cyclopropyl Benzoate (*cis-/trans*-7):** Compounds ***cis*-7** and ***trans*-7** were synthesised following the general procedure, using gold catalyst (13.7 mg, 17.7 μmol), compound **2b** (80.7 mg, 344 μmol), and vinyl benzoate (152.6 mg, 1.03 mmol), at –78 °C for 120 min. The products were purified using an eluent system of 1:9 Et_2O/pentane to give a 63:37 mixture of compounds ***cis*-7** and ***trans*-7** (49.5 mg, 53%).

Data for ***cis*-7**: R_f = 0.09 [1:4 (1:20 EtOAc/pentane)/CH_2Cl_2]; yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.04–8.02 (m, 2 H, CH$_{o\text{-OBz}}$), 7.60–7.56 (m, 1 H, CH$_{p\text{-OBz}}$), 7.48–7.44 (m, 2 H, CH$_{m\text{-OBz}}$), 7.24–7.22 (m, 2 H, C=CHCCHCCH$_{arom}$), 7.22–7.19 (m, 2 H, CH=CCHCCH$_{arom}$), 6.86–6.84 (m, 2 H, CH=CCHCCHCH$_{arom}$), 6.80–6.78 (m, 2 H, C=CHCCHCCHCH$_{arom}$), 4.93–4.92 (m, 1 H, C=CH), 4.35 (br. s, 1 H, CH=CCH), 4.15–4.10 (m, 1 H, CHOBz), 4.091–4.088 (m, 1 H, C=CHCCH), 3.79 (s, 3 H, CH$_3$OPh), 3.78 (s, 3 H, CH$_3$OPh), 3.72 (s, 3 H, C=COCH$_3$), 3.15 (s, 3 H, C=COCH$_3$), 1.12–1.07 (m, 1 H, CH$_2$), 0.99–0.93 (m, 1 H, CH$_2$), 0.61–0.54 (m, 1 H, CHCHOAc) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 167.2 (1 C, C$_{arom\text{-OBz}}$), 160.1 (1 C, C=CH), 158.6 (1 C, CH$_3$OC$_{arom}$), 158.1 (1 C, CH$_3$OC$_{arom}$), 133.0 (1 C, CH$_{p\text{-OBz}}$), 132.6 (1 C, C=CHCCHC$_{arom}$), 130.4 (2 C, CH=CCHCCH$_{arom}$), 130.3 (1 C, C$_{OBz}$), 129.9 (2 C, C=CHCCHCCH$_{arom}$), 129.6 (1 C, CH=CCH-C$_{arom}$), 129.5 (2 C, CH$_{o\text{-OBz}}$), 128.4 (2 C, CH$_{m\text{-OBz}}$), 113.6 (2 C, CH=CCHCCHCH$_{arom}$), 113.1 (2 C, C=CHCCHCCHCH$_{arom}$), 99.3 (1 C, C=CH), 86.1 (1 C, C=CHC), 59.0 (1 C, CH=CCH), 56.7 (1 C, =COCH$_3$), 55.2 (1 C, CH$_3$OC$_{arom}$), 55.1 (1 C, CH$_3$OC$_{arom}$), 53.5 (1 C, CHOBz), 53.3 (1 C, C=CHCCH), 51.9 (1 C, C=CHCOCH$_3$), 22.7 (1 C, CHCHOAc), 9.0 (1 C, CH$_2$) ppm. IR (thin film): $\tilde{\nu}$ = 2951, 2930, 2826, 1721, 1510, 1270, 1245, 1175, 1110, 1034, 712 cm^{-1}. HRMS (EI): calcd. for $C_{31}H_{32}O_6$ [M]$^+$ 500.2199; found 500.2199.

Data for ***trans*-7**: R_f = 0.13 [1:4 (1:20 EtOAc/pentane)/CH_2Cl_2]; yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.03–8.01 (m, 2 H, CH$_{o\text{-OBz}}$), 7.58–7.53 (m, 1 H, CH$_{p\text{-OBz}}$), 7.44–7.39 (m, 2 H, CH$_{m\text{-OBz}}$), 7.28–7.25 (m, 2 H, CH$_3$OCCHCH$_{arom}$), 7.24–7.21 (m, 2 H, CH$_3$OCCHCH$_{arom}$), 6.84–6.81 (m, 4 H, CH$_{arom}$COCH$_3$), 4.71–4.65 (m, 1 H, CHOBz), 4.51–4.49 (m, 1 H, C=CH), 4.25 (br. s, 1 H, CH=CCH), 4.04 (br. s, 1 H, C=CHCCH), 3.79 (s, 3 H, CH$_3$OPh), 3.77 (s, 3 H, CH$_3$OPh), 3.24 (s, 3 H, =COCH$_3$), 2.52 (s, 3 H, =CHCOCH$_3$), 1.62–1.50 (m, 1 H, CH$_2$), 1.62–1.50 (m, 1 H, CHCHOBz), 0.88–0.83 (m, 1 H, CH$_2$) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 167.2 (1 C, C$_{arom\text{-OBz}}$), 158.7 (1 C, C=CH), 158.3 (1 C, CH$_3$OC$_{arom}$), 158.0 (1 C, CH$_3$OC$_{arom}$), 133.5 (1 C, C=CHCCHC$_{arom}$), 133.1 (1 C, C$_{p\text{-OBz}}$), 131.6 (2 C, CH$_3$OCCH-CH$_{arom}$), 130.5 (2 C, CH$_3$OCCHCH$_{arom}$), 129.9 (1 C, CH=CCHC$_{arom}$), 129.6 (2 C, CH$_{o\text{-OBz}}$), 129.5 (1 C, C$_{arom\text{-OBz}}$), 128.4 (2 C, CH$_{m\text{-OBz}}$), 113.2 (2 C, CH$_3$OCCH$_{arom}$), 112.9 (2 C, CH$_3$-OCCH$_{arom}$), 97.6 (1 C, C=CH), 84.5 (1 C, C=CHC), 58.3 (1 C, CH=CCH), 56.2 (1 C, =COCH$_3$), 55.6 (1 C, C=CHCCH), 55.13 (1 C, CH$_3$OC$_{arom}$), 55.11 (1 C, CH$_3$OC$_{arom}$), 52.4 (1 C, C=CHCOCH$_3$), 52.0 (1 C, CHOBz), 24.6 (1 C, CHCHOBz), 9.7 (CH$_2$) ppm. IR (thin film): $\tilde{\nu}$ = 2930, 2831, 1722, 1510, 1267, 1246, 1175, 1035, 711 cm^{-1}. HRMS (EI): calcd. for $C_{31}H_{32}O_6$ [M]$^+$ 500.2199; found 500.2196.

***cis-/trans*-2-[1,3-Dimethoxy-4,5-bis(4-methoxyphenyl)cyclopent-2-en-1-yl]-1-phenylcyclopropyl Acetate (*cis-/trans*-8):** Compounds ***cis*-8** and ***trans*-8** were synthesised following the general procedure, using gold catalyst (10.5 mg, 13.6 μmol), compound **2b** (63.0 mg, 269 μmol), and 1-phenylvinyl acetate (128.0 mg, 0.789 mmol), at –40 °C for 30 min, then 0 °C for 15 min. The products were purified using an eluent system of 1:10 EtOAc/pentane to give a 1:3 mixture of compounds ***cis*-8** and ***trans*-8** (26.0 mg, 19%).

Data for ***cis*-8**: R_f = 0.25 (1% Et_2O/CH_2Cl_2). Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33–7.28 (m, 2 H, C=CHCCHCCH$_{arom}$), 7.16–7.08 (m, 2 H, C=CHCCH$_{arom}$), 7.16–7.08 (m, 2 H, CH$_{m\text{-Ph}}$), 7.16–7.08 (m, 2 H, CH$_{p\text{-Ph}}$), 6.89–6.87 (m, 2 H, C=CHCCHCCHCH$_{arom}$), 6.73–6.71 (m, 2 H, CH$_{o\text{-Ph}}$), 6.65–6.63 (m, 2 H, C=CHCCHCH$_{arom}$), 4.90 (br. s, 1 H, C=CH), 4.31 (br. s, 1 H, C=CH), 4.14 (br. s, 1 H, C=CHCCH), 3.82 (s, 3 H, CH$_3$OPh), 3.71 (s, 3 H, CH$_3$OPh), 3.67 (s, 3 H, C=COCH$_3$), 3.15 (s, 3 H, C=CHCOCH$_3$), 1.62–1.60 (m, 2 H, CH$_2$), 2.17 (s, 3 H, OCOCH$_3$), 0.74–0.69 (m, 1 H, CHCOAc) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 170.1 (1 C, C=O), 160.6 (1 C, MeOC$_{arom}$), 158.4 (1 C, C=), 158.2 (1 C, MeOC$_{arom}$), 141.4 (1 C, C$_{arom}$COAc), 132.5 (1 C, C=CHCCHC$_{arom}$), 130.3 (2 C, C=CHCCH$_{arom}$), 129.9 (2 C, C=CHCCHCCH$_{arom}$), 129.4 (1 C, C=CHC$_{arom}$), 127.9 (2 C, CH$_{m\text{-Ph}}$), 126.1 (1 C, CH$_{p\text{-Ph}}$), 123.4 (2 C, CH$_{o\text{-Ph}}$), 113.6 (2 C, C=CHCCHCH$_{arom}$), 113.3 (2 C, C=CHCCHCCHCH$_{arom}$), 98.7 (1 C, C=CH), 86.6 (1 C, C=CHC), 62.0 (1 C, COAc), 58.2 (1 C, C=CH), 56.8 (1 C, MeOPh), 55.2 (1 C, MeOPh), 55.1 (1 C, C=COCH$_3$), 53.8 (1 C, C=CHCCH), 52.2 (1 C, C=CHCOCH$_3$), 34.9 (1 C, CHCOAc), 21.5 (1 C, OCOCH$_3$), 19.0 (1 C, CH$_2$) ppm. Data for a mixture of ***cis*-8** and ***trans*-8**: IR (thin film): $\tilde{\nu}$ = 2930, 2831, 1751, 1652, 1610, 1510, 1244, 1176, 1034, 731 cm^{-1}. HRMS (EI): calcd. for $C_{32}H_{24}O_6$ [M]$^+$ 514.2355; found 514.2346.

Data for ***trans*-8**: R_f = 0.30 (1% Et_2O/CH_2Cl_2). Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.46–7.44 (m, 2 H, CH$_{o\text{-Ph}}$), 7.33–7.30 (m, 2 H, CH$_{m\text{-Ph}}$), 7.33–7.30 (m, 2 H, CH$_{p\text{-Ph}}$), 7.26–7.24 (m, 2 H, C=CHCCH$_{arom}$), 6.94–6.92 (m, 2 H, C=CHCCHCH$_{arom}$), 6.67–6.65 (m, 2 H, C=CHCCHCCHCH$_{arom}$), 6.47–6.45 (m, 2 H, C=CHCCHCCH$_{arom}$), 4.60 (br. s, 1 H, C=CH), 4.22 (br. s, 1 H, C=CH), 3.85 (s, 3 H, CH$_3$OPh), 3.75 (s, 3 H, CH$_3$OPh), 3.62 (s, 3 H, C=COCH$_3$), 3.31 (br. s, 1 H, C=CHCCH), 2.99 (s, 3 H, C=CHCOCH$_3$), 1.83–1.80 (m, 1 H, CH$_2$), 1.80 (s, 3 H, OCOCH$_3$), 1.46–1.41 (m, 1 H, CHCOAc), 1.28–1.24 (m, 1 H, CH$_2$) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 169.9 (1 C, C=O), 160.2 (1 C, C=), 158.5 (1 C, MeOC$_{arom}$), 157.9 (1 C, MeOC$_{arom}$), 136.7 (1 C, C$_{arom}$-COAc), 132.5 (1 C, C=CHCCHC$_{arom}$), 131.4 (2 C, C=CHCCH$_{arom}$), 130.1 (2 C, CH$_{p\text{-Ph}}$), 130.0 (2 C, C=CHCCHCCH$_{arom}$), 129.8 (1 C, C=CHC$_{arom}$), 127.8 (2 C, CH$_{m\text{-Ph}}$), 127.6 (1 C, CH$_{p\text{-Ph}}$), 113.5 (2 C, C=CHCCHCH$_{arom}$), 112.8 (2 C, C=CHCCHCCHCH$_{arom}$), 98.7 (1 C, C=CH), 85.5 (1 C, C=CHC), 63.9 (1 C, COAc), 58.7 (1 C, C=CH), 56.6 (1 C, C=COCH$_3$), 55.3 (1 C, MeOPh), 55.1 (1 C, MeOPh), 52.0 (1 C, C=CHCOCH$_3$), 51.8 (1 C, C=CHCCH), 30.2 (1 C, CHCOAc), 21.5 (1 C, OCOCH$_3$), 15.9 (1 C, CH$_2$) ppm. IR (thin film): $\tilde{\nu}$ = 2997, 2935, 2831, 1750, 1652, 1610, 1510, 1243, 1176, 1034, 731 cm^{-1}. HRMS (EI): calcd. for $C_{32}H_{34}O_6$ [M]$^+$ 514.2355; found 514.2346.

***cis-/trans*-2-[4,5-Bis(4-chlorophenyl)-1,3-dimethoxycyclopent-2-en-1-yl]cyclopropyl Acetate (*cis-/trans*-9):** Compounds ***cis*-9** and ***trans*-9** were synthesised following the general procedure, using gold catalyst (13.3 mg, 17.2 μmol), compound **2c** (80.8 mg, 338 μmol), and vinyl acetate (93.6 mg, 1.09 mmol), at –40 °C for 15 min. The prod-

ucts were purified using an eluent system of 1:30 EtOAc/pentane to give ***cis*-9** (33.8 mg, 45%) and ***trans*-9** (24.5 mg, 32%) as pale yellow waxes.

Data for ***cis*-9**: R_f = 0.31 (1:10 EtOAc/pentane). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29–7.23 (m, 6 H, CH_{arom}), 7.20–7.17 (m, 2 H, CH_{arom}), 4.81–4.80 (m, 1 H, C=CH), 4.38 (br. s, 1 H, C=C*H*), 4.05–4.01 (m, 1 H, CHOAc), 4.02 (br. s, 1 H, C=CHC*H*), 3.69 (s, 3 H, =COCH_3), 3.03 (s, 3 H, C=CHCOCH_3), 2.08 (s, 3 H, OCOCH_3), 0.90–0.79 (m, 2 H, CH_2), 0.39–0.33 (m, 1 H, AcOCHC*H*) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 171.0 (1 C, OC=O), 159.6 (1 C, CH=*C*OCH$_3$), 139.5 (1 C, C_{arom}CHC=), 135.9 (1 C, C_{arom}CHCHC=), 132.8 (1 C, C_{arom}Cl), 132.2 (1 C, C_{arom}Cl), 130.9 (2 C, CH_{arom}), 130.7 (2 C, CH_{arom}), 128.2 (2 C, CH_{arom}), 127.9 (2 C, CH_{arom}), 99.6 (1 C, C=*C*H), 86.6 (1 C, =CH*C*OCH$_3$), 59.8 (1 C, C=CHCH), 56.8 (1 C, =CO*C*H$_3$), 53.1 (1 C, *C*HOAc), 52.5 (1 C, C=CH*C*H), 51.9 (1 C, =CHCO*C*H$_3$), 21.5 (1 C, *C*HCHOAc), 21.2 (1 C, OCO*C*H$_3$), 9.1 (1 C, CH_2) ppm. IR (neat): $\tilde{\nu}$ = 2934, 1743, 1652, 1489, 1225, 1090, 1014, 907, 730 cm^{-1}. HRMS (EI): calcd. for $C_{24}H_{24}O_4Cl_2$ $[M]^+$ 446.1046; found 446.1043.

Data for ***trans*-9**: R_f = 0.20 (1:10 EtOAc/pentane). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29–7.24 (m, 6 H, CH_{arom}), 7.21–7.19 (m, 2 H, CH_{arom}), 4.61 (t, J = 1.8 Hz, 1 H, C=CH), 4.44 (dt, J = 7.3, 4.1 Hz, 1 H, CHOAc), 4.12 (d, J = 1.0 Hz, 1 H, C=C*H*), 3.96 (br. s, 1 H, C=CHC*H*), 3.59 (s, 3 H, =COCH$_3$), 2.50 (s, 3 H, =CHCOCH$_3$), 2.09 (s, 3 H, OCOCH$_3$), 1.39 (m, 1 H, AcOCHC*H*), 1.31 (m, 1 H, AcOCHC*H*$_2$), 1.15 (td, J = 9.6, 7.3 Hz, 1 H, AcOCHC*H*$_2$) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 171.5 (1 C, O*C*=O), 159.1 (1 C, CH=*C*OCH$_3$), 139.6 (1 C, C_{arom}CHC=), 136.2 (1 C, C_{arom}CHCHC=), 132.6 (1 C, C_{arom}Cl), 132.1 (1 C, C_{arom}Cl), 131.9 (2 C, CH_{arom}), 131.0 (2 C, CH_{arom}), 128.0 (2 C, CH_{arom}), 127.6 (2 C, CH_{arom}), 97.2 (1 C, C=*C*H), 84.8 (1 C, =CH*C*OCH$_3$), 57.4 (1 C, =C*C*HCH), 56.7 (=CO*C*H$_3$), 56.6 (1 C, =CCH*C*H), 52.4 (1 C, =CHCO*C*H$_3$), 51.8 (1 C, *C*HOAc), 24.2 (1 C, *C*HCHOAc), 20.8 (1 C, OCO*C*H$_3$), 9.3 (1 C, CH_2) ppm. IR (neat): $\tilde{\nu}$ = 2933, 1744, 1662, 1489, 1223, 1090, 1014, 908, 730 cm^{-1}. HRMS (EI): calcd. for $C_{24}H_{24}O_4Cl_2$ $[M]^+$ 446.1046; found 446.1050.

***cis*-/*trans*-2-[4,5-Bis(4-chlorophenyl)-1,3-dimethoxycyclopent-2-en-1-yl]cyclopropyl Benzoate (*cis*-/*trans*-10):** Compounds ***cis*-10** and ***trans*-10** were synthesised following the general procedure, using gold catalyst (13.0 mg, 16.8 μmol), compound **2c** (80.5 mg, 337 μmol), and vinyl benzoate (157.2 mg, 1.06 mmol), at –40 °C for 15 min. The products were purified using an eluent system of 1:50–1:9 Et_2O/pentane, followed by a second purification using 1:10 Et_2O/pentane to give ***cis*-10** (33.1 mg, 39%) as a colourless solid and ***trans*-10** (28.2 mg, 33%) as a pale yellow oil.

Data for ***cis*-10**: R_f = 0.35 (10:2 pentane/diethyl ether), m.p. 174–177 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.02 (m, 2 H, $CH_{o\text{-}OBz}$), 7.62–7.58 (m, 1 H, $CH_{p\text{-}OBz}$), 7.49–7.44 (m, 2 H, $CH_{m\text{-}OBz}$), 7.30–7.20 (m, 8 H, CH_{arom}), 4.91–4.90 (m, 1 H, C=CH), 4.37 (br. s, 1 H, =CC*H*), 4.15 (td, J = 7.1, 4.2 Hz, 1 H, CHOBz), 4.09 (d, J = 1.3 Hz, 1 H, =CCHC*H*), 3.71 (s, 3 H, =COCH_3), 3.12 (s, 3 H, =CHCOCH_3), 1.09 (ddd, J = 8.2, 6.5, 4.3 Hz, 1 H, CH_2), 0.96 (dt, J = 9.9, 7.0 Hz, 1 H, CH_2), 0.53 (ddd, J = 10.0, 8.2, 7.2 Hz, 1 H, BzOCHC*H*) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 167.1 (1 C, OC=O), 159.9 (1 C, CH=*C*OCH$_3$), 139.0 (1 C, C_{arom}CHCHC=), 136.0 (1 C, C_{arom}CHC=), 133.2 (1 C, $CH_{p\text{-}OBz}$), 132.9 (1 C, C_{arom}Cl), 132.2 (1 C, C_{arom}Cl), 130.8 (2 C, CH_{arom}), 130.4 (2 C, CH_{arom}), 130.1 (1 C, OCO*C*$_{arom}$), 129.5 (2 C, $CH_{o\text{-}OBz}$), 128.5 (2 C, $CH_{m\text{-}OBz}$), 128.4 (2 C, CH_{arom}), 127.9 (2 C, CH_{arom}), 99.3 (1 C, C=*C*H), 86.2 (1 C, =CH*C*OCH$_3$), 59.4 (1 C, =C*C*HCH), 56.9 (=CO*C*H$_3$), 53.5 (1 C, *C*HOBz), 53.4 (1 C, =CCH*C*H), 52.0 (1 C, =CHCO*C*H$_3$), 22.5 (1 C, *C*HCHOBz), 9.04 (1 C, CH_2) ppm. IR (neat): $\tilde{\nu}$ = 2934, 1721, 1651, 1489, 1266, 1090, 1014, 710 cm^{-1}. HRMS (EI): calcd. for $C_{29}H_{26}O_4Cl_2$ $[M]^+$ 508.1203; found 508.1203.

Data for ***trans*-10**: R_f = 0.27 (10:2 pentane/diethyl ether). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.00 (d, J = 7.2 Hz, 2 H, $CH_{o\text{-}OBz}$), 7.57 (t, J = 7.4 Hz, 1 H, $CH_{p\text{-}OBz}$), 7.42 (t, J = 7.6 Hz, 2 H, $CH_{m\text{-}OBz}$), 7.27–7.26 (m, 2 H, CH_{arom}), 7.25–7.24 (m, 2 H, CH_{arom}), 7.24–7.23 (m, 2 H, CH_{arom}), 7.22–7.20 (m, 2 H, CH_{arom}), 4.68 (dt, J = 7.2, 4.2 Hz, 1 H, CHOBz), 4.49 (t, J = 1.9 Hz, 1 H, C=C*H*), 4.29 (d, J = 1.2 Hz, 1 H, =CC*H*), 4.03 (s, 1 H, =CCHC*H*), 3.20 (s, 3 H, =COCH_3), 2.50 (s, 3 H, =CHCOCH_3), 1.59–1.55 (m, 1 H, CH_2), 1.55–1.53 (m, 1 H, BzOCHC*H*), 1.32–1.27 (m, 1 H, CH_2) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 167.2 (1 C, OC=O), 158.8 (1 C, CH=*C*OCH$_3$), 139.7 (1 C, C_{arom}CHC=), 136.3 (1 C, C_{arom}CHCHC=), 133.3 (1 C, $CH_{p\text{-}OBz}$), 132.6 (1 C, C_{arom}Cl), 132.0 (1 C, C_{arom}Cl), 131.9 (2 C, CH_{arom}), 130.9 (2 C, CH_{arom}), 129.6 (2 C, $CH_{o\text{-}OBz}$), 129.4 (1 C, OCO*C*$_{arom}$), 128.5 (2 C, $CH_{m\text{-}OBz}$), 128.0 (2 C, CH_{arom}), 127.6 (2 C, CH_{arom}), 97.3 (1 C, C=*C*H), 84.7 (1 C, =CH*C*OCH$_3$), 58.6 (1 C, =C*C*HCH), 56.2 (1 C, =CO*C*H$_3$), 55.9 (1 C, =CCH*C*H), 52.5 (1 C, =CHCO*C*H$_3$), 51.9 (1 C, CHOBz), 24.7 (1 C, *C*HCHOBz), 9.7 (1 C, *C*H$_2$) ppm. IR (thin film): $\tilde{\nu}$ = 2933, 1722, 1661, 1489, 1264, 1089, 1014, 709 cm^{-1}. HRMS (EI): calcd. for $C_{29}H_{26}O_4Cl_2$ $[M]^+$ 508.1203; found 508.1202.

***cis*-/*trans*-2-[4,5-Bis(4-chlorophenyl)-1,3-dimethoxycyclopent-2-en-1-yl]-1-methylcyclopropyl Acetate (*cis*-/*trans*-11):** Compounds ***cis*-11** and ***trans*-11** were synthesised following the general procedure, using gold catalyst (13.4 mg, 0.02 mmol), compound **2c** (80.0 mg, 0.33 mmol), and isopropenyl acetate (64.8 mg, 0.65 mmol). The reaction mixture was stirred at room temperature for 16 min. An isocratic eluent of 1:30 Et_2O/pentane was used to isolate a mixture of ***cis*-11** and ***trans*-11** (32.5 mg, 42%). A small amount of ***cis*-11** was isolated from the isomeric mixture as a yellow oil (8.1 mg, 11%). Due to the complexity of the ^{1}H and ^{13}C NMR spectra of the isomeric mixture, the chemical shifts of ***trans*-11** could not be assigned (overall *cis*/*trans* ratio 73:27). ***trans*-11**: R_f = 0.32 (10:3 pentane/diethyl ether). Data for ***cis*-11**: R_f = 0.26 (10:3 pentane/diethyl ether). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31–7.30 (m, 2 H, CH_{arom}), 7.27–7.26 (m, 2 H, CH_{arom}), 7.26–7.24 (m, 2 H, CH_{arom}), 7.24–7.22 (m, 2 H, CH_{arom}), 4.88 (dd, J = 1.8, 1.1 Hz, 1 H, C=CH), 4.28 (s, 1 H, C=C*H*CH), 4.05 (s, 1 H, C=CHC*H*), 3.70 (s, 3 H, C=COCH$_3$), 3.11 (s, 3 H, C=CHCOCH_3), 2.03 (s, 3 H, OCOCH$_3$), 1.14–1.18 (m, 2 H, CH_2), 1.05 (s, 3 H, CHCCH_3), 0.28 (dd, J = 10.0, 7.8 Hz, 1 H, AcOCCH) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 170.2 (1 C, OC=O), 160.7 (1 C, CH=*C*OCH$_3$), 139.0 (1 C, C_{arom}CHCHC=), 136.6 (1 C, C_{arom}CHC=), 132.8 (1 C, C_{arom}Cl), 132.2 (1 C, C_{arom}Cl), 131.0 (2 C, CH_{arom}), 130.2 (2 C, CH_{arom}), 128.4 (2 C, CH_{arom}), 127.9 (2 C, CH_{arom}), 98.5 (1 C, C=*C*H), 86.2 (1 C, C=CH*C*OCH$_3$), 58.8 (1 C, *C*OAc), 58.3 (1 C, C=CH), 57.0 (1 C, C=CO*C*H$_3$), 54.6 (1 C, C=CH*C*H), 52.0 (1 C, C=CHCO*C*H$_3$), 29.4 (1 C, *C*HCOAc), 22.6 (1 C, CHC*C*H$_3$), 21.6 (1 C, OCO*C*H$_3$), 16.7 (1 C, CH_2) ppm. Data for a mixture of ***cis*-11** and ***trans*-11**: IR (thin film): $\tilde{\nu}$ = 2935, 1744, 1653, 1489, 1207, 1089, 1014, 908, 729 cm^{-1}. HRMS (EI): calcd. for $C_{25}H_{26}O_4Cl_2$ $[M]^+$ 460.1203; found 460.1205.

***trans*-2-[4,5-Bis(4-chlorophenyl)-1,3-dimethoxycyclopent-2-en-1-yl]-1-methylcyclopropyl Acetate (*trans*-12):** Compound ***trans*-12** was synthesised following the general procedure, using gold catalyst (9.8 mg, 12.7 μmol), compound **2c** (59.8 mg, 251 μmol), and 1-phenylvinyl acetate (130.6 mg, 0.805 mmol), at –40 °C for 30 min, then 0 °C for 15 min. An isocratic eluent of 1:20 EtOAc/pentane was used to isolate compound ***trans*-12** (11.2 mg, 17%), and an impure mixture of ***cis*-12** and compound **1c** that could not be fully

characterised. The amount of the *cis*-isomer was estimated from the NMR spectrum to be 11.8 mg, 18%.

Data for ***trans*-12**: R_f = 0.21 (1:20 EtOAc/pentane). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.46–7.44 (m, 2 H, CH_{arom} COAc), 7.37–7.35 (m, 2 H, CH=CCHCCHCH_{arom}), 7.33–7.32 (m, 2 H, $CH_{m\text{-Ph}}$), 7.33–7.32 (m, 1 H, $CH_{p\text{-Ph}}$), 7.25–7.24 (m, 2 H, CH=CCHCCH_{arom}), 7.07–7.05 (m, 2 H, C=CHCCHCCHCH_{arom}), 6.40–6.38 (m, 2 H, C=CHCCHCCH_{arom}), 4.60–4.59 (m, 1 H, C=CH), 4.25 (br. s, 1 H, CH=CC*H*), 3.61 (s, 3 H, =COCH_3), 3.29 (br. s, 1 H, CH=CCHC*H*), 3.02 (s, 3 H, C=CHCOCH_3), 1.83–1.79 (m, 1 H, CH_2), 1.82 (s, 3 H, OCOCH_3), 1.39–1.33 (m, 1 H, C*H*COAc), 1.29–1.24 (m, 1 H, CH_2) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 169.8 (1 C, OC=O), 159.9 (1 C, *C*=CH), 138.9 (1 C, C=CHCCH*C*$_{arom}$), 136.33 (1 C, CH=CCH*C*$_{arom}$), 136.31 (1 C, *C*$_{arom}$COAc), 132.8 (1 C, C$_{arom}$Cl), 131.9 (1 C, C$_{arom}$Cl), 131.8 (2 C, CH=CCHC*C*H$_{arom}$), 130.5 (2 C, C=CHCCHCC*H*$_{arom}$), 130.1 (2 C, $CH_{o\text{-Ph}}$), 128.3 (2 C, CH=CCHCCH*C*H$_{arom}$), 128.0 (2 C, $CH_{m\text{-Ph}}$), 127.9 (1 C, $CH_{p\text{-Ph}}$), 127.4 (2 C, C=CHCCHCCH*C*H), 98.7 (1 C, C=*C*H), 85.7 (1 C, C=CH*C*), 63.7 (1 C, *C*OAc), 59.4 (1 C, C=CHC*C*H), 56.7 (1 C, =CO*C*H$_3$), 52.1 (1 C, C=CHCO*C*H$_3$), 51.9 (1 C, C=CHC*C*H), 29.8 (1 C, *C*HCOAc), 21.4 (1 C, OCO*C*H$_3$), 16.0 (1 C, CH_2) ppm. IR (thin film): $\tilde{\nu}$ = 2935, 2831, 1753, 1654, 1489, 1232, 1090, 1015, 732, 699 cm^{-1}. HRMS (EI): calcd. for $C_{30}H_{28}O_4Cl_2$ $[M]^+$ 522.1365; found 522.1355.

***cis*-/*trans*-2-[4-(4-Chlorophenyl)-1,3-dimethoxy-5-(4-nitrophenyl)-cyclopent-2-en-1-yl]cyclopropyl Acetate (*cis*-/*trans*-13):** Compounds ***cis*-13** and ***trans*-13** were synthesised following the general procedure, using gold catalyst (10.1 mg, 13.1 µmol), compound **2c** (67.2 mg, 282 µmol), and compound **3e** (see below; 70.3 mg, 254 µmol), at –40 °C for 30 min. The product was purified using an eluent system of CH_2Cl_2 to give compounds ***cis*-13** (51.7 mg, 45%) and ***trans*-13** (37.1 mg, 32%) as pale yellow oil-foams.

Data for ***cis*-13**: R_f = 0.17 (CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.18–8.15 (m, 2 H, CH_{arom}CNO$_2$), 7.49–7.47 (m, 2 H, CH_{arom}CHCNO$_2$), 7.31–7.29 (m, 2 H, CH_{arom}CCl), 7.21–7.19 (m, 2 H, CH_{arom}CHCCl), 4.84–4.83 (m, 1 H, C=CH), 4.40 (br. s, 1 H, CH=CC*H*), 4.16 (br. s, 1 H, C=CHCC*H*), 4.05–4.00 (m, 1 H, CHOAc), 3.72 (s, 3 H, =COCH_3), 3.07 (s, 3 H, C=CHCOCH_3), 2.09 (s, 3 H, OCOCH_3), 0.88–0.84 (m, 2 H, CH_2), 0.46–0.40 (m, 1 H, C*H*CHOAc) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 170.8 (1 C, OC=O), 160.5 (1 C, *C*=CH), 149.2, 146.7, 135.6, 133.0, 130.8 (2 C, *C*H$_{arom}$CHCCl), 130.1 (2 C, *C*H$_{arom}$CHCNO$_2$), 128.3 (2 C, *C*H$_{arom}$CCl), 122.9 (2 C, *C*H$_{arom}$CNO$_2$), 98.6 (1 C, C=*C*H), 86.7, 59.4 (1 C, CH=C*C*H), 56.9 (1 C, =CO*C*H$_3$), 53.6 (1 C, C=CHC*C*H), 52.8 (1 H, CHOAc), 52.0 (1 C, C=CHCO*C*H$_3$), 21.4 (1 C, C*H*CHOAc), 21.1 (1 C, OCO*C*H$_3$), 9.1 (1 C, CH_2) ppm. IR (thin film): $\tilde{\nu}$ = 2932, 2829, 1745, 1653, 1516, 1345, 1229, 1091, 1015, 835, 729 cm^{-1}. HRMS (EI): calcd. for $C_{24}H_{24}NO_6Cl$ $[M]^+$ 457.1292; found 457.1289.

Data for ***trans*-13**: R_f = 0.23 (CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.16–8.14 (m, 2 H, CH_{arom}CNO$_2$), 7.51–7.49 (m, 2 H, CH_{arom}CHCNO$_2$), 7.28–7.26 (m, 2 H, CH_{arom}CCl), 7.21–7.19 (m, 2 H, CH_{arom}CHCCl), 4.65–4.64 (m, 1 H, C=CH), 4.49–4.44 (m, 1 H, CHOAc), 4.29 (br. s, 1 H, CH=CC*H*), 3.98 (br. s, 1 H, C=CHCC*H*), 3.62 (s, 3 H, =COCH_3), 2.47 (s, 3 H, C=CHCOCH_3), 2.10 (s, 3 H, OCOCH_3), 1.43–1.36 (m, 1 H, CH_2), 1.43–1.36 (m, 1 H, C*H*CHOAc), 1.23–1.18 (m, 1 H, CH_2) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 171.4 (1 C, OC=O), 159.8 (1 C, *C*=CH), 149.3, 146.7, 135.8, 132.8, 131.8 (2 C, *C*H$_{arom}$CHCCl), 130.2 (2 C, *C*H$_{arom}$CHCNO$_2$), 128.0 (2 C, *C*H$_{arom}$CCl), 122.6 (2 C, *C*H$_{arom}$CNO$_2$), 96.2 (1 C, C=*C*H), 85.0 (1 C, C=CH*C*), 58.2 (1 C, CH=C*C*H), 56.8 (1 C, =CO*C*H$_3$), 56.2 (1 C, C=CHC*C*H), 52.5 (1 C, C=CHCO*C*H$_3$), 51.4 (1 C, CHOAc), 24.3 (1 C, C*H*CHOAc), 20.7 (1 C, OCO*C*H$_3$), 9.3 (1 C, CH_2) ppm. IR (thin film): $\tilde{\nu}$ = 2940, 2826, 1744, 1515, 1344, 1224, 1090, 1014, 728 cm^{-1}. HRMS (EI): calcd. for $C_{24}H_{24}NO_6Cl$ $[M]^+$ 457.1292; found 457.1290.

***cis*-/*trans*-2-[1,3-Dimethoxy-4,5-bis(4-nitrophenyl)cyclopent-2-en-1-yl]cyclopropyl Acetate (*cis*-/*trans*-14):** Gold catalyst (13.4 mg, 17.4 µmol) was dissolved in dry CH_2Cl_2 (1.5 mL) at room temperature under a nitrogen atmosphere. A solution of compound **2d** (84.9 mg, 341 µmol) and vinyl acetate (89.0 mg, 1.03 mmol) in dry CH_2Cl_2 (1 mL) was added, and the flask was washed out with CH_2Cl_2 (2 × 0.5 mL). At 15, 30, and 60 min, further **2d** (56.7, 56.6, and 315.1 mg, respectively) was added in CH_2Cl_2 (1 mL each time) (total amount of compound **2d** used: 513.2 mg, 2.06 mmol). After 120 min, reaction was quenched with NEt_3 (5 drops), then the mixture was filtered through Celite, and the filtrate was concentrated in vacuo. The residue was purified by flash chromatography using an eluent of CH_2Cl_2 to give a 58:42 mixture of compounds ***cis*-14** and ***trans*-14** (343.1 mg, 62%).

Data for ***cis*-14**: R_f = 0.17 (CH_2Cl_2). Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.203–8.200 (m, 2 H), 8.19–8.17 (m, 2 H), 7.50–7.48 (m, 2 H), 7.45–7.43 (m, 2 H), 4.89–4.88 (m, 1 H, C=CH), 4.56 (br. s, 1 H, CH=CC*H*), 4.202–4.198 (m, 1 H, CH=CCHC*H*), 4.07–4.02 (m, 1 H, CHOAc), 3.74 (s, 3 H, =COCH_3), 3.05 (s, 3 H, C=CHCOCH_3), 0.94–0.83 (m, 2 H, CH_2), 0.37–0.31 (m, 1 H, C*H*CHOAc) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 170.6 (1 C, OC=O), 159.6 (1 C, *C*=CH), 148.7 (1 C, CH=CCH*C*$_{arom}$), 147.1 (1 C, C$_{arom}$NO$_2$), 146.8 (1 C, C$_{arom}$NO$_2$), 145.1 (1 C, C=CH-CCH*C*$_{arom}$), 130.4 (2 C, *C*H$_{arom}$CNO$_2$), 130.1 (2 C, *C*H$_{arom}$CNO$_2$), 123.2 (2 C, *C*H$_{arom}$CHCNO$_2$), 123.0 (2 C, *C*H$_{arom}$CHCNO$_2$), 99.3 (1 C, C=*C*H), 87.1 (1 C, C=CH*C*), 60.3 (1 C, CH=C*C*H), 57.0 (1 C, =CO*C*H$_3$), 53.2 (1 C, C=CHC*C*H), 52.8 (1 C, CHOBz), 52.1 (1 C, C=CH*C*), 21.3 (1 C, *C*HCHOBz), 21.2 (1 C, OCO*C*H$_3$), 9.1 (1 C, CH_2) ppm. IR (thin film): $\tilde{\nu}$ = 2940, 2842, 1740, 1657, 1517, 1344, 1228, 906, 727, 648 cm^{-1}. HRMS (EI): calcd. for $C_{24}H_{24}N_2O_8$ $[M]^+$ 468.1533; found 468.1533.

Data for ***trans*-14**: R_f = 0.21 (CH_2Cl_2). Pale yellow foam-solid, m.p. 214–216 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.18–8.17 (m, 2 H, CH_{arom}CNO$_2$), 8.16–8.15 (m, 2 H, CH_{arom}CNO$_2$), 7.52–7.50 (m, 2 H, CH_{arom}CHCNO$_2$), 7.44–7.43 (m, 2 H, CH_{arom}CHCNO$_2$), 4.71–4.70 (m, 1 H, C=CH), 4.52–4.48 (m, 1 H, CHOAc), 4.33 (br. s, 1 H, CH=CC*H*), 4.12 (br. s, 1 H, C=CHCC*H*), 3.63 (s, 3 H, =COCH_3), 2.46 (s, 3 H, C=CHCOCH_3), 2.12 (s, 3 H, OCOCH_3), 1.46–1.42 (m, 1 H, C*H*CHOAc), 1.39–1.33 (m, 1 H, CH_2), 1.28–1.22 (m, 1 H, CH_2) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 171.3 (1 C, OC=O), 159.1 (1 C, *C*=CH), 148.8, 147.0, 146.8, 145.3, 131.3 (2 C, *C*H$_{arom}$CNO$_2$), 130.2 (2 C, *C*H$_{arom}$CNO$_2$), 122.9 (2 C, *C*H$_{arom}$CHCNO$_2$), 122.8 (2 C, *C*H$_{arom}$CHCNO$_2$), 97.0, 85.5 (1 C, C=CH*C*), 58.1 (1 C, CH=C*C*H), 56.87 (1 C, C=CHC*C*H), 56.86 (1 C, =CO*C*H$_3$), 52.5 (1 C, C=CHCO*C*H$_3$), 51.6 (1 C, CHOBz), 24.3 (1 C, *C*HCHOBz), 20.7 (1 C, OCO*C*H$_3$), 9.4 (1 C, CH_2) ppm. IR (thin film): $\tilde{\nu}$ = 2940, 2826, 1745, 1663, 1596, 1515, 1343, 1225, 1108, 855, 734 cm^{-1}. HRMS (EI): calcd. for $C_{24}H_{24}N_2O_8$ $[M]^+$ 468.1533; found 468.1528.

Compound **14** could alternatively be prepared from propargyl acetal **2d** and compound **3e** (see below). Gold catalyst (2.6 mg, 3.4 µmol) was dissolved in CH_2Cl_2 (0.5 mL), and the solution was cooled to –40 °C. Compounds **2d** (17.1 mg, 68.6 µmol) and **3e** (17.2 mg, 75.7 µmol) were dissolved in CH_2Cl_2 (1 mL), and this solution was added to the solution of the gold catalyst. The flask was washed out with further CH_2Cl_2 (1 mL). The reaction mixture was stirred at –40 °C for 60 min, then at room temperature for 60 min. The product was purified using an eluent system of 1:2

EtOAc/pentane to give a mixture (52:48) of compounds ***cis*-14** and ***trans*-14** (21.0 mg, 65%) as a pale yellow oil.

The ratio of product **14** to intermediate **3e** could be varied by altering the reaction conditions, depending on which compound was to be obtained. For example, at –40 °C and the standard ratio of compound **2d** to vinyl acetate of 1:3, ***cis*-14** (39%), ***trans*-14** (19%), and **3e** (20%) were formed. When the ratio of compound **2d** to vinyl acetate was increased to 1:10 (see below), a higher yield of **3e** (40%) and lower yields of product **14** (***cis*-14**: 19%, ***trans*-14**: 25%) were obtained. At very low temperatures (–78 °C), only trace amounts of the tandem product were observed (GLC); purification gave compound **3e** (16%).

***cis*-2-[(*Z*)-1-Methoxy-2-(4-nitrophenyl)vinyl]cyclopropyl Acetate (3e):** Compound **3e** was synthesised following the general procedure, using gold catalyst (13.1 mg, 17.0 μmol), compound **2d** (84.6 mg, 340 μmol), and vinyl acetate (295.3 mg, 3.43 mmol), at –40 °C for 15 min. The product was purified using an eluent system of CH_2Cl_2 to give compound **3e** (37.6 mg, 40%) as a bright yellow oil, along with ***cis*-14** (15.0 mg, 19%) and ***trans*-14** (19.2 mg, 24%). Data for **3e**: R_f = 0.30 (CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.13–8.11 (m, 2 H, $CH_{arom}CNO_2$), 7.69–7.67 (m, 2 H, $CH_{arom}CC$=), 5.47 (br. s, 1 H, =CH), 4.45–4.40 (m, 1 H, CHOAc), 3.92 (s, 3 H, OCH_3), 2.00 (s, 3 H, $OCOCH_3$), 1.22 (m, 1 H, C*H*CHOAc), 1.38–1.33 (m, 1 H, CH_2), 1.22–1.18 (m, 1 H, CH_2) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 171.5 (1 C, OC=O), 156.4 (1 C, *C*=CH), 144.8 (1 C, $C_{arom}NO_2$), 143.2 (1 C, $C_{arom}CH$=), 128.3 (2 C, $CH_{arom}CCH$=), 123.6 (2 C, $CH_{arom}CNO_2$), 105.7 (1 C, C=*C*H), 55.3 (1 C, OCH_3), 52.6 (1 C, CHOAc), 20.8 (1 C, OC-O*C*H$_3$), 18.8 (1 C, *C*HCHOAc), 11.0 (1 C, CH_2) ppm. IR (thin film): $\tilde{\nu}$ = 2942, 2914, 2852, 1747, 1589, 1509, 1334, 1230, 1109, 1073, 861 cm^{-1}. HRMS (EI): calcd. for $C_{14}H_{16}NO_5$ $[M + H]^+$ 278.1028; found 278.1026.

***cis*-/*trans*-2-(1,3-Dimethoxy-4,5-dimethylcyclopent-2-en-1-yl)cyclopropyl Acetate (*cis*-/*trans*-15):** Compounds ***cis*-15** and ***trans*-15** were synthesised following the general procedure, using gold catalyst (20.2 mg, 26.2 μmol), compound **2e** (76.3 mg, 537 μmol), and vinyl acetate (149.2 mg, 1.73 mmol), at –40 °C for 90 min, then 0 °C for 30 min. The products were purified using an eluent system of 1:1 (1:20 Et_2O/pentane)/CH_2Cl_2 to give compounds ***cis*-15** (3.2 mg, 7%) and ***trans*-15** (1.9 mg, 4%), and a 1:1 mixture of ***cis*-15** and ***trans*-15** (1.9 mg, 4%), all as yellow oils.

Data for ***cis*-15**: R_f = 0.18 [1:1 (1:20 EtOAc/pentane)/CH_2Cl_2]. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.30 (br. s, 1 H, C=CH), 4.26–4.21 (m, 1 H, CHOAc), 3.57 (s, 3 H, $=COCH_3$), 3.30 (s, 3 H, CHCOC*H*$_3$), 2.91–2.85 (m, 1 H, CH=CCHC*H*), 2.77–2.72 (m, 1 H, CH=CC*H*), 2.04 (s, 3 H, $OCOCH_3$), 1.09–1.03 (m, 1 H, C*H*CHOAc), 1.14 (d, J = 7.4 Hz, 3 H, CH=CCHC*H*$_3$), 0.99–0.94 (m, 2 H, CH_2) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 171.7 (1 C, OC=O), 160.7 (1 C, *C*=CH), 97.2 (1 C, C=*C*H), 84.4 (1 C, C=CH*C*), 56.2 (1 C, =CO*C*H$_3$), 52.2 (1 C, CHOAc), 51.8 (1 C, C=CHCO*C*H$_3$), 45.8 (1 C, CH=C*C*H), 41.6 (1 C, CH=CCH*C*H), 21.1 (1 C, OCO*C*H$_3$), 19.7 (1 C, *C*HCHOAc), 14.7 (1 C, C=CHCCH*C*H$_3$), 13.2 (1 C, CH=CCH*C*H$_3$), 8.01 (1 C, CH_2) ppm. IR (thin film): $\tilde{\nu}$ = 2931, 2834, 1746, 1648, 1228, 1093, 781 cm^{-1}. HRMS (EI): calcd. for $C_{12}H_{19}O_2$ $[M - OAc]^+$ 195.1385; found 195.1384.

Data for ***trans*-15**: R_f = 0.25 [1:1 (1:20 EtOAc/pentane)/CH_2Cl_2]. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.31–4.27 (m, 1 H, CHOAc), 4.31–4.27 (m, 1 H, C=CH), 3.56 (s, 3 H, $=COCH_3$), 3.40 (s, 3 H, C=CHCOC*H*$_3$), 2.68–2.62 (m, 1 H, CH=CC*H*), 2.57–2.52 (m, 1 H, CH=CCHC*H*), 2.03 (s, 3 H, $OCOCH_3$), 1.20–1.16 (m, 1 H, C*H*CHOAc), 1.88 (d, J = 7.0 Hz, 3 H, CH=CCHC*H*$_3$), 1.03 (d, J = 7.0 Hz, 3 H, CH=CCHCHC*H*$_3$), 0.93–0.87 (m, 2 H, CH_2) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 171.6 (1 C, OC=O), 161.3 (1 C, *C*=CH), 96.5 (1 C, C=*C*H), 83.2 (1 C, C=CH*C*), 56.1 (1 C, =CO*C*H$_3$), 52.7 (1 C, C=CHCO*C*H$_3$), 52.3 (1 C, CHOAc), 47.8 (1 C, C=CHC*C*H), 42.5 (1 C, CH=C*C*H), 23.7 (1 C, *C*HCHOAc), 20.8 (1 C, OCO*C*H$_3$), 17.4 (1 C, CH=CCH*C*H$_3$), 14.6 (1 C, C=CHCCH*C*H$_3$), 9.0 (1 C, CH_2) ppm. IR (thin film): $\tilde{\nu}$ = 2931, 2829, 1745, 1228, 1058, 914, 732 cm^{-1}. HRMS (EI): calcd. for $C_{12}H_{19}O_2$ $[M - OAc]^+$ 195.1385; found 195.1383.

***cis*-2-(1,3-Dimethoxy-4,5-dimethylcyclopent-2-en-1-yl)cyclopropyl Benzoate (*cis*-16):** Compound ***cis*-16** was synthesised following the general procedure, using gold catalyst (21.0 mg, 2.72 μmol), compound **3e** (77.3 mg, 0.54 μmol), and vinyl benzoate (142.5 mg, 0.96 mmol), at 0 °C for 15 min, then 20 °C for 15 min. The product was purified using an eluent system of 1:40 Et_2O/pentane to give compound ***cis*-16** (7.8 mg, 5%) as a grey oil. R_f = 0.44 (3:10 Et_2O/pentane). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.00 (d, J = 7.1 Hz, 2 H, $CH_{o\text{-}OBz}$), 7.55 (t, J = 7.4 Hz, 1 H, $CH_{p\text{-}OBz}$), 7.43 (t, J = 7.5 Hz, 2 H, $CH_{m\text{-}OBz}$), 4.51–4.47 (m, 1 H, CHOBz), 4.33 (d, J = 0.8 Hz, 1 H, C=CH), 3.57 (s, 3 H, $=COCH_3$), 3.31 (s, 3 H, $=CHCOCH_3$), 2.89–2.86 (m, 1 H, BzOCHC*H*), 1.26 (s, 1 H, =CC*H*CH), 1.18 (d, J = 7.3 Hz, 3 H, C*H*$_3$CHC=), 1.15–1.13 (m, 1 H, BzOCHC*H*$_2$), 1.11 (s, 1 H, =CCHC*H*), 1.10–1.07 (m, 1 H, BzOCHC*H*$_2$), 1.04 (d, J = 7.0 Hz, 3 H, C*H*$_3$CHCHC=) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 167.4 (1 C, O*C*=O), 160.9 (1 C, CH=*C*OCH$_3$), 132.9 (1 C, $CH_{p\text{-}OBz}$), 130.2 (1 C, OCO*C*$_{arom}$), 129.5 (2 C, $CH_{o\text{-}OBz}$), 128.4 (1 C, $CH_{p\text{-}OBz}$), 97.3 (1 C, C=*C*H), 84.3 (1 C, =CH*C*OCH$_3$), 56.3 (1 C, =CO*C*H$_3$), 52.8 (1 C, *C*HOBz), 52.1 (1 C, =CHCO*C*H$_3$), 45.9 (1 C, *C*HCHOBz), 29.7 (1 C, =*C*CHCH), 20.1 (1 C, =CCH*C*H), 14.6 (1 C, *C*H$_3$CHCHC=), 12.9 (1 C, *C*H$_3$CHC=), 8.0 (1 C, *C*H$_2$CHOBz) ppm. IR (thin film): $\tilde{\nu}$ = 2932, 1722, 1646, 1451, 1269, 1090, 731, 710 cm^{-1}. HRMS (ESI): calcd. for $C_{19}H_{24}NaO_4$ $[M + Na]^+$ 339.1567; found 339.1572.

***cis*-2-(1-Ethoxy-2-methylprop-1-en-1-yl)cyclopropyl Acetate (3f):** Compound **3f** was synthesised following the general procedure, using gold catalyst (16.9 mg, 0.02 mmol), compound **2f**[9] (66.1 mg, 0.43 mmol), and vinyl acetate (74.1 mg, 0.86 mmol). The reaction mixture was stirred at room temperature for 15 min. A gradient eluent of diethyl ether in pentane was used for purification. At the stage of 40:1 pentane/diethyl ether, **3f** (9.3 mg, 6%) was isolated as a colourless oil. R_f = 0.46 (3:10 diethyl ether/pentane). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.35 (dt, J = 3.9, 6.6 Hz, 1 H, CHOAc), 3.78–3.70 (m, 1 H, C*H*$_2$CH$_3$), 3.58–3.50 (m, 1 H, C*H*$_2$CH$_3$), 1.97 (s, 3 H, CO_2CH_3), 1.67 (m, 1 H, AcOCHC*H*), 1.62 [s, 3 H, C=C(C*H*$_3$)CH$_3$], 1.62 [s, 3 H, C=C(C*H*$_3$)CH$_3$], 1.20 (t, J = 7.0 Hz, 3 H, CH$_2$C*H*$_3$), 1.11–1.06 (m, 1 H, AcOCHC*H*$_2$), 1.02–0.98 (m, 1 H, AcOCHC*H*$_2$) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 171.9 (1 C, OC=O), 142.0 [1 C, $(CH_3)_2C$=*C*], 119.4 [1 C, $(CH_3)_2C$=C], 64.9 (1 C, *C*H$_2$CH$_3$), 52.5 (1 C, CHOAc), 20.9 (1 C, CO_2CH_3), 18.6 [1 C, C=C(*C*H$_3$)$_2$] 17.6 [1 C, C=C(*C*H$_3$)$_2$], 16.2 (1 C, *C*HCHOAc), 15.2 (1 C, CH$_2$*C*H$_3$), 9.7 (1 C, *C*H$_2$CHOAc) ppm.

***cis*-(1,8a)-*trans*-(3a,8a)-2,5,8a-Trimethoxy-1-(4-methoxyphenyl)-1,3a,8,8a-tetrahydrocyclopenta[*a*]indene (17):** Gold catalyst (8.4 mg, 11 μmol) was dissolved in dry CH_2Cl_2 (1.5 mL), and the solution was stirred under a nitrogen atmosphere at room temperature. Compound **2b** (50.9 mg, 217 μmol) was dissolved in dry CH_2Cl_2 (1.0 mL), and this solution was added added to the solution of the gold catalyst. The flask was washed out with further dry CH_2Cl_2 (2× 0.5 mL), and this was added to the mixture. The reaction was quenched with NEt_3 (5 drops), the mixture was filtered through Celite™, and the filtrate was concentrated in vacuo. The residue was purified by flash chromatography (1:3 Et_2O/pentane) to give

dimer **17** (3.6 mg, 5%) as a yellow oil. R_f = 0.3 (1:3 Et_2O/pentane). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.24–7.22 (m, 2 H, C*H*$_{arom}$CH-COMe), 7.13 (d, J = 8.2 Hz, 1 H, MeOCCH$_{arom}$), 6.87 (d, J = 2.4 Hz, 2 H, C*H*$_{arom}$COMe), 6.83–6.82 (m, 1 H, CC*H*$_{arom}$COMe), 6.75 (dd, J = 2.4, 8.2 Hz, 1 H, CCC*H*$_{arom}$CH), 4.63–4.61 (m, 1 H, C=CH), 4.18 (br. s, 1 H=CHC*H*), 3.81 (s, 3 H, CCHCOC*H*$_3$), 3.80 (s, 3 H, *p*-OC*H*$_3$), 3.77 (br. s, 1 H, =CCH), 3.51 (s, 3 H, =COC*H*$_3$), 3.44 (d, J = 16.6 Hz, 1 H, CH_2), 3.06 (d, J = 16.8 Hz, 1 H, CH_2), 2.86 (s, 3 H, =CCHCOC*H*$_3$) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 160.1 (1 C, =C), 159.1 (1 C, C$_{arom}$OMe), 158.5 (1 C, CCH-C$_{arom}$OMe), 145.9 (1 C, =CHCHC$_{arom}$), 133.1 (1 C, CH_2C$_{arom}$), 130.6 (1 C, =CCHC$_{arom}$), 130.1 (2 C, C*H*$_{arom}$CHCOMe), 125.1 (1 C, CH_2CC*H*$_{arom}$), 113.6 (2 C, C*H*$_{arom}$COMe), 112.6 [1 C, C*H*$_{arom}$C(OMe)CHC], 109.6 (1 C, MeOC*H*$_{arom}$C), 96.0 (1 C, =CH), 93.9 (1 C, CH_2C*O*Me), 59.1 (1 C, =C*C*H), 57.4 (1 C, =CH*C*H), 56.5 (1 C, =CO*C*H$_3$), 55.4 (1 C, C$_{arom}$O*C*H$_3$), 55.2 (1 C, C$_{arom}$O*C*H$_3$), 52.3 (1 C, CH_2CO*C*H$_3$), 41.5 (1 C, CH_2) ppm. IR (thin film): $\tilde{\nu}$ = 2928, 2829, 1511, 1248, 1177, 1033, 832, 580 cm^{-1}. HRMS (EI): calcd. for $C_{22}H_{24}O_4$ $[M]^+$ 352.1675; found 352.1674.

Supporting Information (see footnote on the first page of this article): Copies of ^1H and ^{13}C NMR spectra.

Acknowledgments

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SUPPORTING INFORMATION

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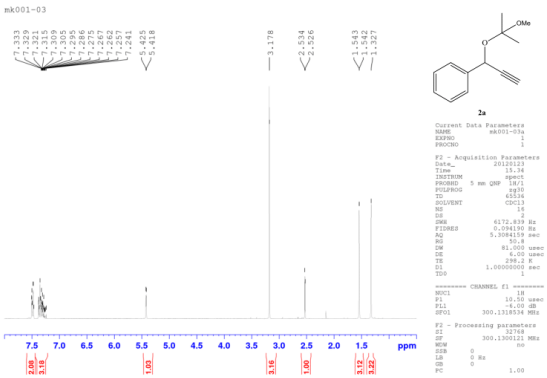
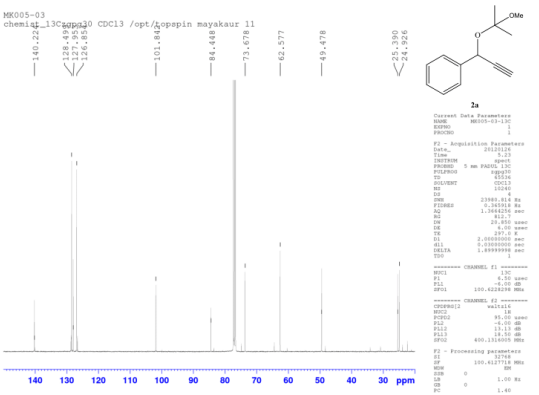
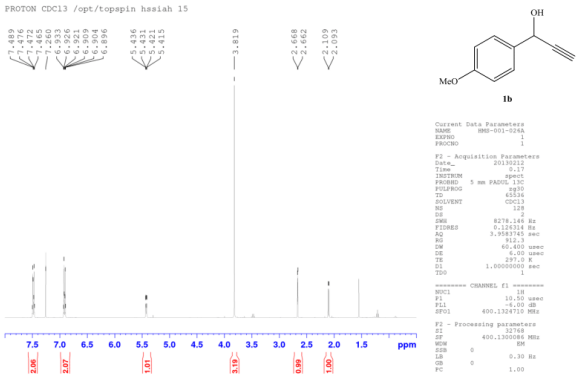
Title: Gold(I)-Catalysed Tandem Cyclisation of Propargyl Acetals and Vinyl Esters
Author(s): Huey-San Melanie Siah, Maya Kaur, Naseem Iqbal, Anne Fiksdahl*

(1-((2-Methoxypropan-2-yl)oxy)prop-2-yn-1-yl)benzene (2a)





1-(4-Methoxyphenyl)prop-2-yn-1-ol (1b)



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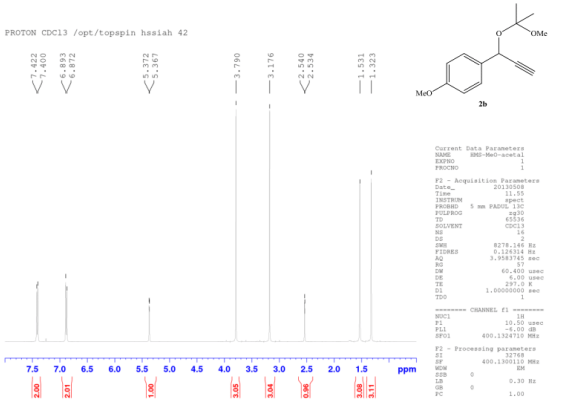
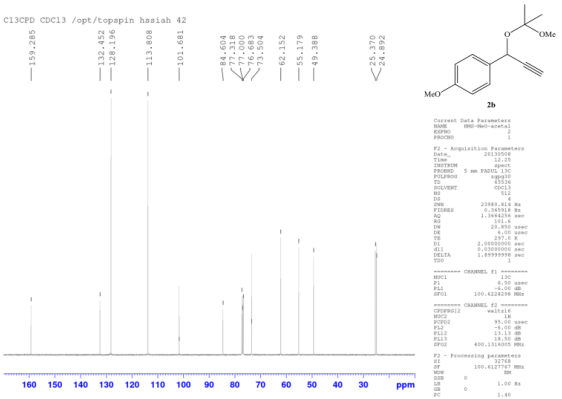
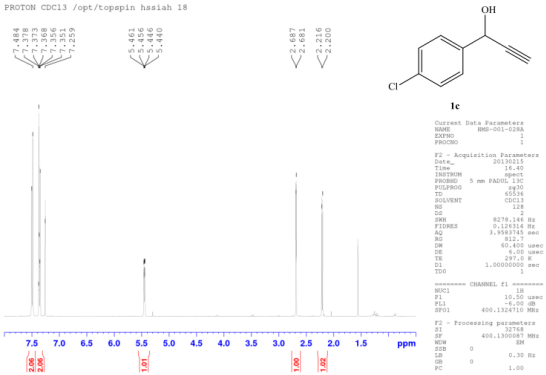
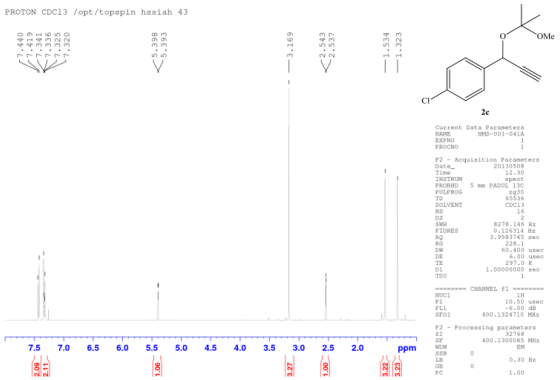


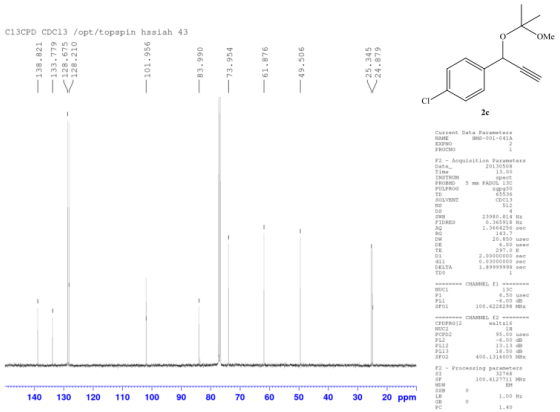


1-(4-Chlorophenyl)prop-2-yn-1-ol (1c)

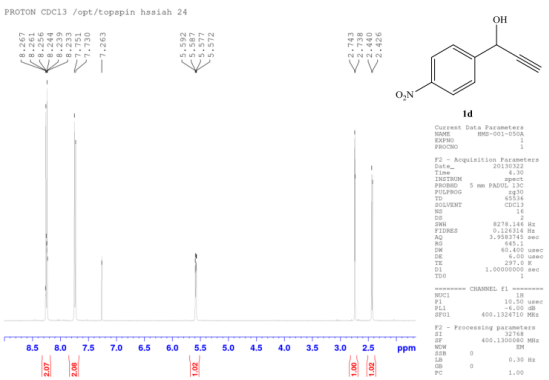


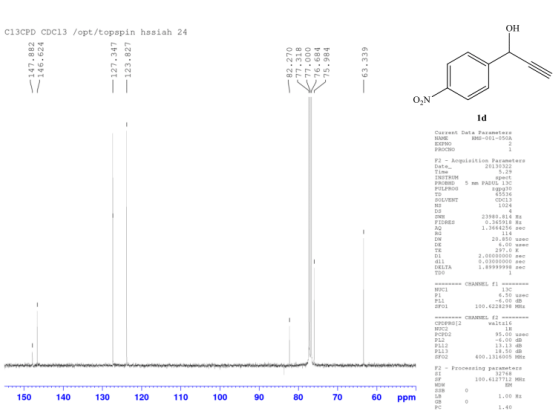
1-Chloro-4-(1-((2-methoxypropan-2-yl)oxy)prop-2-yn-1-yl)benzene (2c)



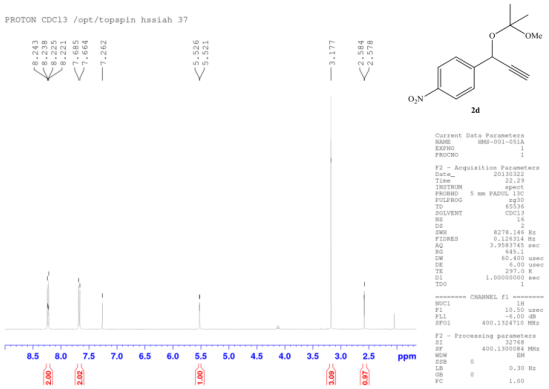


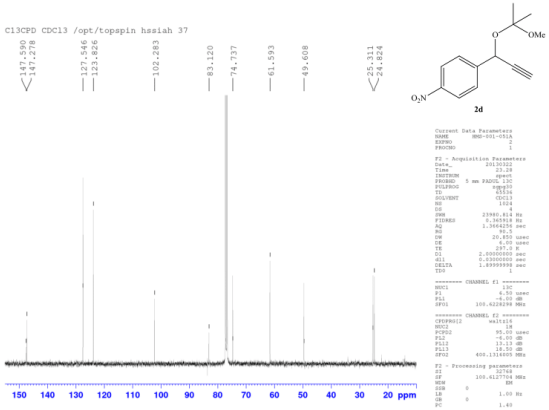
1-(4-Nitrophenyl)prop-2-yn-1-ol (1d)



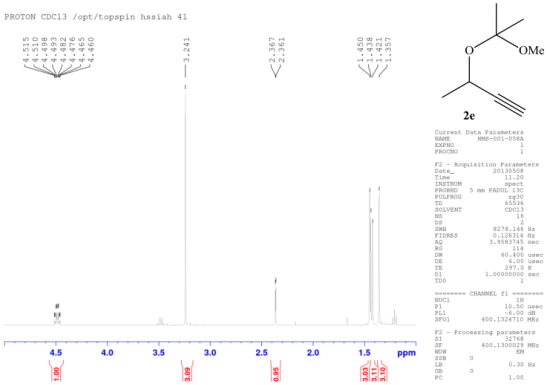


1-(1-((2-Methoxypropan-2-yl)oxy)prop-2-yn-1-yl)-4-nitrobenzene (1d)

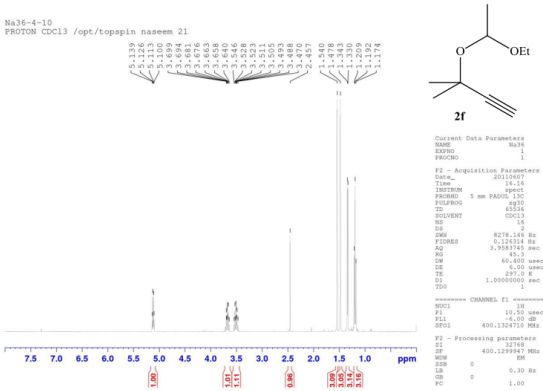


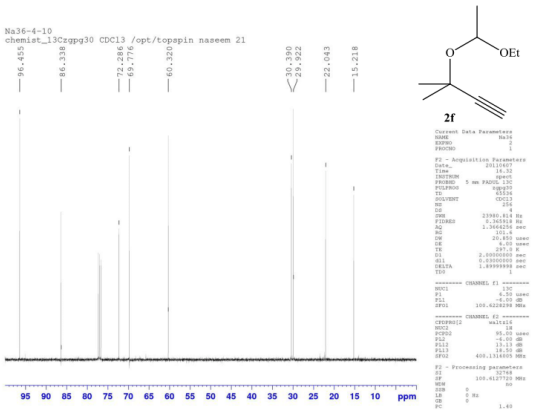


3-((2-Methoxypropan-2-yl)oxy)but-1-yne (2e)

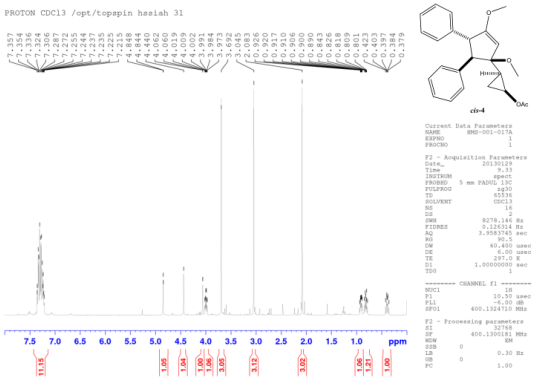


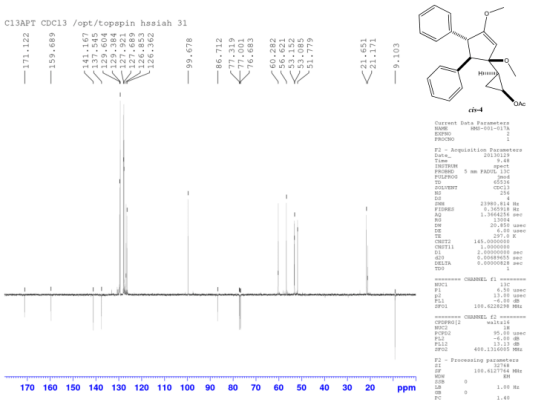
3-(1-Ethoxyethoxy)-3-methylbut-1-yne (2f)



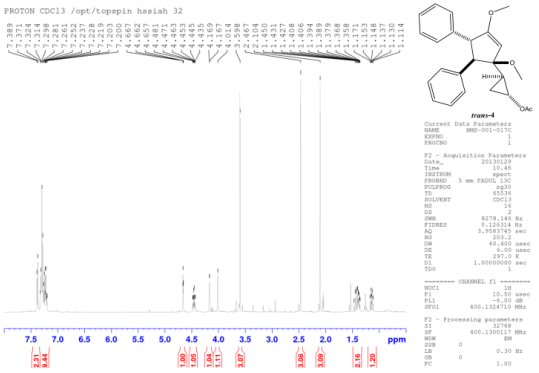


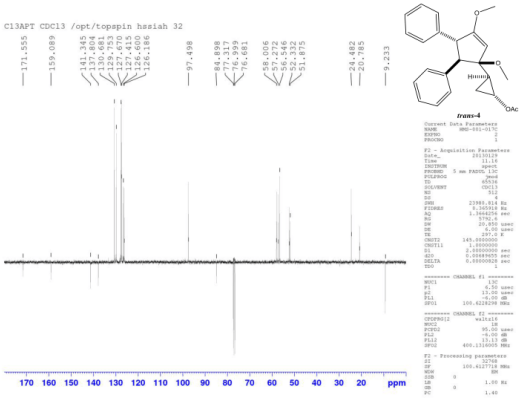
cis-2-(1,3-Dimethoxy-4,5-diphenylcyclopent-2-en-1-yl)cyclopropyl acetate (_cis_-4)



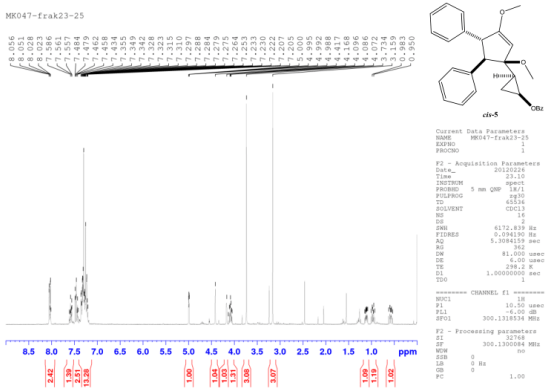


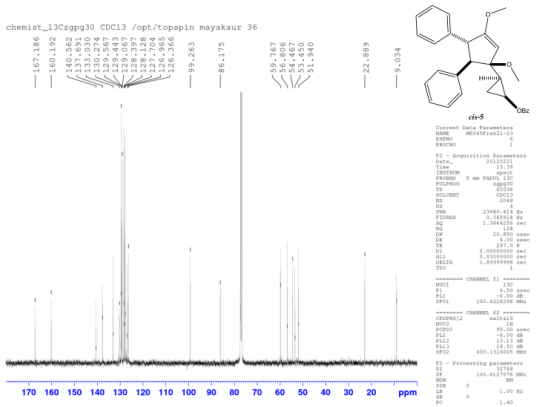
trans-2-(1,3-dimethoxy-4,5-diphenylcyclopent-2-en-1-yl)cyclopropyl acetate (_trans_-4)



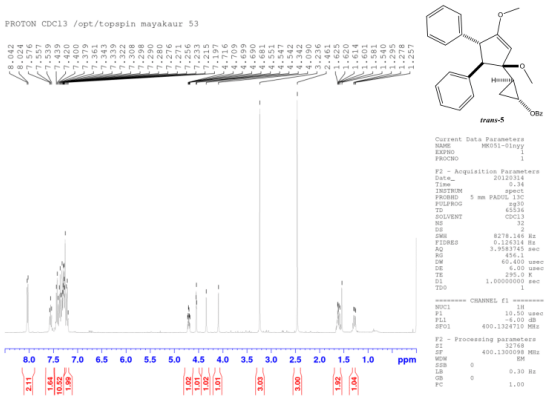


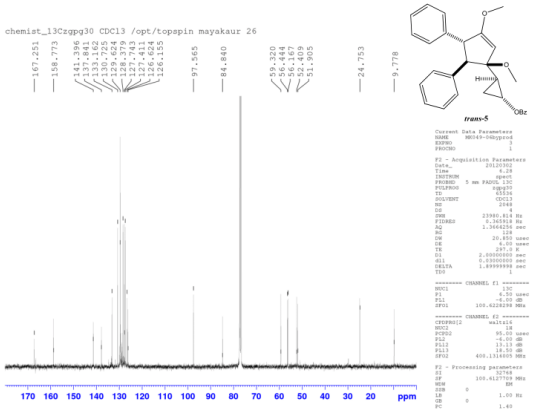
cis-2-(1,3-Dimethoxy-4,5-diphenylcyclopent-2-en-1-yl)cyclopropyl benzoate (_cis_-5)



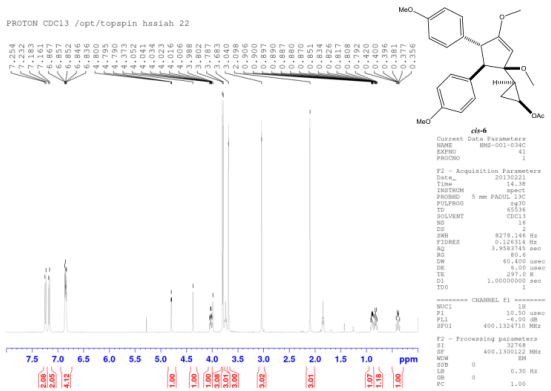


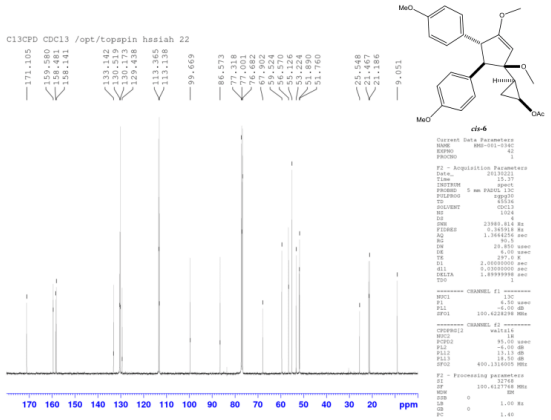
trans-2-(1,3-Dimethoxy-4,5-diphenylcyclopent-2-en-1-yl)cyclopropyl benzoate (_trans_-5)



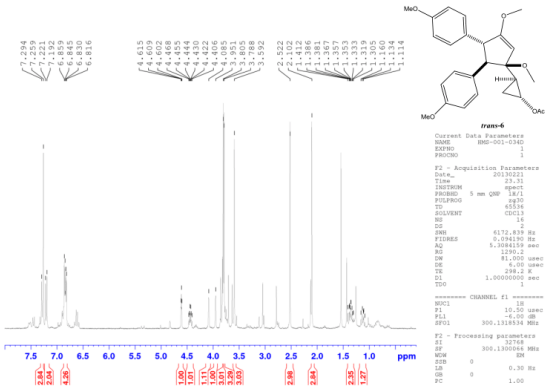


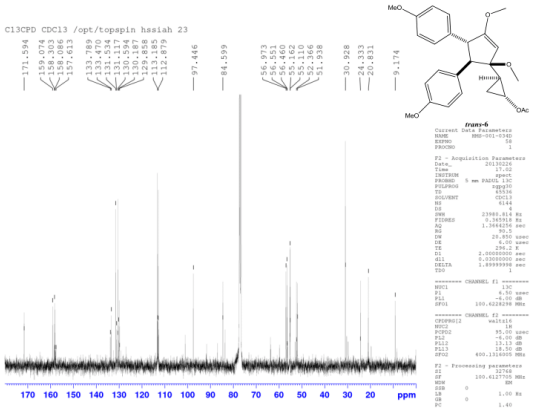
cis-2-(1,3-Dimethoxy-4,5-bis(4-methoxyphenyl)cyclopent-2-en-1-yl)cyclopropyl acetate (_cis_-6)



