Transition Metal-Catalyzed Reactions of Heteroatom-Substituted Alkynes

Margherita Zanini

UNIVERSITAT ROVIRA i VIRGILI

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Supervised by Prof. Antonio M. Echavarren

Institut Català d´Investigació Química (ICIQ)

UNIVERSITAT ROVIRA i VIRGILI

Tarragona 2020

I STATE that the present study, entitled "*Transition Metal-Catalyzed Reactions of Heteroatom-Substituted Alkynes*", presented by Margherita Zanini to award the degree of Doctor, has been carried out under my supervision at the Institut Català d´Investigació Química (ICIQ).

Tarragona, October 2, 2020

Prof. Antonio M. Echavarren

Doctoral Thesis Supervisor

A mutti e baba

"Pain is inevitable. Suffering is optional."

Haruki Murakami (What I Talk About When I Talk About Running)

I would like to thank Prof. Antonio M. Echavarren for accepting me as PhD student in his research group at the Institut Català d'Investigació Quimica (ICIQ) back in 2016 and from that moment guiding me through my studies and trusting in me. I have learnt the importance of "fer la feina ben feta", of analyzing my results with some healthy skepticism, but also to be confident enough to defend my ideas with strength.

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A Doctoral Thesis is for sure made by the results you present in it and hard work, but is also the summary of some years of a life, and this specific summary would not be the same without some special contributions.

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At the moment of writing this Doctoral Thesis, the results presented herein have been published in:

Iridium-Catalyzed β–Alkynylation of Aliphatic Oximes as Masked Carbonyl Compounds and Alcohols

E. Tan*, M. Zanini*, A. M. Echavarren,
Angew. Chem. Int. Ed. **2020**, *59*, 10470–10473.

Gold- or Indium-Catalyzed Cross-Coupling of Bromoalkynes with Allylsilanes through a Concealed Rearrangement

M. E. de Orbe, M. Zanini, O. Quinonero, A. M. Echavarren,
ACS Catal. **2019**, *9*, 7817–7822

Buchwald-type Ligands on Gold(I) Catalysis

G. Zuccarello*, M. Zanini*, A. M. Echavarren.
Isr. J. Chem. **2020**, *60*, 360–371

In addition, other results that are not related to the topic of this Doctoral Thesis have been published in:

Aminoalkyl radicals as halogen-atom transfer agents for activation of alkyl and aryl radicals

T. Constantin, M. Zanini, A. Regni, N. S. Shikh, F. Juliá, D. Leonori.
Science **2020**, *367*, 1021–1026

Variations on the Theme of JohnPhos Gold(I) Catalysts: Arsine and Carbene Complexes with Similar Architectures

J. Carreras, A. Pereira, M. Zanini, A. M. Echavarren,
Organometallics **2018**, *37*, 3588–3597

** Denotes equal contribution*

TABLE OF CONTENTS

Prologue **21**

Abbreviations and Acronyms **23**

Abstract **25**

General objectives **27**

General Introduction **29**

HISTORICAL PERSPECTIVE OF GOLD CATALYSIS 31
CONSEQUENCES OF THE RELATIVISTIC EFFECTS IN HOMOGENEOUS GOLD(I) CATALYSIS 32
GOLD(I)-CATALYZED REACTION OF ALKYNES 34
GOLD(I)-CATALYZED CYCLOISOMERIZATION OF 1,N-ENYNES 36
CYCLOISOMERIZATION OF ENYNES IN PRESENCE OF A NUCLEOPHILE 38
INTERMOLECULAR REACTION OF ALKYNES WITH ALKENES 40

Chapter 1 ..... **49**

INTRODUCTION 51
Formation and Reactivity of Gold(I) Vinylidenes 51
Use of Haloalkynes in Gold(I) Catalysis 57
OBJECTIVES 63
RESULTS AND DISCUSSION 64
Cyclization of 1-Bromo-1,6-Enynes 64
Intermolecular Reaction of Bromoalkynes with Allylsilanes 74
Allylation/Hydroarylation Sequence of Bromoalkynes with Allylsilanes 79
Mechanism of the Gold(I) Catalyzed Reaction of Bromoalkynes. 84
CONCLUSIONS 98
EXPERIMENTAL PART 100
General Information 100
Synthetic Procedures and Characterization Data 101
Experimental mechanistic studies 130
Theoretical DFT Calculations 141
Computational Methods 141
Computed Structures and Energies 142

Chapter 2 ..... **153**

INTRODUCTION 155

Synthesis of Cyclobutanones via [2+2] Cycloaddition of Ketenes with Alkenes 155
Ynol Ethers: A General Introduction 158
Brønsted and Lewis Acid Mediated Reaction of Ynol ethers 161
Gold(I)-Catalyzed Reaction of Ynol ethers 164
OBJECTIVES 167
RESULTS AND DISCUSSION 168
Gold(I)-Catalyzed [2+2] Cycloaddition of Terminal Ynol ethers with Alkenes 168
Gold(I)-Catalyzed Reaction of Internal Ynol ethers with Alkenes 171
One-pot Synthesis of Cyclobutanones Starting from Ynol ethers 180
Mechanism of the Gold(I) Catalyzed Reactions of Ynol ethers 183
CONCLUSIONS 189
EXPERIMENTAL PART 190
General Information 190
Synthetic Procedures and Characterization Data 190
Theoretical DFT Calculations 213
Computational Methods 213
Computed Structures and Energies 214

Chapter 3 221

INTRODUCTION 223
Classical Methods for the Alkynylation Reaction 223
Alkynylation via C-H Activation 224
Oximes as Directing Groups in C(sp^3)-H Functionalization 232
OBJECTIVES 236
RESULTS AND DISCUSSION 237
β-Alkynylation of Ketoximes 237
β-Alkynylation of Oximes Derived from Alcohols 242
CONCLUSIONS 247
EXPERIMENTAL PART 248
General Information 248
Synthetic Procedures and Characterization Data 248

General Conclusions 277

Prologue

This Doctoral Thesis manuscript has been divided into four main parts: a general introduction on gold(I) catalysis and three research chapters. These are preceded by the abstract and the general objective of the Thesis and are followed by the general conclusions. Each research chapter is divided itself into five sections including a specific introduction on the topic of the chapter, the objectives, the results and discussion, the conclusions, and the experimental part. The numbering of the compounds as well as the one of scheme, tables, and figures is organized by chapter, while the refences, reported as footnotes are numbered continuously along the manuscript.

The **General Introduction** covers the basic principles of homogeneous gold(I) catalysis and gives an overview on the activation of alkynes, the cycloisomerization of enynes, and the intermolecular reactions of alkynes with alkenes in presence of gold(I) complexes.

"Chapter I" presents a series of intra- and intermolecular reaction of bromoalkynes with alkenes catalyzed by either gold(I) or indium(III). Detailed mechanistic studies allowed the identification cyclic-bromonium cation as common intermediate for the reactions. In addition, the investigation on the nature of key intermediates of the reaction are presented. This work was conducted in collaboration with Dr. M. Elena de Orbe and Dr. Ophelie Quinonero and, therefore, some of their results are discussed in the chapter for coherence. This work has been published in *ACS Catal.* **2019**, *9*, 7817–7822.

"Chapter II" comprehends our studies on the gold(I)-catalyzed [2+2] cycloaddition and (4+2) cycloaddition of ynol ethers with alkenes to form phenoxycyclobutenes and chromans. This work has not yet been published.

"Chapter III" presents the selective alkynylation of C(sp^3)-H bonds in β–position to an oxime catalyzed by iridium(III). This work was done in collaboration with Dr. E. Tan and his results will be presented too to give a complete picture of the research project. This work has been published in *Angew. Chem. Int. Ed.* **2020**, *59*, 10470-10473.

Abbreviations and Acronyms

In this manuscript, the abbreviations and acronyms most commonly used in organic and organometallic chemistry have been used following the recommendations of "Guidelines of Authors" of the Journal of Organic Chemistry.

Additional abbreviations and acronyms used in this manuscript are listed below:

APCI	atmospheric pressure chemical ionization
BAr_4^{F-}	tetrakis[3,5-bis(trifluoromethyl)phenylborate]
dr	diastereomeric ratio
ESI	electrospray ionization
JohnPhos	(2-biphenyl)di-*tert*-butylphosphine
IBO	intrinsic bond orbital
IMes	1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene
Int	intermediate
IPr	1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene
L	ligand
MALDI	matrix assisted laser desorption ionization
Mes	2,4,6-trimethylphenyl
MS	mass spectrometry/molecular sieves
MW	microwave irradiation
NBO	natural bond orbital
NLMO	natural localized molecular orbital
NTf_2^-	bis(trifluoromethyl)imidiate
OTf^-	triflate
ORTEP	oak ridge thermal ellipsoid plot
*t*BuXPhos	2-(di-*tert*-butylphosphino)-2´,4´,6´-triisopropyl-1,1´-biphenyl
TS	transition state

Abstract

In the past twenty years, homogeneous gold(I) catalysis has been widely used as versatile tools for the generation of molecular complexity starting from simple substrates under mild conditions. In this context, our group focused on the development of reliable methods for the activation of multiple C-C bonds both in intramolecular and intermolecular settings. In general, the intermolecular reaction of alkynes with alkenes are more challenging compared with the intramolecular ones due to competing side reactions and therefore less examples have been reported. In this Doctoral Thesis, we mainly focused on the development of a series of new gold(I)-catalyzed intermolecular reactions of alkynes directly bounded to heteroatoms and the investigation of their mechanisms experimentally and using DFT calculations.

We discovered that 1-bromo-1,6-enyes can undergo a cycloisomerization/elimination sequence in a formal dehydro-Diels-Alder reaction to give substituted naphthalenes. On the other hand, the intermolecular reaction of alkynes with allylsilanes leads to the formation of skipped enynes or skipped dienes in a cross-coupling-type transformation. Mechanistic studies revealed that the two reactions proceed *via* an unprecedented rearrangement of a cyclic bromonium cation intermediate that can evolve either into a gold(I)-vinylidene or a vinylidenephenonium gold(I) cation depending on the substrates. The two intermediates have different reactivity, namely gold(I) vinylidenes can undergo hydroarylation or C-H insertion, while vinylidenephenonium gold(I) cations undergo 1,2-arylmigration. In the context of our study both reactivities have been studied.

Ynol ethers are versatile building blocks that can be involved in the formation of up to four C-C bonds in a single process. However, their high reactivity in the presence of a Lewis acids is limiting to just a few examples their use in gold(I) catalysis. Considering the lack of precedents and our previous experience with haloalkynes, we aimed at the development of intermolecular reactions of ynol ethers with alkenes. In our study, we found that terminal ynol ethers undergo efficiently [2+2] cycloaddition with alkenes to form cyclobutene derivatives that can be easily transformed into the corresponding cyclobutanones. We also found that internal ynol ethers react with α-methyl styrenes in a formal (4+2) cycloaddition. DFT calculations demonstrated that the intermediate (η^2-alkyne)gold(I) complex resemble a metalated ketene.

Considering the presence of alkynes in bioactive molecules and the wide range of transformations that involve alkynes, the development of a direct and selective C-H alkynylation reaction is an important goal. In this regard, an array of transformations that allows the functionalization of C(sp^2)-H bonds has been reported, while the alkynylation of C(sp^3)-H bonds

is still limited. For this reason, to conclude this Doctoral Thesis we focused on the development of an Ir(III)-catalyzed β-alkynylation of oximes derived from both alcohols and carbonyl compounds. The reaction displays an exquisite selectivity towards the primary C(sp^3)-H bonds, even when more activated aliphatic C-H bonds are present.

General Objectives

The objective of this Doctoral Thesis was the development of novel transition metal-catalyzed intermolecular reactions of haloalkynes and ynol ethers. Specifically, we focused on the following goals:

- The study of intra- and intermolecular gold(I)-catalyzed reactions of haloalkynes and the computational and experimental study of their mechanisms.
- The use of ynol ethers in gold(I)-catalyzed intermolecular reactions with alkenes and the study of the reaction mechanism.
- The development of an Ir(III) catalyzed alkynylation of C(sp^3)-H bonds using oximes as directing group.

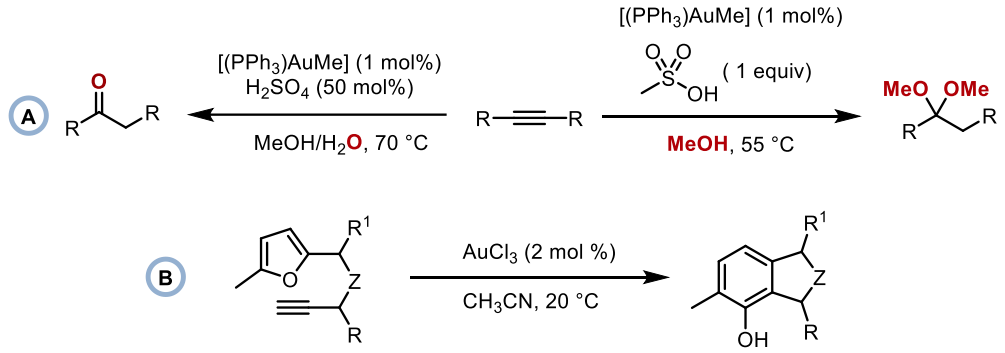
Each Chapter of this manuscript provides a more detailed description of the corresponding objective.

General Introduction

Historical Perspective of Gold Catalysis

For long time gold has been considered in the chemical community as generally inert and a poor catalyst for reactions commonly catalyzed by other transition metals, up to the point to be defined "catalytically dead".[1]

It was necessary to wait until 1986 to see the appearance of homogeneous gold(I) catalysts on the chemical scene, when Ito and Hayashi published the first gold(I)-catalyzed asymmetric nucleophilic attack of isocyanide to aldehydes.[2] However, this ground-breaking work remained the only one in the field for almost other ten years until Teles and coworkers reported in 1998 the synthesis of acetals by addition of alcohols to alkynes catalyzed by gold(I) complexes bearing a phosphine ligand (Scheme 1a).[3] The same gold(I) complex activated by protonolysis allowed later Tanaka and coworkers to achieve the Markovnikov-type hydration of alkynes to access ketones and aldehydes (Scheme 1a).[4] Almost at the same time, Hashmi demonstrated that gold(III) salts could be used for the activation of multiple carbon-carbon bonds, specifically for the synthesis of phenols starting from a furan with an appended alkyne (Scheme 1b). [5]



Scheme 1. A) Gold(I) catalyzed hydration of alkynes to generate acetals or ketones. B) Gold(III) catalyzed synthesis of phenols.

Since then, the number of transformations of multiple C-C bonds catalyzed by gold increased exponentially and homogeneous gold catalysis became a versatile and efficient tool for the construction of complex molecules under mild conditions.[6]

1 Schmidbaur, H *Naturwiss. Rundsch*, **1995**, *48*, 443-451.
2 Y. Ito, M. Sawamura, T. Hayashi, *J. Am. Chem. Soc.* **1986**, *108*, 6405–6406.
3 J. H. Teles, S. Brode, M. Chabanas, *Angew. Chem. Int. Ed.***1998**, *37*, 1415–1518.
4 (a) E. Mizushima, K. Sato, T. Hayashi, M. Tanaka, *Angew. Chem. Int. Ed*. **2002**, *41*, 4563-4565. (b) E. Mizushima, T. Hayashi, M. Tanaka, *Org. Lett*. **2003**, *5*, 3349-3352.
5 A. S. K. Hashmi, T. M. Frost, J. W. Bats, *J. Am. Chem. Soc.* **2000**, *122*, 11553–11554.
6 a) A. Fürstner, *Chem. Soc. Rev.* **2009**, *38*, 3208–3221. b) C. Obradors, A. M. Echavarren, *Acc. Chem. Res.* **2014**, *47*, 902–912.c) L. Fensterbank, M. Malacria, *Acc. Chem. Res.* **2014**, *47*, 953–965.d) E. Jiménez-Núñez, A. M. Echavarren, *Chem. Rev.* **2008**, *108*, 3326–3350. e) R. Dorel, A. M. Echavarren, *Chem. Rev.* **2015**, *115*, 9028–9072.

Consequences of the Relativistic Effects in Homogeneous Gold(I) Catalysis

Compared to other transition metals, gold complexes display a unique reactivity, and a deep understanding of homogeneous gold catalysis can be obtained taking into account the relativistic effects on the gold atom.[7]

The term "relativistic effect" refers in general to every effect generated by the Dirac treatment of the Schrödinger equation, where the special relativity is taken into account and therefore the speed of light is considered as non-infinite and the speed of the particles as significant, relative to *c*.[8] In this context, the mass of a moving particle tends towards infinite as its velocity increases.

For a given atom the radial velocity of its electrons is proportional to the atomic number, therefore for heavy atoms the increase of the speed and consequently of the mass of the electron close to the nucleus is considerable (it has been calculated that for Hg the relativistic mass of the 1*s* electrons is around 20% more of their rest mass). The increase of mass of the internal electrons causes a contraction of the Bohr radius of their orbits, being this inversely proportional to the mass. This contraction applies not only to the *1s* orbitals, but to all the *s* and *p* orbitals. Having contracted internal orbitals makes the electrons on the *d* and *f* orbitals more shielded and makes them suffer a weaker nucleus attraction. As a result, the external *d* and *f* orbitals are highly diffused.

When it comes to practical aspects, a simpler treatment is sufficient for light atoms, but the relativistic contraction of the internal orbitals and the expansion of the external ones become considerable for atoms having the *4f* and the *5d* orbitals filled (such as Pt, Au and Hg), and it reach its maximum for gold.

The relativistic contraction explains the superior Lewis acidity of gold, its high electronegativity (χ = 2.4) and its "aurophilicity"[9] which is the tendency of gold to make strong Au-Au interactions, whose strength is in the order of the one of hydrogen bonds. Also, the electrons located in the expanded *5d* orbital suffer less electron-electron repulsion and can easily interact with *p* filled orbitals of multiple bonds activating preferentially "soft" electrophiles. In addition, the contracted *6s* orbital on gold atom causes a strong Au-L interaction, where L is a general ligand. Therefore, the outcome of gold(I) catalyzed reactions can be tuned by modulating the

7 a) D. J. Gorin, F. D. Toste, *Nature* **2007**, *446*, 395–403. b) P. Pyykkö, *Angew. Chem. Int. Ed.* **2004**, *43*, 4412–4456. c) P. Pyykkö, *Inorg. Chim. Acta* **2005**, *358*, 4113–4130.
8 a) D. R. McKelvey, *J. Chem. Educ.* **1983**, *60*, 111. b) K. S. Pitzer, *Acc. Chem. Res.* **1979**, *12*, 271–276. c) P. Pyykko, J. P. Desclaux, *Acc. Chem. Res.* **1979**, *12*, 276–281.
9 F. Scherbaum, A. Grohmann, B. Huber, C. Krüger, H. Schmidbaur, *Angew. Chem Int. Ed.* **1988**, *27*, 1544–1546.

electronic and the steric of the assisting ligand.[10] As a general trend, the use of phosphite ligands generates highly electrophilic complexes that usually display high reactivity. On the other side, the use of highly σ-donating NHC ligands lowers the electrophilicity of the gold complexes and a general lower reactivity but higher selectivity is observed. Phosphine ligands, instead, present an intermediate behavior between these two extremes, and bulky dialkyl biarylphosphine ligands, initially introduced in the context of Pd-catalyzed reactions, are privileged scaffolds for highly versatile and efficient catalysts.[11]

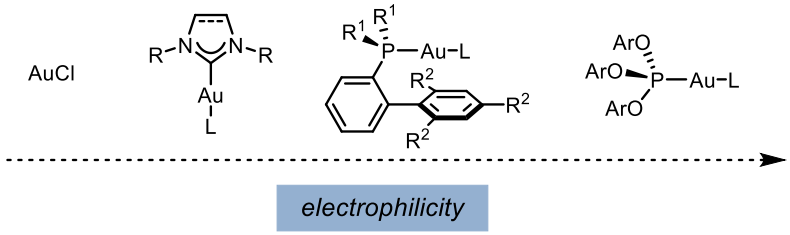


Figure 1. Ligand effect on the electrophilicity and reactivity of gold(I) complexes.