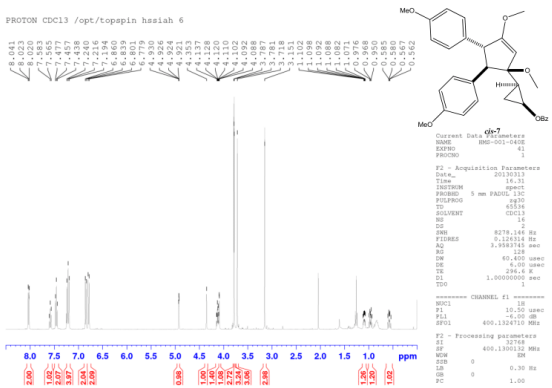


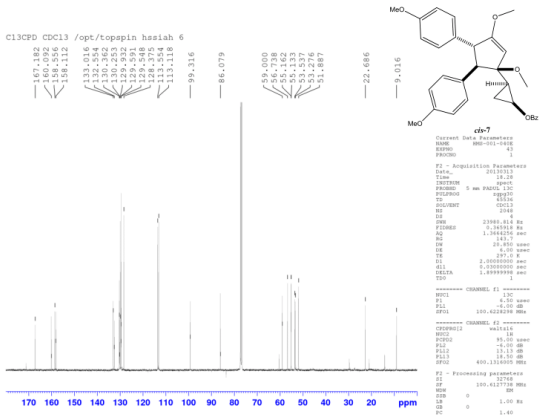
trans-2-(1,3-dimethoxy-4,5-bis(4-methoxyphenyl)cyclopent-2-en-1-yl)cyclopropyl acetate (_trans_-6)



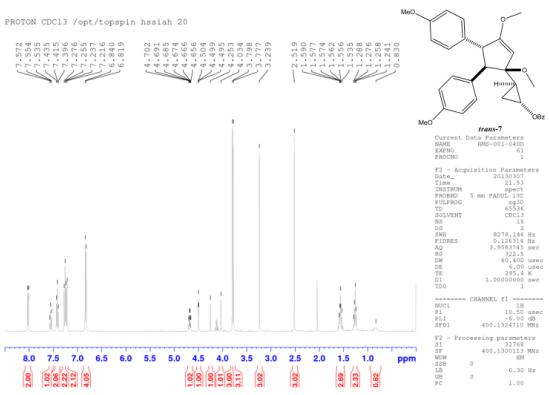


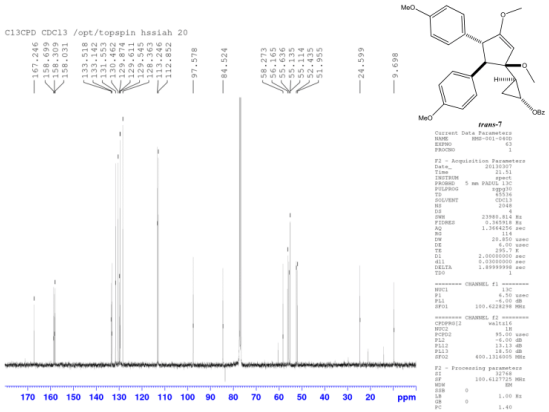
cis-2-(1,3-Dimethoxy-4,5-bis(4-methoxyphenyl)cyclopent-2-en-1-yl)cyclopropyl benzoate (_cis_-7)



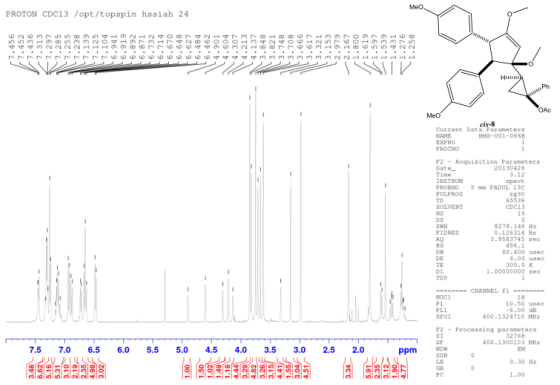


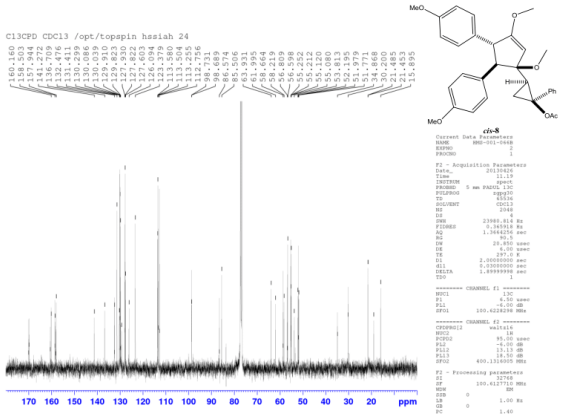
trans-2-(1,3-dimethoxy-4,5-bis(4-methoxyphenyl)cyclopent-2-en-1-yl)cyclopropyl benzoate (_trans_-7)



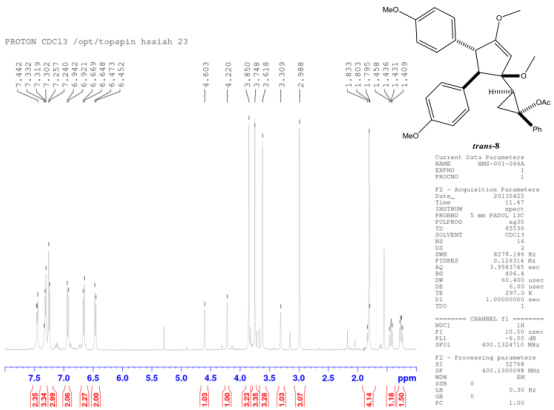


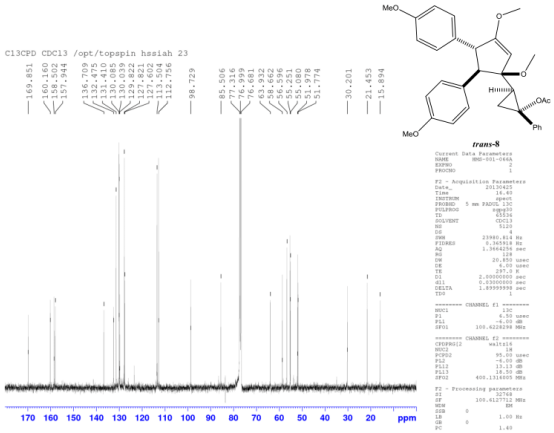
cis-2-(1,3-Dimethoxy-4,5-bis(4-methoxyphenyl)cyclopent-2-en-1-yl)-1-phenylcyclopropyl acetate (_cis_-8) (3:2 mixture of _trans:cis_)



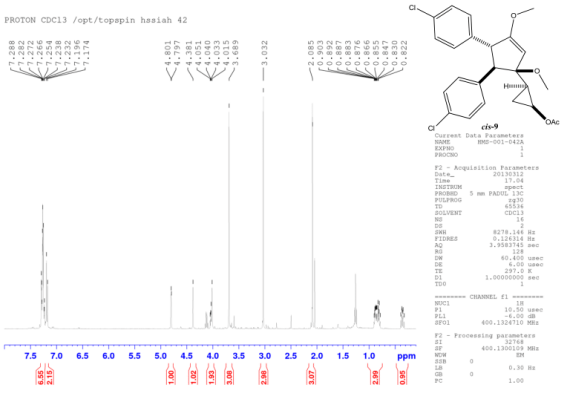


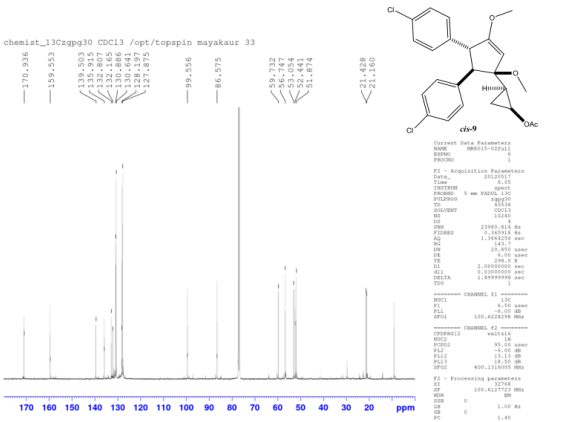
trans-2-(1,3-dimethoxy-4,5-bis(4-methoxyphenyl)cyclopent-2-en-1-yl)-1-phenylcyclopropyl acetate (_trans_-8)



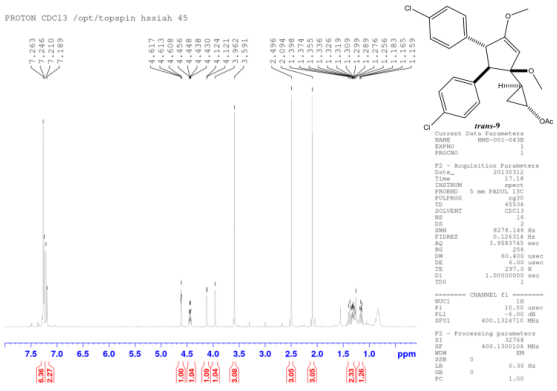


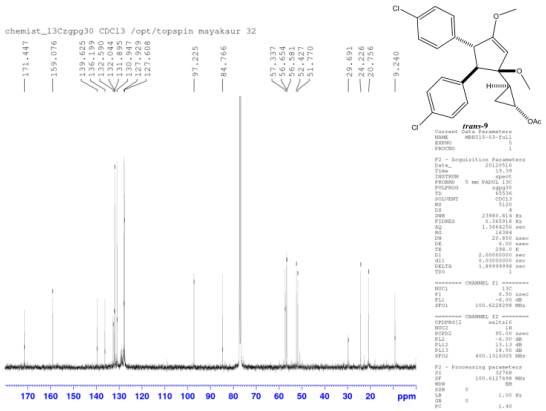
cis-2-(4,5-bis(4-Chlorophenyl)-1,3-dimethoxycyclopent-2-en-1-yl)cyclopropyl acetate (_cis_-9)



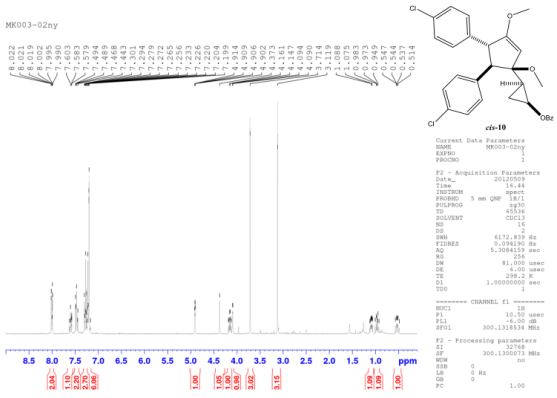


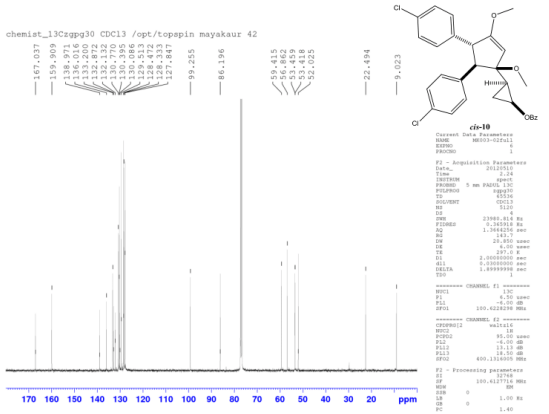
trans-2-(4,5-bis(4-chlorophenyl)-1,3-dimethoxycyclopent-2-en-1-yl)cyclopropyl acetate (_trans_-9)



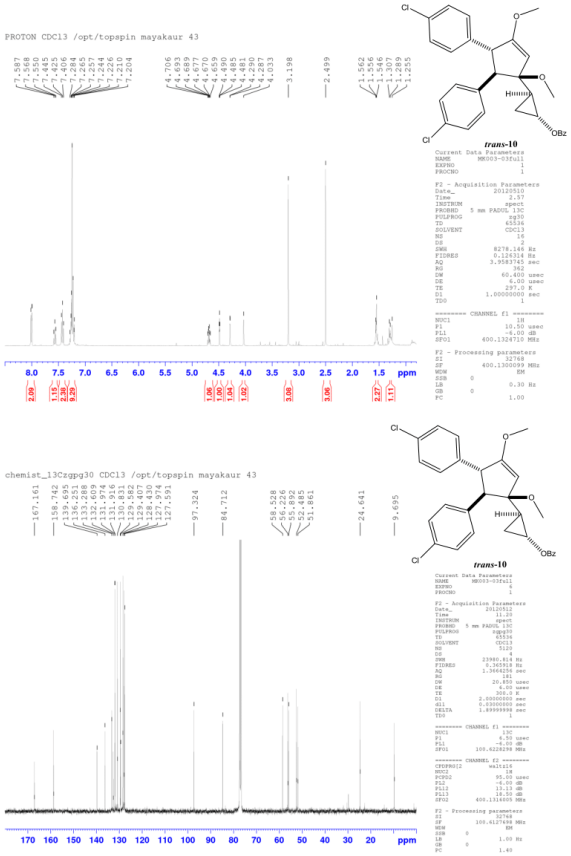


cis-2-(4,5-bis(4-Chlorophenyl)-1,3-dimethoxycyclopent-2-en-1-yl)cyclopropyl benzoate (_cis_-10)

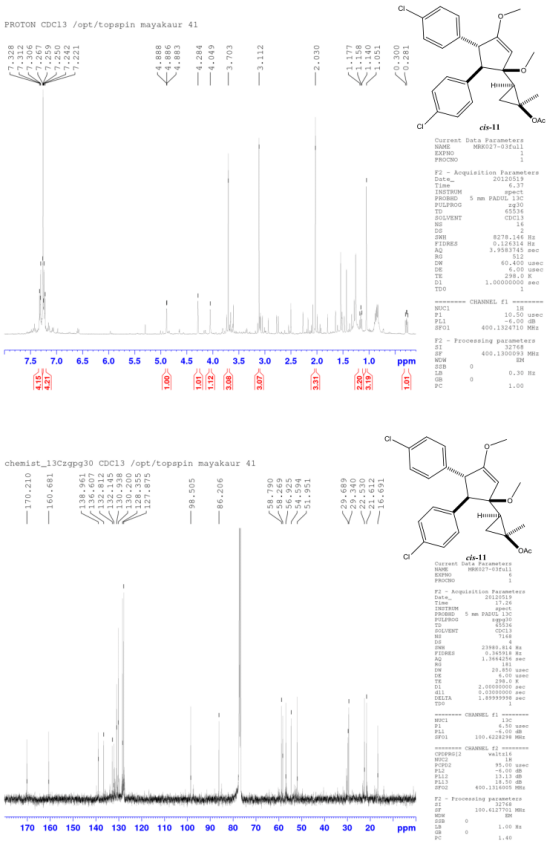




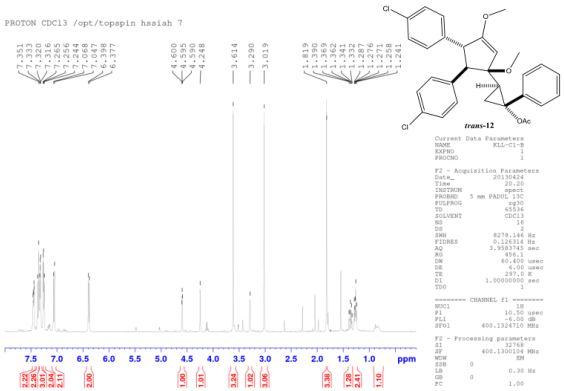
***trans*-2-(4,5-bis(4-chlorophenyl)-1,3-dimethoxycyclopent-2-en-1-yl)cyclopropyl benzoate (*trans*-10)**



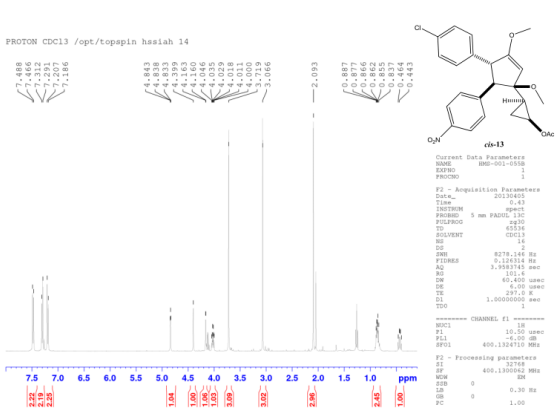
***cis*-2-(4,5-bis(4-Chlorophenyl)-1,3-dimethoxycyclopent-2-en-1-yl)-1-methylcyclopropyl acetate (*cis*-11)**



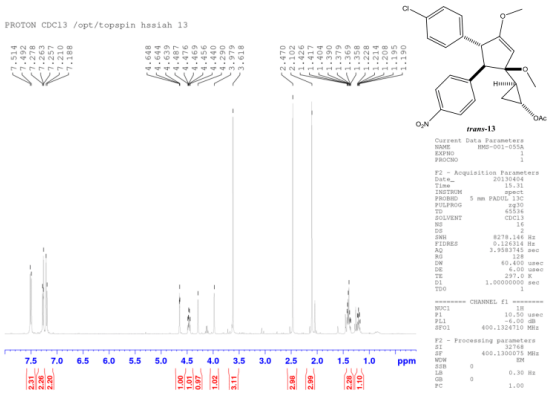
trans-2-(4,5-bis(4-Chlorophenyl)-1,3-dimethoxycyclopent-2-en-1-yl)-1-methylcyclopropyl acetate (_trans_-12)

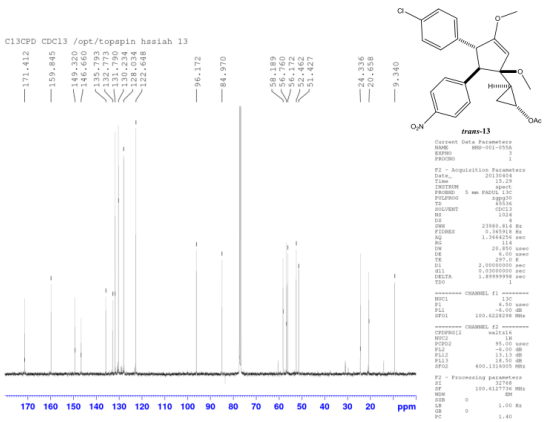


cis-2-(4-(4-Chlorophenyl)-1,3-dimethoxy-5-(4-nitrophenyl)cyclopent-2-en-1-yl)cyclopropyl acetate (_cis_-13)

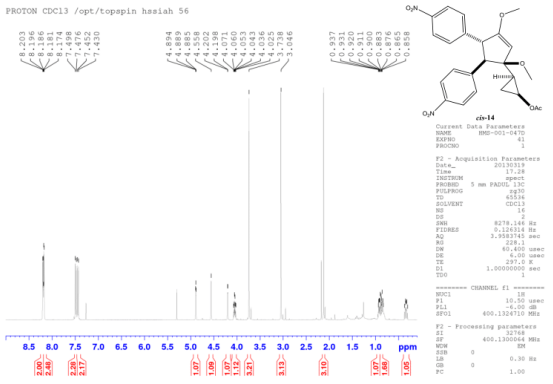


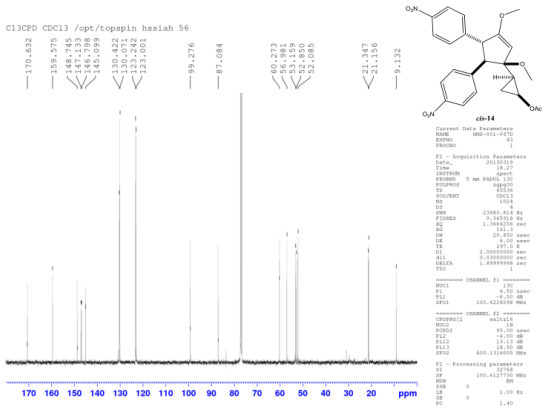
***trans*-2-(4-(4-chlorophenyl)-1,3-dimethoxy-5-(4-nitrophenyl)cyclopent-2-en-1-yl)cyclopropyl acetate (*trans*-13)**



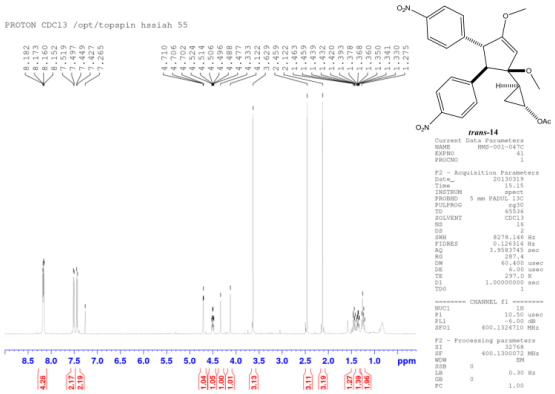


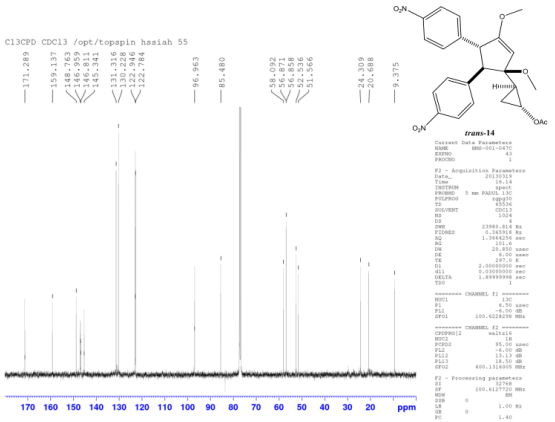
***cis*-2-(1,3-Dimethoxy-4,5-bis(4-nitrophenyl)cyclopent-2-en-1-yl)cyclopropyl acetate (*cis*-14)**



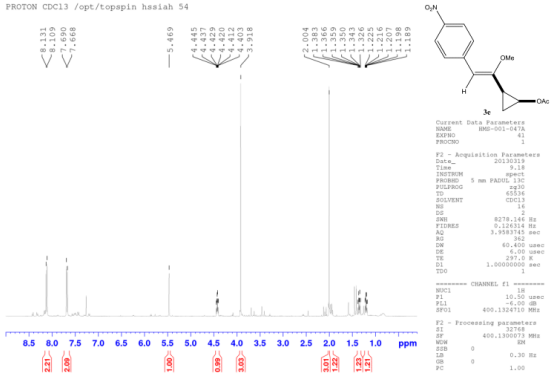


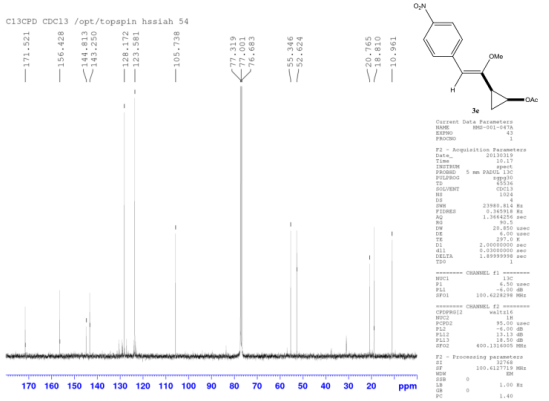
trans-2-(1,3-dimethoxy-4,5-bis(4-nitrophenyl)cyclopent-2-en-1-yl)cyclopropyl acetate (_trans_-14)



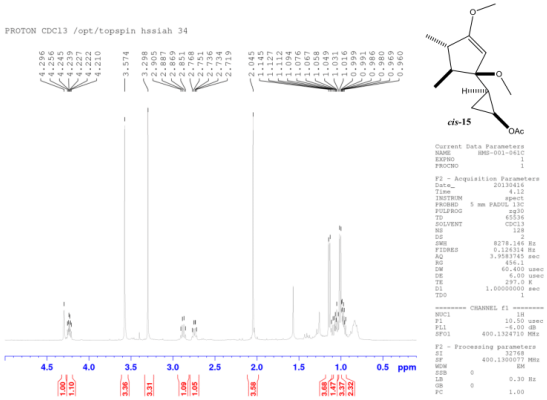


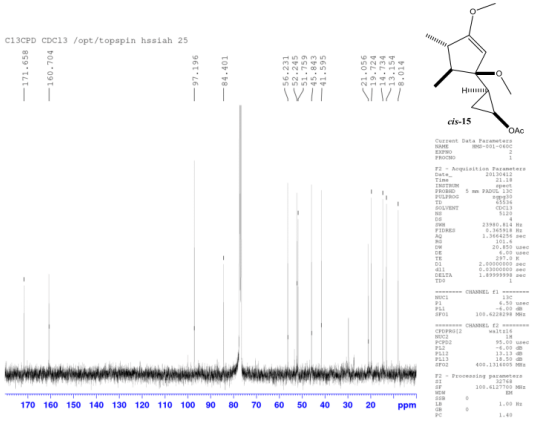
cis-2-((Z)-1-Methoxy-2-(4-nitrophenyl)vinyl)cyclopropyl acetate (3e)



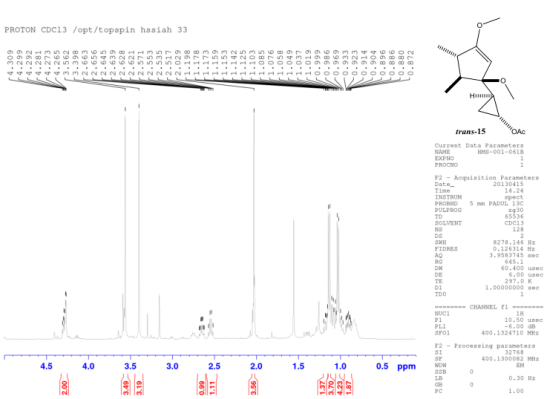


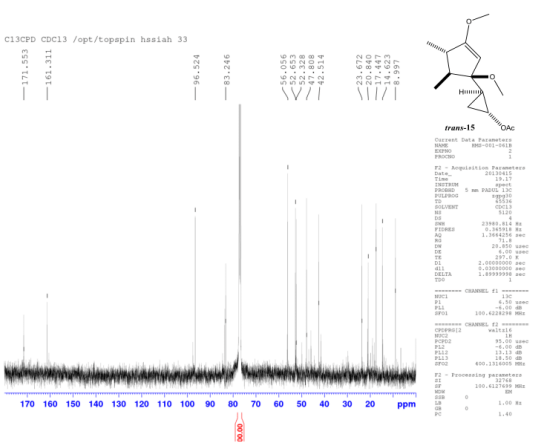
cis-2-(1,3-Dimethoxy-4,5-dimethylcyclopent-2-en-1-yl)cyclopropyl acetate (_cis_-15)





trans-2-(1,3-dimethoxy-4,5-dimethylcyclopent-2-en-1-yl)cyclopropyl acetate (_trans_-15)





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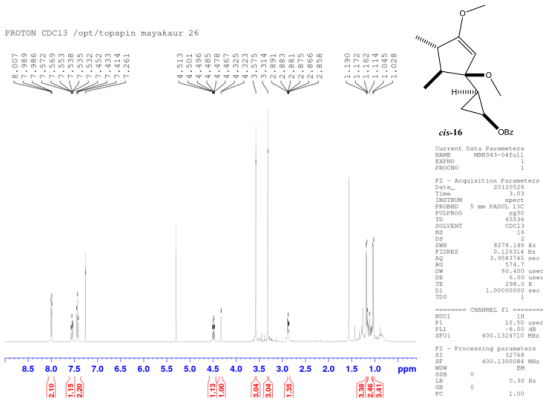

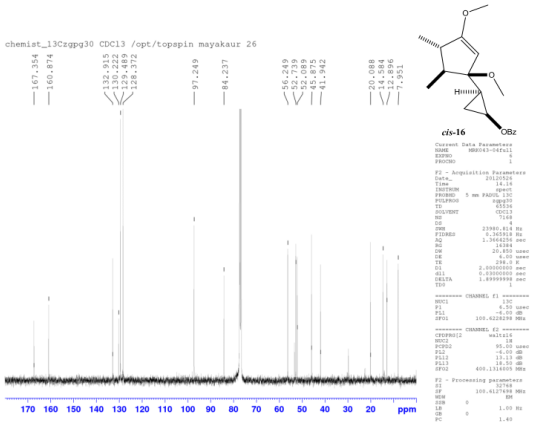

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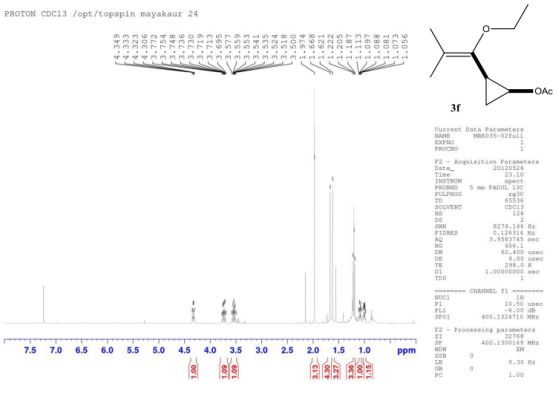

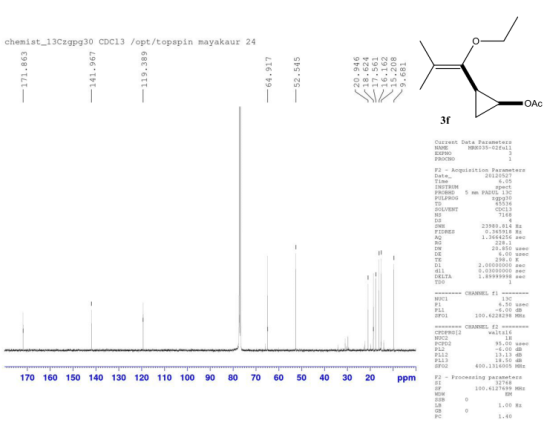

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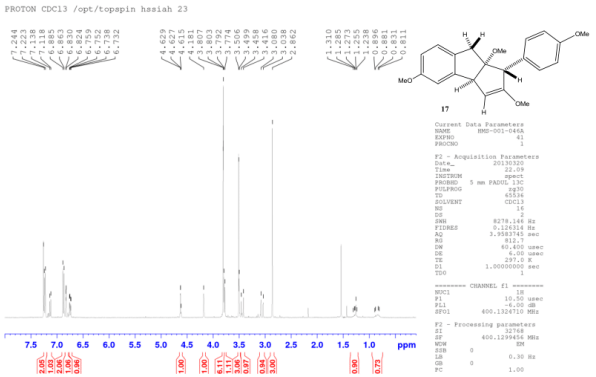


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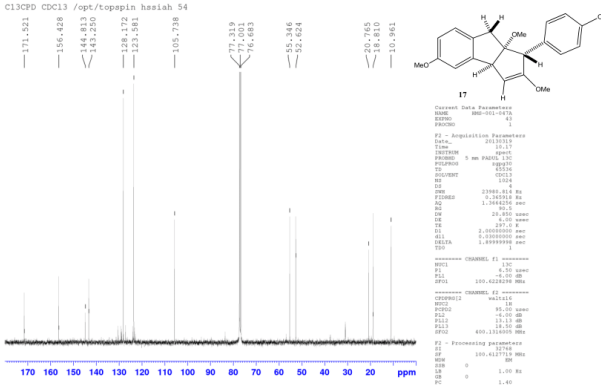


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PAPER II

Gold(I)-catalysed tandem cyclisation of propargyl acetals and alkynes

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Gold(I)-catalysed tandem cyclization of propargyl acetals and alkynes

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ABSTRACT

To expand the understanding of the chemistry of propargyl acetals, their gold(I) catalysed cycloaddition reactions with alkynes have been investigated. We hereby report a novel tandem reaction that allows the construction of a new type of polysubstituted and highly functionalised bicyclic pentalene compounds, 2,6a-dimethoxy-3a-methyl-1,4,5-triphenyl-1,3a,4,6a-tetrahydropentalenes, with four stereogenic centres.

Pure diastereomers were successfully isolated in up to 51% yield from mixtures of diastereomeric products (up to 60% total yield) and characterized individually by NMR spectroscopy. A plausible mechanism for the formation of these novel tandem products, based on subsequent [2+2] and [2+3] cycloadditions, is proposed for this gold(I) catalysed reaction.

1. Introduction

Gold-catalysed reactions of propargyl esters are widely reported in the literature and their ability to undergo very different reaction pathways has been systematically studied and reviewed.[1a–d] The gold catalysed activation process of propargyl esters by 1,2-acyloxy migration has, in particular, been shown to be a versatile strategy for the generation of vinyl gold carbene species (Scheme 1a).[3,4c,i,v] Hence, the propargyl-gold approach represents an important supplement to the conventional vinyl-metal carbenoids, generated in situ by metal-catalysed diazo decomposition, for the preparation of effective vinyl-carbene all-carbon 1,3-dipolar reactants. The efficiency of propargyl esters as safe surrogates of diazo compounds for gold catalysed cyclopropanation has been thoroughly studied.[4a–w] Some applications of propargyl esters in [2+2],[5a–b] [3+2],[6a–d] [4+2],[7] [4+3][8a–d] and [3+3][9] cycloaddition reactions have also been reported.

In contrast to propargyl esters, studies on gold(I)-catalysed reactions of corresponding propargyl acetals are scarce. Gold(I)-catalysed [3+2] cycloaddition of propargyl acetals and aldehydes is reported to afford 2,5-dihydrofurans,[10] recently also in an enantioselective manner.[11] However, it was emphasized that a terminal carboxylate EWG was essential for the reaction to take place.

The Fiksdahl group has shown that propargyl acetals show significantly higher reactivity than the corresponding esters (Scheme 1a).[2] Additionally, cycloaddition reactions of propargyl acetals provide access to a rich chemistry, as the choice of reactants gives rise to a diverse range of products. Hence, the propargyl acetals follow different cyclization pathways in gold(I) catalysed cycloadditions (Scheme 1a–d).[2,12–14] Terminal propargyl acetals were studied, demonstrating that the presence of terminal EWGs[10,11] are not required for such substrates.

Propargyl esters and acetals have been shown to undergo Au(I) triple-bond activation and, respectively, 1,2-acyloxy and 1,5-alkoxy migrations (Scheme 1a,b). The migration-fragmentation processes afford, respectively, the gold-allyl-cation/gold-carbenoid species **I** (Scheme 1a) and the respective highly reactive complex **II** (Scheme 1b).[3]

These intermediates can be trapped with different reagents, typically alkenes. We have shown how the chemoselectivity of the cycloadditions and, hence, the structures of the resulting products are controlled by the nature of the substrates. By changing from propargylic esters to acetals, the reaction pathway switches from cyclopropanation[2] (Scheme 1a) to [2+3] cycloaddition (Scheme 1b),[12] while a study on gold(I) catalysed cycloadditions of propargyl acetals with vinyl acetates, showed that such substrates follow a new tandem cyclization pathway (Scheme 1c).[13] The total outcome of the latter reactions was the formation of the cyclopropyl-cyclopentenyl tandem products **V** by two subsequent cycloaddition reactions. Phenylpropargyl acetals were also shown to undergo intermolecular [5+2] cycloaddition with benzaldimine

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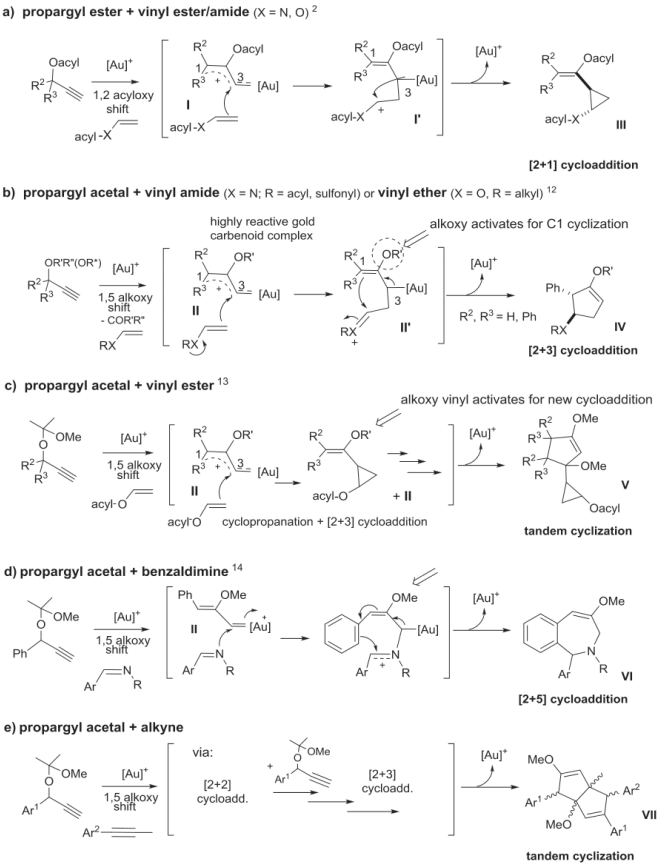
0040-4020/



Scheme 1. Proposed mechanisms of gold(I)-catalysed propargyl cycloadditions.[2,12–14].

substrates in the presence of a gold(I) catalyst to afford benzo[c]azepin-4-ol derivatives **VI** (Scheme 1d).[14] As shown in Scheme 1b–d, the alkyl vinyl ether groups, originating from the propargyl acetal substrates, are incorporated in central intermediates. The proposed mechanisms indicate how the activating and directing effect of these structure moieties are essential for the different chemoselective outcomes of these reactions of propargyl acetals.

The previous results demonstrate that gold-catalysed cycloadditions of propargyl acetals are attractive and valuable synthetic tools. To expand the knowledge of the highly reactive propargyl acetals, it was decided to investigate the potential of other multiple bond substrates, such as alkynes, to undergo chemoselective cycloaddition reactions (Scheme 1e). We herein report the results from our study of gold(I)-catalysed cyclization reactions of propargyl acetals and different alkynes to give rise to highly functionalised pentalene tandem products through double cycloaddition.

2. Results and discussion

2.1. Optimization studies

Results from a brief screening of reaction conditions are summarised in Table 1. The initial reaction conditions were chosen from prior experience and optimization of gold catalysed propargyl acetal cycloadditions.[2–4] The introductory studies of the reaction of propargyl acetal **1b** (1 equiv) and phenylpropyne **2a** (3 equiv) in dichloromethane readily gave complete conversion into a mixture of products after 15 min at room temperature in the presence of 5 mol-% of gold(I) catalyst [Au{P(*t*-Bu)$_2$(*o*-biphenyl)CH$_3$CN}]-SbF$_6$ (Table 1, entry 1). Structural studies utilising NMR spectroscopy and MS spectrometry identified the major product of the reaction as the tandem bicyclic 2,6a-dimethoxy-1,5-bis[4-methoxyphenyl]-3a-methyl-4-phenyl-1,3a,4,6a-tetrahydropentalene compound **4b**, formed in a mixture of diastereomers, due to the formation of four stereogenic centres. Since the bicyclic product **4b** is constructed of two acetal units and one alkyne unit (see *Proposed mechanism* and Scheme 2 below), it would be relevant to test whether a decrease in the amount of alkyne **2a** (from originally 3 equiv above) would favour the tandem reaction. However, reduction to 1 equiv of alkyne **2a** only caused a decrease in isolated total yields of formed diastereomers, dropping from 51% to 42% (Table 1, entry 1, footnotes [c], [d]), indicating that a large excess of alkyne is necessary for the formation of these particular products.

A few other gold catalysts were additionally screened using GLC analysis to ascertain if a change in catalyst affected the outcome of the reaction. Related gold(I) catalytic systems to that used in entry

Table 1
Optimization studies of gold(I)-catalysed tandem cyclization reactions[a]

Entry	Gold catalyst	Time	Conversion [%][b]
1	[Au[I]{P(*t*-Bu)$_2$(*o*-biphenyl)CH$_3$CN}]SbF$_6$	15 min	**95** (51% isol. yield)[c] (42% isol. yield)[d]
2	[Au[I]{P(*t*-Bu)$_2$(*o*-biphenyl)}]Cl+AgSbF$_6$	60 min	80
3	[Au[I]{P(*t*-Bu)$_2$(*o*-biphenyl)}]Cl+AgNTf$_2$	15 min	66
4	[Au[I]{P(*t*-Bu)$_2$(*o*-biphenyl)}]Cl	24 h	nc
5	Au[I](PPh$_3$)Cl+AgSbF$_6$	15 min	nd[e]
6	Au[I](PPh$_3$)Cl	24 h	nc
7	PicAu[III]Cl$_2$	15 min	17
8	AgSbF$_6$	15 min	nd[f]
9	AgNTf$_2$	15 min	nd[f]

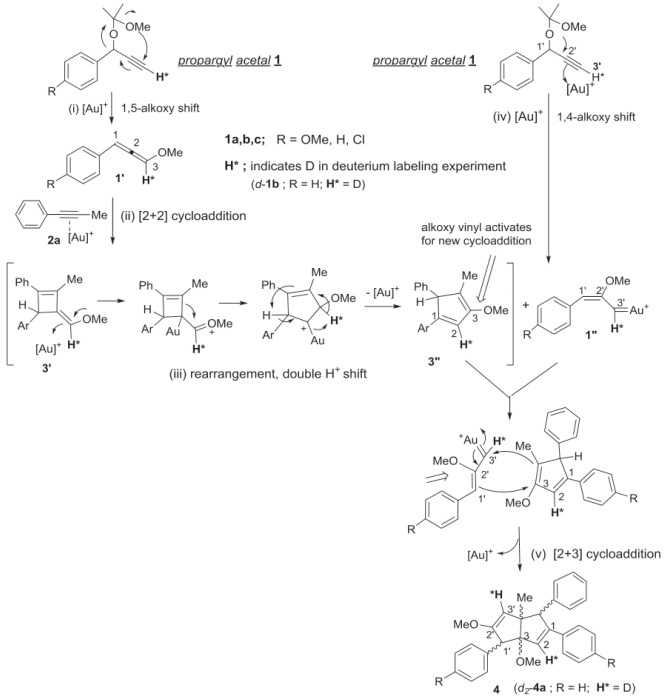
[a] The reactions were performed with **1b** (1 equiv) and **2a** (3 equiv) in DCM (approx. *c*=150 mM) together with 5 mol-% catalyst at rt. The reactions were allowed to stir for the required time before being quenched with NEt$_3$.
[b] The reactions were analysed by GLC. The target compound **4b** was the main product.
[c] Isolated total yield by reaction of **1b** (1 equiv) and **2a** (3 equiv).
[d] Isolated total yield by reaction of **1b** (1 equiv) and **2a** (1 equiv).
[e] Full conversion, but target product **4b** was not detected.
[f] Full conversion, but target product **4b** was not detected; 1-methoxy-4-(1-methoxyprop-2-yn-1-yl)benzene was observed as the main product.

1, but lacking the acetonitrile ligand, were prepared in situ by counterion exchange of the respective gold chloride salt (entries 2, 3). These gave a decrease in conversion at the same or lower rate, but the target diastereomeric compounds **4b** were always the dominating products. As chloride counterion exchange with e.g., SbF_6^- or NTf_2^- is supposed to be crucial for the activity of the gold(I) catalyst,[12–14] no reaction took place with the gold(I) chloride salt, as expected (entry 4). The less bulky triphenylphosphane-based gold(I) catalysts (entries 5, 6) gave no conversion into the desired product **4b**. Consistent with earlier observations, the gold(III) salt,[12–14] PicAu[III]Cl$_2$ (entry 7), gave poor conversion to the desired products. No cycloaddition took place in the presence of the silver salts AgSbF$_6$ or AgNTf$_2$, ruling out a possible silver salt catalysed reaction (entries 8, 9).[12,15]

The original reactions conditions (entry 1) were used in further studies. However, reduced reaction temperature was later shown to increase the reaction effectivity, as discussed below (Table 2, entries 6,7).

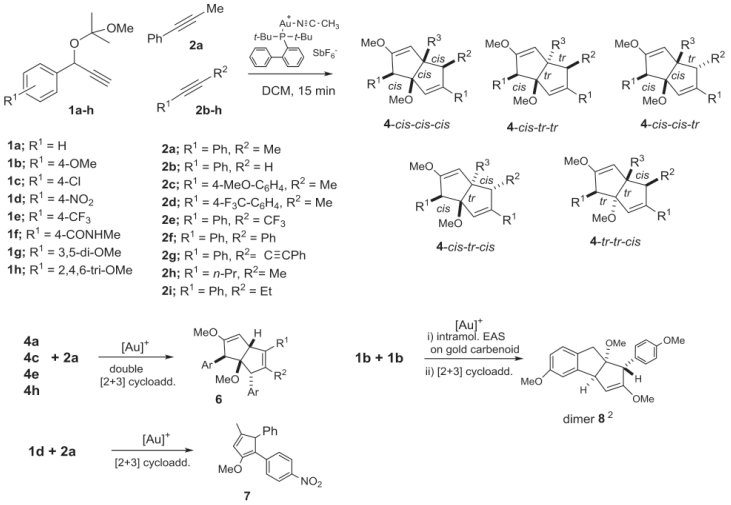
2.2. Proposed mechanism

Based on our previous studies on regioselective cycloadditions of propargyl substrates, the formation of tandem product **4** is proposed to take place via two cycloaddition reactions. The general mechanism is shown for propargyl acetal **1** and alkyne **2a** in Scheme 2. Propargyl acetal **1** can both undergo a 1,5- and a 1,4-alkoxy shift to generate intermediate gold(I) species **1′** and **1″**. It has previously been demonstrated that gold(I)-activated propargyl



Scheme 2. Proposed mechanism for gold(I)-catalysed tandem cyclization reaction of propargyl acetals **1** and alkyne **2a** to afford the pentalene products **4**.

Table 2
Gold(I)-catalysed tandem cyclization reactions of propargyl acetals **1** and alkynes **2**[a]



Entry	Acetal	Alkyne	Temp	Product, yield[b]					
				4 [total yield][c]	4-*cis*-*cis*-*cis*	4-*cis*-*tr*-*tr*	4-*cis*-*cis*-*tr*	4-*cis*-*tr*-*cis*	4-*tr*-*tr*-*cis*
1	**1a**		rt.	**4a** (60)[c]	22	14	6	5	<5
2	**1b**		rt.	**4b** (51)	44	5	<1	<1	—
3	**1c**		rt.	**4c** (29)[c]	—	12	6	4	—
4	**1d**[d]		rt.	n.c.[d]	—	—	—	—	—
5	**1e,f,g,h**		rt.	**4e**, **f**, **g**, **h**[c] (10–30)[e]	10–24[e]	—	—	—	—
6	**1b**		0 °C	**4b** (57)	51	6	—	—	—
7	**1b**		−40 °C	**4b** (57)	51	6	—	—	—
8	**1b**		−78 °C (3 h)	**4b** (14)	14	—	—	—	—
9	**1b**	**2b**	0 °C	**4i**[f]	14	—	—	<2	
10	**1b**	**2c**	0 °C	**4j** (52)	15	—	19	—	18
11	**1b**	**2d**, **e**, **f**, **g**	0 °C	n.c.[g]					
12	**1b**	**2h**	0 °C	n.c.[h]					
13	**1b**	**2i**	0 °C	**4k** (32)	32	—	—	—	

[a] The reactions were performed at rt with propargyl acetal **1** (1 equiv) and alkyne **2** (3 equiv) in DCM (approx. *c*=150 mM) together with 5 mol-% of gold catalyst. The reactions were allowed to stir for 15 min. before being quenched with NEt_3. Diastereomers were isolated by flash chromatography.
[b] Isolated yields refer to chromatographically purified compounds from complex mixtures of diastereomers. These numbers represent the maximum possible yield as the products may contain minor amounts of other diastereoisomers or impurities. However, where necessary, the yields have been adjusted for solvent content. See spectra in the Supplementary data for more information.
[c] Product **6** was isolated in up to 10% yield from reactions with substrates **1a**, **1c**, **1e** and **1h**.
[d] **1d** afforded [2+3] cycloaddition product **7** (15%).
[e] The *cis*-*cis*-*cis* isomers of **4f** (24%) and **4g** (10%) were isolated as well as minor amounts of other diastereomers of **4f**–**g**.
[f] The isolated products were impure and the suggested stereochemistry is based on ^{1}H NMR. Several additional diastereomers and regioisomers seem to be produced.
[g] Full conversion of acetal **1b** in 1–24 h, mainly into propargyl alcohol (up to 10%) and dimer **8** (up to 15%). The alkynes **2d**–**g** were recovered and products **4** were not observed.
[h] The product was impure; several other formed products decomposed over time, even at low temperatures.

substrates exist in rapid equilibrium with gold complexes, such as **1′** and **1″**, which can lead irreversibly to a range of stable products.[3,12]

In this case, alkyne **2a** is believed initially to undergo a gold(I)-catalysed [2+2] cycloaddition[5a,b] reaction (ii) with one unit of propargyl acetal **1** in the allenic form **1′**, generated by a 1,5-methoxy migration (i). The reaction would give rise to a cyclobutylidene intermediate **3′**. We have previously identified[12] similar cyclobutylidene products from [2+2] cycloaddition reactions of propargyl acetal. Subsequent intramolecular rearrangement and double proton shift (iii) are proposed to take place via the oxonium ion to afford the less strained pentadienyl intermediate **3″**. Due to the presence of an activating vinyl ether moiety in **3″**, an additional [2+3] cycloaddition (v) with the active gold(I)-carbenoid species **1″** may take place. In this case, **1″** is generated by a 1,4-alkoxy shift of a second unit of propargyl acetal (iv). As observed in our former

tandem reaction of propargyl acetals (Scheme 1c),[13] the vinylic alkoxy group, which activates for the second cycloaddition, is the key prerequisite of both steps in the present new tandem reaction, as well.

A deuterium-labelling experiment with propargyl acetal, *d*-**1a**, deuterated in the terminal position, afforded the tandem product d_2-**4a** with full incorporation of two deuterium atoms. The ^{1}H NMR spectrum showed the absence of the signals for the two affected vinylic protons. As shown in Scheme 2, where **H*** indicates the specific incorporation of deuterium, the results of the experiment were consistent with the proposed mechanism for the formation of the tandem products by subsequent (ii) [2+2] and (iv) [2+3] cycloadditions including (iii) rearrangement and proton shifts.

The reaction takes place with one unit of an alkyne substrate (**2a**) and two units of propargyl acetals (**1**). Since the two propargyl substrates undergo an initial gold(I) catalysed 1,5- and a 1,4-alkoxy shift, respectively, both the allene derivative (**1′**) and the allylic/carbenoid gold(I) complex (**1″**) are reactive intermediates in this tandem cycloaddition reaction.

2.3. Reactivity

Applying the optimized reaction conditions (Table 1, entry 1), the novel tandem transformation was further studied by modifying the substrate(s), starting with the aryl propargyl moiety. The results of the Au(I) catalysed reactions of propargyl acetals **1a**–**d** with phenylpropyne **2a** are presented in Table 2. All reactions were allowed to stir for 15 min at room temperature before quenching with triethylamine. TLC analysis showed full conversion after this time and the propargyl acetals **1a**–**c** gave the expected tandem cyclization products **4a**–**c**, obtained as diastereomeric mixtures (Table 2, entries 1–3). As discussed below, NOESY ^{1}H NMR experiments were mainly used to propose the relative stereochemistry of the diastereomers. The presence of a *para*-substituent on the aromatic propargyl acetals proved to affect both the reactivity and the outcome of the tandem reactions. Unsubstituted phenyl propargyl acetal **1a** and alkyne **2a** gave mostly the **4a**-*cis*-*cis*-*cis* diastereomer (22%) in addition to several other diastereomers (60% total yield, entry 1). The presence of a strong electron-donating group (OMe) in the *para*-phenyl position (**1b**) improved the selectivity in the tandem reaction, as 44% out of the total yield of 51% represented the **4b**-*cis*-*cis*-*cis* diastereomer (entry 2). In contrast, a halogen (Cl, **1c**, entry 3), gave reduced yield (29%) and selectivity. The nitro-substituted phenylpropargyl substrate **1d** failed to undergo tandem reaction (entry 4). Due to the electron-deficient nature of the substrate acetal **1d**, the reaction with alkyne **2a** afforded a different, single ring structure **7** (15%), analogous to the [2+3] cycloaddition products obtained from propargyl acetals with vinyl compounds (Scheme 1b).[12] This was attributed to the strongly withdrawing nature of the nitro group that favours an unusual [2+3] alkyne cycloaddition with the electrophilic gold carbenoid **II** (Scheme 2b). The less selective substrates (**4a**, **4c**, **4e**, **4g**, entries 1,3,5; footnote [c]) also promoted a second reaction pathway giving the different tandem product **6**. This product appeared to be the result of two [2+3] cycloaddition reactions, proceeding through an intermediate corresponding to product **7** below (entry 4, footnote [d]).

A series of reactions at varying temperature were carried out on the most promising substrate **1b** (entries 6–8). At 0 °C and −40 °C, both the selectivity (51% *cis*-*cis*-*cis* isomer) and the total yield of product **4b** increased (57%, entries 6,7). The reaction rate slowed down significantly at −78 °C, as only 14% conversion of **1b** was observed by GLC after 3 h (entry 8). It was decided to carry out the further experiments with propargyl acetal at 0 °C.

With these results in hand, variation of the alkyne (**2b**–**i**, entries 9–13) was carried out. The reaction with the terminal alkyne **2b** with acetal **1b** afforded product **4i**-*cis*-*cis*-*cis* (14%, entry 9), but also seemed to produce a mixture of several diastereomers and regioisomers, showing that removal of the methyl group appears to lower the selectivity of this reaction substantially, allowing for many other pathways to be accessed. The 4-OMe-phenylalkyne substrate **2c** afforded similar total yield to the non-substituted **2a**, but poor selectivity was obtained (entry 10). The more electron-deficient alkynes (**2d,e,f,g** entry 11) were unable to undergo a tandem reactions. Products **4** were not observed, while the alkynes **2d**–**g** were recovered. However, full conversion of acetal **1b** took place in 1–24 h, mainly into propargyl alcohol, but also the propargyl acetal tricyclic dimer **8** was generated. This is in accordance with our previous[3] observations for the electron-rich *p*-OMe-phenylpropargyl acetal **1b** in other cycloaddition reactions. The formation of dimer **8** has previously been proposed to take place by a tandem dimerization reaction pathway, based on an intramolecular electrophilic aromatic substitution, activated by the *p*-OMe-phenyl group, and a subsequent [2+3] cycloaddition, activated by the vinyl ether moiety of the intermediate.[3] Hence, the competing formation of dimer **8**, could be explained by insufficient nucleophilicity of the second reactant, in the present case the alkynes **2d**–**g** (entry 11), to afford the desired tandem reaction. The dialkylalkyne **2h** (entry 12) showed poor ability to undergo tandem reaction, while the ethyl-phenylalkyne **2i** (entry 13) gave selectively the **4k** *cis*-*cis*-*cis* diastereomer (32%).

^{1}H NMR spectra for each individual diastereomer of product **4** appeared to be quite characteristic. In particular, the distinguishing

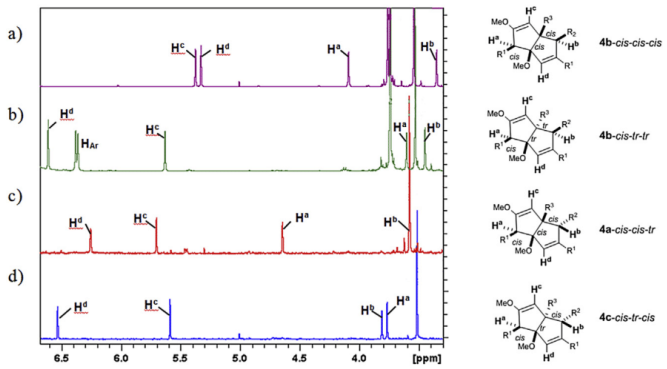


Fig. 1. ^{1}H NMR spectra for individual diastereomers of product **4,** demonstrating the distinguishing shift value patterns for the CH^{a-d} protons.

shift value patterns for the CH^a and CH^b methines and the=CH^c and=CH^d vinylic protons, shown in Fig. 1a–d, represented general recognisable features for all the analogous *cis-cis-cis*, *cis-trans-trans, cis-cis-trans* and *cis-trans-cis* diastereomers of products **4**. As demonstrated, quite large differences in shift values may be observed for some proton-signals (e.g., $\Delta\delta$>1 ppm for CH^a and CH^d).

The identification and characterization of the different diastereomers of products **4** as well as for products **6** and **7** were based on 2D NMR (HMBC/COSY, HSQC, NOESY). In particular, NOESY ^{1}H NMR experiments were essential in order to suggest the relative stereochemistry of the four stereogenic centres in tandem product **4**. Designation of the stereochemistry was based on a thorough comparative study of the observed NOESY correlations with the groups of diastereomeric structures (based on ^{1}H NMR patterns above, Fig. 1a–d). The conformational complexity and size of the products allow a range of NOESY correlations to be obtained, also between *trans* groups, as shown by models. Based on a variety of combinations of NOESY correlations between the CH^a and CH^b methines, the Me- and OMe-groups connected to the quaternary carbons, we have proposed relative stereochemistry of the four chiral centres in four isolated diastereomers (Fig. 1a–d). Examples of how the observed NOESY correlations indicated the designated stereochemistry are shown in Fig. 2.

The generally low isolated yields can be explained by the close chromatographic elution of the several produced diastereomers, which gave overlapping zones both on TLC and flash chromatography. This can be illustrated by e.g., the respective R_f values 0.19/0.23/0.29 (1:10 EtOAc:pentane) of the three main isolated diastereomers of tandem product **4c.** Due to challenging chromatographic separation, the isolation of each diastereomer to the level required for NMR characterization and identification of the particular diastereomers was demanding and loss of material during purification was unavoidable. In addition, the stability of these products was questionable. Thus, the real total amount of tandem products formed in the most successful reactions could be more than 60% of products **4a** and **4b**.

3. Conclusions

In order to contribute to a better understanding of the chemistry of propargyl acetals in the presence of gold(I), we have performed a study on chemoselective gold(I)-catalysed cycloadditions of propargyl acetals **1** with alkynes **2**. We have shown that such substrates undergo a new tandem cyclization pathway to readily afford highly functionalised pentalene tandem products **4**, obtained as diastereomeric mixtures, from one unit of an alkyne substrate (**2**) and two units of propargyl acetal (**1**). The proposed mechanism involves a gold(I)-catalysed [2+2] cycloaddition reaction with an allene derivative. A subsequent rearrangement and a [2+3] cycloaddition with an allylic gold(I) complex afford the tandem products **4**. The allene and allyl intermediates are formed by respectively 1,5- and 1,4-alkoxy shift of two propargyl substrates. Highest yield and stereoselectivity was obtained with phenyl or 4-OMe-phenyl propargyl acetal (**1a** or **1b**) and phenylpropyne **2a** at 0 °C, affording up to 51% yield of the pure **4**-*cis-cis-cis* diastereomer.

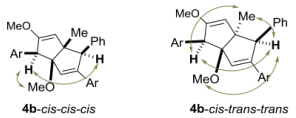


Fig. 2. Examples of NOESY correlations used to suggest stereochemistry of diastereomers.

4. Experimental

4.1. General

All reactions were performed under nitrogen atmosphere. Commercial grade reagents were used as received. Dry solvents were collected from a solvent purification system. All reactions were monitored by GLC and thin-layer chromatography (TLC) using silica gel 60 F254 (0.25 mm thickness). Flash chromatography was carried out using silica gel 60 (0.040–0.063 mm). High Throughput Flash Purification (HPFP) was performed on pre-packed cartridges. ^{1}H and ^{13}C NMR spectra were recorded using a 300, 400 or 600 MHz spectrometer. Chemical shifts are reported in ppm (δ) downfield from tetramethylsilane (TMS) as internal standard. Coupling constants (J) are reported in Hertz (Hz). The attributions of the chemical shifts were determined by means of COSY, HMQC, HMBC and NOESY experiments. Melting points (mp) were determined using a Stuart apparatus and are uncorrected. Accurate mass determination was performed on a 'Synapt G2-S' Q-TOF instrument from Waters. Samples were ionized with the use of ASAP probe, no chromatography separation was used before the mass analysis. IR spectra were obtained using a Smart Endurance reflection cell.

4.2. Preparation of the propargyl acetals

Propargyl acetals **1a**–**d** were generated as previously described.[3] ^{1}H and ^{13}C NMR shifts were consistent with those in the literature. Propargyl acetals **1e**–**h** were generated following a similar procedure:

*4.2.1. 1-(1-((2-Methoxypropan-2-yl)oxy)prop-2-yn-1-yl)-4-(trifluoromethyl)benzene (**1e**). 1-(4-(Trifluoromethyl)phenyl)prop-2-yn-1-ol:* A solution of ethynylmagnesium bromide (7.5 mL, 0.50 M in THF, 3.8 mmol) was cooled to 0 °C and a solution of 4-(trifluoromethyl)benzaldehyde (0.40 mL, 2.9 mmol) in dry THF (3 mL) was added slowly. The reaction mixture was stirred for 5 min at that temperature, then the cooling bath was removed and the reaction mixture was stirred at room temperature for 1 h. The reaction was quenched by addition of 10 mL saturated aqueous ammonium chloride and extracted with DCM (3×20 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by flash chromatography (1:30 EtOAc:pentane) to yield 1-(4-(trifluoromethyl) phenyl)prop-2-yn-1-ol as a bright yellow oil (451.3 mg, 77%). R_f=0.21 (1:30 EtOAc:pentane); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.69–7.64 (m, 4H), 5.54 (d, J=2.4 Hz, 1H), 2.71(s, 1H), 2.32 (dd, J=2.4, 3.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 143.7, 130.7 (q, J=32.4 Hz), 126.8, 125.6 (q, J=3.8 Hz), 124.0 (q, J=270.4 Hz), 82.7, 75.5, 63.7; HRMS (EI) calcd for $C_{10}H_6F_3$ $[M-OH]^+$ 183.0422, obsd 183.0425.

A mixture of 1-(4-(trifluoromethyl)phenyl)prop-2-yn-1-ol (449.0 mg, 2.243 mmol) and 2-methoxypropene (5.0 mL, 52 mmol) was cooled to 0 °C, then pyridinium *p*-toluenesulfonate (PPTS, catalytic amount, <5 mg) was added. The cooling bath was removed and the mixture stirred at room temperature for 1 h. The mixture was diluted with DCM (50 mL), washed with water (3×50 mL), then dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by flash chromatography (1:50 EtOAc:pentane) to yield 1-(1-((2-methoxypropan-2-yl) oxy)prop-2-yn-1-yl)-4-(trifluoromethyl)benzene (**1e**) as a pale yellow oil (520.1 mg, 85%). R_f=0.31 (1:30 EtOAc:pentane); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.62 (s, 4H, H), 5.48 (s, 1H, OCH), 3.18 (s, 3H, OCH_3), 2.56 (s, 1H, ≡CH), 1.55 (s, 3H, CH_3), 1.33 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 144.1, 130.2 (q, J=32.1 Hz), 127.1, 125.5 (q, J=3.72 Hz), 124.0 (q, J=270.4 Hz), 102.1, 83.7, 74.2, 61.9, 49.6, 25.3, 24.9; ^{13}C NMR (376 MHz, $CDCl_3$, C_6F_6 used as reference) δ ppm

264.1; IR (neat, cm^{-1}) 3300, 2993, 2938, 2828, 1616, 1323, 1123, 1066, 1015, 848, 826; HRMS (EI) calcd for $C_{14}H_{15}O_2F_3$ $[M]^+$ 272.1024, obsd 272.1019.

*4.2.2. 4-(1-((2-Methoxypropan-2-yl)oxy)prop-2-yn-1-yl)-N-methylbenzamide (**1f**). 4-(1-Hydroxyprop-2-yn-1-yl)-N-methylbenzamide:* A solution of ethynylmagnesium bromide (8.0 mL, 0.50 M in THF, 4.0 mmol) was cooled to 0 °C and 4-formyl-*N*-methylbenzamide (517.0 mg, 3.168 mmol) in dry THF (50 mL) was added slowly. The reaction mixture was stirred for 5 min at that temperature, then the cooling bath was removed and the reaction mixture was stirred at room temperature for 2 h. Additional ethynylmagnesium bromide (6.0 mL, 0.50 M in THF, 3.0 mmol) was added and the mixture stirred for a further 30 min. Additional ethynylmagnesium bromide (3.0 mL, 0.50 M in THF, 1.5 mmol) was added and the mixture stirred for a further 30 min. Complete conversion was not obtained. The reaction was quenched by addition of saturated aqueous ammonium chloride (20 mL) and solvents were evaporated. The residue was dissolved in DCM (100 mL) and water (50 mL) added. The phases were separated and the water phase extracted with DCM (2×50 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by flash chromatography (1:1 EtOAc:pentane) to yield 4-(1-hydroxyprop-2-yn-1-yl)-*N*-methylbenzamide as a colourless oil (263.7 mg, 44%). R_f=0.13 (1:1 EtOAc:pentane). The product was used directly without further analysis.

A mixture of 4-(1-hydroxyprop-2-yn-1-yl)-*N*-methylbenzamide (263.7 mg, 1.394 mmol) and 2-methoxyprop-1-ene (5.0 mL, 52 mmol) were stirred at 0 °C. PPTS (catalytic, <5 mg) was added and the mixture stirred for 5 min. The mixture was allowed to come to ambient temperature and stirred for 1 h. The mixture was diluted with DCM (50 mL), washed with water (3×50 mL), the combined water phase extracted with DCM (3×50 mL), then the combined organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by recrystallization (DCM/pentane) to yield 4-(1-((2-methoxypropan-2-yl)oxy)prop-2-yn-1-yl)-*N*-methylbenzamide (**1f**) as a colourless powder (136.7 mg, 38%). Mp 127–129 °C; R_f=0.25 (1:1 EtOAc:pentane); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.51–7.49 (m, 2H), 7.46–7.44 (m, 2H), 7.20 (br s, NH), 5.39 (s, 1H, OCH), 3.18 (s, 3H, OCH_3), 2.54 (s, 1H, ≡CH), 2.18 (s, 3H, NCH_3), 1.54 (s, 3H, CH_3), 1.32 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 168.2, 137.6, 136.2, 127.6, 119.8, 101.8, 84.3, 73.7, 62.1, 49.5, 25.4, 24.9, 24.6; IR (neat, cm^{-1}) 3299, 3184, 2987, 1668, 1608, 1549, 1319, 1014, 858, 668; HRMS (EI) calcd for $C_{15}H_{20}NO_3$ $[M+H]^+$ 262.1443, obsd 262.1440.

*4.2.3. 1,3-Dimethoxy-5-(1-((2-methoxypropan-2-yl)oxy)prop-2-yn-1-yl)benzene (**1g**). 1-(3,5-Dimethoxyphenyl)prop-2-yn-1-ol:* A solution of ethynylmagnesium bromide (8.0 mL, 0.50 M in THF, 4.0 mmol) was cooled to 0 °C. 3,5-Dimethoxybenzaldehyde (521.6 mg, 3.139 mmol) in dry THF (10 mL) was added slowly. The reaction mixture was stirred for 5 min at that temperature, then the cooling bath was removed and the reaction mixture was stirred at room temperature for 1 h. The reaction was quenched by addition of saturated aqueous ammonium chloride (10 mL), the phases separated and the water phase extracted with DCM (3×50 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo. The crude product of 1-(3,5-dimethoxyphenyl)prop-2-yn-1-ol (557.1 mg) was reacted directly without further purification. R_f=0.23 (1:4 EtOAc:pentane); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 6.72 (d, *J*=2.1 Hz, 2H), 6.43 (t, *J*=2.3 Hz, 1H), 5.40 (dd, *J*=6.3, 2.2 Hz, 1H), 3.81 (s, 6H), 2.66 (d, *J*=2.24 Hz, 1H), 2.18 (d, *J*=6.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 161.0, 142.3, 104.5, 100.6, 83.3, 74.8, 64.4, 55.4.

A mixture of the crude product of 1-(3,5-dimethoxyphenyl) prop-2-yn-1-ol and 2-methoxyprop-1-ene (5.0 mL, 52 mmol) was stirred at 0 °C. PPTS (catalytic, <5 mg) was added and the mixture stirred for 5 min. The mixture was allowed to come to ambient temperature and stirred for 1 h. The mixture was diluted with DCM (100 mL), washed with water (3×50 mL), the combined water phase extracted with DCM (100 mL), then the combined organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by flash chromatography (1:10 EtOAc:pentane) to yield 1,3-dimethoxy-5-(1-((2-methoxypropan-2-yl)oxy)prop-2-yn-1-yl)benzene (**1g**) as a colourless oil (640.4 mg, 84% over two steps). R_f=0.09 (1:30 EtOAc:pentane); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 6.66 (d, *J*=2.2 Hz, 2H), 6.40 (t, *J*=2.3 Hz, 1H), 5.36 (d, *J*=2.2 Hz, OCH), 3.80 (s, 6H, 2×$ArOCH_3$), 3.21 (s, 3H, OCH_3), 2.53 (d, *J*=2.2 Hz, 1H, ≡CH), 1.53 (s, 3H, CH_3), 1.33 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 160.8, 142.5, 104.8, 101.9, 99.9, 84.2, 73.6, 62.5, 55.4, 49.5, 25.3, 24.9; IR (neat, cm^{-1}) 3268, 2982, 2940, 2831, 1609, 1319, 1151, 1023, 864, 646; HRMS (EI) calcd for $C_{15}H_{20}O_4$ $[M+H]^+$ 264.1362, obsd 264.1358.

*4.2.4. 1,3,5-Trimethoxy-2-(1-((2-methoxypropan-2-yl)oxy)prop-2-yn-1-yl)benzene (**1h**). 1-(2,4,6-Trimethoxyphenyl)prop-2-yn-1-ol:* A solution of ethynylmagnesium bromide (6.5 mL, 0.50 M in THF, 3.3 mmol) was cooled to 0 °C. 2,4,6-Trimethoxybenzaldehyde (505.3 mg, 2.575 mmol) in dry THF (15 mL) was added slowly. The reaction mixture was stirred for 5 min at that temperature, then the cooling bath was removed and the reaction mixture was stirred at room temperature for 30 min. The reaction was quenched by addition of saturated aqueous ammonium chloride (20 mL), the phases separated and the water phase extracted with DCM (3×20 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo. The crude product of 1-(2,4,6-trimethoxyphenyl)prop-2-yn-1-ol (554.4 mg) was reacted directly without further purification. R_f=0.15 (1:4 EtOAc:pentane).

A mixture of the crude product of 1-(2,4,6-trimethoxyphenyl) prop-2-yn-1-ol and 2-methoxyprop-1-ene (10.0 mL, 104 mmol) were stirred at 0 °C. PPTS (catalytic, <5 mg) was added and the mixture stirred for 5 min. The mixture was allowed to come to ambient temperature and stirred for 1 h. The mixture was diluted with DCM (50 mL), washed with water (3×50 mL), the combined water phase extracted with DCM (100 mL), then the combined organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by flash chromatography (1:4 EtOAc:pentane) to yield 1,3,5-trimethoxy-2-(1-((2-methoxypropan-2-yl)oxy)prop-2-yn-1-yl)benzene (**1h**) as a colourless oil (696.9 mg, 95% over two steps). R_f=0.29 (1:4 EtOAc:pentane); ^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 6.13 (s, 2H), 6.05 (d, *J*=2.4 Hz, 1H, OCH), 3.86 (s, 6H, 2×$ArOCH_3$), 3.81 (s, 3H, $ArOCH_3$), 3.14 (s, 3H, OCH_3), 2.36 (dd, *J*=2.4, 0.66 Hz, 1H, ≡CH), 1.48 (s, 3H, CH_3), 1.26 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 161.2, 110.1, 101.4, 91.3, 84.8, 70.1, 56.1, 55.3, 53.4, 49.0, 25.1, 24.8; IR (neat, cm^{-1}) 3268, 3231, 2982, 2940, 1589, 1413, 1194, 1107, 967, 815; HRMS (EI) calcd for $C_{16}H_{22}O_5$ $[M]^+$ 294.1467, obsd 294.1470.

4.3. Preparation of alkynes

Alkynes **2a, 2b, 2f** and **2h** were purchased from Sigma Aldrich and used as received. Alkynes **2c** and **2d** were synthesised through base-induced methylation of their relevant terminal alkynes. Alkyne **2e** was synthesised through copper-catalysed trifluoromethylation of phenylacetylene. The dimeric alkyne **2g** was synthesised through Sonogashia self-cross-coupling of phenylacetylene.

*4.3.1. 1-Methoxy-4-(prop-1-yn-1-yl)benzene (**2c**).* To a flame-dried round-bottom flask under nitrogen was added 1-ethynyl-4-methoxybenzene (520.9 mg, 3.941 mmol) in THF (20 mL). The

flask was placed in an ice-water/salt bath and allowed to cool. *n*-Butyllithium (5.0 mL, 8.0 mmol) was added slowly and the reaction was allowed to stir for 1 h. Iodomethane (0.50 mL, 8.0 mmol) was added at that temperature and the reaction was stirred at room temperature for 1 h. The reaction was quenched with saturated solution of ammonium chloride (20 mL) and extracted with dichloromethane. The organic phases were dried over $MgSO_4$ and the solvent removed in vacuo. The residue was purified by flash chromatography (100% pentane—2% EtOAc/pentane) to give 1-methoxy-4-(prop-1-yn-1-yl)benzene (**2c**) as a colourless oil (194.5 mg, 34%). R_f=0.16 (1:100 EtOAc:pentane); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.34–7.31 (m, 2H), 6.82–6.79 (m, 2H), 3.80 (s, 3H), 2.03 (s, 3H). ^{1}H NMR shifts were consistent with those in the literature.[16]

*4.3.2. 1-(Prop-1-yn-1-yl)-4-(trifluoromethyl)benzene (**2d**).* Product **2d** was generated using a similar procedure as that used for product **2c**. ^{1}H and ^{13}C NMR shifts were consistent with those in the literature.[17]

*4.3.3. (3,3,3-Trifluoroprop-1-yn-1-yl)benzene (**2e**).* Under dry conditions, copper(I) iodide (58.7 mg, 0.308 mmol), 1,10-phenanthroline (108.7 mg, 0.6032 mmol) and potassium bicarbonate (295.4 mg, 2.951 mmol) were weighed into a Schlenk flask and Togni's reagent 1 (3,3-dimethyl-1-(trifluoromethyl)-1,2-benziodoxole, 501.4 mg, 1.519 mmol) was added. Freshly distilled DCM (5 mL) was added into this tube. Ethynylbenzene (158.1 mg, 1.548 mmol) in DCM (5 mL) was added to the tube over 6 h, using a syringe pump. After addition, the reaction mixture was stirred for another 18 h at room temperature. The reaction was quenched with NH_4Cl (10 mL) and water (10 mL) added. The aqueous phase was extracted with DCM (3×20 mL) and the combined organic phases were dried over anhydrous Na_2SO_4 and concentrated in vacuo (moderate vacuum, approx. 500 mbar at rt, was used to avoid product evaporation). The product was purified by flash chromatography (pentane) to give (3,3,3-trifluoroprop-1-yn-1-yl)benzene (**2e**) (92.5 mg, 35%) as a colourless oil. R_f=0.67 (pentane); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.54–7.49 (m, 2H), 7.48–7.46 (m, 1H), 7.41–7.37 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 132.4 (d, J=1.2 Hz), 130.9, 128.6, 118.5 (q, J=1.9 Hz), 114.9 (q, J=256.6 Hz), 86.5 (q, J=6.4 Hz), 75.7 (q, J=53.0 Hz). ^{1}H and ^{13}C NMR shifts were consistent with those in the literature.[18]

*4.3.4. 1,4-Diphenylbuta-1,3-diyne (**2g**).* In an open flask, copper(I) iodide (77.0 mg, 0.404 mmol), potassium bicarbonate (410.4 mg, 4.099 mmol) were stirred in DCM (2 mL). Ethynylbenzene (204.7 mg, 2.004 mmol) was dissolved in DCM (1 mL) and added to the reaction mixture, then 1,10-phenanthroline (145.4 mg, 0.8069 mmol) and the reaction mixture was stirred for 24 h. Water (25 mL) was added and the mixture was extracted with DCM (3×25 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated in vacuo. The product was purified by flash chromatography (pentane) to give 1,4-diphenylbuta-1,3-diyne (**2g**) (92.2 mg, 46%) as a white crystalline solid. R_f=0.30 (pentane); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.56–7.54 (m, 2H), 7.40–7.36 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 132.5, 129.2, 128.4, 121.7, 81.5, 73.9. ^{1}H and ^{13}C NMR shifts were consistent with those in the literature.[19]

4.4. General procedure for gold-catalysed reactions

The relevant propargyl acetal **1a**–**h** (1 equiv) and alkyne **2a**–**h** (3 equiv) were dissolved in dichloromethane (2–3.4 mL) and added to a solution of the gold catalyst, Au[P(*t*-Bu)$_2$(*o*-biphenyl)]SbF_6 (5 mol-%), in dichloromethane (1.7–3 mL). The reaction was stirred for 15 min at the required temperature. The reaction mixture was filtered through Celite and concentrated in vacuo. The products **4, 6, 7** and **8**[3] were isolated by flash chromatography using an appropriate eluent system.

*4.4.1. 2,6a-Dimethoxy-3a-methyl-1,4,5-triphenyl-1,3a,4,6a-tetrahydropentalene (**4a**) and 5,6a-dimethoxy-2-methyl-1,3,6-triphenyl-1,3a,6,6a-tetrahydropentalene (**6a**).* Compounds **4a** and **6a** were synthesised according to the General Procedure at rt, using propargylic acetal **1a** (149.8 mg, 0.7334 mmol) and alkyne **2a** (261.4 mg, 2.250 mmol). Flash chromatography (1:50 EtOAc:pentane) gave products **4a** and **6a** as off-white or pale yellow oils.

4a-*cis-cis-cis* (33.0 mg, 22%, mixture with two unknown isomers, yield calculated from ^{1}H NMR): R_f=0.44 (1:10 EtOAc:pentane); ^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 7.15–7.02 (m, 15H), 5.40 (d, J=1.0 Hz, 1H, H^c), 5.34 (s, 1H, H^d), 4.15 (s, 1H, H^a), 3.54 (s, 3H,=$COCH_3$), 3.42 (s, 1H, H^b), 3.01 (s, 3H, -$COCH_3$), 1.03 (s, 3H, CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ ppm 128.1, 152.6, 138.5, 138.2, 136.3, 136.2, 129.4, 128.4, 128.2, 127.9, 127.6, 127.3, 127.0, 126.7, 109.6, 90.2, 69.9, 54.6, 51.2, 50.8, 49.4, 20.5; IR (thin film, cm^{-1}) 3018, 2925, 2821, 1644, 1492, 1453, 1096, 753, 701, 699; HRMS (EI) calcd for $C_{29}H_{28}O_2$ [M]$^+$ 408.2089, obsd 408.2085.

4a-*cis-tr-tr* (21.3 mg, 14%): R_f=0.29 (1:10 EtOAc:pentane); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.61–7.13 (m, 10H), 6.98 (t, 1H, J=7.2 Hz), 6.90 (t, 2H, J=8.0 Hz), 6.64 (s, 1H, H^d), 6.31 (d, 2H, J=7.2 Hz), 5.66 (s, 1H, H^c), 3.66 (s, 1H, H^a), 3.53 (s, 3H,=$COCH_3$), 3.52 (s, 1H, H^b), 3.16 (s, 3H,-$COCH_3$), 0.99 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 156.8, 142.0, 138.7, 138.1, 138.0, 136.1, 132.0, 128.2, 128.1, 127.8, 127.6, 127.4, 127.0, 126.7, 126.5, 105.3, 86.1, 72.3, 57.5, 57.2, 54.5, 51.2, 20.8; IR (thin film, cm^{-1}) 3012, 2952, 2925, 1646, 1490, 1453, 1231, 1096, 1032, 751; HRMS (EI) calcd for $C_{29}H_{28}O_2$ [M]$^+$ 408.2089, obsd 408.2087.

4a-*cis-cis-tr* (6%): R_f=0.33 (1:10 EtOAc:pentane); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.09–6.95 (m, 15H), 6.26–6.25 (m, 1H, H^d), 5.72 (s, 1H, H^c), 4.70 (s, 1H, H^a), 3.62 (s, 1H, H^b), 3.59 (s, 3H,=$COCH_3$), 3.08 (s, 3H, −$COCH_3$), 1.05 (d, 3H, J=1.4 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 156.6, 139.7, 138.8, 138.3, 137.8, 135.4, 129.6, 128.8, 127.6, 127.2, 126.5, 125.9, 125.7, 106.3, 86.4, 71.5, 66.6, 54.4, 51.4, 51.3, 16.7; IR (thin film, cm^{-1}) 2987, 2955, 2925, 2587, 1490, 1454, 1376, 1183, 1147, 1068, 1013, 872; HRMS (EI) calcd for $C_{29}H_{28}O_2$ [M]$^+$ 408.2089, obsd 408.2090.

4a-*cis-tr-cis* (5%): R_f=0.33 (1:10 EtOAc:pentane); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.68–6.84 (m, 15H), 6.53 (m, 1H, H^d), 5.59 (s, 1H, H^c), 3.81 (s, 1H, H^b), 3.77 (s, 1H, H^a), 3.51 (s, 3H,=$COCH_3$), 3.21 (s, 3H, −$COCH_3$), 0.49 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 156.6, 142.1, 140.5, 139.5, 137.6, 128.2, 127.9, 127.6, 127.1, 127.0, 126.4, 106.2, 100.0, 87.1, 61.1, 54.8, 54.6, 54.6, 51.7, 20.8 (not possible to assign all ^{13}C shifts); IR (thin film, cm^{-1}) 2954, 2924, 2869, 2853, 1492, 1453, 1230, 1097, 699, 581, 570; HRMS (EI) calcd for $C_{29}H_{28}O_2$ [M]$^+$ 408.2089, obsd 408.2086.

6a (10.4 mg, 7%): R_f=0.51 (1:10 EtOAc:pentane); ^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 7.44–7.39 (m, 4H), 7.31–7.19 (m, 11H), 4.78 (dd, J=2.1, 1.5 Hz, 1H), 4.34–4.34 (m, 1H), 4.09 (br s, 1H), 4.070–4.066 (m, 1H), 3.58 (s, 3H), 2.52 (s, 3H), 1.70 (d, J=1.1 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ ppm 159.8, 138.9, 137.9, 137.7, 137.5, 135.7, 130.2, 129.5, 128.23, 128.21, 127.9, 126.7, 126.6, 126.5, 95.9, 93.6, 66.6, 60.1, 57.1, 56.5, 54.7, 14.5; IR (thin film, cm^{-1}) 3049, 3023, 2925, 1695, 1494, 1452, 1104, 758, 731, 698; HRMS (EI) calcd for $C_{29}H_{28}O_2$ [M]$^+$ 408.2089, obsd 408.2082.

*4.4.2. 2,6a-Dimethoxy-1,5-bis(4-methoxyphenyl)-3a-methyl-4-phenyl-1,3a,4,6a-tetrahydropentalene (**4b**).* Compounds **4b** were synthesized according to the General Procedure at 0 °C, using propargylic acetal **1b** (153.3 mg, 0.6543 mmol) and alkyne **2a** (223.0 mg, 2.250 mmol). Flash chromatography (1:20 EtOAc:pentane) gave products **4b** as pale yellow or yellow oils.

4b-*cis-cis-cis* (77.7 mg, 51%): R_f=0.24 (1:10 EtOAc:pentane); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.56–7.51 (m, 1H), 7.35–7.26 (m, 5H),

7.16–7.04 (m, 1H), 6.94 (d, 2H, *J*=8.5 Hz), 6.77 (d, 4H, *J*=8.7 Hz), 5.37 (s, 1H, H^c), 5.33 (s, 1H, H^d), 4.09 (s, 1H, H^a), 3.77 (s, 3H), 3.75 (s, 3H), 3.54 (s, 3H,=$COCH_3$), 3.35 (s, 1H, H^b), 3.02 (s, 3H, −$COCH_3$), 1.02 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 158.3, 158.2, 158.2, 152.6, 136.3, 130.3, 128.4, 128.2, 127.3, 127.0, 126.9, 113.2, 113.1, 109.6, 90.1, 69.0, 55.13, 55.08, 54.6, 51.1, 49.9, 49.4, 25.6, 20.5; IR (film, cm^{-1}) 2919, 2824, 1644, 1610, 1509, 1243, 1177, 1124, 1034, 903, 826, 730, 699; HRMS (EI) calcd for $C_{31}H_{32}O_4$ $[M]^+$ 468.2301, obsd 468.2299.

4b-*cis-tr-tr* (8.6 mg, 6%): R_f=0.14 (1:10 EtOAc:pentane); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.53–7.51 (m, 1H), 7.05–6.92 (m, 6H), 6.79–6.72 (m, 4H), 6.61 (s, 1H, H^d), 6.38 (d, 2H, *J*=7.2 Hz), 5.63 (s, 1H, H^c), 3.74 (s, 3H), 3.74 (s, 3H), 3.60 (s, 1H, H^a), 3.53 (s, 3H,=$COCH_3$), 3.45 (s, 1H, H^b), 3.16 (s, 3H, −$COCH_3$), 0.98 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 158.8, 158.3, 156.8, 142.1, 138.0, 136.2, 132.9, 130.9, 130.2, 128.9, 127.6, 127.4, 126.5, 113.2, 105.3, 86.0, 71.4, 57.2, 56.6, 55.4, 55.1, 54.5, 51.2, 20.8; IR (cm-1) 2900, 2240, 1710, 1302, 1223, 905, 734; HRMS (EI) calcd for $C_{31}H_{32}O_4$ $[M]^+$ 468.2301, obsd 468.2299.

4b-*cis-cis-tr* *and* **4-*cis-tr-cis*** were isolated as a mixture (trace): ^{1}H NMR of the mixture is supplied. Identification of the isomers was carried out by comparison with the **4a** analogue. The characteristic ^{1}H NMR signals are given below.

4b-*cis-cis-tr:* ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 6.22 (s, 1H, H^d), 5.69 (s, 1H, H^c), 4.62 (s, 1H, H^a), 3.58 (s, 3H,=$COCH_3$), 3.55 (s, 1H, H^b), 3.08 (s, 3H, −$COCH_3$), 1.09 (s, 3H, CH_3).

4b-*cis-tr-cis:* ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 6.50 (s, 1H, H^d), 5.56 (s, 1H, H^c), 3.81 (s, 1H, H^b), 3.72 (s, 1H, H^a), 3.51 (s, 3H,=$COCH_3$), 3.20 (s, 3H, −$COCH_3$), 0.49 (s, 3H, CH_3).

*4.4.3. 1,5-Bis(4-chlorophenyl)-2,6a-dimethoxy-3a-methyl-4-phenyl-1,3a,4,6a-tetrahydropentalene (**4c**) and 1,6-bis(4-chlorophenyl)-5,6a-dimethoxy-2-methyl-3-phenyl-1,3a,6,6a-tetrahydropentalene (**6c**).* Compounds **4c** and **6c** were synthesized according to the General Procedure at rt, using propargylic acetal **1c** (110 mg, 0.461 mmol) and alkyne **2a** (161 mg, 1.38 mmol). Flash chromatography (1:100 EtOAc:pentane) gave the products **4c** and **6c** as off-white oils.

4c-*cis-tr-tr* (12 mg, 12%): R_f=0.19 (1:10 EtOAc:pentane); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.55–7.53 (m, 1H), 7.23–7.06 (m, 6H), 7.06–7.03 (m, 2H), 6.98–9.95 (m, 2H), 6.63 (s, 1H, H^d), 6.39–6.37 (m, 2H), 5.64 (d, 1H, *J*=1.1 Hz, H^c), 3.61 (s, 1H, H^a), 3.52 (s, 3H,=$COCH_3$), 3.47 (s, 1H, H^b), 3.14 (s, 3H, −$COCH_3$), 0.99 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 156.4, 141.5, 138.1, 137.1, 136.4, 135.7, 133.2, 133.0, 132.6, 129.5, 128.2, 128.1, 127.6, 127.4, 126.9, 105.3, 85.9, 71.4, 57.0, 56.8, 54.5, 51.3, 20.9; IR (thin film, cm^{-1}) 2919, 2839, 1639, 1490, 1445, 1226, 1091, 1014, 838, 813, 741, 702; HRMS (EI) calcd for $C_{29}H_{26}O_2{}^{35}Cl_2$ $[M]^+$ 476.1310, obsd 476.1309.

4c-*cis-cis-tr* (6.4 mg, 6%, isolated as a mixture with **4c-*cis-tr-cis*):** R_f=0.23 (1:10 EtOAc:pentane); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.51–7.49 (m, 1H), 7.37–7.35 (m, 3H), 7.18–7.16 (m, 1H), 7.06 (d, 4H, *J*=8.4 Hz), 7.02–7.00 (m, 2H), 6.88 (d, 2H, *J*=8.6 Hz), 6.26–6.25 (m, 1H, H^d), 5.70 (s, 1H, H^c), 4.64 (s, 1H, H^a), 3.58 (s, 4H,=$COCH_3$ and H^b, overlapping), 3.07 (s, 3H, −$COCH_3$), 1.09 (d, 3H, *J*=1.3 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 138.6, 106.3, 70.7, 54.5, 51.5, 50.8, 17.0 (not possible to assign all carbon shifts); IR (film, cm^{-1}) 2955, 2923, 2867, 1490, 1257, 1091, 1014, 817, 742, 703, 568; HRMS (EI) calcd for $C_{29}H_{28}O_2{}^{35}Cl_2$ $[M]^+$ 476.1310, obsd 476.1309.

4c-*cis-tr-cis* (3.6 mg, 4%, isolated as a mixture with **4c-*cis-cis-tr***): ^{1}H NMR of the mixture is supplied. Identification of the isomers was carried out by comparison with the **4a** analogue. The characteristic ^{1}H and ^{13}C NMR signals are given below. R_f=0.29 (1:10 THF:pentane); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 6.50 (m, 1H, H^d), 6.58 (s, 1H, H^c), 3.71 (s, 1H, H^b), 3.69 (s, 1H, H^a), 3.51 (s, 3H,=$COCH_3$, overlapping with **4c-*cis-cis-tr***), 3.18 (s, 3H, −$COCH_3$), 0.48 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 156.6, 142.1, 140.5, 139.5, 137.6, 128.2, 127.9, 127.6, 127.1, 127.0, 126.4, 106.2, 100.0, 87.1, 61.1, 54.8, 54.6, 54.6, 51.7, 20.8 (not possible to assign all carbon shifts); IR (film, cm^{-1}) 2955, 2923, 2867, 1490, 1257, 1091, 1014, 817, 742, 703, 568; HRMS (EI) calcd for $C_{29}H_{26}O_2{}^{35}Cl_2$ $[M]^+$ 476.1310, obsd 476.1310.

6c (7 mg, 7%): R_f=0.58 (1:10 EtOAc:pentane); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.41 (d, 4H, *J*=4.3 Hz), 7.32–7.26 (m, 2H), 7.26–7.23 (m, 2H), 7.17–7.11 (m, 5H), 4.78 (s, 1H), 4.32 (s, 1H), 4.03 (s, 1H), 3.99 (s, 1H), 3.58 (s, 3H), 2.64 (s, 3H), 1.68 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 159.3, 138.1, 137.1, 137.1, 136.2, 135.1, 132.5, 131.4, 130.8, 128.3, 128.2, 128.2, 128.1, 127.8, 96.1, 93.1, 66.1, 59.5, 56.6, 56.0, 54.7, 14.4; IR (thin film, cm^{-1}) 2950, 2919, 1646, 1490, 1340, 1225, 1090, 1014, 701; HRMS (EI) calcd for $C_{29}H_{26}{}^{35}Cl_2O_2$ $[M]^+$ 477.1385, obsd 477.1388.

*4.4.4. Products **4e** and **6e** were synthesized according to the General Procedure at rt, using propargylic acetal **1e** (150.3 mg, 0.5520 mmol) and alkyne **2a** (191.9 mg, 1.652 mmol).* Flash chromatography (2:1 EtOAc:pentane) gave products **4e** and **6e** as a mixture of pale yellow oils. This mixture was inseparable by flash chromatography and appeared to contain both compounds of type **4e** and **6e**, but their identity could not be determined conclusively. (^{1}H NMR in Supplementary data).

*4.4.5. 4,4′-(2,6a-Dimethoxy-3a-methyl-4-phenyl-1,3a,4,6a-tetrahydropentalene-1,5-diyl)bis(N-methylbenzamide) (**4f**).* Compounds **4f** were synthesized according to the General Procedure at rt, using propargylic acetal **1f** (136.0 mg, 0.5204 mmol) and alkyne **2a** (181.0 mg, 1.561 mmol). Flash chromatography (2:1 EtOAc:pentane) gave products **4f** as pale yellow or yellow oils.

4f-*cis-cis-cis* (32 mg, 24%): R_f=0.29 (2:1 EtOAc:pentane); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.57–7.50 (m, 2H), 7.47–7.43 (m, 2H), 7.39–7.32 (m, 4H), 7.18–7.05 (m, 3H), 6.97–6.95 (m, 2H), 5.37 (s, 1H, H^c), 5.32 (s, 1H, H^d), 4.10 (s, 1H, H^a), 3.52 (s, 3H,=$COCH_3$), 3.36 (s, 1H, H^b), 3.00 (s, 3H, −$COCH_3$), 2.10 (s, 6H), 1.01 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 168.3, 168.2, 157.9, 152.9, 136.6, 136.4, 135.9, 134.0, 132.3, 129.9, 128.2, 127.4, 126.9, 126.5, 119.1, 109.6, 90.2, 69.2, 60.4, 54.6, 51.1, 50.1, 49.4, 24.5, 24.4, 20.5; IR (thin film, cm^{-1}) 3304, 3049, 2925, 1669, 1601, 1533, 1517, 1412, 1317, 768, 699; HRMS (EI) calcd for $C_{33}H_{34}N_2O_4$ $[M]^+$ 522.2519, obsd 522.2518.

4f-*cis-tr-tr* was isolated as a mixture (8 mg, 6%): ^{1}H NMR of the mixture is supplied. Identification of the isomers was carried out by comparison with the **4a** analogue. The characteristic ^{1}H NMR signals are given below.

4f-*cis-tr-tr:* ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 6.62 (s, 1H, H^d), 5.63 (s, 1H, H^c), 3.62 (s, 1H, H^a), 3.51 (s, 3H,=$COCH_3$), 3.47 (s, 1H, H^b), 3.15 (s, 3H, −$COCH_3$), 0.99 (s, 3H, CH_3).

*4.4.6. 1,5-Bis(3,5-dimethoxyphenyl)-2,6a-dimethoxy-3a-methyl-4-phenyl-1,3a,4,6a-tetrahydropentalene (**4g**).* Compound **4g** was synthesized according to the General Procedure at rt, using propargylic acetal **1f** (153.4 mg, 0.5804 mmol) and alkyne **2a** (206.5 mg, 1.778 mmol). Flash chromatography (1:10 EtOAc:pentane) gave products **4f** as colourless oils.

4g-*cis-cis-cis* (14.8 mg, 10%): R_f=0.22 (1:4 EtOAc:pentane); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.32–7.26 (m, 5H), 6.86 (s, 1H), 6.37 (s, 1H), 6.34 (s, 1H), 6.31 (s, 1H), 6.21 (s, 2H), 5.42 (s, 1H, H^c), 5.37 (s, 1H, H^d), 4.07 (s, 1H, H^a), 3.61 (s, 6H), 3.55 (s, 3H,=$COCH_3$), 3.32 (s, 1H, H^b), 3.11 (s, 3H, −$COCH_3$), 1.05 (s, 3H, CH_3); ^{13}C NMR was not obtained due to impurity. Identification of the isomer was carried out by comparison with the **4a** analogue. HRMS (EI) calcd for $C_{33}H_{36}O_6$ $[M]^+$ 528.2512, obsd 528.2511.

*4.4.7. 3a,5-Dimethoxy-2,4-bis(4-methoxyphenyl)-1-phenyl-1,3a,4,6a-tetrahydropentalene (**4i**).* Compounds **4i** were synthesized according to the General Procedure at 0 °C, using propargylic acetal **1b** (152.4 mg, 0.6505 mmol) and alkyne **2b** (197.5 mg, 1.934 mmol). Flash chromatography (1:20 EtOAc:pentane) gave mixtures of products **4i** as pale yellow oils. One compound was identified as the **4i-*cis-cis-cis*** isomer, while another also seemed to be a stereoisomer of **4**, but did not correspond to any of the already identified isomers. The minor amount did not to allow for characterisation. ^{1}H NMR of both compounds is provided.

4i-*cis-cis-cis* (20.5 mg, 14%): Identification of the isomer was carried out by comparison with the **4a** analogue. The characteristic ^{1}H signals are given below. HRMS (EI) calcd for $C_{30}H_{30}O_4$ $[M]^+$ 454.2144, obsd 454.2145.

Not determined isomer of **4**: ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 5.54 (s, 1H, H^c), 5.47 (s, 1H, H^d), 4.14 (s, 1H, H^a), 3.59 (s, 1H, H^b), 3.54 (s, 3H,=$COCH_3$), 2.97 (s, 3H, $-COCH_3$).

*4.4.8. 2,6a-Dimethoxy-1,4,5-tris(4-methoxyphenyl)-3a-methyl-1,3a,4,6a-tetrahydropentalene (**4j**).* Compounds **4j** were synthesized according to the General Procedure at 0 °C, using propargylic acetal **1b** (70.4 mg, 0.300 mmol) and alkyne **2c** (130.4 mg, 0.8920 mmol). Flash chromatography (1:10 EtOAc:pentane) gave products **4j** as yellow oils/waxes.

4j-*cis-cis-cis* (11 mg, 15%, isolated as a mixture with an unknown isomer): Identification of the isomer was carried out by comparison with the **4a** analogue. The characteristic ^{1}H signals are given below. R_f=0.12 (1:10 EtOAc:pentane); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 5.35 (s, 1H, H^d), 5.25 (s, 1H, H^c), 4.08 (s, 1H, H^a), 3.81 (s, 3H), 3.76 (s, 3H), 3.75 (s, 3H), 3.53 (s, 3H,=$COCH_3$), 3.33 (s, 1H, H^b), 3.01 (s, 3H, $-COCH_3$), 1.02 (s, 3H, CH_3).

4j-*cis-cis-tr* (14.0 mg, 19%): R_f=0.10 (1:10 EtOAc:pentane); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 6.93 (d, 2H, J=8.2 Hz), 6.87 (d, 2H, J=8.7 Hz), 6.94–6.85 (m, 2H, overlapping), 6.64 (d, 2H, J=8.6 Hz), 6.59 (d, 2H, J=8.8 Hz), 6.65–6.42 (m, 2H, overlapping), 6.20 (s, 1H, H^d), 5.68 (s, 1H, H^c), 4.53 (s, 1H, H^a), 3.71 (s, 3H), 3.70 (s, 3H), 3.67 (s, 3H), 3.57 (s, 3H,=$COCH_3$), 3.53 (s, 1H, H^b), 3.07 (s, 3H, -$COCH_3$), 1.07 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 158.2, 157.6, 157.4, 156.7, 138.0, 135.9, 132.1, 130.9, 130.5, 130.2, 129.9, 113.0, 112.6, 112.4, 106.2, 86.3, 70.6, 65.8, 55.1, 55.04, 55.00, 54.4, 51.3, 50.9, 16.8; IR (thin film, cm^{-1}) 2935, 2826, 1609, 1509, 1463, 1245, 1178, 1035, 910, 826, 794, 730; HRMS (EI) calcd for $C_{32}H_{34}O_5$ $[M]^+$ 498.2406, obsd 498.2398.

4j-*tr-tr-cis* (13.2 mg, 18%): R_f=0.15 (1:10 EtOAc:pentane); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 6.94 (d, 2H, J=8.8 Hz), 6.85 (d, 2H, J=8.5 Hz), 6.75 (d, 2H, J=8.8 Hz), 6.62 (d, 2H, J=8.7 Hz), 7.19–6.61 (m, 4H, overlapping), 5.76 (s, 1H, H^c), 5.16 (s, 1H, H^d), 4.13 (s, 1H, H^a), 3.81 (s, 3H), 3.73 (s, 3H), 3.69 (s, 3H), 3.60 (s, 3H,=$COCH_3$), 3.36 (s, 1H, H^b), 3.06 (s, 3H, -$COCH_3$), 1.74 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 158.7, 158.3, 157.8, 157.6, 146.5, 133.0, 130.2, 130, 129.4, 128.3, 127.1, 113.2, 112.8, 107.1, 89.5, 68.7, 59.1, 55.19, 55.16, 55.0, 54.7, 50.5, 48.7, 13.8; IR (thin film, cm^{-1}) 2930, 2909, 2826, 1610, 1510, 1463, 1246, 1177, 1099, 1036, 824, 732; HRMS (EI) calcd for $C_{32}H_{34}O_5$ $[M]^+$ 498.2406, obsd 498.2402.

*4.4.9. 3a-Ethyl-2,6a-dimethoxy-1,5-bis(4-methoxyphenyl)-4-phenyl-1,3a,4,6a-tetrahydropentalene (**4k**).* The title compound was synthesized according to the General Procedure at 0 °C, using propargylic acetal **1b** (151.1 mg, 0.6449 mmol) and alkyne **2i** (260.0 mg, 1.997 mmol). Flash chromatography (1:20 EtOAc:pentane) gave product **4k** as a pale yellow oil.

4k-*cis-cis-cis* (50.1 mg, 32%): R_f=0.21 (1:10 EtOAc:pentane); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.60–7.53 (m, 1H), 7.37–7.28 (m, 5H), 7.20–7.14 (m, 1H), 6.94 (d, 2H, J=8.6 Hz), 6.75 (d, 4H, J=8.7 Hz), 5.41 (s, 1H, H^d), 5.29 (s, 1H, H^c), 4.02 (s, 1H, H^a), 3.76 (s, 3H), 3.73 (s, 3H), 3.56 (s, 3H,=$COCH_3$), 3.43 (s, 1H, H^b), 2.90 (s, 3H, -$COCH_3$), 1.82–1.70 (m, 1H, CH_2), 1.45–1.33 (m, 1H, CH_2), 0.75 (t, J=7.3 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 158.4, 158.3, 158.2, 153.9, 136.5, 130.3, 130.2, 128.4, 128.2, 127.3, 127.2, 126.2, 113.0, 107.3, 90.8, 66.5, 55.1, 55.0, 54.6, 53.3, 51.9, 51.5, 24.5, 8.5; IR (thin film, cm^{-1}) 2962, 2930, 2826, 1704, 1610, 1510, 1244, 178, 1034, 809, 824, 729, 699; HRMS (EI) calcd for $C_{32}H_{34}O_4$ $[M]^+$ 482.2457, obsd 482.2462.

*4.4.10. 5,6a-Dimethoxy-2-methyl-3-phenyl-1,6-bis(2,4,6-trimethoxyphenyl)-1,3a,6,6a-tetrahydropentalene (**6h**).* The title compound was synthesized according to the General Procedure at rt, using propargylic acetal **1h** (151.2 mg, 0.5137 mmol) and alkyne **2a** (184.0 mg, 1.584 mmol). Flash chromatography (1:3 EtOAc:-pentane) gave product **6h** as a pale yellow oil (16.4 mg, 11%): R_f=0.18 (1:3 EtOAc:pentane); ^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 7.41–7.39 (m, 2H), 7.37–7.35 (m, 2H), 7.23–7.20 (m, 1H), 6–11 (d, J=2.4 Hz, 1H), 6.10 (d, J=2.4 Hz, 1H), 6.08 (d, J=2.3 Hz, 1H), 6.06 (d, J=2.3 Hz, 1H), 4.92 (s, 1H), 4.84 (t, J=1.5 Hz, 1H), 4.57 (t, J=2.1 Hz), 4.47–4.46 (m, 1H), 3.808 (s, 3H), 3.806 (s, 3H), 3.77 (s, 3H), 3.76 (s, 3H), 3.71 (s, 3H), 3.70. (s, 3H), 3.50 (s, 3H), 2.84 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ ppm 159.8, 159.7, 159.6, 159.5, 139.2, 135.0, 134.9, 128.2, 127.9, 125.6, 109.5, 108.1, 95.2, 92.9, 91.5, 90.8, 90.8, 90.5, 60.4, 59.5, 56.2, 56.0, 55.9, 55.7, 55.4, 55.2, 55.1, 54.1, 49.4, 14.2; IR (thin film, cm^{-1}) 2935, 2836, 1692, 1590, 1226, 1204, 1127, 812, 732; HRMS (EI) calcd for $C_{35}H_{40}O_8$ $[M]^+$ 588.2723, obsd 588.2719.

*4.4.11. 1-(3-Methoxy-4-methyl-5-phenylcyclopenta-1,3-dien-1-yl)-4-nitrobenzene (**7**).* The title compound was synthesized according to the General Procedure at rt, using propargylic acetal **1d** (202 mg, 0.810 mmol) and alkyne **2a** (284 mg, 2.43 mmol). Flash chromatography (1:60 EtOAc:pentane) gave compound **7** as an orange solid/wax (18 mg, 15%): R_f=0.43 (1:5 EtOAc:pentane); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.97 (d, 2H, J=9.2 Hz), 7.56 (d, 2H, J=9.1 Hz), 7.27–7.08 (m, 5H), 6.34 (s, 1H), 4.27 (s, 1H), 4.04 (s, 3H), 1.86 (d, 3H, J=1.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 162.7, 155.3, 143.3, 141.7, 138.5, 129.0, 127.8, 127.0, 125.2, 123.7, 120.0, 116.5, 58.5, 58.1, 15.5; IR (film, cm^{-1}) 2924, 2841, 1589, 1515, 1331, 1315, 1107, 852, 752, 735, 699; HRMS (EI) calcd for $C_{19}H_{17}NO_3$ $[M]^+$ 308.1287, obsd 308.1287.

*4.4.12. 2,5,8a-Trimethoxy-1-(4-methoxyphenyl)-1,3a,8,8a-tetrahydrocyclopenta[a]indene (**8**).*[3] Propargylic acetal **1b** and alkynes **2e**, **f**, **g**, **h** were mixed according to the General Procedure. Full conversion of acetal **1b** at 0 °C (1–24 h) afforded dimer **8**[13] (up to 15%) and propargyl alcohol (up to 10%), while products **4** could not be detected.

Acknowledgements

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Supplementary data

Supplementary data (spectroscopic data ^{1}H and ^{13}C NMR) associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2015.12.080.

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Supporting Information

^{1}H and ^{13}C NMR Spectral data for new compounds

Gold(I)-catalysed tandem cyclization of propargyl acetals and alkynes

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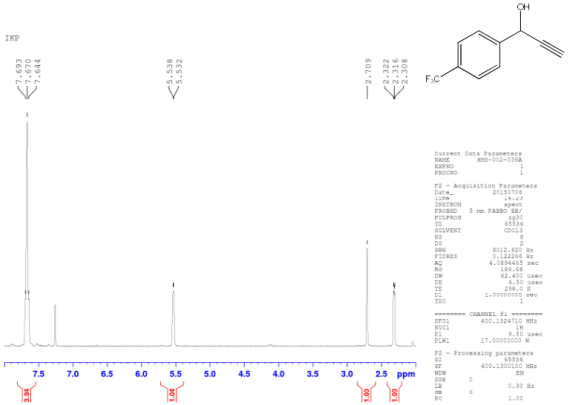
S1- S8 **Propargyl alcohols and acetals**

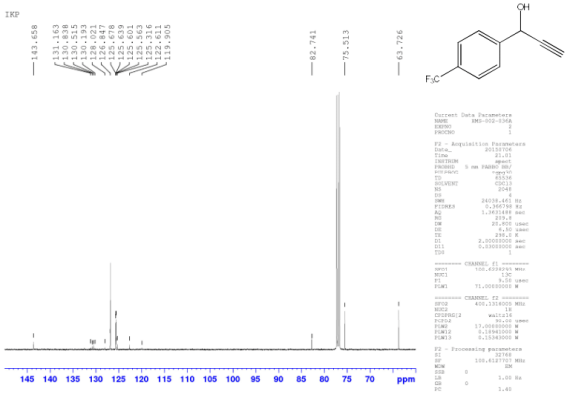
S9-S25 **Products 4a-c, 4e (& 6e), 4f, 4g, 4i, 4j, 4k**

S26-S29 **Products 6a, 6c, 6h**

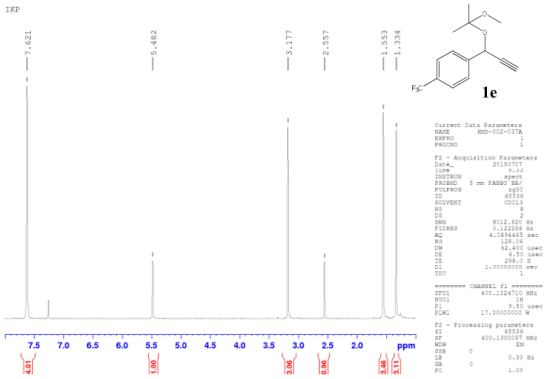
S30 **Product 7**

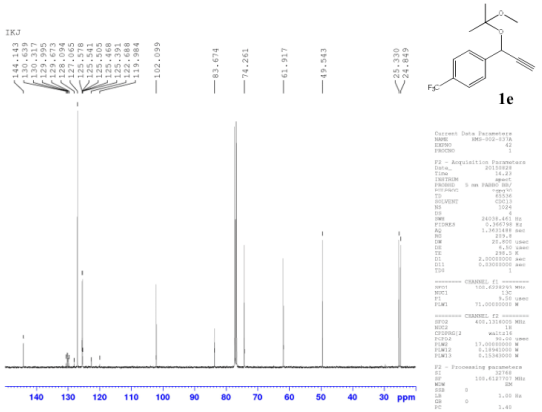
Propargyl alcohols and acetals

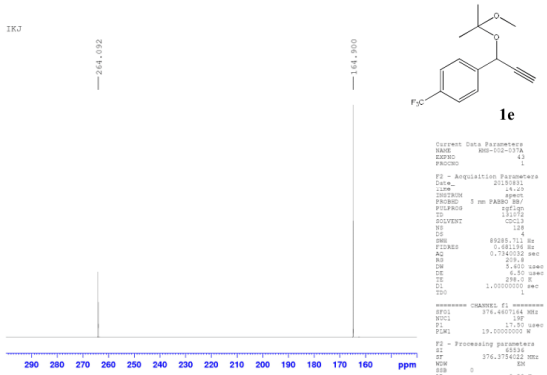




Propargyl acetal 1e







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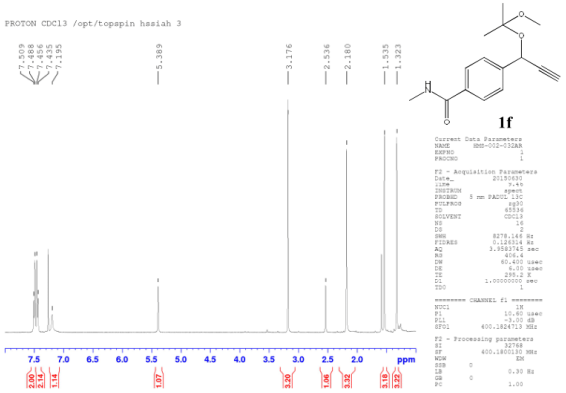

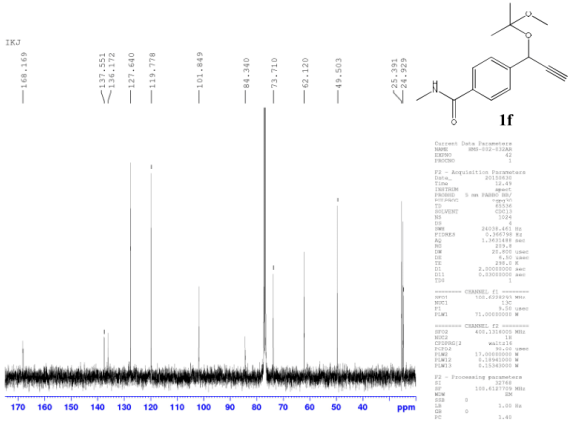

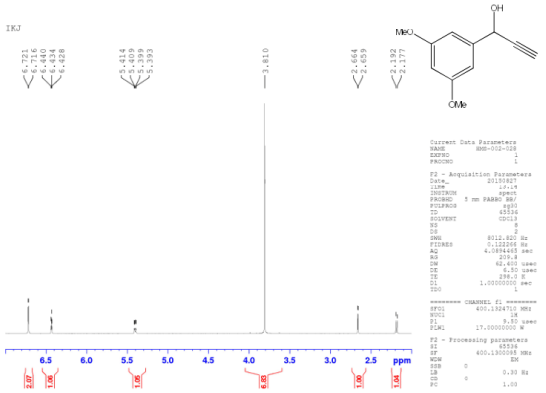

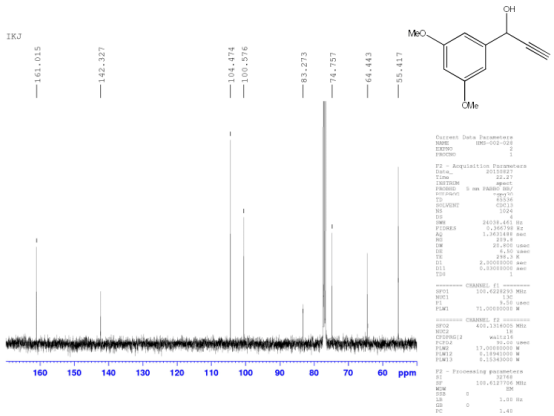

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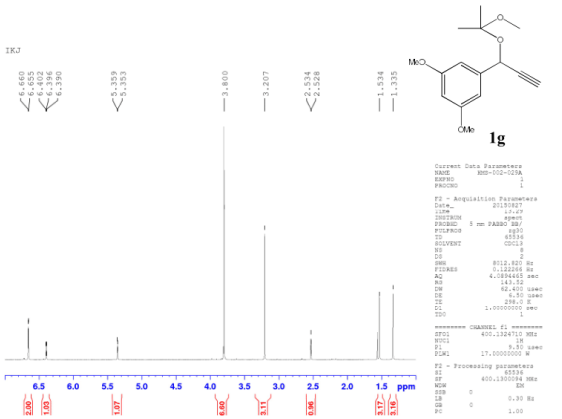

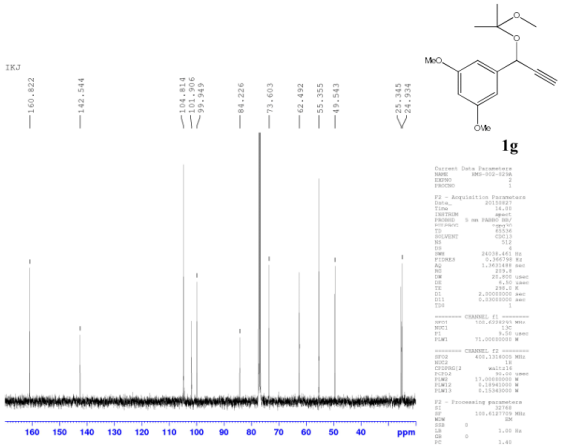

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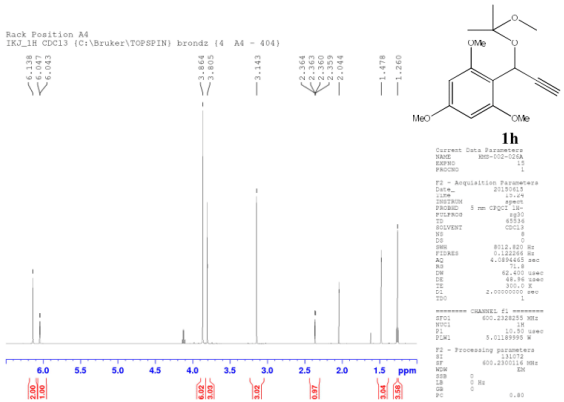
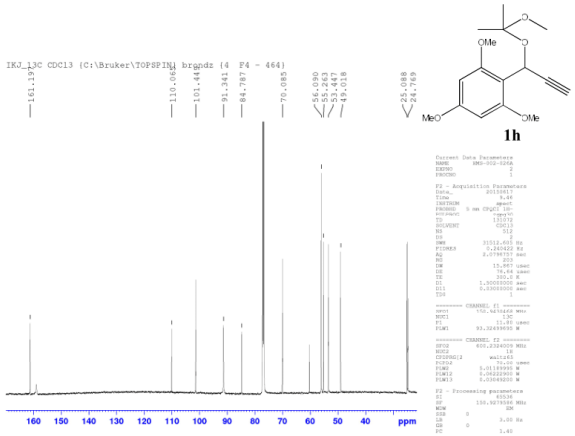
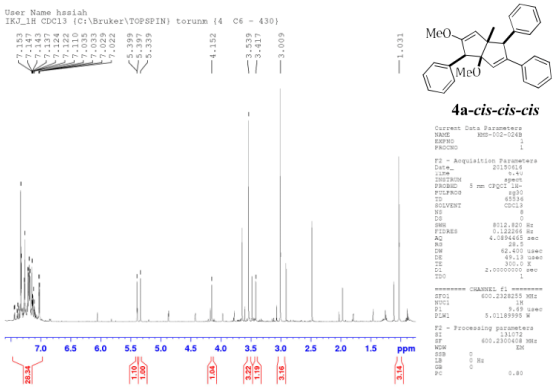




Compounds 4a



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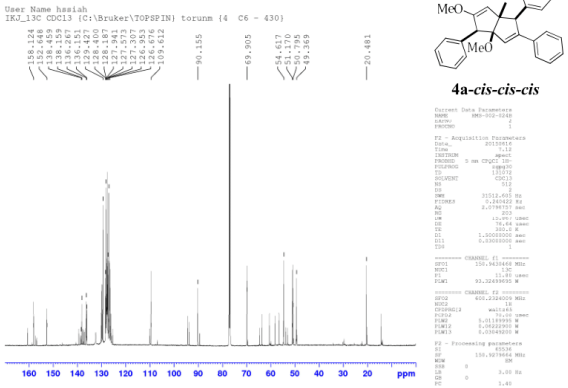

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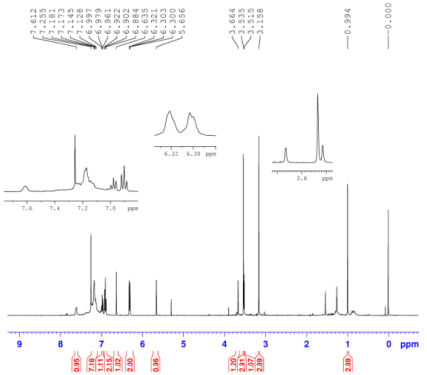
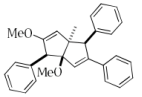
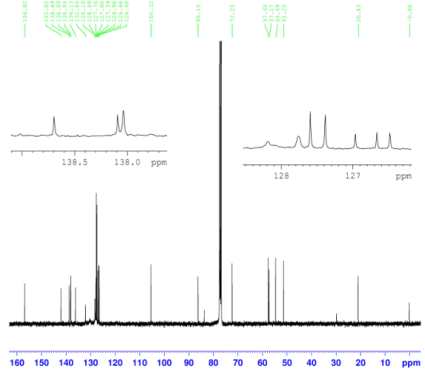
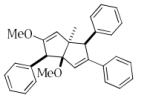


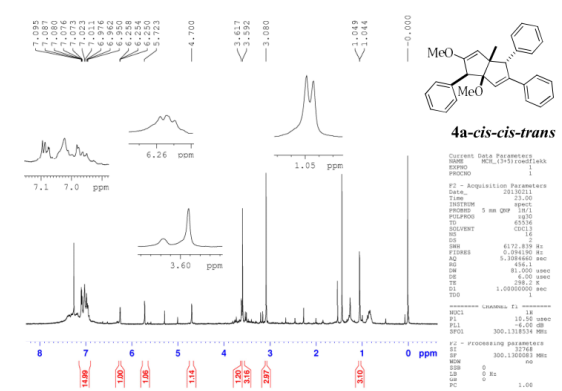


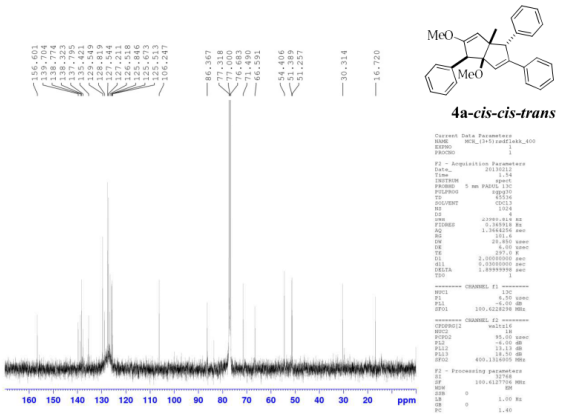
4a-*cis-trans-trans*

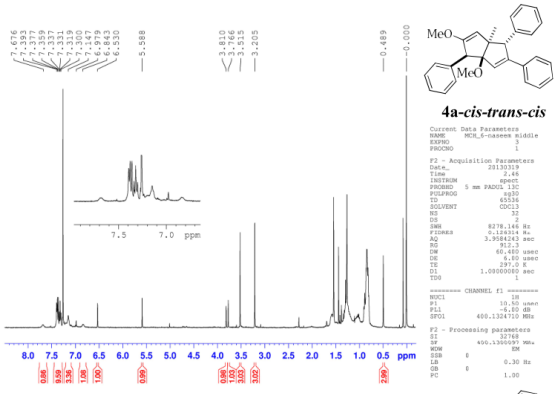


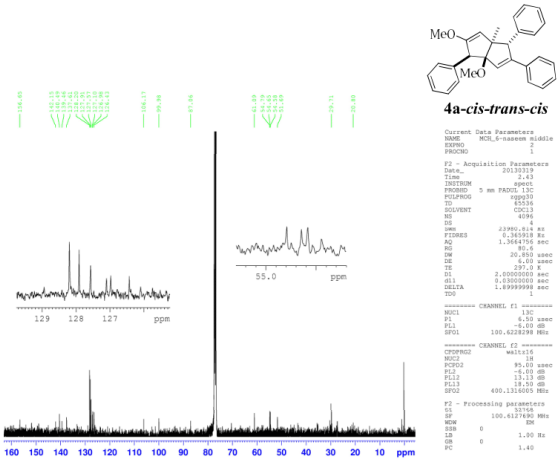


4a-*cis-trans-trans*

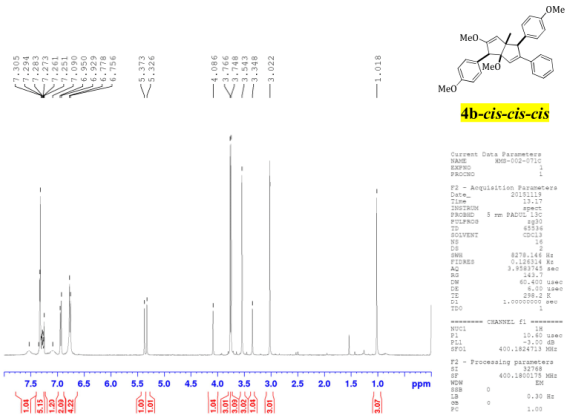

MeO
MeO
4a-cis-cis-trans
6.26 ppm
1.05 ppm
7.1 7.0 ppm
3.60 ppm
8 7 6 5 4 3 2 1 0 ppm


MeO
MeO
4a-cis-cis-trans
160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

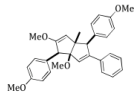

MeO
MeO
4a-cis-trans-cis
7.5 7.0 ppm
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm


MeO
MeO
4a-cis-trans-cis
55.0 ppm
129 128 127 ppm
160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

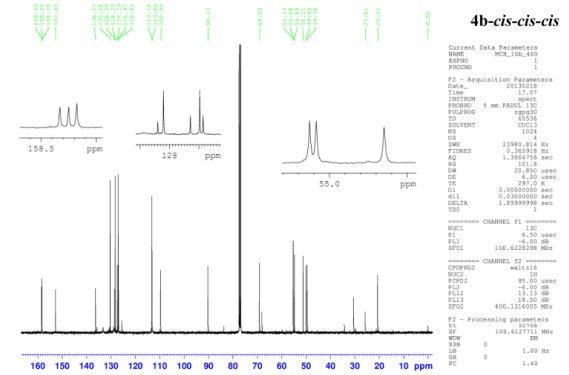
Compounds 4b

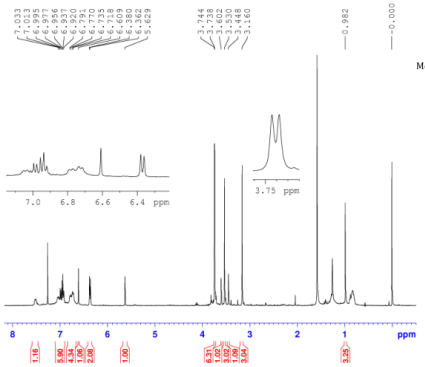


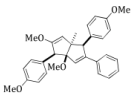
4b-*cis-cis-cis*



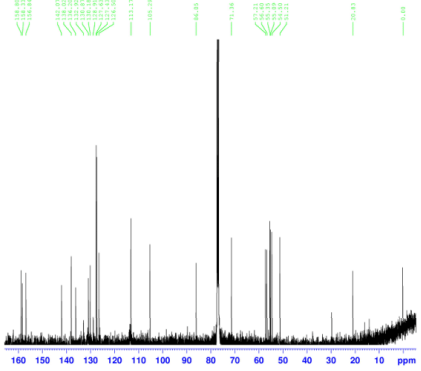
4b-*cis-cis-cis*

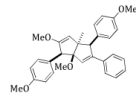






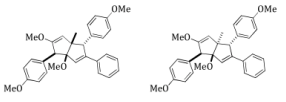
4b-*cis-trans-trans*



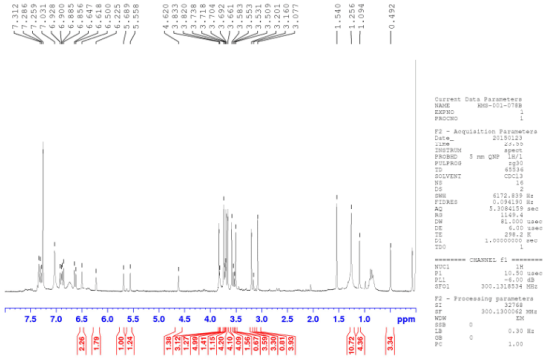


4b-*cis-trans-trans*

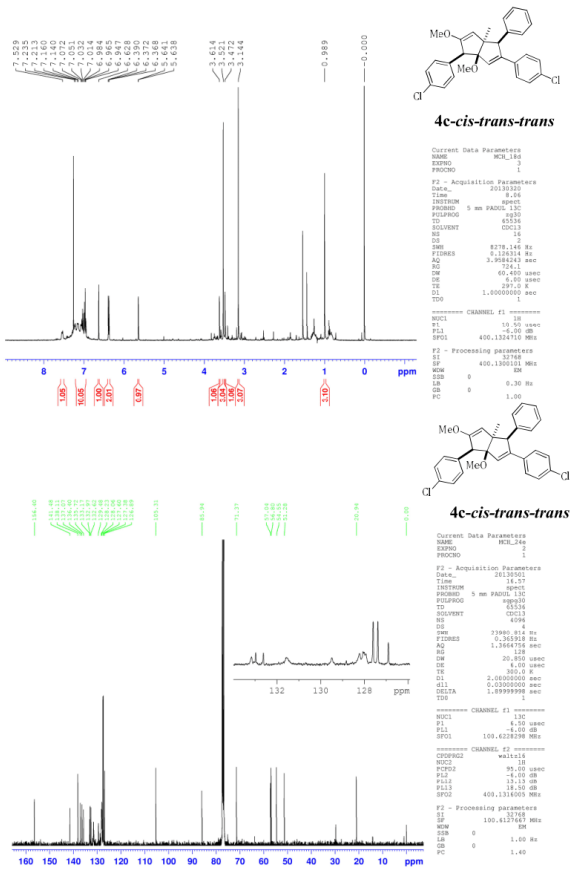
Trace mixture identified by comparison of proton shifts with analogues



4b-*cis-cis-trans* **4b-*cis-trans-cis***

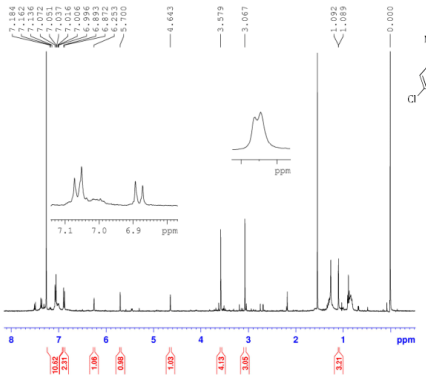


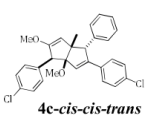
Compounds 4c



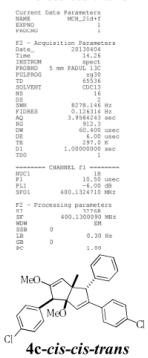
4c-*cis-trans-trans*

4c-*cis-trans-trans*

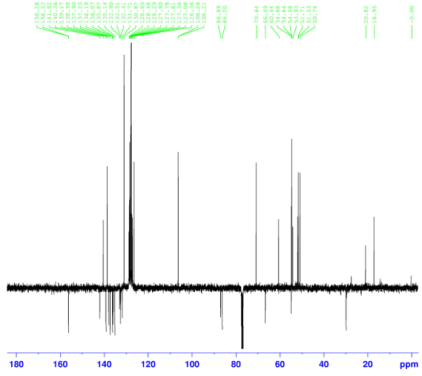




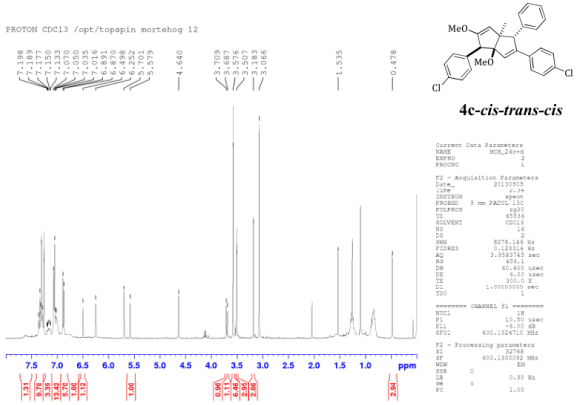
4c-*cis-cis-trans*



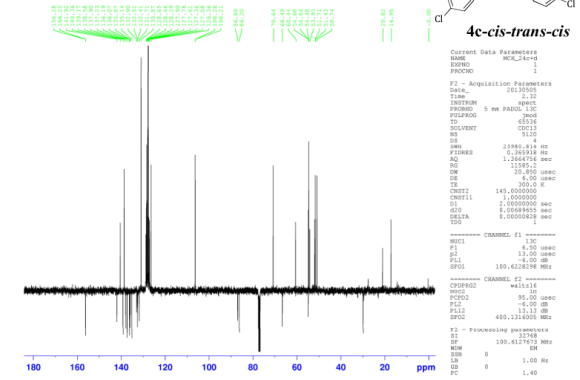
4c-*cis-cis-trans*
(characterised in a mixture with **4c**-*cis-trans-cis* (see next page))

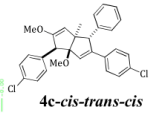


4c-*cis-trans-cis*, characterised in a mixture with **4c**-*cis-cis-trans* (see previous page).



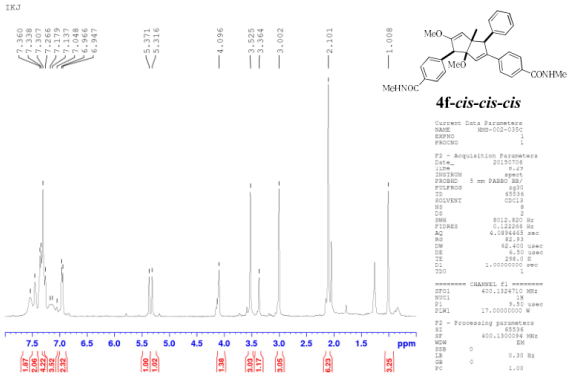
4c-*cis-trans-cis*

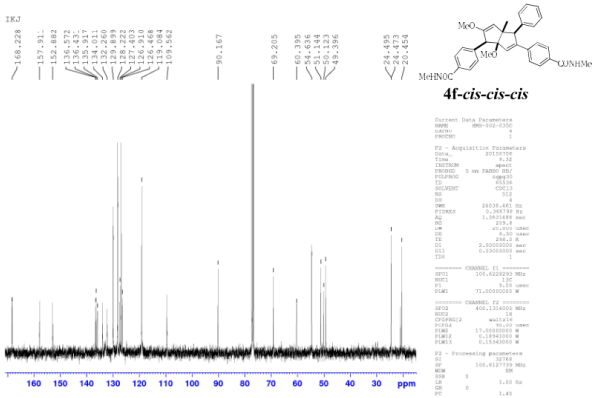




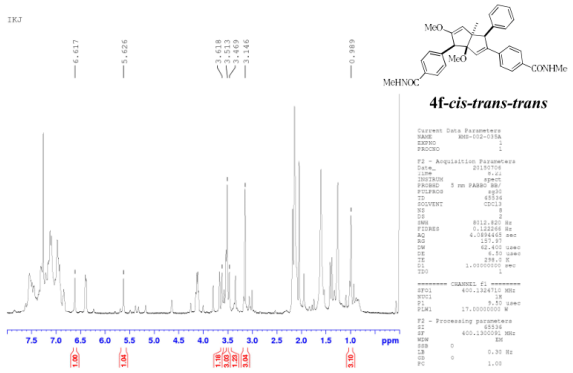
4c-*cis-trans-cis*

Compounds 4f

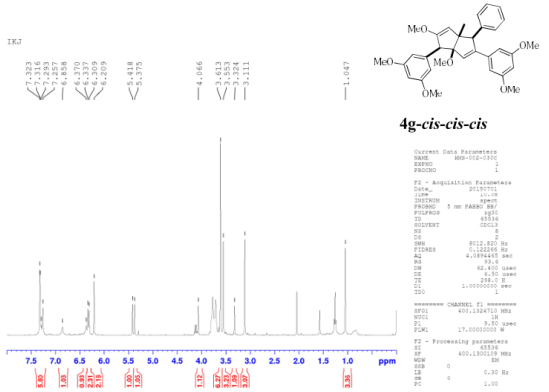




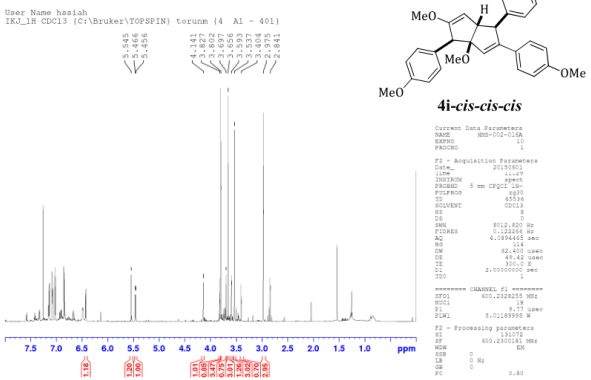
Trace of 4f-*cis-trans-trans*

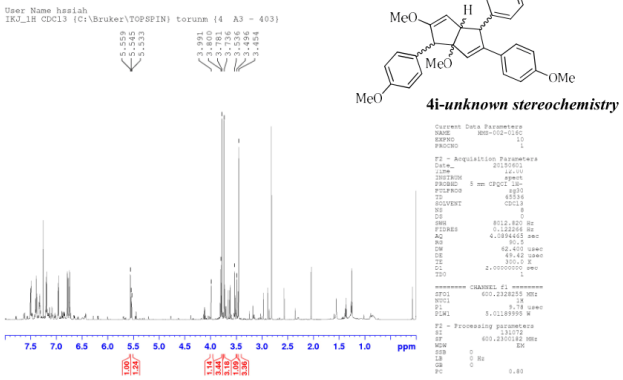


Compound 4g

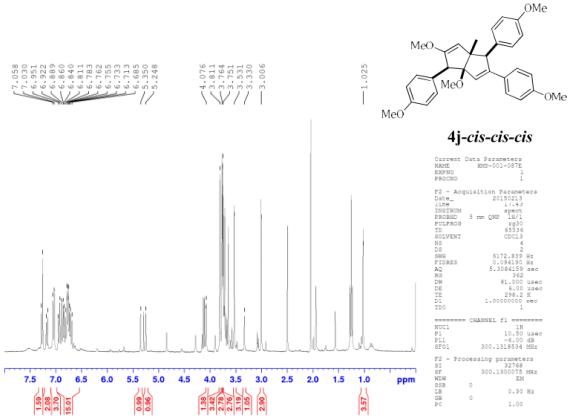


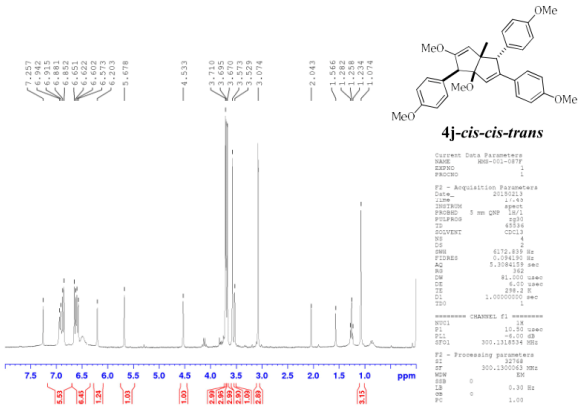
Compounds 4i



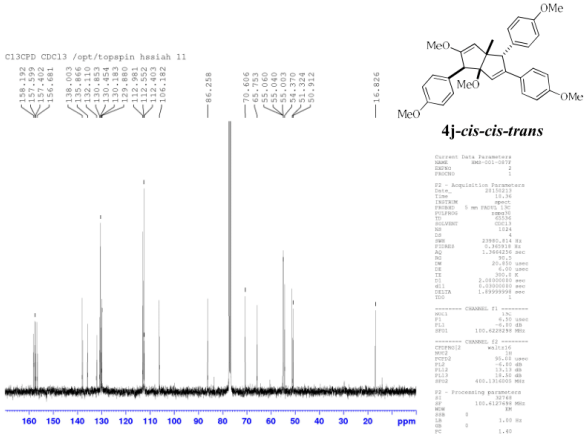


Compounds 4j

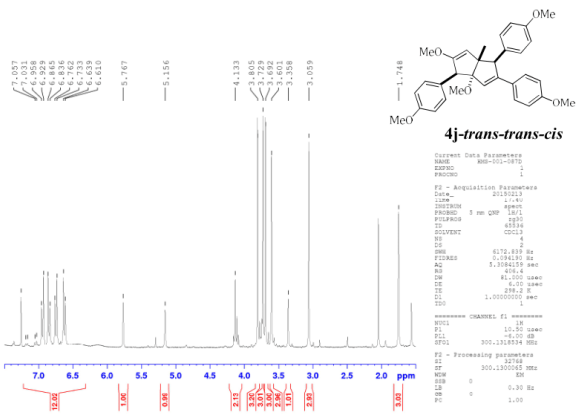




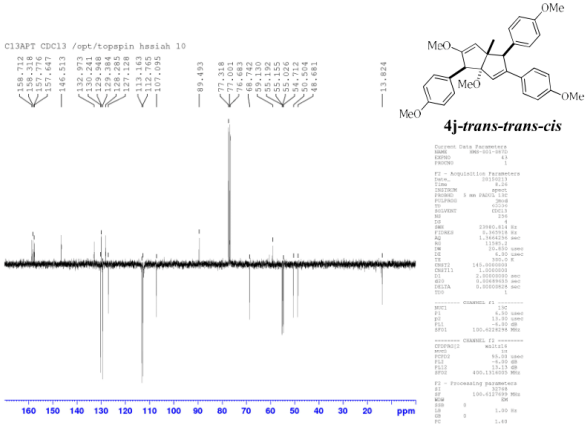
4j-*cis-cis-trans*



4j-*cis-cis-trans*

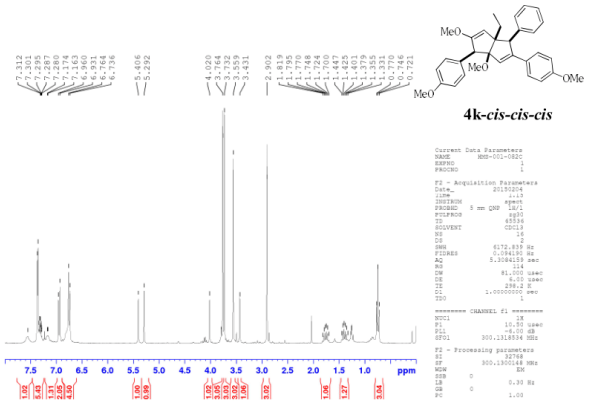


4j-*trans-trans-cis*

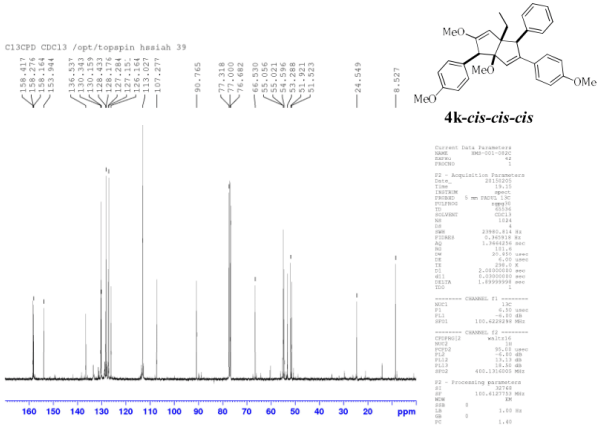


4j-*trans-trans-cis*

Compound 4k

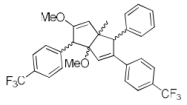


4k-*cis-cis-cis*

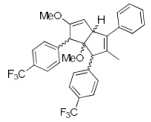


4k-*cis-cis-cis*

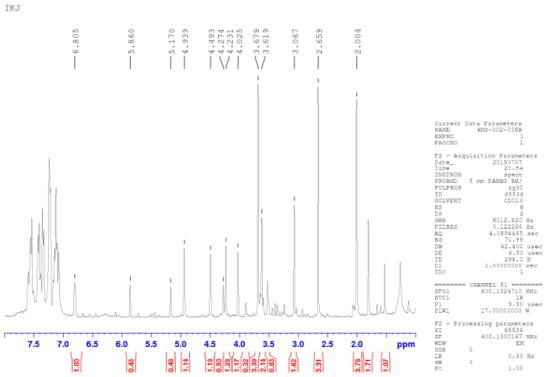
Mixture of compounds 4e and 6e



4e-*unknown stereochemistry*

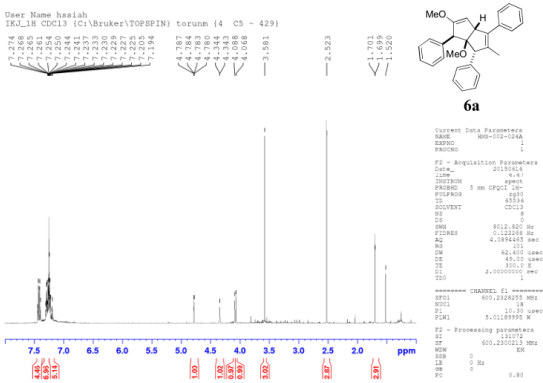


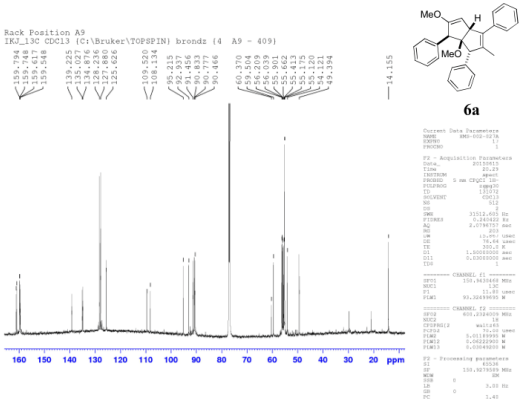
6e-*unknown stereochemistry*



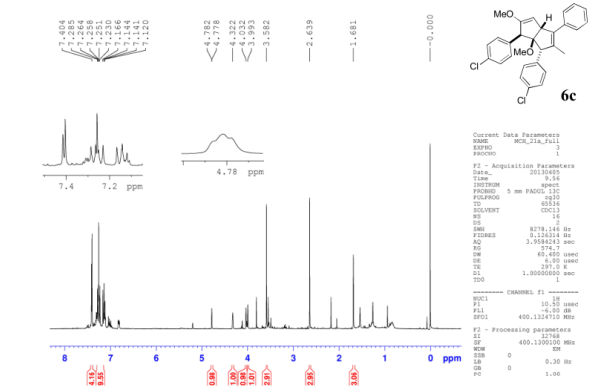
Compounds 6

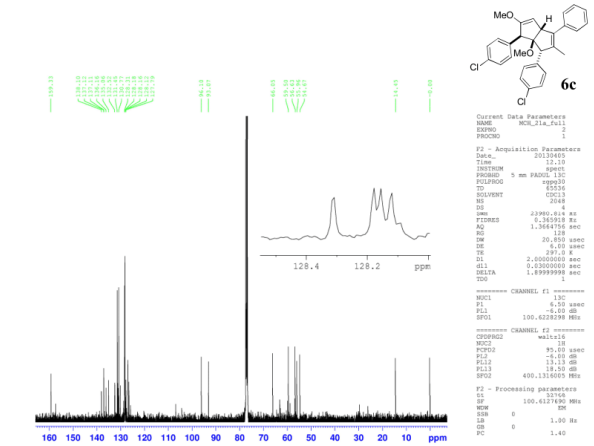
Compound 6a



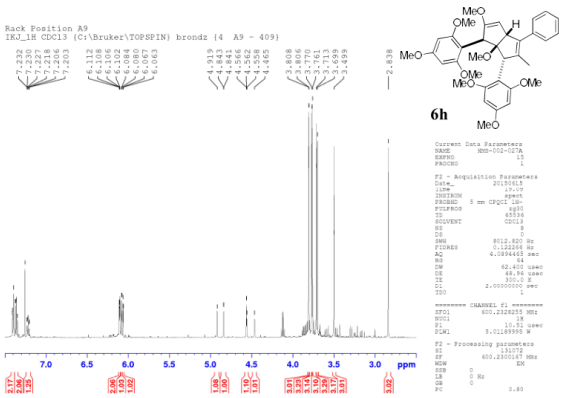


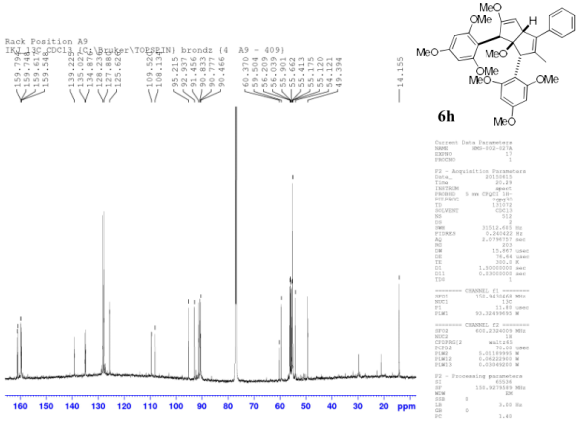
Compound 6c



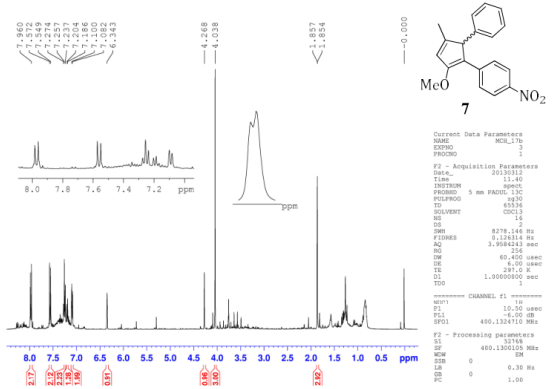


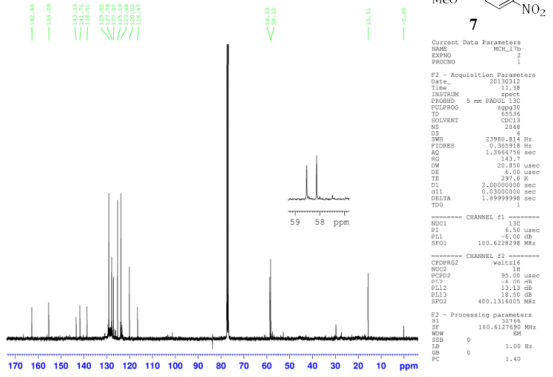
Compound 6h





Compound 7





PAPER III

Dual-gold(I)-generated trifluoromethylation of terminal alkynes with Togni's reagent

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Dual-gold(I)-generated trifluoromethylation of terminal alkynes with Togni's reagent

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σ,π-alkyne-dual-Au complex
Transfer reagent

ABSTRACT

The interaction of a Au(I) catalyst (JohnPhosAu(I)-MeCN/SbF_6) and the Togni's reagent 1, as a source of electrophilic trifluoromethyl group, has been studied in order to develop gold-catalysed alkyne trifluoromethylation reactions. Alkyne-CF_3 products were prepared in moderate yields (up to 46%) by electrophilic trifluoromethylation of terminal arylalkynes with Togni's reagent 1 in the presence of sub-stoichiometric amounts of gold catalyst (25%). The proposed addition-elimination reaction mechanism proceeds through a Au-Togni Reagent complex with a linear Togni Reagent-O-Au(I)-P-(phosphane) coordination mode (X-ray analysis). Alkyne deprotonation gives rapid formation of protonated Togni Reagent and a σ,π-acetylide dual-Au complex, confirmed by X-ray analysis. It was shown that the σ,π-dual-Au complex activates for trifluoromethylation, most likely by transfer of a $[LAu]^+$ fragment to the alkyne substrate. The resulting reactive π-Au^+-alkyne intermediate probably undergoes O-/CF_3-addition of Togni Reagent, and final elimination of Togni alcohol gives the alkyne-CF_3 product.

1. Introduction

Important effects on biological activity have resulted in a dramatic increase in the interest for fluorinated drugs and precursors. Incorporation of fluorine into a molecule is known to give compounds with interesting and beneficial chemical and medicinal properties [1]. In particular, trifluoromethyl groups are strongly electron-withdrawing and may increase the lipophilicity and affect the metabolic properties of compounds [2]. Electrophilic fluorination is known to proceed by gold(I) catalyst/Selectfluor combinations. On the other hand, Selectfluor can also induce oxidative coupling of substituents on gold [3,4]. Such reactions are proposed to proceed via oxidation of the Au(I) complex by Selectfluor to give an active cationic Au(III)-F species. Final fluorodeauration or reductive elimination allows the formation of monofluorinated products [5,6]. Earlier work on homopropargyl acetals performed in the Fiksdahl group [7,8] demonstrates a one-pot pyrane cyclization-fluorination process, applying a combined Au(I)-Selectfluor system. In analogous ways as above, we envisioned that a trifluoromethyl moiety could be incorporated in relevant substrates by combining gold catalysis with an electrophilic source of trifluoromethyl.

Togni's trifluoromethylating reagents (Scheme 1) are convenient and stable sources of electrophilic trifluoromethyl groups [9], and are part of a larger group of hypervalent iodine reagents that have been used increasingly in a variety of syntheses [10]. Among the many applications of these reagents are *O*-, *N*-, *P*- and *S*-trifluoromethylations and trifluoromethylations of aryl, saturated and unsaturated compounds. The reactions can be acid-, base-, and/or transition metal-catalysed [10]. The present investigation of Au-generated electrophilic trifluoromethylation of terminal alkynes was inspired by the fact that, to the best of our knowledge, no reactions applying a Au(I) catalyst-Togni reagent combination has been reported. We wanted to study two possible outcomes for the incorporation of a trifluoromethyl group in alkynes with Togni's reagent 1 in the presence of gold(I) catalyst. Firstly, gold-catalysed addition of OMe/CF_3 to the alkyne bond in MeOH could give the MeO-vinyl-CF_3 product **2"** (Scheme 1). Moreover, trifluoromethyl could be incorporated in the terminal alkyne position to give CF_3-alkynes **5** (Schemes 2 and 3) in the absence of MeOH or other nucleophiles. The studies are reported below.

2. Results and discussion

2.1. Formation of Au(I) – Togni reagent complex *II*

In order to prepare vinyl-CF_3-products (**2"**, **3"** and/or **4"**, Scheme 1a) by alkyne trifluoromethylation in methanol,

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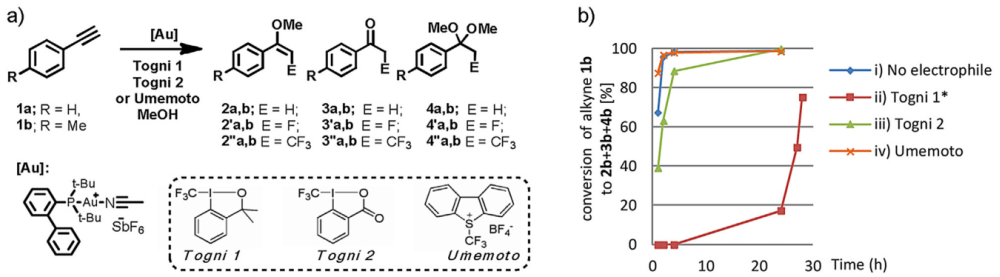


Scheme 1. a) Au(I)-catalysed electrophilic addition to phenylalkynes. b) Au(I)-catalysed conversion of alkyne **1b** at r.t. into products **2b**, **3b** and **4b** in MeOH in the absence (i) or presence (ii-iv) of trifluoromethylating agents (GLC). *) Reaction ii) was heated at 70 °C for 2 h after 26 h at r.t.

phenylacetylenes (**1a**,**b**) were subjected to introductory studies at room temperature with JohnPhos-Au(I) catalyst and Togni's 1, 2 and Umemoto's [11,12] reagents, respectively. These conditions are related to those presented (methanol/Selectfluor) by Nevado et al. [6] for gold-catalysed electrophilic fluorination of alkynes to give corresponding mono-fluoro products **2′**, **3′** and **4′**. The attempted trifluoromethylation reactions were monitored by GLC (see Supplementary data). The reactions did not give the trifluoromethylated products (**2"**, **3"**, **4"**), and only the non-trifluoromethylated products **2**, **3** and **4** were observed from the addition of methanol over the triple bond, both in the absence and presence of trifluoromethylating agents (Scheme 1b). However, it became apparent that the presence of Togni 1 reagent (Scheme 1b, ii) slowed down the reaction significantly, compared to the full conversion observed in the reference reaction with no electrophile added (Scheme 1b, i). Also, quantitative conversions into products **2**, **3** and **4** were obtained in the reactions with Togni 2 and Umemoto's reagents (Scheme 1b, iii, iv). The Togni 1 reagent reaction (ii) gave only 17% conversion into products **2**, **3** and **4** after 26 h at room temperature. However, upon heating at 70 °C for 2 h, the reaction rate increased dramatically and 75% conversion was obtained, indicating that the catalyst is reversibly deactivated or that a new catalytically active Au complex is formed at higher temperatures.

Investigation of the interactions between the Au catalyst and Togni 1 reagent ("Togni Reagent") was carried out by a series of experiments studied by NMR, which indicated that an acetonitrile ligand displacement and Au(I) coordination of Togni Reagent took place immediately. The Au-Togni Reagent interaction was observed by ^{1}H and ^{19}F NMR by preparation of a 1:1 mixture of these compounds in $CDCl_3$ (Fig. 1a and b). It was seen that the ^{1}H NMR signal for the Au(I)-MeCN ligand (2.42 ppm, Fig. 1a, ii) shifted to a broader signal at 2.20 ppm (Fig. 1a, iii), in the 1:1 mixture. This indicates ligand exchange to give the non-ligated "free" acetonitrile. Furthermore, the observed shift of the ^{19}F NMR CF_3-Togni Reagent signal from −40.1 ppm to −31.2 ppm (Fig. 1b, i, ii) indicated an interaction between the Au catalyst and Togni Reagent. Minor ^{1}H NMR shifts of the methyl groups in the Togni Reagent (1.48 ppm to 1.50 ppm; Fig. 1a, i, iii) and the *t*-butyl groups of the gold ligand (1.42 ppm to 1.43 ppm) were also seen. This led us to believe that a new Au-Togni Reagent complex was formed by MeCN/Togni Reagent ligand replacement.