The tendency of gold(I) to form di-coordinated linear complexes can be explained by an efficient *s/p* and *s/d* orbital hybridization due to a reduced energy gap between atomic orbitals resulting from relativistic effects. This fact, together with a general lower nucleophilicity compared to other coinage metals, justifies the reluctance of gold(I) complexes towards oxidative addition, a fundamental step in redox catalytic cycles common for other late transition metals.[12] Besides practical aspects, like the possibility to run gold(I) catalyzed reaction without exclusion of air and a general functional group tolerance, the redox stability of gold(I) complexes allows accessing activation modes usually precluded to other transition metals. Nevertheless, in recent years, it has been demonstrated that by careful ligand design, gold(I) can also undergo oxidative addition with activated substrates bringing the reactivity of gold beyond the π-activation.[13]

Due to the difficulty in increasing the coordination number, to activate the substrate it is necessary to generate a formal vacancy by ligand abstraction. A first approach to generate catalytic active species is to activate *in situ* neutral gold(I)-chloride complexes upon chloride abstraction, which is usually done with a silver salt. However, these commonly used chloride scavengers can lead to the formation of less reactive chloride-bridged dinuclear gold(I) complexes or other side-species, a type of phenomena that has been named as “the silver

10 D. J. Gorin, B. D. Sherry, F. D. Toste, *Chem. Rev.* **2008**, *108*, 3351–3378.
11 G. Zuccarello, M. Zanini, A. M. Echavarren, *Isr. J. Chem.* **2020**, *60*, 360–372.
12 M. Livendahl, C. Goehry, F. Maseras, A. M. Echavarren, *Chem. Commun.* **2014**, *50*, 1533–1536.
13 For a review: M. Joost, A. Amgoune, D. Bourissou, *Angew. Chem. Int. Ed.* **2015**, *54*, 15022–15045.

effect".[14] Another approach is to use neutral complexes [LAuX] where X is a weakly coordinating anionic ligand (like TfO^- or Tf_2N^-) or cationic complexes with general structure [LAuL']X, where L' is a neutral labile ligand and X a weakly coordinating anion (like SbF_6^-, PF_6^-, BF_4^-, etc.).[15] In most of the cases such species are bench stable solids that can be stored under ambient conditions and can be engaged directly in the catalytic cycle *via* associative ligand exchange with the substrate.

Gold(I)-Catalyzed Reaction of Alkynes

Since the beginning of the investigation on gold(I) catalysis it was observed that gold(I) complexes have an "alkynophilic" character, meaning that gold(I) complexes are able to activate selectively alkynes in complex molecular settings. The binding mode of gold(I) with unsaturated bonds is usually described with the Dewar-Chatt-Duncanson model for donor-acceptor complexes, characterized by a substrate-to-metal σ-donation into an empty *d*-orbital of the metal and a metal-to-substrate π-backdonation into an antibonding orbital of the unsaturated ligand.[16] However, the full *5d* orbitals of gold are too low in energy to provide a meaningful overlap with the π* of the substrate and the contribution of the π-backdonation to the metal-substrate bond is minimal, leading to an electron-deficiency on the substrate that can then easily attacked by a nucleophile.

Studies on the coordination of gold(I) with different C-C π-bonds revealed that in many cases gold(I) prefers to coordinate alkenes over alkynes.[17] However, gold(I) complexes with alkynes have lower LUMOs compared to the corresponding gold(I)-alkene complex and the former are therefore activated preferentially towards nucleophilic attack.[18] This nucleophilic attack usually occurs in an *anti*-fashion and *via* an outer-sphere mechanism leading to the formation of the *trans*-alkenyl species **I** with a Markovnikov selectivity (Scheme 2).[19] A wide range of carbon and heteronucleophiles can be involved in this process, such arene, heteroarenes, alcohols,

14 a) A. Homs, I. Escofet, A. M. Echavarren, *Org. Lett.* **2013**, *15*, 5782–5785. b) A. Zhdanko, M. E. Maier, *ACS Catal.* **2015**, *5*, 5994–6004.c) Z. Lu, J. Han, G. B. Hammond, B. Xu, *Org. Lett.* **2015**, *17*, 4534–4537.

15 B. Ranieri, I. Escofet, A. M. Echavarren, *Org. Biomol. Chem.* **2015**, *13*, 7103–7118.

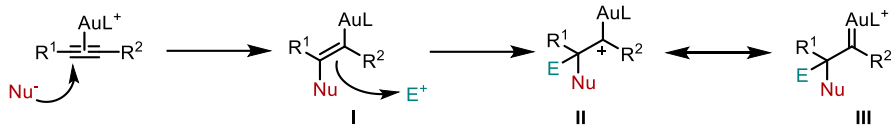
16 The description of this model is reported in M.J.S. Dewar, *Bull. Soc. Chim. Fr*. **1951**, 18 ,C71-C79, however the publication cannot be found online. Good description of the model can be found anyway online

17 R. E. M. Brooner, R. A. Widenhoefer, *Angew. Chem. Int. Ed.* **2013**, *52*, 11714–11724.

18 M. García-Mota, N. Cabello, F. Maseras, A. M. Echavarren, J. Pérez-Ramírez, N. Lopez, *ChemPhysChem* **2008**, *9*, 1624–1629.

19 a) A. S. K. Hashmi, J. P. Weyrauch, W. Frey, J. W. Bats, *Org. Lett.* **2004**, *6*, 4391–4394. b) J. J. Kennedy-Smith, S. T. Staben, F. D. Toste, *J. Am. Chem. Soc.* **2004**, *126*, 4526–4527. c) A. Fürstner, *Chem. Soc. Rev.* **2009**, *38*, 3208–3221

thiols, amines, imines, sulfoxides and *N*-oxides. The resulting *trans*-alkenyl gold species **I** can be involved in further transformations to generate the corresponding products.[20]



Scheme 2. Nucleophilic attack to (η^2-alkynes)-gold(I) complexes and subsequent trapping with an electrophile

Often, the alkenyl-gold intermediate can react with an electrophile generating carbocationic intermediate **II** partially stabilized by backdonation from the expanded *5d* orbital of gold. Whether these intermediates should be defined as gold(I) stabilized carbocation (**II**) or gold(I)-Fischer-type carbene (**III**) has been a matter of certain debate.[21]

To describe the bonding situation for gold(I) carbene, Goddard and Toste proposed a three-center four-electron σ-hyper bond, where both the ancillary ligand and the carbene are donating electrons to gold.[22] At the same time, gold(I) can backdonate electrons to both the ligand and the carbene fragment that compete for the electron density of the metal (Figure 2, top).

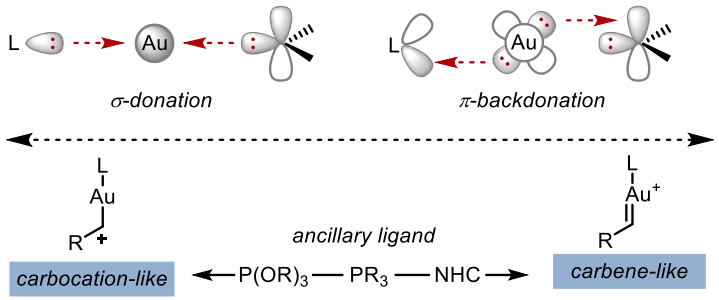


Figure 2. Nature of the gold(I) carbene/gold(I) carbocation intermediate and influence of the ancillary ligand.

Under these premises, is it clear that both the carbocationic and the carbenic description of this intermediate represent extreme resonance forms of the same species displaying intermediate properties and it is possible to generate species displaying either enhanced carbenic or carbocationic reactivity modulating the substituent R or the ancillary ligand L. In this context,

20 a) W. Debrouwer, T. S. A. Heugebaert, B. I. Roman, C. V. Stevens, *Adv. Synth. Catal.* **2015**, *357*, 2975–3006. b) R. Dorel, A. M. Echavarren, *Chem. Rev.* **2015**, *115*, 9028–9072. c) A. M. Echavarren, M. E. Muratore, V. López-Carrillo, A. Escribano-Cuesta, N. Huguet, C. Obradors, *Org. React.* **2017**, *92*, 1–411.

21 Reviews on the topic: a) Y. Wang, M. E. Muratore, A. M. Echavarren, *Chem. Eur. J.* **2015**, *21*, 7332–7339. B) R. J. Harris, R. A. Widenhoefer, *Chem. Soc. Rev.* **2016**, *45*, 4533–4551.

22 D. Benitez, N. D. Shapiro, E. Tkatchouk, Y. Wang, W. A. Goddard, F. D. Toste, *Nat. Chem.* **2009**, *1*, 482–486.

the use of σ-donating and poor π-acceptor NHC ligands favors the π-backdonation on the carbon fragment, leading to more carbene-like intermediates, whereas phosphorous-based ligands favor more carbocation-like species (Figure 2, bottom).

Gold(I)-Catalyzed Cycloisomerization of 1,*n*-Enynes

Homogeneous gold(I) catalysis is associated with the cycloisomerization of 1,*n*-enynes and related substrates. This reaction allows the assembly of complex molecular framework starting from relatively simple substrates in a single step and it is usually catalyzed by electrophilic metal complexes, among which gold(I) outstands for its higher reactivity and selectivity, as well as for the variety of transformations that can induce.

In this context, the most studied reaction is the cycloisomerization of 1,6-enynes.[23] This reaction starts by activation of the alkyne of the enyne by gold(I) in intermediate **IV** *via* η^2-coordination, which allows the nucleophilic attack of the alkene to form intermediates **V** or **VI** by 5-*exo*-dig and 6-*endo*-dig cyclization, respectively (Scheme 3). Intermediates of type **V** and **VI** are usually drawn as a cyclopropyl gold(I) carbene, although, as discussed in the previous section, these species have a significant carbocationic character.[24] According to computational studies, cyclopropyl gold(I) carbenes **V** are in most cases highly distorted with a relatively long C2-C4 bond and are in equilibrium with the corresponding homoallylic gold(I) stabilized carbocation (Scheme 3, **V** and **V'**).[24c] In this manuscript the intermediates like **V** and **VI** will be presented, for conciseness, as the carbene form.

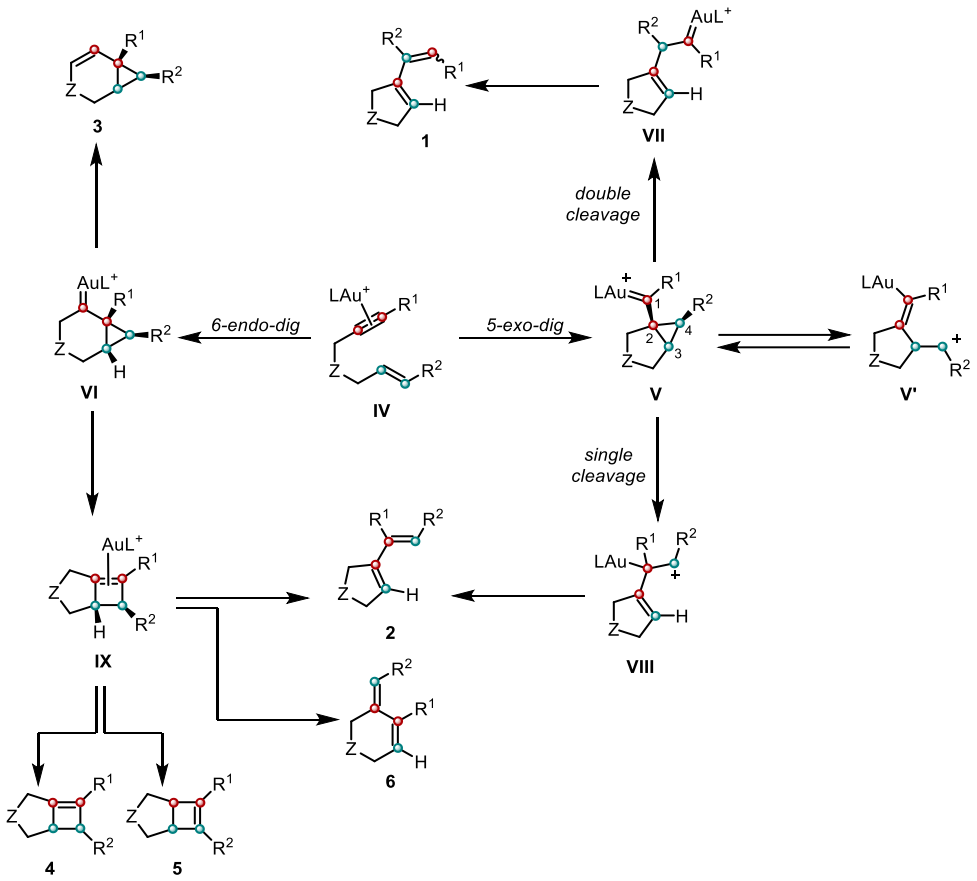
In absence of an external nucleophile, **V** and **VI** can undergo several skeletal rearrangements depending on the ligand and the substituents on the enyne.[25] Intermediate **V** can open to form carbene **VII** in a process known as "double cleavage rearrangement", in which the external carbon of the alkene is formally inserted in between the two carbons of the alkyne. Upon 1,2-H-shift and protodeuration, 1,3-diene **1** is formed, usually favoring the formation of the *Z* isomer. Alternatively, intermediate **VIII** is formed from **V** upon "single cleavage rearrangement". This process corresponds to a migration of the terminal carbon of the alkene on the terminal carbon of the alkyne, in a formal cleavage of the alkene. Homoallyl-carbocation **VIII** then evolves into compounds **2** in a stereospecific manner in which the configuration of

23 a) C. Obradors, A. M. Echavarren, *Acc. Chem. Res.* **2014**, *47*, 902–912. b) Y. C. Lee, K. Kumar, *Isr. J. Chem.* **2018**, *58*, 531–556. c) E. Jiménez-Núñez, A. M. Echavarren, *Chem. Rev.* **2008**, *108*, 3326–3350.

24 a) C. Nieto-Oberhuber, S. López, M. P. Muñoz, D. J. Cárdenas, E. Buñuel, C. Nevado, A. M. Echavarren, *Angew. Chem. Int. Ed.* **2005**, *44*, 6146–6148. b) A. Fürstner, P. W. Davies, *Angew. Chem. Int. Ed.* **2007**, *41*, 3410-3449. c) I. Escofet H. Armengol-Relats, H. Bruss M. Besora, A. M. Echavarren, *Chem. Eur. J.* (chem.202004237, under revision)

25 J. M. Mattalia, P. Nava, *J. Organomet. Chem.* **2014**, *749*, 335–342.

the alkene is maintained in the *exo*-double bond of the product. Weather intermediate **V** undergoes single or double cleavage depends on the substituents on the alkyne. Thus, electron-withdrawing substituents favors the double cleavage rearrangement, while electron-donating ones lead preferentially to the single cleavage diene. 1,3-Dienes **2** can be also formed from the six-membered cyclopropyl gold(I) carbene **VI** upon ring expansion of the cyclopropane into the cyclobutene **IX** and subsequent ring opening.[26] Cyclopropyl gold(I) carbene **VI** can form bicyclo[4.1.0]hept-2-ene derivatives **3** *via* 1,2-H shift and protodeauration.



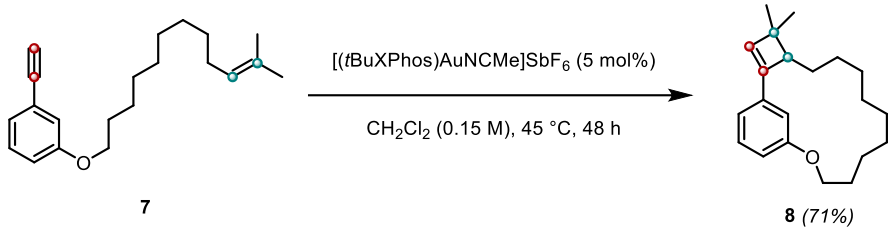
Scheme 3. Gold(I)-catalyzed cycloisomerization of 1,6-enynes

Compounds of general structure **6** are also formed from the same intermediate **IX** in an *endo*-type single cleavage rearrangement, where the internal carbon of the alkene migrates to the external carbon of the alkyne.[27]

26 A. Escribano-Cuesta, P. Pérez-Galán, E. Herrero-Gómez, M. Sekine, A. A. C. Braga, F. Maseras, A. M. Echavarren, *Org. Biomol. Chem.* **2012**, *10*, 6105–6111.

27 N. Cabello, E. Jiménez-Núñez, E. Buñuel, D. J. Cárdenas, A. M. Echavarren, *Eur. J. Org. Chem.* **2007**, *8*, 4217–4223.

Interestingly, cyclobutenes **4**, the product of direct intramolecular [2+2] cycloaddition, are formed in just few cases, while their isomers **5** are formed more often by acid catalyzed migration of the double bond driven by a less constrain on the ring fusion.[28] In contrast, the double bond remains located at the ring fusion in the reaction of longer 1,*n*-enynes (n = 10-16), providing macrocycles of up to 15 carbons that incorporate a cyclobutene (Scheme 4). [29]



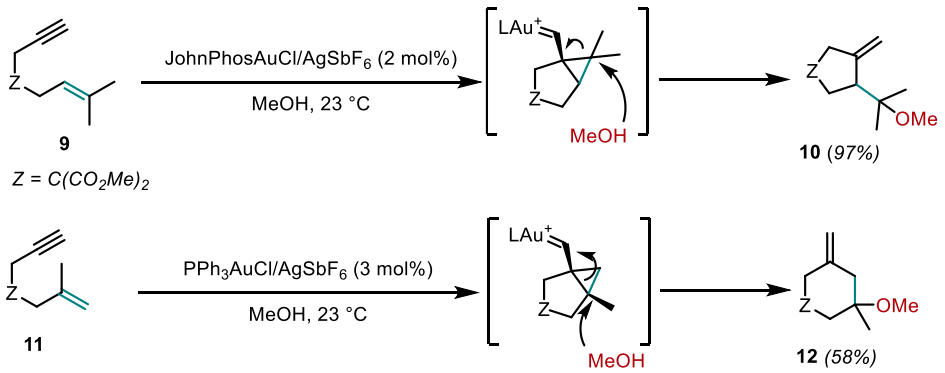
Scheme 4. Gold(I)-catalyzed intermolecular [2+2] cycloaddition of 1,6-enyne to form a 15-membered macrocycle

The reactions of 1,5- and 1,7-enynes follow analogous pathways. In the case of 1,5-enynes the *endo*-pathway in the formation of the cyclopropyl gold(I) carbene is generally favored due to the formation of a bicyclo[3.1.0]hexane system less strained compared to the bicyclo[2.8.0]pentane system formed in the 4-*exo*-cyclization. Less studied 1,7-enynes usually undergo single cleavage rearrangement through both *endo*- and *exo*-cyclopropyl gold(I) carbenes.[30]

Cycloisomerization of Enynes in Presence of a Nucleophile

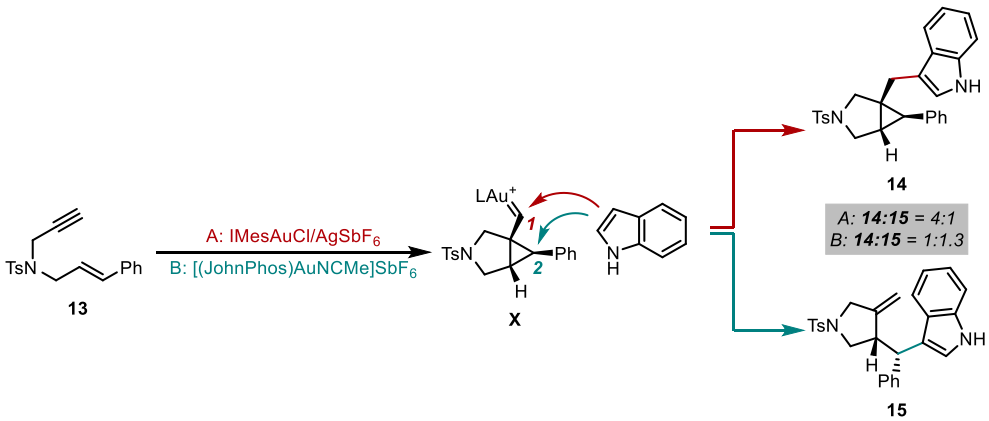
The cyclopropyl gold(I) carbene formed in the first step of the cycloisomerization of a 1,*n*-enyne can be also trapped by a nucleophile. These reactions occur regioselectively and stereospecifically and the overall process can be considered as an *anti*-addition of the nucleophile and the electrophilic alkyne to the alkene with Markovnikov selectivity (Scheme 5).