A similar, but weaker interaction, was observed for Togni 2 reagent, probably due to the lower electron density of the ester oxygen than the alkoxy-oxygen in Togni 1 reagent. No interaction was observed in the case of Umemoto's reagent. The observed Au-Togni Reagent interaction provides an explanation for the difference in the rates of reaction seen in Scheme 1b, as a Au-Togni Reagent complex would be less catalytically active than the

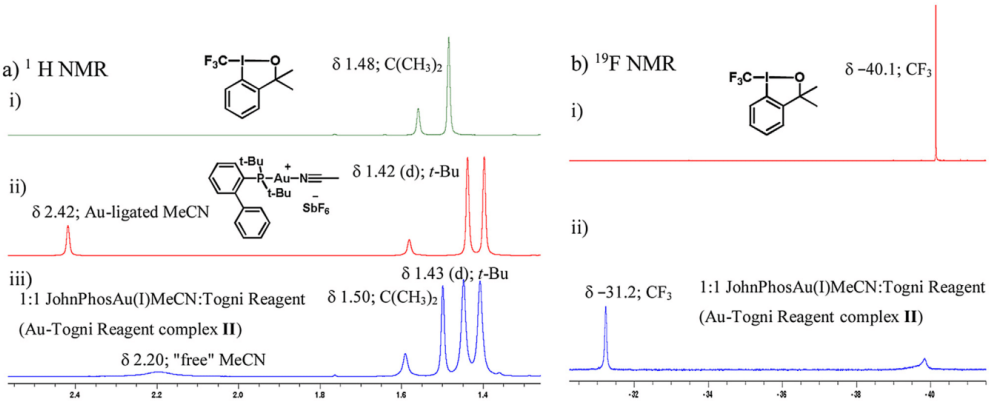


Fig. 1. a) ^{1}H NMR of i) Togni Reagent; ii) JohnPhosAu(I)-MeCN; iii) formation of Au-Togni Reagent complex **II**, registered 15 min after preparation of the 1:1 Au-Togni Reagent mixture; b) ^{19}F NMR of i) Togni Reagent; ii) formation of Au-Togni Reagent complex **II** (after 15 min).

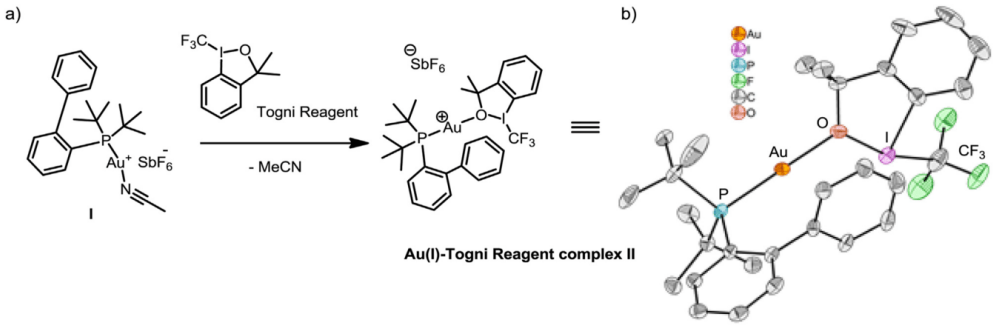


Fig. 2. Au(I)-Togni Reagent complex **II**; a) formation from JohnPhos-Au(I)-MeCN **I** and Togni Reagent; b) X-ray structure analysis.

Table 1
Relationships between Togni Reagent I-O and I-CF_3 bond lengths (X-ray) and CF_3 shift values (^{19}F NMR).

	I-O bond length	I-CF_3 bond length	^{19}F NMR, CF_3
a) Togni 1 Reagent [14]	2.118 Å	2.267 Å	−40.1 ppm
b) Protonated Togni 1 Reagent [10]	2.440 Å	2.214 Å	−20 ppm
c) Au-Togni Reagent complex **II**	2.281 Å	2.219 Å	−31.2 ppm

original catalyst. It was also observed that a weakly coordinating counterion, such as SbF_6, in the gold catalyst was important, as mixtures of JohnPhosAuCl or (Ph_3P)AuCl with Togni Reagent did not show any coordination.

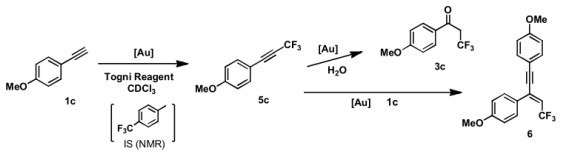
X-ray analysis of crystalline Au(I)-Togni Reagent complex **II**, obtained from an equimolar mixture of JohnPhos-Au(I)-MeCN **I** and Togni Reagent from DCM/diethyl ether (Fig. 2a), revealed for the first time O-binding of Togni Reagent to the Au(I) centre (Fig. 2b). The linear Togni Reagent-*O-Au(I)-P*-(phosphane) coordination mode is clearly verified. NMR spectra of the crystalline complex **II** were identical to NMR of 1:1 mixtures of gold(I)-Togni Reagent in solution, discussed above (Fig. 1a, iii) and 1b, ii)). To the best of our knowledge, previous evidence of metal coordination with Togni reagents is limited to Zn interactions [9,13].

It has previously been proposed [10] that O-protonation of Togni Reagent reagent weakens, lengthens and polarises the iodine-oxygen bond and activates the CF_3 moiety. Thus, a coordination site on the iodine atom may become accessible, allowing nucleophilic addition of a heteroatom X to the iodine atom. Subsequent reductive elimination would give the X-CF_3 product and the "Togni alcohol" (**7**, Scheme 4). The interaction of Togni Reagent with JohnPhosAu(I) catalyst **I** is most likely more complex than activation with simple Brönsted acids, but some conclusions can be drawn from comparison of the crystal structure data of the Au-Togni Reagent complex **II** to that of protonated reagent. Table 1 shows the I-O and I-CF_3 bond lengths in the Togni Reagent (a), the protonated Togni Reagent (b) and the Au-Togni Reagent complex **II** (c). Activation of Togni Reagent by protonation has been explored with a strong acid ($BArF_{24}$-acid) and a crystal structure for protonated Togni Reagent is reported [10], showing that protonation does indeed weaken and lengthen the I-O bond (from 2.118 Å to 2.440 Å; Table 1a,b) and shortens the I-CF_3 bond (from 2.267 Å to 2.214 Å), compared with data of the Togni Reagent [14]. Data for the Au(I)-Togni Reagent complex **II** (c) shows similarly that Togni Reagent coordination to the gold centre also shortens the I-CF_3 bond. The lengthening of the O-I bond length is less than by protonation. In accordance, ^{19}F NMR shift values indicate that the Togni Reagent-CF_3 group becomes less shielded by complexation, although this effect is less significant for the Au (I)-Togni Reagent complex **II** (c) than by protonation (b).

Overall, JohnPhosAu(I)-MeCN **I** and Togni Reagent form a relatively stable Au(I)-Togni Reagent complex **II**, which is less active than the original Au(I) catalyst, thus, retarding the addition of MeOH over the alkyne triple bond (Scheme 1b ii).

2.2. Trifluoromethylation of terminal alkynes

As X-ray and NMR studies pointed to a CF_3 activating effect by Au(I) complexation of Togni Reagent, attempts on Au-catalysed activation of Togni Reagent for addition of CF_3/Nu to alkynes **1c** were carried out in aprotic reaction conditions (LiI in acetone-d_6). However, no CF_3/I-incorporation took place, as shown by ^1H and ^{19}F NMR monitoring over several days. Nevertheless, minor amounts of alkyne-CF_3 **5c** (Scheme 2) were formed, also in the absence of LiI. Neither addition of an organic base nor water affected the reaction. In contrast to Cu-catalysed electrophilic trifluoromethylation of terminal alkynes with Togni Reagent [15], corresponding reactions with alkyne and Togni Reagent in the presence of a Au(I) catalyst have, to the best of our knowledge, not previously been described. Based on these initial results of Au generated electrophilic trifluoromethylation of terminal alkyne, quantification and optimization experiments were carried out with alkyne **1c**, JohnPhosAu(MeCN) and Togni Reagent (Scheme 2). The relative amounts of gold, alkyne and Togni Reagent were varied, as well as catalyst counterion, reaction temperature, time and concentration (entries 1–30). Also, the addition of acids or organic bases was tested (entries 31, 32). The alkyne-CF_3 **5c** was formed as the main product, but also the alkyne-alkene-CF_3 product **6** and small amounts of the α-CF_3-ketone product **3c** were observed. Ketone **3c** [16] may be formed by Au- or acid-catalysed hydration of the alkyne-CF_3 product **5c** [17,18]. The presence of water is caused by elimination of the "Togni alcohol" (**7**, Scheme 4) which is produced in the trifluoromethylation reaction, affording "Togni-alkene" **8**. Reactions being allowed to run for longer time after maximum yields had been achieved (at r.t. or 50 °C), showed that the alkyne-CF_3 product **5c** was converted into ketone-CF_3 **3c**. The formation of the alkyne-alkene-CF_3 product **6** may be



Amounts of reactants (eq)				Conditions			Yield [%][a]			
Entry	Au	Togni Reagent	**1c**	T (° C)	time (h)	[alkyne] (approx.. mM)	**5c**	**6**	**3c**	Total
1	2	1	**1**	r.t.	120	26	0	0	0	0[b]
2	1	1	**1**	r.t.	16	26	16	1	1	18
3	0.5	1	**1**	r.t.	16	26	29	3	0	32
4	0.5	1	**1**	r.t.	24	25	24	4	3	31[c]
5	0.25	1	**1**	r.t.	24	26	24	3	1	29
6	0.5	2	**1**	r.t.	8	26	33	3	1	36
7	0.5	3	**1**	r.t.	16	25	31	2	0	34
8	0.5	2	**1**	0	24	25	0	0	0	0
9	0.5	2	**1**	50	2	26	32	3	3	38
10	0.5	2	**1**	80	2	26	21	5	-[d]	26
11	0.5[e]	2	**1**	50	2	26	32	3	-[d]	35[e]
12	0.5[f]	2	**1**	50	2	26	15	3	-[d]	18[f]
13	0.5[g]	2	**1**	50	2	26	13	3	2	18[g]
14	0.5[h]	2	**1**	50	2	21	0	0	0	0[h]
15	0.5	1	**1**	50	2	26	26	3	-[d]	30
16	0.5	3	**1**	50	2	26	28	4	-[d]	32
17	0.05	2	**1**	50	2	26	0	5	-[d]	5
18	0.25	2	**1**	50	2	26	23	4	-[d]	27
19	1	**1**	4	50	2	52	15	9	6	30
20	1	**2**	4	50	2	52	24	7	4	35
21	1 (0.25)	**4** (**1**)	4 (1)	50	2	52	27	5	3	35
22	1 (0.10)	**10** (**1**)	10 (1)	50	2	52	15	7	1	22
23	0.25	**1**	2.5	50	2	134	24	15	2	41
24	0.25	**1**	2.5	r.t.	24	115	25	17	3	46
25	0.25	**1**	5	50	2	70	12	19	3	34
26	0.25	**1**	10	50	2	187	8	23	2	33
27	0.25	**1**	1	r.t.	16	52	30	5	1	37
28	0.25	**1**	1	r.t.	4	97	36	5	1	42
29	0.25	**1**	1	r.t.	8	222	32	6	1	38
30	0.25	**1**	1	50	2	119	29	5	3	36
31	0.25	**1**	0.12+1	r.t.	72	52	11	8	0	19[i]
32[j]	0	**1**	1	r.t.	2	0	0	0	0	0

a) Reaction conditions; JohnPhosAu(I)(MeCN)SbF_6 **I** and Togni Reagent were dissolved in $CDCl_3$ in an NMR tube. Alkyne **1c** and internal standard (4-CF_3-toluene) in $CDCl_3$ were added to the NMR tube. The reaction was left at the appropriate temperature and the reaction mixture was analysed by NMR. The reported yields are based on the amounts of the limiting reagent, indicated by bold font; b) Dual gold complex **III** was generated immediately; c) 1 eq $HSbF_6$ was added; d) product **3c** could not be seen by ^{1}H NMR; e) Au = JohnPhosAuSbF_6; f) Au = JohnPhosAu(NTf_2); g) Au = JohnPhosAuBArF; h) 1.6 eq DBU added; i) 0.12 eq DBU+alkyne **1c** was added to the Au-Togni Reagent mixture, then 1 eq alkyne and IS added; j) reactions were carried out in the presence of either acids ($HSbF_6$ or TFA) or bases (DBU or BuLi.; 1 eq); no gold catalyst was added.

Scheme 2. Studies on alkyne trifluoromethylation.[a,]

explained by Au-catalysed addition of alkyne **1c** over the alkyne-CF_3 **5c** triple bond. The *cis* configuration of alkene **6** is assigned from the absence of NOE ^{1}H NMR correlations between the vinyl proton and the vinyl-aromatic protons. The formation of the trifluoromethylated products **5c**, **3c** and **6** was analysed by ^{1}H and ^{19}F NMR.

By initial variation of the amount of Au catalyst, it was observed that, relative to a 1:1:1 mixture of Au:Togni Reagent:alkyne **1c**, which gave 16% alkyne-CF_3 **5c** (Scheme 2, entry 2), the yields increased by reducing the amount of Au catalyst. Maximum yields were obtained with 0.5:1:1 or 0.25:1:1 mixtures of Au:Togni Reagent:alkyne (up to 29% alkyne-CF_3 **5c** and 32% total yield of **5c**, **6** and **3c** in 16–24 h; entries 3, 5). Two eq of Au catalyst (entry 1) gave no CF_3-products, as immediate generation of the dual gold complex **III** took place (Section 2.3 below), thereby deactivating for the desired transformation by trapping the alkyne substrate **1c**. The fully protonated Togni Reagent was also observed (^{19}F NMR), as discussed below (Scheme 4). Activation of Togni Reagent by addition of $HSbF_6$ (1 eq generated in situ from *tert*-BuCl and $AgSbF_6$, entry 4) gave no increase in the yield. Based on the most efficient Au:Togni Reagent:alkyne (0.5:1:1) reaction conditions (entry 3), the amount of Togni Reagent was increased. The use of 2-3 eq of Togni Reagent speeded up the reaction and slightly increased the yields (up to 33% alkyne-CF_3 **5c** and 36% total yield in 8 h; entries 6, 7). No increase in yields was obtained by varying the reaction temperature. Lower temperature gave no reaction (0 °C, 24 h, entry 8), while reaction at 50 °C reduced the reaction time significantly (32% of **5c** in 2 h, entry 9). Further heating to 80 °C, conducted in a sealed vessel, gave lower yield (21% of **5c** in 2 h, entry 10). The non-MeCN-ligated catalyst (entry 11) gave similar results to the original JohnPhosAuSbF_6-MeCN catalyst (entry 9). The nature of the counter-ion is essential for Au(I) catalyst activity and selectivity. By varying the Au(I) catalyst counter-ion in reactions at 50 °C (as in entry 9), a negative effect was observed for the more weakly coordinating anions, as only 13–15% of product **5c** was obtained with JohnPhosAuNTf_2 and AuBArF (entries 12, 13), afforded by treatment of JohnPhosAuCl with, respectively, $AgNTf_2$ and NaBArF, followed by filtration into the reaction tube. The addition of base (DBU, 1.6 eq, entry 14) was thought to assist the reaction by alkyne deprotonation, but might rather have neutralised the activated Togni Reagent, as the reaction gave no products (GLC). Based on the reaction conditions in entry 9,

it was shown that changing the amount of Togni Reagent (1 and 3 eq, entries 15, 16) did not affect the outcome of the reaction. However decreasing the amount of gold (0.25–0.05 eq, entries 17, 18) gave a corresponding decrease in total yields of CF_3 products. Hence it seemed like the Au complex was consumed stoichiometrically.

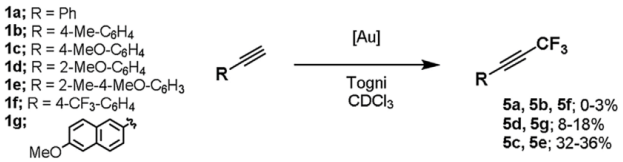
In further experiments, the ratio of alkyne relative to Togni Reagent was tested (entries 19–21) and the limiting Togni Reagent was used to calculate product yields. The Au:alkyne ratio was kept at 0.25:1 (1:4 as in entry 18), and the amount of Togni Reagent was varied (1–4 eq,). Highest total yields of CF_3-products were obtained with excess Togni Reagent (2–4 eq) relative to Au (entries 20, 21). Most interestingly, the results proved that the Au(I) complex promoted alkyne trifluoromethylation with Togni Reagent in a catalytic manner, as the total yields of CF_3 products were higher (up to 35%, entry 21) than the sub-stoichiometric amounts of Au (25% Au). A further decrease in the relative amount of gold (10%, entry 22) gave lower yield with respect to Togni Reagent and alkyne substrates, but showed higher catalytic effect and more than two-fold yield with respect to gold (22% total yield of CF_3 products). Based on the reaction conditions in entry 21, it was shown that excess of alkyne (2.5–10 eq, entries 23–26), shifted the selectivity of the reaction away from alkyne-CF_3 **5c**, towards the alkyne-alkene-CF_3 product **6**. This appears to be rational, given that two units of alkyne are incorporated in product **6**. Nevertheless, the obtained total yields with 25% Au were raised to 46% at room temperature (entry 24). Based on the reactant ratio in entry 21, higher yields were obtained by increasing the reaction concentration (entries 27–30). Highest yield was obtained at 97 mM of alkyne **1c** at room temperature (36% alkyne-CF_3 **5c**, total yield 42%, 4 h, entry 28). The potential effect of a base additive was tested (entry 31). The addition of alkyne and DBU (0.12 eq of each) to a mixture of the Au (25%) and Togni Reagent (1eq) caused immediate formation of dual-gold complex **III** (Section 2.3) and non-protonated Togni Reagent (^{1}H and ^{19}F NMR). Interestingly, when the remaining 1 eq alkyne was added, the reaction still generated CF_3 products (19% in total), indicating that the dual-Au complex **III** is capable of activating for the trifluoromethylation reaction. Finally, the fact that the alkyne trifluoromethylation reaction was promoted by gold, was supported by the unsuccessful reactions of alkyne and Togni Reagent without Au catalyst, but in the presence of acids or bases ($HSbF_6$, TFA, DBU (1 eq) or BuLi (1 eq), entry 32).

Thus, the screening of reaction conditions showed that highest yields of the alkyne-CF_3 target product **5c** were obtained from a 0.25:1:1 mixture of Au:Togni Reagent:alkyne (97 mM) at room temperature (entry 28) or, alternatively, from a 0.5:2:1 mixture of Au:Togni Reagent:alkyne (26 mM) at 50 °C (entry 9). Comparative studies of other aryl-alkyne substrates (**1a,b, 1d-g**) showed that the success of the trifluoromethylation method was highly dependent on the aryl-alkyne **1** electron-density, as only the activated 4-MeO-phenylalkynes **1c** and **1e** were reasonably reactive (Scheme 3).

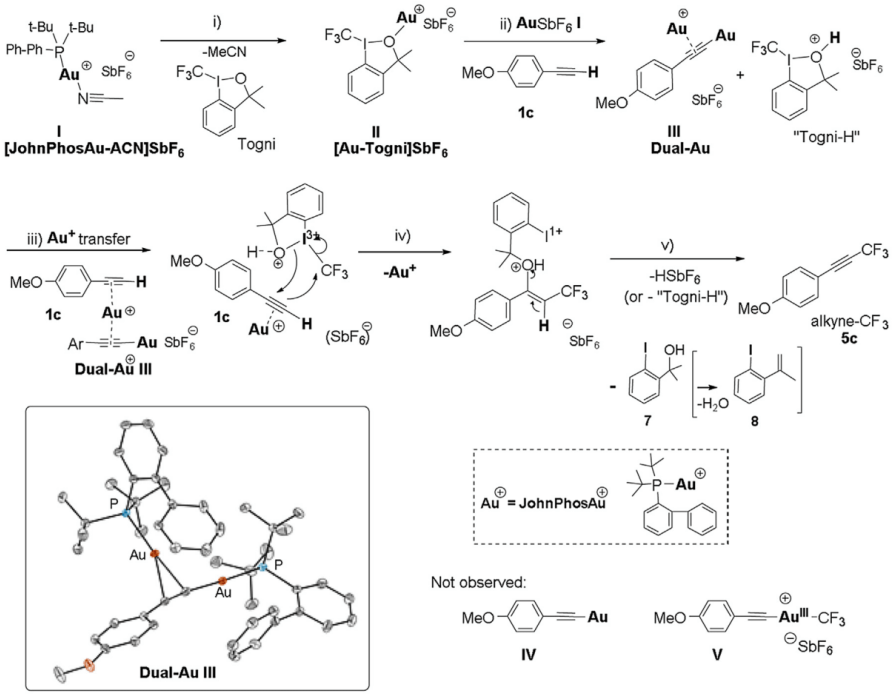
2.3. Proposed mechanism

Attempts to experimentally prove the Au-catalysed trifluoromethylation reaction mechanism with Togni Reagent were made [19]. Previous studies of reactions with Togni reagents[10] have mainly focused on transformations with Togni reagents, based on different activating reagents and catalysts. A proposed reaction mechanism is presented below and the supporting experimental evidences are discussed (Scheme 4 and Fig. 2).

In all the reactions above (Schemes 2 and 3) it seems that the JohnPhosAu catalyst **I** and Togni Reagent immediately generate Au-Togni Reagent complex **II** (Fig. 1 and Scheme 4, step i). ^{19}F NMR studies of arylalkyne **1c** support this hypothesis, as ^{19}F NMR shift of Togni Reagent $-CF_3$ (originally at −40.1 ppm, Fig. 3a) was seen at −31.2 ppm for Au-Togni Reagent complex **II** (Fig. 3a step i). The activated Au-Togni Reagent **II** is stable at r.t. for several days, but gradually decomposes into the original Au catalyst **I** and Togni Reagent by-products over some weeks. A new complex **III** was immediately formed after the addition of alkyne **1c** to the mixtures of JohnPhosAuMeCN-Togni Reagent (Scheme 4, step ii), as shown by ^{1}H NMR (MeO signal shifts from 3.81 to 3.90 ppm; Fig. 3b, step ii). The formation of complex **III** also generates the protonated activated "Togni-H" by deprotonation of alkyne **1c**, as shown by the change of ^{19}F NMR shifts for Togni Reagent-CF_3 to −37.6 ppm (Fig. 3a step ii). As the CF_3 of fully protonated "Togni-H", prepared with excess Au (Table, entry 1), gave ^{19}F NMR shift at −22 ppm (visible in Fig. 3a, step v), it is proposed that the NMR shifts at −37.6 ppm arose from partial protonation of Togni Reagent, due to limited amount of acid (0.125 eq) generated from conversion of 0.25 eq JohnPhosAu **I** into dual-Au complex **III** (Scheme 4b, step ii). This is in accordance with results from titration of Togni Reagent with superacid (^{19}F NMR approx. −37 ppm) [10,14]. With twice excess of Au **I**, no CF_3 products were formed, as only gold complex **III** immediately was generated (Scheme 2, entry 1). Isolation of the crystalline complex allowed full characterization (NMR, HRMS and X-ray) and revealed the structure of the σ,π-dual-Au complex **III** (Scheme 4). The complex is relatively stable in solution, but decomposes over time, possibly to gold nanoparticles, when left in the reaction mixture in the presence of the generated $HSbF_6$. It is also significantly less stable when subjected to silica chromatography. This kind of dual-Au complex has previously been reported with phosphine [20] or NHC-ligands [21], and they are shown to be catalytically active for a limited number of reactions [20,22–24]. It has previously been reported [20,21] that the generation of dual-Au complexes similar to **III**, goes through metal-π coordination of Au – alkyne triple bond, switching to a metal-σ-coordination of the Au centre. The σ-complex then undergoes metal-π coordination with a second Au unit to give the dual-Au complex **III** [21]. The coordination of the second $[LAu]^+$ fragment to the gold acetylide complex is thermodynamically favoured over a coordination of the same [LAu]+ fragment to the corresponding non-aurated alkyne [25]. These transformations occur very fast, even at sub-zero temperatures. This is in accordance with the lack of observable intermediate complexes in the present investigation. Although the



Scheme 3. Au(I)-promoted trifluoromethylation studies on arylalkynes (performed as in Scheme 2, entries 9 or 28).



Scheme 4. Proposed mechanism for Au(I)-promoted trifluoromethylation of alkyne **1c**, incl. X-ray structure analysis of dual-Au **III**.

crystal structure of complex **III** showed π,σ-alkyne coordination of the dual-Au complex, ^{13}C NMR studies revealed that the two Au atoms are interchangeable in solution, as both alkyne carbons (118.6 ppm, J = 11.5 Hz and 124.6 ppm, 68.5 Hz) appear as triplets, due to coupling to the two equivalent phosphorous atoms, in accordance with earlier reports for dual-Au complexes[20] and for related heterobimetallic gold-platinum alkyne complexes [26].

Based on the fact that the dual-Au complex **III** was immediately formed by addition of alkyne **1c**, it seemed likely that the alkyne trifluoromethylation (Scheme 4, steps iii–v) was activated by the dual-Au complex **III**. Previous computational studies have described similar σ,π-dual-(NHC-)gold complexes as a thermodynamic sink for $[LAu]^+$ species, as both $[LAu]^+$ units prefer to be on the same alkyne group. There is a low barrier for the π-bonded $[LAu]^+$ to interact with and transfer to a second alkyne to give a more reactive complex [25]. Hence, dual-gold **III** may act as a resting state for the catalyst by transferring the $[JohnPhos-Au]^+$ to another unit of alkyne **1c** to give a reactive $[JohnPhos-Au]^+$-**1c** π-intermediate (Scheme 4, step iii). The present alkyne activation mechanism represents a rare intermolecular case of dual-gold as a transfer reagent. Most reported reactions apply the dual-gold transfer concept in cyclization reactions, involving an almost equal intramolecular interaction of the cationic gold between two alkynes of di-yne substrates. [17] The generation of CF_3 products (**5c**, **6**, **3c**) occurred over time, as shown by NMR (Fig. 3a,b, step v). The transformation is believed to proceed through an addition-elimination process (Scheme 4, steps iv-v). The O-/CF_3-addition to the activated **1c**-Au^+ triple bond may take place in a concerted or stepwise manner, including iodine(III)-reduction and de-auration. The resulting CF_3-vinyl-ether intermediate undergoes final elimination of the "Togni alcohol" **7** and regains the alkyne triple bond to give the alkyne-CF_3 product **5c**.

^{1}H and ^{19}F NMR studies of other arylalkynes (**1a,b, 1d-g**, Supplementary data, Table 3) showed the formation of corresponding dual-Au complexes **III**. Since alkyne-CF_3 products were not observed in all cases (Scheme 3), not all dual-Au manage to activate the trifluoromethylation reaction by $[LAu]^+$ transfer, or not all alkynes **1a-g** are able to act as an effective substrate. The proposed complexes **III** from alkynes **1a,b** and **1d-g** were not isolated, but the results indicate that isolation could be possible, e.g. in order to test the reactivity of the different complexes.

In contrast to JohnPhosAuMeCN **I**, the isolated dual-gold complex **III** did not give any coordination or reaction with Togni Reagent (or acid-activated Togni Reagent, ^{1}H and ^{19}F NMR). Hence, it was concluded that the dual Au complex **III** was neither activating Togni Reagent, nor a reactive intermediate towards the CF_3 products. It was also observed (Scheme 2, entry 31) that even when the acid generated from the formation of dual-gold **III** was neutralised with DBU, the reaction still took place, albeit slower and with lower total yields. It was thus concluded that the acid assists the conversion, but is not essential for the reaction.

Additional mechanistic experiments (Scheme 5), included selective stepwise preparation of dual-Au complex **IIIc** (0.125 eq from Togni Reagent, Au(I) **I** and alkyne **1c**, Scheme 4, steps i-ii), followed by addition of alkyne **1e** (0.875 eq, steps iii-v). The reactions showed conversion into only CF_3 product **5e** (37%), as this procedure allow selective formation of dual-Au complex **IIIc** and CF_3-product **5e**, respectively. Only trace amounts of **1c** and other CF_3 products were seen. Similar amounts of CF_3 product **5e** (32%) were formed with the original method using only alkyne **1e**. These

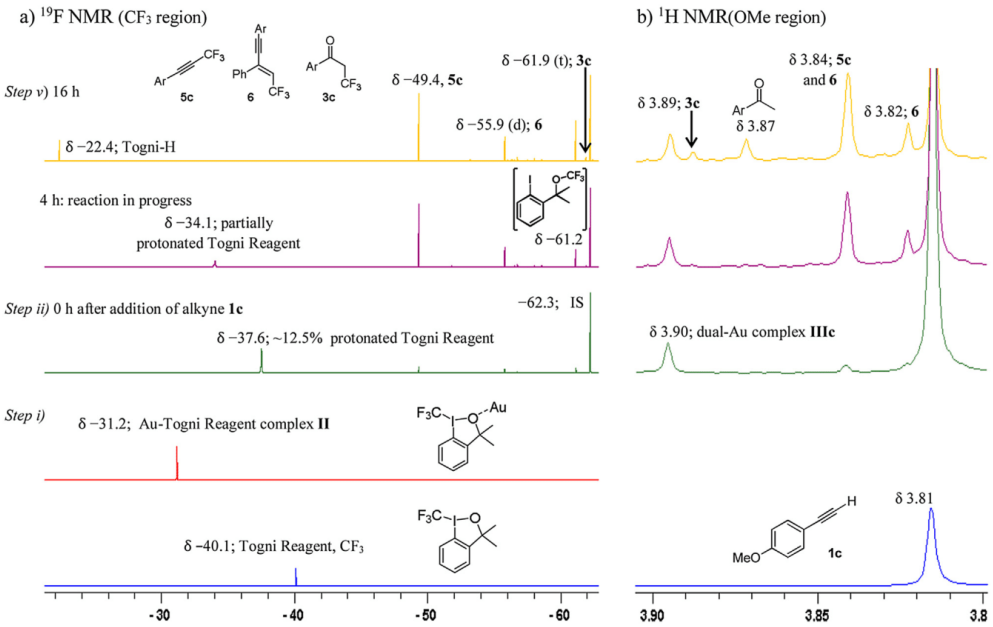
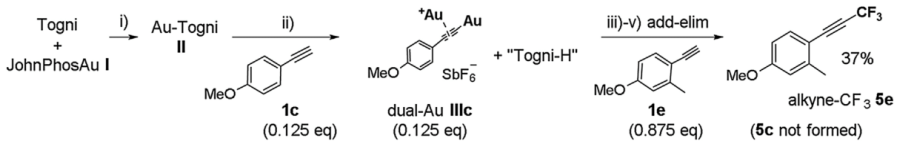


Fig. 3. Selected ^{19}F and ^{1}H NMR spectra, following the trifluoromethylation reaction progress (Scheme 4, steps i-v; reaction conditions shown in Scheme 2, entry 24), as shown by respectively CF_3 and MeO-alkyne **1c** signal from dual-Au complex **IIIc**, and products **5c**,**6** and **3c**.



Scheme 5. Selective transformation of alkynes **1c** and **1e** into, respectively, dual-Au **IIIc** and **5e**.

results show that acetylide (**1c**), incorporated in the initially formed dual-Au **IIIc**, was not converted into CF_3 products, but only acted as a transfer agent in trifluoromethylation of the different alkyne **1e** to selectively give CF_3 product **5e**. The "real" Au catalytic loading is hence only 14%. In general, the present reaction via intermediate formation of dual-Au complex **IIIc** and Togni-H, does not enable further alkyne **1e** deprotonation, and thus, allow selective triple bond activation of alkyne **1e**, which seems to be crucial for the success of the present trifluoromethylation method.

In order to exclude the possibility that a Au-acetylide complex was involved in the reaction, the Au-acetylide complex **IV** was prepared (from the JohnPhosAuCl and alkyne **1c** in the presence of base) and mixed with non-activated or activated Togni Reagent (TFA, $HNTf_2$, $HSbF_6$ or Au complex **II**). No product was formed in these reactions, indicating that Au-acetylide **IV** was not acting as an acetylide nucleophilic species by attacking the CF_3-Togni Reagent to yield the alkyne-CF_3 product **5c**.

Another theory included a possible generation of a CF_3-Au(III)-acetylide intermediate **V**, which would give the CF_3- product by reductive elimination in analogy with the Au-Selectfluor reaction pathways [5]. It was hypothesised that a potential gold(III) complex **V** would be observed in experiments at low temperature, where no products were supposed to be formed (Scheme 2, entry 8). As identification of Au(III)-F intermediates, formed in Au-Selectfluor reactions, has previously been made by ^{19}F NMR [5], possible Au(III)-CF_3 intermediates would potentially be seen in the Au-Togni Reagent reaction. NMR experiments (^{1}H, ^{13}C, ^{19}F and ^{31}P) were carried out on a 1:4:4 mixture of Au:Togni Reagent:alkyne **1b** at −20 °C. Careful integration and comparison with spectra of relevant compounds (complexes **I**, **II** and **III**, alkyne **1b**, Togni Reagent and Togni-H) confirmed that the reaction mixture only contained dual-Au complex **III**, partially protonated Togni Reagent and alkyne **1c**, which indicated that a possible Au(III)-CF_3 complex **V** is not involved in the reaction.

3. Conclusion

The interaction of a Au(I) catalyst (JohnPhos-Au(I)-MeCN/SbF_6) and the Togni's reagent 1, as a source of electrophilic trifluoromethyl group, has been studied in order to develop gold-catalysed alkyne trifluoromethylation reactions. ^{1}H, ^{13}C, ^{19}F and ^{31}P

NMR studies were essential in this work. We have developed a simple experimental procedure for trifluoromethylation of terminal arylalkynes (1 eq) with Togni Reagent (1 eq) in the presence of sub-stoichiometric amounts of the JohnPhosAuI-MeCN catalyst (25%) to give alkyne-CF_3 product (3,3,3-trifluoroprop-1-yn-1-yl) benzene, **5c**). Although the yields are low, the total amounts of CF_3-alkyne products (up to 46%) are higher than the Au(I) catalyst loading. This indicates that the JohnPhosAu(I) complex promotes alkyne trifluoromethylation with Togni Reagent in a catalytic manner. Future catalyst or substrate optimizations may provide possibilities to increase the yields. The analogous Cu-catalysed method [15] requires 20% CuI and 1:1.5:0.4:0.4 alkyne:Togni Reagent:phenantroline:$KHCO_3$ as well as syringe pump addition of alkyne, to give 70–98% yields.

The proposed addition-elimination reaction mechanism is based on immediate generation of Au-Togni Reagent complex **II** from the JohnPhosAu complex **I** and Togni Reagent. Alkyne deprotonation takes place by subsequent addition of alkyne **1c** to give rapid formation of a σ,π-dual-Au complex **III** and "Togni-H". It is believed that the alkyne trifluoromethylation step is activated by $[LAu]^+$ transfer from dual-Au **III** to a new unit of alkyne **1c**. The triple bond activation allows O-/CF_3-addition of Togni-H" to the alkyne. This step proceeds through iodine-reduction by cleavage of the I-CF_3 and I-O bonds and de-auration. Finally, the CF_3-vinyl-ether intermediate regains the alkyne triple bond to give the alkyne-CF_3 product **5c** by elimination of "Togni alcohol".

Three new Au(I) complexes, gold-Togni Reagent complex **II**, dual-gold complex **III** and gold-acetylide complex **IV** were generated and characterised in the course of the studies. The JohnPhosAu-MeCN catalyst **I** and Togni Reagent rapidly interact to form the relatively stable Au-Togni complex **II** by ligand exchange of the acetonitrile ligand with the Togni Reagent molecule. Complex **II** is less active than the original Au(I) catalyst **I**, e.g. retarding the addition of MeOH over alkyne triple bonds. X-ray analysis of the Au-Togni Reagent complex **II** confirmed the linear Togni Reagent-*O-Au(I)-P-*(phosphane) coordination mode by O-binding of the Togni Reagent oxygen to the gold(I) centre. The structure of the dual-gold complex **III**, proposed to be the $[LAu]^+$ transfer reagent in the trifluoromethylation reaction after immediate formation from Au(I) and alkyne **1c**, was confirmed by X-ray analysis.

In summary, the present study on gold-catalysed electrophilic alkyne trifluoromethylation has contributed to the complex picture of gold catalysis and introduced the use of hypervalent iodine reagents into this field.

4. Experimental

4.1. General experimental procedures

Commercial grade reagents were used as received. Flash chromatography was carried out using silica gel 60 (0.040–0.063 mm) and analysed using thin-layer chromatography (TLC) with silica gel 60 F254 (0.25 mm thickness). Melting points (m.p.) were determined using a Stuart apparatus and are uncorrected. ^1H, ^{13}C, ^{19}F and ^{31}P NMR spectra were recorded using 400 MHz or 600 MHz spectrometer. Chemical shifts are reported in ppm (δ) downfield from tetramethylsilane for ^1H NMR (0 ppm), $CDCl_3$ for ^{13}C NMR (77.0 ppm), 1-methyl-4-(trifluoromethyl)benzene for ^{19}F NMR (−62.27 ppm) [27] and triphenylphosphine for ^{31}P NMR (−6.00 ppm) as internal standards. The PPh_3 standard was in a sealed tube to prevent interaction with the compounds, especially the gold complexes. Coupling constants (J) are reported in Hertz (Hz). The attributions of the chemical shifts were determined by means of COSY, HSQC, HMBC and NOESY NMR experiments. Accurate mass determination in positive and negative mode was performed on a "Synapt G2-S" Q-TOF instrument from Waters™. Samples were ionized by the use of ASAP probe (APCI) or ESI probe. No chromatographic separation was used previous to the mass analysis. Calculated exact mass and spectra processing was done by Waters™ Software Masslynx V4.1 SCN871. IR spectra were obtained using a Smart Endurance reflection cell. UV spectra were obtained using a Cary 60 UV–vis spectrophotometer from Agilent Technologies with accompanying fiber optic dip probe accessory. GLC analyses were carried out on a 7890A GC System from Agilent Technologies with a TR-5 column from Thermo Scientific. Single crystal X-ray data was acquired using a Bruker D8 Venture diffractometer with the APEX3 suit, integrated with SAINT V9.32B, solved with XT, and refined with XL using Olex2 as GUI. The cif files were edited with encipher v1.4, and molecular graphics were produced with Diamond v4.0. ORTEP plots are shown in the main document, and all metric data including reflection data are contained in the respective cif files. This data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html, or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK. Fax: +44 1223 336 033; or deposit@ccdc.cam.ac.uk.

4.2. General procedure for NMR experiments

The required amounts of (acetonitrile)[(2-biphenyl)di-*tert*-butylphosphine]gold(I) hexafluoroantimonate **I** and Togni Reagent (3,3-dimethyl-1-(trifluoromethyl)-1,2-benziodoxole) were weighed into an NMR tube and dissolved in a small amount of $CDCl_3$. The required amount of alkyne **1** and 1-methyl-4-(trifluoromethyl)benzene (internal standard, IS)[27] was dissolved in a small amount of $CDCl_3$ and added to the NMR tube. The NMR tube was then left at the appropriate temperature and the reaction mixtures analysed by NMR at the required times. Sometimes, stock solutions were used when several reactions were run in a short period.

For example, for (Scheme 2, entry 3): A stock solution of 1-ethynyl-4-methoxybenzene (**1c**, 20.9 mg, 0.158 mmol) and 1-methyl-4-(trifluoromethyl)benzene (IS, 23.2 mg, 0.145 mmol) was dissolved in 20 mL $CDCl_3$ using a volumetric flask. (Acetonitrile)[(2-biphenyl)di-*tert*-butylphosphine]gold(I) hexafluoroantimonate (**I,** 6.3 mg, 8.16 μmol) and Togni Reagent (5.7 mg, 0.017 mmol) were weighed into an NMR tube and dissolved in 0.2 mL $CDCl_3$, and 0.5 mL of the stock solution was added containing alkyne **1c** (2.09 mg, 0.0158 mmol) and internal standard (2.32 mg, 0.0145 mmol). The reaction mixture was analysed at 2, 4, 8, 16, 24, 36, 48, 60, 72, 96 and 120 h with ^1H and ^{19}F NMR, at 400 MHz and 376 MHz respectively.

All the trifluoromethylated alkyne products (**5a-g**) and 3,3,3-trifluoro-1-(4-methoxyphenyl)propan-1-one[16] (**3c**) reported in the present work have been reported earlier [28–31]. Identification was based on NMR spectra (^1H, ^{19}F and/or ^{13}C) and yields reported in Scheme 3 are calculated from a known amount of added IS. Novel compound alkene **6** is characterised below. Analogous alkene compounds for the other substrates were observed in only trace amounts under the reaction conditions used and therefore not isolated and no yields are reported.

(*E*)-4,4′-(5,5,5-Trifluoropent-3-en-1-yne-1,3-diyl)bis(methoxybenzene) (alkene-CF_3 **6**) was obtained using the general procedure for NMR experiments, with (acetonitrile)[(2-biphenyl)di-*tert*-butylphosphine]gold(I) hexafluoroantimonate (**I**, 5.8 mg, 7.5 μmol), Togni Reagent (10.8 mg, 0.0327 mmol) and 1-ethynyl-4-methoxybenzene (**1c**, 38.3 mg, 0.290 mmol) in $CDCl_3$ (0.5 mL). The mixture was heated at 50 °C for 2 h and the solvent was removed *in vacuo*. The crude mixture was purified using pipette chromatography with only pentane (note: not all of the crude mixture was soluble in pentane), giving the desired product, (*Z*)-

4,4′-(5,5,5-trifluoropent-3-en-1-yne-1,3-diyl)bis(methoxybenzene, **6**), as an off-white oil (1.5 mg, 15%): R_f = 0.15 (1:30 EtOAc:pentane); ^{1}H NMR (600 MHz, $CDCl_3$): δ ppm 7.48-7.45 (m, 2H, CH_{Ar}), 7.41-7.39 (m, 2H, CH_{Ar}), 6.93-6.90 (m, 2H, CH_{Ar}), 6.87-6.85 (m, 2H, CH_{Ar}), 6.09 (q, 1H, *J* = 8.9 Hz, $CHCF_3$), 3.84 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3); ^{13}C NMR (150 MHz, $CDCl_3$): δ ppm 160.34 ($\underline{C}OCH_3$), 160.32 ($\underline{C}OCH_3$), 134.8 (q, *J* = 6.6 Hz, $\underline{C}$=$CHCF_3$), 133.4 (2$\underline{C}$, CH_{Ar}), 129.9 (q, 2$\underline{C}$, *J* = 2.0 Hz, CH_{Ar}), 127.8 ($\underline{C}_{Ar}$), 122.7 (q, *J* = 269.9 Hz, CF_3), 120.5 (q, *J* = 34.2 Hz, $\underline{C}HCF_3$), 114.1 (2C, CH_{Ar}), 113.6 (2C, CH_{Ar}), 113.4 (q, *J* = 13.3 Hz, ≡C-$\underline{C}_{Ar}$), 94.2 (C≡$\underline{C}C_{Ar}$), 88.0 ($\underline{C}$≡CC_{Ar}), 55.33 (OCH_3), 55.29 (OCH_3); ^{19}F NMR (376 MHz, $CDCl_3$): δ ppm −55.81 (d, 3F, *J* = 8.4 Hz, CF_3); IR (film, cm^{-1}) 2953, 2919, 1602, 1509, 1252, 1134, 1033, 833, 555; HRMS (ESI), *m/z*: calcd for $C_{19}H_{16}O_2F_3$ $[M+H]^+$ 333.1102, found 333.1106.

4.3. Mechanistic experiments; stepwise reaction of alkynes **1c** and **1e** to allow selective formation of dual-Au complex **IIIc** and CF_3-product **5e**

4.3.1. Exp 1

*(Au:Togni Reagent:**1c** 0:25:1:1);* According to the General procedure, using gold catalyst **I** (5.1 mg, 6.6 μmol, 0.25 eq) and Togni Reagent (8.9 mg, 0.027 mmol, 1eq) in 0.2 mL $CDCl_3$, and alkyne **1e** (4.0 mg, 0.027 mmol, 1eq) and IS (2.9 mg, 0.018 mmol) in 0.4 mL $CDCl_3$. The mixture was monitored at r.t for 120 h with ^{1}H and ^{19}F NMR spectroscopy. Product **5e** was formed in 32% at 48 h ^{1}H and ^{19}F NMR data were in accordance with previous reports [30].

4.3.2. Exp 2

*(Au:Togni Reagent:**1c** 0:25:1:0.125) + (**1e** 0.875);* Gold catalyst **I** (11.7 mg, 0.015 mmol) and Togni Reagent (20.3 mg, 0.061 mmol) were dissolved in 0.1 mL $CDCl_3$ in an NMR tube and, after 10 min, alkyne **1b** (1.0 mg, 7.6 μmol) in 0.2 mL $CDCl_3$ was added and the mixture shaken. The mixture was allowed to react at r.t. for ca. 2 min and then alkyne **1e** (7.8 mg, 0.053 mmol) and IS (5.4 mg, 0.034 mmol) in 0.3 mL $CDCl_3$ was added. The mixture was monitored at r.t. with ^{1}H and ^{19}F NMR spectroscopy for 72 h. Product **5e** was formed in 37% (based on alkyne **1e**) at 16 h. Only trace amounts of other CF_3-products were observed.

4.3.3. Exp 3

*(Au:Togni Reagent:**1c** 0:25:0.125:0.125) + (Togni Reagent 0.875) + (**1e** 0.875);* Gold catalyst **I** (11.9 mg, 0.015 mmol) and Togni Reagent (2.6 mg, 7.88 μmol) were dissolved in 0.1 mL $CDCl_3$ and alkyne **1c** (1.03 mg, 7.79 μmol) in 0.1 mL $CDCl_3$ was added and shaken. The mixture was allowed to react for 10 min and then Togni Reagent (17.6 mg, 0.053 mmol) was added. The mixture was allowed to react for another 10 min and alkyne **1e** (8.7 mg, 0.060 mmol) and IS (5.4 mg, 0.034 mmol) in 0.3 mL $CDCl_3$ was added. The reaction was monitored with ^{1}H and ^{19}F NMR spectroscopy for 72 h. Product **5e** was formed in 37% (based on alkyne **1e**) at 16 h. Only trace amounts of other CF_3-products were observed.

4.4. Procedure for generation and isolation of Au-Togni reagent complex **II**

(Acetonitrile)[(2-biphenyl)di-*tert*-butylphosphine]gold(I) hexafluoroantimonate (**I**, 40.7 mg, 0.053 mmol) and Togni Reagent (3,3-dimethyl-1-(trifluoromethyl)-1,2-benziodoxole, 18.9 mg, 0.057 mmol) were weighed into a small vial and dissolved in DCM (400 μL). Crystals, suitable for X-ray diffraction, were obtained by slow diffusion of diethyl ether into this vial at −20 °C, giving the desired Au-Togni Reagent complex (**II**) as colourless needles (40.7 mg, 73%): mp 125.5-127.6 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ ppm 7.90-7.87 (m, 1H, CH_{Ar}), 7.63 (t, 1H, *J* = 7.3 Hz, CH_{Ar}), 7.61 (d, 1H, *J* = 8.5 Hz, CH_{Ar}), 7.57-7.53 (m,3H, CH_{Ar}), 7.47-7.45 (m, 3H, CH_{Ar}), 7.29-7.15 (m, 3H, CH_{Ar}), 1.51 (s, 6H, 2×$OC(CH_3)_2$), 1.44 (d, 18H, *J* = 16.0 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ ppm 149.2 (d, *J* = 11.9 Hz, C_{Ar}), 148.0 (br s, $\underline{C}CO$), 142.7 (d, *J* = 6.7 Hz, C_{Ar}), 133.4 (d, *J* = 7.7 Hz, CH_{Ar}), 133.2 (d, *J* = 3.8 Hz, CH_{Ar}), 131.8 (CH_{Ar}), 131.3 (CH_{Ar}), 131.2 (d, *J* = 2.3 Hz, CH_{Ar}), 129.9 (CH_{Ar}), 129.0 (CH_{Ar}), 128.7 (CH_{Ar}), 128.3 (br s, IC$\underline{C}$H), 128.1 (CH_{Ar}), 127.2 (d, *J* = 7.4 Hz, CH_{Ar}), 123.5 (d, *J* = 49.5 Hz, P$\underline{C}_{Ar}$), 107.90 (br s, CI), 106.1 (br q, *J* = 380.7 Hz, CF_3), 79.0 (CO), 38.3 (d, *J* = 27.6 Hz, $PC_{t\text{-}Bu}$), 32.8 (br s, $OC(\underline{C}H_3)_2$), 30.8 (d, *J* = 5.8 Hz, $CH_{3,\ t\text{-}Bu}$); ^{19}F NMR (376 MHz, $CDCl_3$): δ ppm −31.21 (3F, CF_3); ^{31}P NMR (162 MHz, $CDCl_3$): δ ppm 56.34 (AuP); IR (film, cm^{-1}) 2960, 2920, 1466, 1159, 1073, 913, 759, 727, 661; HRMS (ESI), *m/z*: calcd for $C_{30}H_{37}OF_3PIAu$ $[M]^+$ 825.1244, found 825.1259. X-ray data; CCDC ID: 1508694.

4.5. Procedure for generation and isolation of σ,π-dual-Au complex **III**

(Acetonitrile)[(2-biphenyl)di-*tert*-butylphosphine]gold(I) hexafluoroantimonate (**I**, 11.7 mg, 0.015 mmol) and potassium carbonate (2.1 mg, 0.015 mmol, note: base not strictly necessary but used in order to try to absorb the acid that could destroy the product) were weighed into a flask and 1 mL DCM was added. 1-*E*thynyl-4-methoxybenzene (**1c**, 5.5 mg, 0.042 mmol) in 1 mL DCM was added. The mixture rapidly became dark purple. The solvent was removed in vacuo and the residue was purified via pipette chromatography (1:2 acetone:pentane). The fractions containing the desired product were filled to the top with pentane (ca. 1/3 of the vial volume), corked and placed in the freezer. Long needles formed and the solvents were pipetted out and the crystals were washed with pentane to give the product **III** as long colourless needles (5.1 mg, 50%, note: this method also works with or without base to give crystals of X-ray quality): mp decomp. ca. 200 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ ppm 7.89-7.86 (m, 2H, CH_{Ar}), 7.55-7.53 (m, 4H, CH_{Ar}), 7.43-7.40 (m, 2H, $CH_{Ar,\ acetylide}$), 7.37-7.31 (m, 6H, CH_{Ar}), 7.26-7.23 (m, 2H, CH_{Ar}), 7.10-7.08 (m, 4H, CH_{Ar}), 6.97-6.95 (m, 2H, $CH_{Ar,\ acetylide}$), 3.90 (s, 3H, OCH_3), 1.41 (d, 36H, *J* = 15.7 Hz, 6C $(CH_3)_3$); ^{13}C NMR (200 MHz, CDCl3): δ ppm 161.2 (1C, $\underline{C}OCH_3$), 149.2 (2C, d, *J* = 14.5 Hz, C_{Ar}), 142.6 (2C, d, *J* = 6.8 Hz, C_{Ar}), 134.8 (2C, $CH_{Ar,\ acetylide}$), 133.8 (2C, CH_{Ar}), 133.2 (2C, d, *J* = 7.9 Hz, CH_{Ar}), 131.1 (2C, CH_{Ar}), 129.3 (4C, CH_{Ar}), 129.0 (4C, CH_{Ar}), 128.0 (2C, CH_{Ar}), 127.4 (2C, d, *J* = 6.9 Hz, CH_{Ar}), 125.3 (2C, d, *J* = 44.7 Hz, PC_{Ar}), 124.6 (1C, t, *J* = 68.5 Hz, AuC≡), 118.6 (1C, t, *J* = 11.5 Hz), 114.3 (2C, $CH_{Ar,\ acetylide}$), 112.4 (1C, ≡CC), 55.6 (1C, OCH_3), 37.9 (4C, d, *J* = 23.8 Hz, P$\underline{C}(CH_3)_3$), 30.9 (6C, d, *J* = 7.0 Hz, $PC(\underline{C}H_3)_3$); ^{31}P NMR (162 MHz, $CDCl_3$): δ ppm 62.35 (AuP); IR (film, cm^{-1}) 2954, 2890, 1600, 1504, 1252, 1169, 756, 731, 701, 657; HRMS (ESI) calcd for $C_{49}H_{61}OP_2Au_2$ $[M]^+$ 1121.3529, found 1121.3551. X-ray data; CCDC ID: 1508697.

4.6. Procedure for generation and isolation of Au-acetylide complex **IV**

Chloro[(1,1′-biphenyl-2-yl)di-*tert*-butylphosphine]gold(I) (JohnPhosAuCl, 38.4 mg, 0.072 mmol), 1-ethynyl-4-methoxybenzene (**1c**, 20.3 mg, 0.154 mmol) and *N*-ethyl -*N*-isopropylpropan-2-amine (1.0 mL) were dissolved in dry DCM (3 mL) and NaH (8.9 m, 0.371 mmol) was added. The reaction was stirred at r.t. for 9 h, at which time the reaction was complete. The solvent was evaporated almost to dryness *in vacuo* and a small amount of DCM/pentane was added. Slow evaporation afforded precipitation of the product, which was washed with pentane, giving the Au-acetylide complex **IV** as a white solid (39.1 mg, 86%): mp decomp. ca. 115 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ ppm 7.88-7.85 (m, 1H, CH_{Ar}), 7.56-7.54 (m, 1H, CH_{Ar}), 7.52-7.49 (m, 2H, CH_{Ar}), 7.48-7.47 (m, 1H, CH_{Ar}), 7.47-7.44 (m, 1H, CH_{Ar}), 7.41- 7.39 (m, 2H, CH_{Ar}), 7.29-7.27 (m, 1H, CH_{Ar}), 7.19-7.18 (m, 2H, CH_{Ar}), 6.79-6.77 (m, 2H, $CH_{Ar,acetylide}$), 3.79 (s, 3H, OCH_3), 1.42 (d, *J* = 15.0 Hz, 18H, $C(CH_3)_2$); ^{13}C NMR (200 MHz, $CDCl_3$): δ

ppm 157.9 ($\underline{C}OCH_3$), 150.3 (d, J = 14.7 Hz, C_{Ar}), 142.4 (d, J = 5.7 Hz, C_{Ar}), 134.3 ($\underline{C}H_{Ar}$), 133.4 (2C, $CH_{Ar,acetylide}$), 133.1 (d, J = 7.5 Hz, CH_{Ar}), 132.2 (d, J = 132.1 Hz, AuC), 130.1 (d, J = 1.8 Hz, CH_{Ar}), 129.2 (2C, CH_{Ar}), 129.0 (2C, CH_{Ar}), 128.0 (CH_{Ar}), 127.6 (d, J = 39.6 Hz, PC_{Ar}), 126.6 (d, J = 6.2 Hz, CH_{Ar}), 118.5 (d, J = 2.4 Hz, $AuCC\underline{C}_{Ar}$), 102.0 (d, J = 23.6 Hz, Au$\underline{C}C$), 55.1 (OCH_3), 37.4 (d, 2C, J = 22.1 Hz, $\underline{C}(CH_3)_3$), 31.0 (d, J = 7.0 Hz, 6C, $C(\underline{C}H_3)_3$); ^{31}P NMR (162 MHz, $CDCl_3$): δ ppm 64.06 (AuP); IR (neat, cm^{-1}) 2961, 2852, 1766, 1504, 1461, 1243, 1037, 828, 751, 698; HRMS (ESI) calcd for $C_{29}H_{35}OPAu$ $[M+H]^+$ 627.2091, found 627.2098.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jfluchem.2017.01.004. jfluchem . . . . Crystallographic data of Au-Togni Reagent complex II (CCDC 150869) and dual-Au complex III (CCDC 1508697)can be obtained free of charge at http://www.ccdc.cam.ac.uk/conts/retrieving.html or from the Cambridge Crystallographic Data Centre (CCDC).

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Supplementary Data

Dual-Gold(I)-generated trifluoromethylation of terminal alkynes with Togni's reagent

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1. **i) Procedure for initial experiments and GLC analysis** (Section 2.1)

   ii) NMR studies of Au(I) promoted trifluoromethylation of alkynes 1a-g (Section 2.3)

2. **NMR Spectra of** compound **6,**

   Au-Togni Reagent complex **II**

   Dual-Au complex **III**

   Au-acetylide complex **IV**

1. *i) Procedure for initial experiments and GLC analysis* (Section 2.1)

Two stock solutions were made up in volumetric flasks: 1-ethynyl-4-methylbenzene (**1b**, 250.4 mg in 25 mL MeOH, *Solution A*) and (acetonitrile)[(2-biphenyl)di-tert-butylphosphine]gold(I) hexafluoroantimonate **I** ([25.4 mg + 250 µL DCM] in 5 mL MeOH, *Solution B*). DCM was added to *Solution B* due to poor solubility of the gold complex in MeOH. The required source of electrophilic CF_3 reagent (Scheme 1) was weighed into a flask and *Solution A* (1000 µL, 10.02 mg, 86.22 µmol alkyne) and *Solution B* (700 µL, 3.56 mg, 4.61 µmol) were added successively, while stirring. The flask was flushed with nitrogen and the vessel stoppered. 100 µL of the reaction mixture was transferred after the requisite time to a vial with 1 drop triethylamine and 250µL:500µL water:EtOAc was used for work-up. The organic phase was analysed by GLC. The experiments were analysed at 1, 2, 4 and 24 h at room temperature. From 26 h, the Togni 1 experiment (Scheme 1b, ii) was heated to 70 °C and analysed at 27 h and 28 h.

GLC method: A temperature program of 50-200 °C with a gradient of 10 °C/min was used to monitor the reactions, and retention times for the necessary reference compounds were obtained from a previous project in the Fiksdahl group (see Table 1). 1-Methyl-4-(3,3,3-trifluoroprop-1-yn-1-yl)benzene **5b** had been obtained via a literature method[1]and the gold-catalysed addition of methanol over the triple bond of 1-methyl-4-(3,3,3-trifluoroprop-1-yn-1-yl)benzene **5b** gave the required CF_3 compounds **2b"-4b"**, via another literature method.[2] Applying the same method for 1-ethynyl-4-methylbenzene **1b** gave the non-fluorinated compounds **2-4**. Peak integration was carried out manually and reported as percentage of the total area of the integrated peaks (see Table 2).

Table 1. GLC retention times for possible products formed by Au catalysed conversion of alkynes.

Compound	Non-CF_3 (Scheme 1)	CF_3 compounds
Alkyne	**1b** 4.3 min	**5b** 4.6 min
Ketone	**3b** 7.0 min	**3"b** 7.5 min
Enol ether	**2b** 7.4 min	**2"b** 7.7 min
Acetal	**4b** 7.8 min	**4"b** 8.1 min

Table 2. GLC data from Au(I)-catalysed electrophilic addition of MeOH to alkyne **1b** in the presence of CF_3 source (Scheme 1).

Electrophilic source of CF_3	Conversion into non-fluorinated products [Area%] **3**:**2**:**4**					
Reaction time:	1 h	2 h	4 h	24 h	27 h	28 h
No electrophile	47:0:20	65:1:30	69:1:28	79:1:19	-	-
Togni 1 (42.6 mg, 129 mmol)	0:0:0	0:0:0	0:0:0	0:0:17	9:0:41*	23:0:52*
Togni 2 (60% wt, 68.0 mg, 129 mmol)	18:9:13	35:8:20	58:4:27	86:2:11	-	-
Umemoto (42.9 mg, 126 mmol)	65:3:20	76:2:19	80:2:16	72:2:25	-	-

* Reaction was heated to 70 °C for 2 h after 26 h at r.t.

ii) NMR studies of Au(I) promoted trifluoromethylation of aryl-alkynes 1a-g (Section 2.3).

Table 3. NMR studies of Au(I) promoted trifluoromethylation of aryl-alkynes **1a-g** (Scheme 3). a) NMR signals of characteristic Me, MeO and CF_3 groups of substrates **1a-g**; b) and c): ^1H or ^{19}F NMR signals of characteristic Me, MeO and CF_3 groups in dual-Au complexes **IIIa-g** (b) and CF_3-Togni (c) registered 15 min after preparation of the Au-Togni- alkyne reaction mixtures (based on conditions given in Scheme 2, entry 28).

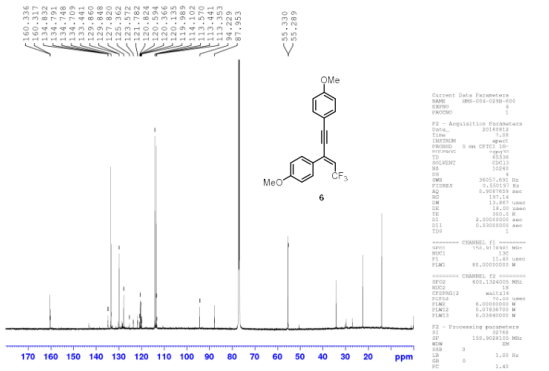
Substrate	a) $^1H^{a)}$ or $^{19}F^{b)}$ NMR; alkynes **1a-g**	b) NMR shift of dual-Au complex **IIIa-g**	c) CF_3-Togni shift (partially protonated) ^{19}F NMR
1a; R = Ph	-	-	-37.8 ppm
1b; R = 4-Me-C_6H_4	4-Me[a)] 2.35 ppm	2.45 ppm	-37.9 ppm
1c; R = 4-MeO-C_6H_4	4-MeO[a)] 3.81 ppm	3.90 ppm	-37.7 ppm
1d; R = 2-MeO-C_6H_4	2-MeO [a)] 3.91 ppm	3.95 ppm	-37.9 ppm
1e; R = 2-Me-4-MeO-C_6H_3	2-Me [a)] 2.43 ppm 4-MeO [a)] 3.80 ppm	2.47 ppm 3.88 ppm	-37.6 ppm
1f; R = 4-CF_3-C_6H_4	4-CF_3 [b)] -62.92 ppm	-62.88 ppm	-37.8 ppm
1g; 6-MeO-2-naphthyl	MeO [a)] 3.92 ppm	3.97 ppm	-37.8 ppm

2. NMR Spectra

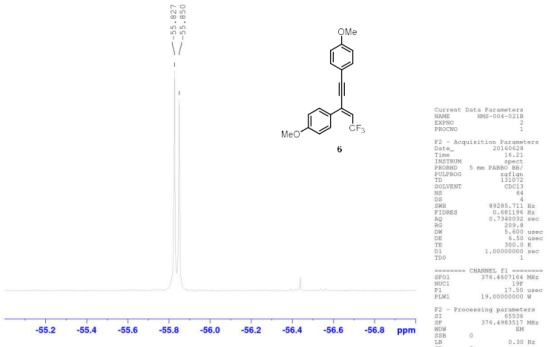
(E)-4,4'-(5,5,5-Trifluoropent-3-en-1-yne-1,3-diyl)bis(methoxybenzene); alkene-CF_3 (6)

^{1}H NMR

^{13}C NMR

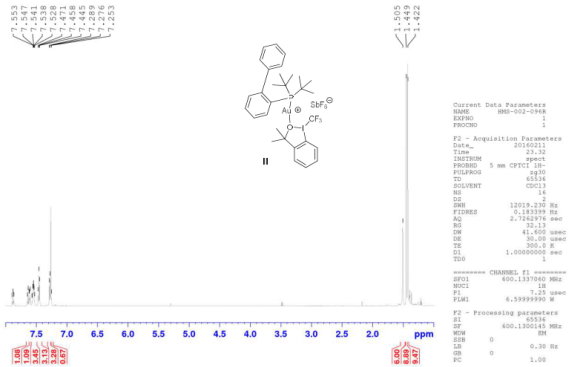


^{19}F NMR

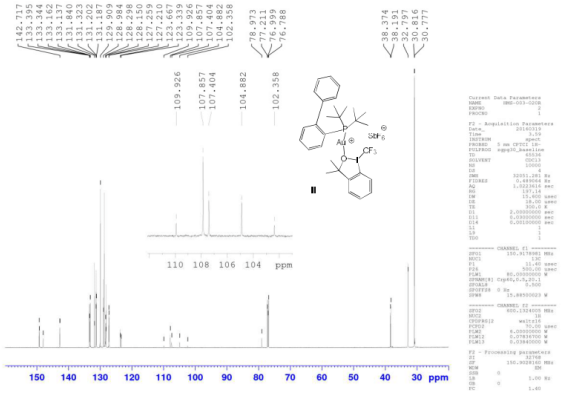


Au-Togni Reagent complex II

^{1}H NMR



^{13}C NMR



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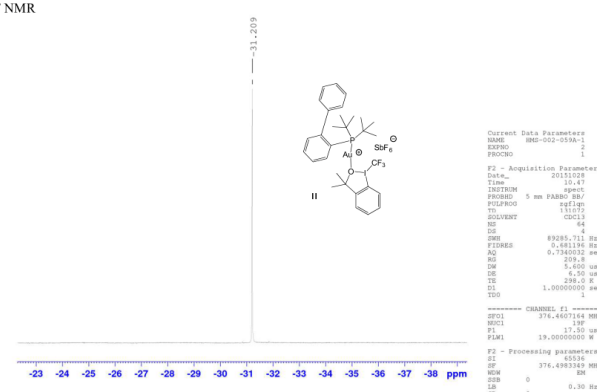
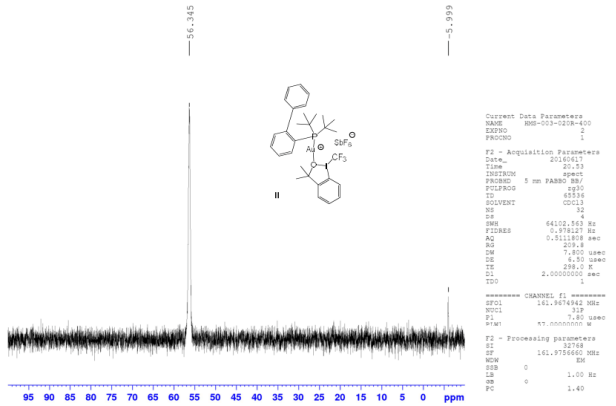
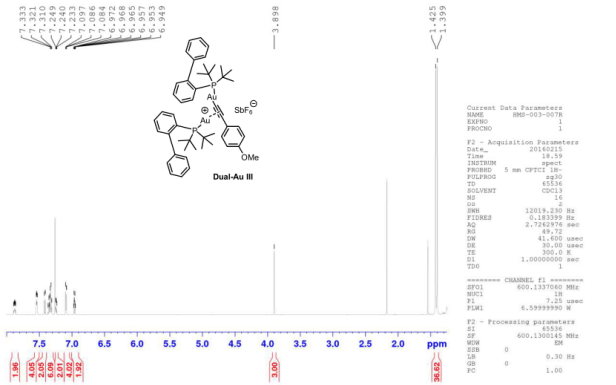


^{31}P NMR

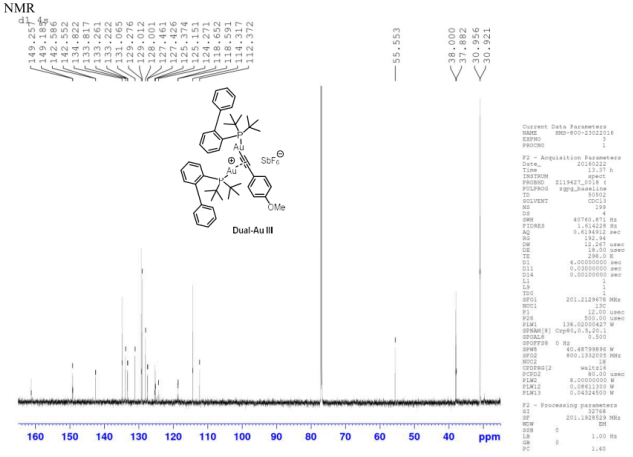


Dual-Au complex III

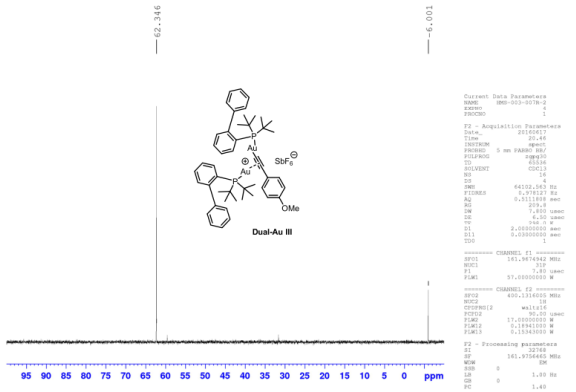
^{1}H NMR



^{13}C NMR

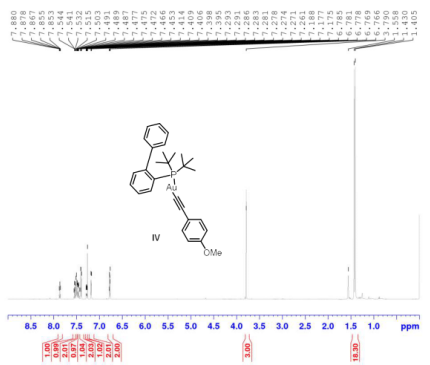


^{31}P NMR



Au-acetylide complex IV

^{1}H NMR



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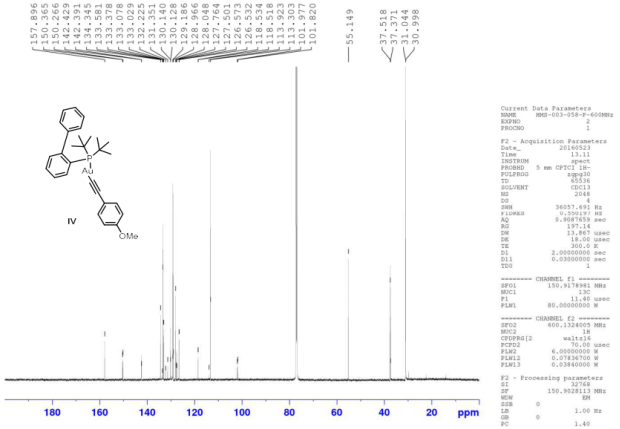
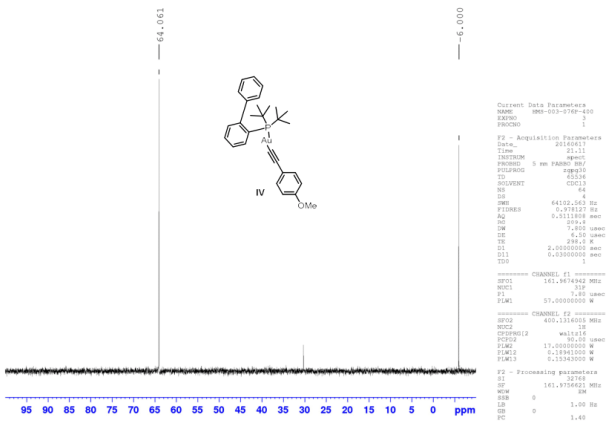


^{31}P NMR



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PAPER IV

Preparation and Catalytic Activity of Novel σ,π-Dual Gold(I) Acetylide Complexes

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Full Paper

Gold Catalysis

Preparation and Catalytic Activity of Novel σ,π-Dual Gold(I) Acetylide Complexes

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Abstract: Synthesis, characterisation and catalytic activity of a series of novel σ,π-dual gold(I) acetylide complexes are presented. σ,π-Dual gold(I) complexes based on the JohnPhos ligand or the bridging chiral MeO-BIPHEP ligand were generated from terminal alkynes in the presence of an organic base. The catalytic activity of the complexes was explored in a range of gold(I)-catalysed reactions of propargylic alcohol derivatives and their catalytic and enantioselective potentials were compared to corresponding monogold(I) phosphane and chiral digold(I) diphosphane species.

Introduction

σ,π-Dual gold(I) acetylide complexes, mainly based on NHC ligands, have been reported to be active catalytic species in organic transformations, and there is a growing interest for use of such complexes.[1] Investigations of isolated σ,π-dual gold catalysts show different catalytic activity or regioselectivity when compared to monogold complexes.[1a,2] The Fiksdahl group has previously identified dual gold complexes as the catalytically active species in electrophilic trifluoromethylation of terminal alkynes (Figure 1).[3] It was proposed that the JohnPhos σ,π-dual-Au(I) complex **Ib** (Figure 1a) promoted alkyne

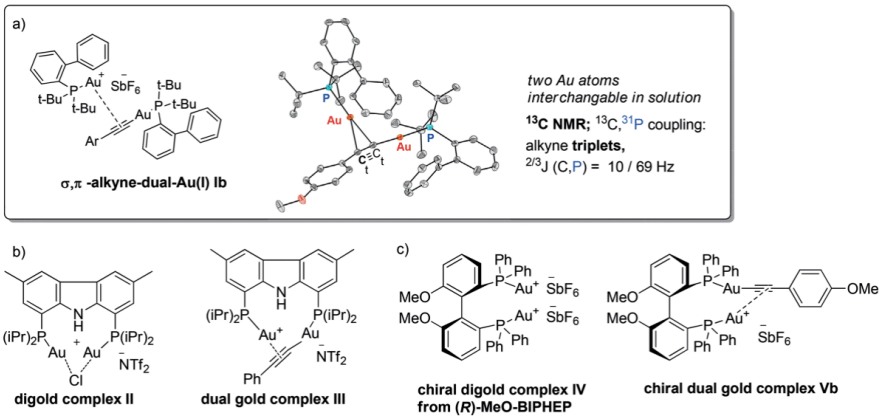

Figure 1. a) σ,π-Dual gold(I) acetylide complex **Ib**, reported by the Fiksdahl group.[3] Structures of b) digold and dual gold complexes[4] (**II**, **III**) and c) chiral digold and dual gold complexes (**IV**, **Vb**).

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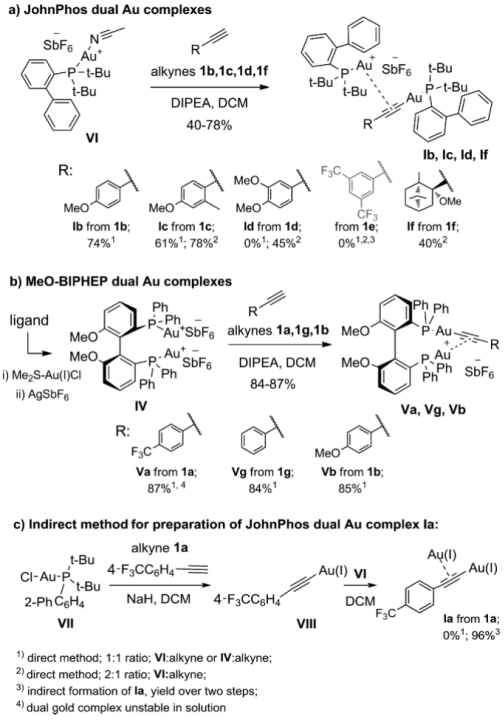
-CF_3 product formation in a catalytic manner by transfer of a $[LAu]^+$ fragment from the σ,π-dual-Au complex to the alkyne substrate, activating for trifluoromethylation.

The structures of digold complex **II** and σ,π-dual gold complex **III** (Figure 1b) have recently been reported. The catalytic ability of digold complex **II** has been tested in one reaction,[4] while the catalytic potential of bridged σ,π-dual gold complexes has not been explored so far. In contrast to chiral bridged σ,π-dual gold complexes, such as complex **Vb** (Figure 1c), chiral digold complex **IV** and similar complexes have been applied in enantioselective reactions.[5] Bridged chiral

σ,π-dual gold acetylide complexes can be generated from chiral digold complexes and alkynes and may have potential to give different catalytic activity, including enantioselectivity.

The aim of the present study was to acquire more knowledge on the synthesis and properties, as well as the catalytic ability, of new σ,π-dual gold complexes. We also wanted to observe whether the two closer gold atoms in chiral σ,π-dual gold(I) acetylide complexes would provide different regioselectivity or enantioselectivity from the corresponding monogold JohnPhos phosphane complex **VI** and the chiral digold diphosphane complex **IV** (Scheme 1a, b). We hereby present further studies on synthesis and characterisation of novel σ,π-dual gold(I) complexes. Their catalytic activity in different gold(I)-catalysed propargyl reaction is discussed, as well.



Scheme 1. Preparation of a) JohnPhos dual gold complexes and b) chiral MeO-BIPHEP σ,π-dual gold complexes. c) Indirect preparation method. Yields calculated from amount of gold complex used.

Results and Discussion

Synthesis of JohnPhos and MeO-BIPHEP σ,π-Dual Gold Complexes I and V

In order to probe the catalytic activity in reactions of propargylic alcohol derivatives, a series of σ,π-dual gold(I) complexes, with coordinated JohnPhos ligand or the bridging chiral MeO-BIPHEP ligand were synthesised from a range of alkynes, including a chiral alkyne (Scheme 1a–c).

JohnPhos Dual Gold Complexes I

The complexes were prepared from aryl alkynes (**1b**, **1c** and **1d**) and the chiral alkylalkyne **1f** by a procedure based on our previous experience from trifluoromethylation studies (Scheme 1a).[3] By mixing the JohnPhos-Au(I) cationic species **VI** with the appropriate alkyne (**1b**, **1c**, **1d**, **1f**; 1:1 or 2:1 ratio) in the presence of diisopropylethylamine, the dual gold complexes **Ib, Ic, Id** and **If** were obtained in moderate to high yields (40–78 %) in a single step. The most electron-rich alkyne **1d**, required excess of the Au(I) source (2:1 ratio **VI**:**1d**), as only the gold-acetylide was formed using a 1:1 ratio. A similar 2:1 ratio of **VI**:alkyne **1c** improved the yield of the dual gold complex **Ic** (from 61 % to 78 %).

The electron-deficient alkyne **1a** initially failed to give a dual gold complex via the direct method (Scheme 1a), as only the gold-acetylide was formed. However, an indirect method (Scheme 1c), via the gold-acetylide intermediate **VIII** (generated

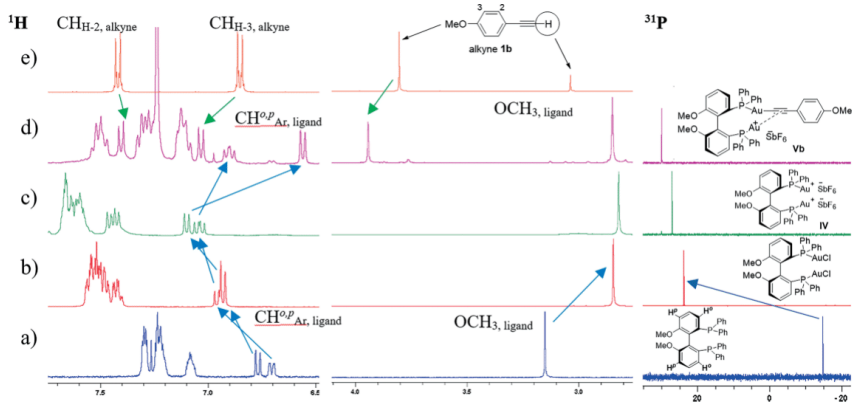


Figure 2. ^{1}H and ^{31}P NMR studies of a) the (*R*)-MeO-BIPHEP ligand through b) complexation with gold chloride, c) counterion exchange (**IV**) and d) formation of dual gold complex **Vb** with e) alkyne **1b**.

from alkyne **1a** and sodium hydride, and chloride replacement of the JohnPhos gold(I) chloride species **VII**) and final π-coordination of a second cationic gold unit **VI**, gave excellent yield of the desired JohnPhos dual gold complex **Ia** (96 % over two steps).

The formation of dual gold complex from the most electron-deficient alkyne **1e** was not successful with any of the methods, as only gold-acetylide was obtained, with no further coordination of a second gold unit. This demonstrates how the nature of the alkyne may favor either dual gold complex or gold-acetylide formation.

(R)-MeO-BIPHEP Bridged Dual Gold Complexes V

In initial studies, digold complexes, such as (*R*)-MeO-BIPHEP-digold **IV** (Scheme 1b), were generated in situ[5e] from five chiral diphosphane ligands ((*R*)-BINAP, (*R*,*R*)-DIOP, (*R*)-Phanephos, (*R*)-MeO-BIPHEP and (*S*)-*i*Pr-MeOBIPHEP) by complexation with gold chloride (Me_2S-Au(I)Cl) and counterion exchange, as shown by NMR (Figure 2). The digold complexes were identified by ^{1}H and ^{31}P NMR. Synthesis of the target bridged dual gold complexes from the digold complexes and alkyne **1b** gave products with varied purity and stability (NMR, MS). However, the stable bridged (*R*)-MeO-BIPHEP σ,π-dual gold complex **Vb** was successfully obtained from digold species **IV** and alkyne **1b.**

Thus, mixing the digold species **IV** with the appropriate electron-rich or electron deficient arylalkyne (**1a**, **1b** and **1g**) (1:1 ratio **IV**:alkyne) in the presence of diisopropylethylamine, afforded the (*R*)-MeO-BIPHEP bridged dual gold complexes **Va, Vb** and **Vg** in high yields in a single step (84–87 %, Scheme 1b). The dual gold complexes were characterised and identified by NMR (^{1}H, ^{19}F, ^{13}C, ^{31}P) and HRMS.

NMR Studies

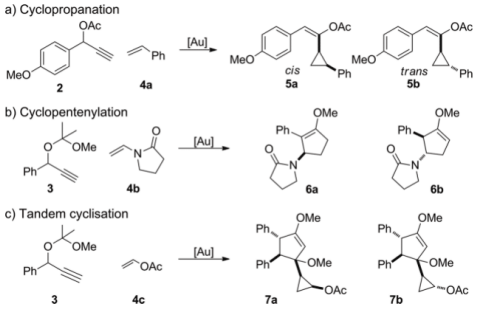
The dual gold(I) complex **Ib** has previously been studied by the Fiksdahl group.[3] The crystal structure (XRD, Figure 1a) confirmed the σ,π-coordination of the gold units in the solid state, while NMR data indicated that the gold units are interchangeable in solution, as both alkyne ^{13}C NMR signals were recorded as triplets (^{13}C-^{31}P coupling). Only a single set of proton signals and a single phosphorus signal from the gold ligand was seen in ^{1}H and ^{31}P NMR, in accordance with previous reports.[6] Similar NMR observations were made for complexes **Ia**, **Ic, Id, If** and **Va**, **Vb**, **Vg** in the present study.

The generation of the (*R*)-MeO-BIPHEP dual gold complex **Vb** (Figure 2a-e) from the diphosphane ligand (a) by complexation with gold chloride to give the digold complex (b), subsequent exchange with a non-coordinating anion (c) and by final formation of the target dual gold complex **Vb** (d) of alkyne **1b** (e), was clearly followed by ^{1}H and ^{31}P NMR studies. The methoxy ^{1}H NMR signal from the MeO-BIPHEP ligand showed a significant shielding effect by ligand coordination to give the digold complex. Smaller changes were also observed by further transformation into the dual gold complex **Vb**. The effect on the aromatic ligand protons, particularly in biphenyl *ortho* and *para* positions, was noticeable all through the process a)-d) to give the target dual gold complex **Vb**. Also, coordination is shown by distinct ^{1}H NMR patterns of alkyne **1b**, as the methoxy signal and the aromatic H-3 protons experience a deshielding effect and move to higher shift values. As expected, the terminal alkyne proton disappears by complexation. The changes in the phosphorus environment were also seen by ^{31}P NMR. In particular, a characteristic deshielding effect was observed as a large change to a higher ^{31}P NMR shift value (from −15 ppm to 24 ppm) by initial ligand coordination to AuCl to give the digold complex. Smaller deshielding effects were also observed throughout the next steps towards the final dual complex **Vb**.

Reactivity of JohnPhos Dual Gold Complexes I in Reactions of Propargylic Alcohol Derivatives

Based on our previous studies,[7] the catalytic activity of the synthesised JohnPhos dual-gold complexes **I** was tested in

Table 1. Gold(I)-catalysed propargyl test reactions; a) cyclopropanation,[7a] b) cyclopentenylation[7b] and c) tandem cyclisation reactions[7c] with known monogold complex **VI** and dual gold complexes **I**.



Entry	Complex	Temp.	Time	Yield	Ratio
a) Cyclopropanation[a] **2**+**4a**:					**5a/5b**
1	**VI**	r.t.	30 min	98 %	2:1
2	**Ia**	r.t.	24 h	89 %	8:1
3	**Ib**	40 °C	4 h	97 %	8: 1
4	**Ic**	40 °C	24 h	91 %	9:1
5	**Id**	r.t.	2 h	94 %	8:1
6	**If**	r.t.	24 h	99 %	8:1
b) Cyclopentenylation[b] **3**+**4b**:					**6a/6b**
7	**VI**[7b]	r.t.	15 min	61 %	1:0
8	**Ia**	r.t.	2 h	66 %	1:2
9	**Ib**	r.t.	24 h	36 %	1:1
10	**Ic**	r.t.	2 h	68 %	1:2.4
11	**Id**	40 °C	24 h	19 %	0:1
12	**If**	r.t.	24 h	66 %	1:3
c) Tandem cyclisation[c] **3**+**4c**:					**7a/7b**
13	**VI**[7c]	r.t.	15 min	54 %	60:40
14	**Ia**	r.t.	15 min	48 %	55:45
15	**Ib**	r.t.	2 h	55 %	57:43
16	**Ic**	r.t.	1 h	61 %	56:44
17	**Id**	r.t.	1 h	31 %	55:45
18	**If**	r.t.	24 h	57 %	56:44

[a] Reaction conditions: propargyl ester **2** (1 equiv.) and alkene **4a** (4 equiv.) in CH_2Cl_2 ($c \approx 50$ mM) with gold catalyst (5 mol-%). [b] Reaction conditions: Propargyl acetal **3** (1 equiv.) and alkene **4b** (3 equiv.) in CH_2Cl_2 ($c \approx 80$ mM) with gold catalyst (5 mol-%). [c] Reaction conditions: Propargyl acetal **3** (1 equiv.) and alkene **4c** (3 equiv.) in CH_2Cl_2 ($c \approx 80$ mM) with gold catalyst (5 mol-%).

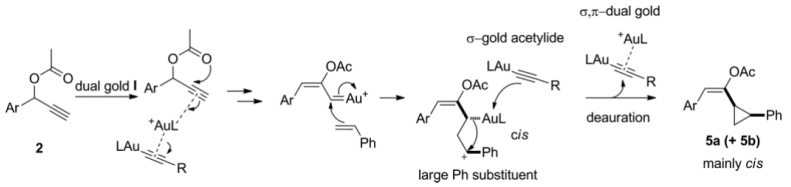
three gold(I)-catalysed propargyl ester and acetal reactions. The results from a) cyclopropanation,[7a] b) cyclopentenylation[7b] and c) tandem cyclisation[7c] were compared with our results obtained with JohnPhos monogold(I) complex **VI** previously[7b,7c] or in the current study (Table 1a–c).

The five dual gold complexes **I** gave excellent yields in cyclopropanation of propargyl ester **2** with styrene **4a** (89–99 % of **5**, Table 1a, entries 2–6), low to good yields for the cyclopentenylation of propargyl acetal **3** with 1-vinylpyrrolidin-2-one **4b** (19–68 % of **6**, Table 1b, entries 8–12), and moderate yields for the tandem cyclisation reaction between propargyl acetal **3** with vinyl acetate **4c** (31–61 % of **7**, Table 1c, entries 14–18). In all reactions, more than one of the new dual gold complexes gave higher yields than JohnPhos monogold complex **VI** (entries 1,7,13). In addition, higher *cis*-diastereoselectivity was obtained in cyclopropanation with all dual gold complexes (up to 80 % de, entries 2–6, Table 1a). A regioselectivity shift for cyclopentenylation into the other enol ether product **6b** (up to 100 %, entry 11, Table 1b) was observed, as well. The selective formation of the *trans* isomer was in accordance with previous studies.[7b]

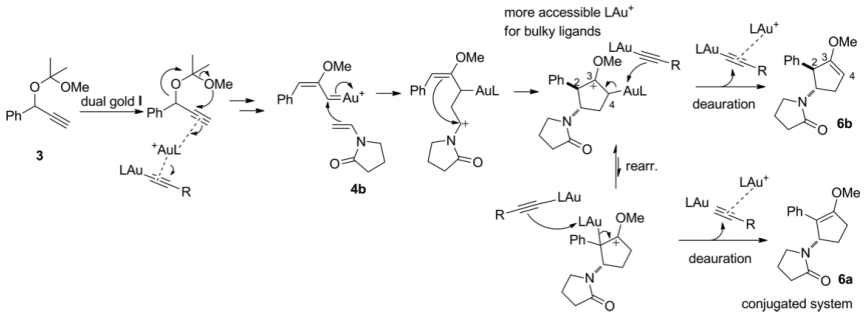
The preferences for other isomers may generally be explained by the cyclisation deauration step, where the stereo- or regioselectivity is determined by transfer of the substrate-connected gold unit back to the σ-gold-acetylide to regenerate the σ,π-dual gold complex (Scheme 2, Scheme 3, and Scheme 4). In the deauration step, favouring *cis*-cyclopropanation (Table 1a, entries 2–6), the bulky departing gold unit may prefer *cis* relation to the rigid phenyl ring in the substrate, to enable approach and coordination of the σ-gold-acetylide (Scheme 2) to regenerate the σ,π-dual gold complex.

Cyclopentenylation, catalysed by the dual gold complexes **I**, with electron-withdrawing or bulky ligands, gives mainly enol ether product **6b** (up to 100 % of total **6**, entries 8–12). The reaction may be rationalised by cleavage of the bulky gold unit from the most accessible 4-position of the substrate to regenerate the σ,π-dual gold complex (Scheme 3). The exclusive formation of isomer **6a** with the less bulky monogold (JohnPhos) complex **VI** (entry 7) may be enabled by formation of a stabilised conjugated system in product **6a** by rearrangement into the more crowded Au-benzylic intermediate.

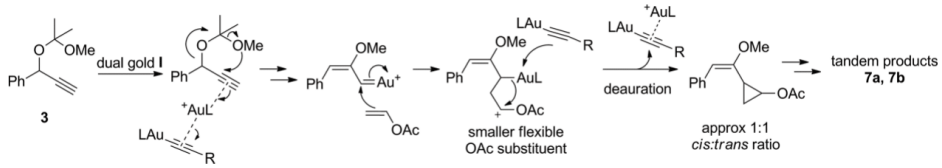
No significant change in stereoselectivity was apparent for the tandem cyclisation reaction, as the smaller and more flexible acetyl group may not interfere with the incoming σ-gold-acetylide (Scheme 4) to the same extent as the more



Scheme 2. Proposed mechanism of dual gold-catalysed cyclopropanation (Table 1a) of propargyl ester **2** and styrene, **4a**.



Scheme 3. Proposed mechanism of dual gold-catalysed cyclopentenylation (Table 1b) of propargyl acetal **3** and vinyl amide **4b**.



Scheme 4. Proposed mechanism of the cyclopropanation step of dual gold-catalysed tandem cyclisation (Table 1c) of propargyl acetal **3** and vinyl acetate, **4c**.

rigid and bulky phenyl group in the cyclopropanation reaction above (Scheme 2).

All reactions using dual gold complexes **I** required longer times or higher temperatures than the commercially available monogold complex **VI**. The lower reactivity may be caused by the necessary transfer of the π-bonded gold unit from the dual gold complex to the propargyl substrates, to act as a catalytic species (Scheme 2, Scheme 3, and Scheme 4).

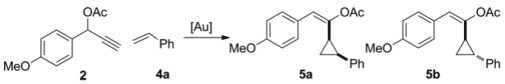
The electronic and steric properties of the substituents on alkynes **1b–f** affect the reactivity of the dual gold complexes, but the trend is not clear, as the overall reactivity is influenced by at least two opposing factors. The initial step, where the catalytic active gold unit is disconnected from the dual gold-acetylide complex and transferred to the propargyl substrate (Scheme 2, Scheme 3, and Scheme 4), would likely require an energy barrier crossing. Electron-rich (e.g. complex **Id**, entries 11 and 17) or sterically non-hindered gold-acetylides may deactivate for initial disconnection and transfer of the π-bonded gold unit, but would, in contrast, activate for final deauration to regenerate the σ,π-dual gold complex by re-connection to the σ-gold-acetylide.

The chiral dual gold complex **If**, based on the chiral MeO-camphorylalkyne **1f**, did not induce any enantioselectivity in cyclopropanation or cyclopentenylation reactions (HPLC, GLC), probably due to the long distance between the chiral acetylide unit and the propargyl substrate in the stereogenerating deauration step. The proposed mechanisms (Scheme 2, Scheme 3, and Scheme 4) are supported by results from our earlier trifluoromethylation study where the dual gold complex was the sole gold species observed.[3]

Reactivity of Chiral (R)-MeO-BIPHEP Dual-Gold Complexes V in Reactions of Propargylic Alcohol Derivatives

Based on our previous studies,[7c,8] the catalytic activity and stereoselectivity of chiral dual gold complexes **V** were tested

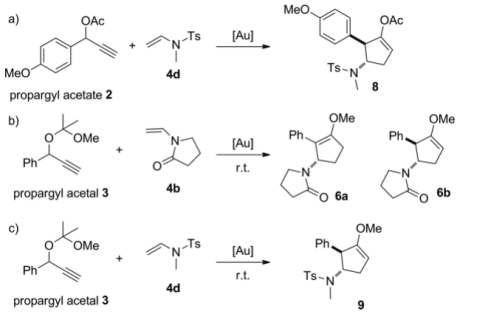
Table 2. Gold(I)-catalysed propargyl cyclopropanation with monogold (**VI**), digold (**IV**) and dual gold complexes (**V**).[a]



Entry	[Au]	Temp.	Time	Yield	**5a**:**5b**	ee[b] **5a**; *cis*	ee[b] **5b**; *trans*
1	**VI**	r.t.	15 min	98 %	2:1	–	–
2	**IV**	r.t.	2 h	58 %	1:0	65 %	–
3	**Va**	–40 °C	6 h	0 %	–	–	–
4		–40 °C to 10 °C	18 h	40 %	14:1	43 %	35 %
5		–20 °C	24 h	40 %	6:1	52 %	15 %
6		0 °C	3 h	66 %	3:1	50 %	10 %
7		r.t.	2 h	36 %	1:0	38 %	–
8	**Vg**	0–4 °C	24 h	56 %	11:1	51 %	20 %
9		r.t.	6 h	76 %	1:0	40 %	–
10	**Vb**	r.t.	24 h	40 %	1:0	44 %	–
11		40 °C	4 h	61 %	1:0	40 %	–

[a] Reactions performed with propargyl ester **2** (1 equiv.) and alkene **4a** (4 equiv.) in CH_2Cl_2 ($c \approx 50$ mM) together with gold catalyst (5 mol-%). [b] % ee determined by HPLC (Chiralpak AD Column 5:95 2-propanol:hexane, 0.8 mL/min).

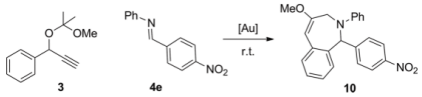
Table 3. Gold(I)-catalysed propargyl cyclopentenylation with gold complexes **IV**, **VI** and **V**.[a]



Entry	Au (I)	Alkene	Temp.	Time	Product yield	ee[c]
a) Propargyl acetate **2**:					**8:**	
1	**VI**	**4d**	r.t.	15 min	64 %	–
2	**IV**	**4d**	r.t.	5 h	58 %[b]	9 %
3		**4d**	40 °C	3 h	40 %[b]	16 %
4	**Va**	**4d**	r.t.	5 h	19 %	42 %
5		**4d**	40 °C	2 h	38 %[b]	36 %
6	**Vg**	**4d**	r.t.	72 h	18 %[b]	46 %
7		**4d**	40 °C	24 h	29 %	44 %
8	**Vb**	**4d**	r.t.	3 h	67 %[b]	44 %
9		**4d**	40 °C	3 h	32 %[b]	39 %
b) Propargyl acetal **3**:					**6a:**	
10	**VI**	**4b**	r.t.	15 min	61 %	–
11	**IV,Va,Vb**	**4b**	r.t.	48 h	5–24 %[b]	–
12	**Vg**	**4b**	r.t.	48 h	31 %	14 %
c) Propargyl acetal **3**:					**9:**	
13	**VI**	**4d**	r.t.	15 min	54 %	–
14	**IV**	**4d**	r.t.	48 h	26 %	32 %
15	**Va**	**4d**	r.t.	48 h	33 %	32 %
16	**Vg**	**4d**	r.t.	48 h	30 %	36 %
17	**Vb**	**4d**	r.t.	24 h	55 %	38 %

[a] Reactions performed with propargyl ester **2** (1 equiv.) and alkene **4d** (2 equiv.) in CH_2Cl_2 ($c \approx 17$ mM); or acetal **3** (1 equiv.) and alkene **4b** or **4d** (3 equiv.) in CH_2Cl_2 ($c \approx 80$ mM) in the presence of gold catalyst (5 mol-%). [b] Yield calculated by NMR from product mixture. [c] % ee of products **6**, **8** and **9** determined by HPLC (Chiralpak AD Column 10:90 2-propanol:hexane, 0.8 mL/min for product **8**; 1.0 mL/min for products **6a**/**6b**; 0.5 mL/min for **9**).

Table 4. Gold(I)-catalysed [2+5]-cycloaddition of propargyl acetal **3** and imine **4e**.[a]



Entry	Complex	Solvent	Time	Yield	ee[b]
1	**VI**	DCM	30 min	60 %	–
2	**IV**	DCM	42 h	17 %	9 %
3	**Va**	DCM	42 h	25 %	9 %
4	**Vg**	DCM	42 h	27 %	8 %
5	**Vb**	DCM	42 h	42 %	2 %

[a] Reactions performed with propargyl acetal **3** (1 equiv.) and imine **4e** (1.5 equiv.) in CH_2Cl_2 or CH_3CN ($c \approx 50$ mM) together with gold catalyst (5 mol-%). [b] % ee determined by HPLC (Chiralpak AD Column 10:90 2-propanol:hexane, 0.8 mL/min).

in gold(I)-catalysed reactions of propargylic alcohol derivatives (Table 2, Table 3, Table 4, and Table 5 and Scheme 5). The results were compared with our corresponding results with digold complex **IV** and JohnPhos monogold complex **VI**.[7c,8]

Fair yields of products **5** (61–76 %) were obtained in cyclopropanation of propargyl ester **2** and alkene **4a** in the presence of (*R*)-MeO-BIPHEP complexes **V** (Table 2).[7a] Reaction times with digold complex **IV** and dual gold complexes **V**, were longer than the monogold complex **VI** (Table 2, entries 1, 2, 7, 9 and 10), as also seen for dual gold complexes **I** above (Table 1a). The reaction times to give full conversion increased with increasing electron-density of the acetylide (entries 7, 9 and 10; 2 h to 24 h at r.t.), which indicates that the rate-determining step in this reaction is the disconnection of the π-bound gold unit from the σ,π-dual gold complex.

The digold and bridged dual gold complexes **V** give exclusive *cis* diastereomer formation at r.t. (entries 2, 7, 9, 10), as seen for complexes **I**, likely for the same deauration reason as discussed above (Scheme 2). The enantioselectivity of the reactions was positively affected by temperature reduction. All the tested chiral (*R*)-MeO-BIPHEP complexes **IV** and **V** gave substantial enantioselectivity (65 % ee of *cis*-**5a** with digold complex **IV**, entry 2; and up to 52 % ee *cis*-**5a** with dual gold complexes **V**, entries 5, 8, 10). The lower enantioselectivity obtained with dual gold complexes than the digold complex **IV**, may be explained by a conceivable *gem*-digold intermediate,[1b,9] which is possible for monogold complex **VI** and digold complex **IV**, but not for the bridged dual gold complexes **V** (Figure 3a).

The cyclopentenylation reaction of propargyl ester **2** and sulfonamide **4d**[8] with bridged dual gold complexes **V** (Table 3a, entries 5–9) gave selectively the vinyl acetate product **8** (up to 67 %). In contrast to cyclopropanation results (Table 2), the bridged dual gold complexes **V** gave higher enantioselectivity (42–46 % ee of **8** at r.t.; entries 4–9) than the digold complex **IV** (<16 % ee, entries 2 and 3).

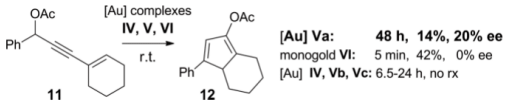
An explanation for the higher enantioselectivity of the dual gold complexes in cyclopentenylation reactions, may be seen in the cyclisation step, which determines the enantioselectivity (Figure 3b). As a larger ring is formed, the gold centres are less directly involved. Therefore, the effect of a possible *gem*-digold complex on the enantioselectivity of the reaction is reduced, and the selectivity is likely mainly dependent on the bulkiness of the overall gold complex.

Corresponding cyclopentenylation reactions of the more reactive propargyl acetal **3** with vinyl amide **4b**[7b] (Table 3b, entries 10–12) were studied, as well. However, the di-/dual gold complexes **IV** and **V** performed poorly, and only low yields of product **6a**, were estimated from complex product mixtures (NMR; 5–31 % yield in 48 h). Analysis of isolated enol ether **6a** (31 %) indicated low enantioselectivity (14 % ee, entry 12).

The reaction was further studied by replacing the electron deficient vinyl amide **4b** with the moderately deactivated vinyl sulfonamide **4d**[10] (Table 3c, entries 13–17).[7b] The effect was apparent, and higher yields and greater enantiomeric excess of the enol ether product **9** were obtained for the dual gold complexes **V** (33–55 % yield of **9**, 32–38 % ee), relative to the digold complex **IV** (26 % yield of **9**, 32 % ee), as discussed above (Table 3a and Figure 3b). Highest yield (55 % of product **9**, entry 17), comparable to monogold complex **VI** (54 %, entry 13), was obtained with the dual gold complex **Vb** with electron-rich acetylide (4-OMe-C_6H_4). This result may imply that the catalytic efficiency is controlled by regeneration step of the σ,π-dual gold complex in the final deauration.

The slow gold-catalysed [2+5] cycloaddition of propargyl acetal **3** and imine **4e**[11] afforded benzazepine product **10** less efficiently with di-/dual gold complexes **IV** and **V** (17–42 % in 42 h, Table 4, entries 2–5) than monogold catalyst **VI** (60 %, entry 1). The yields improved (from 25 % to 42 %, entries 3–5) with increased acetylide electron density (from 4-CF_3 to 4-OMe). Low enantioselectivity (up to 9 % ee) was observed with dual gold complex **Va**.

Gold-catalysed reactions of non-terminal propargyl esters were also tested (Scheme 5, Table 5). Only dual gold complex **Va** was sufficiently active to generate product **12** (14 %) with some enantioselectivity (20 % ee), but the reaction was slow and challenging, due to substrate and product instability. Fast cycloisomerisation of propargyl ester **11**[12] took place with monogold complex **VI** (5 min, 42 %).



Scheme 5. Gold(I)-catalysed cycloisomerisation of 1,3-enyne propargyl ester **11**.

Non-terminal propargyl ester **13** was subjected to gold-catalysed acetate migration[13] to afford allene product **14**. The outcome of the reaction is in accordance with previous reports on selective allene formation with Au(I)-phosphine, whereas indene products were generated with Au(I) NHC complexes.[14] Monogold complex **VI** readily afforded high yield of allene product **14** (70 %, 30 min, Table 5, entry 1). Similar yields were only obtained by very slow reactions in the presence of digold

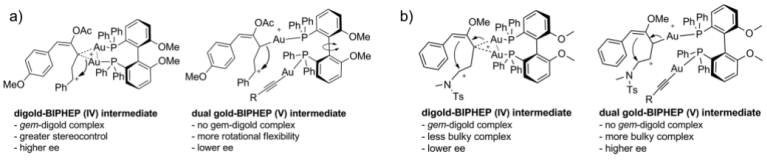
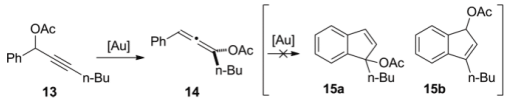


Figure 3. Possible gold-intermediates with digold complex **IV** and dual gold complexes **V** in the deauration step of the a) cyclopropanation reaction (Scheme 2) and b) cyclopentenylation reactions (Scheme 3).

Table 5. Gold(I)-catalysed generation of allene by rearrangement of propargyl ester **13**.[a]



13 **14** **15a** **15b**

Entry	Complex	Time	**13** amount	Conversion of **13** to **14** (NMR)	Yield **14**	ee[c]
1	VI	30 min	20 mg	–	70 %	–
2	IV	7 d	6.0 mg	93 %	65 %[b]	0 %
3	Va	7 d	6.0 mg	82 %	75 %[b]	0 %
4	Vg	7 d	6.0 mg	20 %	–	–
5	Vb	7 d	6.0 mg	7 %	–	–

[a] The reactions were performed with propargyl ester **13** (1 equiv.) in CH_2Cl_2 ($c \approx 50$ mM) together with gold catalyst (5 mol-%). [b] Isolated with starting material; yield calculated from NMR. [c] % ee determined by HPLC (Chiralpak AD Column 2:98 2-propanol:hexane, 0.8 mL/min).

complex **IV** or the dual gold complex **Va** (65–75 %, 7 days, Table 5, entries 2 and 3). No enantioselectivity was observed (HPLC). Only trace amounts of indene product **15**[15] were formed by separate gold-catalysed cyclisation of isolated allene **14** with complexes **IV** and **V**.

Conclusions

A series of new σ,π-dual gold(I)-acetylide complexes were prepared by gold coordination of selected ligands and a range of alkynes, and characterised (^{1}H, ^{19}F, ^{13}C, ^{31}P NMR; HRMS). The catalytic activity of the JohnPhos dual-gold complexes **I** and the bridged chiral MeO-BIPHEP dual-gold complexes **V** was tested in several reactions of propargylic alcohol derivatives. The results from the dual gold(I)-catalysed reactions (cyclopropanation, cyclopentenylation, tandem cyclisation, selective allene generation, and cycloisomerisation of propargyl 1,3-enyne) were compared with corresponding results based on the monogold(I) phosphane (JohnPhos) complex **VI** as well as the chiral digold(I) diphosphane complex **IV**.

The JohnPhos dual gold complexes **I** gave excellent yields and high *cis*-diastereoselectivity in cyclopropanation (89–99 % yield; up to 80 % de). Electron-rich dual gold complexes afforded higher yields than the monogold(I) JohnPhos complex **VI** in propargyl cyclopentenylation and tandem cyclisation. The catalytic activity of bridged chiral dual gold(I) MeO-BIPHEP complexes **V** was demonstrated, as well. Both digold and bridged dual gold complexes **IV** and **V** afforded *cis*-diastereoselective (>99 % de) and enantioselective (up to 65 % ee) cyclopropanations. Higher yields (up to 76 %) were obtained with dual gold **V** than digold **IV** complexes. The chiral dual gold complexes **V** were also catalytically active in cyclopentenylation reactions (up to 67 % product yields) and were more enantioselective (up to 46 % ee) than the chiral digold complex **IV** (<16 % ee). Dual gold complexes **V** were not promising for tandem cyclisation, the allene generation reaction or the cycloisomerisation reaction, as very slow conversion of propargyl substrates were observed.

The present study demonstrates that dual gold complexes have different catalytic potential than the monogold **VI** or digold **IV** complexes in a variety of reactions of propargylic alcohol derivatives. The chiral dual gold(I) complexes **V** exhibit comparable catalytic activity and similar or higher enantioselectivity than the corresponding digold species **IV** in selected reactions. Mechanistic explanations are proposed for the differing regio- or stereoselective outcome of some reactions, rationalised by bulkiness or proximity effects in the deauration and product formation step.

The dual gold(I) complexes **I** and **V** appear to be less catalytically active than the monogold JohnPhos complex **VI**. However, the resulting selectivity may be useful in certain reactions to obtain specific target products, as hereby demonstrated for enantio-, diastereo- and regioselective reactions. To the best of our knowledge, the catalytic activity of bridged dual gold(I) complexes has not previously been studied. Thus, the present work contributes to new understanding of the synthesis, properties and catalytic potential of dual gold(I) complexes, including enantioselective chiral bridged dual gold(I) species.

Experimental Section

General: Commercial grade reagents were used as received. Dry solvents were collected from a solvent-purification system. All reactions were monitored by thin-layer chromatography (TLC) using silica gel 60 F254 (0.25-mm thickness) or by ^{1}H-NMR. Flash chromatography was carried out using silica gel 60 (0.040–0.063 mm). High Throughput Flash Purification (HPFP) was performed on pre-packed cartridges. ^{1}H and ^{13}C NMR spectra were recorded using a 400 or 600 MHz spectrometer. Chemical shifts are reported in ppm (δ) relative to d-$CDCl_3$ or d-DCM. Coupling constants (J) are reported in Hertz (Hz). The attributions of the chemical shifts were determined using COSY, HSQC and HMBC NMR experiments and cis/trans isomers by NOESY experiments. Accurate mass determination in either positive or negative mode was performed with a "Synapt G2-S" Q-TOF instrument from Waters. Samples were ionised with an ASAP probe, and no chromatographic separation was used before the mass analysis. IR spectra were obtained using a Bruker Alpha FT-IR spectrometer using OPUS V7 software to analyse the spectra. Compounds **1a**–**1e**, **1g**, **4a**, **4b** and **4c** were used as received from Sigma-Aldrich. Propargyl acetates **2**,[7a] **11**[12] and **13**,[14a] propargyl acetal **3**[7c] and imine **4e**[16] were synthesised from known procedures. Products **5a**, **5b**, **6a**, **7a**, **7b**, **9**, **10**, **14**, **15a** and **15b** are reported in literature.[7,8,11,13] Compound **4d** is a known compound that has been previously synthesised in the Fiksdahl group, but not fully characterised. Missing spectroscopic data is included here for posterity. Compounds **1f**, **6b**, **8** and **12** are novel and are fully characterised here. Test reactions were carried out following literature procedures with any variations in conditions specified in the text.

Complex **IV** (and the other chiral digold complexes) were generated following a literature procedure[5e] to obtain the dichloride salt and subsequent reaction with silver hexafluoroantimonate and filtration gave the required complex in situ. The syntheses of complexes **I** and **V** are described below.

Preparation of (*1R,2S,4R*)-2-ethynyl-2-methoxy-1,7,7-trimethylbicyclo[2.2.1]heptane (1f)

Compound **1f** was synthesised from (*1R,2S*)-2-ethynyl-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol through a known procedure.[17] (*1R,4R*)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one (541.9 mg, 3.56 mmol) was added to a solution of ethynylmagnesium bromide in THF (0.5 M, 10.0 mL, 5.00 mmol). The reaction mixture was heated under reflux for 24 h. After cooling to room temperature, the solution was quenched by the addition of H_2O (1 mL). The crude mixture was concentrated until most of the THF was removed. The residue was dissolved in Et_2O (25 mL) and sat. aq. NH4Cl (25 mL) was added. The phases were separated, and the aqueous layer was extracted with Et_2O (3 × 25 mL). The combined organic phases were washed with brine (25 mL) and dried with Na_2SO_4. After filtration and removal of the solvents in vacuo the crude product was purified by column chromatography (gradient pentane - 1:30 EtOAc/pentane -, 1:4 EtOAc/pentane to give 201.9 mg of a colourless wax (ca. 60 % pure (*1R,2S*)-2-ethynyl-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol). This product was dissolved in DMF (2 mL), cooled to 0 °C and sodium hydride (47.0 mg, 1.96 mmol) was added slowly. After stirring for 30 min at the same temperature, iodomethane (100 µL, 1.61 mmol) was added. The solution was warmed to r.t. and the DMF was extracted with diethyl ether (10 mL) and water (5 mL). The ether phase was washed with water (2 × 10 mL) and the combined aqueous washes were extracted with diethyl ether (4 × 10 mL). The combined ether extracts were concentrated in vacuo and the crude oil was chromatographed (1:10 Et_2O:pentane) to give (*1R,2S,4R*)-2-ethynyl-2-methoxy-1,7,7-trimethylbicyclo[2.2.1]heptane as a colourless volatile wax (60.4 mg, 9 % yield over two steps). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 3.25 (s, 3H, OCH_3), 2.40 (s, 1H, ≡CH), 2.28–2.23 (m, 1H, CH_3OCCH_2), 2.02–1.95 (m, 1H, CCH_2CH_2), 1.74–1.72 (m, 1H, CH_2CHCH_2), 1.69–1.64 (m, 1H, $CHCH_2CH_2$), 1.51 (d, 1H, *J* = 13.2 Hz, (CH_3OCCH_2), 1.47–1.39 (m, 1H, CCH_2CH_2), 1.14–1.08 (m, 1H, $CHCH_2CH_2$), 0.96 (s, 3H, $CH_{3,\ bridge}$), 0.90 (s, 3H, CH_3), 0.85 (s, 3H, $CH_{3,\ bridge}$); ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 85.0 (≡C), 83.7 (OC), 72.7 (≡CH), 54.0 (CCH_3), 50.2 (OCH_3), 48.1 ($C(CH_3)_2$), 45.5 (CH_2CHCH_2), 42.9 (CH_3OCCH_2), 32.6 (CCH_2CH_2), 26.9 ($CHCH_2CH_2$), 21.2 ($CH_{3,\ bridge}$), 20.9 ($CH_{3,\ bridge}$), 10.6 (CH_3); IR (neat, cm^{-1}) 3306, 2949, 2823, 1451, 1120, 1086, 1057, 1034, 645, 623; HRMS (ASAP+) calcd. for $C_{16}H_{20}NO_2$ [M + H] 258.1494, found 258.1490.

***N*,4-Dimethyl-N-vinylbenzenesulfonamide (4d)**

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 7.62 (d, 2H, *J* = 8.3 Hz, CH_{Ar}), 7.28 (d, 2H, *J* = 7.9 Hz, CH_{Ar}), 6.98 (dd, 1H, *J* = 15.6/9.0 Hz, =CH), 4.31 (dd, 1H, *J* = 9.0/1.2 Hz, $=CH_2$), 4.16 (dd, 1H, *J* = 15.5/1.0 Hz, $=CH_2$), 2.84 (s, 3H, NCH_3), 2.40 (s, 3H, $PhCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.8 (CH_3C_{Ar}), 134.8 (SC_{Ar}), 133.8 (=CH), 129.7 (CH_{Ar}), 127.0 (CH_{Ar}), 93.1 ($=CH_2$), 31.2 (NCH_3), 21.5 ($PhCH_3$); HRMS (ASAP+) calcd. for $C_{10}H_{14}NO_2S$ [M + H] 212.0745, found 212.0745.

1-((*1S,2R*)-3-Methoxy-2-phenylcyclopent-3-en-1-yl)pyrrolidin-2-one (6b)

Compound **6b** was synthesised from a literature procedure[7b] using propargyl acetal **3** (1 equiv.) and alkene **4b** (3 equiv.) in CH_2Cl_2 (*c* ≈ 80 mM) together with gold catalyst (5 mol-%) for the required time at the required temperature. The crude mixture was purified using silica chromatography (2 % MeOH/DCM) to give products **6a** and **6b** as yellow oils. **6b:** ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 7.29–7.26 (m, 2H, CH_{Ar}), 7.21–7.17 (m, 1H, CH_{Ar}), 7.16–7.14 (m, 2H, CH_{Ar}), 4.68–4.64 (m, 2H, =CH and NCH), 3.71 (br d, 1H, *J* = 4.3 Hz, PhCH), 3.59 (s, 3H, OCH_3), 3.46–3.34 (m, 2H, NCH_2), 2.70 (dtt, 1H, *J* = 15.5/8.1/1.9 Hz, $=CHCH_2$), 2.37–2.33 (m, 2H, $COCH_2$), 2.27–2.21 (m, 1H, $=CHCH_2$), 2.04–1.96 (m, 2H, NCH_2CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 174.5 (CO), 159.6 (C=), 140.4 (C_{Ar}), 128.6 (2C, CH_{Ar}), 127.6 (1C, CH_{Ar}), 126.9 (CH_{Ar}), 93.5 (=CH), 57.7 (NCH), 56.8 (OCH_3), 53.8 (PhCH), 43.7 (NCH_2), 31.43 and 31.40 (overlapping, 2C, $OCCH_2$ and $=CHCH_2$), 18.2 (NCH_2CH_2); IR (neat, cm^{-1}) 2933, 2855, 1676, 1645, 1419, 1284, 1250, 1231, 1161, 1024, 754, 699, 628; HRMS (ASAP+) calcd. for $C_{16}H_{20}NO_2$ [M + H] 258.1494, found 258.1490.

(*4S,5R*)-4-((*N*,4-Dimethylphenyl)sulfonamido)-5-(4-methoxyphenyl)cyclopent-1-en-1-yl acetate (8)

Compound **8** was synthesised from a literature procedure[8] using propargyl ester **2** (1 equiv.) and alkene **4d** (2 equiv.) in CH_2Cl_2 (*c* ≈ 17 mM) together with gold catalyst (5 mol-%) for the required time at the required temperature. The crude mixture was purified using silica chromatography (1:10–1:4 EtOAc/pentane) to give product **8** as a colourless oil. **8:** ^{1}H NMR (600 MHz, $CDCl_3$): δ ppm 7.45–7.44 (m, 2H, $CH_{Ar,\ Ts}$), 7.13 (d, *J* = 8.2 Hz, 2H, $CH_{Ar,\ Ts}$), 6.87–6.74 (m, 2H, CH_{Ar}), 6.76–6.74 (m, 2H, CH_{Ar}), 5.48–5.47 (m, 1H, =CH), 4.56 (dt, *J* = 8.5/4.6 Hz, 1H, NCH), 3.80–3.79 (m, overlapping, 1H, ArCH), 3.78 (s, 3H, OCH_3), 2.88 (s, 3H, NCH_3), 2.61 (ddt, *J* = 17.0/8.6/2.4 Hz, 1H, CH_2), 2.38 (s, 3H, $ArCH_3$), 2.15 (dm, *J* = 17.0 Hz, 1H, CH_2), 1.90 (s, 3H, $COCH_3$); ^{13}C NMR (150 MHz, $CDCl_3$): δ ppm 168.4 (C=O), 158.7 ($C_{Ar}OCH_3$), 150.2 (=C), 142.9 ($C_{Ar}CH_3$), 136.7 (SC), 131.7 ($C_{Ar}CH$), 129.5 ($CH_{Ar,\ Ts}$), 128.6 (CH_{Ar}), 127.1 ($CH_{Ar,\ Ts}$), 114.0 (CH_{Ar}), 112.8 (=CH), 63.4 (NCH), 55.2 (OCH_3), 51.9 (ArCH), 31.2 (CH_2), 29.1 (NCH_3), 21.5 ($ArCH_3$), 20.7 ($COCH_3$); IR (neat, cm^{-1}) 2929, 2837, 1753, 1511, 1337, 1244, 1203, 1178, 1155, 1088, 1032, 969, 814, 654, 569, 549; HRMS (ES+) calcd. for $C_{22}H_{25}NO_5NaS$ $[M + Na]^+$ 438.1351, found 438.1353.

3-Phenyl-3a,5,6,7-tetrahydro-4H-inden-1-yl acetate (12)

The reactions were performed with propargyl ester **11** (1 equiv.) in CH_2Cl_2 (*c* ≈ 20 mM) together with gold catalyst (5 mol-%) for the required time at the required temperature. The crude mixture was purified using silica chromatography (1:50 EtOAc/pentane) to give product **12** as a yellow oil. **12:** ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 7.39–7.38 (m, 2H, CH_{Ar}), 7.32–7.30 (m, 2H, CH_{Ar}), 7.19–7.16 (m, 1H, CH_{Ar}), 6.65 (s, 1H, =CH), 3.13 (dd, *J* = 12.7/5.8 Hz, 1H, CH), 2.70–2.66 (m, 1H, $=CCH_2$), 2.40–2.36 (m, 1H, $CHCH_2$), 2.23 (s, 3H, $COCH_3$), 2.09 (td, *J* = 13.4/5.4 Hz, 1H, $=CCH_2$), 1.96–1.92 (m, 1H, $=CCH_2CH_2$), 1.82–1.79 (m, 1H, $CHCH_2CH_2$), 1.48 (qt, *J* = 13.4/3.3 Hz, 1H, $CHCH_2CH_2$), 1.28–1.16 (m, 1H, $=CCH_2CH_2$), 0.90 (qd, *J* = 12.8/3.2 Hz, 1H, $CHCH_2$); ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 169.0 (C=O), 147.9 (CC_{Ar}), 142.1 (=CO), 135.0 (C_{Ar}), 132.6 (OC=C), 128.5 (CH_{Ar}), 126.7 (CH_{Ar}), 125.6 (CH_{Ar}), 123.8 (=CH), 48.5 (CH), 33.2 ($CHCH_2$), 28.4 ($=CCH_2CH_2$), 25.6 ($CHCH_2CH_2$), 24.4 ($=CCH_2$), 20.8 ($COCH_3$); IR (neat, cm^{-1}) 2931, 2852, 1753, 1652, 1492, 1444, 1368, 1352, 1211, 1169, 1148, 1015, 889, 757, 693; HRMS (ES+) calcd. for $C_{15}H_{17}O$ $[(M+H_2O\text{-}HOCOCH_3)+H]^+$ 213.1279, found 213.1276. The mass of the product was not observed. However, the product is unstable and previous work has identified it only by deacetylation.[18] It is proposed that in the conditions in the MS instrument the compound undergoes deacetylation to give the mass given above.

Preparation of gold complexes I and V

Complex Ia (CF_3)

Method B: Chloro[(1,1′-biphenyl-2-yl)di-*tert*-butylphosphine]gold(I) (41.5 mg, 1 equiv.) and alkyne **1a** (21.1 mg, 2 equiv.) were dissolved in dry DCM (5 mL) and NaH (21.1 mg, 11 equiv.) was added. The reaction mixture was stirred until complete conversion of the gold

complex as analysed by TLC (2–7 days). The mixture was filtered through Celite and evaporated to give the gold-acetylide **VIII** as a colourless powder. The gold-acetylide (20.7 mg, 1 equiv.) and (acetonitrile)[(2-biphenyl)di-*tert*-butylphosphine]gold(I) hexafluoroantimonate (23.5 mg, 1 equiv.) were dissolved in DCM (0.5 mL) and stirred for 30 min. The mixture was evaporated to give complex **Ia** as a colourless solid (96 % over two steps).

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 7.89–7.84 (m, 2H, $CH_{Ar,\ ligand}$), 7.68 (d, 2H, *J* = 8.0 Hz, $CH_{Ar,\ acetylide}$), 7.57–7.51 (m, 6H, 4 × $CH_{Ar,\ ligand}$ and 2 × $CH_{Ar,\ acetylide}$), 7.30–7.27 (m, 6H, $CH_{Ar,\ ligand}$), 7.25–7.22 (m, 2H, $CH_{Ar,\ ligand}$), 7.11–7.09 (m, 4H, $CH_{Ar,\ ligand}$), 1.42 (d, 36H, *J* = 16.0Hz, *t*Bu); ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 149.1 (d, *J* = 13.8 Hz, $C_{Ar,\ ligand}$), 142.7 (d, *J* = 6.7 Hz, $C_{Ar,\ ligand}$), 133.8 (d, *J* = 1.8 Hz, $CH_{Ar,\ ligand}$), 133.3 (d, *J* = 7.7 Hz, $CH_{Ar,\ ligand}$), 132.6 ($CH_{Ar,\ acetylide}$), 131.5 (q, *J* = 33.1 Hz, **C**CF_3), 131.2 (br s, $CH_{Ar,\ ligand}$), 129.4 (s, $CH_{Ar,\ ligand}$), 129.1 ($CH_{Ar,\ ligand}$), 128.0 ($C_{Ar,\ acetylide}$), 127.6 (d, *J* = 6.9 Hz, $CH_{Ar,\ ligand}$), 125.7 (q, *J* = 3.5 Hz, $CH_{Ar,\ acetylide}$), 125.1 ($C_{Ar,\ ligand}$), 124.9 (d, *J* = 12.9 Hz, $C_{Ar,\ ligand}$), 124.7 (t, *J* = 80.2 Hz, AuC), 123.5 (q, *J* = 272.2 Hz, CF_3), 113.0 (t, *J* = 12.7 Hz, Au**C**C), 38.1 (d, *J* = 24.4 Hz, PC), 31.0 (d, *J* = 5.8 Hz, PC(**C**H_3)$_3$); ^{19}F NMR (376 MHz, $CDCl_3$): δ ppm –62.9; ^{31}P NMR (162 MHz, $CDCl_3$): δ ppm 62.57; IR (neat, cm^{-1}) 2956, 2900, 2869, 1465, 1320, 1168, 1125, 1065, 755, 801, 654, 525, 495, 477; HRMS (ES+) calcd. for $C_{49}H_{59}F_3P_2Au_2$ [M + H]$^+$ 1160.3375, found 1160.3376.

Complex Ib (OMe)

Method A: (Acetonitrile)[(2-biphenyl)di-*tert*-butylphosphine]gold(I) hexafluoroantimonate (43.8 mg, 1 equiv.) and DIPEA (10 μL, 1.0 equiv.) were mixed in DCM (1 mL), then alkyne **1b** (8.8 mg, 1.2 equiv.) in DCM (1 mL) was added. After stirring for 5 min, the mixture was filtered through Celite and precipitated with pentane to give complex **Ib** as a colourless solid (23.6 mg, 74 %). The ^{1}H NMR spectrum was in accordance with reported literature.[3]

Complex Ic (MeO/Me)

Method A (1 eq alkyne): (Acetonitrile)[(2-biphenyl)di-*tert*-butylphosphine]gold(I) hexafluoroantimonate (40.8 mg, 1 equiv.) and DIPEA (10 μL, 1.1 equiv.) were mixed in DCM (0.5 mL), then alkyne **1c** (7.8 mg, 1.0 equiv.) in DCM (0.5 mL) was added. After stirring for 5 min, 2 mL DCM was added and the mixture was washed with water (5 × 2 mL), the organic phase dried with Na_2SO_4, filtered and the solvents evaporated. The resulting powder was dissolved in ca. 0.25 mL DCM and 4 mL pentane added carefully and placed in the freezer overnight. The crystals were washed with pentane (5 × 1 mL) and dried in vacuo to give complex **Ic** as a colourless solid (22.0 mg, 61 %).

Method A (0.5 eq alkyne): (Acetonitrile)[(2-biphenyl)di-*tert*-butylphosphine]gold(I) hexafluoroantimonate (20.0 mg, 1 equiv.) and DIPEA (5 μL, 1.1 equiv.) were mixed in DCM (1.0 mL), then alkyne **1c** (3.8 mg, 1.0 equiv.) in DCM (1.0 mL) was added. was added. After stirring for 5 min, 2 mL DCM was added and the mixture was washed with water (5 × 2 mL), the organic phase dried with Na_2SO_4, filtered and the solvents evaporated. The resulting powder was dissolved in ca. 0.25 mL DCM and 4 mL pentane added carefully and placed in the freezer overnight. The crystals were washed with pentane (5 × 1 mL) and dried in vacuo to give complex **Ic** as a colourless solid (13.8 mg, 78 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 7.88–7.84 (m, 2H, $CH_{Ar,\ ligand}$), 7.53–7.50 (m, 4H, $CH_{Ar,\ ligand}$), 7.38 (d, *J* = 8.3 Hz, $CH_{Ar,\ acetylide}$), 7.28–7.19 (m, 8H, $CH_{Ar,\ ligand}$), 7.08–7.05 (m, 4H, $CH_{Ar,\ ligand}$), 6.81–6.77 (m, 2H, $CH_{Ar,\ acetylide,\ ortho\ to\ OMe}$), 3.86 (s, 3H, OCH_3), 2.45 (s, 3H, CH_3), 1.39 (d, *J* = 15.6 Hz, *t*Bu); ^{13}C NMR (150 MHz, $CDCl_3$): δ ppm 161.5 (**C**OCH_3), 149.3 (d, *J* = 13.9 Hz, $C_{Ar,\ ligand}$), 144.5 (CH_3**C**$_{Ar,\ acetylide}$), 142.3 (d, *J* = 7.4 Hz, $C_{Ar,\ ligand}$), 136.0 ($CH_{Ar,\ acetylide,\ meta\ to\ OMe}$), 133.9 (br s, $CH_{Ar,\ ligand}$), 133.3 (d, *J* = 8.0 Hz, $CH_{Ar,\ ligand}$), 131.1 ($CH_{Ar,\ ligand}$), 129.3 ($CH_{Ar,\ ligand}$), 129.0 ($CH_{Ar,\ ligand}$), 128.0 ($CH_{Ar,\ ligand}$), 127.4 (d, *J* = 7.5 Hz, $CH_{Ar,\ ligand}$), 125.2 (d, C, *J* = 44.3 Hz, $C_{Ar,\ ligand}$), 123.7 (t, *J* = 69.3 Hz, AuC), 123.5 (t, *J* = 10.8 Hz, Au**C**C), 115.3 ($CH_{Ar,\ acetylide,\ ortho\ to\ OMe}$), 112.1 ($C_{Ar,\ acetylide,\ ortho\ to\ OMe}$), 111.8 ($CH_{Ar,\ acetylide}$), 55.5 ($OCH_3$), 38.1 (d, *J* = 24.7 Hz, PC), 31.0 (d, *J* = 7.5 Hz, PC**C**), 21.4 (CH_3); ^{31}P NMR (162 MHz, $CDCl_3$): δ ppm 62.31; IR (neat, cm^{-1}) 2954, 2898, 2865, 2018, 1603, 1561, 1466, 1366, 1295, 1247, 754, 733, 699, 656, 525, 498; HRMS (ES+) calcd. for $C_{50}H_{63}OP_2Au_2$ [M]$^+$ 1135.3685, found 1135.3696.

Complex Id (diOMe)

Method A: (Acetonitrile)[(2-biphenyl)di-*tert*-butylphosphine]gold(I) hexafluoroantimonate (40.5 mg, 1 equiv.) and DIPEA (10 μL, 1.1 equiv.) were mixed in DCM (1 mL), then alkyne **1d** (4.2 mg, 0.5 equiv.) in DCM (1 mL) was added. After stirring for 5 min, 2 mL DCM was added and the mixture was washed with water (5 × 2 mL), the organic phase dried with Na_2SO_4, filtered and the solvents evaporated. The resulting powder was dissolved in ca. 0.25 mL DCM and 4 mL pentane added carefully and placed in the freezer overnight. The crystals were washed with pentane (5 × 1 mL) and dried in vacuo to give complex **Id** as a colourless powder (32.5 mg, 45 %).

^{1}H NMR (600 MHz, $CDCl_3$): δ ppm 7.87–7.85 (m, 2H, $CH_{Ar,\ ligand}$), 7.54–7.51 (m, 4H, $CH_{Ar,\ ligand}$), 7.36–7.30 (m, 6H, $CH_{Ar,\ ligand}$), 7.24–7.21 (m, 2H, $CH_{Ar,\ ligand}$), 7.11 (dd, 1H, *J* = 8.3/1.9 Hz, $CH_{Ar,\ acetylide}$), 7.09–7.07 (m, 4H, $CH_{Ar,\ ligand}$), 6.94 (dd, 1H, *J* = 8.4/1.5 Hz, $CH_{Ar,\ acetylide}$), 6.89 (d, 1H, *J* = 1.8 Hz, $CH_{Ar,\ acetylide}$), 3.95 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 1.39 (d, 36H, *J* = 15.7 Hz, *t*Bu); ^{13}C NMR (150 MHz, $CDCl_3$): δ ppm 151.3 ($C_{Ar,\ acetylide}$), 149.2 (d, *J* = 14.0 Hz, $C_{Ar,\ ligand}$), 148.6 ($C_{Ar,\ acetylide}$), 142.6 (d, *J* = 6.8 Hz, $C_{Ar,\ ligand}$), 133.9 (br s, $CH_{Ar,\ ligand}$), 133.3 (d, *J* = 7.7 Hz, $CH_{Ar,\ ligand}$), 131.1 (br s, $CH_{Ar,\ ligand}$), 129.3 $CH_{Ar,\ ligand}$), 129.0 $CH_{Ar,\ ligand}$), 128.0 ($CH_{Ar,\ ligand}$), 127.5 (d, *J* = 7.5 Hz, $CH_{Ar,\ ligand}$), 127.3 ($CH_{Ar,\ acetylide}$), 125.2 (d, *J* = 44.8 Hz, PC_{Ar}), 124.6 (t, *J* = 68.5 Hz, AuC), 118.2 (t, *J* = 11.4 Hz, Au**C**C), 115.3 ($CH_{Ar,\ acetylide}$), 112.5 ($C_{Ar,\ acetylide}$), 111.2 ($CH_{Ar,\ acetylide}$), 56.1 (2 × OCH_3), 38.0 (d, *J* = 22.7, **C**$(CH_3)_3$), 31.0 (d, *J* = 7.0 Hz, PC(**C**H_3)$_3$); ^{31}P NMR (162 MHz, $CDCl_3$): δ ppm 62.35; IR (neat, cm^{-1}) 2947, 2899, 2865, 2017, 1592, 1508, 1463, 1263, 1136, 1023, 753, 699, 655, 525; HRMS (ESI) calcd. for $C_{50}H_{63}O_2P_2Au_2$ [M]$^+$ 1151.3634, found 1151.3649.

Complex If (camphorOMe)

Method A: (Acetonitrile)[(2-biphenyl)di-*tert*-butylphosphine]gold(I) hexafluoroantimonate (21.2 mg, 1 equiv.) and DIPEA (10 μL, 2.1 equiv.) were mixed in DCM (0.5 mL), then alkyne **1f** (5.0 mg, 0.9 equiv.) in DCM (0.5 mL) added. After 10 min stirring, the mixture was washed with water (5 × 1 mL), the organic phase dried with Na_2SO_4, filtered and precipitated with pentane. The solvents were evaporated and the resulting powder was washed with pentane and dried in vacuo to give complex **If** as a colourless powder (15.5 mg, 40 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 7.90–7.86 (m, 2H, $CH_{Ar,\ ligand}$), 7.54–7.52 (m, 4H, $CH_{Ar,\ ligand}$), 7.35–7.26 (m, 6H, $CH_{Ar,\ ligand}$), 7.22–7.18 (m, 2H, $CH_{Ar,\ ligand}$), 7.13–7.08 (m, 4H, $CH_{Ar,\ ligand}$), 3.23 (s, OCH_3), 2.37–2.32 (m, 1H, CH_3OCCH_2), 1.85–1.76 (m, 3H, CCH_2CH_2 and CH_2CHCH_2 and $CHCH_2CH_2$), 1.49 (d, 1H, *J* = 13.6 Hz, CH_3OCCH_2), 1.42 (dd, 37H, *J* = 15.5/11.3 Hz, *t*Bu and CCH_2CH_2), 1.26–1.22 (m, 1H, $CHCH_2CH_2$), 0.950 (s, 3H, CH_3), 0.946 (s, 3H, CH_3), 0.88 (s, 3H, CH_3); ^{13}C NMR (150 MHz, $CDCl_3$): δ ppm 149.1 (d, *J* = 13.8 Hz, C_{Ar}), 133.8 (br s, CH_{Ar}), 133.4 (d, *J* = 7.5 Hz, CH_{Ar}), 132.1 (t, *J* = 11.8 Hz, Au**C**C), 131.2 (br s, CH_{Ar}), 129.4 (d, *J* = 5.4 Hz, CH_{Ar}), 129.3 (CH_{Ar}), 129.0 (CH_{Ar}), 127.8 (CH_{Ar}), 127.5 (d, *J* = 7.1 Hz, CH_{Ar}), 124.6 (d, *J* =

44.7 Hz, PC_{Ar}), 117.0 (t, J = 68.7 Hz, AuC), 85.0 (OC), 55.1 (CCH_3), 50.1 (OCH_3), 48.6 ($C(CH_3)_2$), 45.4 (CH_2CHCH_2), 44.0 (CH_3OCCH_2), 38.4 (dd, 24.4/24.4 Hz, P**C**$(CH_3)_3$), 32.8 (**C**CH_2CH_2), 31.0 (dd, J = 20.0/6.8 Hz, PC(**C**$H_3)_3$), 27.1 (C), 21.3 (CH_3), 20.8 (CH_3), 11.7 (CH_3); ^{31}P NMR (162 MHz, $CDCl_3$): δ ppm 61.95; IR (neat, cm^{-1}) 2950, 2900, 1471, 1391, 1369, 1170, 1084, 755, 702, 655, 526, 475; HRMS (ESI) calcd. for $C_{52}H_{71}OP_2Au_2$ $[M]^+$ 1167.4311, found 1167.4329.

General procedure for synthesis of Complexes V

A solution of (*R*)-(6,6′-dimethoxy-[1,1′-biphenyl]-2,2′-diyl)bis(diphenylphosphine) (9.9 mg, 0.017 mmol) in DCM (1 mL) was added to chloro(dimethyl sulfide)gold (10 mg, 0.034 mmol) in DCM (1 mL). The resulting solution was stirred for 5–10 min then silver hexafluoroantimonate (11.7 mg, 0.034 mmol) was added and the mixture filtered. A mixture of N-ethyl-N-isopropylpropan-2-amine (5 μL, 0.029 mmol) and alkyne **1a**, **1b** or **1g** (0.017 mmol) in a small amount of DCM was added. The mixture was stirred for 5–10 min then washed with water 5 × 1 mL, dried with Na2SO4, filtered and the solvents evaporated. The residue was washed with pentane (3 × 1 mL) to give the required gold complex. The complexes tended to retain a small amount of pentane and where necessary, the yield was calculated from ^{1}H NMR.

Complex Va (BIPHEP-CF3)

Complex **Va** was synthesised according to the general procedure above using alkyne **1a** (2.9 mg, 1.0 equiv.) to give the desired complex as a yellow solid (20.5 mg, 87 %). ^{1}H NMR (600 MHz, CD_2Cl_2): δ ppm 7.75 (d, 2H, $CH_{Ar,\ acetylide}$), 7.60–7.56 (m, 4H, 2 × $CH_{Ar,\ ligand,\ Ph}$, 2 × $CH_{Ar,\ acetylide}$), 7.54–7.51 (m, 4H, $CH_{Ar,\ ligand,\ Ph}$), 7.37–7.27 (m, 6H, $CH_{Ar,\ ligand,\ Ph}$), 7.29 (dt, 2H, J = 8.1/2.1 Hz, $CH_{Ar,\ ligand}$), 7.20–7.17 (m, 4H, $CH_{Ar,\ ligand,\ Ph}$), 7.13 (dd, 4H, J = 13.3/7.5 Hz, $CH_{Ar,\ ligand,\ Ph}$), 6.93 (dd, 2H, J = 9.8/8.1 Hz, $CH_{Ar,\ ligand}$), 6.61 (d, 2H, J = 8.4 Hz, $CH_{Ar,\ ligand}$), 2.91 (s, 6H, OCH_3); ^{13}C NMR (150 MHz, CD_2Cl_2): δ ppm 159.4–159.3 (m, 2C, **C**$OCH_{3,\ ligand}$), 136.1–136.0 (m, 4C, $CH_{Ar,\ ligand,\ Ph}$), 134.7–134.6 (m, 4C, $CH_{Ar,\ ligand,\ Ph}$), 133.4 (s, (m, 2C, $CH_{Ar,\ acetylide}$), 133.3 (m, 2C, $CH_{Ar,\ ligand,\ Ph}$), 132.5 (m, 2C, $CH_{Ar,\ ligand,\ Ph}$), 131.0–130.9 (m, 2C, $CH_{Ar,\ ligand}$), 130.3 (dm, 2C, J = 62.3 Hz, $PC_{Ar,\ ligand}$), 129.75–129.68 (m, 4C, $CH_{Ar,\ ligand,\ Ph}$), 129.3–129.2 (m, 4C, $CH_{Ar,\ ligand,\ Ph}$), 128.3 (d, 2C, J = 61.4 Hz, $PC_{Ar,\ Ph}$), 128.3–128.2 (m, 2C, P**C**$_{Ar,\ ligand}$), 126.7 (q, 1C, J = 3.3 Hz, **C**$HCCF_3$), 126.2 (d, 2C, J = 63.7 Hz, $PC_{Ar,\ Ph}$),125.2 (br s, 2C, P**C**$CH_{Ar,\ ligand}$), 123.9 (q, 1C, J = 272.8 Hz, CF_3), 123.8 (1C, $C_{Ar,\ acetylide}$), 117.6 (only HMBC, AuC**C**), 114.7 (s, 2C, $CH_{Ar,\ ligand}$), missing, AuC and **C**CF_3; ^{19}F NMR (376 MHz, CD_2Cl_2): δ ppm –63.34; ^{31}P NMR (162 MHz, $CDCl_3$): δ ppm 29.29; IR (neat, cm^{-1}) 3056, 2936, 2837, 1567, 1460, 1435, 1156, 1123, 1097, 1064, 1043, 845, 743, 691, 654, 500; HRMS (ES+) calcd. for $C_{47}H_{36}O_2F_3P_2Au_2$ [M+] 1145.1474, found 1145.1473.

Complex Vb (BIPHEP-OMe)

Complex **Vb** was synthesised according to the general procedure above using alkyne **1b** (2.3 mg, 1.0 equiv.) to give the desired complex as a yellow solid (19.4 mg, 85 %). ^{1}H NMR (600 MHz, CD_2Cl_2): δ ppm 7.58–7.52 (m, 6H, $CH_{Ar,\ ligand}$), 7.40–7.37 (m, 2H, $CH_{Ar,\ acetylide}$), 7.34–7.31 (m, 4H, $CH_{Ar,\ ligand}$), 7.29 (td, 2H, J = 8.3/2.5 Hz, $CH_{Ar,\ ligand}$), 7.28–7.23 (m, 2H, $CH_{Ar,\ ligand}$), 7.17–7.11 (m, 8H, $CH_{Ar,\ ligand}$), 7.03–7.01 (m, 2H, $CH_{Ar,\ acetylide}$), 6.97 (dd, 2H, J = 10.5/7.9 Hz, $CH_{Ar,\ ligand}$), 6.57 (d, 2H, J = 8.5 Hz, $CH_{Ar,\ ligand}$), 3.95 (s, 3H, $OCH_{3,\ acetylide}$), 2.87 (s, 6H, $OCH_{3,\ ligand}$); ^{13}C NMR (150 MHz, CD_2Cl_2): δ ppm 163.3 (s, 1C, **C**$OCH_{3,\ acetylide}$), 159.3–159.2 (m, 2C, **C**$OCH_{3,\ ligand}$), 136.2–136.1 (m, 4C, $CH_{Ar,\ ligand,\ Ph}$), 135.8 (s, 2C, $CH_{Ar,\ acetylide}$), 134.8–134.7 (m, 4C, $CH_{Ar,\ ligand,\ Ph}$), 133.0 (s, 2C, $CH_{Ar,\ ligand,\ Ph}$), 132.1 (s, 2C, $CH_{Ar,\ ligand,\ Ph}$), 130.81–130.74 (m, 2C, $CH_{Ar,\ ligand,\ Ar}$), 130.7 (dm, 2C, J = 63.1 Hz, PC_{Ar}), 129.44–129.37 (m, 4C, $CH_{Ar,\ ligand,\ Ph}$), 129.07–128.99 (m, 4C, $CH_{Ar,\ ligand,\ Ph}$), 128.4 (dm, 2C, J = 61.5 Hz, PC_{Ph}), 128.2–128.1 (m, 2C, PCC), 126.3 (dm, 2C, J = 63.2 Hz, PC_{Ph}), 125.2 (br s, 2C, $CH_{Ar,\ ligand,\ Ar}$), 119.5 (t, J = 72.2 Hz, AuC), 115.4 (s, 2C, $CH_{Ar,\ acetylide}$), 114.4 (s, 2C, $CH_{Ar,\ ligand,\ Ar}$), 110.9 (s, 1C, C≡**C**C), 56.3 (s, 1C, $OCH_{3,\ acetylide}$), 55.2 (s, 2C, $OCH_{3,\ ligand}$), AuC**C** not visible; ^{31}P NMR (162 MHz, CD_2Cl_2): δ ppm 29.42; IR (neat, cm^{-1}) 3053, 2936, 2837, 1998, 1597, 1435, 1255, 1167, 1156, 1086, 1042, 1025, 836, 785, 743, 653, 500; HRMS (ES+) calcd. for $C_{47}H_{39}O_3P_2Au_2$ [M+] 1107.1705, found 1107.1721.

Complex Vg (BIPHEP-H)

Complex **Vg** was synthesised according to the general procedure above using alkyne **1g** (1.7 mg, 1.0 equiv.) to give the desired complex as a yellow solid (18.8 mg, 84 %). ^{1}H NMR (600 MHz, CD_2Cl_2): δ ppm 7.64–7.61 (m, 1H, $CH_{Ar,\ acetylide}$), 7.59–7.50 (m, 9H, 2 × $CH_{Ar,\ acetylide}$ and 7 × $CH_{Ar,\ ligand,\ Ph}$), 7.44–7.43 (m, 2H, $CH_{Ar,\ acetylide}$), 7.34–7.32 (m, 4H, $CH_{Ar,\ ligand,\ Ph}$), 7.30–7.28 (m, 4H, 2 × $CH_{Ar,\ ligand}$ and 2 × $CH_{Ar,\ ligand,\ Ph}$), 7.16–7.12 (m, 7H, $CH_{Ar,\ ligand,\ Ph}$), 6.97 (dd, 2H, J = 10.8/8.0 Hz, $CH_{Ar,\ ligand}$), 6.58 (d, 2H, J = 8.3 Hz, $CH_{Ar,\ ligand}$), 2.88 (s, 6H, OCH_3); ^{13}C NMR (150 MHz, CD_2Cl_2): δ ppm 159.3–159.2 (m, 2C, **C**$OCH_{3,\ ligand}$), 136.2–136.1 (m, 4C, $CH_{Ar,\ ligand,\ Ph}$), 134.8–134.7 (m, 4C, $CH_{Ar,\ ligand,\ Ph}$), 133.4 (s, 2C, $CH_{Ar,\ acetylide}$), 133.1 (s, 2C, $CH_{Ar,ligand,\ Ph}$), 132.4 (s, 2C, $CH_{Ar,ligand,\ Ph}$), 132.2 (s, 1C, $CH_{Ar,\ acetylide}$), 130.9–130.8 (m, 2C, $CH_{Ar,\ ligand}$), 130.5 (dm, 2C, J = 62.7 Hz, PC_{Ar}), 129.8 (s, 2C, $CH_{Ar,\ acetylide}$), 129.53–129.47 (m, 4C, $CH_{Ar,\ ligand,\ Ph}$), 129.07–128.99 (m, 4C, $CH_{Ar,\ ligand,\ Ph}$), 128.3 (dm, 2C, J = 61.4 Hz, PC_{Ph}), 128.3–128.2 (m, 2H, PC**C**), 126.3 (dm, 2C, J = 63.2 Hz, PC_{Ph}),125.2 (br s, 2C, $CH_{Ar,\ ligand}$), 122.9 (t, J = 72.2 Hz, AuC), 121.4 (t, J = 6.6 Hz, AuC**C**), 119.7 (s, $C_{Ar,\ acetylide}$), 114.5 (s, 2C, $CH_{Ar,ligand}$), 55.2 (s, 2C, $OCH_{3,\ ligand}$); ^{31}P NMR (12 × $CH_{Ar,\ acetylide}$ and 7 × $CH_{Ar,\ Ph}$), 62 MHz, $CDCl_3$): δ ppm 29.35; IR (neat, cm^{-1}) 3053, 2935, 2836, 1567, 1460, 1434, 1264, 1155, 1086, 1042, 743, 690, 653, 501; HRMS (ES+) calcd. for $C_{46}H_{37}O_2P_2Au_2$ [M+] 1077.1600, found 1077.1621.