28 N. Kim, R. E. M. Brooner, R. A. Widenhoefer, *Organometallics* **2017**, *36*, 673–678.
29 C. Obradors, D. Leboeuf, J. Aydin, A. M. Echavarren, *Org. Lett.* **2013**, *15*, 1576–1579.
30 a) N. Cabello, C. Rodríguez, A. M. Echavarren, *Synlett* **2007**, 1753–1758. b) C. Huang, P. Kothandaraman, B. Q. Koh, P. W. H. Chan, *Org. Biomol. Chem.* **2012**, *10*, 9067–9078.



Scheme 5. Markovnikov alkoxycyclization of 1,6-enynes **9** and **11**.

In this context, nitrogen- and oxygen-containing nucleophiles have been widely used in intermolecular and intramolecular processes.[20b] In the same way, 1,3-dicarbonyl compounds and electron-rich aromatics can react with cyclopropyl gold(I) carbenes as carbon nucleophiles.[31] In the case of carbon nucleophiles, whether the attack will occur on the cyclopropyl ring or on the carbenic carbon is dependent on the assisting ligand. Thus, for example, in the reaction of nitrogen-tethered 1,6-enyne **13** with indole, the cyclopropyl gold(I) carbene **X** is attacked preferentially on carbon ***1*** when IMesAuCl activated with $AgSbF_6$ is used, delivering a 4:1 mixture of products **14** and **15.** On the other hand, using a phosphine-based ligand, slightly favors the attack on carbon ***2*** (**14**/**15** = 1:1.3) (Scheme 6).

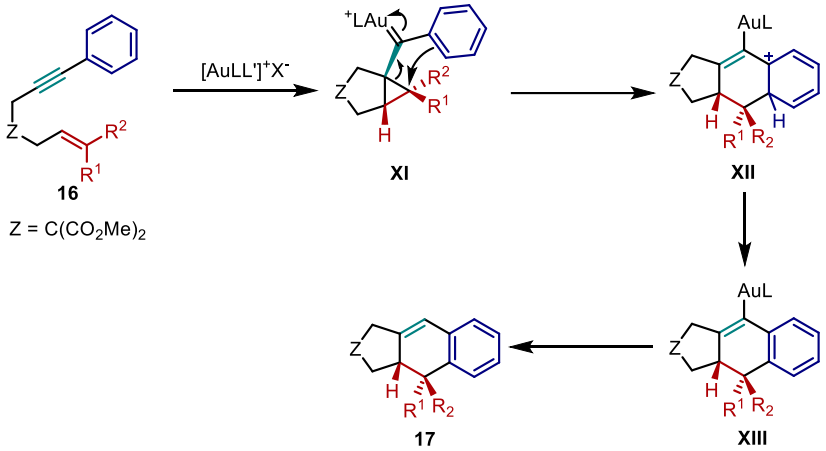


Scheme 6. Catalyst-dependent chemoselectivity in the reaction of 1,6-enyne **13** with indole.

Aryl rings can be used also as internal nucleophiles as shown in the reaction of 1,6-enynes **16** with an aryl-substituted alkyne that undergo formal [4+2] cycloaddition in presence of gold(I)

31 C. H. M. Amijs, V. López-Carrillo, M. Raducan, P. Pérez-Galán, C. Ferrer, A. M. Echavarren, *J. Org. Chem.* **2008**, *73*, 7721–7730.

to form the tricyclic products **17** (Scheme 7).[32] The reaction is initiated with 5-*exo*-dig cyclization of the enyne to form **XI**, which undergo opening of the cyclopropyl ring *via* Friedel-Crafts-type reaction to form **XII**, followed by re-aromatization and protodeauration leading to the desired product.



Scheme 7. Gold(I) catalyzed formal [4+2] cycloaddition of 1-aryl-1,6-enynes

Intermolecular Reaction of Alkynes with Alkenes

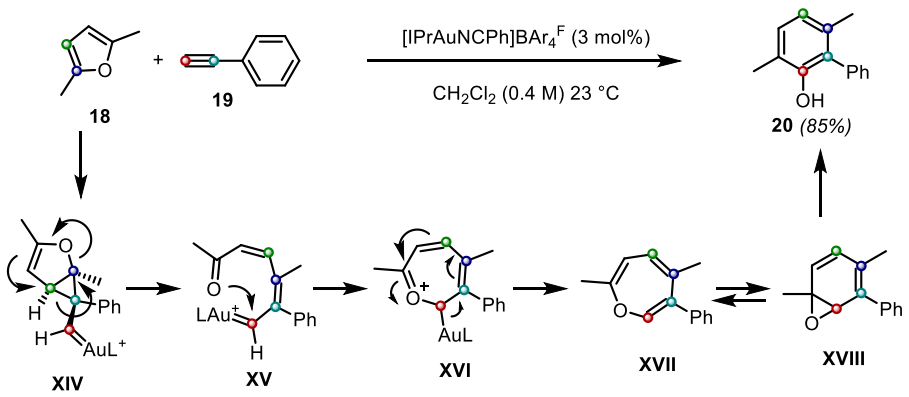
Compared to the many transformations developed intramolecularly, the number of intermolecular reactions involving alkynes and alkenes to form new C-C bonds is more limited.[33] In the intermolecular setting in fact, two separate and independent unsaturations with analogous affinities for coordination are competing for the binding site of the metal, which would slow down the reaction or even suppress the reactivity. In addition, the intrinsic acidity of the gold(I)-catalyzed reactions can lead to undesired Brønsted acid-catalyzed dimerizations or oligomerizations of electron-rich alkenes[34] or other side reactions, which are minimized in intramolecular transformations. On top of this, the products of intermolecular reactions of alkynes and alkenes usually contain double bonds that can compete with the substrates for the coordination with the catalyst and with the starting alkene for the reaction with the alkyne, giving rise to the formation of byproducts.

32 a) C. Nieto-Oberhuber, S. López, A. M. Echavarren, *J. Am. Chem. Soc.* **2005**, *127*, 6178–6179.b) C. Nieto-Oberhuber, P. Pérez-Galán, E. Herrero-Gómez, T. Lauterbach, C. Rodríguez, S. López, C. Bour, A. Rosellón, D. J. Cárdenas, A. M. Echavarren, *J. Am. Chem. Soc.* **2008**, *130*, 269–279. c) M. C. P. Yeh, W. C. Tsao, B. J. Lee, T. G. Lin, *Organometallics* **2008**, *27*, 5326–5332. d) C. M. Chao, M. R. Vitale, P. Y. Toullec, J. P. Genêt, V. Michelet, *Chem. Eur. J.* **2009**, *15*, 1319–1323.

33 For a review see: a) M. E. Muratore, A. Homs, C. Obradors, A. M. Echavarren, *Chem.: Asian J.* **2014**, *9*, 3066–3082. b) C. Garciá-Morales, A. M. Echavarren, *Synlett* **2018**, *29*, 2225–2237.

34 J. Urbano, A. J. Hormigo, P. De Frémont, S. P. Nolan, M. M. Díaz-Requejo, P. J. Pérez, *Chem. Commun.* **2008**, *4*, 759–761.

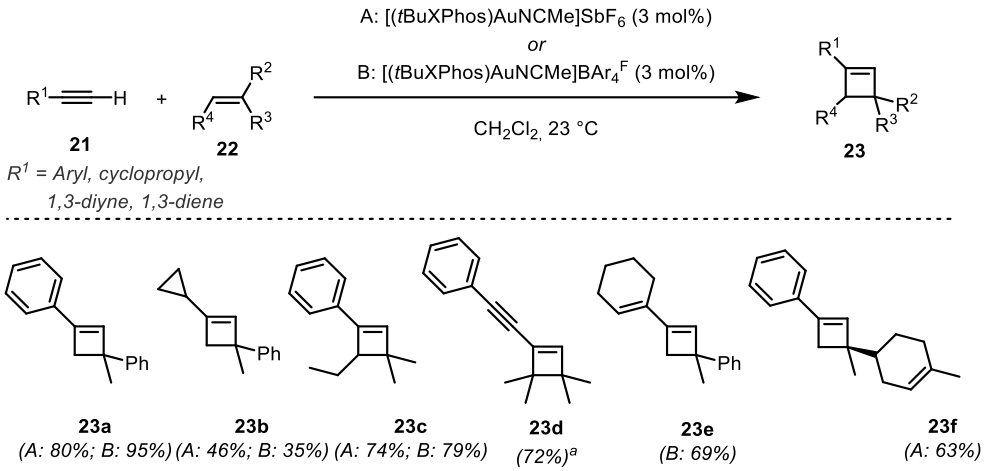
As introduced at the beginning of this manuscript, one of the first developed reaction in the field of homogeneous gold catalysis has been the synthesis of substituted phenols starting from furans.[5] Despite the many reported variations of this reaction, its intermolecular version remained limited to one single example with low yields for almost a decade[35] until our group reported that the use of an IPr-based complex allowed to obtain substituted phenols from furans such as **18** and phenyl acetylene **19** or other aryl acetylenes (Scheme 8). [36] The reaction starts with the formation of the cyclopropyl gold(I) carbene **XIV,** which rearranges to form gold(I) carbene **XV**. This carbene then undergoes cyclization to form **XVI**, which leads to oxepine **XVII**. Oxepine **XVII** is in equilibrium with the arene-oxide tautomer **XVIII**, whose opening leads to the formation of the final phenol **20**.



Scheme 8. Mechanism of the gold(I) catalyzed synthesis of phenols starting from furan and alkynes.

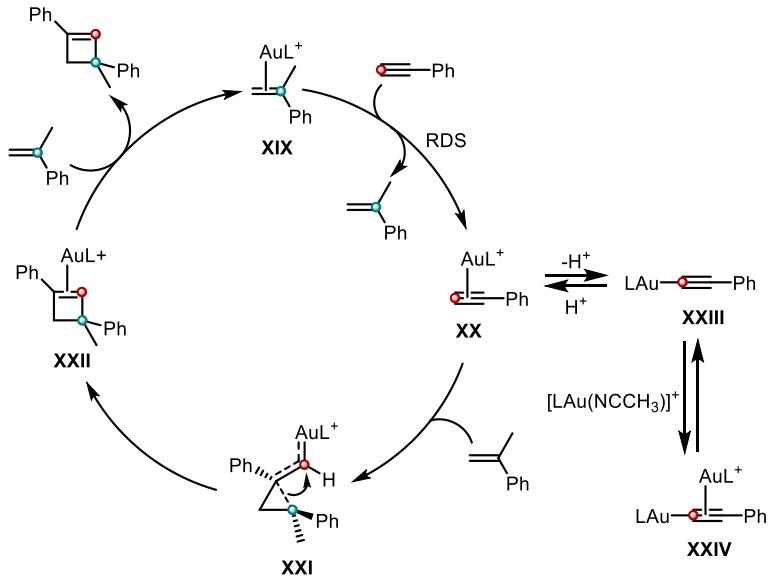
Our group reported in 2010 the first intermolecular cycloaddition of terminal alkynes with alkenes to form cyclobutenes in a regioselective fashion (Scheme 9).[37] The reaction was initially reported for aryl and cyclopropyl-alkynes and was later extended to 1,3-dienes[38] and 1,3-diynes.[39] In a following study by our group, it was found that the nature of the counterion of the cationic catalyst was crucial in many cases to afford better yields.[40] Specifically, switching from SbF_6^- to the less coordinating and less basic BAr_4^{F-} was the best choice in most of the cases.

35 A. S. K. Hashmi, M. C. Blanco, E. Kurpejović, W. Frey, J. W. Bats, *Adv. Synth. Catal.* **2006**, *348*, 709–713.
36 N. Huguet, D. Lebœuf, A. M. Echavarren, *Chem. Eur. J.* **2013**, *19*, 6581–6585.
37 V. López-Carrillo, A. M. Echavarren, *J. Am. Chem. Soc.* **2010**, *132*, 9292–9294.
38 M. Elena de Orbe, A. M. Echavarren, *Eur. J. Org. Chem.* **2018**, *2018*, 2740–2752.
39 M. E. De Orbe, L. Amenós, M. S. Kirillova, Y. Wang, V. López-Carrillo, F. Maseras, A. M. Echavarren, *J. Am. Chem. Soc.* **2017**, *139*, 10302–10311.
40 A. Homs, C. Obradors, D. Leboeuf, A. M. Echavarren, *Adv. Synth. Catal.* **2014**, *356*, 221–228.



Scheme 9. Gold(I) catalyzed [2+2] cycloaddition of alkynes with alkenes and selected examples of the product obtained with this methodology. [a] $[IPrAuNCMe]BAr_4^F$ was used as catalyst.

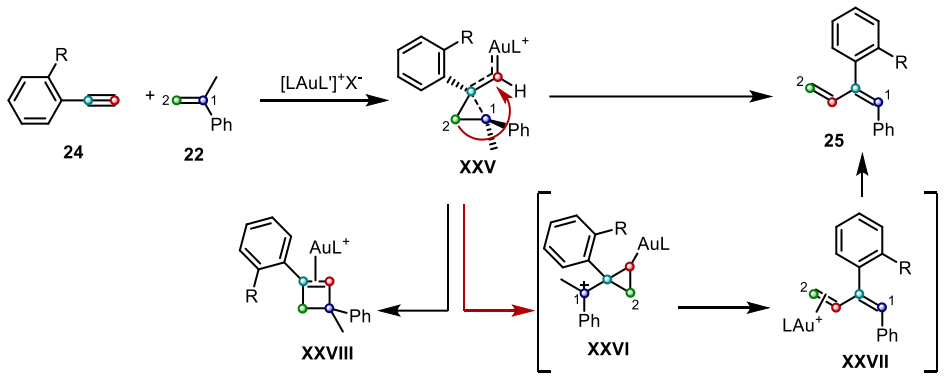
The reaction starts with the formation of (η^2-alkene) gold(I) complex **XIX**, the productive (η^2-alkyne) gold(I) complex **XX** is then formed by an associative ligand exchange that is in many cases the rate-determining-step of the reaction. Complex **XX** reacts with the alkene to form cycloproyl gold(I) carbene **XXI**, analogous to the one formed in the cycloisomerization of the enynes (Scheme 10). Complex **XXII** is formed then *via* ring expansion and the final product is then released though an associative ligand exchange with another molecule of alkene. Additionally, **XX** can evolve into the σ-complex **XXIII** and then react with another molecule of the catalyst to form the σ–π-digold(I) complex **XXIV.**



Scheme 10. Mechanism of the gold(I)-catalyzed [2+2] cycloaddition of alkynes with alkenes.

σ–π-Digold complexes can be catalysts for a series of transformations with diyenes,[41] but they are poor catalysts for enyne cycloisomerizations,[42] and unproductive for the intermolecular [2+2] cycloaddition and other intermolecular reactions.[40,43] ^{31}P-NMR studies on the gold(I)-catalyzed intermolecular [2+2] cycloaddition showed that σ–π-digold complex **XXIII** is, together with **XIX**, the only long-living species formed during the reaction, and its formation causes a decrease in the amount of catalytically active gold species. Among the counterions tested, BAr_4^{F-} was the one that led to the lowest amount of **XXIII**, probably because of its lower basicity, resulting in an improvement of the efficiency of the reaction.

Interestingly, under the same conditions a mixture of 1,3-diene **25** and cyclobutene was obtained starting from *ortho*-substituted aryl alkynes (Scheme 11).[39] Detailed mechanistic studies mainly based on DFT calculations showed that the diene is formed from the same cyclopropyl gold(I) carbene **XXV** that would generate the cyclobutene, but in the case *ortho*-substituted arylalkynes, **XXV** is also in equilibrium with cyclopropyl cation **XXVI** generated via C2-migration. Upon ring opening, the corresponding 1,3-diene-gold(I) complex **XXVII** is formed that upon ligand exchange forms product **25**.

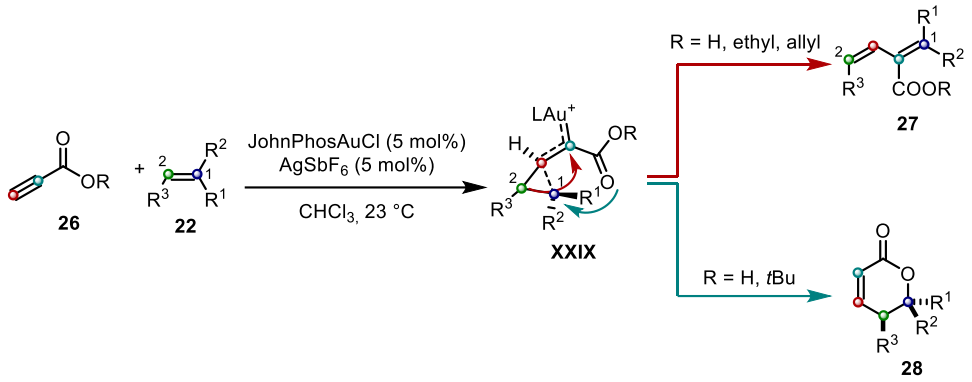


Scheme 11. Gold(I)-catalyzed formation of dienes **25**.

Replacing the aryl ring on the alkyne for a more electron-withdrawing group changes the outcome of the reaction. For example, the gold(I)-catalyzed reaction of propiolic acids or esters (**26** in Scheme 12) with 1,1-di- or trisubstituted alkenes leads selectively to α,β-unsaturated γ-lactones by a formal [4+2] cycloaddition (Scheme 12, blue path).[44] On the other hand, reaction of propiolic derivatives with 1,2-disubstituted alkenes leads to the stereospecific synthesis of

41 These transformations are usually defined as "dual gold catalysis" and will be discussed in more detail in the introduction of Chapter 1.
42 S. Ferrer, A. M. Echavarren, *Organometallics* **2018**, *37*, 781–786.
43 C. Obradors, A. M. Echavarren, *Chem. Eur. J.* **2013**, *19*, 3547–3551.
44 H. S. Yeom, J. Koo, H. S. Park, Y. Wang, Y. Liang, Z. X. Yu, S. Shin, *J. Am. Chem. Soc.* **2012**, *134*, 208–211.

1,3-dienes (**27**, Scheme 12, red path) as observed in the reaction of *ortho*-substituted arylalkynes. Mechistically, the two products are branching from the same cyclopropyl gold(I) carbene intermediate **XXIX**.