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Keywords: Chirality · Gold(I) complexes · Acetylides · Propargylic substrates · Catalytic activity

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Supporting Information

Preparation and Catalytic Activity of Novel σ,π-Dual Gold(I) Acetylide Complexes

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Contents:

1. ^{1}H and ^{13}C NMR Spectra of compounds 1f, 4d, 6b, 8, 12……S2
2. ^{1}H and ^{13}C NMR Spectra of complexes I and V……S7

Figure S1. ^{1}H NMR spectrum of (*1R*,*2S*,*4R*)-2-Ethynyl-2-methoxy-1,7,7-trimethylbicyclo[2.2.1]heptane (**1f**)

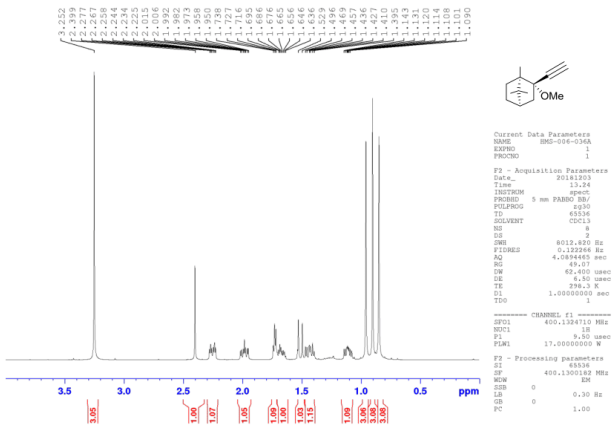


Figure S2. ^{13}C NMR spectrum of (*1R*,*2S*,*4R*)-2-Ethynyl-2-methoxy-1,7,7-trimethylbicyclo[2.2.1]heptane (**1f**)

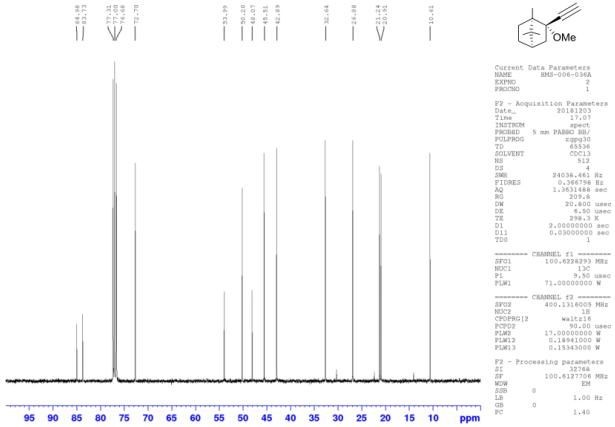


Figure S3. ^{1}H NMR spectrum of *N*,4-dimethyl-N-vinylbenzenesulfonamide (**4d**)

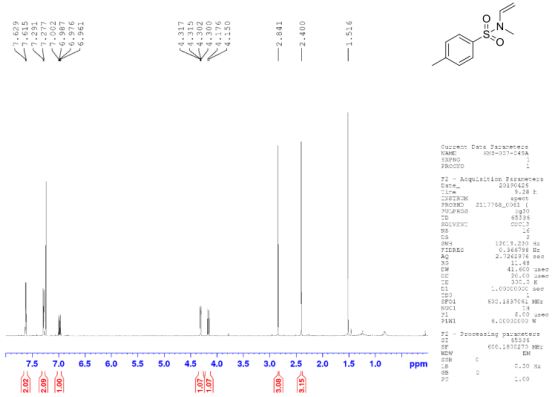


Figure S4. ^{13}C NMR spectrum of *N*,4-dimethyl-N-vinylbenzenesulfonamide (**4d**)

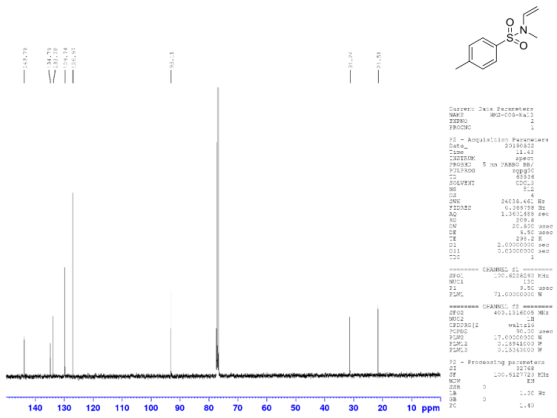


Figure S5. ^{1}H NMR spectrum of 1-((*1S,2R*)-3-methoxy-2-phenylcyclopent-3-en-1-yl)pyrrolidin-2-one (**6b**)

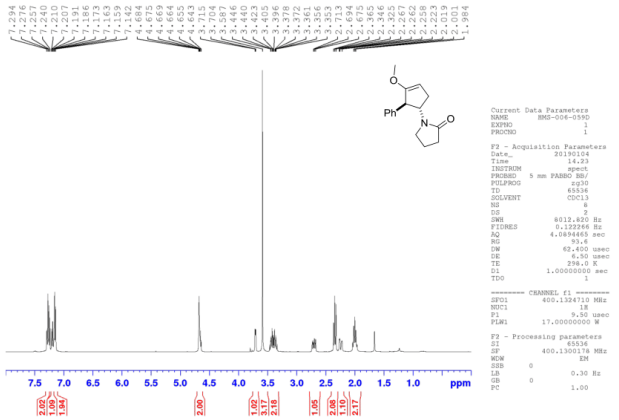


Figure S6. ^{13}C NMR spectrum of 1-((*1S,2R*)-3-methoxy-2-phenylcyclopent-3-en-1-yl)pyrrolidin-2-one (**6b**)

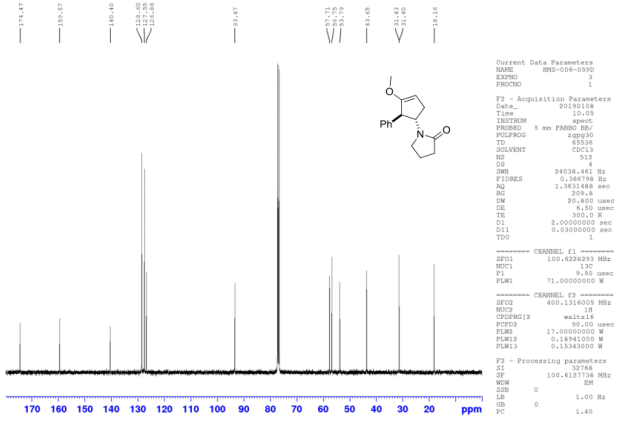


Figure S7. ^{1}H NMR spectrum of (*4R,5R*)-4-((N,4-dimethylphenyl)sulfonamido)-5-(4-methoxyphenyl)cyclopent-1-en-1-yl acetate (**8**)

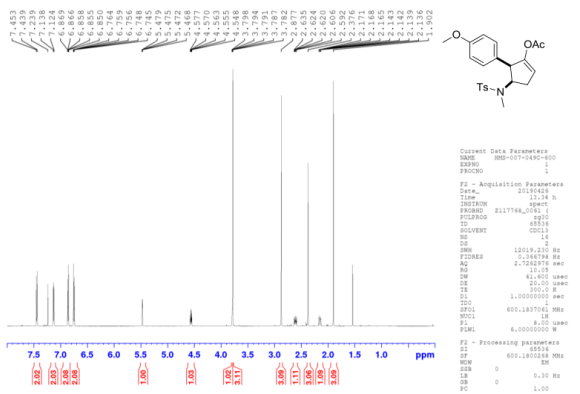


Figure S8. ^{13}C NMR spectrum of (*4R,5R*)-4-((N,4-dimethylphenyl)sulfonamido)-5-(4-methoxyphenyl)cyclopent-1-en-1-yl acetate (**8**)

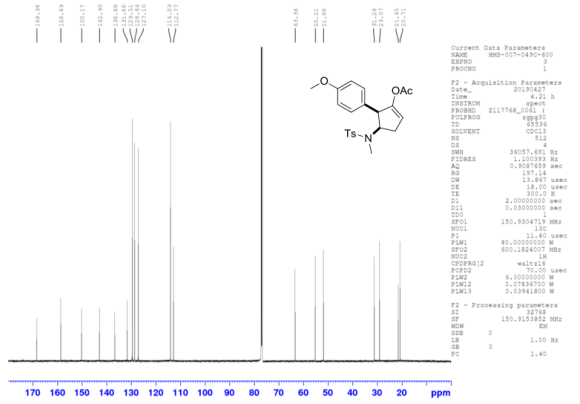


Figure S9. ^{1}H NMR spectrum of 3-phenyl-3a,5,6,7-tetrahydro-4H-inden-1-yl acetate (**12**)

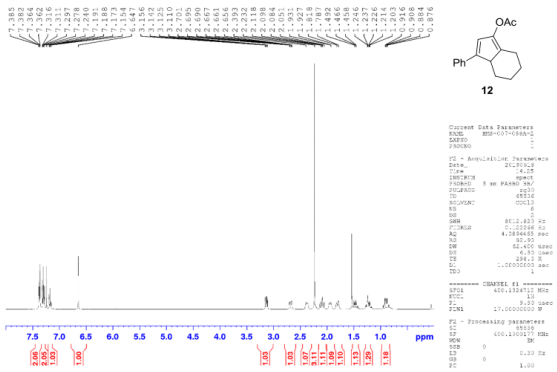


Figure S10. ^{13}C NMR spectrum of 3-phenyl-3a,5,6,7-tetrahydro-4H-inden-1-yl acetate (**12**)

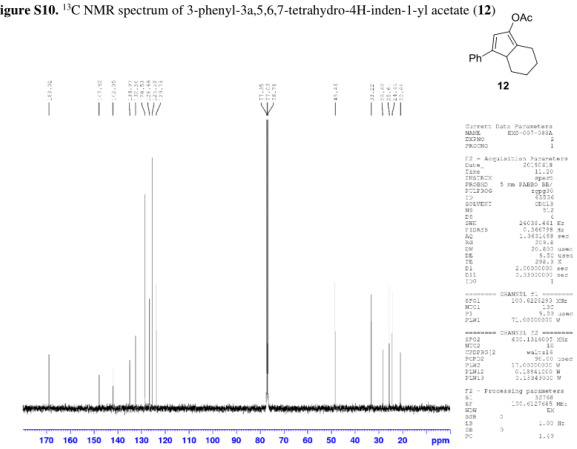


Figure S11. ^{1}H NMR spectrum of Complex **Ia** (CF_3)

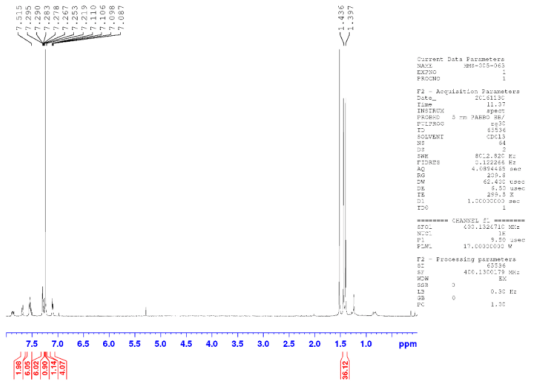


Figure S12. ^{13}C NMR spectrum of Complex **Ia** (CF_3)

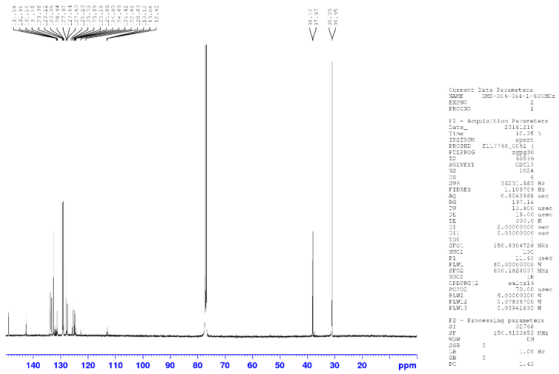


Figure S13. ^{1}H NMR spectrum of Complex **Ic** (Me/OMe)

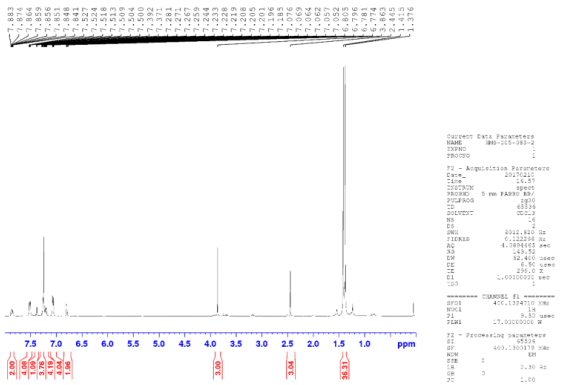


Figure S14. ^{13}C NMR spectrum of Complex **Ic** (Me/OMe)

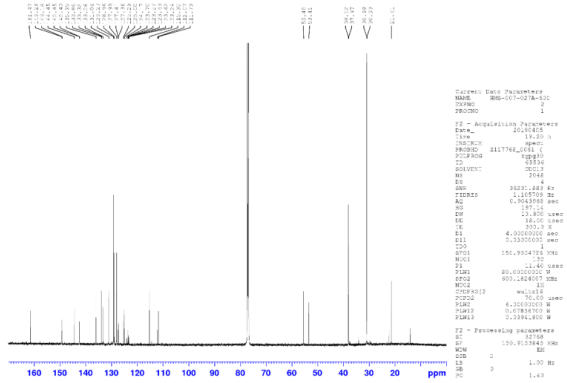


Figure S15. ^{1}H NMR spectrum of Complex **Id** (diOMe)

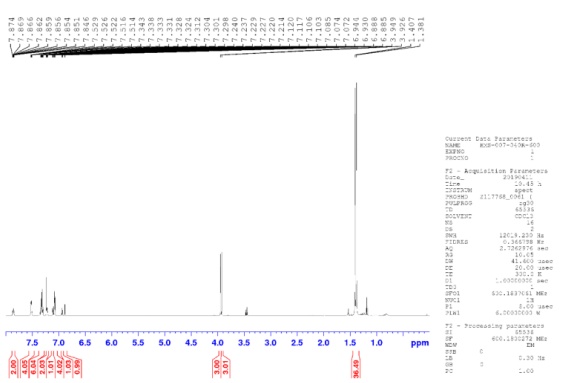


Figure S16. ^{13}C NMR spectrum of Complex **Id** (diOMe)

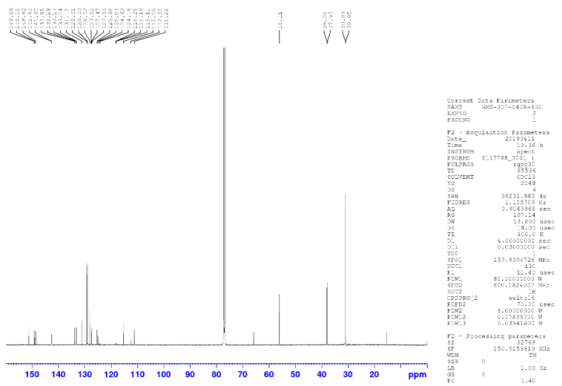


Figure S17. ^{1}H NMR spectrum of Complex **If** (camphorOMe)

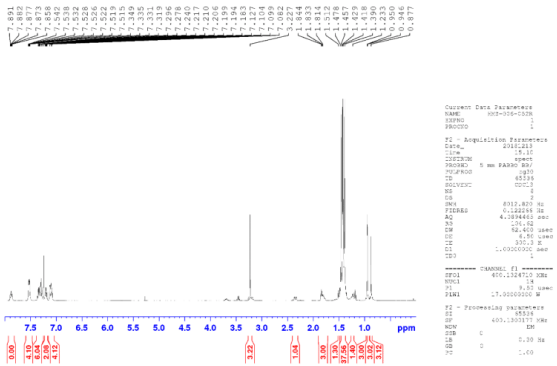


Figure S18. ^{13}C NMR spectrum of Complex **If** (camphorOMe)

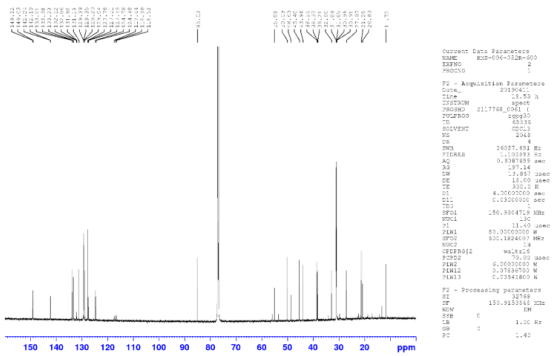


Figure S19. ^{1}H NMR spectrum of Complex **Va** (BIPHEP-CF_3)

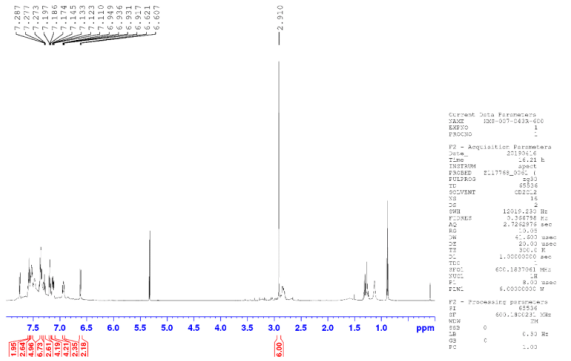


Figure S20. ^{13}C NMR spectrum of Complex **Va** (BIPHEP-CF_3)

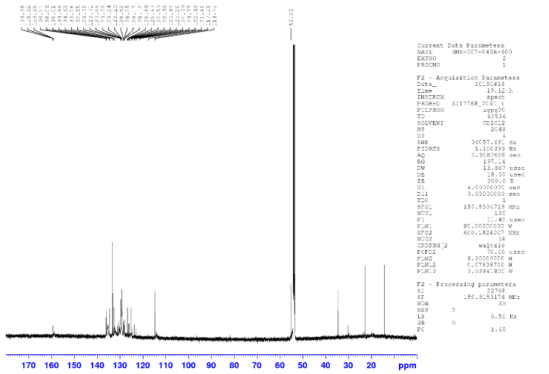


Figure S21. ^{1}H NMR spectrum of Complex **Vg** (BIPHEP-H)

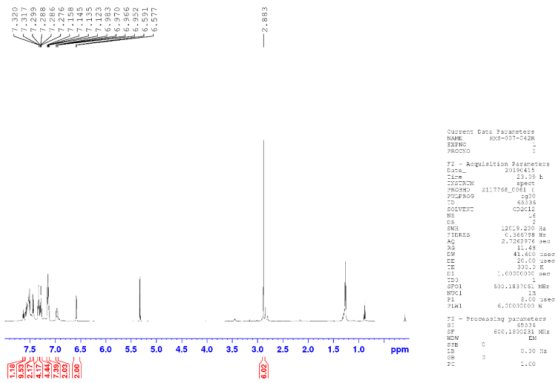


Figure S22. ^{13}C NMR spectrum of Complex **Vg** (BIPHEP-H)

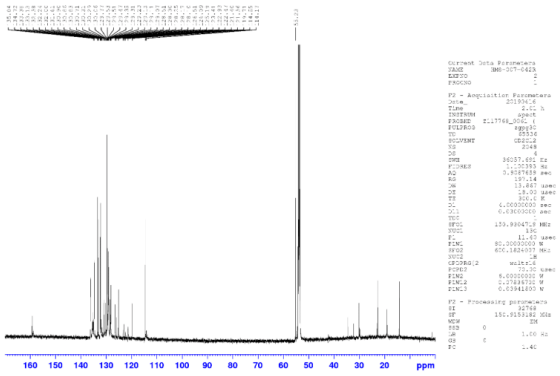


Figure S23. ^{1}H NMR spectrum of Complex **Vb** (BIPHEP-OMe)

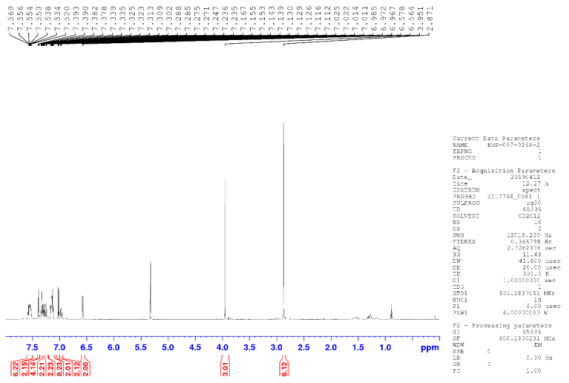
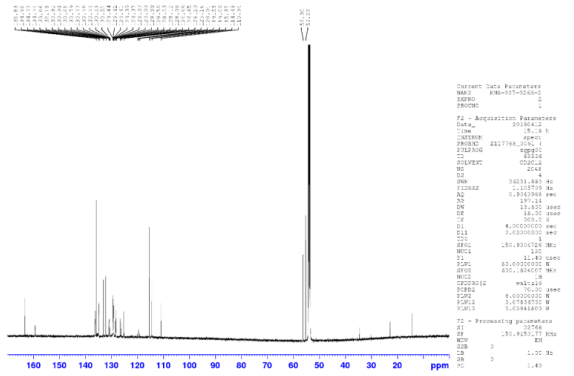


Figure S24. ^{13}C NMR spectrum of Complex **Vb** (BIPHEP-OMe)



PAPER V

Au(I)-catalyzed cycloaddition pathways of non-terminal propargyl substrates

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Au(I)-catalysed cycloaddition pathways of non-terminal propargyl substrates

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Abstract:

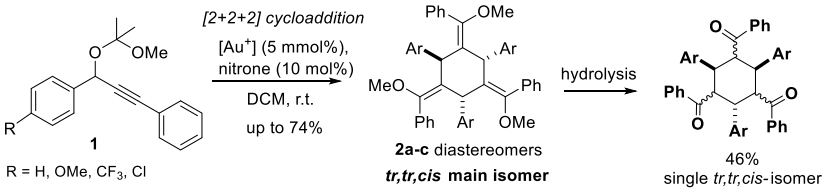
Novel chiral menthol-based pyridyl nitrone ligands were synthesised and Au(I) coordination of the ligands gave chiral Au(I)-nitrone complexes. ^{1}H NMR studies of the gold(I) coordination experiments with nitrone ligands afforded a convenient method for monitoring complex formation. The catalytic effect of Au(I)-nitrone complexes, shown to tune catalytic systems to produce uncommon products, was evaluated in [2+2+2] cyclotrimerization and [2+4] cyclodimerization reactions of non-terminal propargyl acetals. Alternative gold(I)-catalysed [2+2], [2+4] and [3+4] cycloaddition reaction pathways of non-terminal propargyl acetals with imine substrates gave a diverse range of *N*-heterocyclic products. The present screening study demonstrates the potential and the versatility of non-terminal propargyl acetals in gold(I)-catalyzed cycloaddition reactions.

Key words: non-terminal propargyl acetals; cyclo-trimerization/-dimerization; gold(I)-nitrone complexes; azetidine; benzazepine; piperidine

Introduction

The intensive development of gold chemistry the last decade has mainly focused on the discovery and understanding of new gold(I)-catalysed reactions as well as the construction of new gold(I)-ligated complexes. We have contributed to the development of gold catalysis in organic synthesis in recent years by the development of a number of cycloaddition reactions based on the highly reactive terminal propargyl acetal substrates and a series of reactants, including nitrones.[1-10]

We have previously studied the interesting dual aspect of nitrones in gold-catalysed reactions, both as substrate in gold(I)-catalysed [3+3] cycloaddition with propargyl acetals,[5] but also as catalytic additives in gold(I)-catalysed reactions, tuning the catalytic system to produce uncommon products. We have shown that gold(I)-nitrone complexes, either generated *in situ* or isolated prior to reaction, may catalyse unusual transformations, such as regio- and chemoselective [2+2+2] cyclotrimerization of non-terminal 1,3-diaryl propargyl acetals **1** (Scheme 1).[8, 10] The cyclohexylidene trimeric products **2a-c** (up to 74% yield) were obtained as a mixture of three stereoisomers. Hydrolysis allowed isolation of 46% of the main *trans,trans,cis*-diastereomer.



Scheme 1. Gold(I)-nitrone-catalyzed [2+2+2] cyclotrimerization of diarylpropargyl acetal **1**.

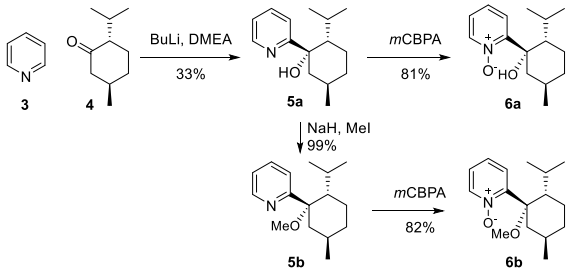
The cyclotrimerization approach demonstrates the ability of nitrones to tune the catalytic activity of Au(I) complexes and that unusual transformations may take place in the presence of Au(I)-nitrone complexes, which represent an interesting group of Au(I) catalysts with specific properties. Chiral nitrones have been used as Lewis bases to induce enantioselectivity in organic reactions[11, 12] and would have the potential to act as chiral ligands and thereby afford enantioselective gold-catalysed reactions.

Our previous results show that non-terminal propargyl substrates have ability to undergo uncommon cycloaddition reactions. Therefore, we have further studied the potential cycloaddition pathways which may take place with non-terminal propargyl acetals in the presence of either new prepared chiral Au(I)-nitrone complexes or conventional Au(I) catalysts.

Results and Discussion

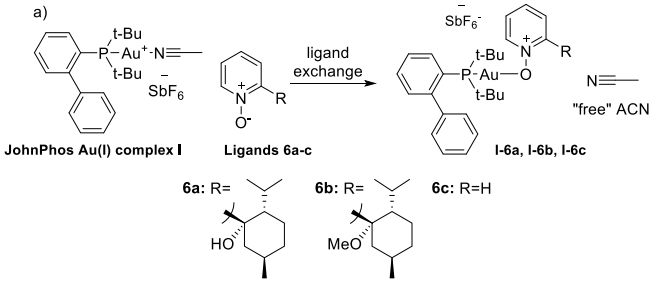
1. Synthesis of chiral nitrone ligands and Au(I)-nitrone complexes

The chiral nitrone ligands **6a** and **6b** were synthesised via 2-pyridyl-menthol intermediate **5a**, which was formed (33%, Scheme 2) by enantioselective addition of lithiated pyridine to (-)-menthone **4**.[9] The methyl-ether **5b** was obtained in quantitative yields by methylation of alcohol **5a**. Oxidation of pyridyl-menthol derivatives **5a** and **5b** gave the chiral nitrone ligands **6a** and **6b** in high yields (81-82%).



Scheme 2. Synthesis of chiral nitrone ligands **6a** and **6b.**

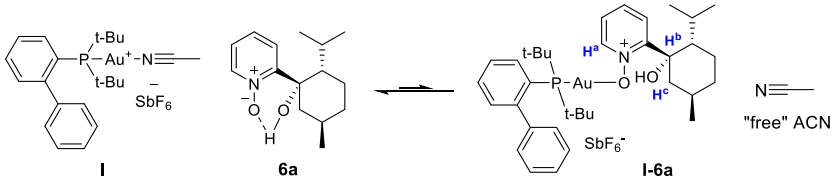
Prior to use in reactions, Au(I)-nitrone complexes **I-6a**, **I-6b** and **I-6c** were generated in situ by acetonitrile ligand exchange of the JohnPhos Au(I)-ACN complex **I** with the chiral pyridyl-nitrone ligands **6a** and **6b** as well as the non-substituted pyridine *N*-oxide **6c** (Scheme 3; 1:2 ratio of complex **I**:nitrone **6**).



Scheme 3. In situ generation of Au(I)-nitrone complexes (**I-6a,b,c**) by ligand exchange of JohnPhosAu(I)(ACN)SbF_6 complex **I** with nitrones **6a-c**.

2. ^{1}H NMR coordination studies

^{1}H NMR analysis of gold(I) coordination experiments with nitrone ligands, afforded a convenient method for monitoring Au(I) coordination (Scheme 4). The coordination abilities of pyridine-nitrones **6a** and **6b** to JohnPhosAu(I)SbF_6 complex **I** to give chiral nitrone complexes **I-6a** and **I-6b** were clearly ascertained by comparing the changes in ^{1}H NMR shifts going from pure nitrone (**6a** or **6b**) and gold(I) complex **I**, respectively (Figures 1a,b and d), to 1:1 mixtures of the relevant nitrone (**6a** or **6b**) and Au(I) complex **I** (Figures 1c and e).



Scheme 4. Coordination of nitrone **6a** with JohnPhosAu(ACN)SbF_6 **I**, shown as an equilibrium between [complex **I** + **6a**] and [complex **I-6a** + "free" ACN].

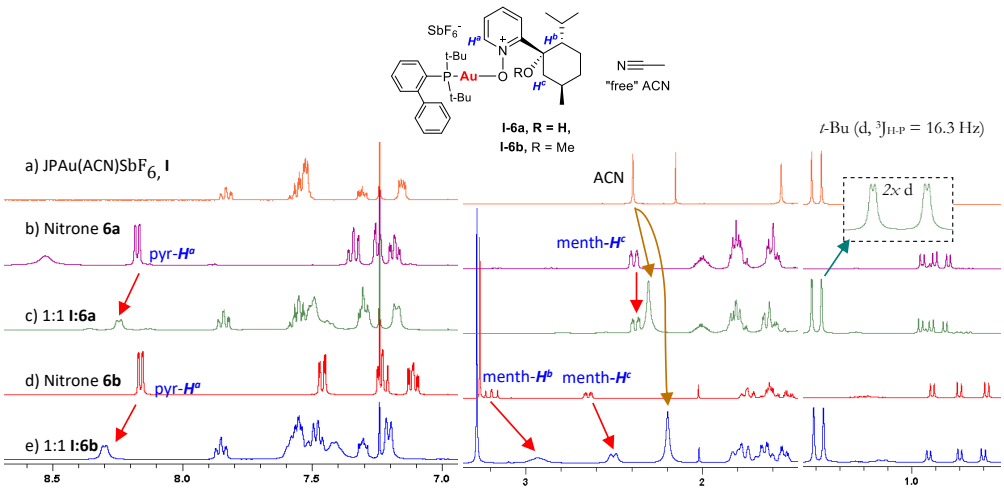


Figure 1. ^{1}H NMR study of nitrones **6a** and **6b** coordination with JohnPhosAu(ACN)SbF_6 **I** (1:1 in $CDCl_3$).

Formation of gold complex **I-6b** by **c**oordination of nitrone ligand **6b** with Au(I) complex **I** is clearly visible by ^{1}H NMR (Figure 1d,e). All pyridine protons of nitrone **6b** are deshielded, but the most significant increases in chemical shifts ($\Delta\delta^{1}H_{coord} = \delta^{1}H_{complex} - \delta^{1}H_{ligand}$) were observed for the pyr-***H***^{a} proton signal ($\Delta\delta^{1}H_{coord}$ 0.11 ppm). The opposite effect was seen for menthyl protons ROCC***H***^{b} and ROCC***H***$^{c}_{2}$, which were strongly shielded ($\Delta\delta^{1}H_{coord}$ −0.29 ppm and −0.17 ppm, respectively). The up-field shift of the ligated ACN signal of Au(I)-complex **I** (from 2.39 ppm to 2.20 ppm; $\Delta\delta^{1}H_{coord}$ −0.19 ppm, Figure 1a,e) is a characteristic proof of ACN de-coordination and ligand exchange to give non-ligated "free" acetonitrile.[13] Also the aromatic protons of the phosphane ligand experienced minor deshielding effects.

Similar changes were observed for the **I:6a** mixture, indicating coordination of nitrone **6a**, as well. However, a weaker observed effect on the Au(I)-ACN signal (Figure 1a,c), may indicate less efficient displacement of the ACN ligand and, hence, that nitrone **6a** is less strongly coordinated to the Au(I) than nitrone **6b**. A minor change of the *t*-Bu doublet ($^{3}J_{H-P}$ = 16.3 Hz), which appears as two doublets in the **I:6a** mixture, indicates that diastereotopic *t*-Bu groups are formed by coordination of the chiral ligand (Figure 1b, expanded). Thus, the chiral nitrone **6a** may have a greater steric effect on the phosphane ligand than nitrone **6b** when coordinated to the Au(I) center.

Generally, the nitrone (**6a** and **6b**) signals in the 1:1 mixtures are broader, indicating a dynamic ligand exchange (Scheme 4). Several observations confirm that nitrone **6b** is more strongly bonded to the Au center than nitrone **6a**, as the menthol proton signals are more strongly shielded and the ligated ACN peak is more affected for mixture **I:6b** compared to mixture **I:6a**. Intramolecular H-bonding in the non-methylated nitrone **6a** unit (Scheme 4), shown in the crystal structure for **I-6a** (X-ray, Figure 3), provides one explanation for the weaker coordination of ligand **6a**, compared to ligand **6b**, as H-bonding is not possible in the methylated nitrone **6b**

The Au(I) complexation of chiral nitrones **6a** and **6b** appears to be weaker compared to previously reported gold-nitrone complexes[10] which gave sharp ^{1}H NMR peaks for 1:1 mixtures of complex **I** and nitrones. The bulkiness of the chiral nitrones **6a** and **6b** may affect the ability to undergo coordination to gold(I). To get better understanding of the dynamics of the Au(I)-nitrone coordination and the equilibrium between coordinated and uncoordinated states (Scheme 4), further ^{1}H NMR studies of complex **I** and nitrone **6a** were carried out with increasing amounts of nitrone (ratio **I:6a** 1:1, 1:2, 1:5 and 1:10, Figure 2 and Table 1).

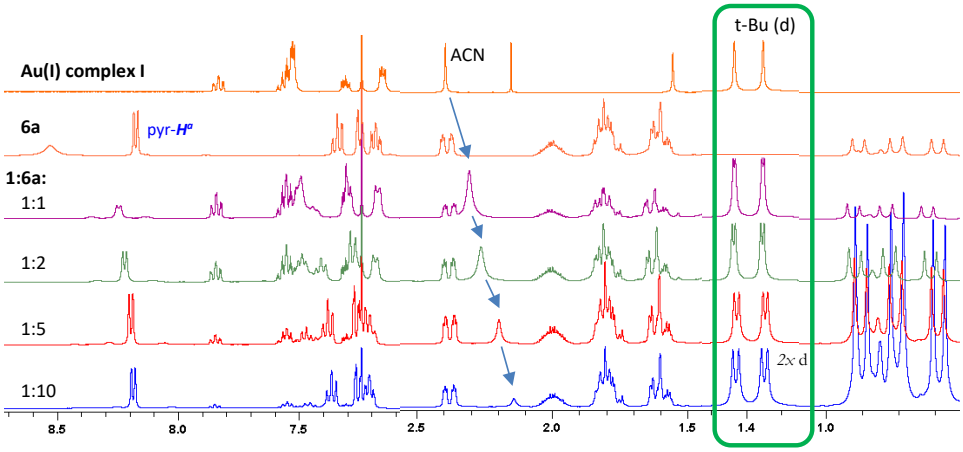


Figure 2. ^{1}H NMR coordination study of nitrone **6a** with Au(I) complex **I** with different **I:6a** ratios.

A minor deshielding effect on the pyr-***H***^{a} proton was initially observed by a 1:1 ratio (Table 1, entry 1). By increasing to excess amount of ligand **6a**, the presence of only one pyr-***H***^{a} doublet indicates a dynamic process, and not two distinct nitrone states. ^{1}H NMR of the mixtures showed that the ACN methyl signal was strongly affected by increased amount of nitrone **6a**, almost reaching the expected value of 2.10 ppm[14] for "free" acetonitrile at 1:10 (**I:6a**) ratio (Table 1, entry 2). In contrast to ligand **6b** (Figure 1a,e), ligand exchange of nitrone **6a** with the ACN is less favoured, as excess of nitrone appears necessary to promote full coordination to the gold centre. By excess amount of ligand **6a**, the phosphane *tert*-butyl doublet splits into two doublets with increased difference in chemical shift ($\Delta\delta_{diastereomer}$ up to 0.009 ppm), demonstrating a significant diastereotopic effect by Au(I)-nitrone **2a** coordination (Table 1, entry 4), as also seen to a lesser extent above (Figure 1c).

Table 1. Changes in ^{1}H NMR peak shifts, $\Delta\delta^1H_{coord}$[a] (ppm), of mixtures with decreasing **I:6a** ratio.

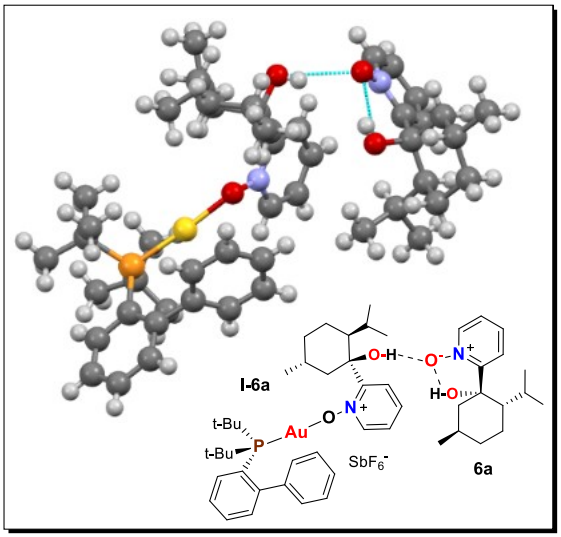
Entry	Signal observed	δ (ppm)	I:6a ratio: 1:1	1:2	1:5	1:10
				$\Delta\delta^1H_{coord}$[a]		
1	**6a**: *H*^{a}	8.17	0.07	0.05	0.04	0.01
2	**I**; ACN	2.39	0.08	0.13	0.19	0.25 (δ 2.14)
3	**I:** *t*-Bu (d)	1.40	0	0	−0.01	−0.01
4	**I-6a** (2x d)	1.40	0.003[b]	0.005[b]	0.007[b]	0.009[b]

[a] $\Delta\delta^1H_{coord} = \delta^1H_{complex} - \delta^1H_{ligand}$; [b] $\Delta\delta^1H_{diastereomer} = \delta^1H_{isomer\ 1} - \delta^1H_{isomer\ 2}$

Similar ^{1}H NMR coordination studies of nitrones **6a** and **6b** with the Au(I)-phosphane complex $Ph_3PAuSbF_6$ showed possible Au(I) coordination, in addition to decomposition of the phosphane or nitrone ligand. Coordination of $Me_3PAuSbF_6$ failed. The previously isolated Ph_3PAu(I)-nitrone complex **II-6d**[10] (Figure 3) was obtained in much lower yields (38%) than the corresponding JohnPhos-Au(I)-nitrone complex **I-6d** (74%), indicating lower coordination ability of the less electron-rich PPh_3 ligand to give stable gold(I)-nitrone complexes.

3. Crystal structures (X-ray)

Crystalline complex **I-6a** was successfully obtained and the crystal structure was confirmed by X-ray analysis (Figure 3), which showed the expected nearly linear nitrone-O-Au(I)-P coordination mode (176.9°). The deviation from linearity is less than for previously characterised[10] complex **I-6d**, and slightly more than observed for pyridine-*N*-oxide complex **I-6c**, likely due to steric effects. The shorter O-Au bond length (2.064 Å) of chiral complex **I-6a** than for **I-6c** and benzaldimine nitrone **I-6d**, indicates that nitrone ligand **6a** is more strongly bonded to the Au(I) center. This may be due to an electron donating effect of the menthol unit. The short N-O bond length of complex **I-6a** (1.349 Å) was similar to complex **I-6c**, indicating a N-O double bond character. The Au-P bond length (2.225 Å) in complex **I-6a** was comparable to that for complex **I-6c**, but shorter than for complex **I-6d**, likely due to the size of nitrone.



Complex	O-Au	Au-P	N-O	O-Au-P angle
I-6a	2.064	2.225	1.349	176.9
I-6c[10]	2.074	2.230	1.349	177.4
I-6d[10]	2.096	2.243	1.340	174.9

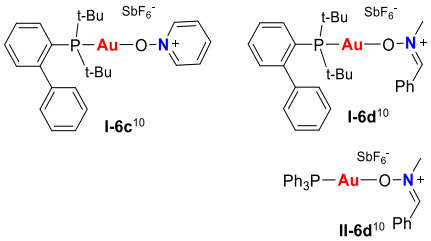


Figure 3. Crystal structure (X-ray) of Au(I)-nitrone complex **I-6a**. Selected bond lengths (Å) and angles (°) in gold(I)-nitrone complexes **I-6a**, **I-6c** and **I-6d** are given.

An uncoordinated nitrone **6a** unit, also visible in the crystal structure (Figure 3, right), enables Au(I)-nitrone coordination by hindering intramolecular hydrogen-bonding of ligand **6a**, as the O-atom of the "free" nitrone unit forms an intermolecular H-bond to the OH group of the ligated nitrone **6a**. The intramolecular H-bond within the uncoordinated nitrone also supports the theory that nitrone **6a** has a poorer coordination ability to the Au center than MeO-nitrone **6b** because of competing internal H-bonds.

4. Cycloaddition reactions of non-terminal propargyl acetals

The catalytic properties of the gold-nitrone complexes **I-6a, I-6b** and **I-6c** were evaluated in gold-catalysed [2+2+2] cyclotrimerization[8] and [2+4] cyclodimerisation of novel propargyl acetal **10** (Tables 2-4).

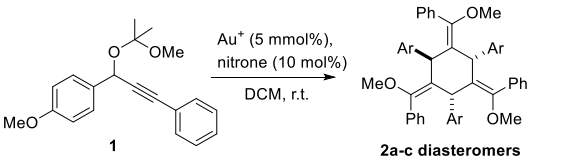
4.1 Catalytic effect of gold-nitrone complexes.

- *[2+2+2] Cyclotrimerisation.* The catalytic ability of complexes **I-6a, I-6b** and **I-6c** were tested in the gold(I)-nitrone-catalysed [2+2+2] cyclotrimerization reaction of 1,3-diarylpropargyl acetals (**1**), which we have reported[10] to give cyclohexylidene products **2**. The presence of catalytic amounts of different nitrones was previously shown to be essential for successful selective cyclotrimerization, as Au(I) complex **I** gave no product **2** and complex product mixtures from diarylpropargyl acetal **1** in the absence of nitrone (Table 2, entry 1). A relevant hypothesis is that Au catalyst **I** is too active to afford selective trimerization, and that the reduced Au-catalyst activity by nitrone-Au coordination allows controlled chemoselective trimerization to take place.

The trimer **2** was obtained in moderate to good yields (40-73%) as mixtures of three diastereomers (**2a-c**, Table 2, entries 2-4). Complex **I-6b** gave highest yield (73%, entry 3), similar to the best yields reported[8] for this reaction (74%, entry 5, nitrone **6c**, counterion NTf_2). Complex **I-6a** gave lower yield (40%, entry 2), possibly because nitrone **6a** is more poorly coordinated to gold(I) than nitrone **6b**, as discussed above. The success of the cyclotrimerisation reaction demands careful tuning of catalytic activity of the gold complex, and a stronger deactivation of the gold center than that provided by nitrone **6a** appears to be necessary.

Some differences in the diastereoisomeric product distribution (**2a-c**) were observed. Complex **I-6a** gave highest stereoselectivity towards the main *trans,trans,cis*-diastereomer (55%, entry 2), while nitrone complex **I-6b** was slightly more selective towards isomer **2b** than nitrone complex **I-6c** (35% vs 25%). The different isomer ratios could be attributed to a combination of factors, such as the bulk of the nitrones, as well as the strength of nitrone coordination to the gold center. Chiral HPLC separation of the three pairs of enantiomers in the product mixture for determination of possible % ee, was unsuccessful in our hands.

Table 2. Gold(I)-catalysed [2+2+2] cyclotrimerisation of propargyl acetal **1** to trimer **2**.

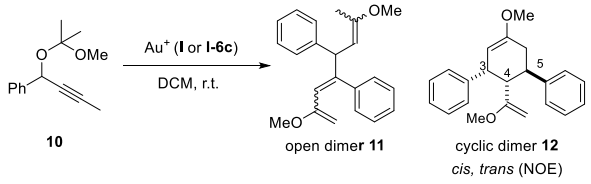


Entry	Au(I) complex	Time	Yield	**2a**[b]:**2b**:**2c**
1	**I**	2-24 h	-[8]	-
2	**I-6a**	18 h	40%	55:25:20
3	**I-6b**	18 h	73%	45:35:20
4	**I-6c**[10]	18 h	66%	45:25:30
5	**I-6c**[c, 8]	2 h	74%	n.r.[d]

a) complex product mixture; b) **2a** = *trans,trans,cis*; main product; c) (JohnPhosAuCl)$AgNTf_2$-**6c**,[8] d) n.r.: ratio not reported.

- *[2+4] Cyclodimerisation:* As previous studies on non-terminal propargyl substrates only included phenyl-substituted propargyl acetals, such as diarylpropargyl substrate **1**[10] above, the reactivity of methyl-aryl-propargyl acetal **10** was explored. Catalytic amounts of both complexes **I** and **I-6c** gave full conversion of acetal **10**, however, to different products; proposed to be the open and the cyclic dimeric products **11** (25%) and **12** (30%), respectively (Table 3). Both products were rather unstable.

Table 3. Gold(I)-catalysed dimerisation of propargl acetal **10**.

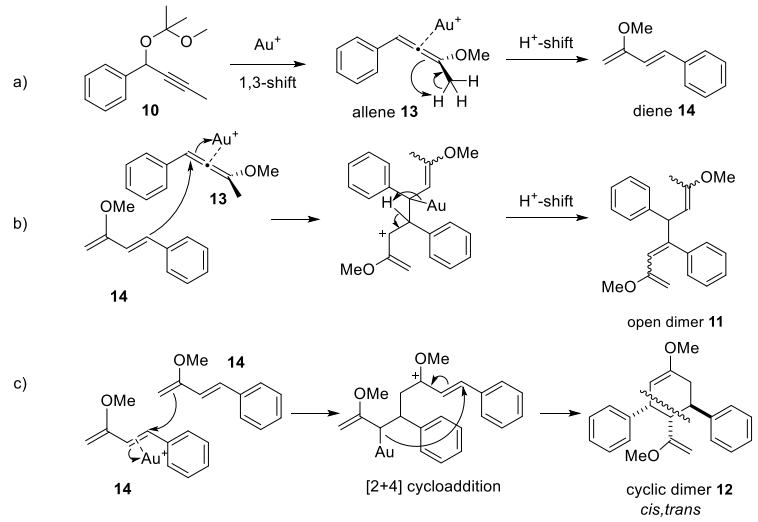


Au(I) complex	Time	Yield
I	2 h	**11**, 25%[a]
I-6c	24 h	**12**, 30%[a]

a) Unstable.

The different dimerization reaction pathway of methyl-aryl-propargyl acetal **10** from the trimerization taking place with diaryl-propargyl substrate **1**, may be explained by the proposed pathways for the formation of the octatriene **11** and *cis,trans*-cyclohexene **12** dimer products (Scheme 5). The trimerization of diaryl substrate **1** is proposed to proceed through [2+2+2] cycloaddition of allenic intermediates after gold-catalysed 1,3-alkoxy rearrangement.[10] In accordance with literature,[8] the propargyl acetal **10** undergoes a gold-catalyzed 1,3-methoxy shift to give allenic intermediate **13**. However, unlike the mechanism for diaryl-propargyl acetals, the methyl-substituted allene **13** may undergo proton shift and isomerization to give diene **14** (Scheme 5a). Such gold catalysed transformations are reported[15, 16] to be faster for electron-rich than electron-deficient allenes.[17] Diene **14**, formed by isomerization of allene **13** may subsequently undergo two alternative dimerization pathways; either with allene **13** or with a second unit of diene **14** to give the open and the cyclic dimers **11** and **12**, respectively (Scheme 5b,c). NMR analysis of cyclohexene dimer **12** showed NOE correlations, such as between benzylic H3 and allylic H4 protons, which were used to establish the relative *cis-trans* stereochemistry of the diphenyl-vinyl-trisubstituted cyclohexene **12**.

In contrast to Au(I) complex **I**, producing the open dimer **11**, the results indicate that nitrone complex **I-6c** may have higher catalytic capacity for allene-to-diene isomerization (Scheme 5a), which enables dimerization of two units of diene **14** to give cyclic dimer **12** by a Diels-Alder-like [2+4] cycloaddition.

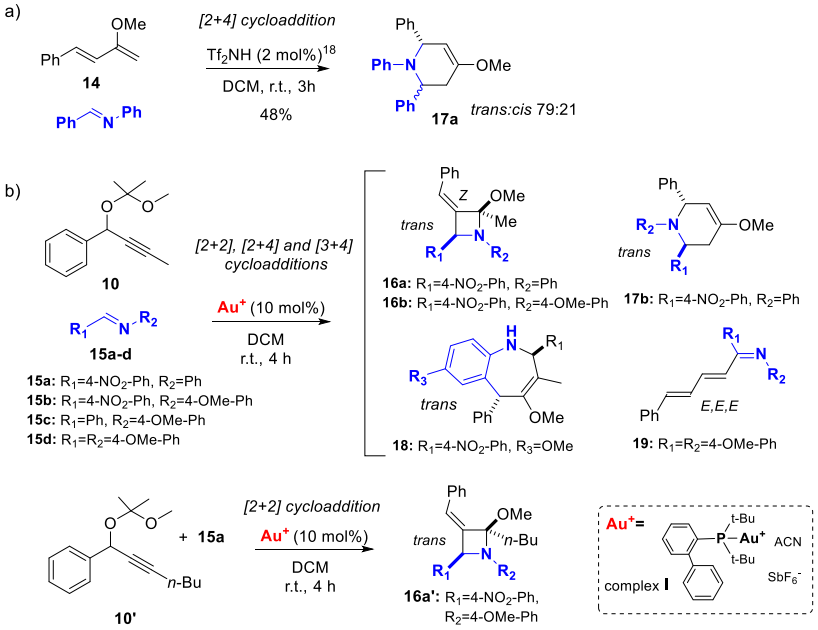


Scheme 5. Proposed pathways for a) gold-catalysed generation of allene **13** and diene **14** intermediates from propargyl acetal **10**; b) dimerization of diene **14** with allene **13** to give open dimer **11** and c) dimerization of two units of diene **14** to give cyclic dimer **12**.

4.2 Cycloaddition studies of in situ generated intermediates from non-terminal propargyl acetals.

Since alkyl-arylpropargyl acetal **10** seemed to generate allene **13** or diene **14** intermediates in the presence of Au(I) complexes, a series of possible Diels Alder reactions were tested with substrate **10** and dienophiles. The reactions with alkene, alkyne, nitrile and carbonyl compounds failed to incorporate the dienophiles, and only dimers such as **11** and **12** (21-53%) were formed. However, as diene **14** is known to undergo hetero-Diels-Alder reactions with imines (48% yield of piperidine product **17a**, Table 4a),[18] the ability of gold(I) to catalyse possible cycloaddition reactions of imines with in situ generated allene **13** or diene **14** from alkyl-arylpropargyl acetal **10**, was more promising. In fact, propargyl acetal **10** and aldimines **15a-d** did undergo several cycloaddition reactions in the presence of Au(I) complex **I** with in situ generated intermediates **13** or **14** (Table 4b). The polarised nitro-phenyl imines (**15a** and **15b**) mainly afforded the novel *E,trans*-benzylidene-diarylazetidine **16** (30-33%, entries 1 and 2), explained by the proposed [2+2] cycloaddition of imine and allene **13** (Scheme 6a). The more sterically hindered *n*-butyl-propargyl acetal **10'** gave similar product **16a'** in lower yield (<15%, entry 5). An analogous [2+2] cycloaddition is reported by the Fiksdahl group for dimerization of a diaryl propargyl ester to give a di-benzylidene-cyclobutyl product.[8] Azetidines, such as products **16**, are relatively stable; useful as biological scaffolds, reactive intermediates and chiral ligands.[19, 20] They can be synthesised by several routes, commonly by intramolecular ring-closing, ring expansion or ring contraction, and a few intermolecular methods are known.[19-21] Further chemical transformations of the azetidine moiety are useful in organic synthesis.[20] A few copper-catalysed [2+2] cycloadditions between allenes and imines are reported to give azetidines.[20, 22] The presently reported gold(I)-catalysed [2+2] cycloaddition of propargyl acetal **10** and imines **15a,b** via in situ generated allene **13** represents a novel synthetic pathway to azetidines.

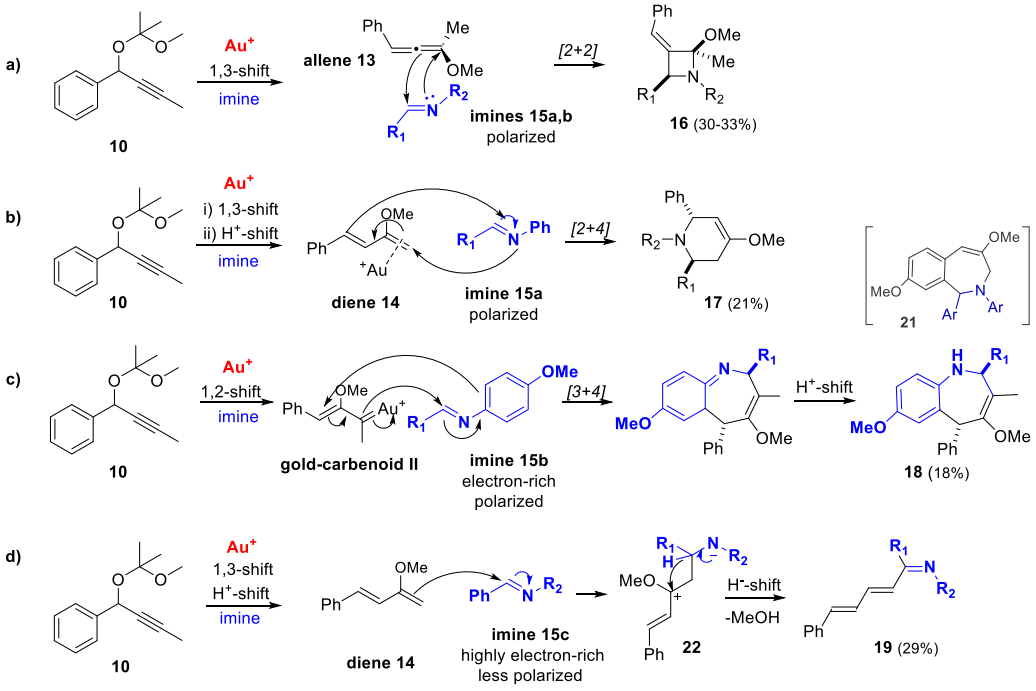
Table 4. Cycloaddition reactions of a) diene **14** with phenylbenzaldimine[18] and b) aryl-alkyl-propargyl acetals **10** and **10'** with imines **15a-d**.



Entry	Acetal	Imine	Yield			
			16	**17b**	**18**	**19**
1	**10**	**15a**	**16a**, 33%	21%	-	-
2	**10**	**15b**	**16b**, 30%	-	18%	-
3	**10**	**15c**	-	-	-	29%
4	**10**	**15d**	Full conv. of **10**, no prod. isolated			
5	**10'**	**15a**	**16a'** <15%	-	-	-

The reaction of polarised imine **15a** with diene **14** also generated the [2+4] cycloaddition by-product **17b** (21%, Table 4, entry 1 and Scheme 6b), while the more polarized and electron-rich **15b** followed an unusual competing [3+4] cycloaddition, involving the e-rich MeO-phenyl unit to give the benzazepine-type by-product **18** via an uncommon gold-carbenoid **II** (18%, Table 4, entry 2 and Scheme 6c). This product is similar to the [2+5] cycloaddition product **21** formed with imine and terminal aryl-propargyl acetals, reported in earlier studies,[3] but the mechanism is different. The *trans* stereochemistry of heterocyclic products **16**-**18** was established from NMR NOE correlations between the respective substituents on the ring. The *Z*-configuration of **16** was based on NOE correlations between the relevant benzylidene protons and the R_1-aryl and Me/MeO groups.

Reaction with the less polarized and more electron-rich methoxy-phenyl imine **15c** followed a different reaction pathway than the cycloaddition seen for the polarised imine **15a** (Scheme 6b). The main product was a fully conjugated *E,E,E*-pentadien-1-imine **19** (29%, Table 4, entry 3), which may be formed by diene **14** attack on imine **15c**, followed by hydride shift and methanol elimination (Scheme 6d). The *E,E,E*-configuration of product **19** was assigned based on ^{1}H NMR coupling constants and NOE correlations. Reaction with very electron-rich aldimine **15d** gave no products, indicating that the polarisation of the imine bond is important to enable nucleophilic attack on the imine.



Scheme 6. Proposed mechanisms for formation of products **16-19**.

Conclusions

Two novel chiral menthol-based pyridyl nitrones **6a** and **6b** were synthesized. Au(I)-nitrone complexes (**I-6a** and **I-6b**) were prepared by coordination of ligands **6a** and **6b** to JohnPhosAu(ACN)SbF_6 complex **I**. ^{1}H NMR coordination studies indicated that the new nitrones coordinated poorer to Au(I) than previously studied nitrones, probably due to the bulk of the chiral menthol-based substituent, as well as the competing intramolecular hydrogen-bonds in non-methylated ligand **6a**.

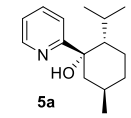
The catalytic effect of Au(I)-nitrones **6a** and **6b** was evaluated in [2+2+2] cyclotrimerization and [2+4] cyclodimerization reactions. Complex **I-6b** gave highest yield (73%, entry 3), similar to the best yields reported previously (74%, nitrone **6c** with counterion NTf_2).[8] The obtained diastereoisomeric ratio of the Au(I)-nitrone catalyzed cyclotrimerization products **2** from diaryl-propargyl substrate **1**, was different than in previous studies,[8] indicating that the nitrones have a special effect in this particular reaction. Chiral HPLC analysis of trimeric products **2a-c** failed to give enantioseparation. Methyl-aryl-propargyl acetal **10** followed a different dimerization reaction pathway, based on in situ generated allene **13** and diene **14** intermediates, compared to the trimerization of diaryl-propargyl substrate **1**. The Au(I) nitrone complex **I-6c** afforded the cyclic dimer **12** by a Diels-Alder-like [2+4] cycloaddition from methyl-aryl-propargyl **10**, in contrast to Au(I) complex **I**, producing the open dimer **11**.

Alternative pathways of non-terminal methyl-aryl propargyl acetal **10** were explored by testing the ability to undergo possible gold(I)-catalysed cycloaddition reactions with different imines. Specific [2+2], [2+4] and [3+4] cycloaddition reactions of imines **15a-d** with in situ generated allene **13** and diene **14** intermediates from acetal **10** gave a diverse range of *N*-heterocyclic products **16-19** (18-30%). Mechanistic discussions of the selective reaction pathways are

The present screening study demonstrates the potential and the versatility of non-terminal propargyl acetals in gold(I) catalyzed cycloaddition reactions. Further optimization of reaction conditions, substrate variation and gold catalyst tuning may give improved yields and more efficient synthetic methods for preparation of selective cycloaddition products.

Experimental

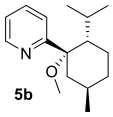
(1S,2S,5R)-2-Isopropyl-5-methyl-1-(pyridin-2-yl)cyclohexanol (5a)



5a

Butyllithium (2.0 M in cyclohexane, 2.9 mL, 5.8 mmol) under inert atmosphere was cooled to 0 °C and 2-(dimethylamino)ethanol (0.29 mL, 2.9 mmol) in dry heptane (2 mL) was added slowly. The mixture was stirred at the same temperature for 15 min. The mixture was then cooled to −78 °C and pyridine (0.12 mL, 1.5 mmol) in dry heptane (2 mL) was added. The mixture became bright orange over 30 mins, then (2S,5R)-2-isopropyl-5-methylcyclohexanone (0.50 mL, 2.9 mmol) in dry THF (5 mL) was added slowly. The mixture was stirred at this temperature for 1 h. The reaction was quenched with sat. aq. NH_4Cl (25 mL) and extracted with DCM (3 x 25 mL), dried with brine and Na_2SO_4, filtered and evaporated *in vacuo*. Flash chromatography (1:1 DCM:pentane) gave the desired product as a colourless oil (114.6 mg, 33%). ^1H and ^{13}C NMR data were in accordance with published literature.[9]

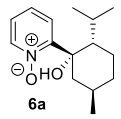
2-((1S,2S,5R)-2-Isopropyl-1-methoxy-5-methylcyclohexyl)pyridine (5b)



5b

Compound **5a** (114.6 mg, 0.491 mmol) in dry THF (3 mL) was added dropwise to a suspension of NaH (93.8 mg, 3.91 mmol) in dry THF (12 mL). The mixture was stirred at r.t. for 30 mins then MeI (0.30 ml, 4.8 mmol) was added and the solution was stirred at r.t. for 3 h. The reaction was quenched carefully dropwise with sat. aq. NH_4Cl (20 mL) and extracted with EtOAc (3 x 20 mL). The combined organic phases were dried with sat. aq. NaCl (20 mL), dried over Na_2SO_4, filtered and evaporated *in vacuo*. Flash chromatography (1:30 EtOAc:pentane) gave **5b** as a colourless oil (119.6 mg, 99%). $[\alpha]_D^{20}$ = −51.1° (c 1.01, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): δ 8.61 (ddd, 1H, *J* = 4.8/1.7/0.9 Hz, NCH_{Ar}), 7.65 (td, 1H, *J* = 7.8/1.8 Hz, CH_{Ar}), 7.45 (dt, 1H, *J* = 7.9/1.0 Hz, CH_{Ar}), 7.12 (ddd, 1H, *J* = 7.4/4.8/1.2 Hz, CH_{Ar}), 3.22 (s, 3H, OCH_3), 2.03-1.94 (m, 2H, $CH_3OCC\underline{H}_2$), 1.85-1.82 (m, 1H, $CH_3OCCH_2CHC\underline{H}_2$), 1.73-1.63 (m, 2H, $CH_3C\underline{H}$ and $CH_3OCCHC\underline{H}_2$), 1.56-1.49 (m, 2H, $(CH_3)_2CHC\underline{H}$ and $CH_3OCCHC\underline{H}_2$), 1.29 (sepd, 1H, *J* = 6.9/1.5 Hz, $(CH_3)_2C\underline{H}$), 1.11 (qd, 1H, *J* = 12.6/3.4 Hz, $CH_3OCCH_2CHC\underline{H}_2$), 0.96 (d, 3H, *J* = 6.5 Hz, CH_3), 0.87 (d, 3H, *J* = 6.7 Hz, $(CH_3)_2$), 0.58 (d, 3H, *J* = 6.9 Hz, $(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 164.0, 149.4, 135.3, 121.5, 121.2, 84.8, 51.7, 50.3, 39.9, 35.2, 28.0, 26.5, 23.6, 22.4, 21.2, 18.2; HRMS (ASAP) calcd for $C_{16}H_{26}NO$ $[M+H]^+$ 248.2014, found 248.2012.

2-((1S,2S,5R)-1-Hydroxy-2-isopropyl-5-methylcyclohexyl)pyridine 1-oxide (6a)



6a

Compound **5a** (95.0 mg, 0.41 mmol) was dissolved in dry DCM (2 mL) under inert atmosphere at 0 °C. 3-chlorobenzoperoxoic acid (210.3 mg, 0.938 mmol) was added. The reaction mixture was stirred at 0 °C for 5 min then the ice bath was removed and the reaction was allowed to come to r.t. overnight (17.5 h). The reaction mixture was diluted with DCM (10 mL) and washed with aq. KOH (6N, 3x5 mL) and the organic layer was dried over Na_2SO_4, filtered and the solvent evaporated *in vacuo*. Flash chromatography (1:1 EtOAc:pentane) gave **6a** as a colourless oil (82.0 mg, 81%). $[\alpha]_D^{20}$ = −79.4° (c 1.01, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): δ ppm 8.58 (br s, 1H, OH), 8.20 (dd, 1H, *J* = 6.5/0.8 Hz, CH_{Ar}), 7.38 (td, 1H, *J* = 7.8/1.3 Hz, CH_{Ar}), 7.28 (dd, 1H, *J* = 8.2/1.8 Hz, CH_{Ar}), 7.21 (td, 1H, *J* = 6.9/2.0 Hz, 1H, CH_{Ar}), 2.43-2.39 (m, 1H, $C\underline{H}_2COH$), 2.09-1.96 (m, 1H, $C\underline{H}COH$), 1.87-1.77 (m, 3H, $C\underline{H}_2CHCOH$ and $C\underline{H}_2CH_2CHCOH$ and $C\underline{H}(CH_3)_2$), 1.66-1.59 (m, 2H, $C\underline{H}CH(CH_3)_2$ and $C\underline{H}_2CH_2CHCOH$), 0.98 (d, 3H, *J* = 6.7 Hz, $CH(\underline{C}H_3)_2$), 0.93 (d, 3H, *J* = 7.0 Hz, $CH(\underline{C}H_3)_2$), 0.87 (d, 3H, *J* = 6.7 Hz, $CH\underline{C}H_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 155.1 (C_{Ar}), 141.3 (CH_{Ar}), 127.8 (CH_{Ar}), 123.7 (CH_{Ar}), 123.6 (CH_{Ar}), 79.6 (COH), 47.8 ($\underline{C}HCH(CH_3)_2$), 46.6 ($\underline{C}H_2COH$), 35.0 ($\underline{C}H_2CHCOH$), 27.8 ($\underline{C}H(CH_3)_2$), 27.2 ($\underline{C}HCH_3$), 23.8 ($CH(\underline{C}H_3)_2$), 22.0 ($CH\underline{C}H_3$), 21.1 ($C\underline{H}_2CH_2CHCOH$), 18.7 ($CH(\underline{C}H_3)_2$); HRMS (ASAP) calcd for $C_{15}H_{24}NO_2$ $[M+H]^+$ 250.1807, found 250.1809.

General Procedure for gold(I)-catalysed reaction of propargyl acetal 10 and imines 15a-d.

JohnPhosAu(ACN)SbF_6 (4.5 µmol) was dissolved in DCM (0.5 mL) and a mixture of acetal **10** (46 µmol) and the appropriate imine (0.138 mmol) in DCM (1 mL) was added. The reaction mixture was stirred at r.t. for 4 h, then the reaction was quenched with NEt_3 and solvent removed *in vacuo*. Product isolation and purification was done by silica chromatography (EtOAc:pentane).

Supporting information: Additional Supporting information with Full experimental detail, ^1H and ^{13}C NMR spectra, may be found online in the supporting information section for this article.

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Au(I)-catalysed cycloaddition pathways of non-terminal propargyl substrates

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Supporting Information

Table of Contents

General and Synthesis of compounds **6a**, **I-6a**, **I-6b**, **10**, **10'**, **11**, **12**.....S2

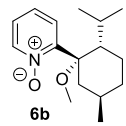
General Procedure; gold(I)-catalysed reaction of propargyl acetal **10** and imines **15a-d**, and synthesis of compounds **16-19** S4

^{1}H and ^{13}C NMR spectra for all compounds S6

General

Commercial grade reagents were used as received. Dry solvents were collected from a solvent-purification system. All reactions were monitored by thin-layer chromatography (TLC) using silica gel 60 F254 (0.25-mm thickness) or by ^{1}H-NMR. Flash chromatography was carried out using silica gel 60 (0.040-0.063 mm). High Throughput Flash Purification (HPFP) was performed on pre-packed cartridges. ^{1}H and ^{13}C NMR spectra were recorded using a 400 or 600 MHz spectrometer. Chemical shifts are reported in ppm (δ) relative to d-$CDCl_3$ or d-CD_2Cl_2. Coupling constants (J) are reported in Hertz (Hz). The attributions of the chemical shifts were determined using COSY, HSQC and HMBC NMR experiments and cis/trans isomers by NOESY experiments. Accurate mass determination in either positive or negative mode was performed with a "Synapt G2-S" Q-TOF instrument from Waters. Samples were ionised with an ASAP probe, and no chromatographic separation was used before the mass analysis. Optical rotation was measured on an Anton Paar MCP 5100 Polarimeter and the concentration is given in g/100 mL. Acetals **1** and **7** and aldimines **15a-d** were synthesised using published methods.[1-3] Compound **8** was purchased from Sigma-Aldrich and used as received.

2-((1S,2S,5R)-2-Isopropyl-1-methoxy-5-methylcyclohexyl)pyridine 1-oxide (6b)


6b

Compound **5b** (see main article) (119.7 mg, 0.484 mmol) was dissolved in dry DCM (2 mL) under inert atmosphere at 0 °C. 3-Chlorobenzoperoxoic acid (234.6 mg, 1.047 mmol) was added. The reaction mixture was stirred at 0 °C for 5 min, then the ice bath was removed and the reaction was allowed to come to r.t. overnight (18 h). The reaction mixture was diluted with DCM (10 mL) and washed with aq. KOH (6N, 3x5 mL) and the organic layer was dried over Na_2SO_4, filtered and the solvent evaporated *in vacuo*. The residue was purified by silica chromatography (EtOAc) to give **6b** as a colourless oil (104.2 mg, 82%). $[\alpha]_D^{20}$ = −92.0° (c 1.01, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 8.18 (dd, *J* = 6.4/0.9 Hz, 1H, NCH), 7.48 (dd, *J* = 8.1/2.0 Hz, 1H, NCCH), 7.25 (ddd, *J* = 8.1/7.5/1.3 Hz, 1H, NCHC<u>H</u>), 7.13 (ddd, *J* = 7.4/6.5/2.1 Hz, 1H, NCCHC<u>H</u>), 3.28 (s, 3H, OCH_3), 3.22 (dd, *J* = 14.5/12.5 Hz, 1H, 1 of $OCCH_2$), 2.67 (ddd, *J* = 12.5/3.7/2.3 Hz, 1H, OCCH), 1.81-1.73 (m, 2H, 1 of $OCCH_2$ and 1 of $CH_3CHC\underline{H}_2CH_2$), 1.69-1.59 (m, 2H, $CH_3C\underline{H}$ and 1 of $OCCHC\underline{H}_2$), 1.56-1.50 (m, 1H, 1 of $OCCHC\underline{H}_2$), 1.26-1.13 (m, 2H, 1 of $CH_3CHC\underline{H}_2CH_2$), 0.94 (d, *J* = 6.6 Hz, 3H, CH_3), 0.82 (d, *J* = 6.8 Hz, 3H, $CH(C\underline{H}_3)_2$), 0.71 (d, *J* = 7.0 Hz, 3H, $CH(C\underline{H}_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 153.1 (NC), 142.2 (NCH), 126.1 (NCCH), 125.0 (NCH<u>C</u>H), 123.8 (NCCH<u>C</u>H), 84.8 (OC), 50.4 (OCH_3), 43.4 (OC<u>C</u>H), 34.7 ($CH_3CH\underline{C}H_2CH_2$), 33.7 ($OC\underline{C}H_2$), 28.3 ($\underline{C}H(CH_3)_2$), 28.2 ($\underline{C}HCH_3$), 23.6 ($CH(\underline{C}H_3)_2$), 22.2 ($CH\underline{C}H_3$), 20.8 ($OCCH\underline{C}H_2$), 18.4 ($CH(\underline{C}H_3)_2$); HRMS (ASAP) calcd for $C_{16}H_{26}NO_2$ [M+H] 264.1964, found 264.1959.

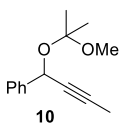
(JohnPhosAu-nitrone 6a)SbF_6 complex (I-6a)

A 1:5 mixture of **I:6a** dissolved in DCM and vapour diffused with pentane gave crystals of sufficient quality for X-ray analysis to obtain the crystal structure of complex **I-6a**, co-crystallised with an uncoordinated nitrone (Figure 4, X-ray; CCDC ID: 1979616). Crystallization of 1:1 **I:6a** was attempted, but due to the weak coordination of nitrone **6a**, this method was unsuccessful. The 1:1 mixture was suitable for MS analysis. HRMS (ESI) calcd for $C_{35}H_{50}NO_2AuP$ $[M]^+$ 744.3245, found 744.3251.

(JohnPhosAu-nitrone 6b)SbF_6 complex (I-6b)

Crystallization of a 1:1 mixture, **I:6b**, was attempted, but due to the weak coordination of nitrone **6b**, this method was unsuccessful. The 1:1 mixture was suitable for MS analysis. A HRMS (ESI) calcd for $C_{36}H_{52}NO_2AuP$ $[M]^+$ 758.3401, found 758.3403.

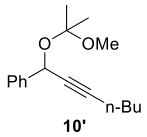
(1-((2-Methoxypropan-2-yl)oxy)but-2-yn-1-yl)benzene (10)


10

Prop-1-yn-1-ylmagnesium bromide (10 ml, 5,00 mmol) was stirred under nitrogen gas at 0 °C and benzaldehyde (0.51 ml, 5.02 mmol) in THF (10 ml) was added slowly. The mixture was stirred for 1 h at this temperature. The reaction mixture was quenched with sat. aq. NH_4Cl (25 mL) and extracted with DCM (3x25mL), the combined organic phase was dried over Na_2SO_4, filtered and dried *in vacuo*. The crude product was used without further purification. Crude 1-phenylbut-2-yn-1-ol (602,9 mg, 4,12 mmol) was dissolved in 2-methoxyprop-1-ene (5 ml, 52,2 mmol) and stirred. PPTS (catalytic amount) was added and the mixture stirred at ambient temperature and stirred for 1 h. The reaction mixture was diluted with DCM (50 mL), washed with water (3x50mL), the aqueous phase extracted with DCM (100 mL), and the combined organic phases were dried over sodium sulfate, filtered and concentration *in vacuo*. The residue was purified by silica chromatography (1:30 EtOAc:pentane + 0.5% NEt_3) to give **10** as a colourless

oil (758.9 mg, 69% over two steps). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 7.47-7.46 (m, 2H, 2xCH_{Ar}), 7.35-7.30 (m, 2H, 2xCH_{Ar}), 7.28-7.23 (m, 1H, CH_{Ar}), 5.36 (q, *J* = 2.0 Hz), 3.16 (s, 3H, OCH_3), 1.83 (d, *J* = 2.2 Hz, 3H, ≡CCH_3), 1.51 (CH_3), 1.29 (CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 141.4 (C_{Ar}), 128.4 (CH_{Ar}), 127.7 (CH_{Ar}), 126.8 (CH_{Ar}), 101.6 ($\underline{C}(CH_3)_2$), 81.8 (≡$\underline{C}CH_3$), 79.9 (≡$\underline{C}CH$), 63.1 (CH), 49.4 (OCH_3), 25.4 ($C(\underline{C}H_3)_2$), 25.1, 3.8 (≡CCH_3); HRMS (ASAP) calcd for $C_{14}H_{18}O_2$ [M*+] 218.1307, found 218.1309.

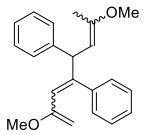
(1-((2-Methoxypropan-2-yl)oxy)hept-2-yn-1-yl)benzene (10')



10'

To a solution of hex-1-yne (0.78 mL, 6.79 mmol) in anhydrous THF (5 mL) was added butyllithium (3 mL, 1.6 M solution in hexanes, 7.50 mmol) at −78 °C under inert atmosphere. The reaction was stirred at this temperature for 30 mins. Benzaldehyde (0.69 mL, 6.79 mmol) was added and the mixture stirred for 30 min before being allowed to warm to room temperature gradually for an additional 30 min before being quenched with sat. aq. NH_4Cl. The mixture was extracted with ether, and the combined organic phases were washed with water and brine, dried over anhydrous Na_2SO_4 and filtered. The solvents were removed *in vacuo* and the residue was purified by SiO_2 column chromatography (1:10 EtOAc:pentane) to provide 1-phenylhept-2-yn-1-ol as a colourless oil (1.150 g, 90%). 1-Phenylhept-2-yn-1-ol (250.1 mg, 1.328 mmol) was dissolved in 2-methoxyprop-1-ene (1 mL, 10.44 mmol) and PPTS (catalytic amount) was added and the reaction was stirred at r.t. for 1 h. The reaction mixture was diluted with DCM (20 mL), washed with water (3x20mL), the aqueous phase extracted with DCM (20 mL), and the combined organic phases were dried over sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified via silica chromatography (1:30 EtOAc:pentane) to give **10'** as a colourless oil (262.2 mg, 76%). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 7.47-7.45 (m, 2H, CH_{Ar}), 7.34-7.30 (m, 2H, CH_{Ar}), 7.28-7.23 (m, 1H, CH_{Ar}), 5.39 (t, *J* = 1.9 Hz, 1H, CH), 3.17 (s, 3H, OCH_3), 2.20 (td, *J* = 6.9/2.1 Hz, 2H, ≡CCH_2), 1.52 (s, 3H, CCH_3), 1.50-1.43 (m, 2H, CH_2), 1.41-1.33 (m, 2H, CH_2), 1.31 (s, 3H, CCH_3), 0.87 (t, *J* = 7.2 Hz, 3H, $CH_2\underline{CH_3}$); ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 141.3 (C_{Ar}), 128.3 (CH_{Ar}), 127.6 (CH_{Ar}), 126.9 (CH_{Ar}), 101.6 ($\underline{C}(CH_3)_2$), 86.4 (≡CCH_2), 80.7(≡CCH), 63.1 (CH), 49.4 (OCH_3), 30.7 (CH_2), 25.5 (CCH_3), 25.0(CCH_3), 21.9 (CH_2), 18.6 (≡CCH_2), 13.6 (CH_2CH_3); HRMS (ESI) calcd for $C_{17}H_{24}O_2Na$ [M+Na]$^+$ 283.1674, found 283.1679.

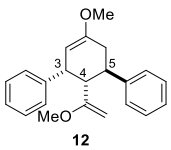
2,7-Dimethoxyocta-1,3,6-triene-4,5-diyl)dibenzene, open dimer 11



11

JohnPhosAu(ACN)SbF_6 (9.20 mg, 0.012 mmol) was dissolved in DCM (1 mL) and acetal **10** (52.0 mg, 0.238 mmol) in DCM (1 mL) was added. The reaction mixture was stirred at r.t. and followed on TLC. After 2 h, full consumption of **10** was observed and the reaction was quenched with NEt_3 and solvent removed *in vacuo*. The residue was purified by silica chromatography (1:60 EtOAc:pentane) to give **11** as a yellow oil (9.4 mg, 25%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34-7.14 (m, 10H, CH_{Ar}), 6.35 (br s, 1H, C=CHPh), 4.71 (d, *J* = 9.0 H, 1H, CH=CO), 4.43 (dd, *J* = 9.2/0.9 Hz, 1H, CHPh), 4.02 (d, *J* = 2.3 Hz, 1H, =CH_2), 3.86 (d, *J* = 2.4 Hz, 1H, =CH_2), 3.56 (s, 3H, OCH_3), 3.45 (s, 3H, OCH_3), 1.84 (s, 3H, CH_3). Compound decomposed before any other analyses could be carried out. Structure is proposed from possible intermediates and ^{1}H NMR spectrum.

***Cis,trans*-5'-Methoxy-2'-(1-methoxyvinyl)-1',2',3',4'-tetrahydro-1,1':3',1''-terphenyl, cyclic dimer 12**

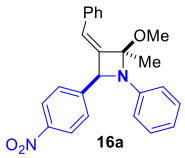


12

Propargyl acetal **10** (79 mg, 0.36 mmol) was dissolved in dry DCM (4 mL) under nitrogen atmosphere. JohnPhosAu(ACN)SbF_6 (14 mg, 0.018 mmol) and nitrone **6d** were added and the solution stirred for 24 h. The reaction was quenched with NEt_3 and the solvent removed *in vacuo*. The residue was purified by silica chromatography (1:40-1:20 EtOAc:pentane) to give **12** as a yellow oil (17 mg, 30%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27-7.10 (m, 10H, CH_{Ar}), 4.81 (dd, *J* = 5.2/1.6 Hz, 1H, CHC=), 3.84 (br t, *J* = 5.2 Hz, 1H, =CCHPh), 3.58 (s, 3H, OCH_3), 3.55 (d, *J* = 2.4 Hz, 1H, CH_2=), 3.47 (d, *J* = 2.3 Hz, 1H, CH_2=), 3.16 (dd, *J* = 11.2/6.0 Hz, 1H, CHPh), 3.05 (dd, *J* = 12.0/5.9 Hz, 1H, CHC(OCH_3)=), 2.91 (s, 3H, OCH_3), 2.49 (dd, *J* = 17.3/5.8 Hz, 1H, CH_2), 2.34 (ddt, *J* = 17.2/11.9/1.8 Hz, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 162.5 (O$\underline{C}$=C), 155.3 (O$\underline{C}$=C), 144.9 (C_{Ar}), 143.2 (C_{Ar}), 129.5 (C_{Ar}), 127.9 (C_{Ar}), 127.7 (C_{Ar}), 127.3 (C_{Ar}), 126.2 (C_{Ar}), 125.8 (C_{Ar}), 96.3 (CH=), 83.7 (CH_2=), 54.26 (OCH_3), 53.6 (OCH_3), 49.6 (CH), 44.9 (CHPh), 37.7 ($C\underline{H}_2$CHPh), 37.6 (CH_2); HRMS (ASAP) calcd for $C_{22}H_{25}O_2$ [M+H]$^+$ 321.1855, found 321.1854. Compound **12** was stable in solution, but unstable on silica.

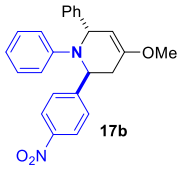
General Procedure for gold(I)-catalysed reactions of propargyl acetal 10 and imines 15a-d.
JohnPhosAu(ACN)SbF_6 (4.5 µmol) was dissolved in DCM (0.5 mL) and a mixture of acetal **10** (46 µmol) and the appropriate imine (0.138 mmol) in DCM (1 mL) was added. The reaction mixture was stirred at r.t. for 4 h, then the reaction was quenched with NEt_3 and solvent removed *in vacuo*. The products were isolated and purified by silica chromatography (EtOAc:pentane).

***cis*-3-((*Z*)-Benzylidene)-2-methoxy-2-methyl-4-(4-nitrophenyl)-1-phenylazetidine (16a) and *trans*-4-methoxy-2-(4-nitrophenyl)-1,6-diphenyl-1,2,3,6-tetrahydropyridine (17b)**
Compounds **16a** and **17** were synthesised by the General Procedure using gold(I) catalyst (4.5 µmol), **10** (46 µmol) and imine **15a** (0.138 mmol) to give **16a** (5.8 mg, 33%) and **17** (3.8 mg, 22%) as yellow oils.



16a

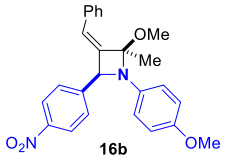
16a: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.25-8.22 (m, 2H, $CH_{Ar,\ No2}$), 7.68-7.64 (m, 2H, $CH_{Ar,\ No2}$), 7.45-7.43 (m, 2H, $CH_{Ar,\ Ph}$), 7.32-7.28 (m, 2H, $CH_{Ar,\ Ph}$), 7.23-7.17 (m, 3H, $CH_{Ar,\ Ph}$), 6.87-6.84 (m, 1H, $CH_{Ar,\ Ph}$),6.67-6.65 (m, 2H, $CH_{Ar,\ Ph}$), 6.08 (d, *J* = 2.1 Hz, 1H, =CH), 5.11 (d, *J* = 1.8 Hz, 1H, CH), 3.46 (s, 3H, OCH_3), 1.66 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.6 ($C_{Ar,\ NO2}$), 146.4 ($C_{Ar,\ NO2}$), 145.0 ($C_{Ar,\ Ph}$), 140.4 (C=), 134.1 ($C_{Ar,\ Ph}$), 129.2 ($CH_{Ar,\ Ph}$), 128.8 ($CH_{Ar,\ Ph}$), 128.6 ($CH_{Ar,\ Ph}$), 128.0 ($CH_{Ar,\ Ph}$), 127.2 ($CH_{Ar,\ NO2}$), 124.9 (=CH), 124.3 ($CH_{Ar,\ NO2}$), 120.3 ($CH_{Ar,\ Ph}$), 115.5 ($CH_{Ar,\ Ph}$), 98.9 ($\underline{C}OCH_3$), 62.7 (CH), 51.3 (OCH_3), 19.2 (CH_3); HRMS (ASAP) calcd for $C_{24}H_{23}N_2O_3$ $[M+H]^+$ 387.1709, found 387.1709.



17b

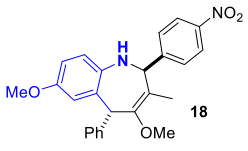
17b: ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.09-8.06 (m, 2H, $CH_{Ar,\ No2}$), 7.33-7.31 (m, 2H, $CH_{Ar,\ NO2}$), 7.29-7.26 (m, 4H, $CH_{Ar,\ Ph}$), 7.20-7.17 (m, 1H, $CH_{Ar,\ Ph}$), 7.02-6.99 (m, 2H, $CH_{Ar,\ Ph}$), 6.68-6.65 (m, 1H, $CH_{Ar,\ Ph}$), 6.56-6.54 (m, 2H, $CH_{Ar,\ Ph}$), 5.30-5.29 (m, 2H, 2 x ArCH), 5.01 (dd, *J* = 5.4/1.5 Hz, =CH), 3.43 (s, 3H, OCH_3), 3.11 (ddt, *J* = 14.4/5.8/1.6 Hz, 1H, CH_2), 2.48 (dd, *J* = 16.1/3.4 Hz, 1H, CH_2); ^{13}C NMR (150 MHz, $CDCl_3$): δ 151.7 (=C), 150.4 ($C_{Ar,\ NO2}$), 147.0 ($C_{Ar,\ Ph}$), 146.9 ($C_{Ar,\ NO2}$), 144.1 ($C_{Ar,\ Ph}$), 128.74 ($CH_{Ar,\ Ph}$), 128.65 ($CH_{Ar,\ Ph}$), 128.0 ($CH_{Ar,\ NO2}$), 126.8 ($CH_{Ar,\ Ph}$), 126.3 ($CH_{Ar,\ Ph}$), 123.5 ($CH_{Ar,\ NO2}$), 119.0 ($CH_{Ar,\ Ph}$), 117.5 ($CH_{Ar,\ Ph}$), 97.2 (=CH), 59.7 (ArCH), 57.9 (ArCH), 54.5 (OCH_3), 35.0 (CH_2); HRMS (ASAP) calcd for $C_{24}H_{23}N_2O_3$ $[M+H]^+$ 387.1709, found 387.1709.

***cis*-3-((*Z*)-Benzylidene)-2-methoxy-1-(4-methoxyphenyl)-2-methyl-4-(4-nitrophenyl)azetidine (16b) and *trans*-4,7-dimethoxy-3-methyl-2-(4-nitrophenyl)-5-phenyl-2,5-dihydro-1H-benzo[b]azepine (18)**
Compounds **16b** and **18** were synthesised by the General Procedure using gold(I) catalyst (4.7 µmol), **10** (47 µmol) and imine **15b** (0.142 mmol) to give **16a** (5.8 mg, 30%) and **17** (3.7 mg, 19%) as yellow oils.