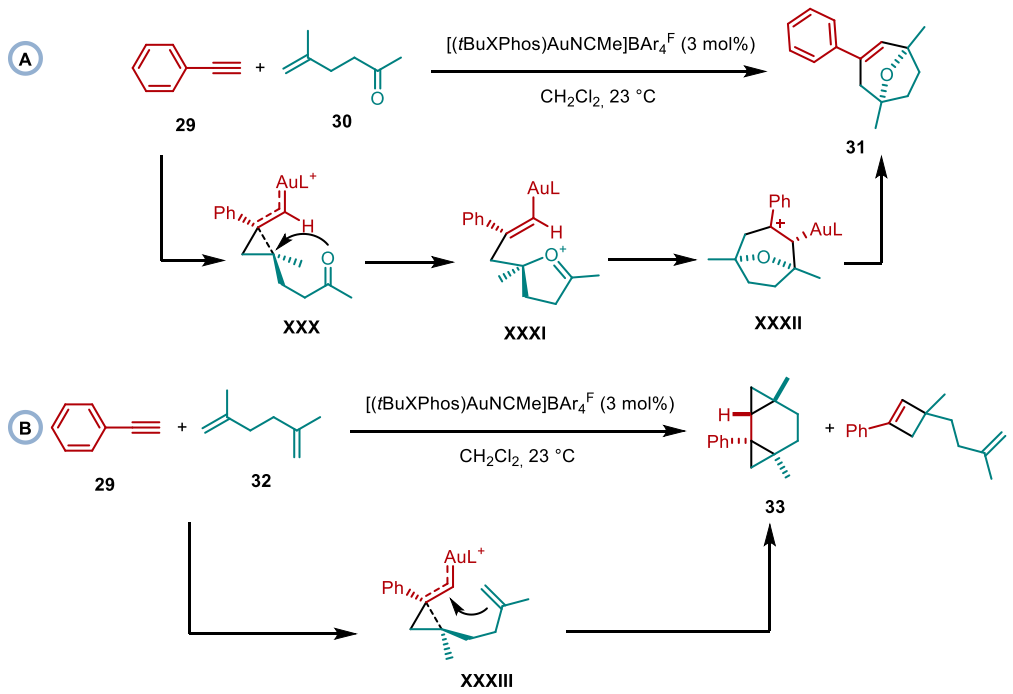


Scheme 12. Gold(I) catalyzed reaction of propiolic acids and esters with alkenes.

It is important to note that, differently from the cases mentioned above, in this reaction the gold(I) carbene is located on the more substituted carbon, highlighting a general trend in the selectivity of the formation of cyclopropyl gold(I) carbenes: in the intermolecular formation of cyclopropyl gold(I) carbenes the gold(I) carbene is usually located on the carbon bearing the most electron-withdrawing substituent.

In the case of highly substituted alkenes, the partial positive charge on C1 in **XXIX** is more stabilized allowing the attack of the carboxylic moiety leading to the lactone. According to DFT calculations, instead, when a 1,2-disubstituted alkene is used, the most accessible transition state is the one leading to product **27** through a carbocation intermediate analogous of **XXI** in Scheme 11.

Increasing the complexity of the alkenes partner it is possible to reach high molecular complexity in one step. Our group discovered that in presence of a cationic gold(I) complex, aryl akynes react with ketoalkenes in a formal [2+2+2] cycloaddition in which two C-C bonds and one C-O bond are formed to finally deliver oxabicyclo[3.2.8]oct-3-enes **31** (Scheme 13a).[43] The reaction occurs stepwise starting as usual with the formation of **XXX**, followed by the attack of the carbonyl to the most substituted carbon of the cyclopropyl ring forming oxonium cation **XXXI**. Finally, the seven membered ring is formed by a Prins-type reaction leading to **XXXII** and then to **31** upon metal elimination and ligand exchange.

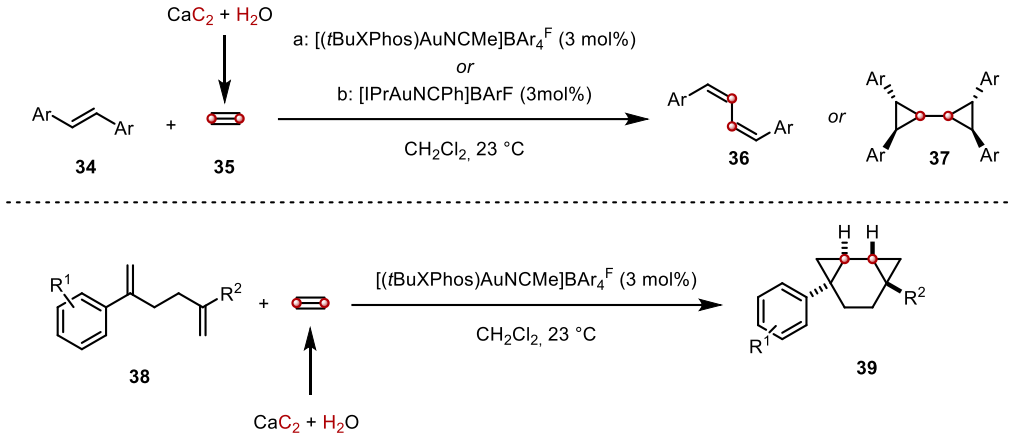


Scheme 13. A) Gold(I) catalyzed [2+2+2] cycloaddition of arylalkynes with ketoalkenes. B) Gold(I)-catalyzed double cyclopropanation of dienes.

In contrast, cyclopropyl gold(I) carbene **XXXIII** formed in the reaction of aryl alkynes with 1,5-dienes reacts at the carbene by cyclopropanation with the pendant double bond forming the tricyclic product **33** (Scheme 13b).[37] In this transformation, the (η^2-alkyne) gold(I) complex of phenylacetylene behaves as an equivalent of a 1,2-dicarbene that undergoes double cyclopropanation.

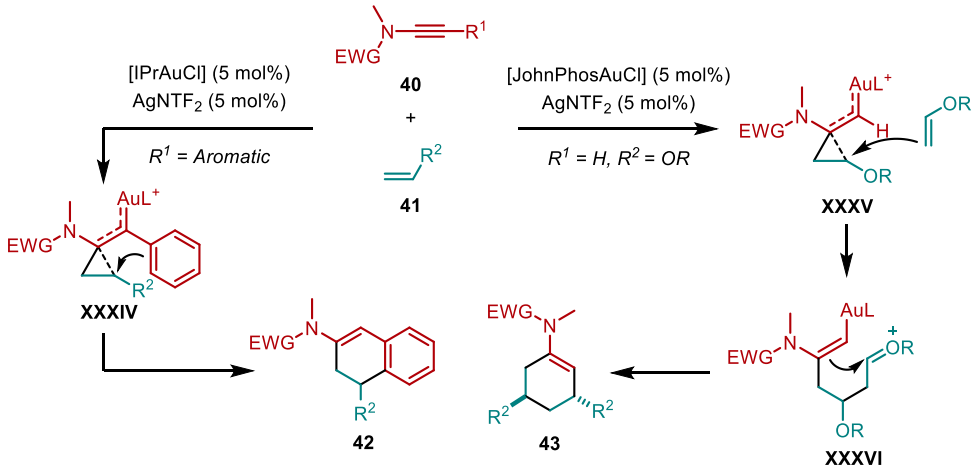
Recently, our group developed a catalytic system that engages acetylene gas in a gold(I)-catalyzed reaction that leads to the cyclopropanation of alkenes or to the formation of 1,3-dienes (Scheme 14).[45] Depending on the catalyst used, *trans*-stilbenes react with acetylene gas, generated *in situ* from CaC_2 and H_2O, to form stereoselectively ***ZZ*-36** or the bis-cyclopropane **37** (Scheme 14, top). Moreover, in presence of 1,5-dienes, acetylene **35** undergoes bis-cyclopropanation to form tricyclic derivatives **39** as single diastereoisomer in analogy with what already observed in the case of phenylacetylene.

45 D. Scharnagel, I. Escofet, H. Armengol-Relats, M. E. de Orbe, J. N. Korber, A. M. Echavarren, *Angew. Chem. Int. Ed.* **2020**, *59*, 4888–4891.



Scheme 14. Gold(I)-catalyzed intermolecular reaction of acetylene gas with alkenes.

Ynamides can also be involved in intermolecular reactions with alkenes (Scheme 15).[46] Aryl-substituted ynamides react in presence a NHC-based gold(I) complex *via* formal [4+2] cycloaddition to form products **42**. In this case, the cyclopropyl gold(I) carbene **XXXIV** undergoes Friedel-Crafts-type reaction to furnish the bicyclic product. The cyclopropyl gold(I) carbene formed in the reaction of a terminal ynamide with an enol ether reacts with another molecule of the alkene, then cation **XXXVI** undergoes a cyclization forming stereoselectively 1,3,5-substituted cyclohexenes **43**.[47]



Scheme 15. Gold(I)-catalyzed intermolecular [4+2] and [2+2+2] cycloaddition of ynamides and alkenes.

46 R. B. Dateer, B. S. Shaibu, R. S. Liu, *Angew. Chem. Int. Ed.* **2012**, *51*, 113–117.
47 The gold(I)-catalyzed reactions of alkynes substituted with other heteroatoms will be discussed in the introduction of Chapter 1 and Chapter 2.

Chapter 1

Gold (I) and Indium(III)-Catalyzed Reactions on Bromo-Alkynes

Introduction

Formation and Reactivity of Gold(I) Vinylidenes

Transition metal vinylidenes are highly versatile species involved as intermediates in the catalytic formation of C-C and C-heteroatom bonds.[48] Despite the proposal for the involvement of gold(I) vinylidenes as reactive intermediate in certain transformations back in 2004,[49] the systematic investigation on their generation and reactivity has only been carried out in the last 10 years. [50]

Structurally related to gold(I) carbenes, gold(I) vinylidenes present an additional unsaturation on the carbene causing an intrinsic destabilization due to the inhibition of the π-donation from the substituents that usually stabilizes gold(I) carbenes (Figure 1.1).[51] Intrinsic bond orbital (IBO) analysis of different gold(I) vinyldenes and the comparison with the analogous gold(I) carbenes showed that for gold(I) vinylidenes the metal participates with a higher π-backdonation on the carbene from one of the *d*-occupied orbitals to compensate the absence of stabilizing substituents, which results in a higher reactivity of these elusive species. In fact, only in one case it has been possible to characterize in solution a gold(I)-vinylidene stabilized by β,β-silyl groups.[52]

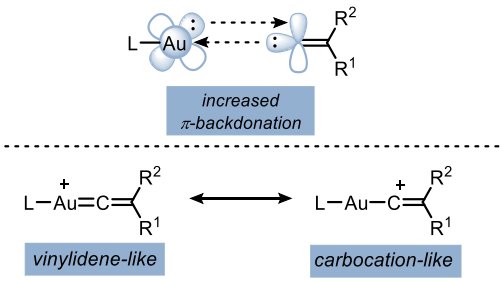


Figure 1.1. Structure and resonance forms of gold (I)-vinylidenes.

48 (a) B. M. Trost, A. McClory, *Chem.: Asian J.* **2008**, *3*, 164–194. (b) S. W. Roh, K. Choi, C. Lee, *Chem. Rev.* **2019**, *119*, 4293–4356. (c) *Metal Vinylidenes and Allenylidenes in Catalysis: From Reactivity to Applications in Synthesis; Bruneau, C.*, Dixneuf, P. H., Eds.; WILEY-VCH: Weinheim, Germany, 2008

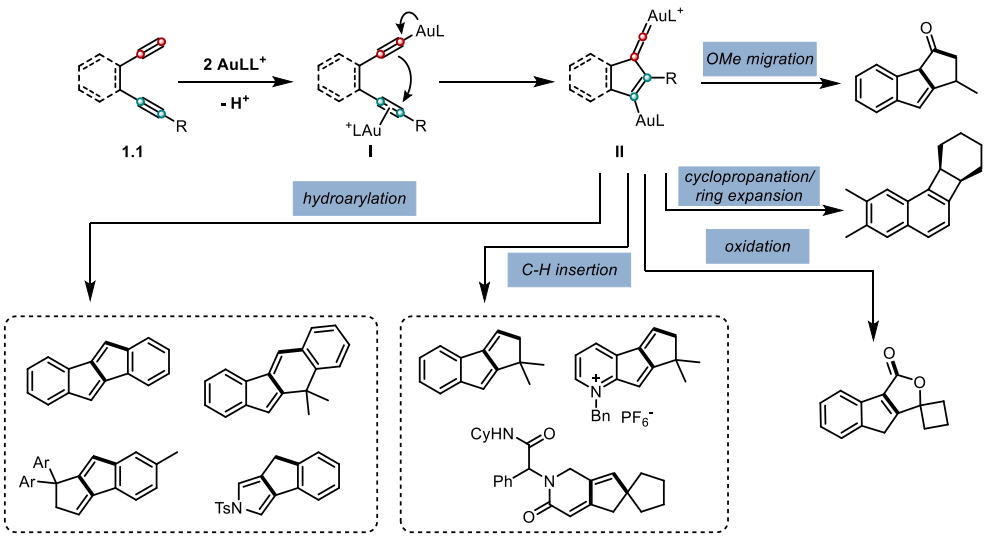
49 V. Mamane, P. Hannen, A. Fürstner, *Chem. Eur. J.* **2004**, *10*, 4556–4575.

50 For a review on generation and reactivty of gold(I) vinylidenes: F. Gagosz, *Synth.* **2019**, *51*, 1087–1099.

51 L. Nunes Dos Santos Comprido, J. E. M. N. Klein, G. Knizia, J. Kästner, A. S. K. Hashmi, *Chem. Eur. J.* **2016**, *22*, 2892–2895.

52 R. J. Harris, R. A. Widenhoefer, *Angew. Chem. Int. Ed.* **2015**, *54*, 6867–6869.

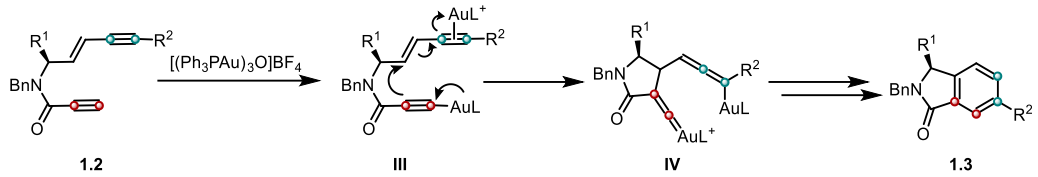
The most common way of access to gold(I) vinylidenes is *via* the so called "dual gold catalysis" on a diyene,[53] a transformation discovered separately by Zang[54] and Hashmi[55] in 2012 (Scheme 1.1). In these reactions, both triple bonds in **1.1** are activated by the gold(I) catalyst, but in two different and complementary ways: in **I** the terminal alkyne forms a nucleophilic σ-gold acetylide complex that attacks the other triple bond activated by π-coordination of another cationic gold complex forming the digold species **II** bearing a gold(I) vinylidene and a σ-vinyl gold(I) moiety. Vinylidenes generated in this way can then undergo hydroarylation, insertion in C-H, N-H or O-H bonds, cyclopropanation or nucleophilic attack of oxygen nucleophile.



Scheme 1.1. Generation of gold(I) vinylidenes via dual gold activation and subsequent reactions.

This mode of activation has been also extended by Hyland and Pyne to enediyenes (Scheme 1.2).[56] In this case, the gold acetylide in **III** attacks the gold(I)-activated conjugated enyne on the double bond forming intermediate **IV**, having at the same time the vinylidene and an allenyl-gold moiety, that finally undergoes a cyclization to form isoindolinones **1.3**.

53 (a) A. S. K. Hashmi, *Acc. Chem. Res.* **2014**, *47*, 864–876. (b) X. Zhao, M. Rudolph, A. S. K. Hashmi, *Chem. Commun.* **2019**, *55*, 12127–12135.
54 L. Ye, Y. Wang, D. H. Aue, L. Zhang, *J. Am. Chem. Soc.* **2012**, *134*, 31–34.
55 A. S. K. Hashmi, I. Braun, P. Nösel, J. Schädlich, M. Wieteck, M. Rudolph, F. Rominger, *Angew. Chem. Int. Ed.* **2012**, *51*, 4456–4460.
56 F. Zamani, R. Babaahmadi, B. F. Yates, M. G. Gardiner, A. Ariafard, S. G. Pyne, C. J. T. Hyland, *Angew. Chem. Int. Ed.* **2019**, *58*, 2114–2119.

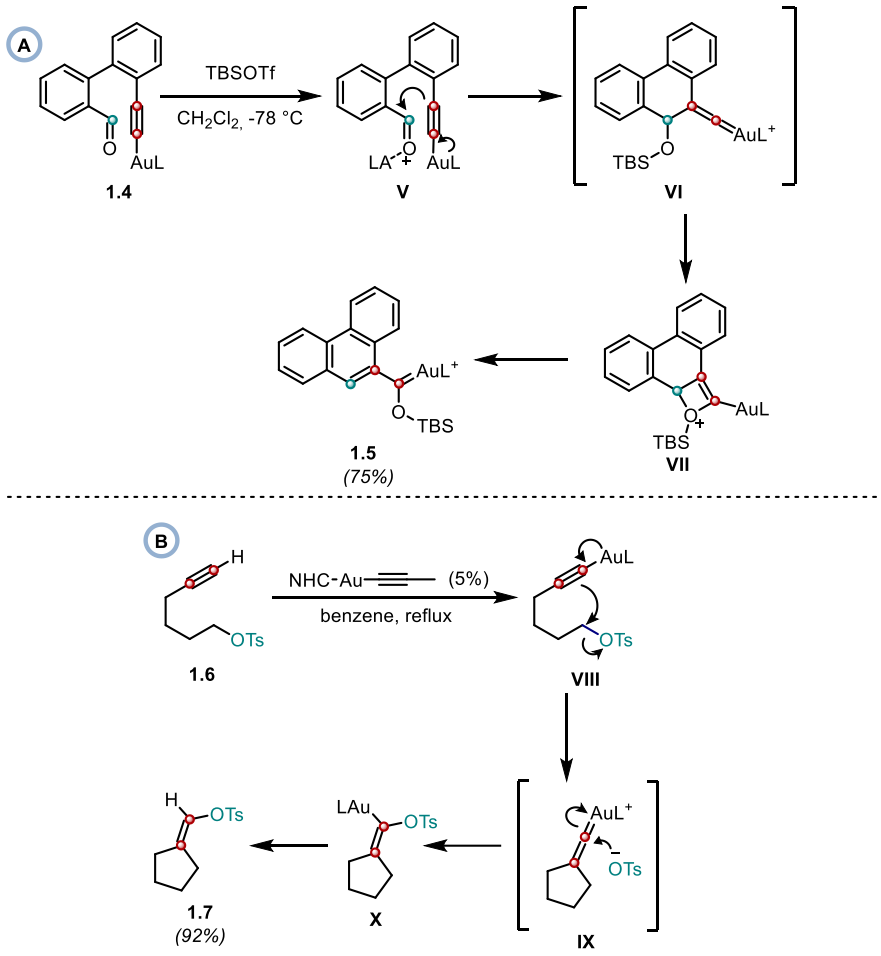


Scheme 1.2. Dual gold catalysis on enediynes

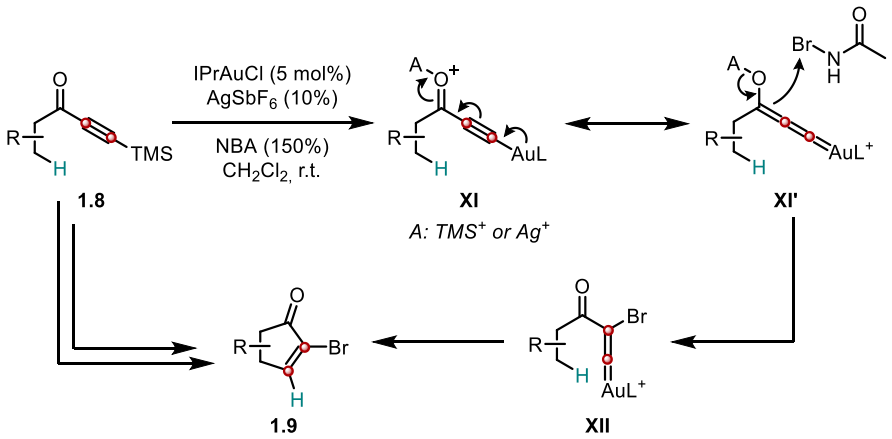
In an extension of the "dual gold catalysis" approach, the electrophilic alkyne can be replaced by other electrophilic moieties like a Lewis acid-activated aldehyde (Scheme 1.3a)[57] or a carbon bearing an aryl sulfonate leaving group (Scheme 1.3b).[58] In the first case, vinylidene **VI** rearranges immediately into the stable gold(I) carbene **1.5** *via* a four-membered oxonium cation **VII**. In the second one, the vinylidene generated from **VIII** forms a tight ion pair with the tosylate, which then attacks the vinylidene to form the tosyl enol ether **1.7**.

Finally, the group of Zhang reported the synthesis of 2-bromocyclopentenones **1.9** passing through a gold(I)-bromo vinylidene intermediate (Scheme 1.4).[59] The proposed mechanism starts with the formation of the gold acetylide species **XI** from TMS-protected ynone **1.8**, that can also be viewed as gold(I)-allenylidene **XI'**. This intermediate reacts with NBS to form vinylidene **XII**, which leads to the final product *via* C-H insertion. Overall, the formation of the gold(I) vinylidene can be seen as the formal nucleophilic attack of the σ-gold acetylide complex in **XI** on the electrophilic bromine source.

57 W. Debrouwer, A. Fürstner, *Chem. Eur. J.* **2017**, *23*, 4271–4275.
58 J. Bucher, T. Wurm, K. S. Nalivela, M. Rudolph, F. Rominger, A. S. K. Hashmi, *Angew. Chem. Int. Ed.* **2014**, *53*, 3854– 3858.
59 Y. Wang, M. Zarca, L. Z. Gong, L. Zhang, *J. Am. Chem. Soc.* **2016**, *138*, 7516–7519.

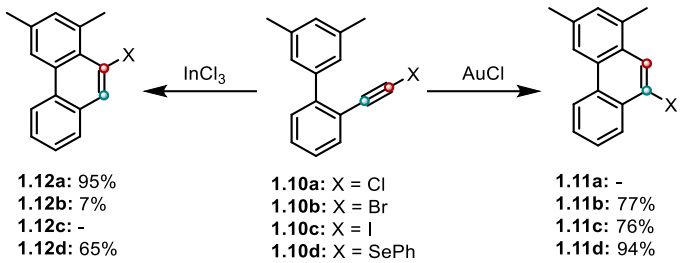


Scheme 1.3. A) Synthesis of gold(I) vinylidenes via nucleophilic attack of a gold acetylide on an aldehyde. B) Synthesis of gold (I) vinylidenes via nucleophilic substitution.



Scheme 1.4. Generation of gold(I) vinylidenes in presence of an electrophilic bromide.

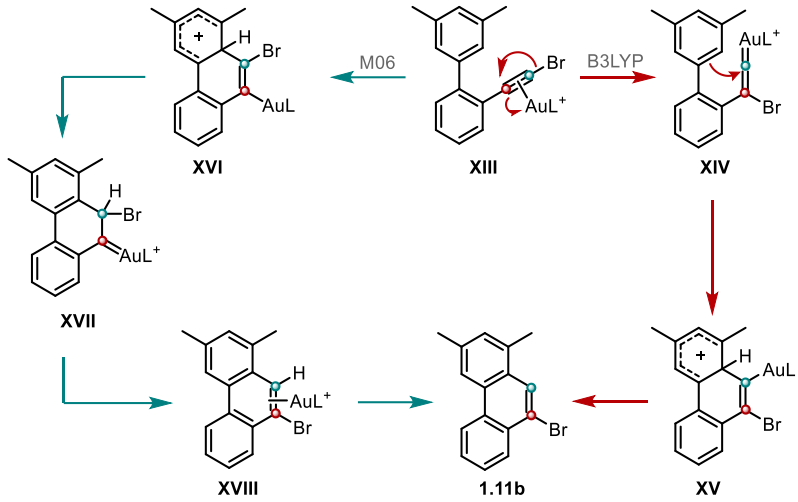
In addition, gold(I) vinylidenes can be generated *via* 1,2 migration of a halogen or a silyl-, stannyl-, or germanyl group attached to an alkyne activated by π-coordination of gold. The gold(I)-catalyzed alkyne-vinylidene isomerization was initially proposed in the context of hydroarylation of *ortho*-alkynylbiaryls by the group of Furstner (Scheme 1.5).[49] In that work, this group observed that for bromoalkyne **1.10b** and iodoalkyne **1.10c** phenanthrenes **1.11b** and **1.11c** were formed selectively instead of the regioisomer formed by direct hydroarylation of the triple bond (**1.12b,c**). Instead, chloroalkyne **1.10a** does not undergo cyclization in presence of AuCl, but it reacts with $InCl_3$ to form selectively **1.12a** *via* direct hydroarylation. Both phenanthrenyl selenides **1.11d** and **1.12d** can be formed starting from **1.10d** using AuCl or $InCl_3$ respectively.[60]



Scheme 1.5. Gold(I)- or indium(III)-catalyzed synthesis of phenanthrenes.

The first mechanistic proposal for the formation of **1.11b** hypothesized an initial 1,2-halogen migration to form gold(I) vinylidene **XIV**, followed by a hydroarylation to give **1.23b** (Scheme 1.6, red path). An initial DFT study on the reaction using B3LYP as functional confirmed the hypothesis,[61] however according to calculations performed with the M06 functional, another pathway is favored in which the hydroarylation occurs first forming **XVI**, followed by 1,2-H shift leading to carbene **XVIII** and a 1,2-Br shift to form the observed product (Scheme 1.6, blue path).[62]

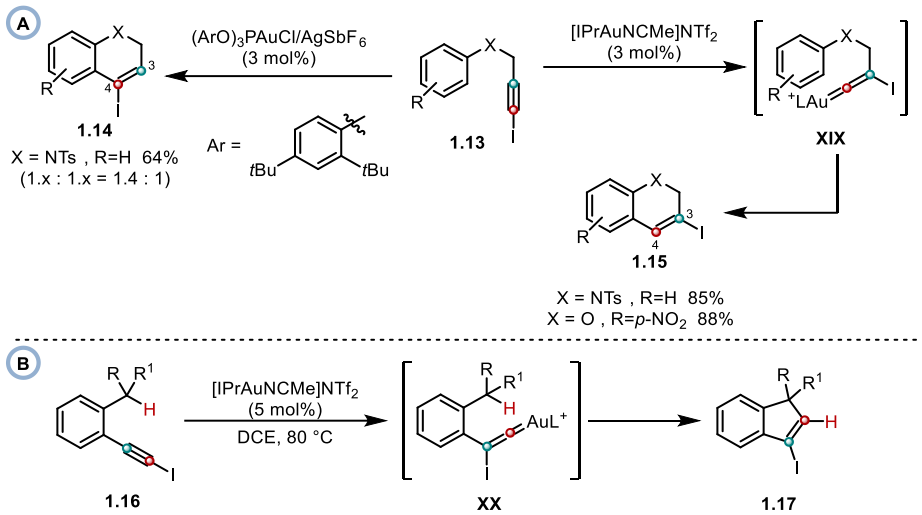
60 W. Lim, Y. H. Rhee, *Eur. J. Org. Chem.* **2013**, 460–464.
61 E. Soriano, J. Marco-Contelles, *Organometallics* **2006**, *25*, 4542–4553.
62 G. Huang, B. Cheng, L. Xu, Y. Li, Y. Xia, *Chem. Eur. J.* **2012**, *18*, 5401–5415.



Scheme 1.6. Proposed mechanisms for the gold-catalyzed synthesis of phenanthrene **1.11b**.

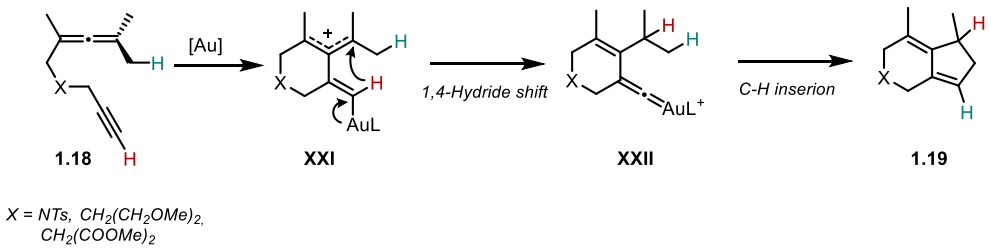
1,2-Halogen migration in iodoalkynes has also been found as the initial step for the synthesis of dehydro-iodoquinolines[63] and 3-iodo-2*H*-chromenes[64] **1.15** *via* hydroarylation of the corresponding vinylidene **XIX** (Scheme 1.7a). In this case, there is a competition between the 1,2-iodo migration and the direct hydroarylation of the alkyne and the outcome of the reaction can be modulated tuning the ligand: NHC ligands, that are known to stabilize gold(I) vinylidenes, deliver the product with the iodine in position 3 on the quinoline **1.15**, while a phosphite-based ligand favors the direct hydroarylation of the iodoalkyne giving product **1.14.** Gold(I)-iodo vinylidenes formed in this way can be also involved in C-H insertion reaction for the synthesis of indenes **1.17** (Scheme 1.7b).[65]

63 P. Morán-Poladura, S. Suárez-Pantiga, M. Piedrafita, E. Rubio, J. M. González, *J. Organomet. Chem.* **2011**, *696*, 12–15.
64 P. Morán-Poladura, E. Rubio, J. M. González, *Beilstein J. Org. Chem.* **2013**, *9*, 2120–2128.
65 P. Morán-Poladura, E. Rubio, J. M. González, *Angew. Chem. Int. Ed.* **2015**, *54*, 3052–3055.



Scheme 1.7. A) Gold(I)-catalyzed synthesis of dehydroiodoquinolines and 3-iodo-2*H*-chromoenes **1.15** starting from iodoalkynes. B) Gold(I)-catalyzed synthesis of 2-iodoindene **1.17**.

A different way for the generation of gold(I) vinylidenes was proposed to occur by in the cycloisomerization of 1,6-allenynes **1.18** to form hydrindene **1.19**.[66] It was proposed that, after nucleophilic attack of the allene on the activate alkyne, an unusual 1,4-H shift in intermediate **XXI** provides vinylidene **XXII**, followed by C-H insertion to form the final product (Scheme 1.8).



Scheme 1.8. Generation of gold vinylidenes via 1,4-H shift.

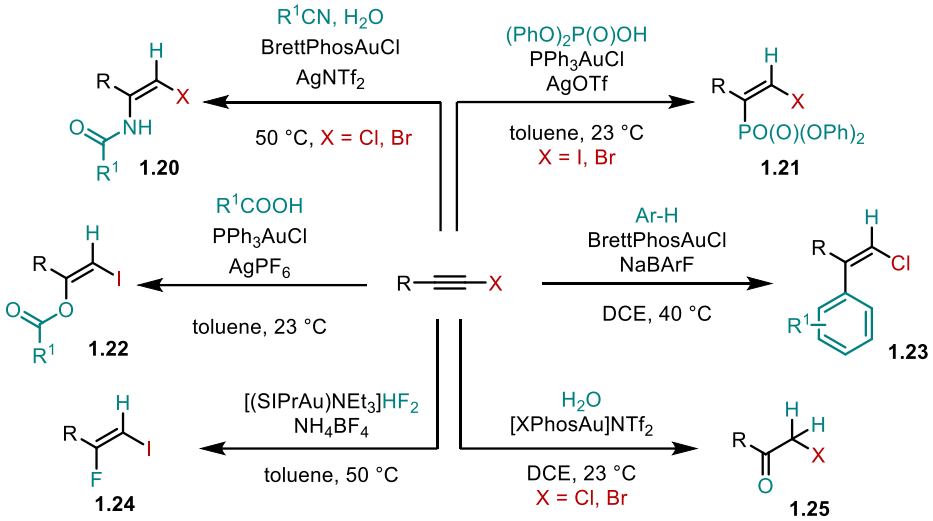
Use of Haloalkynes in Gold(I) Catalysis

Apart from their use as vinylidene precursors presented in the previous section, the main use of haloalkynes in gold(I) catalysis is to generate highly functionalized alkenes by hydrofunctionalization (Scheme 1.9).[67]

66 F. Jaroschik, A. Simonneau, G. Lemière, K. Cariou, N. Agenet, H. Amouri, C. Aubert, J. P. Goddard, D. Lesage, M. Malacria, Y. Gimbert, V. Gandon, L. Fensterbank, *ACS Catal.* **2016**, *6*, 5146–5160.

67 For a review on metal-catalyzed hydrofunctionalization of haloalkynes with a focus on gold-catalyzed processes see: V. Cadierno, *Eur. J. Inorg. Chem.* **2020**, *2020*, 886–898. In this manuscript, only selected examples will be reported.

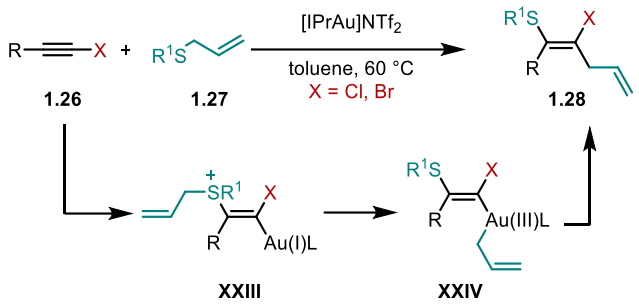
(*Z*)-β-Haloenamides **1.20** can be accessed by Ritter reaction of bromo-and chloro-alkynes with nitriles.[68] Additionally, the Markovnikov addition of a diphenyl phosphate or a carboxylic acid delivers alkenyl-halophosphates **1.21**[69] and (*Z*)-β-iodoenol esters **1.22**.[70] The hydroarylation with aromatic and heteroaromatic compounds leading to products **1.23** has been achieved for chloroalkynes.[71] The hydrohalogenation is also possible, for instance treatment of iodoalkynes with NHC-gold(I) bifluoride complexes in presence of NH_4BF_4 leads to the formal *anti*-addition of hydrogen fluoride to form **1.24**.[72] Finally, the addition of water to chloro- and bromo-alkynes leads to the formation α-haloketones.[73]



Scheme 1.9. Selected examples of hydrofunctionalization of haloalkynes

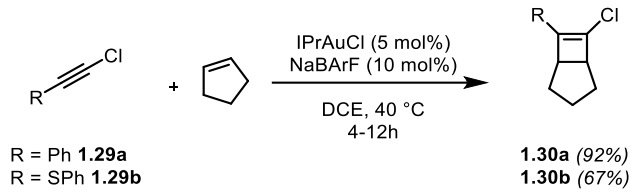
In this context, an interesting example is the *anti*-thioallylation of haloalkynes for which a Au(I)/Au(III) catalytic cycle has been proposed, with the sulfonium cation acting as mild oxidant (Scheme 1. ***10***).[74]

68 C. Liu, F. Yang, *Eur. J. Org. Chem.* **2019**, *2019*, 6867–6870.
69 B. C. Chary, S. Kim, D. Shin, P. H. Lee, *Chem. Commun.* **2011**, *47*, 7851–7853.
70 P. J. González-Liste, J. Francos, S. E. García-Garrido, V. Cadierno, *J. Org. Chem.* **2017**, *82*, 1507–1516.
71 C. Liu, Y. Xue, L. Ding, H. Zhang, F. Yang, *Eur. J. Org. Chem.* **2018**, *2018*, 6537–6540.
72 A. Gómez-Herrera, F. Nahra, M. Brill, S. P. Nolan, C. S. J. Cazin, *ChemCatChem* **2016**, *8*, 3381–3388.
73 L. Xie, Y. Wu, W. Yi, L. Zhu, J. Xiang, W. He, *J. Org. Chem.* **2013**, *78*, 9190–9195.
74 J. Wang, S. Zhang, C. Xu, L. Wojtas, N. G. Akhmedov, H. Chen, X. Shi, *Angew. Chem. Int. Ed.* **2018**, *57*, 6915–6920.



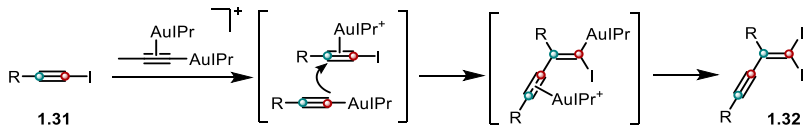
Scheme 1. 10. Proposed mechanism for the thioallylation of haloalkynes.

In contrast, the use of haloalkynes in gold(I)-catalyzed reaction with unsaturated C-C bond is very limited. For the reaction with alkenes, only few examples of cycloisomerization of 1-bromo-1,5-enynes are reported in the literature,[75] while the intermolecular reaction of (chloroethynyl)arenes **1.29a** and phenyl chloroethynyl sulfides **1.29b** with alkenes has been reported to lead to the formation of differently substituted cyclobutenes **1.30** upon [2+2] cycloaddition (Scheme 1.11).[76]



Scheme 1.11. Gold(I) catalyzed [2+2] cycloaddition of **1.29a** or **1.29b** with alkenes.

When we started the PhD research project just few other examples involving another alkyne as reaction partner were reported. For instance, the head-to-tail dimerization of iodoalkynes **1.31** under "dual gold catalysis" to give products **1.32** (Scheme 1.12).[77]

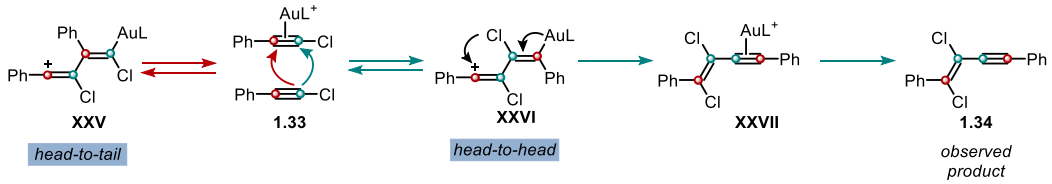


Scheme 1.12. Head-to-tail dimerization of iodoalkynes **1.31**.

However, several relevant studies have been reported in the last two years on the investigation of the reactivity of haloalkynes under gold(I) catalysis. The first example was the head-to-head

75 (a) K. Speck, K. Karaghiosoff, T. Magauer, *Org. Lett.* **2015**, *17*, 1982–1985. (b) Z. Rong, A. M. Echavarren, *Org. Biomol. Chem.* **2017**, *15*, 2163–2167.
76 Y. Bin Bai, Z. Luo, Y. Wang, J. M. Gao, L. Zhang, *J. Am. Chem. Soc.* **2018**, *140*, 5860–5865.
77 S. Mader, L. Molinari, M. Rudolph, F. Rominger, A. S. K. Hashmi, *Chem. Eur. J.* **2015**, *21*, 3910–3913.