16b

16b: ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.27-8.24 (m, 2H, $CH_{Ar,\ NO2}$), 7.69-7.67 (m, 2H, $CH_{Ar,\ NO2}$), 7.47-7.46 (m, 2H, $CH_{Ar,\ Ph}$), 7.34-7.31 (m, 2H, $CH_{Ar,\ Ph}$), 7.25-7.22 (m, 1H, $CH_{Ar,\ Ph}$), 6.82-6.79 (m, 2H, $CH_{Ar,\ OMe}$), 6.64-6.62 (m, 2H, $CH_{Ar,\ OMe}$), 6.09 (d, *J* = 1.9 Hz, 1H, =CH), 5.07 (d, *J* = 1.8 Hz, 1H, CH), 3.73 (s, 3H, $ArOCH_3$), 3.48 (s, 3H, OCH_3), 1.62 (s, 3H, CH_3); ^{13}C NMR (150 MHz, $CDCl_3$): δ 154.1 (C_{Ar}OMe), 147.6 ($C_{Ar,\ NO2}$), 146.7 ($C_{Ar,\ NO2}$), 140.7 (C=), 138.6 ($C_{Ar,\ OMe}$), 134.2 ($C_{Ar,\ Ph}$), 128.8 ($CH_{Ar,\ Ph}$), 128.6 ($CH_{Ar,\ Ph}$), 127.9 ($CH_{Ar,\ Ph}$), 127.3 ($CH_{Ar,\ NO2}$), 124.7 (=CH), 124.2 ($CH_{Ar,\ NO2}$), 116.6 ($CH_{Ar,\ OMe}$), 114.8 ($CH_{Ar,\ OMe}$), 98.7 (CMe), 62.5 (CHAr), 55.6 ($ArOCH_3$), 51.2 (OCH_3), 19.0 (CH_3); HRMS (ASAP) calcd for $C_{25}H_{25}N_2O_4$ $[M+H]^+$ 417.1814, found 417.1808.



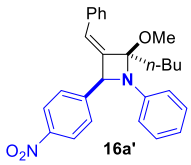
18

18: ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.03-8.01 (m, 2H, $CH_{Ar,\ NO2}$), 7.40 (d, *J* = 7.6 Hz, 2H, $CH_{Ar,\ Ph}$), 7.25-7.22 (m, 2H, $CH_{Ar,\ Ph}$), 7.18-7.16 (m, 2H $CH_{Ar,\ NO2}$), 7.16-7.13 (m, 1H, $CH_{Ar,\ Ph}$), 6.86 (d, *J* = 2.7 Hz, $CH_{Ar,\ OMe}$), 6.54 (dd, *J* = 8.4/2.7 Hz, $CH_{Ar,\ OMe}$), 6.27 (d, *J* = 8.4 Hz, $CH_{Ar,\ OMe}$), 5.44 (br s, NCHAr), 4.74 (br s, CHAr), 3.75 (s, 3H, $ArOCH_3$), 3.06 (OCH_3), 1.80 (d, *J* = 1.1 Hz, CH_3); ^{13}C NMR (150 MHz, $CDCl_3$): δ 154.7 ($C_{Ar,\ NO2}$), 153.6 (C_{Ar}OMe), 148.9 (=COMe), 146.5 ($C_{Ar,\ NO2}$), 144.7 ($C_{Ar,\ Ph}$), 136.5 (NC_{Ar}), 130.3 (NCC), 128.4 ($CH_{Ar,\ Ph}$), 127.1 ($CH_{Ar,\ Ph}$), 127.0 ($CH_{Ar,\ NO2}$), 126.2 ($CH_{Ar,\ Ph}$), 123.5 ($CH_{Ar,\ NO2}$), 119.0 (=CMe), 117.3 ($CH_{Ar,\ OMe}$), 114.9 ($CH_{Ar,\ Ph}$), 112.5 ($CH_{Ar,}$

$_{Ph}$), 58.3 (CHAr), 55.6 (ArOCH$_3$), 54.4 (=COCH$_3$), 45.8 (CHPh), 13.0 (CH$_3$); HRMS (ASAP) calcd for $C_{25}H_{25}N_2O_4$ $[M+H]^+$ 417.1814, found 417.1808.

***cis*-3-((*Z*)-Benzylidene)-2-butyl-2-methoxy-4-(4-nitrophenyl)-1-phenylazetidine (16a')**

Compound **16a'** was synthesised by the General Procedure using gold(I) catalyst (4.7 µmol), **10** (46 µmol) and imine **15c** (0.139 mmol) to give **16a'** (3.0 mg, impure, <15%) as a yellow oil.

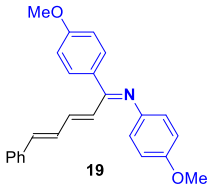


16a'

16a': ^{1}H NMR (600 MHz, CDCl$_3$): δ 8.26-8.24 (m, 2H, CH$_{Ar, NO2}$), 7.66-7.64 (m, 2H, CH$_{Ar, NO2}$), 7.48-7.47 (m, 2H, CH$_{Ar, Ph}$), 7.33-7.31 (m, 2H, CH$_{Ar, Ph}$), 7.25-7.23 (m, 1H, CH$_{Ar, Ph}$), 7.22-7.19 (m, 2H, CH$_{Ar, Ph}$), 6.87-6.84 (m, 1H, CH$_{Ar, Ph}$), 6.67 (br d, *J* = 7.9 Hz, 2H, CH$_{Ar, Ph}$), 6.22 (d, *J* = 1.9 Hz, 1H, =CH), 5.24 (d, *J* = 1.3 Hz, 1H, CHAr), 3.49 (s, 3H, OCH$_3$), 2.36-2.31 (m, 1H, CCH$_2$) 2.16-2.11 (m, 1H, CCH$_2$), 1.15-1.04 (m, 4H, 2xCH$_2$), 0.64 (t, *J* = 7.1 Hz, 3H, CH$_3$); ^{13}C NMR (150 MHz, CDCl$_3$): δ 147.5 (C$_{Ar, NO2}$), 146.5 (C$_{Ar, NO2}$), 144.6 (C$_{Ar, Ph}$), 139.0 (C=), 134.2 (C$_{Ar, Ph}$), 129.2 (CH$_{Ar, Ph}$), 128.7 (CH$_{Ar, Ph}$, 4C), 128.0 (CH$_{Ar, Ph}$), 127.0 (CH$_{Ar, NO2}$), 126.2 (=CH), 124.2 (CH$_{Ar, NO2}$), 119.8 (CH$_{Ar, Ph}$), 114.7 (CH$_{Ar, Ph}$), 102.1 (COCH$_3$), 63.5 (CHAr), 51.3 (OCH$_3$), 33.0 (CCH$_2$), 25.4 (CH$_2$), 22.6 (CH$_2$), 13.7 (CH$_3$); HRMS (ASAP) calcd for $C_{27}H_{29}N_2O_3$ $[M+H]^+$ 429.2178, found 429.2182.

(*1E,2E,4E*)-N,1-bis(4-Methoxyphenyl)-5-phenylpenta-2,4-dien-1-imine (19)

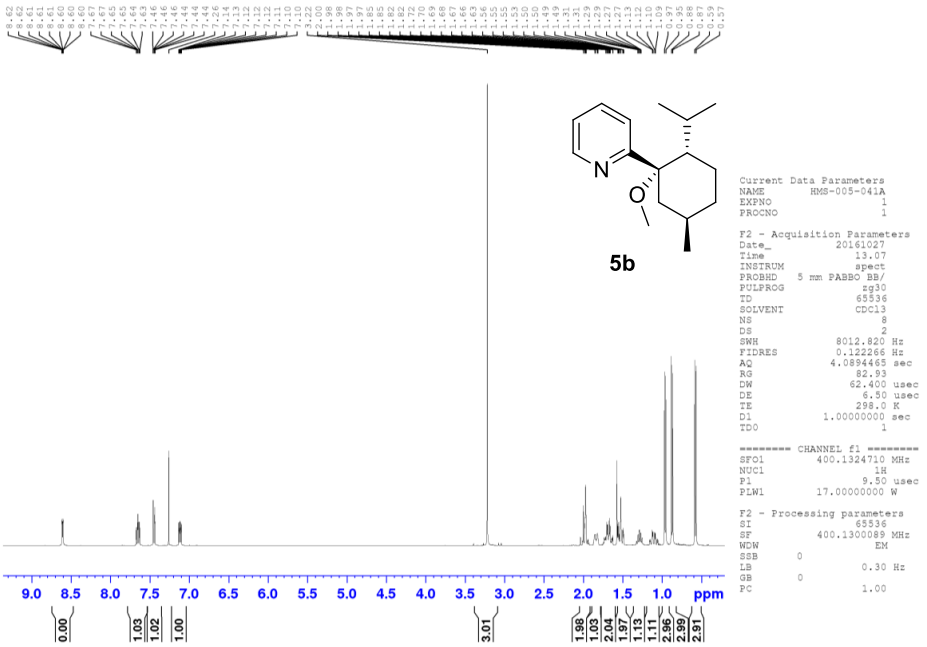
Compound **19** was synthesised via the General Procedure using gold catalyst (4.5 µmol), **10** (46 µmol) and aldimine **15c** (0.137 mmol) to give **19** (4.5 mg, 29%) as a yellow oil.



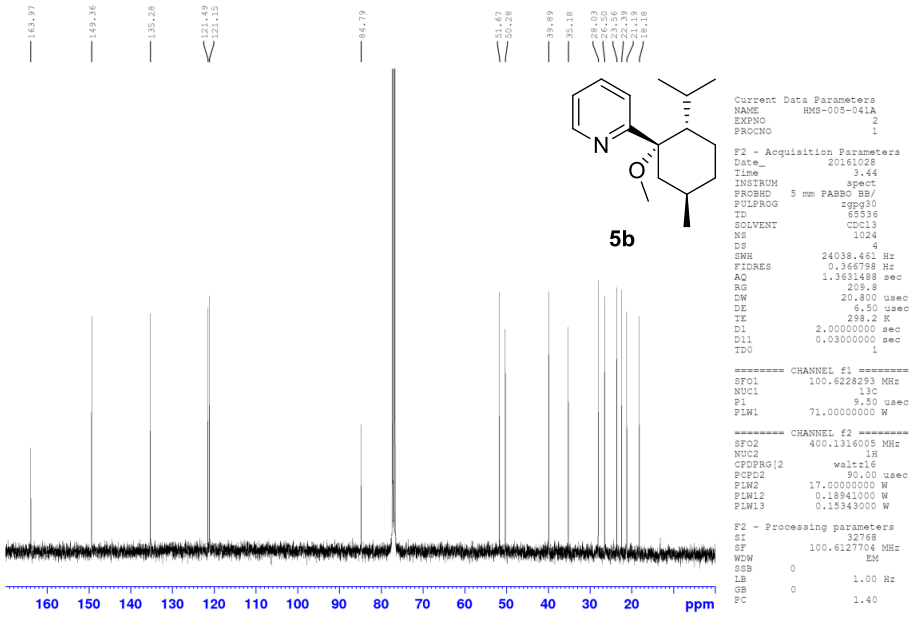
19

19: ^{1}H NMR (600 MHz, CDCl$_3$): δ 7.58 (d, *J* = 7.7 Hz, (CH$_{Ar, Ph}$), 7.49 (d, 15.8 Hz, =CH), 7.39-7.37 (m, 4H, CH$_{Ar, Ph}$), 7.34-7.28 (m, 4H, CH$_{Ar, Ph}$), 7.22 (d, *J* = 15.8 Hz, =CH), 7.17 (d, *J* = 16.6 Hz, =CH), 6.91-6.87 (m, 4H, CH$_{Ar, OMe}$), 6.81 (d, *J* = 16.6 Hz, =CH), 3.82 (s, 3H, OCH$_3$); ^{13}C NMR (100 MHz, CDCl$_3$): δ 162.9 (C=N), 156.6 (C$_{Ar, OMe}$), 143.9 (NC$_{Ar}$), 137.9 (=CH), 137.7 (=CH), 136.3 (C$_{Ar, Ph}$), 135.9 (C$_{Ar, Ph}$), 129.2 (CH$_{Ar, Ph}$), 128.9 (CH$_{Ar, Ph}$), 128.83 (CH$_{Ar, Ph}$), 128.76 (CH$_{Ar, Ph}$), 127.5 (CH$_{Ar, Ph}$), 127.3 (CH$_{Ar, Ph}$), 126.6 (=CH), 122.75 (=CHAr), 122.72 (CH$_{Ar, OMe}$), 114.1 (CH$_{Ar, OMe}$), 55.4 (OCH$_3$); HRMS (ESI) calcd for $C_{24}H_{22}NO$ $[M+H]^+$ 340.1701, found 340.1698.

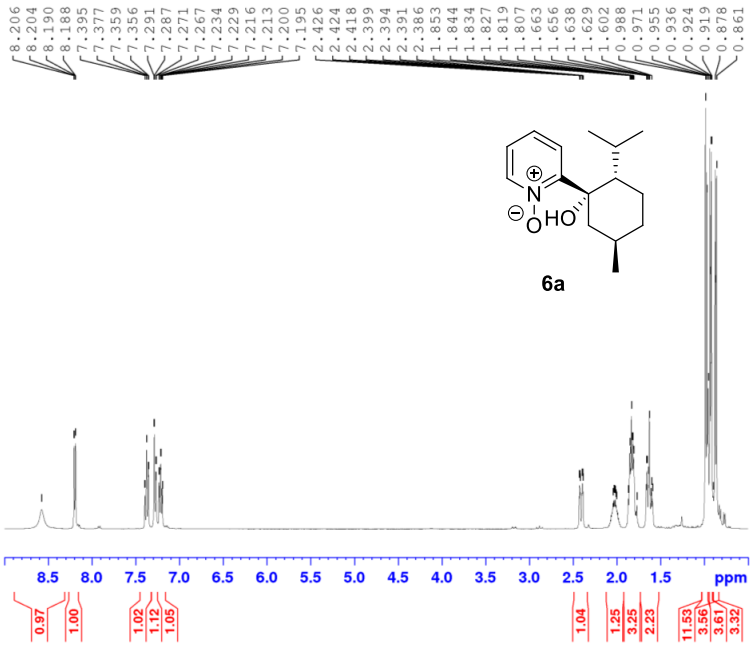
^{1}H NMR spectrum of 2-((1S,2S,5R)-2-sopropyl-1-methoxy-5-methylcyclohexyl)pyridine (5b)



^{13}C NMR spectrum of 2-((1S,2S,5R)-2-isopropyl-1-methoxy-5-methylcyclohexyl)pyridine (5b)



^{1}H NMR spectrum of 2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexyl)pyridine 1-oxide (6a)

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FIDRES            0.122266 Hz
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RG                    31.85
DW                   62.400 usec
DE                    6.50 usec
TE                   301.0 K
D1                1.00000000 sec
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NUC1                    1H
P1                    9.50 usec
PLW1           17.00000000 W

F2 - Processing parameters
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WDW                     EM
SSB          0
LB                    0.30 Hz
GB           0
PC                    1.00
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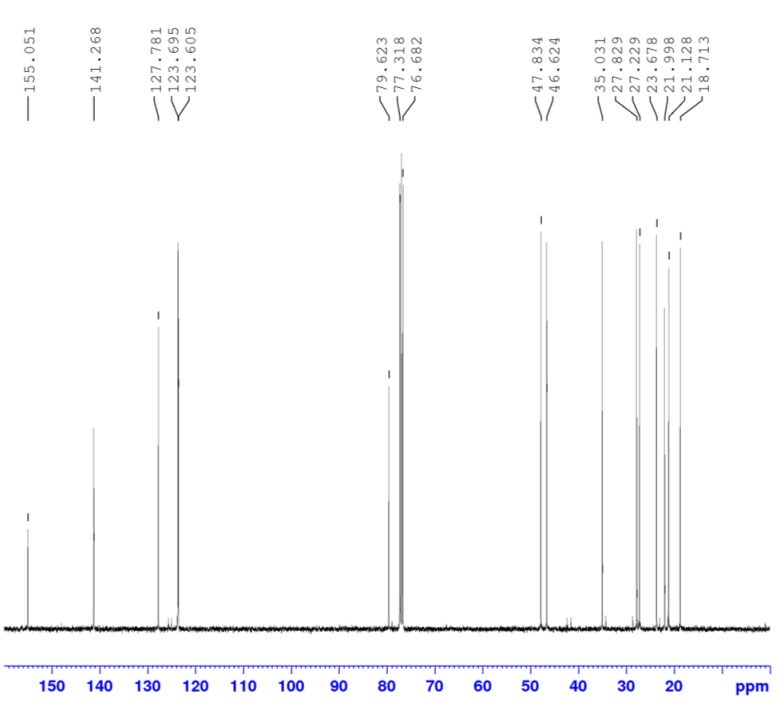
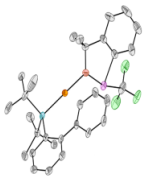
^{13}C NMR spectrum of 2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexyl)pyridine 1-oxide (6a)





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PROCNO                   1

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DS                       4
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FIDRES            0.366798 Hz
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DE                    6.50 usec
TE                   301.0 K
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D11               0.03000000 sec
TD0                      1

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NUC1                    13C
P1                    9.50 usec
PLW1           71.00000000 W

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PLW2           17.00000000 W
PLW12           0.18941000 W
PLW13           0.15343000 W

F2 - Processing parameters
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WDW                     EM
SSB          0
LB                    1.00 Hz
GB           0
PC                    1.40
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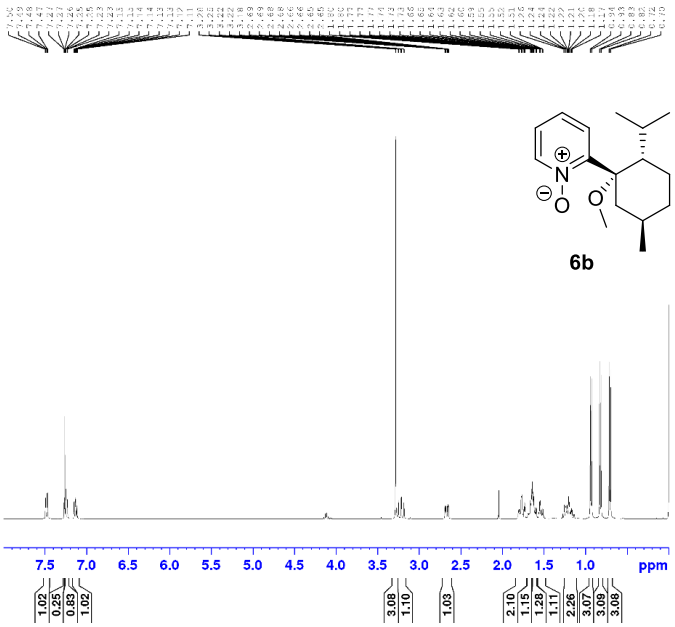
^{1}H NMR spectrum of 2-((1S,2S,5R)-2-isopropyl-1-methoxy-5-methylcyclohexyl)pyridine 1-oxide (6b)



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PROCNO 1

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DS 2
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FIDRES 0.122266 Hz
AQ 4.0894465 sec
RG 82.93
DW 62.400 usec
DE 6.50 usec
TE 298.0 K
D1 1.00000000 sec
TD0 1

======== CHANNEL f1 ========
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NUC1 1H
P1 9.50 usec
PLW1 17.00000000 W

F2 - Processing parameters
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SF 400.1300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
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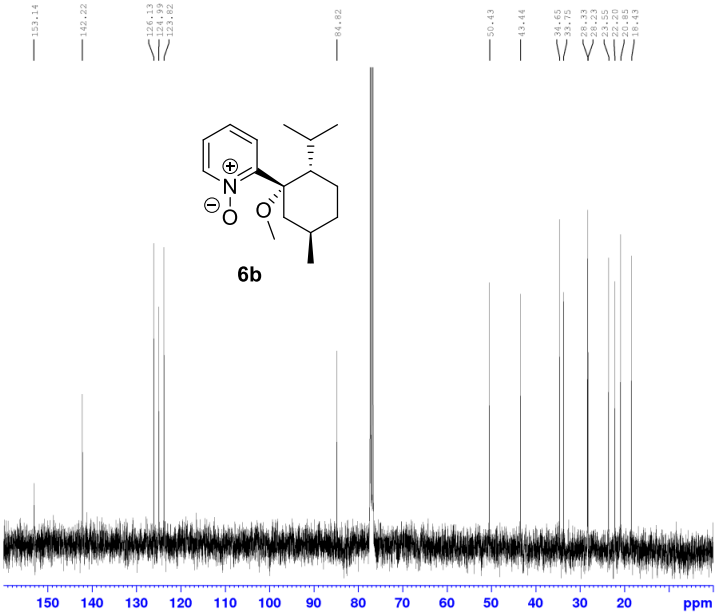
^{13}C NMR spectrum of 2-((1S,2S,5R)-2-isopropyl-1-methoxy-5-methylcyclohexyl)pyridine 1-oxide (6b)



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PROCNO 1

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SOLVENT CDCl3
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DS 4
SWH 24038.461 Hz
FIDRES 0.366798 Hz
AQ 1.3631488 sec
RG 209.8
DW 20.800 usec
DE 6.50 usec
TE 298.0 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1

======== CHANNEL f1 ========
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NUC1 13C
P1 9.50 usec
PLW1 71.00000000 W

======== CHANNEL f2 ========
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NUC2 1H
CPDPRG[2 waltz16
PCPD2 90.00 usec
PLW2 17.00000000 W
PLW12 0.18941000 W
PLW13 0.15343000 W

F2 - Processing parameters
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SF 100.6127709 MHz
WDW EM
SSB 0
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GB 0
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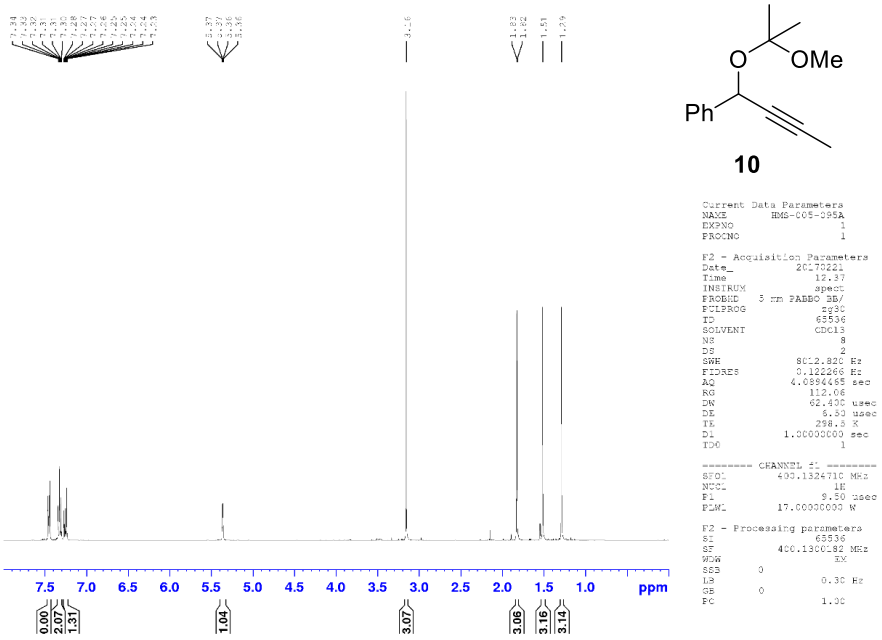
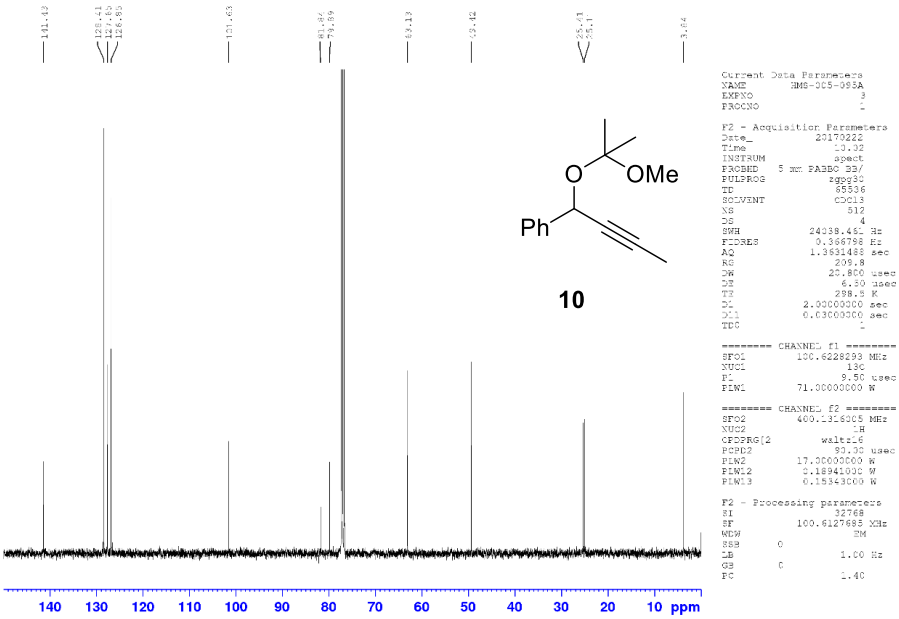
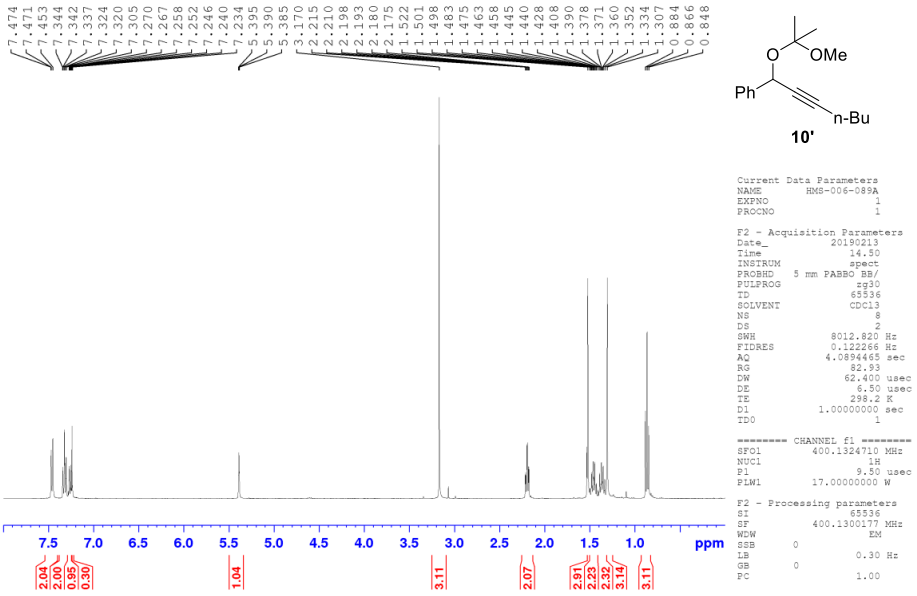
^{1}H NMR spectrum of (1-((2-methoxypropan-2-yl)oxy)but-2-yn-1-yl)benzene (10)



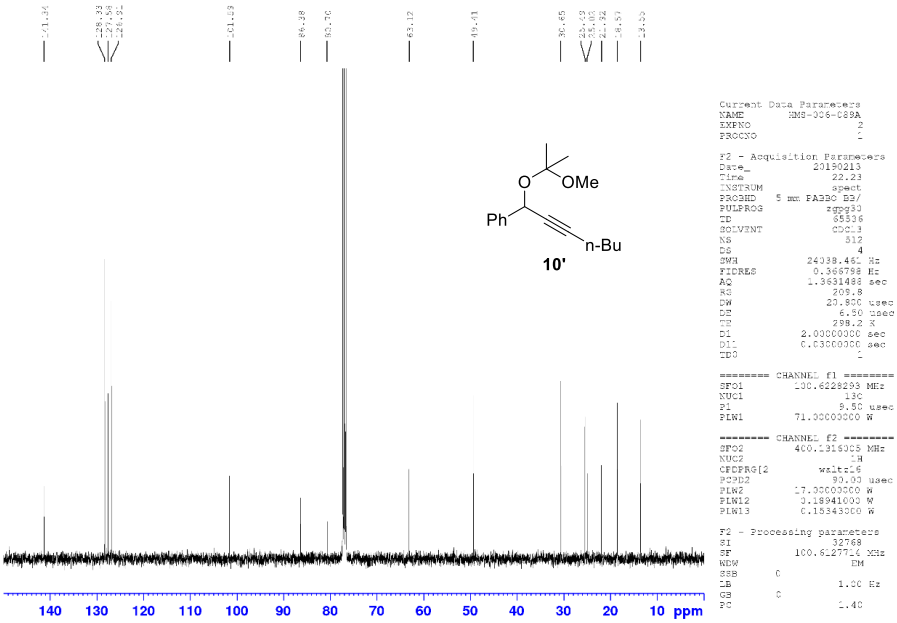
^{13}C NMR spectrum of (1-((2-methoxypropan-2-yl)oxy)but-2-yn-1-yl)benzene (10)



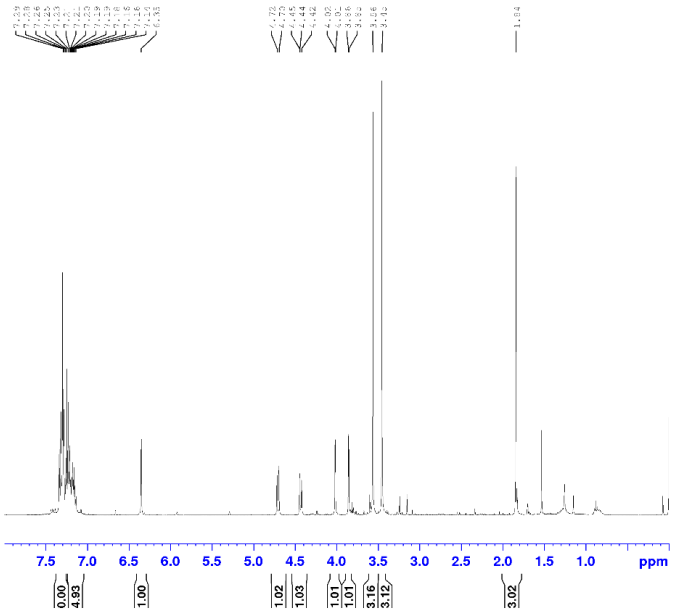
^{1}H NMR spectrum of (1-((2-methoxypropan-2-yl)oxy)hept-2-yn-1-yl)benzene (10')

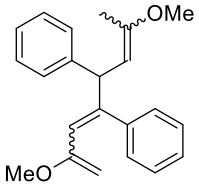


^{13}C NMR spectrum of (1-((2-methoxypropan-2-yl)oxy)hept-2-yn-1-yl)benzene (10')



^{1}H NMR spectrum of 2,7-Dimethoxyocta-1,3,6-triene-4,5-diyl)dibenzene, open dimer 11





11

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TD0                    1

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P1                 9.50 usec
PLW1        17.00000000 W

F2 - Processing parameters
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SSB                    0
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GB                     0
PC                  1.00
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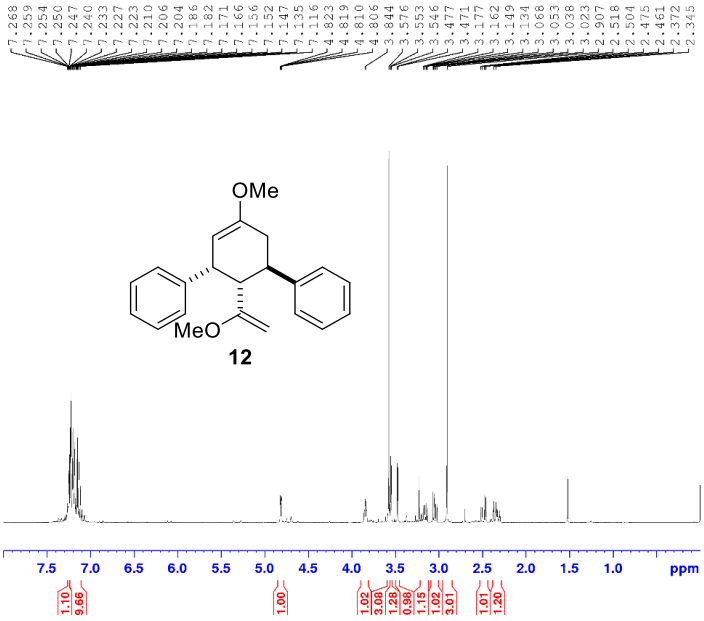
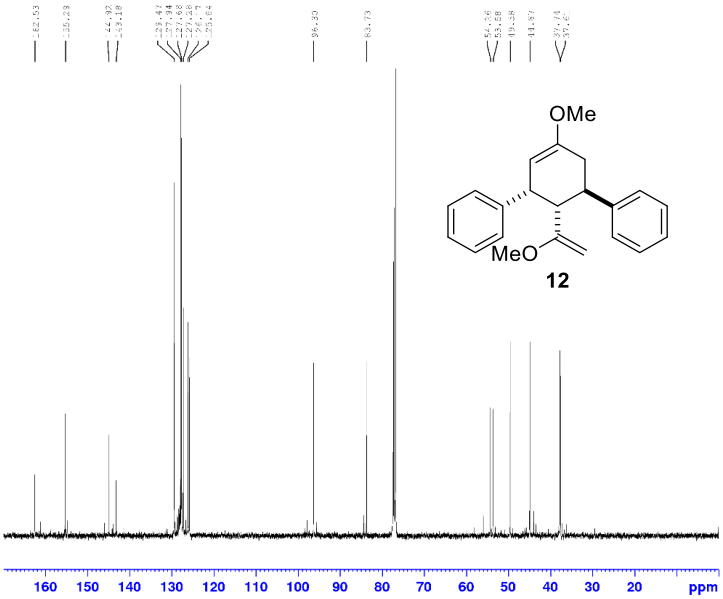
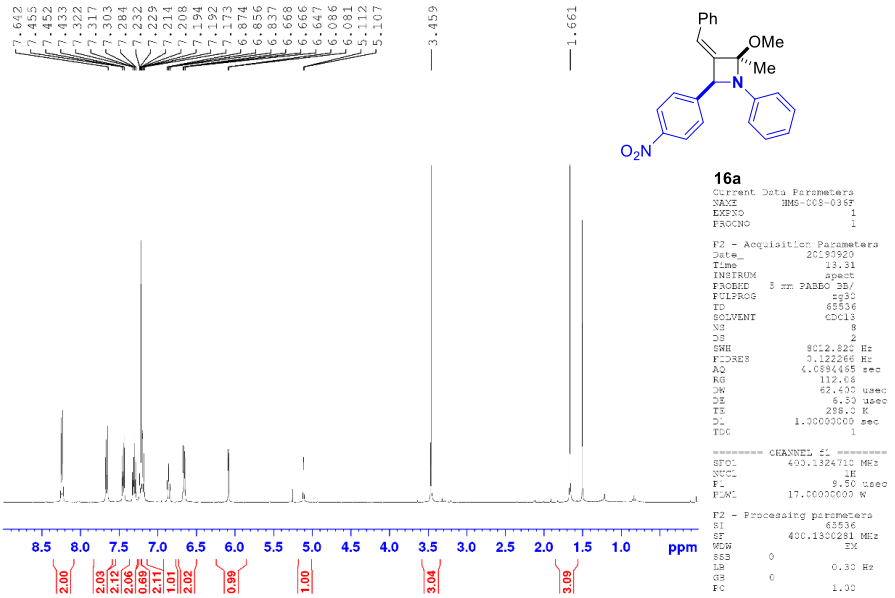
^{1}H NMR spectrum of *Cis,trans*-5'-Methoxy-2'-(1-methoxyvinyl)-1',2',3',4'-tetrahydro-1,1':3',1''-terphenyl, cyclic dimer 12



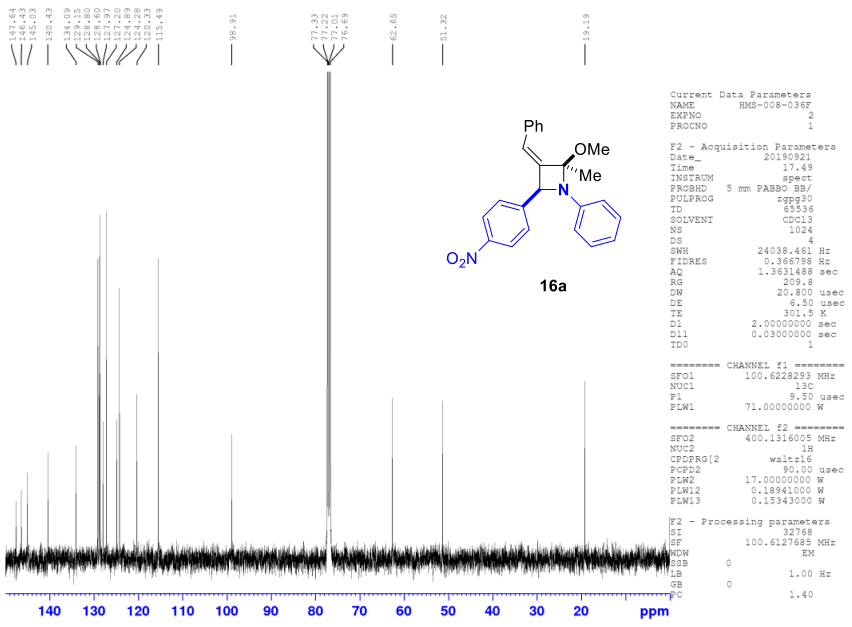
^{13}C NMR spectrum of *Cis,trans*-5'-Methoxy-2'-(1-methoxyvinyl)-1',2',3',4'-tetrahydro-1,1':3',1''-terphenyl, cyclic dimer 12



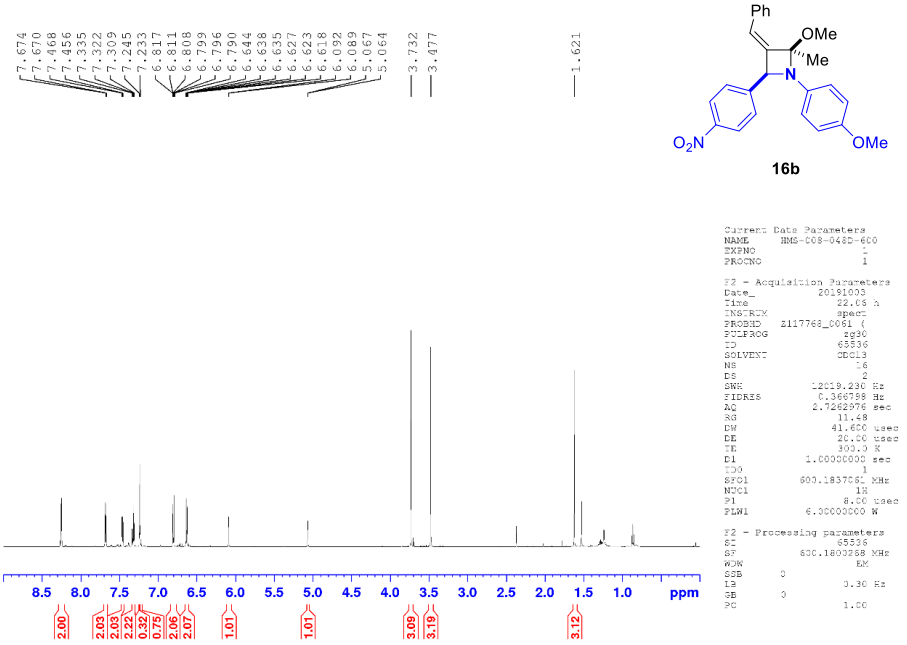
^{1}H NMR spectrum of *cis*-3-((Z)-benzylidene)-2-methoxy-2-methyl-4-(4-nitrophenyl)-1-phenylazetidine (16a)



^{13}C NMR spectrum of *cis*-3-((Z)-benzylidene)-2-methoxy-2-methyl-4-(4-nitrophenyl)-1-phenylazetidine (16a)



^{1}H NMR spectrum of *cis*-3-((Z)-benzylidene)-2-methoxy-1-(4-methoxyphenyl)-2-methyl-4-(4-nitrophenyl)azetidine (16b)



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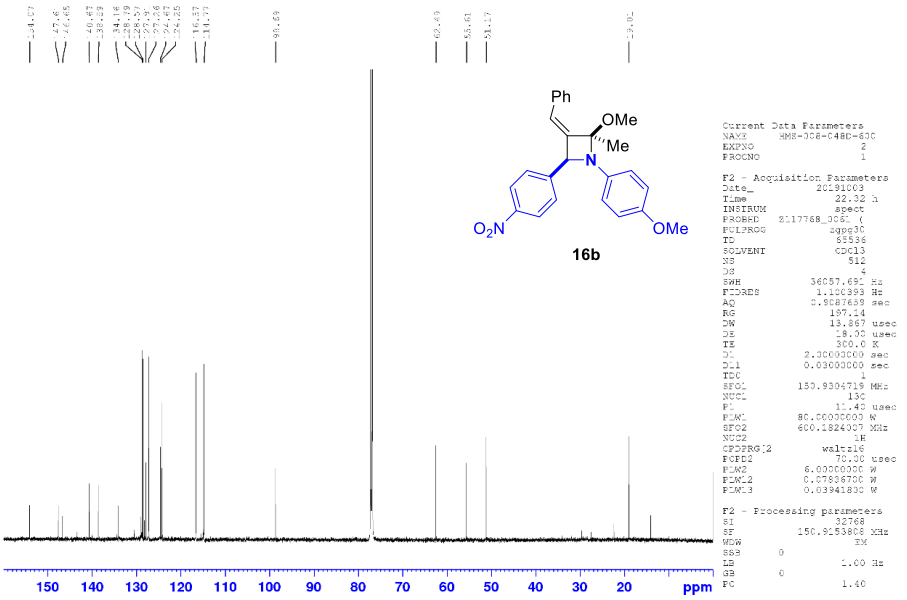

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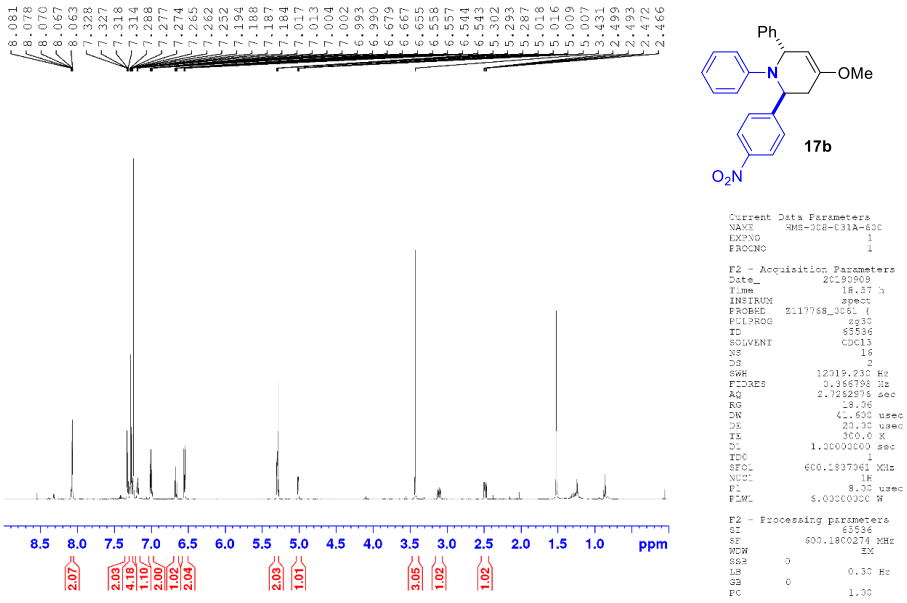

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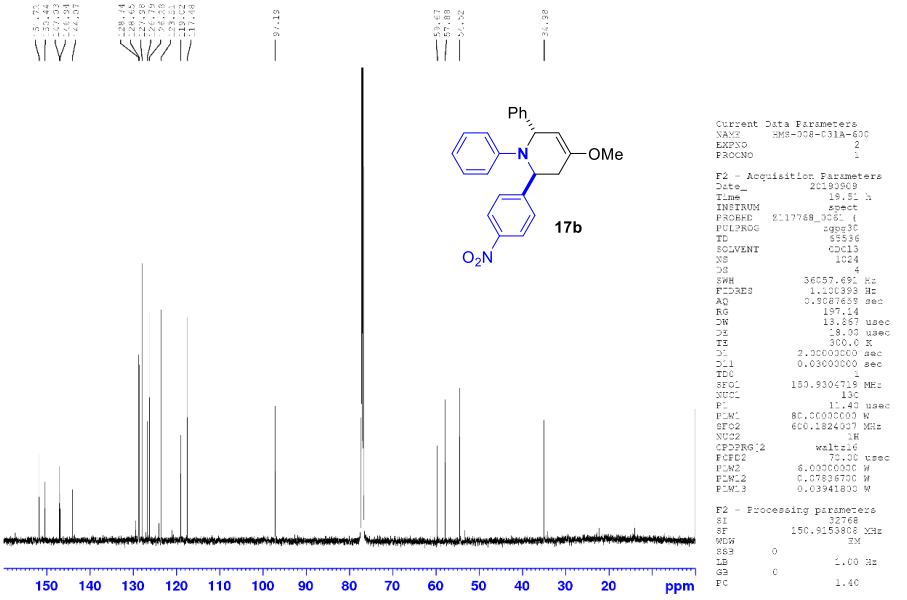

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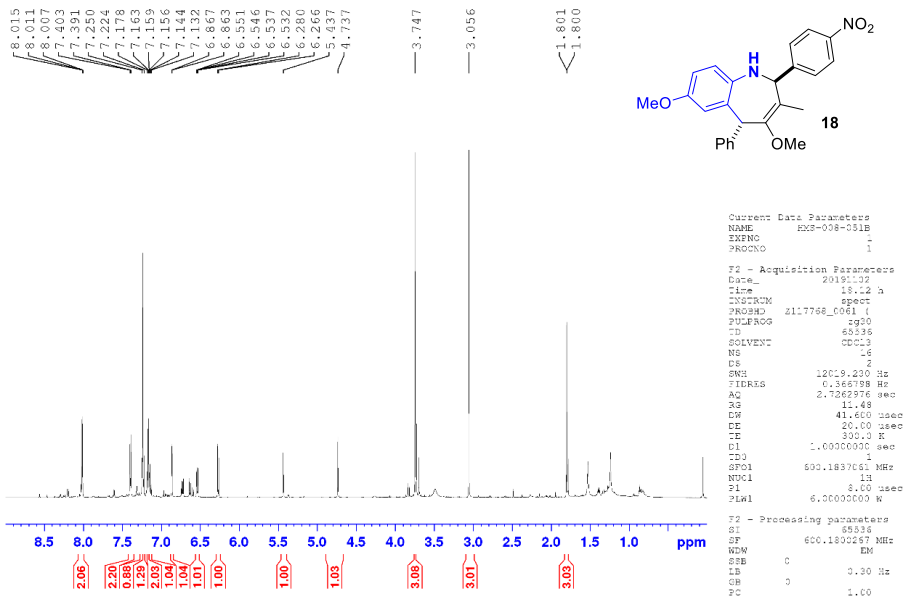
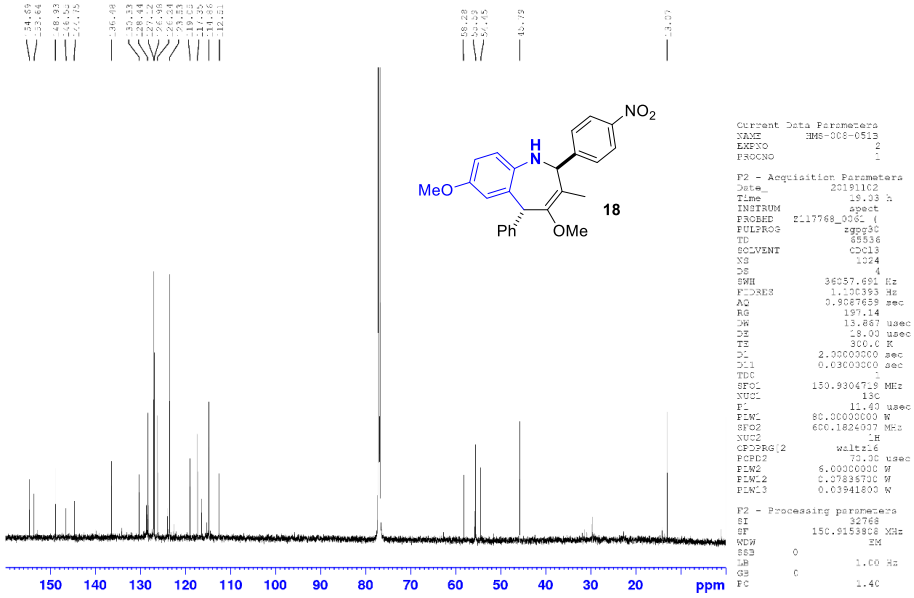
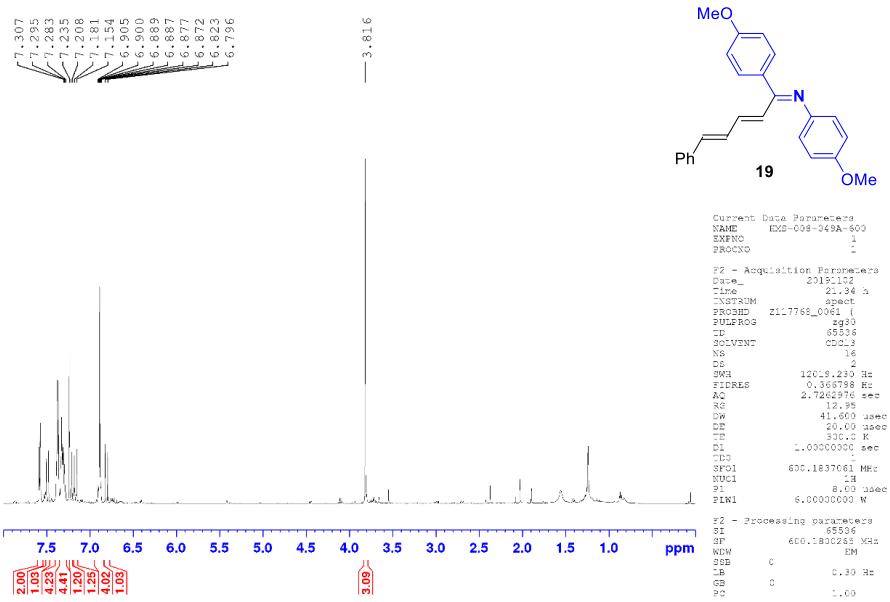
^{1}H NMR spectrum of *trans*-4,7-dimethoxy-3-methyl-2-(4-nitrophenyl)-5-phenyl-2,5-dihydro-1H-benzo[b]azepine (18)



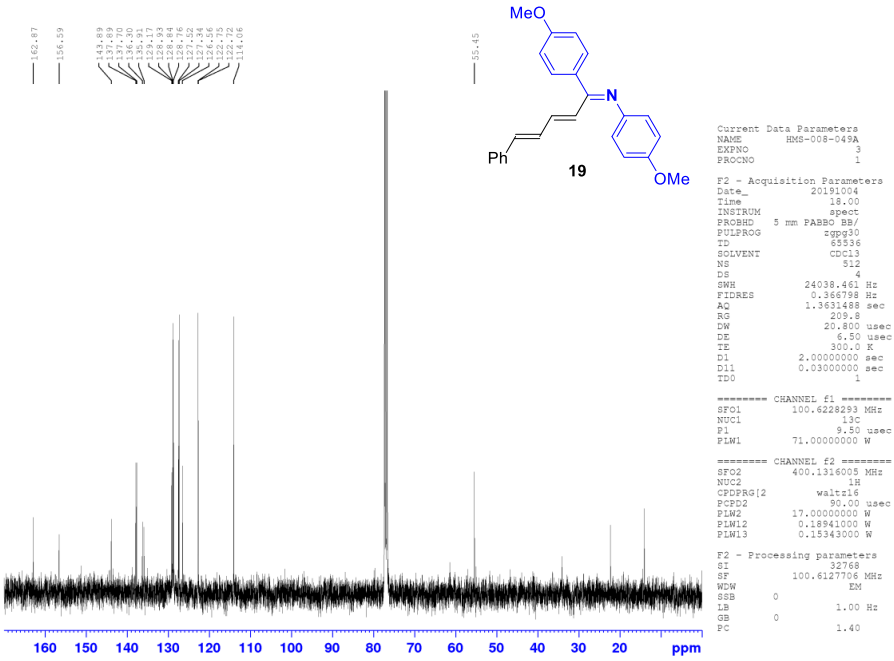
^{13}C NMR spectrum of *trans*-4,7-dimethoxy-3-methyl-2-(4-nitrophenyl)-5-phenyl-2,5-dihydro-1H-benzo[b]azepine (18)



^{1}H NMR spectrum of (1E,2E,4E)-N,1-bis(4-methoxyphenyl)-5-phenylpenta-2,4-dien-1-imine (19)



^{13}C NMR spectrum of (1E,2E,4E)-N,1-bis(4-methoxyphenyl)-5-phenylpenta-2,4-dien-1-imine (19)



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PAPER VI

Catalytic studies of cyclometalated gold(III) complexes and their related UiO-67 MOF

Manuscript submitted to *Molecular Catalysis*. Volodymyr A. Levchenko, Huey-San Melanie Siah, Sigurd Øien-Ødegaard, Anne Fiksdahl, Mats Tilset.

Catalytic studies of cyclometalated gold(III) complexes and their related UiO-67 MOF

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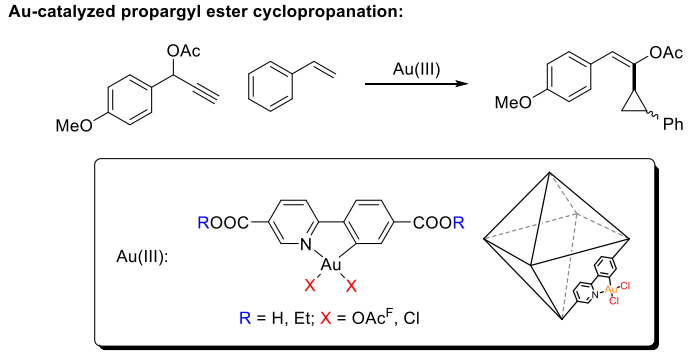
Catalytic studies of cyclometalated gold(III) complexes and their related UiO-67 MOF

Volodymyr A. Levchenko, Huey-San Melanie Siah, Sigurd Øien-Ødegaard, Anne Fiksdahl, and Mats Tilset*

Abstract

Cyclometalated gold(III) complexes Au(L)$(OAc^F)_2$ (L= phenylpyridine dicarboxylic diester (ppyde) or phenylpyridine dicarboxylic acid (ppydc)) have been prepared reacting $Au(OAc)_3$ with corresponding phenyl pyridines (ppyde or ppydc) in trifluoroacetic acid ($HOAc^F$) under microwave heating. Further treatment of Au(L)$(OAc^F)_2$ with *aqua regia* resulted in dichloro complexes Au(L)Cl_2. Au-functionalized UiO-67 MOF has been synthesized by exchanging linkers of UiO-67 with Au(ppydc)Cl_2, furnishing the MOF with (N^C)-cyclometalated Au(III) centers. The catalytic activities of the molecular cyclometalated complexes and the Au-incorporated MOF were studied in gold-catalyzed propargyl ester cyclopropanations. Almost all complexes and the MOF showed catalytic activity to the cyclopropanation product (up to 97% conversion), with a preference for the *trans* diastereoisomer (up to 14:86 d.r.). The recyclability of the most active molecular complex has also been investigated.

Graphical abstract



Keywords

Gold, catalysis, propargyl ester, MOF, *aqua regia*, UiO-67, cyclometalation.

1. Introduction

Gold catalysis comprises one of the most effective methods for the activation of C-C double and triple bonds leading to broad diversity of follow-up chemical transformations, such as heterocycles and natural compounds syntheses.[1-5] In the field of gold catalysis, the development of Au(I) catalysts has dominated over Au(III) catalysts, due to the superior stability of Au(I) salts compared to Au(III) salts. However, stable Au(III)-ligated complexes have been developed and studied for their bioactivity, such as anticancer and inhibition of DNA/RNA synthesis.[6, 7] Au(III) complexes that have been used in catalysis have been primarily less robust and ligand-free Au(III) species, with some exceptions such as pincer (C^C^N)Au and (C^C)Au complexes.[8-12] In the past decade, Au(III) complexes as catalysts have gained popularity due, in part, to the development of robust synthetic procedures.[13] The Tilset group has reported the syntheses of various cyclometalated Au(III) complexes using microwave heating.[14-16] (N^C)Au complexes bearing a phenyl pyridine ligand (ppy) are extensively studied complexes with various substituents on aromatic rings. This class of cyclometalated complexes has proven to be active in the catalysis of a large range of reactions, including aromatic addition to vinyl ketones,[17] AAA-coupling reaction[18, 19] and oxazole synthesis.[20]

The ppy motif, as a ligand in cyclometalated metal complexes, has potential uses in the MOF community, especially in heterogeneous catalysis.[21] One family of MOFs that has attracted widespread attention is the UiO-series – UiO-66, UiO-67 and UiO-68.[22] Due to their high thermal and chemical stability and ease of modification, they have been utilized for incorporation of various metal-functionalized linkers. However, the incorporation of the ppy ligand into UiO-67 is yet to be explored with gold, although reports with Ir, Ru and Rh exist (Figure 1).[21, 23-25]

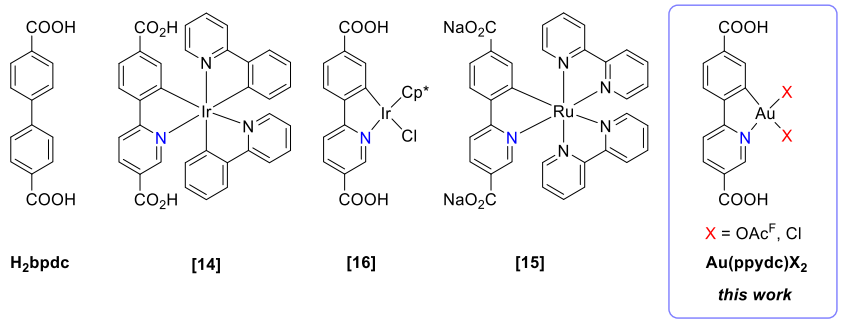


Figure 1. Reported cyclometalated metal complexes, from left to right: Linker for the UiO-67 MOF, cyclometalated iridium complexes[23, 25], cyclometalated ruthenium complexes[24] and cyclometalated gold complexes described in this work.

The introduction of a gold linker with a covalent Au-C bond is expected to increase the robustness and recyclability of the catalytic material and give better catalytic performance. Existing reports on covalently-bonded Au-MOFs are limited. While this work was in preparation, Toste and co-workers reported a stabilization of (C^C)Au(III) complexes by inclusion into MOFs.[26] The catalytic results indicated an enhanced stability of the supported Au complex compared to its molecular analogue. The attempted inclusion of (salen)-Au(III) complex into a IRMOF-3 framework has been reported, but was discovered to contain mostly Au(0) species.[27] Later, a proline-functionalized IRMOF-3 with Au active centers was reported, but analysis revealed inclusion of both Au(III) and Au(0) species.[28] Other than one Schiff base Au(III)-functionalized IRMOF-3 and the recent work by Toste,[26,[29] no other stable covalently-bonded Au(III) complexes have been incorporated into a MOF. The goal of this investigation was to incorporate the Au(ppydc) unit into the UiO-67 MOF framework and study the catalytic activity of the Au(III)-MOF in a gold-catalyzed reaction. The Au(ppydc) unit contains a stable Au-metallacycle

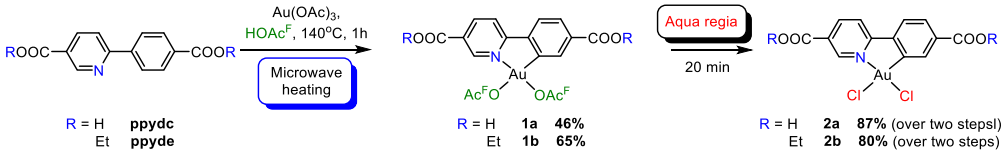
comprised of covalent Au-C and coordinative Au-N bonds and is expected to give a robust, heterogeneous catalyst, capable of carrying out a range of gold-catalyzed reactions.[30]

This work demonstrates the successful incorporation of an Au(III)-functionalized linker into the framework of the UiO-67 MOF. The resulting MOF was tested in a cyclopropanation reaction and compared to its molecular cyclometalated Au(III) analogs in solution.

2. Results and Discussion

2.1. Synthesis and characterization of cyclometalated Au(III) complexes

The cyclometalation of ppydc and ppyde with $Au(OAc)_3$ in $HOAc^F$ under microwave heating resulted in formation of complexes **1a** and **1b** in 46% and 65% yields, respectively (Scheme 1).



Scheme 1. Synthesis of complexes 1a and 1b followed by ligand exchange in aqua regia furnishing complexes 2a and 2b.

The ^{1}H NMR spectra of the complexes **1a** and **1b** were compared to those of uncomplexed ligands ppydc and ppyde and revealed one proton less in the cyclometalated complexes. The loss of a proton at the chelating C and appearance of a singlet to its neighbor H at δ 7.50 and 7.51 in the ^{1}H NMR spectra of **1a** and **1b**, respectively, indicated the formation of the Au-C covalent bond**.** Also, the ^{19}F NMR spectrum revealed two signals corresponding to OAc^F groups.

Initial attempts to substitute OAc^F groups by Cl in treatment with aqueous NaCl or HCl resulted in full exchange of OAc^F groups and led to formation of **2a** and **2b**. The reaction was followed by ^{19}F NMR spectroscopy and the disappearance of the two fluorine signals confirmed complete Cl-ion exchange. One major drawback of this method of preparation is that the reaction results in 2b and **2a** which appears as a grey material presumably due to contamination with NMR-silent inorganic gold species. The inorganic gold species can be removed by washing **1a** with *aqua regia*, in a protocol that was previously employed in our group [31,39]. In addition to the dissolution of inorganic Au species, *aqua regia* substituted OAc^F groups with Cl, furnishing pure **2a** and **2b** in 87% and 80% yields, respectively, after two steps.

The absence of signals in the ^{19}F NMR spectra of the complexes **2a-b** indicated the successful exchange of the OAc^F groups with halides. A strong deshielding for the proton α to the chelating N in the ^{1}H NMR spectrum of **2a** (δ 10.02) and **2b** (δ 10.06) compared with that of the free ppydc and ppyde ligands (δ 9.18 in both ligands) indicated a successful cyclometalation. A similar deshielding effect was observed for protons α to chelating C atom in **2a** (δ 8.33) and **2b** (δ 8.39) compared to those in ppydc (δ 8.27) and ppyde (δ 8.29) (see ESI). The molecular ions with expected isotope distribution were observed in the high-resolution mass-spectra of the complexes – two ^{35}Cl, one $^{35/37}$Cl and two ^{37}Cl ions for **2a-b** confirming the presence of two halogen atoms in the complex (see ESI).

Crystals suitable for structure determination by X-Ray diffraction analysis were obtained by vapor diffusion of dichloromethane into the trifluoroacetic acid solution for **1a**, pentane into dichloromethane solution for **1b** and dichloromethane into DMSO solution for **2a**. The ORTEP figures and the selected bond distances as well as angles are summarized and depicted in Figure 2.

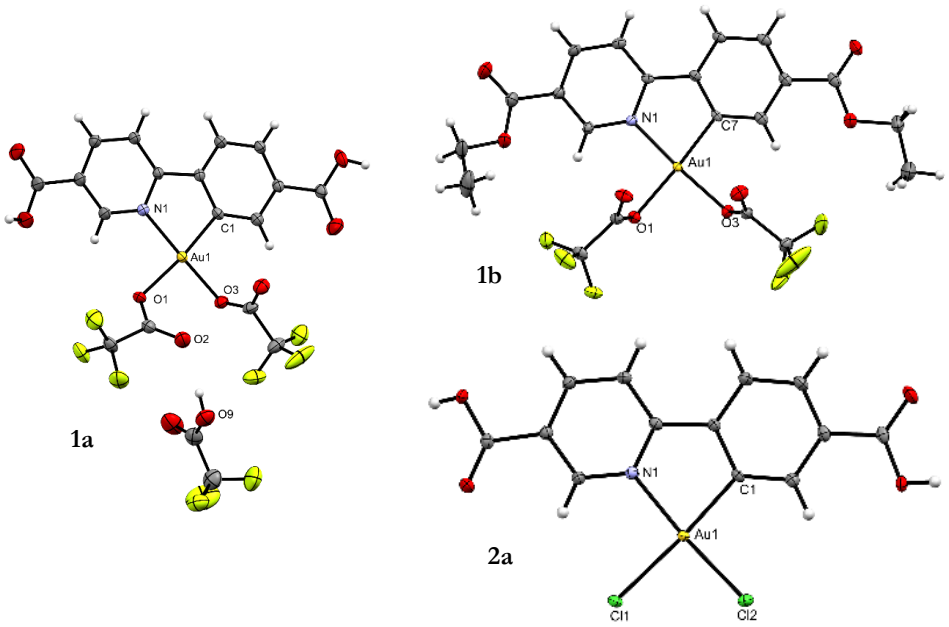


Figure 2. ORTEP representation of crystal structures of 1a-b and 2a with atoms drawn using 50% probability ellipsoids. Selected bond distances (Å) and angles (deg), for 1a: Au1-N1 2.008(2), Au1-C1 1.991(3), Au1-O3 2.006(2), Au1-O1 2.088(3), O2-O3 2.677(3), N1-Au1-C1 81.9(1), C1-Au1-O3 93.7(1), O3-Au-O1 92.51(9), O1-Au1-N1 91.8(1). For 1b: N1-Au1 2.002(3), Au1-C7 1.993(3), Au1-O1 2.064(3), Au1-O3 2.047(3); N1-Au1-C7 81.7(1), C7-Au1-O3 94.8(1), O3-Au1-O1 88.5(9), O1-Au1-N1 95.0(1). For 2a: N1-Au1 2.008(2), Au1-C1 1.991(3), Au1-O1 2.088(3), Au1-O3 2.006(2); N1-Au1-C1 81.9(1), C1-Au1-O3 93.7(1), O3-Au1-O1 92.51(9), O1-Au1-N1 91.8(1).

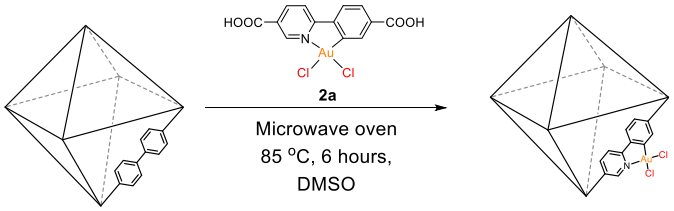
The solid-state structures of **1a** and **1b** reveal the expected square-planar geometry around the Au(III)-center. In both complexes the Au-O bond which is *trans* to carbon atom is elongated compared to the one *trans* to nitrogen due to the stronger *trans* influence of aryl-C *vs* pyr-N (2.064(3) *vs* 2.047(3) Å in **1b** and 2.088(3) *vs* 2.006(2) Å in **1a**). The Au-C distances are similar, 1.993(3) and 1.991(3) Å in **1b** and **1a** respectively. The bond angles around the central Au atom are also similar in **1a** and **1b** with no differences greater than 3° for both complexes. The carbonyl groups in **1a** and **1b** were found to be planar with respect to aromatic system. The Au-Cl bond distances in **2a** of 2.2713(6) (*trans* to N) and 2.3613(6) (*trans* to C) Å are typical for (N^C)$AuCl_2$ complexes, which span the range 2.262-2.282 Å for *trans* to N and 2.361-2.372 Å for *trans* to C.[32-34]

2.2. Synthesis and characterization of MOF

Our initial attempts to synthesize a Au(III)-functionalized UiO-67 MOF focused on direct assembly from the starting building blocks ($ZrCl_4$, H_2bpdc and complex **1a** or **2a**) in DMF at 120 °C in the presence of

benzoic acid as a modulator. Despite the success of the direct assembly for other metal-functionalized MOFs,[25] this synthesis method resulted in UiO-67 with no incorporation of Au as evidenced by single-crystal X-ray diffraction analysis. The absence of Au in the isolated material may be attributed to the reduction of Au(III) with amines that were generated during the synthesis. Such reduction during the synthesis was also observed for other types of Au-functionalized MOFs [27].

The destructive reduction of the Au-linker has been overcome by employing a post-synthetic linker exchange (PSLE)[35] protocol to substitute the biphenyl linker in UiO-67 with a gold(III) ppy unit (Scheme 3). The PSLE was carried out by heating UiO-67 with **1a** or **2a** in DMSO at 85 °C in the microwave oven for 6 h. This method was successful for complex **2a** to give MOF **UiO-67-[Au]Cl**, but **1a** was thermally unstable under these conditions and incorporation of **1a** into the MOF failed.



Scheme 3. Post synthetic linker exchange in reaction between UiO-67 MOF and 2a under microwave heating in DMSO.

The obtained **UiO-67-[Au]Cl** was isolated as a pale-yellow powder, after washing with hot DMSO and acetone followed by activation under dynamic vacuum. The crystallinity of UiO-67 was retained after incorporation of **2a**, as evidenced by powder X-ray diffraction analysis and SEM (Figures 3a and c). Energy-dispersed X-ray spectroscopy (EDS) was used to study the spatial distribution of gold in MOF. EDS elements mapping on **UiO-67-[Au]Cl** showed a homogeneous distribution of Au within the MOF (Figure 3f). Activated **UiO-67-[Au]Cl** exhibited a Braunauer-Emmett-Teller (BET) surface area of 867 m^2/g, which is less than half the BET of the original UiO-67 (2113 m^2/g), and their nitrogen absorption isotherms are depicted in Figure 3d. The decrease in surface area can be attributed to the smaller pore size due to the presence of the Au-functionalized linkers in the pores. The Au-functionalization had surprisingly a little impact on MOF's thermal stability, which is stable up to 400 °C and is comparable to the unfunctionalized UiO-67 MOF (Figure 3b), according to TGA measurements.

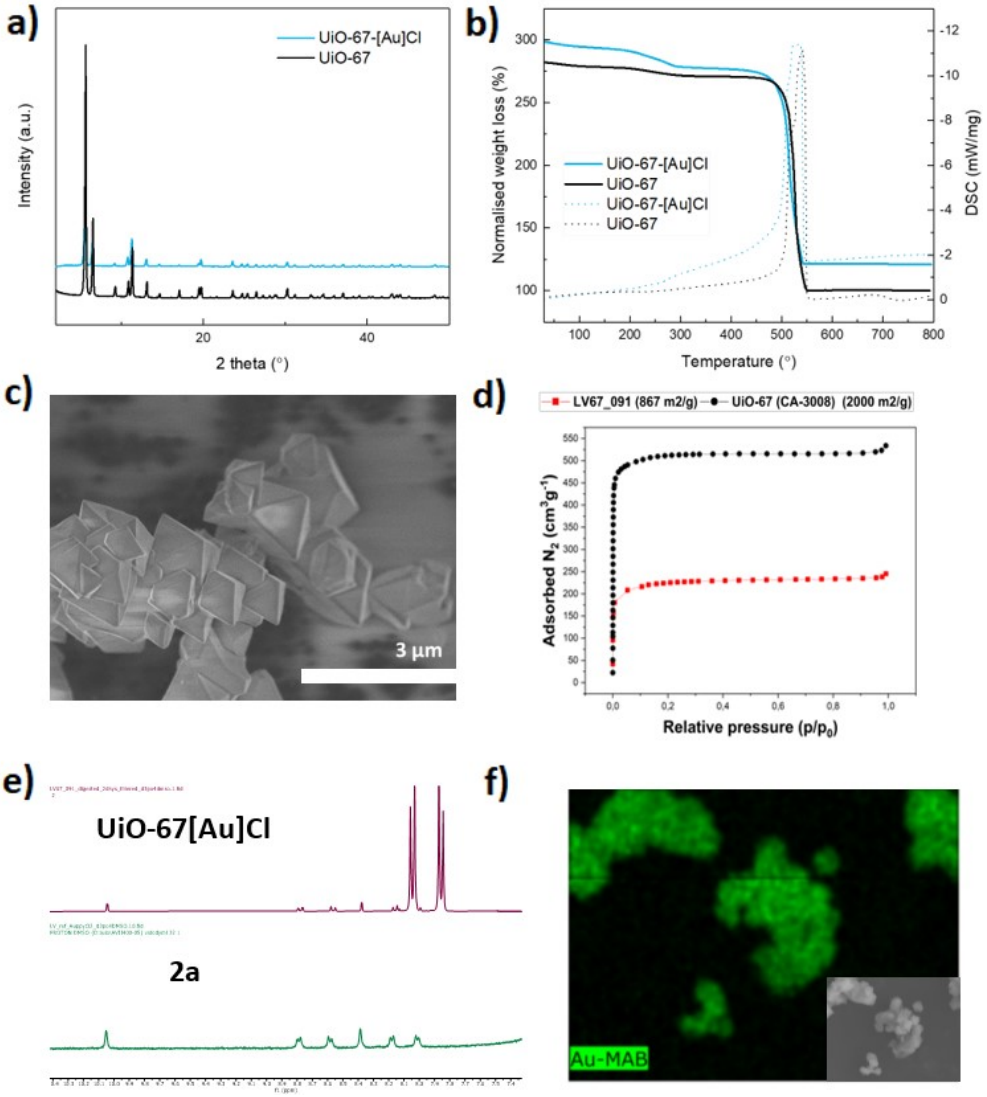


Figure 3. (a) PXRD patterns of UiO-67 and UiO-67-[Au]Cl. (b) TGA plots of UiO-67 and UiO-67-[Au]Cl. (c) SEM image of UiO-67-[Au]Cl. (d) Nitrogen sorption isotherm of UiO-67-[Au]Cl. (e) ^{1}H NMR (400 MHz, DMSO-d_6) spectra of 2a and UiO-67-[Au]Cl. (f) Au mapping of UiO-67-[Au]Cl by EDX.

The presence of the Au(ppy) units in **UiO-67-[Au]Cl** was confirmed by ^{1}H NMR spectroscopy of the digested material in 1M D_3PO_4 in DMSO-d_6. The degree of functionalization was calculated by integration of the proton resonances for bpdc and ppy in ^{1}H NMR spectrum, which showed 16% Au-incorporation (see ESI for calculations). Linker exchange in single crystals of UiO-67 was carried out under the same conditions used for the bulk samples. Single crystal X-ray structure determination of **UiO-67-[Au]Cl** showed a successful incorporation of the Au(ppy) unit into the UiO-67 framework (**Figure 4**). One of the linkers shows thermal vibrations of the aryl groups of the linker, and the position and thermal vibrations of the partially occupied Au atom. The occupancy of the Au atom is slightly below 1%, and it is disordered by symmetry over four equivalent sites. Other ligands of the Au atom are missing from the structure due to disorder and their poor scattering power.

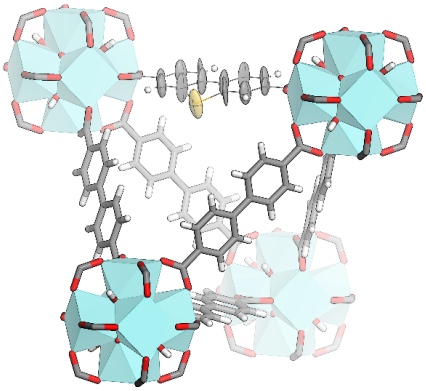
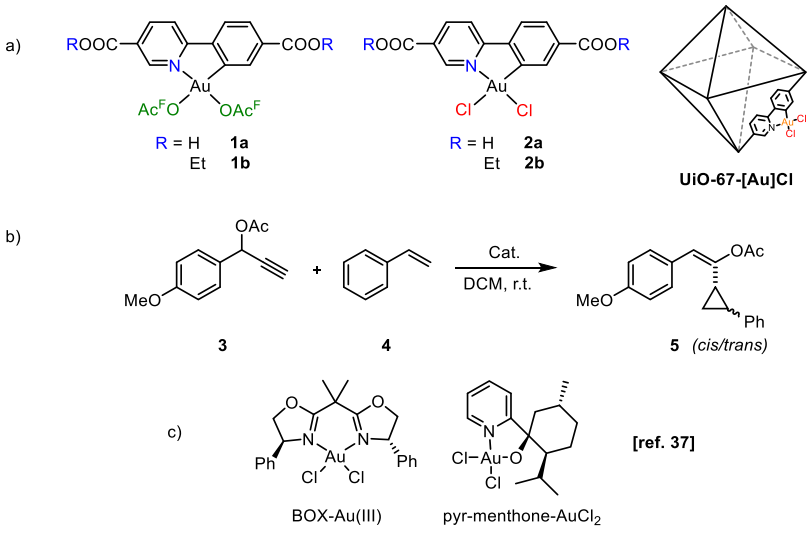


Figure 4. Structure of **UiO-67[Au]Cl** showing a partial unit cell.

2.3. Catalytic studies of gold complexes

The catalytic activity of diesters **1-2b**, diacids **1-2a**, and **UiO-67-[Au]Cl** was studied in the cyclopropanation reaction between **3** and **4** [36] in DCM at room temperature using 10 mol% of gold catalyst (Scheme 2b). The reaction progress was monitored by ^{1}H NMR spectroscopy (Figure 5 and Table 1). The previously published NMR study of this reaction with butyl-bisoxazoline-Au(III) (BOX) complexes showed high activity with gold(III) complexes and an interesting *cis-trans* isomerization (Scheme 2c) [36].



Scheme 2. a) Cyclometalated complexes and Au(III)-MOF utilized in the current study; b) Propargyl ester cyclopropanation test reaction used to study the catalytic activity of the Au(III) species in the current study; c) complexes studied before in the catalytic cyclopropanation reaction.

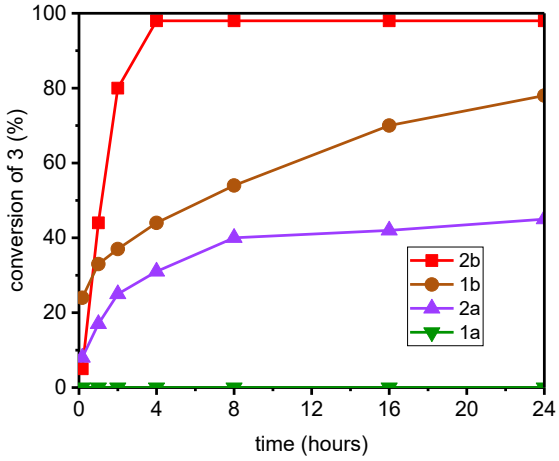


Figure 5. Comparison of the catalytic activity of complexes 1a, 1b, 2a and 2b.

Complexes **1b**, **2a** and **2b** showed catalytic activity over 24 h (45-97% conversion, Figure 5 and Table 1, entries 2-4) with **2b** as the most efficient catalyst (conversion >95% after 4 h), giving quantitative yield after isolation (Figure 5 and Table 1, entry 4). Changing the solvent from CH_2Cl_2 to DMSO-d_6 or MeCN-d_3 completely retarded the catalytic activity of **2b**.

Table 1. Results from NMR studies of the gold-catalyzed cyclopropanation reaction between 3 and 4.[a]

Entry	Catalyst	Conversion of **3** (1 h) [%]	*Cis:trans* (1 h)	Conversion of **3** (24 h) [%] (isolated yield in parenthesis)	*Cis:trans* (24 h)
1	**1a**	0	-	0	-
2	**2a**	17	32:68	45	23:77
3	**1b**	33	22:78	77 (80[b])	22:78
4	**2b**	43	10:90	97 (>99)	16:84
5	**2b**/AgOTf	>99[c, d]	50:50	>99	50:50
6	**UiO-67-[Au]Cl**	48	20:80	56	14:86
7	**UiO-67-[Au]Cl**	49	20:80	80[e]	18:82
8	**UiO-67**	0	-	0	-
9	**UiO-67@AuNPs[37]**	0	-	0	-

[a] Reagents and conditions: 5 mg of **1** with 11 µL of styrene with 10 mol% Au catalyst with 0.6 mL of CD_2Cl_2 in NMR tube. Conversions and *cis*/*trans* ratios were determined by ^{1}H NMR; [b] Dark precipitate in dark solution after 4 hours observed; [c] approx. 30% of species of unknown nature also generated within 1 h; [d] Immediate decomposition observed with similar observations when $NaBAr^F$ and $NaPF_6$ were attempted; [e] Double scale compared to the NMR scale and stirred.

The bis(trifluoroacetate) analogue **1b** resulted in lower conversion (77%, 24 h, Table 1, entry 3), which is presumably due to the decomposition of the catalyst. After only 4 h, a deep purple color had evolved, indicating the possible reduction of the catalyst to gold nanoparticles. Examination of the ^{1}H NMR data also revealed a reduction in the concentration of complex **1b**. In comparison, complex **2b** remained stable through the whole catalytic run, with no signs of degradation.

Generally, the complexes **1b** and **2b** are much more active than **1a** and **2a** (Figure 5 and Table 1, entries 3 and 4 *vs* 1 and 2), where the differences appeared to correspond to catalyst solubility in DCM-d_2

(soluble **1**-**2b** and insoluble **1**-**2a**). Despite the insolubility of **2a**, the complex showed moderate activity (45% conversion, 24 h, Table 1, entry 2). The catalytic nature of the apparently insoluble **2a** was investigated by stirring **2a** in DCM-d_2 for 24 h, filtering off the solids and mixing the filtrate with the propargyl ester **3** and styrene. NMR analysis of the mixture over 24 h showed no conversion, indicating that catalysis occurs in a heterogeneous manner for complex **2a**. The reactions were conducted several times and, in all cases, catalytic activity was observed, although results appeared to be sensitive to the quality of the substrate, styrene or catalyst.

Recent literature on the catalytic activity of cationic BOX-Au(III) complexes and neutral Au(III) complexes ($AuCl_3$ and pyr-menthone-$AuCl_2$) report that cationic Au(III) complexes show higher catalytic activity than the neutral complexes (Scheme 2c) [36]. Ligand exchange of complex **2b** was therefore attempted with AgOTf, $NaPF_6$ and $NaBAr^F$ prior to mixture with the reagents.

The cyclopropanation reaction catalyzed by complex **2b**/AgOTf resulted in immediate formation of Au nanoparticles, but also full conversion within the first few minutes of the reaction with no further changes over the next 24 h (Table 1, entry 5). Reactions using **2b**/$NaPF_6$ or $NaBAr^F$ resulted in immediate decomposition of the gold complex and/or propargyl acetate **3** to unknown products (Table 1, footnote d).

UiO-67-[Au]Cl was tested at 10% catalyst loading and gave moderate conversion (56%, 24 h, NMR scale, Table 1, entry 6). Notably, after 8 h, a pink discoloration was observed on the walls of the NMR tube. The pink material is suspected to be Au nanoparticles that originate from decomposition of the **UiO-67-[Au]Cl** catalyst. When the experiment was repeated at larger scale with stirring, high conversion was obtained (80%, 24 h, Table 1, entry 7). The heterogeneous nature of the catalyst was investigated by filtering the catalyst from the reaction mixture after stirring for 1 h. NMR monitoring of the filtrate showed that conversion of **3** continued the solid **UiO-67-[Au]Cl** was removed, indicating leaching of gold species into the solution, which gave moderate conversion (52%, 24 h). Reference reactions with UiO-67 and UiO-67 with AuNPs gave no conversion (entries 8-9).

2.4. Cis and trans selectivity in NMR studies

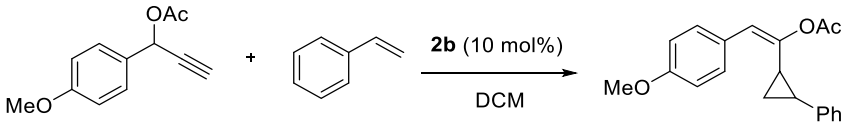
In published reports, the *cis* isomer of the cyclopropanation product is usually formed, although subsequent *cis-trans* isomerization is observed with different rates dependent on the gold ligand and the substrate.[36] In contrast, all experiments with our neutral gold complexes gave high *trans* selectivity (up to 14:86 dr), and no further change in *cis:trans* ratio. The results indicate that our substituted ppy-ligands give a different stereoselectivity than other gold(III) complexes and are not active for *cis*:*trans* isomerization within the time span the reactions were carried out in (24 h). The cationic **2b**/AgOTf complex decomposed during the reaction and gave equal amounts of *cis* and *trans* isomers, supporting our theory that a different gold species is the catalytic species in this reaction.

2.5. Optimization and recyclability of complex ***2b***

Monitoring of the integrity of the catalysts was possible during the catalytic runs by means of ^{1}H NMR and complex **2b** was observed to be intact after a reaction time of 24 h (see ESI). This observation prompted an investigation of the catalyst's recyclability. The experiments were scaled up and optimized, and recovery of the catalyst was carried out after completion of the reaction. First, the experiment was optimized with respect to temperature and heating method (conventional or microwave) (Table 2). When the reaction was repeated at larger scale (108 mg propargyl acetate **3**, 30 mg complex **2b**), the conversion was slower at r.t. and conversion was moderate after 24 hours (50%, Table 2, entry 1). Utilization of microwave heating resulted in high conversions of **3**

over short periods of time, but the reaction did not go to completion (79-85%, Table 2, entries 2-4). An increase in temperature and reaction time resulted in eventual decomposition of the gold catalyst, although high conversion of the substrate was obtained (90%, Table 2, entry 5). Further studies showed that heating in an oil bath at 65 °C for 5 hours gave full conversion of **3** and generated the product **5** in high yield (Table 2, entry 7).

Table 2. Optimization of the reaction conditions for the scaled-up reaction between 3 and 4 catalyzed by 2b (10 mol%).



3 **4** **5**

Entry	Heating source	Time	Temperature, °C	Conversion of **3**, %	*cis*:*trans*
1	-	24 h	25	50	20:80
2	MW	30 min	100	79	20:80
3	MW	45 min	100	84	20:80
4	MW	1 h 30 min	85	85	20:80
5	MW	1 h 30 min	100	90[a]	20:80
6	oil bath	9 h	55	>95	20:80
7	**oil bath**	**5 h**	**65**	**>95**[b]	20:80
8[c]	**oil bath**	**5 h**	**65**	**>95**[d]	20:80

[a]: decomposition of catalyst occurred; [b]: Isolated yield 73%, *cis*/*trans* 26/74; [c] Recovered catalyst from entry 7; [d] Yield of **3** = 89% and was measured by ^{1}H NMR with dimethyl sulfone as internal standard

As anticipated, complex **2b** was stable (^{1}H NMR) under the optimized conditions (Table 2, entry 7) and after full conversion of **3**, the isolation of complex **2b** was carried out by precipitating the complex from the reaction mixture with pentane. The recovery degree was found to be 93% (by mass) and the identity of complex **2b** was confirmed by ^{1}H NMR (see ESI). The recovered complex **2b** was subjected to a second round of catalyzing the cyclopropanation reaction and demonstrated the same level of activity giving high yield (89%, calculated by ^{1}H NMR using an internal standard, Table 2, entry 8). To our knowledge, reports of the recyclability of Au(III) complexes are scarce and the catalytic ability and recyclability of complex **2b** is an exciting discovery.[19, 38]

Recyclability of complex **2b** *in situ* was also studied by conducting an experiment under the optimized conditions depicted in Table 2, entry 7. After 5 h, the substrate conversion was determined by ^{1}H NMR analysis and an additional 1 equivalent of **3** and 1 equivalent of **4** was introduced to the reaction mixture. The reaction was repeated with an additional 3 cycles and the results are given in Table 3.

Table 3. Recyclability of 2b.

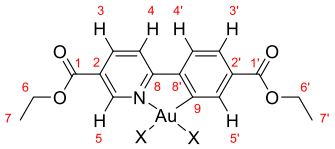
Cycle	1	2	3	4
Conversion of **3**, %	>95	>95	>95	>95
Stability of **2b**	yes	yes	yes	decomposed

The cyclopropanation reaction catalyzed by **2b** could be repeatedly used for 3 cycles with no degradation of **2b**, which was observed only at the 4th cycle.

3. Conclusions

A convenient and robust method of synthesizing stable cyclometalated gold(III) complexes has been developed. Their structures have been confirmed through NMR and X-ray crystal analysis. The first Au(ppy)-functionalized linker has successfully been incorporated into the framework of MOF UiO-67. The resulting MOF has been analyzed by X-ray spectroscopy analysis, ^{1}H NMR, TGA and nitrogen adsorption analysis. The results indicate the integrity of the Au(ppy) unit in the framework of UiO-67 MOF. NMR studies on the catalytic activity of the gold(III) complexes and Au-MOF were carried out in a known cyclopropanation reaction. Most of the catalysts showed moderate to excellent conversions on the NMR scale. When the reaction was scaled up with complex **2b**, the catalyst was found to be recoverable and recyclable in new reactions.

4. Experimental



4.1. Synthesis of **1a**

The teflon liner for the microwave oven synthesis reactor was filled with gold(III) acetate (68 mg, 0.182 mmol, 1.1 equiv.), 6-(4-carboxyphenyl)nicotinic acid (40 mg, 0.164 mmol, 1.0 equiv.) and trifluoroacetic acid (15 mL). The reaction mixture was heated in the microwave oven at 130°C for 1 hour. Still warm, the suspension was centrifuged and clear solution was decanted. The flask with solution was kept overnight in a dark place at room temperature until the crystalline product started to precipitate. The crystals were filtered and washed with water (until pH of the filtrate was 7), diethyl ester (10 mL) and dried under a stream of air giving the 50 mg of the complex **1a** as white solid (46% yield). X-ray-quality crystals were obtained by cooling the warm reaction mixture to room temperature.

Notes: material for NMR spectra was prepared by removing trifluoroacetic acid under reduced pressure immediately after the microwave synthesis and decomposes in solution over short period of time making spectra acquisition troublesome. Complex **1a** that precipitates out of the TFA solution is insoluble in DMSO-d_6, DMF-d_7 and CD_3CN.

^{1}H NMR (400 MHz, DMSO-d_6): δ_H 9.07 – 8.95 (1H, m, *H*-5), 8.93 – 8.81 (1H, m, *H*-3), 8.71 – 8.58 (1H, m, *H*-4), 8.28 – 8.14 (1H, m, *H*-4'), 8.13 – 8.00 (1H, m, *H*-3'), 7.50 (1H, s, *H*-5'). **^{1}H NMR** (400 MHz, CD_3CN): δ_H 9.10 (1H, s, *H*-5), 8.81 (1H, dd, *J* = 8.4, 1.8 Hz, *H*-3), 8.28 (1H, d, *J* = 8.5 Hz, *H*-4), 8.13 (1H, d, *J* = 8.0 Hz, H-*4'*), 7.90 (1H, d, *J* = 8.0 Hz, *H*-3'), 7.62 (1H, s, *H*-5'). **^{13}C{^{1}H} NMR** (151 MHz, DMSO-d_6): δ_C 165.2, 164.7, 163.2, 158.4 (q, *C*O, *J* = 37.9, 36.9 Hz), 148.1, 145.1, 145, 140.3, 133.4, 130.9, 128.4, 127.9, 127.2, 123.4, 115.7 (q, *C*F_3, *J* = 292.2, 290.3 Hz). **^{13}C{^{1}H} NMR** (151 MHz, CD_3CN): δ_C 166.8, 165.5, 163.3, 158.9 (q, *C*O, *J* = 39.5 Hz), 150, 146.3, 146.1, 141.6, 134.2, 132.4, 129.3, 129.2, 128.4, 124.2 (Signals of CF_3 group overlapped with solvent signal). **MS** (ESI$^+$, CH_3OH): *m/z* 697.658 ([M+CH_3OH]$^+$, 7%). **HRMS** (ESI$^+$, CH_3OH): *m/z* 697.6582 [$C_{17}H_8AuF_6NO_8$+CH_3OH]$^+$ (calculated for $C_{14}H_{12}AuF_6NO_9$ 697.0080 (+0.65 ppm)).

4.2. Synthesis of **1b**

The teflon liner for the microwave oven synthesis reactor was filled with gold(III) acetate (45 mg, 0.120 mmol, 1.2 equiv.), ethyl 6-(4(ethoxycarbonyl)phenyl)nicotinate (30 mg, 0.1 mmol, 1.0 equiv.) and trifluoroacetic acid (20 mL). The reaction mixture was heated in the microwave oven at 130°C for 1

hour. After cooling down to room temperature, the volatiles were removed in vacuum and solid crude was extracted with warm (40-45 °C) CH_2Cl_2 (2 x 15 mL). Combined fractions were filtrated through a folded filter and volume of the filtrate was reduced to 10 mL under vacuum. Product was precipitated as a white solid upon addition of the pentane (20 mL). The filtration resulted in 47 mg of **1b** as a white powder in 65% yield.

^{1}H NMR (600 MHz, CD_2Cl_2): δ_H 9.23 (1H, dd, *J* = 1.8, 0.6 Hz, *H5*), 8.84 (1H, dd, *J* = 8.4, 1.8 Hz, *H3*), 8.16 (1H, dd, *J* = 8.0, 1.4 Hz, *H3'*), 8.11 (1H, d, *J* = 8.4 Hz, *H4*), 7.76 – 7.71 (2H, m, *H4'* and *H5'*), 4.47 (2H, q, *J* = 7.2 Hz, C*H*2(6)), 4.38 (2H, q, *J* = 7.1 Hz, C*H*2(6')), 1.41 (6H, dt, *J* = 19.0, 7.2 Hz, C*H*3(7 and 7')). **^{1}H NMR** (400 MHz, DMSO-d_6): δ_H 9.03 (s, 1H), 8.92 (dd, *J* = 8.4, 1.9 Hz, 1H), 8.66 (d, *J* = 8.5 Hz, 1H), 8.22 (d, *J* = 8.1 Hz, 1H), 8.11 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.51 (s, 1H), 4.42 (q, *J* = 7.2 Hz, 2H), 4.35 (q, *J* = 7.0 Hz, 2H), 1.34 (dt, *J* = 13.6, 7.1 Hz, 6H).**^{13}C{^{1}H} NMR** (151 MHz, CD_2Cl_2): δ_C 166.6 (C8), 164.3 (C1'), 161.8 (C1), 161.3 (CO, *J* = 37.8 Hz), 160.9 (CO, *J* = 39.3 Hz) 149.7 (CH-5), 145.6 (CH-3), 144.5 (C-2), 141.6 (C-8'), 134.8 (CH-2'), 131.9 (CH-3'), 129.4 (CH-4'*)*, 129.0 (CH-5'), 127.1 (C8'), 122.7 (CH-4), 118.1 (CF3, *J* =289.9 Hz), 116.1 (CF3, *J* =288.4 Hz), 63.9 (-CH2-(6)), 62.7 (-CH2-(6')), 14.3 (CH-3(7)), 14.2 (CH-3(7')). **^{19}F NMR** (376 MHz, CD_2Cl_2): δ_F -77.05, -75.98. (ref. C_6F_6). **MS** (ESI$^+$, CH_3OH): *m/z* 580.100 ([M-OAc^F-Et+H]$^+$, 100%).

4.3. Synthesis of **2a**

The Teflon liner for the microwave oven synthesis reactor was filled with 6-(4-carboxyphenyl)nicotinic acid (60 mg, 0.248 mmol, 1.0 equiv.), $Au(OAc)_3$ (102 mg, 0.273 mmol, 1.1 equiv.) and trifluoroacetic acid (15 mL). The mixture was heated in the microwave oven at 130 °C for 1 hour. After cooling to room temperature, the solvent was removed under reduced pressure. After the solvent removal, the solid crude was stirred with aqua regia solution (9 mL HCl and 3 mL HNO_3) for 30 min. The pale yellow precipitate was filtered through a fine frit, washed with water and dried under a stream of air for 30 min. The product was obtained in 87% yield (110 mg).

^{1}H NMR (600 MHz, DMSO-d_6): δ_H 10.02 (1H, d, *J* = 1.9 Hz, *H*5), 8.78 (1H, dd, *J* = 8.4, 1.9 Hz, *H*3), 8.57 (1H, d, *J* = 8.5 Hz, *H*4), 8.33 (1H, d, *J* = 1.5 Hz, *H*5'), 8.15 (1H, d, *J* = 8.1 Hz, *H*4'), 7.98 (1H, dd, *J* = 8.0, 1.6 Hz, *H*3'). **^{13}C NMR** (151 MHz, DMSO-d_6): δ_C 165.9 (C1'), 165.5 (C8), 163.8 (C1), 151.1 (C2'), 149.1 (CH-5), 145.9 (C8'), 143.9 (CH-3), 133.3 (C9), 130.3 (CH-5'), 129.9 (CH-3'), 128.1 (C2), 127.6 (CH-4'), 122.9 (CH-4). **MS** (ESI$^+$, CH_3OH): *m/z* 531.939 ([^{35}M+Na]$^+$, 100%), 533.936 ([$^{35/37}$M+Na]$^+$, 63.7%), 535.933 ([^{37}M+Na]$^+$, 10.6%). **HRMS** (ESI$^+$, CH_3OH): *m/z* 531.9386 (calculated for $C_{13}H_8AuCl_2NNaO_4$ 531.9388 (+0.5 ppm)).

4.4. Synthesis of **2b**

The teflon liner for the microwave oven synthesis reactor was filled with gold(III) acetate (90 mg, 0.24 mmol, 1.2 equiv.), ethyl 6-(4-(ethoxycarbonyl)phenyl)nicotinate (60 mg, 0.20 mmol, 1.0 equiv.) and trifluoroacetic acid (15 mL). The reaction mixture was heated in the microwave oven at 130 °C for 1 hour. The volatiles were removed under reduced pressure and afforded Au(ppyde)(OAc^F)$_2$ as a pale-yellow solid which was used without further purification. The crude was then taken up with aqua regia solution (9 mL HCl and 3 mL HNO_3) for 30 min. The pale yellow precipitate was filtered through a fine frit, washed with water and dried under a stream of air for 30 min. The product was obtained in 80% yield (90 mg).

^{1}H NMR (600 MHz, DMSO-d_6): δ_H 10.06 (1H, d, *J* = 1.9 Hz, *H*5), 8.84 (1H, dd, *J* = 8.4, 2.0 Hz, *H*3), 8.63 (1H, d, *J* = 8.4 Hz, *H*4), 8.39 (1H, d, *J* = 1.6 Hz, *H5'*), 8.23 (1H, d, *J* = 8.1 Hz, *H4'*), 8.04 (1H, dd, *J* = 8.0, 1.6 Hz, *H3'*), 4.44 (2H, q, *J* = 7.1 Hz, *H6*), 4.37 (2H, q, *J* = 7.1 Hz, *H6'*), 1.36 (6H, dt, *J* = 14.3, 7.1 Hz, *H7* and *7'*). ^{1}H NMR (600 MHz, $CDCl_3$): δ_H 10.41 (d, *J* = 1.8 Hz, 1H), 8.78 (dd, *J* = 8.4, 1.8 Hz, 1H), 8.67 (d, *J* = 1.4 Hz, 1H), 8.12 (dd, *J* = 8.1, 1.5 Hz, 1H), 8.07 (d, *J* = 8.4 Hz, 1H), 7.72 (d, *J* = 8.1 Hz, 1H), 4.52 (q, *J* = 7.1 Hz,

2H), 4.44 (q, *J* = 7.1 Hz, 2H), 1.45 (dt, *J* = 19.8, 7.1 Hz, 7H). **$^{13}C\{^{1}H\}$ NMR** (151 MHz, DMSO-d_6): δ_C 165.7 (C1), 164.4 (C1'), 162.3 (C8), 151.0 (C9), 148.8 (CH5), 146.2 (C8'), 143.8 (CH3), 132.3 (C2'), 129.9 (CH5'), 129.8 (CH3'), 127.9 (CH4'), 127.1 (C2), 123.1 (CH4), 62.4 (CH_2(6)), 61.6 (CH_2(6')), 14.14 (CH_3(7)), 14.06 (CH_3(7')). **MS** (ESI$^+$, CH_3OH): *m/z* 588.002 ([*M*+Na^+], 7%), 584.051 ([*M*+H_3O^+], 100%). **HRMS** (ESI$^+$, CH_3OH): calculated for $C_{17}O_4H_{16}AuNCl_2Na^+$ [*M*+Na^+] 588.0014, found 588.0016 (Δ -0.2 ppm).

4.5. Synthesis of **3**

To a stirred ethynylmagnesium bromide solution (38 mL of 0.5 M solution in THF, 19 mmol) on ice bath, a solution of *p*-anisaldehyde (2 g, 14.69 mmol) in THF (5 mL) was added under nitrogen atmosphere. Solution was stirred for 15 min on ice bath and overnight at room temperature. Water (50 mL) with Et_2O (40 mL) were added and the organic phase was separated. The aqueous phase was extracted with Et_2O (2 x 40 mL) and the combined phases were dried with Na_2SO_4. Filtration followed by solvent removal under reduced pressure resulted in 1-phenylprop-2-yn-1-ol as a viscous, yellow-brown oil which was used for next step without further purification. Mixture of 1-phenylprop-2-yn-1-ol (2.17 g, 13.38 mmol) acetic anhydride (3.6 mL) and trimethylamine (5.3 mL) in DCM (20 mL) was stirred at room temperature overnight. The solution was poured into 1M NaOH until pH = 14 and mixed with DCM (25 mL). After the organic layer was separated, the compound was extracted with DCM (2 x 25 mL). The combined organic layer was dried over Na_2SO_4, filtered off, and purified by column chromatography using ethyl acetate/hexane mixture (1:10) as an eluent. The obtained pale-yellow oil solidified in the freezer. Yield: 2.43 g, 89%. The compound must be stored in the freezer under vacuum in a Schlenk flask.

4.6. Synthesis of UiO-67[Au]Cl

A mixture of UiO-67 MOF (200 mg) and **2a** (67 mg, 0.118 mmol) in DMSO (8 mL) was heated at 85 °C for 6 hours in the microwave oven. The resulted powder was washed with hot DMSO (3 times) and acetone (3 times). The material was then dried under dynamic vacuum overnight yielding **UiO-67[Au]Cl** (240 mg).

4.7. Digestion of MOF

Digestion solution: To 54 mg of D_3PO_4 (86% in D_2O) was added 3.3 mL DMSO-d_6 (for 1 mL of DMSO-d_6 was used 18 mg of 86% D_3PO_4).

Procedure: To 15 mg of MOF material 600 µL of digestion solution added and sonicated for 1 min. The suspension was then placed on a shaker and left overnight. The suspension was then placed in the NMR tube and the ^{1}H NMR spectrum recorded.

4.8. General procedure for catalysis

Catalytic tests were carried out following published procedure.[36] A mixture of **3** (5 mg, 0.024 mmol, 1 equiv.) and styrene (11 µl, 0.096 mmol, 4 equiv.) in CD_2Cl_2 (0.6 mL) was added to the gold catalyst. The reaction's development was monitored by ^{1}H NMR at 10 min, 1 h, 2 h, 4 h, 8 h, 16 h and 24 h.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.mcat.xxxx.xxxxxx.

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SUPPORTING INFORMATION

Catalytic studies of cyclometallated gold(III) complexes and their related MOF

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Contents

Experimental Section 2
Synthesis of ethyl 6-(4-(ethoxycarbonyl)phenyl)nicotinate, ppyde 3
Synthesis of 6-(4-carboxyphenyl)nicotinic acid, ppydc 4
Spectra of Au(ppyde/dc)X_2 (X = OAc^F, Cl) complexes 5
Au(ppydc)$(OAc^F)_2$ (1a) 5
Au(ppyde)$(OAc^F)_2$ (1b) 7
Au(ppydc)Cl_2 (2a) 9
Au(ppyde)Cl_2 (2b) 10
UiO-67-[Au]Cl characterization 12
Catalysis data 14
Crystallographic data 14
References 18

Experimental Section

All chemicals and solvents were sourced commercially and used as received. The microwave oven used was of the type Milestone MicroSYNTH with a rotor of type SK-10. NMR spectra were recorded on a Bruker Avance AV600 operating at 600 MHz (^{1}H), DRX500 operating at 500 MHz (^{1}H), AVII400 operating at 400 MHz (^{1}H) and DPX200 operating at 200 MHz (^{1}H). All spectra were recorded at 25 ^{o}C. Values for chemical shifts (δ) are reported in ppm relative to CDCl3 (7.26 ppm for ^{1}H NMR and 77.0 ppm for ^{13}C NMR) and DMSO-d_6 (2.50 ppm for ^{1}H NMR and 39.5 ppm for ^{13}C NMR). DCM was used from solvent purifier MB SPS-800 from MBraun. DCM-d_2 was purchased from Euroisotop. Styrene was stabilized with 4-tert-butylcatechol and purchased from Alfa Aesar. Mass spectra were taken on a Micromass QTOF II spectrometer and a Bruker Daltronics maXisII spectrometer. Ethyl 6-Chloronicotinate, Pd_2dba_3, HBF_4·P(t-Bu)$_3$, KF·2H_2O and LiOH were purchased from Sigma Aldrich, 4-ethoxycarbonylphenylboronic acid was purchased from AK Scientific, and used as received. THF was purified by using a MB SPS-800 solvent purifier system from MBraun. All other solvents and chemicals were purchased from VWR or Sigma Aldrich and used as received. UiO-67 MOF was synthesized according to the procedures developed in our group.[1] TGA analysis was performed on a Netzsch STA 449 F3-Jupiter instrument. Ca. 20 mg of the sample was weighed and transferred into an Al_2O_3 sample holder and the data was collected for the temperature range of 30 °C to 800 °C. SEM images were taken on a Hitachi SU8230 Field Emission Scanning Electron Microscope (FE-SEM). Nitrogen sorption were performed with a BelSorp mini II instrument. In each measurement, ~40 mg of the sample was weighed into a 9.001 cm3 glass cell and pretreated at 80 °C for 30 min and 200 °C for 60 minutes, under vacuum. For powder X-ray diffraction (PXRD) samples were prepared using ~20 mg of the sample on a glass plate XRD sample holder by spreading it evenly and covering with transparent plastic film. The plastic film gives a small signal in the PXRD patterns observed at 2θ = ~22 ° and 34 ° as broad peaks. PXRD patterns (Cu Kα radiation, λ = 1.5418 2 Å, 2θ range = 2-50 °, time scale = 1, resulting in a d-spacing to 1.82 Å) were collected in reflectance Bragg-Brentano geometry with a Bruker D8 Discovery diffractometer equipped with a focusing Gemonochromator and a Bruker LYNXEYE detector.

Aqua regia is prepared by slow addition of 2 mL of concentrated nitric acid (HNO_3, 65%) to 6 mL of hydrochloric acid (HCl, 37%) and used immediately after preparation. The filtration of

the suspension was performed in a glass frit (pore size 4) under reduced pressure in a vacuum filtering flask equipped with a NaOH solution for immediate neutralization of the *aqua regia*.

Aqua regia handling protocol: Wear lab protection (gloves, protective googles, lab coat). Do not handle outside of a fume hood (gaseous toxic species are produced in aqua regia). Do not store in a closed vessel. All safety protocols for the handling of strong acid apply. Disposal: neutralize aqua regia with a NaOH solution.

Synthesis of ethyl 6-(4-(ethoxycarbonyl)phenyl)nicotinate, ppyde

Synthesis was carried out according to published procedure.[2] Ethyl 6-Chloronicotinate (4.65 g, 25.1 mmol, 1.0 equiv.), 4-Ethoxycarbonylphenylboronic acid (5.09 g, 26.2 mmol, 1.05 equiv.) and $KF{\cdot}2H_2O$ (7.79 g, 82.8 mmol, 3.3 equiv.) were mixed in THF (50 mL). The mixture were bubbled with Ar for 20 minutes before Pd_2dba_3 (0.118 g, 0.129 mmol, 0.0051 equiv.) and $HBF_4{\cdot}P(t\text{-Bu})_3$ (0.0866 g, 0.299 mmol, 0.012 equiv.) were added. The bubbling was continued for 5 minutes before the reaction mixture was heated to reflux. The mixture was then refluxed for 20 h under Ar, after which it was evaporated. The residue was dissolved in DCM and filtered through a silica column (washing with DCM). The combined fractions were evaporated to dryness and the solid obtained was recrystallized from EtOH. This gave ethyl 6-(4-(ethoxycarbonyl)phenyl)nicotinate as a colorless solid. Yield: 6.78 g, 22.6 mmol, 90 %. NMR spectra matched those of reported compound. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.18 (dd, J = 2.2, 0.8 Hz, 1H), 8.38 (dd, J = 8.4, 2.3 Hz, 1H), 8.33 – 8.25 (m, 2H), 8.20 (d, J = 8.6 Hz, 1H), 8.12 – 8.04 (m, 2H), 4.42 – 4.30 (m, 4H), 1.35 (td, J = 7.1, 3.1 Hz, 6H).

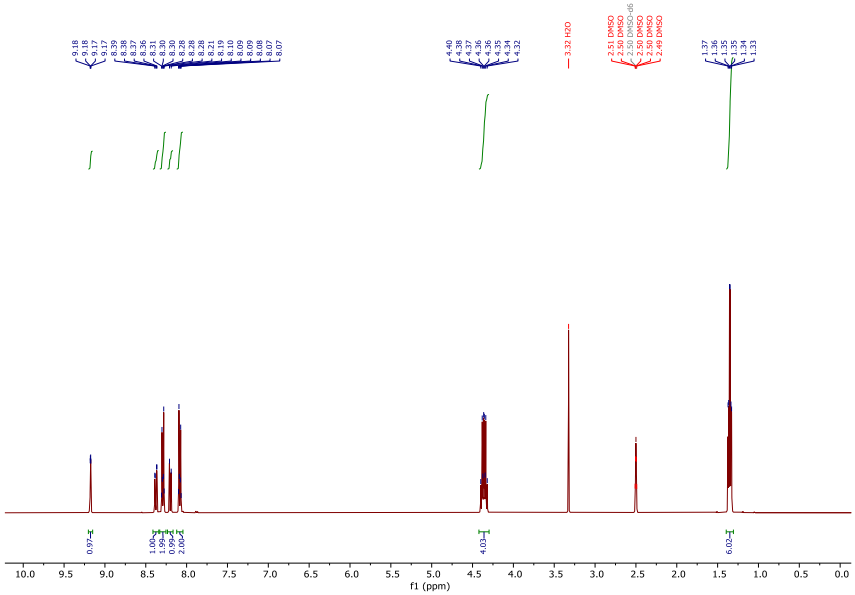


Figure S2. ^{1}H NMR spectrum of ppyde (400 MHz, DMSO-d_6).

Synthesis of 6-(4-carboxyphenyl)nicotinic acid, ppydc

Ethyl 6-(4-(ethoxycarbonyl)phenyl)nicotinate (6.00 g, 20.0 mmol, 1.0 equiv.) was dissolved in a mixture of THF (80 mL) and MeOH (40 mL). LiOH (1.94 g, 80.9 mmol, 4.05 equiv.) and H_2O (80 mL) were then added. Within few minutes a homogenous solution was obtained. The reaction mixture was stirred at room temperature for 24 h, after which THF and MeOH were removed under reduced pressure. Water (100 mL) was added, and the solution was stirred for 30 min at room temperature before it was filtered. Conc. AcOH was then added to the filtrate to a pH of 4-5 was reached. The precipitated product was filtered and air-dried overnight, after which it was broken up in small pieces and stirred with water (200 mL) for several hours. The product was filtered and dried in an oven at 110°C for 3 days. This gave 6-(4-carboxyphenyl)nicotinic acid as a colorless solid. Yield: 4.20 g, 17.2 mmol, 86 %. NMR spectra matched those of reported compound.[3] ^{1}H NMR (DMSO-d_6, 400 MHz): δ_H 13.29 (2H, bs), 9.18 (1H, d, J = 1.6 Hz), 8.37 (1H, dd, J = 8.3, 2.1 Hz), 8.27 (2H, d, J = 8.5 Hz), 8.19 (1H, d, J = 8.3 Hz), 8.07 (2H, d, J = 8.4 Hz). ^{13}C{^{1}H} NMR (DMSO-d_6, 100 MHz): δ_C 166.9, 166.0, 158.1, 150.4, 141.4, 138.2, 131.8, 129.8, 127.2, 125.7, 120.6.

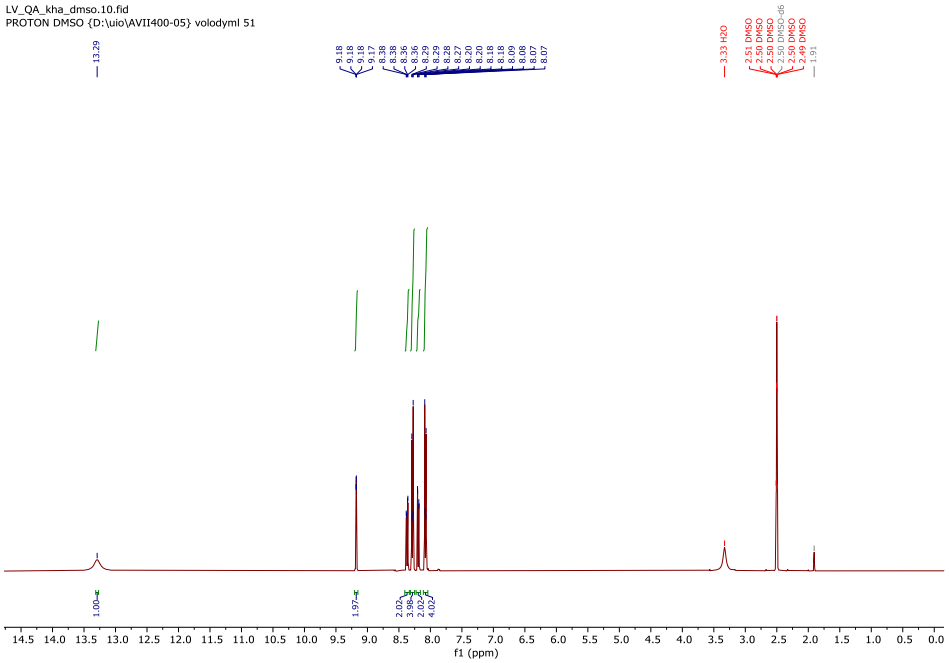
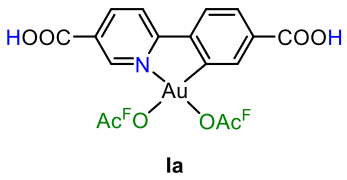


Figure S3. ^{1}H NMR spectrum of **ppydc** (400 MHz, DMSO-d_6).

Spectra of Au(ppyde/dc)X_2 (X = OAc^F, Cl) complexes

Au(ppydc)$(OAc^F)_2$ **(1a)**



Ia

Figure S4. ^{1}H NMR spectrum of Au(ppydc)$(OAc^F)_2$, **1a** (400 MHz, DMSO-d_6).

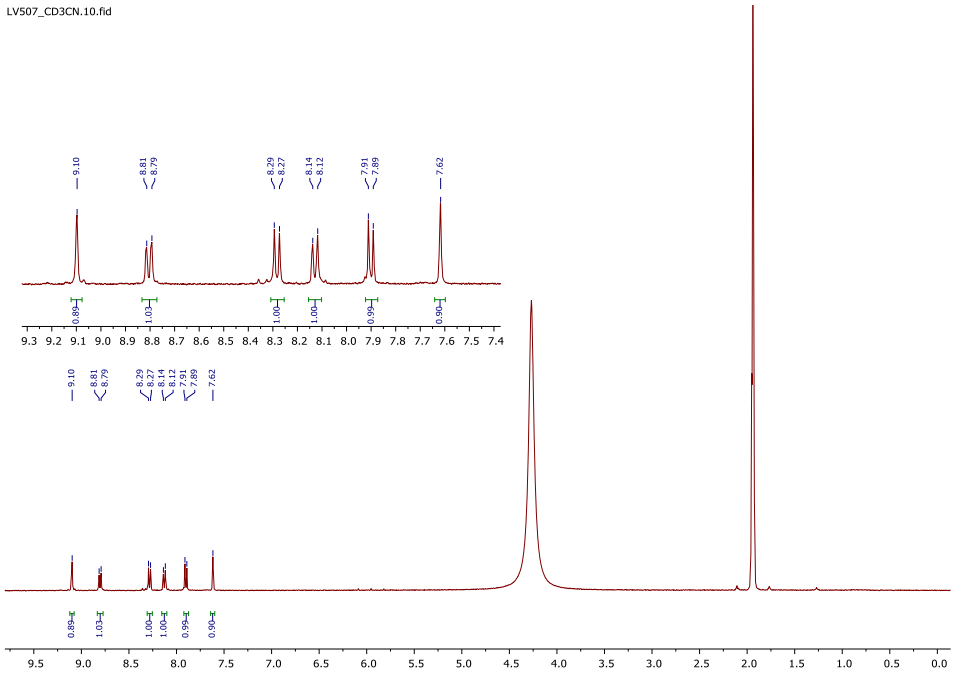


Figure S5. ^{1}H NMR spectrum of Au(ppydc)(OAc^{F})$_2$, **1a** (400 MHz, CD_3CN).

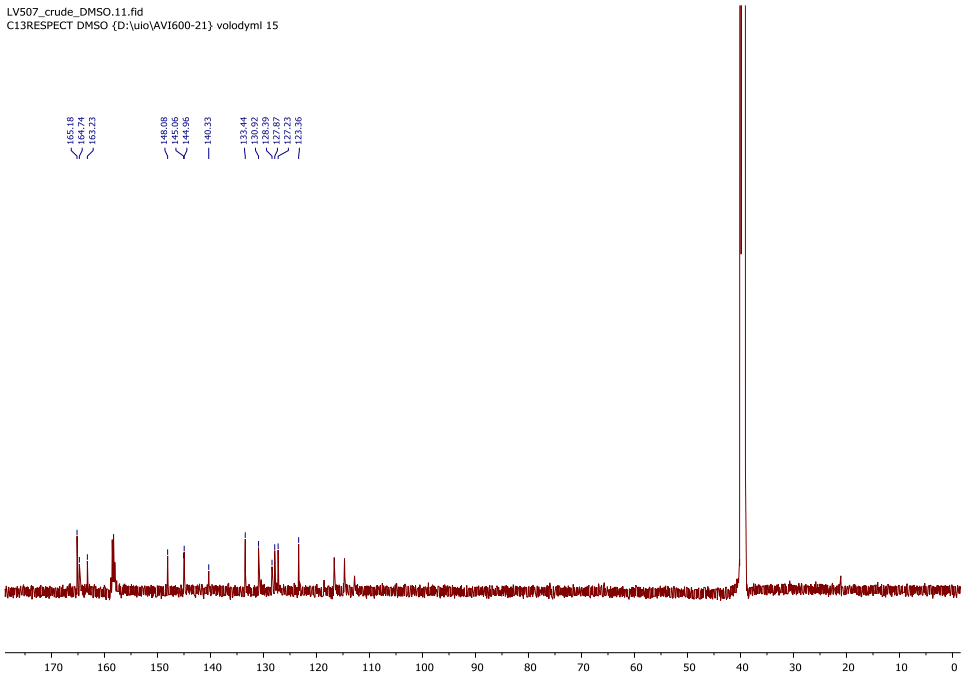


Figure S6. ^{13}C{^{1}H} NMR spectrum of Au(ppydc)(OAc^{F})$_2$, **1a** (151 MHz, DMSO-d_6). To observe carbons in $OCOCF_3$ group d1=6 and ns=10k was necessary.

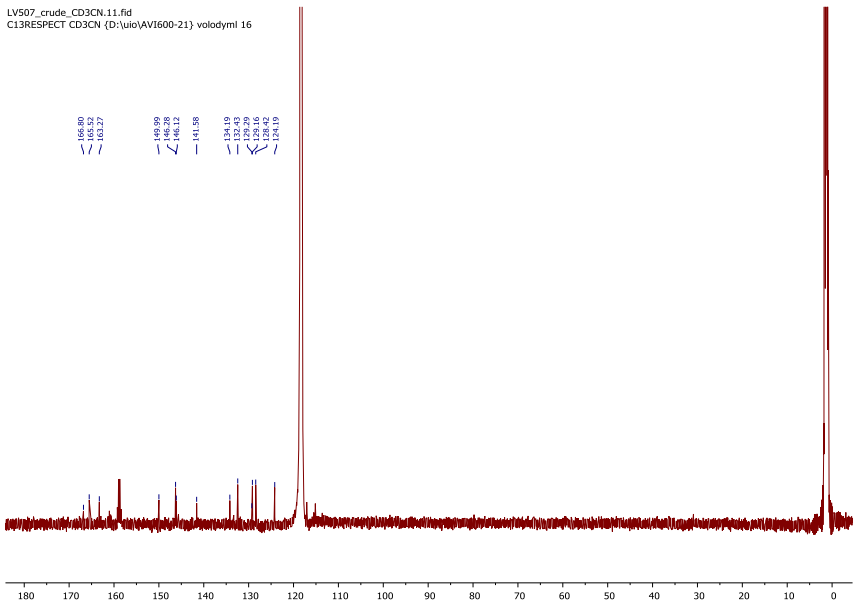


Figure S7. $^{13}C\{^{1}H\}$ NMR spectrum of Au(ppydc)(OAc^{F})$_2$, **1a** (151 MHz, CD_3CN). To observe carbons in $OCOCF_3$ group d1=6 and ns=10k was necessary. The signals from CF_3 groups are overlapping with solvent signals.

Au(ppyde)(OAc^{F})$_2$ **(1b)**

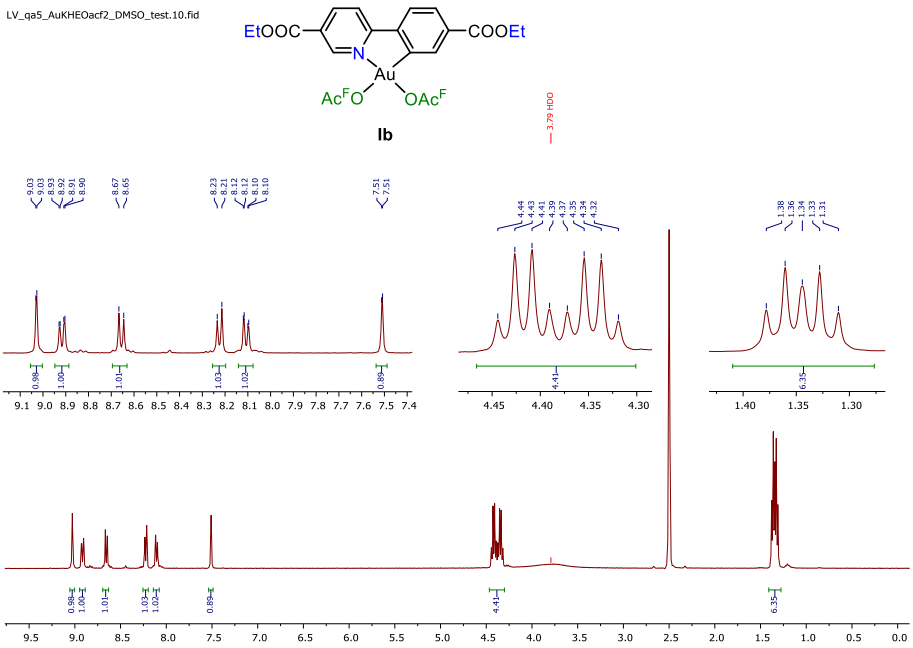


Figure S8. ^{1}H NMR spectrum of Au(ppyde)(OAc^{F})$_2$ (**1b**), (DMSO-d_6, 400 MHz).

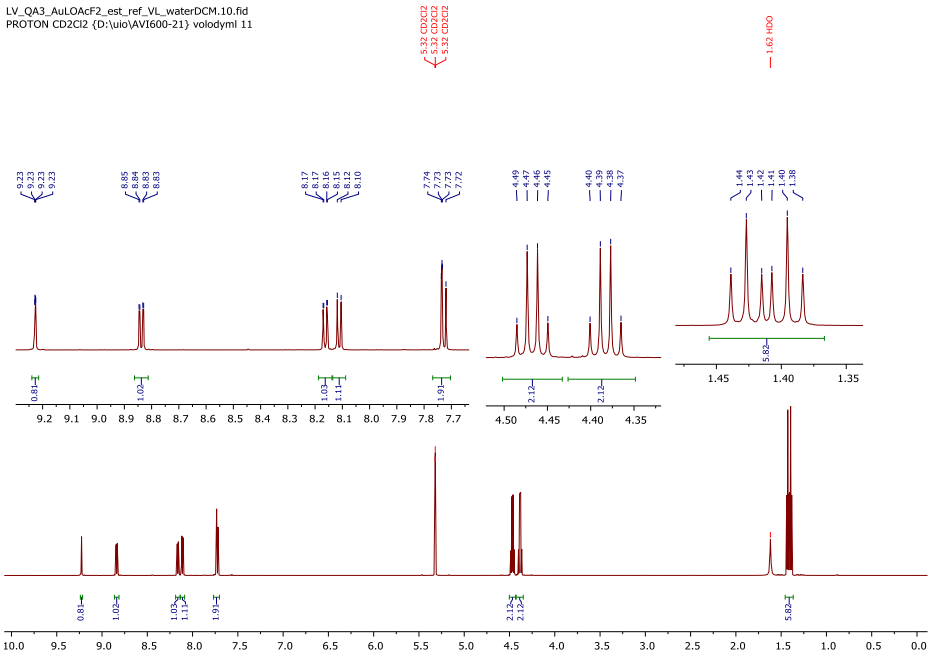


Figure S9. ^{1}H NMR spectrum of Au(ppyde)(OAc^{F})$_2$ (**1b**), (CD_2Cl_2, 600 MHz).

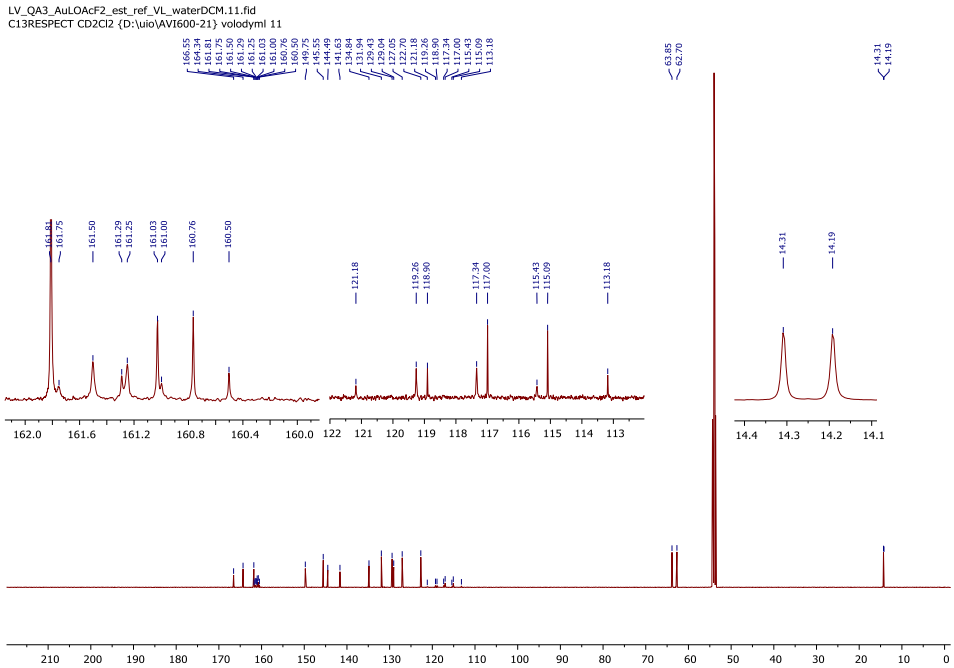


Figure S10. ^{13}C NMR spectrum of Au(ppyde)(OAc^{F})$_2$ (**1b**), (CD_2Cl_2, 150 MHz).

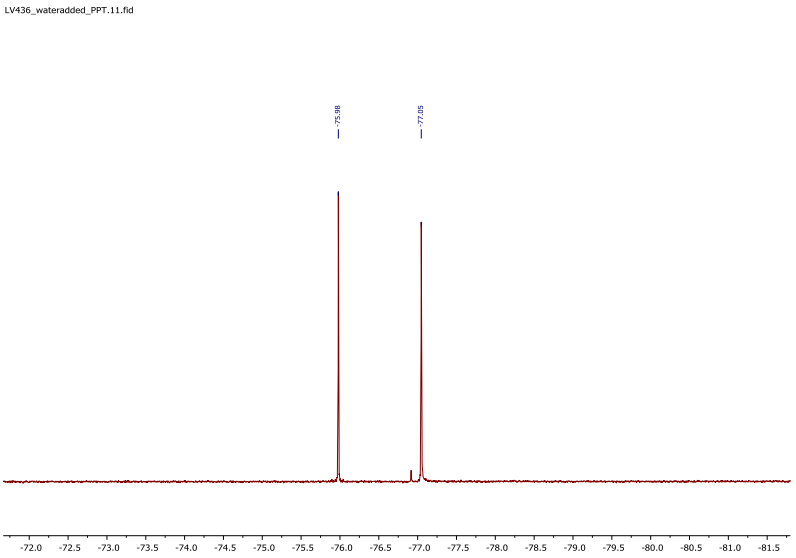


Figure S11. ^{19}F NMR spectrum of Au(ppyde)$(OAc^F)_2$ (**1b**), (CD_2Cl_2, 376 MHz). Internal standard is not show on the spectrum.

$Au(ppydc)Cl_2$ **(2a)**

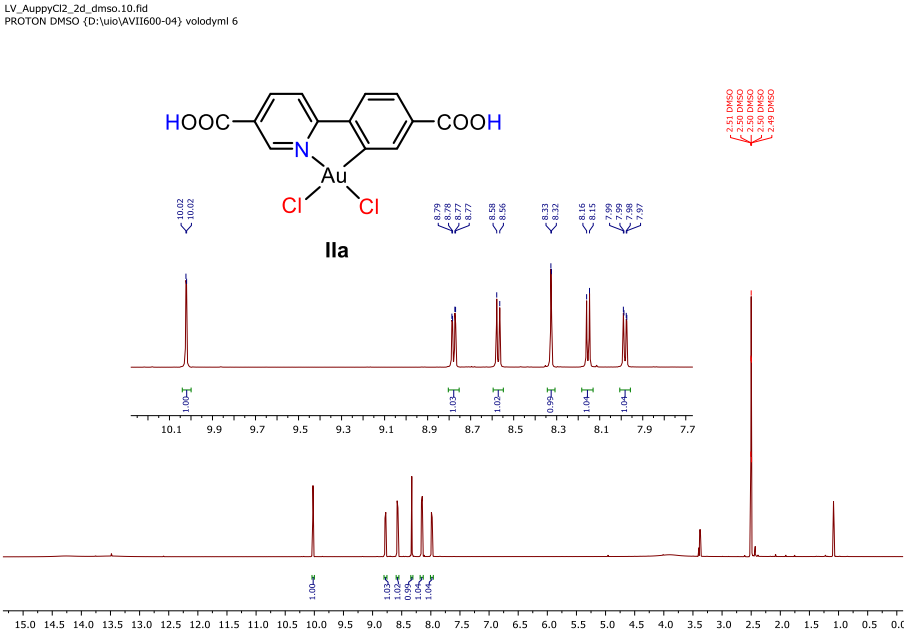


Figure S12. ^1H NMR spectrum of $Au(ppydc)Cl_2$ (**2a**) (600 MHz, DMSO-d_6). Triplet at 1.09 ppm and quartet at 3.39 ppm are diethyl ether signals.

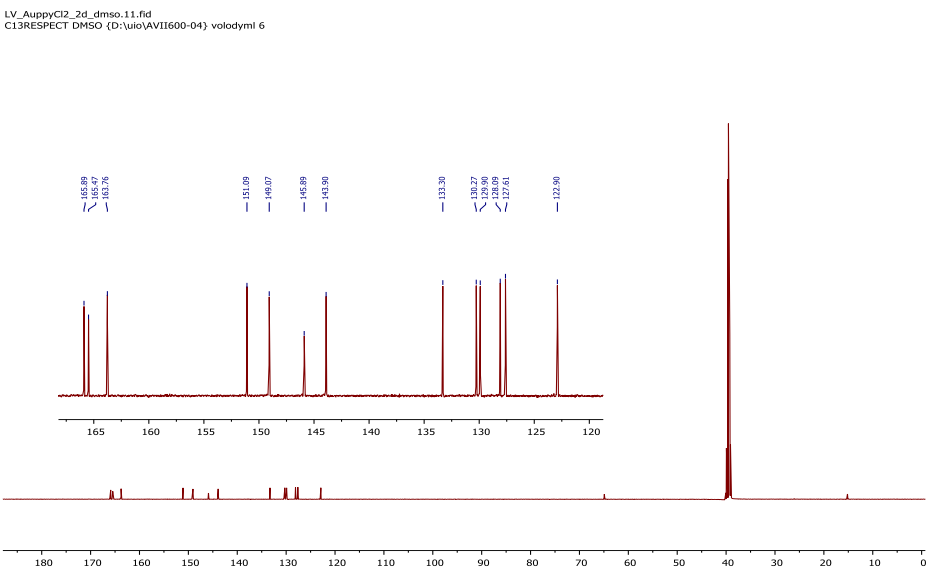


Figure S13. ^{13}C NMR spectrum of Au(ppydc)Cl_2 (**2a**) (151 MHz, DMSO-d_6). Resonances at 64.9 and 15.2 ppm belong to diethyl ether.

Au(ppyde)Cl_2 **(2b)**

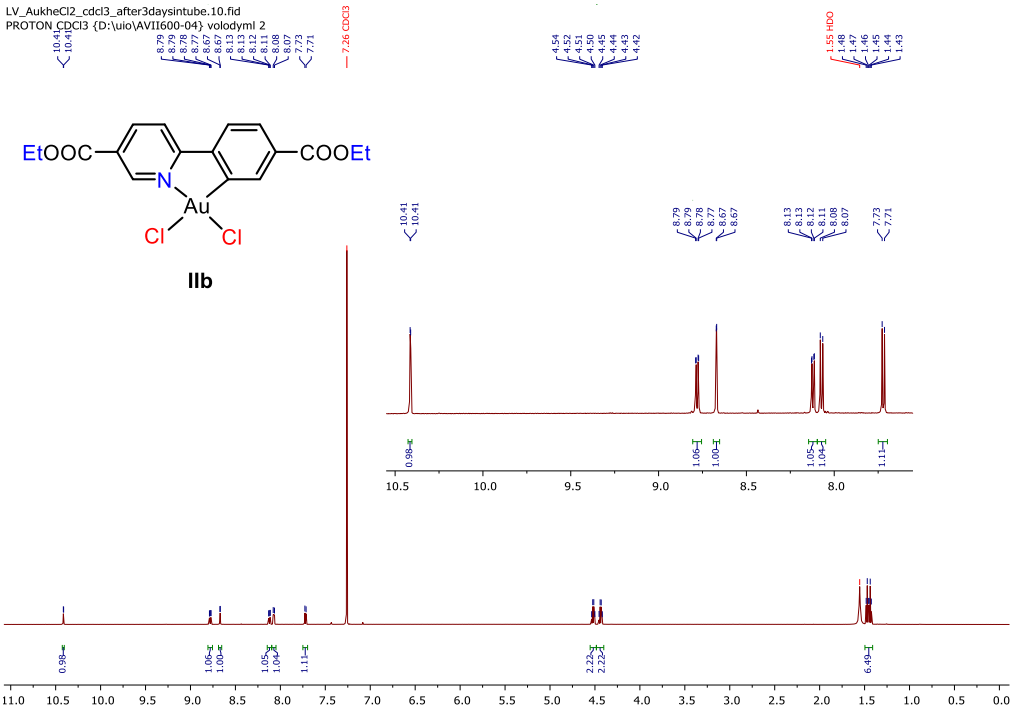


Figure S14. ^{1}H NMR spectrum of Au(ppyde)Cl_2 (**2b**) (600 MHz, $CDCl_3$).

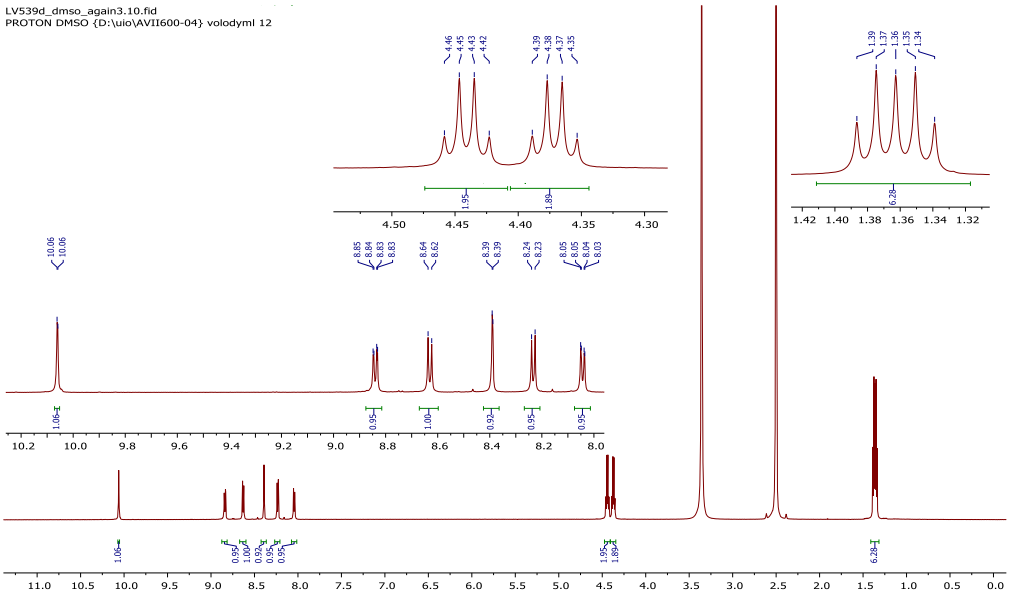


Figure S15. ^{1}H NMR spectrum of Au(ppyde)Cl$_2$ (**2b**) (600 MHz, DMSO-d_6).

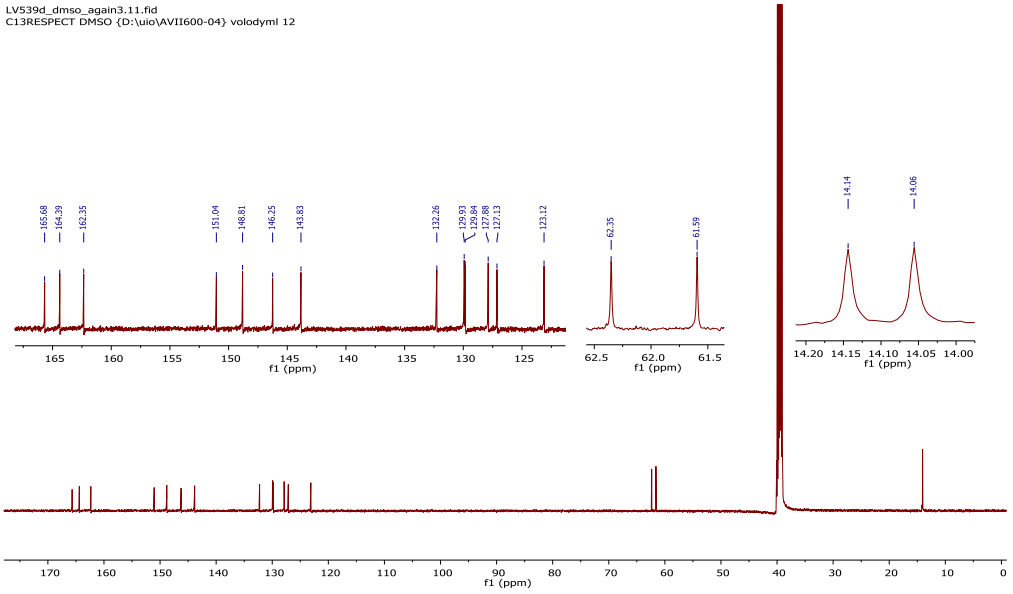


Figure S16. ^{13}C NMR spectrum of Au(ppyde)Cl$_2$ (**2b**) (150 MHz, DMSO-d_6).

UiO-67-[Au]Cl characterization

Au incorprotation calculations:

Incorporation of Au into the UiO-67 MOF was investigated by the ^{1}H NMR spectroscopy.

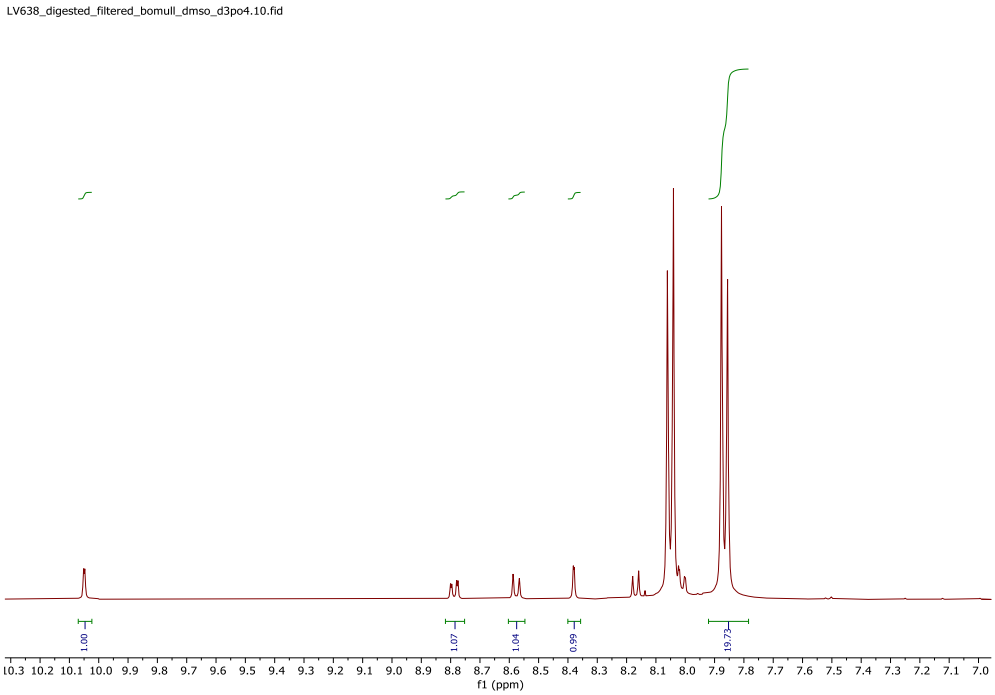
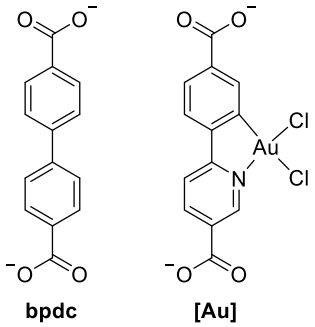


Figure S17. ^{1}H NMR spectrum (400 MHz, DMSO-d_6) of the digested **UiO-67[Au]Cl** in 1M D_3PO_4 in DMSO-d_6.



Cluster: $Zr_6O_4(OH)_4(bpdc)_6$

Fw ($Zr_6O_4(OH)_4$) = 679.3

Fw (bpdc) = 240.2

Fw ([Au]) = 508.06

Au-functionalized cluster: $Zr_6O_4(OH)_4(bpdc)_{6-x}([Au])_x$

$$mol\ fraction(bpdc) = \frac{integral(bpdc)}{4}$$

$$mol\ fraction([Au]) = \frac{integral([Au])}{1}$$

$$n = \frac{mol\ fraction([Au])}{mol\ fraction\ (bpdc) + mol\ fraction([Au])}$$

x = n*6

$$n = \frac{1}{4.9325 + 1} = 0.169$$

x = 6 * 0.169 ≈ 1

Fw ($Zr_6O_4(OH)_4(bpdc)_5([Au])_1$) = 679.3 + 5*240.2 + 508.06 = 2388.36

Incorporation of [Au] = 1/6 *100% ≈ 16%

Catalyst loading calculations:

For 10 mol% catalyst:

10 mol% of **3** (5 mg) = 0.002448 mmol

m(**UiO-67[Au]Cl**) = 0.002448 * 2388.36 ≈ 6 mg

Catalysis data

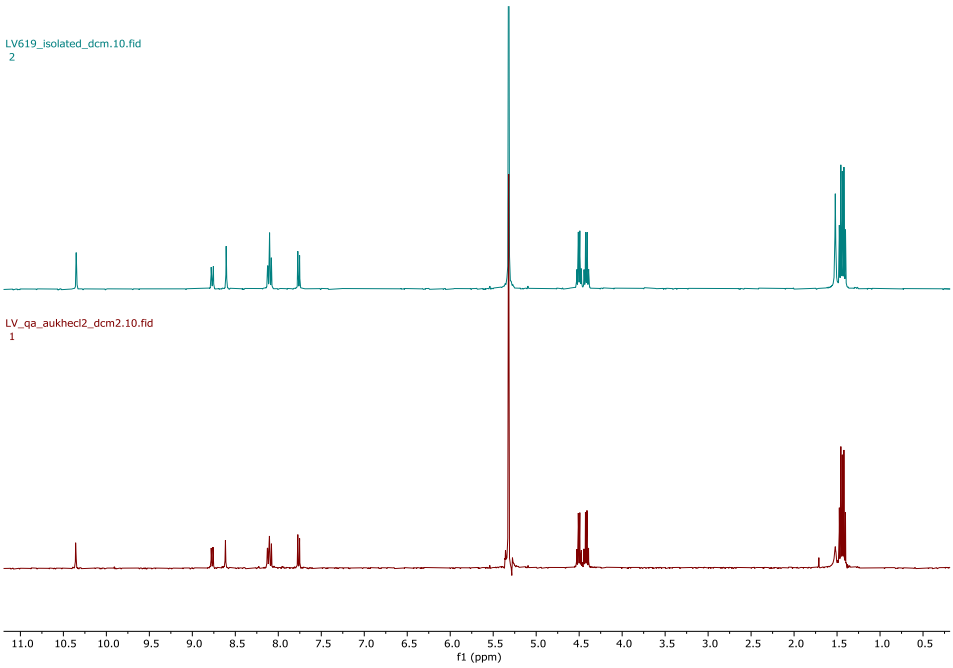


Figure S18. ^{1}H NMR (400 MHz, CD_2Cl_2) spectrum of **2b** before (bottom) and after (top) the catalysis.

Upscaled catalysis with recovery of IIb:

Mixture of **3** (108 mg, 0.529 mmol, 1 equiv.) and styrene (245 µl, 2.166 mmol, 4 equiv.) in CH_2Cl_2 (13 mL) was added to **2b** (30 mg, 0.053 mmol, 10 mol%) in a round-bottom flask. The reaction mixture was heated at 65 °C for 5 hours in the closed flask before it was concentrated under reduced pressure. Pentane was added to the concentrated solution and the catalyst was recovered by filtration (28 mg, recovery degree 93%).

Crystallographic data

Single crystal diffraction data was acquired on a Bruker D8 Venture equipped with a Photon 100 detector and using Mo Kα radiation (λ = 0.71073 Å) from an Incoatec iµS microsource. Data reduction was performed with the Bruker Apex3 Suite,[4] the structure was solved with ShelXT[5] and refined with ShelXL.[6] Olex2 was used as user interface.[7] The CIF files were edited with enCIFer v1.4,[8] and molecular graphics were produced with Mercury 4.2.0.[9]

Full details of the data collection, structure solution and refinement are contained in the CIF file, available as ESI and from https://www.ccdc.cam.uk/ (CCDC numbers: 1972306 for **1a**, 1972307 for **1b**, 1972305 for **2a** and 1972304 for **UiO-67-[Au]Cl**) and are summarized in Table S1.

Table S2. Crystallographic data

Crystal data	**1a**	**1b**	**2a**	**UiO-67-[Au]Cl Single Crystal**
Chemical formula	$C_{17}H_8AuF_6NO_8$·2($C_2HF_3O_2$)	$C_{21}H_{16}AuF_6NO_8$	$C_{13}H_8AuCl_2NO_4$·2(C_2H_6OS)	0.25($C_{336}H_{208}Au_{0.23}O_{128}Zr_{24}$)·2.67(C)
M_r	893.27	721.31	666.33	2163.94
Crystal system, space group	Triclinic, $P\bar{1}$	Monoclinic, $P2_1$	Triclinic, $P\bar{1}$	Cubic, $Fm\bar{3}m$
Temperature (K)	100	100	100	100
a, *b*, *c* (Å)	8.0544 (7), 12.4028 (10), 15.6474 (13)	7.4239 (5), 29.797 (2), 10.6117 (8)	9.1094 (10), 10.0291 (11), 12.2185 (14)	26.784
□ (°)	107.632 (2), 102.761 (2), 98.721 (2)	100.687 (2)	89.129 (2), 83.777 (2), 75.627 (2)	-
V (Å^3)	1412.2 (2)	2306.7 (3)	1074.9 (2)	19214.2
Z	2	4	2	4.0
Radiation type	Mo *K*a	Mo *K*a	Mo *K*a	Mo *K*a
□ (mm^{-1})	5.35	6.48	7.32	0.40
Crystal size (mm)	0.20 × 0.11 × 0.08	0.22 × 0.08 × 0.07	0.12 × 0.10 × 0.07	0.05 × 0.05 × 0.03
Diffractometer	Bruker Photon100 area detector	Bruker Photon100 area detector	Bruker Photon100 area detector	Bruker D8 Venture, CMOS detector
Absorption correction	Multi-scan	Multi-scan	Multi-scan	Multi-scan
T_{min}, T_{max}	0.576, 0.746	0.485, 0.749	0.533, 0.746	0.662, 0.746
No. of measured, independent and observed [I > 2□(I)] reflections	49476, 9117, 8611	48420, 28381, 26753	26928, 6569, 6022	18094, 911, 749
R_{int}	0.029	0.025	0.033	0.133
(sin □/□)$_{max}$ (Å^{-1})	0.729	0.926	0.715	0.595
$R[F^2 > 2□(F^2)]$, $wR(F^2)$, S	0.025, 0.073, 1.09	0.029, 0.065, 1.02	0.018, 0.037, 1.04	0.033, 0.065, 1.11
No. of reflections	9117	28381	6569	911
No. of parameters	428	672	271	58
CCDC no.	1972306	1972307	1972305	1972304

Crystallographic structure determination of 1a

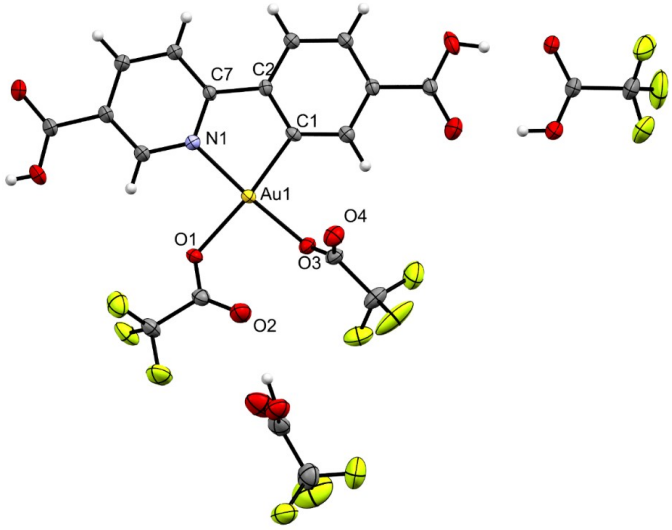


Figure S19. ORTEP plot of **1a** with 50% ellipsoids. Selected bond distances (Å) and angles (°): N1-Au1 2.008(2), Au1-C1 1.991(3), Au1-O1 2.088(3), Au1-O3 2.006(2); N1-Au1-C1 81.9(1), C1-Au1-O3 93.7(1), O3-Au1-O1 92.51(9), O1-Au1-N1 91.8(1).

Crystallographic structure determination of 1b

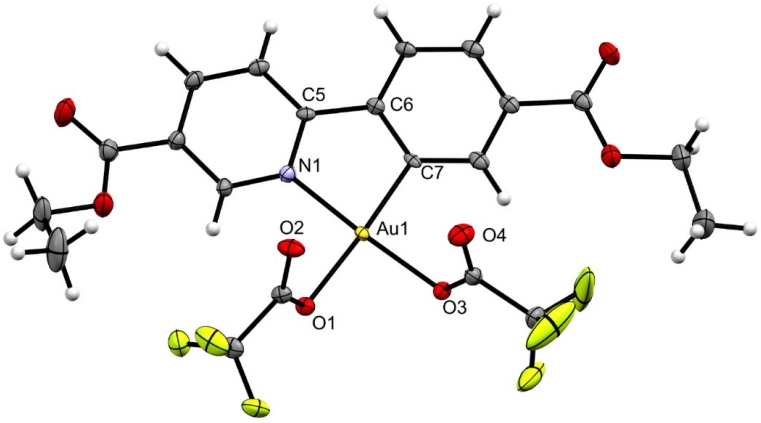


Figure S20. ORTEP plot of **1b** with 50% ellipsoids. Only one molecule in asymmetric unit is shown. Selected bond distances (Å) and angles (°): N1-Au1 2.002(3), Au1-C7 1.993(3), Au1-O1 2.064(3), Au1-O3 2.047(3); N1-Au1-C7 81.7(1), C7-Au1-O3 94.8(1), O3-Au1-O1 88.5(9), O1-Au1-N1 95.0(1).

Crystallographic structure determination of 2a

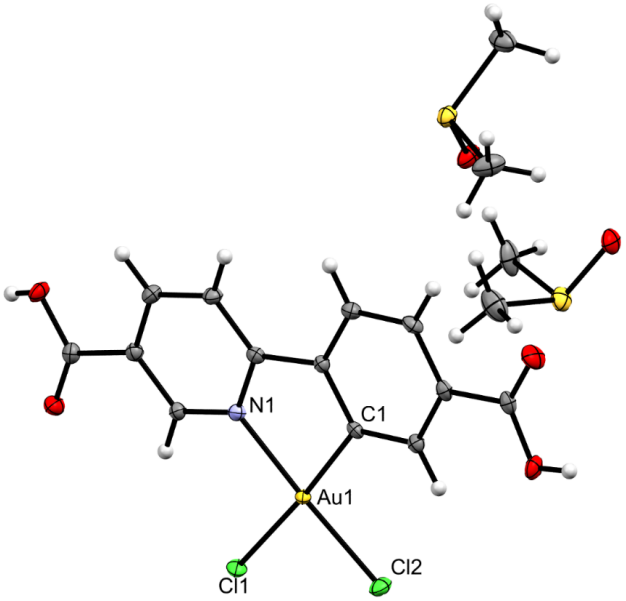


Figure S21. ORTEP plot of **2a** with 50% ellipsoids. Selected bond distances (Å) and angles (°): N1-Au1 2.041(2), Au1-C1 2.025(2), Au1-Cl2 2.2713(6), Au1-Cl1 2.3613(6); N1-Au1-C1 81.63(7), C1-Au1-Cl2 93.67(6), Cl2-Au1-Cl1 90.43(2), Cl1-Au1-N1 94.29(5).

Crystallographic structure determination of UiO-67-[Au]Cl

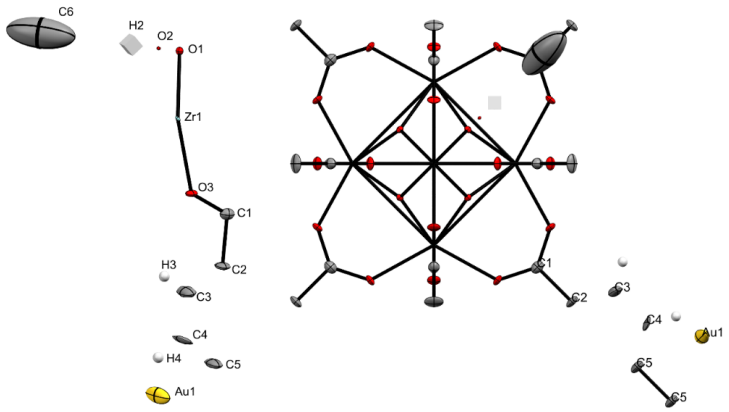


Figure S22. ORTEP plot of **UiO-67-[Au]Cl** with 50% ellipsoids. The asymmetric unit (left) and Zr-cluster (right) are shown along c* axis.

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