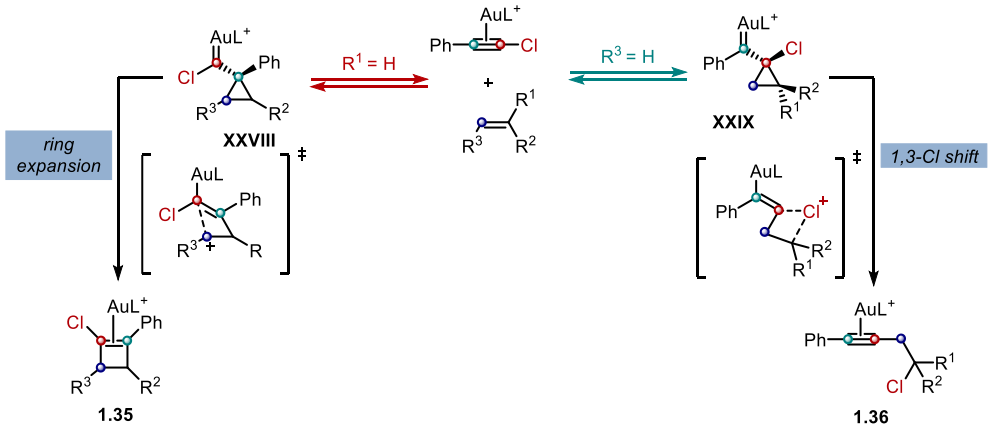
dimerization of chloroalkynes **1.33** (Scheme 1.13).[78] The C-Cl bond is not labile enough to allow the formation of the σ-goldacetylide complex observed for the iodoalkynes, so the reaction starts with the direct attack of one of the chloroalkynes to another one activated by π-coordination with gold(I). On the base of DFT calculations, the head-to-tail (Scheme 1.13, red path, intermediate X**XV**) and head-to-head (Scheme 1.13, blue path, intermediate X**XVI**) pathways are in competition, and the formation of **XXV** is energetically favored over **XXVI**. However, this first step is proposed to be reversible and the selectivity is determined then by the energy of the following steps. Considering this, it was proposed that an irreversible 1,3-chloride shift in vinyl cation X**XVI** to form **XXVII** shifts the equilibrium towards the formation of the observed product **1.34**.



Scheme 1.13. Gold(I)-catalyzed head-to-head dimerization of chloroalkynes.

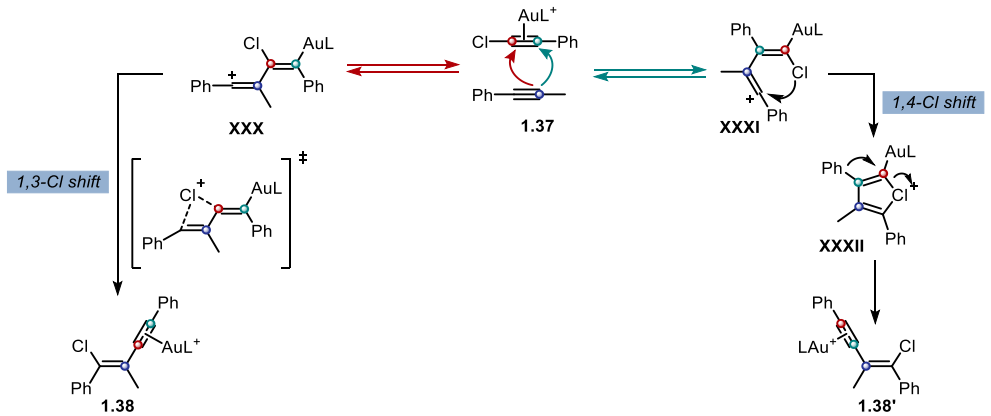
An analogous mechanism was also proposed later for the gold(I)-catalyzed 1,2-chloroalkynylation of 1,1-disubstituted alkenes (Scheme 1.14).[79] According to DFT calculations, the two possible products (**1.35** and **1.36**) arise from the evolution of two regioisomeric cyclopropyl gold(I) carbene intermediates, **XXVII** and **XXIX,** respectively. For 1,2-disubstituted alkenes the formation of **XXVIII** and its ring expansion towards the cyclobutene is favored (Scheme 1.14, red path). In contrast, for 1,1-disubstituted alkenes, the irreversible 1,3-chloride shift (only possible from **XXIX**) is shifting the equilibrium towards the formation of cyclopropyl gold(I) carbene **XXXIX** and allows the formation of **1.36** over **1.35** (Scheme 1.14, blue path).

78 M. Kreuzahler, A. Daniels, C. Wölper, G. Haberhauer, *J. Am. Chem. Soc.* **2019**, *141*, 1337–1348.
79 M. Kreuzahler, G. Haberhauer, *J. Org. Chem.* **2019**, *84*, 8210–8224.



Scheme 1.14. Proposed mechanism for the gold(I)-catalyzed 1,2-haloalkynylation of 1,1-disusbstituted alkenes.

Very recently, the haloalkynylation of aryl alkynes to form **1.38** has been reported (Scheme 1.15).[80] Two possible mechanistic pathways have been suggested: 1) the product can be obtained from **XXX** *via* a 1,3-chloride shift as proposed before. 2) The product is obtained from **XXXI** *via* formation of chloronium cyclic intermediate **XXXII**, followed by 1,2-aryl shift. It has to be noted that the two enynes **1.38** and **1.38'** are identical apart from the inverted positions of the two carbons on the alkyne and can only be distinguished by isotope labelling. According to experimental results, the two mechanisms coexist, being the second one the most favored (blue path).

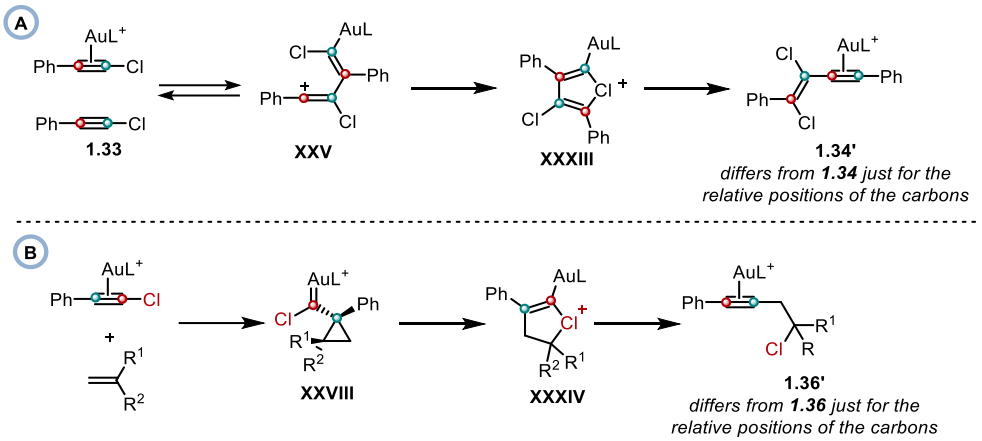


Scheme 1.15. Proposed mechanism for the 1,2-chloroalkynylation of alkynes.

80 M. Kreuzahler, G. Haberhauer, *Angew. Chem Int. Ed.* **2020**, *59*, 9433-9437.

The formation of analogous bromonium cyclic intermediate starting from bromoalkynes and alkenes and its evolution into a vinylidenephenonium-gold(I) cation is the main topic of this Chapter and it will be discussed in detail in the Results and Discussion section.

Considering the experimental evidences in the context of the 1,2-chloroalkynylation of alkynes and the results presented in this PhD Thesis, it is reasonable to reconsider the mechanism of the head-to-head dimerization and the 1,2-chloroalkynylation of alkenes (Scheme 1.13 and Scheme 1.14) under a unified scenario where the products are formed *via* the formation of a 5-membered halonium cyclic cation (intermediate **XXXII** and **XXXIV)** and subsequent rearrangement (Scheme 1.16).



Scheme 1.16. A) alternative mechanism for the formation of **1.34**. B) Alternative mechanism for the formation of **1.36.**

A thorough mechanistic study of these reactions published during the preparation of this manuscript confirmed this hypothesis, although depending on the catalyst and the substituents on the alkyne the reaction can follow both mechanisms. [81] As mention before, the product obtained from each mechanism differs from the other just by the relative position of the carbons of the alkyne, so practically there is no difference between them unless one of the alkyne carbons is isotopically labelled.

81 M. Kreuzahler, G. Haberhauer, *Angew. Chem Int. Ed.* **2020**, *59*, 17739-17749.

Objectives

Haloalkynes are versatile functionalities largely employed in transition metal catalysis. However, only few examples of their involvement in gold(I) catalyzed reaction with alkenes were reported in the literature, in contrast with the extensively studied reactions of terminal and other internal alkynes. Even more, little was known about the mechanisms taking place in their reactions. With this basis, we aimed first to explore the intra- and intermolecular reactivity of bromoalkynes with alkenes under gold(I) catalysis.

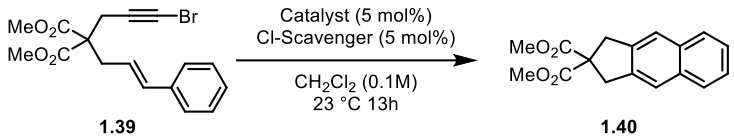
In the second part of this Chapter, we focus on the elucidation of the reaction mechanism and on the determination of the nature of the intermediates involved with the aid of both experimental and computational studies.

Results and Discussion

Cyclization of 1-Bromo-1,6-Enynes

As already mentioned in the General Introduction, gold(I)-catalyzed cycloisomerizations of 1,6-enynes are well established and widely studied processes. However, haloalkynes are scarcely involved in these reactions. So, we selected 1-bromo-1,6-enynes like **1.39** as first class of substrates to study.

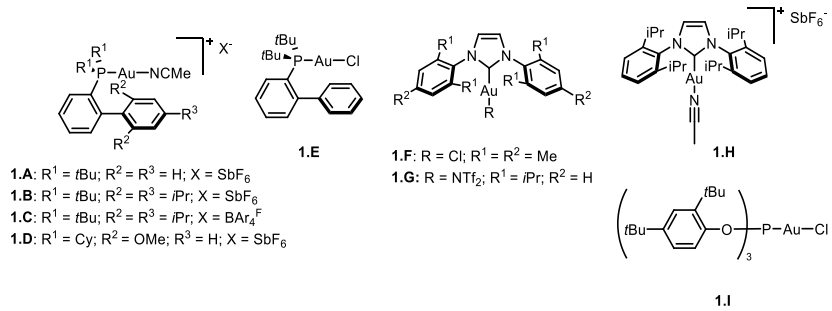
Table 1.1 Catalyst screening for the cyclization of 1-bromo-1,6-enyne **1.39**.



1.39 **1.40**

Entry	Catalyst	Cl-scavenger	Conversion (%)[a]	Yield (%)[a]
1	**1.A**	-	53	21
2	**1.B**	-	35	11
3	**1.C**	-	8	10
4	**1.D**	-	30	5
5	**1.E**	$NaBAr_4^F$	100	19
6	**1.F**	$AgNTf_2$	40	15
7	**1.G**	-	14	6
8	**1.H**	-	61	18
9	**1.I**	$AgNTf_2$	100	10

[a] Conversion and yield determined by ^{1}H-NMR using mesitylene as internal standard

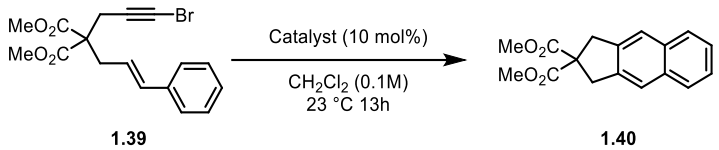


1.A: R^1 = *t*Bu; R^2 = R^3 = H; X = SbF_6
1.B: R^1 = *t*Bu; R^2 = R^3 = *i*Pr; X = SbF_6
1.C: R^1 = *t*Bu; R^2 = R^3 = *i*Pr; X = BAr_4^F
1.D: R^1 = Cy; R^2 = OMe; R^3 = H; X = SbF_6

We chose enyne **1.39** as model substrate and tested its reactivity with different gold(I) complexes (Table 1.1). We discovered that in presence of catalyst **1.A**, 2,3-dihydro-1*H*-cyclopenta[*b*]naphthalene **1.40** was formed as exclusive product, albeit in only 21% yield (Table 1.1, entry 1). Screening of other phosphine gold complexes (**1.B-1.D**, Table 1.1, entries 2-4) led to lower yields and conversions. By changing the counter ion to BAr_4^F (Table 1.1, entry 5), the starting material was completely consumed, but just 19% of the desired product was obtained. It is important to note that in this case, as well as in the others, no other major by-product was identified in the NMR of the crude reaction mixture. Precatalyst **1.F** together with $AgNTf_2$ as chloride scavenger delivered product **1.40** in 15% yield and 40% conversion (Table 1.1, entry 6). Poor results were obtained with IPr ligand with the coordinanting counterion NTf_2 (**1.G**), while the cationic complex with acetonitrile and SbF_6^- as counterion **1.H** gave analogous results (Table 1.1, entries 7 and 8). Finally, complex **1.I** with a phosphite ligand caused an increase in the decomposition of the starting material leading to a poor yield of **1.40** (Table 1.1, entry 9).

In addition to gold(I) complexes, we screened a small library of other Lewis acids (Table 1.2). Among them, only $PtCl_2$ delivered the desired naphthalene in 35% yield and full conversion of the starting enyne (Table 1.2, entry 1). In all the other cases, full decomposition of the starting material was observed (Table 1.2, Entries 2-6). At this point, catalysts **1.A, 1.F** and **1.H**, together with $PtCl_2$ were tested at higher temperatures in order to achieve better conversions (Table 1.3). With **1.A** at 50 °C and 80 °C, **1.40** was obtained in 15% and 28 % yield, respectively, however an increase of decomposition of the starting material was observed (Table 1.3, entries 1 and 2). The reaction with $PtCl_2$ as catalyst at 80 °C gave the same results than at room temperature (Table 1.3, entry 6), while with NHC ligands the increase of temperature caused a slight increase of yields being **1.F**/$AgNTf_2$ at 80 °C the best catalytic system so far, leading to **1.40** in 45% yield after complete conversion of the starting material (Table 1.3, entry 5). Additionally, the reaction time decreased to 3 h.

Table 1.2. Screening of Lewis acids as catalysts for the cyclization of 1-bromo-1,6-enyne **1.39**.

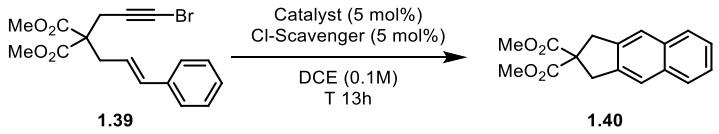


1.39 **1.40**

Entry	Catalyst	Conversion (%)[a]	Yield (%)[a]
1	$PtCl_2$	100	35
2	$GaCl_3$	100	-[b]
3	$InCl_3$	100	-[b]
4	$InBr_3$	100	-[b]
5	AuCl	100	-[b]
6	$AuCl_3$	100	-[b]

[a] Conversion and yield determined by ^{1}H-NMR using mesitylene as internal standard. [b] Decomposition of the starting material.

Table 1.3 Temperature screening for the cyclization of 1-bromo-1,6-enyne **1.39.**



1.39 **1.40**

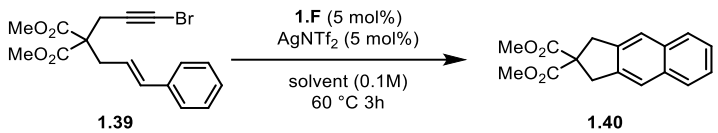
Entry	Catalyst	Cl-scavenger	T (°C)	Conversion (%)[a]	Yield (%)[a]
1	**1.A**	-	50	63	15
2	**1.A**	-	80	85	28
3	**1.H**	-	80	82	23
4	**1.F**	$AgNTf_2$	50	88	32
5[c]	**1.F**	$AgNTf_2$	80	100	**45**

6	$PtCl_2$[b]	-	80	100	35

[a] Conversion and yield determined by ^{1}H-NMR using mesitylene as internal standard.
[b] 10% of $PtCl_2$ was used. [c] Reaction time = 3h.

Different solvents where screened a 60 °C with the best catalytic system (Table 1.4). All of them gave poor conversion and yields.

Table 1.4. Solvent screening for the cyclization of 1-bromo-1,6-enyne **1.39**.



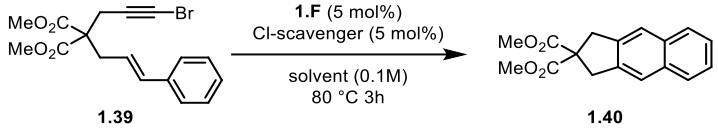
1.39 **1.40**

Entry	solvent	Conversion (%)[a]	Yield (%)[a]
1	DCE	83	31
2	1,4-dioxane	30	<10
3	Toluene	35	<10
4	THF	20	<10
5	Cyclohexane	37	<10
6	EtOAc	20	<10
7	Acetone	20	<10
8	MeOH	90	- [b]

[a] Conversion and yield determined by ^{1}H-NMR using mesitylene as internal standard.
[b] A major unidentified product is formed instead.

Finally, different chloride scavengers were tested (Table 1.5). Thus, $AgSbF_6$, $AgBF_4$, AgOTf and $NaBAr_4^F$ led to complete conversion of the starting material, however the yields were lower compared to $AgNTf_2$ (Table 1.5, entries 1, 3, 4, and 5). With $AgPF_6$, half of the starting material was recovered, and the product was obtained in 25% yield (Table 1.5, entry 2). In presence of AgOAc no reaction was observed, and the starting material was fully recovered (Table 1.5, entry 6).

Table 1.5. Screening of chloride scavengers for the cyclization of 1-bromo-1,6-enyne **1.39**.



1.39 **1.40**

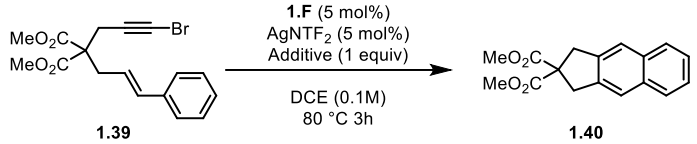
Entry	Cl-scavenger	Conversion (%)[a]	Yield (%)[a]
1	$AgSbF_6$	90	30
2	$AgPF_6$	45	25
3	$AgBF_4$	100	35
4	AgOTf	100	27
5	$NaBAr_4^F$	100	25
6	AgOAc	0	-

[a] Conversion and yield determined by ^{1}H-NMR using mesitylene as internal standard.

It is important to note that product **1.40** was recovered when submitted to the above reaction conditions, excluding its decomposition as a reason for the relatively low yields observed in these experiments.

We also screened a series of additives that could inhibit the decomposition of the starting material. The use of KOtBu as well as 3,5-dichloropyrinde and proton sponge suppresses completely the reactivity (Table 1.6, entries 1,7, and 9). On the other hand, using NaOtBu, NaOAc and 2,6-*tert*buthyl pyridine, very low conversion and poor yields were obtained (Table 1.6, entries 2, 6, and 8). In contrast MgO or K_2CO_3 have no influence on the reaction giving analogous results than in absence of additives. Finally, the yield of the product increased to 68% by using BHT as additive (Table 1.6, entry 10).

Table 1.6. Additive screening for the cyclization of 1-bromo-1,6-enyne **1.39**.

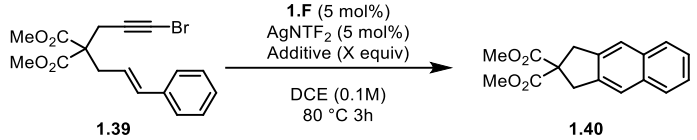


Entry	Additive	Conversion (%)[a]	Yield (%)[a]
1	KO*t*Bu	0	-
2	NaO*t*Bu	30	8
3	MgO	100	50
4	MgO[b]	100	33
5	K_2CO_3[c]	100	50
6	NaOAc	20	10
7	3,5-Cl-Py	0	-
8	2,6-*t*Bu-Py	10	5
9	Proton sponge	0	-
10	BHT	100	68

[a] Conversion and yield determined by ^{1}H-NMR using mesitylene as internal standard. [b] 4 equiv of MgO were used. [c] 10% of K_2CO_3 was used. BHT = 2,6-Di-*tert*-butyl-4-methylphenol.

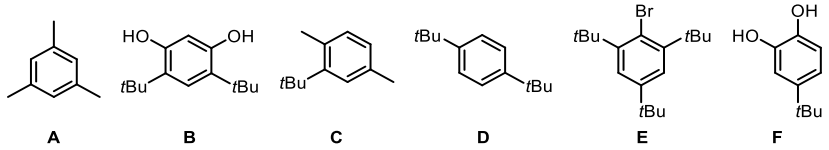
Other known radical scavengers were tested as additives, as well as compounds structurally related with BHT. Interestingly, reducing the amount of BHT or using Na-ascorbate or TEMPO in different amounts was detrimental for the reaction (Table 1.7 entries 1-4). However, addition of other arenes related in structure with BHT led to **1.40** in *ca.* 50% yield (Table 1.7, entries 5-10). Finally, the best results were obtained using 0.7 equiv of BHT at 70 °C, allowing the isolation of **1.40** in 69% yield (Table 1.7, entry 12).

Table 1.7. Second screening of additives for the cyclization of 1-bromo-1,6-enyne **1.39.**



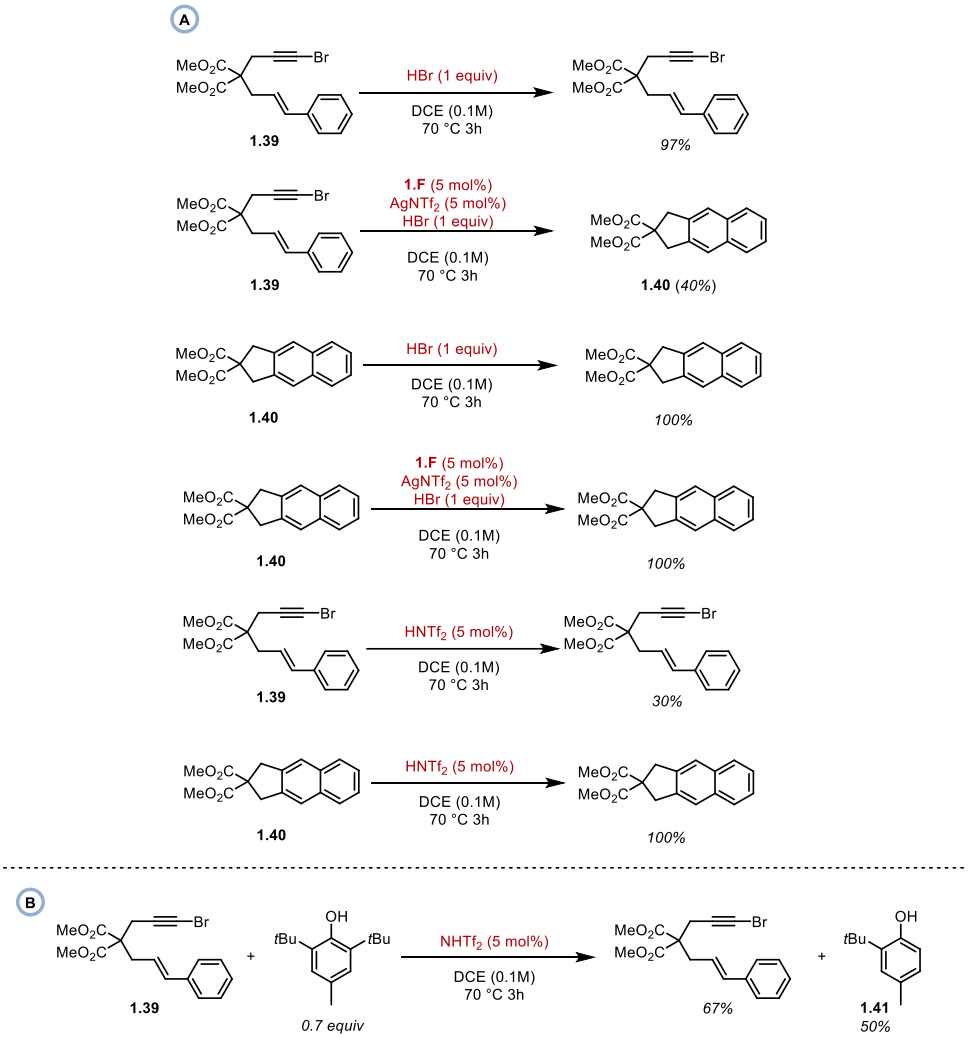
Entry	Additive (equiv)	Conversion (%)[a]	Yield (%)[a]
1	BHT (0.2)	100	60
2	Na-Ascorbate (1)	10	8
3	TEMPO (1)	0	-
4	TEMPO (0.2)	0	-
5	**A** (1)	100	49
6	**B** (1)	100	50
7	**C** (1)	100	49
8	**D** (1)	100	48
9	**E** (1)	100	52
10	**F** (1)	100	47
11	BHT (2)	100	67
12	BHT (0.7)[b]	100	71 (69)

[a] Conversion and yield determined by ^{1}H-NMR using trichloroethylenes as internal standard. Isolated yields in parenthesis. [b] Reaction performed at 70 °C.



The reason why the use of BHT as additive improved the outcome of this reaction was initially unclear. To answer this question, we investigated the possible decomposition of the starting

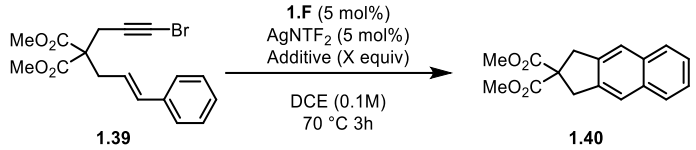
material. Considering that the formation of **1.40** involves the formation of HBr, we treated enyne **1.39** with HBr in DCE at 70 °C, in presence or absence of the catalyst (Scheme 1.17). In the first case, the starting material was unchanged, whereas in the second one the reaction proceeded normally. In the same way, product **1.40** is stable in presence of HBr, in presence or absence of the catalyst. The partial decomposition of silver salts can generate an acidic media as well, in this case generating $HNTf_2$ that could be responsible of the decomposition. Considering this, we treated compound **1.39** with 5% of $HNTf_2$ and, after 3 h at 70 °C, *ca.* 70% of the starting material was decomposed and no formation of the product was observed. Again, **1.40** was stable under these conditions.



Scheme 1.17. A) assessment of the stability of **1.39** and **1.40** in presence of acids generated in the reaction media. B) Effect of BHT on the decomposition of **1.39** in presence of $HNTf_2$.

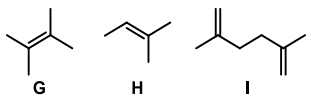
Under the same conditions, but with the addition of 0.7 equiv of BHT, **1.39** was recovered in 67% yield after 3 h together with **1.41** resulting from the protodealkylation of BHT (Scheme 1.17b). Since simple alkenes are known to act as acid traps in reaction such as the Pinnick oxidation, we also tested the reaction in the presence of alkenes **G-I**. Using 2-methyl-2-butene (**H**), we obtained analogous results to those observed before with BHT, although a larger excess of alkene and longer reaction times are required (Table 1.8).

Table 1.8 Screening of simple alkenes as mild acid quenchers.



Entry	Additive (equiv)	Conversion (%)[a]	Yield (%)[a]
1	**G** (30)	75	44
2	**H** (30)	90	64
3	**I** (30)	24	14
4	**H** (100)	100	56
5	**H** (20)	72	58
6	**H** (10)	100	69[b]

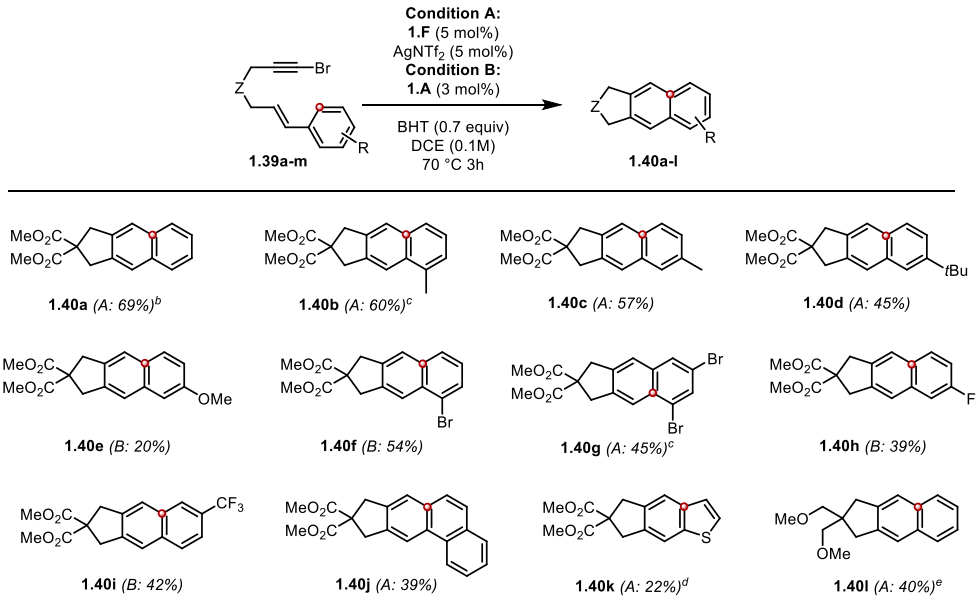
[a] Conversion and yield determined by ^{1}H-NMR using mesitylene as internal standard.
[b] reaction time 14 h.



Having defined the optimal conditions for the reaction, we explored the scope of the cyclization on 1-bromo-1,6-enynes **1.39** into the corresponding naphthalenes **1.40** (Table 1.9). First, we demonstrated that both *E* and *Z* enynes (**1.39a** and **1.39b**) can form efficiently the same naphthalene product. However, we discovered that the reaction is very sensitive to the substitution pattern on the aromatic ring. Although the cyclization of enynes with a methyl either in *ortho* or *para* position of the aryl (**1.39c-d**) occurs giving the products **1.40c-d** in 60% and 57% yields, respectively, increasing the electron density on the ring led to a drop in yields for

compounds **1.40e-g** that were obtained in yields ranging from 20 to 45%. Under the standard reaction conditions, enynes with electron poor aromatic rings gave poor conversions. The use of 3 mol% **1.A** instead of the **1.F**/$AgNTf_2$ system led to better results (conditions B in Table 1.9). Under these new conditions, a series of electron-withdrawing groups can be tolerated on the aromatic ring with yields ranging from 39 to 54% (**1.40g-j**). Also, naphthyl-substituted enyne **1.39k** under conditions A led to the desired product **1.40k** in 39% yield. Thiophene substituted enyne **1.39l** was cyclized under conditions A in poor yield (22%). Finally, the malonate spacer can be replaced for methyl-protected alcohols in enyne **1.39m** leading to **1.40m** in 40% yield.

Table 1.9. Scope of the cyclization of 1-bromo-1,6-enynes[a].



[a] Isolated yields. [b] **1.40a** was obtained in 70% yield starting from **1.39b**. [c] 75% pure. [d] yield corrected on conversion. [e] reaction time: 14h

Substrates that failed or gave less satisfactory results in this gold(I) cyclization are shown in Figure 1.2. In the case of **1.39n**, two regioisomers were formed in 2:1 ratio and in poor yield, being favored the attack of the carbon *para*- to the methoxy (red labelled carbon). The reaction of enyne **1.39o-q** led to a complex mixture of products. In contrast, enyne **1.39s** with an *ortho*-methoxy group on the aromatic ring was recovered unchanged. 1-Iodo-1,6-enyne **1.39t** was found to be light sensitive, while when covering the reaction vial with aluminum foil to avoid decomposition, it was fully recovered.

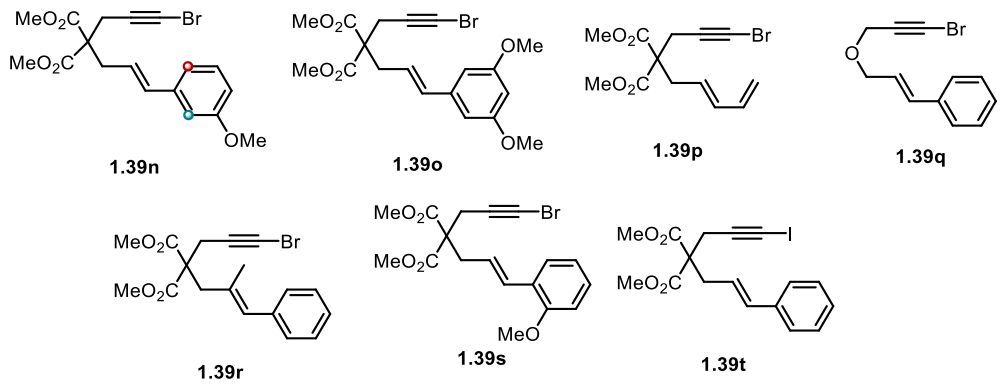


Figure 1.2. Other enynes tested in the gold(I) catalyzed cyclization.

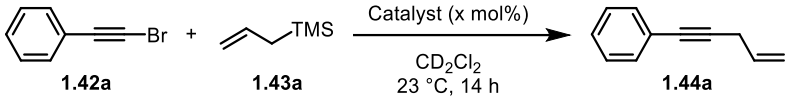
Intermolecular Reaction of Bromoalkynes with Allylsilanes

We also found that (bromoethynyl)benzene **1.42a** reacts with allyltrimethylsilane **1.43a** in presence of cationic gold(I) complexes in a formal cross-coupling reaction with loss of TMSBr forming the skipped enyne **1.44a**. Upon optimization,[82] we found that both complex **1.C** and $InBr_3$ can catalyze the reaction giving **1.44a** at 23 °C after 14 h in 77% and 81% yield, respectively. (Table 1.10, entries 7 and 11).

We also tested different substitution patterns on both substrates.[82] With chloroalkyne **1.42b** product **1.44a** was formed in good yields, although the reaction proceeded slowly (Table 1.11, entry 2). In contrast, iodoalkyne **1.42c** failed in this reaction (Table 1.11, entry 3). We screened also different allyl derivatives and we found that also allyltriphenylsilane **1.43d** reacted with **1.42a** giving **1.44a** in 66% yield (Table 1.11, entry 6). However, for sake of atom economy, we continued in our studies with allyltrimethylsilanes. The reaction of phenylacetylene **1.42e** with **1.43a** led to the exclusive formation of cyclobutene **1.45** *via* [2+2] cycloaddition.

82 Experiments performed by Dr. M. Elena de Orbe.

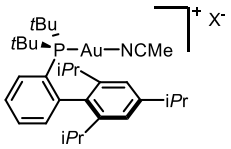
Table 1.10. Reaction of bromoalkyne **1.42a** with allylsilane **1.43a** to form 1,4-enyne **1.44a**.



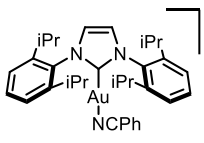
1.42a **1.43a** **1.44a**

Entry	Catalyst (mol%)	**1.42a:1.43a**	Yield (%)[a]
1	**1.B** (5)	1:1	13 (7)
2	**1.C** (3)	1:1	50
3	**1.K** (5)	1:1	14
4	**1.L** (5)	1:1	traces
5	AuCl (5)	1:1	0
6	$AuCl_3$(5)	1:1	0
7	**1.C** (3)	1:2	(77)
8	$PtCl_2$ (3)	1:1	traces
9	$GaCl_3$ (3)	1:1	28-45[b]
10	$InBr_3$ (3)	1:1	50-55[b]
11	$InBr_3$ (3)	1:2	(81)

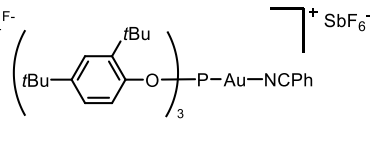
[a] Yields determined by ^{1}H-NMR using mesitylene as internal standard. Isolated yields in parentheses. [b] Range of yields obtained in different runs.



1.B: X = SbF_6
1.C: X = BAr_4^F

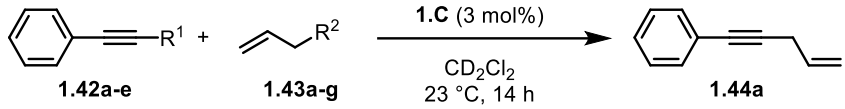


1.K



1.L

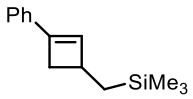
Table 1.11. Optimization of the substitution pattern of the Substrates to form **1.44a**[a].



1.42a-e **1.43a-g** **1.44a**

Entry	**1.42a-e**	R^1	**1.43a-g**	R^2	Yield (%)[b]
1	**1.42a**	Br	**1.43a**	$SiMe_3$	(77)
2	**1.42b**	Cl	**1.43a**	$SiMe_3$	68[c]
3	**1.42c**	I	**1.43a**	$SiMe_3$	9
4	**1.42a**	Br	**1.43b**	$Si(OMe)_3$	21
5	**1.42a**	Br	**1.43c**	$Si(iPr)_3$	23
6	**1.42a**	Br	**1.43d**	$SiPh_3$	66
7	**1.42a**	Br	**1.43e**	Bpin	16
8	**1.42a**	Br	**1.43f**	$Sn(nBu)_3$	14
9	**1.42d**	SiMe3	**1.43g**	Br	-[d]
10	**1.42e**	H	**1.43a**	$SiMe_3$	-[e,f]

[a] Substrates **1.42**:**1.43** in a 1:2 ratio. [b] Yields determined by ^{1}H-NMR using mesitylene as internal standard. Isolated yields in parentheses. [c] Reaction time was 48 h. [d] No reaction. [e] Product **1.45** was formed instead. [f] Reaction at 50 °C.



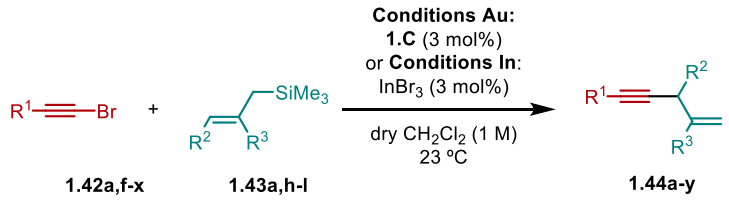
1.45

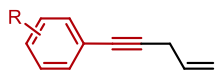
With the two sets of conditions in hands, we then studied the scope of the formation of 1,4-enyne under both conditons.[82] Substituents on the aromatic ring of the bromoalkyne were well tolerated as demonstrated by the synthesis of skipped enynes **1.44a-l** with yields ranging from 40% to 96% for gold(I) and from 43% to 92% in the indium-catalyzed reaction. Polyaromatics and heteroaromatic rings at the alkyne led to lower yields compared to phenylacetylene (Table 1.12, **1.44n-s**). The aromatic ring can be substituted by a simple alkene to form **1.44l** in moderate

yields (Au: 31%, In: 21%). Furthermore, 1,3-di(pent-4-en-1-yn-1-yl)benzene **1.44y** is formed in a 2-fold formal cross-coupling reaction starting from 1,3-bis(bromoethynyl)benzene (**1.42x**) in 44% and 66% yield with **1.C** and $InBr_3$ respectively.

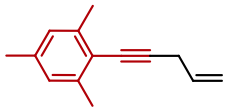
Regarding the allylsilane partner, different substituents in position 2 can be accommodated, furnishing the desired skipped enyne **1.44t-v** in moderate to good yields using gold. However, the indium-catalyzed synthesis of **1.44u,v** failed. Interestingly, the reaction of 3-substituted allylsilanes led exclusively to 1,4-enynes **1.44w,x** by reaction at the γ-position of the allylsilane.

Table 1.12. Scope of the gold(I)- or indium catalyzed synthesis of skipped enyne **1.44a-y**[a]



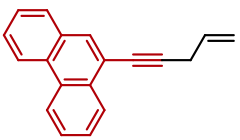


1.44a: R = H (**Au**: 77%, **In**: 81%)
1.44b: R = *p*-OMe (**Au**: 67%, **In**: 64%)
1.44c: R = *p*-Ph (**Au**: 62%, **In**: 80%)
1.44d: R = *p*-*t*Bu (**Au**: 71%, **In**: 53%)
1.44e: R = *p*-Br (**Au**[b]: 60%. **In**[b]: 73%)
1.44f: R = *p*-CF_3 (**Au**[b]: 62%, **In**[b]: 74%)
1.44g: R = *o*-Me (**Au**[d]: 77%, **In**: 70%)
1.44h: R = *o*-Et (**Au**[e]: 40%, **In**: 53%)
1.44i: R = *o*-F (**Au**: 50%, **In**: 78%)
1.44j: R = *m*-OH (**Au**[c]: 63%, **In**[c]: 56%)
1.44k: R = *m*-Cl (**Au**[b]: 45%, **In**[b]: 43%)

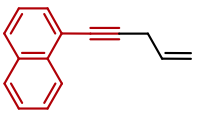


1.44l (**Au**: 96%, **In**: 92%)

1.44m (**Au**: 31%, In: 21%)

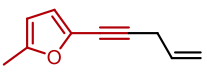


1.44n (**Au**: 61%, **In**: 55%)

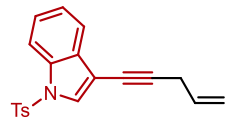


1.44o (**Au**: 55%, **In**: 65%)

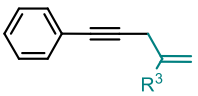
1.44p: X = S (**Au**: 48%, **In**: 44%)
1.44q: X = O (**Au**: 23 %, **In**: 20 %)



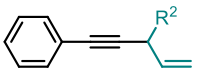
1.d4r (**Au**: 31%, **In**: 22%)



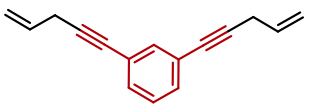
1.44s (**Au**: 87%, **In**: 19%)



1.44t: R = Me (**Au**: 54%, **In**: 54%)
1.44u: R = Br (**Au**[b]: 64%, **In**: 0%)
1.44v: R = CH_2Cl (**Au**: 48%, **In**: 0%)



1.44w: R = Et (**Au**[b]: 47 %, **In**[b]: 73%)
1.44x: R = Ph (**Au**: 35 %, **In**: 55%)

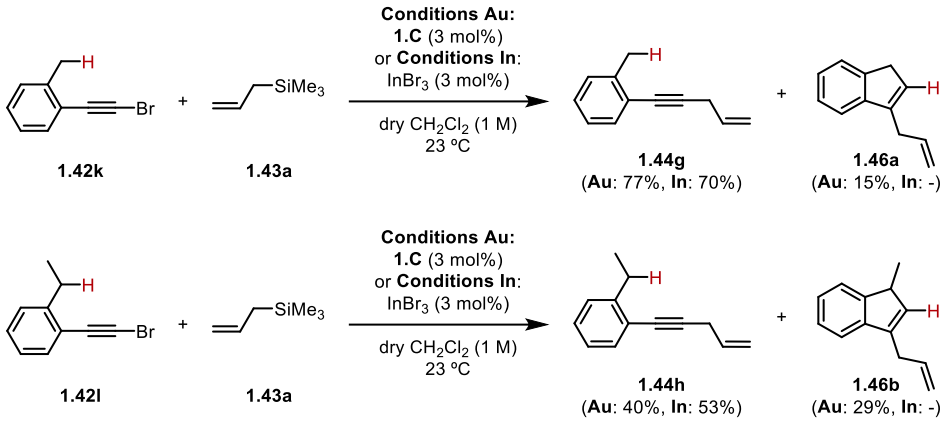


1.44y (**Au**: 44%, **In**: 63%)

[a] Isolated yields. [b] Reaction at 50 ºC. [c] Yields determined by ^{1}H-NMR using mesitylene as internal standard.

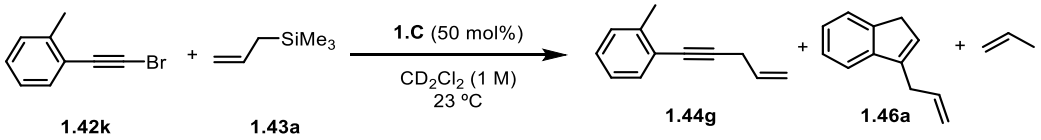
It is important to note that in the reaction of *o*-methyl or *o*-ethyl substituted (bromoethynyl)benzenes **1.42k** and **1.42l**, 3-allylindenes **1.46a** and **1.46b** were isolated in poor

yields, together with the expected enynes when **1.C** was used as catalyst (Scheme 1.18). In contrast, **1.46a** and **1.46b** were not detected in the reaction with $InBr_3$.



Scheme 1.18. Gold(I)-catalyzed reaction of ortho-substituted bromoalkynes **1.42k** and **1.42l** with allylsilane **1.43a**. (**1.42**/**1.43a** in a 1:2 ratio).

By monitoring the reaction by ^{1}H-NMR, we observed the formation of both **1.44g** and **1.46a** (Figure 1.3). In addition, we found that allylsilane **1.43a** partially decomposes into propene after the addition of the gold(I) catalyst, although this decomposition stops as the desired gold(I) catalyzed reaction starts and the amount of allylsilane decreases linearly with the formations on the product. The formation of **1.46a-b** is related to the gold(I)-catalyzed synthesis of 2-iodoindene via C-H insertion shown in Scheme 1.7 and suggests the involvement of a gold(I) vinylidene intermediate in the reaction.



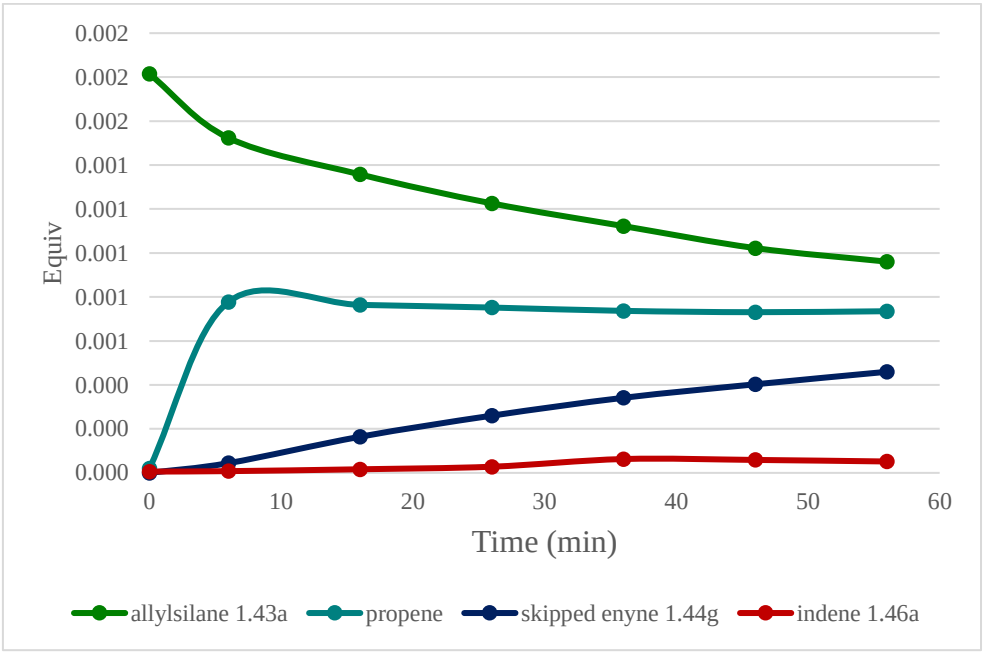


Figure 1.3. Evolution of the gold(I) catalyzed reaction of **1.42k** with **1.43a** for the formation of **1.44g** and **1.46a**. Substrates **1.42k:1.43a** in a 1:2 ratio. Yields determined by ^{1}H-NMR using bromo-mesitylene as internal standard.

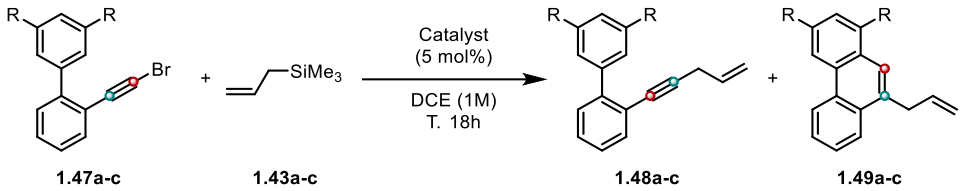
Allylation/Hydroarylation Sequence of Bromoalkynes with Allylsilanes[83]

Inspired by the C-H insertion observed in *o*-substituted (bromoethynyl)benzenes leading to indenes **1.46a-b**, we envisioned that other functionalities could be involved in cascade reactions after the initial allylation of the bromoalkyne. In this context, we expected that an aryl substituent in *ortho* position would be involved in an allylation/hydroarylation cascade. To test our hypothesis, we submitted biphenyl derivative **1.47a** to the standard reaction conditions and **1.49a** was obtained in 33% yield. However, skipped enyne **1.48a** was obtained in this reaction as the major product (Table 1.13, entry 1). The indium-catalyzed reaction gave **1.48a** in 68% yield as single product.

By heating up to 75 °in DCE, a mixture of the 1,4-enyne **1.48a** and cyclized product **1.49a** were obtained in ratio 2:1 in moderate to good yields (Table 1.13, entries 3 and 4).

83 Experiments done in collaboration with Dr. M.Elena de Orbe and Dr. Ophelie Quinonero

Table 1.13 Reaction of bromoalkynes **1.47a-c** with allysilane **1.43a**. [a]



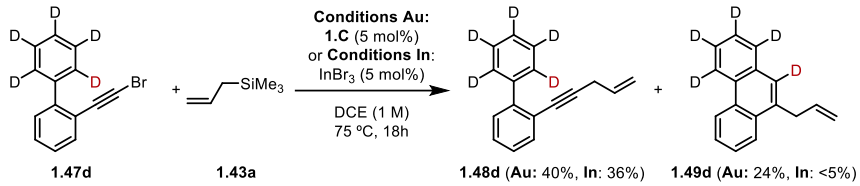
Entry	**1.47**	R	Catalyst	T (°C)	**1.48** (%)[b]	**1.49** (%)[b]
1	**1.47a**	H	**1.C**	23	58	33
2	**1.47a**	H	$InBr_3$	23	68	0
3	**1.47a**	H	**1.C**	75	53	23
4	**1.47a**	H	$InBr_3$	75	32	17
5	**1.47b**	Me	**1.C**	23	58	16
6	**1.47b**	Me	$InBr_3$	23	24	0
7	**1.47b**	Me	**1.C**	75	41	26
8	**1.47b**	Me	$InBr_3$	75	21	0
9	**1.47c**	CF_3	**1.C**	23	10	0
10	**1.47c**	CF_3	$InBr_3$	23	16	0
11	**1.47c**	CF_3	**1.C**	75	85	0
12	**1.47c**	CF_3	$InBr_3$	75	90	0

[a] **1.47a-c:1.43a** in 1:2 ratio. [b] Isolated yields

In order to distinguish the two aromatic rings and hence be able to define the position of the allyl chain, we prepared also *o*-alkylbiaryls **1.47b** and **1.47c** bearing two methyl and two trifluoromethyl groups, respectively. In the case of **1.47b**, the gold catalyzed reaction delivered a mixture of the skipped enyne **1.48b** and the allyl phenanthrene **1.49b** both at room temperature and at 75 °C (Table 1.13, entries 5 and 7). The reaction catalyzed by $InBr_3$ gave only **1.48b** in

poor yields (Table 1.13, entries 6 and 8). On the other hand, substrate **1.47c** substituted with CF_3 groups gave exclusively 1,4-enyne **1.48c** (Table 1.13, entries 9-12)

According to these results, allyl-phenanthrene **1.49b** is not the product of direct hydroarylation of **1.48b** but is the product of a formal 1,2-shift of the allyl chain. Additionally, in the reaction of deuterated bromoalkyne **1.47d**, the deuterium remains on position 10 in phenanthrene **1.49d** (Scheme 1.19)



Scheme 1.19 reaction of bromoalkyne **1.47d** with trimethylallylsilane.

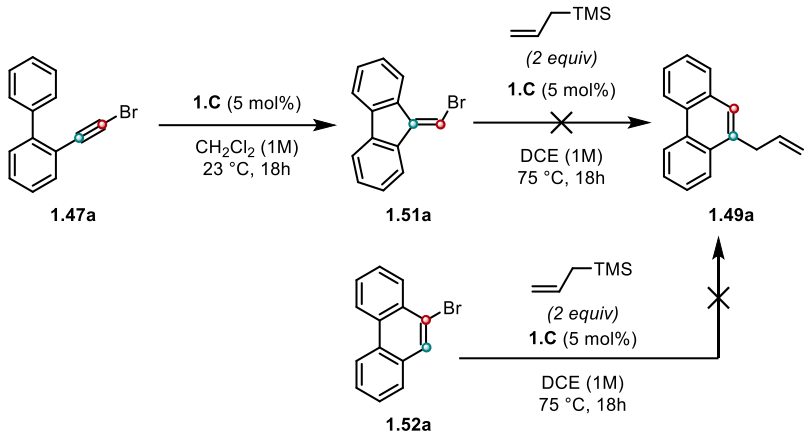
We also investigated the cyclization of substrates **1.48a-c** to form phenanthrenes (Table 1.14). Using **1.C** as catalyst, **1.48a** forms the hydroarylation product **1.50a** (Table 1.14, entries 1-3), which in this case is indistinguishable from **1.49a**. The more electron-rich **1.48b** delivers quantitatively phenanthrene **1.50b**, a regioisomer of **1.49b**. As expected, **1.48c** did not undergo hydroarylation under these conditions.

Table 1.14. hydroarylation of **1.48a-c** to form allylphenanthrenes **1.50a-c**.

Entry	**1.47**	R	T (°C)	**1.48:1.50**[a]
1	**1.48a**	H	75	2.5:1
2	**1.48a**	H	100	1:1.7
3	**1.48a**	H	120	1:1.7
4	**1.48b**	Me	100	0:1 (quant. yield)[b]
5	**1.48c**	CF_3	100	1:0 (no reaction)

[a] Determined by ^{1}H-NMR. [b] Isolated yield.

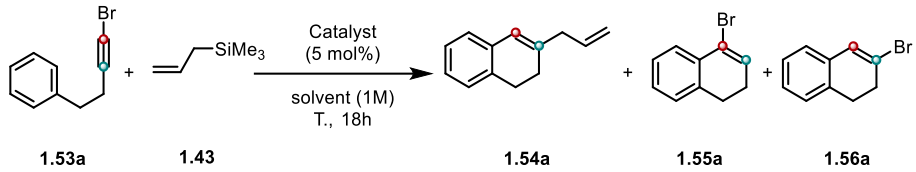
Once we have demonstrated that 1,4-enynes **1.48** are not precursor of phenanthrenes **1.49**, we evaluated the possibility of an initial hydroarylation of **1.47** followed by an intermolecular allylation with **1.43a** to form allyl phenanthrene **1.50**. Thus, in the absence of allyltrimethylsilane **1.43a**, **1.47a** undergoes 5-*exo*-hydroarylation even at room temperature forming fluorene **1.51**, while decomposition was observed when the reaction is carried out at 75 °C (Scheme 1.20). Treatment **1.51a** with allyltrimethylsilane under the optimized reaction conditions failed to give any phenanthrene **1.49a**. In the same way, commercially available bromo phenanthrene **1.52a** was fully recovered after the reaction with allylsilane **1.43a**.



Scheme 1.20. Studies on the formation of allyl phenantherene **1.49a**.

We also aimed to investigate the role of the spacer aromatic ring by replacing it in **1.53a** with an aliphatic chain. The reaction of **1.53a** with allylsilane **1.43a** proceeded slowly at room temperature using **1.C** as catalyst giving rise to 1,2-dihydronaphtalene **1.54a** in 41% yield, together with unreacted starting material (Table 1.15, entry 1). To our surprise, the expected skipped enyne was not observed in this reaction. Product **1.54a** is the result of a formal 1,2-allyl shift from the product of direct hydroarylation of the skipped enyne. Rising the temperature to 75 °C led to full conversion in 18 h and **1.54a** was isolated in 64% yield (Table 1.15, entry 2). In addition, a 6:1 mixture of 4-bromo- and 3-bromo-dihydronaphthalene (**1.55a** and **1.56a** respectively) was isolated in 15% yield. In contrast, $InBr_3$ led to **1.54a** in poor yield (Table 1.15, entry 3,4).

Table 1.15. Reaction of bromoalkyne **1.53a** with allylsilane **1.43a**[a].



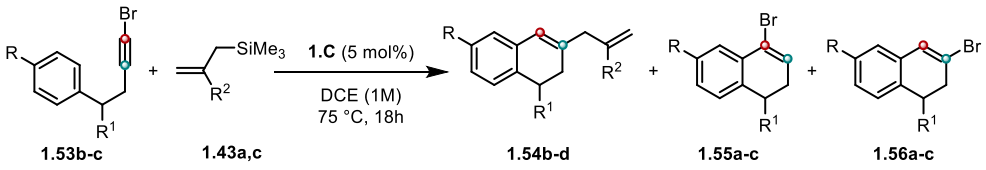
1.53a **1.43** **1.54a** **1.55a** **1.56a**

Entry	T (°C)	solv	cat	**1.53a** (%)[b]	**1.54a** (%)[b]	**1.55a:1.56a** (%)[b]
1	23	CH_2Cl_2	**1.C**	19	41[c]	-
2	75	DCE	**1.C**	-	64	15% (6:1)
3	50	CH_2Cl_2	$InBr_3$	61	4	-
4	75	DCE	$InBr_3$	85[d]	11[d]	-

[a] Substrates **1.53a**:**1.43a** in a 1:2 ratio. [b] Isolated yields. [c] Reaction time 10d. [d] Yields determined by ^{1}H-NMR using mesitylene as internal standard.

The reaction is very sensitive to the substitution pattern on both the bromoalkyne and the allylsilane. Substrates with a methyl group either in *para*-position on the aromatic ring or on the aliphatic chain led to an increase of the direct hydroarylation of bromoalkynes **1.53b** and **1.53c** respectively (Table 1.16, entries 1, 2). With 3-substituted allyltrimethylsilane **1.43c**, the desired product was obtained in 13% yield, while **1.55a** and **1.56a** were isolated as 3:1 mixture in 61% yield (Table 1.16, Entry 3).

Table 1.16. Reaction of bromoalkynes **1.53b-c** with allylsilane **1.43a,c**.[a]



1.53b-c **1.43a,c** **1.54b-d** **1.55a-c** **1.56a-c**

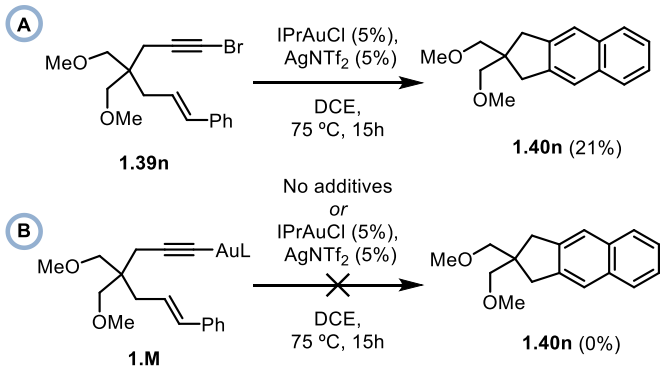
Entry	1.53	R, R^1	**1.43**	R^2	**1.54** (%)[b]	**1.55:1.56** (ratio)[b]
1	1.53b	Me, H	**1.43a**	H	20[c]	53% (1:0)[c]
2	1.53c	H, Me	**1.43a**	H	42	36% (5:1)
3	1.53a	H, H	**1.43c**	CH_2Cl	13	61% (3:1)

[a] Substrates **1.53b-c**:**1.43a,c** in a 1:2 ratio. [b] Isolated yields. [c] Yields determined by ^{1}H-NMR using mesitylene as internal standard.

Mechanism of the Gold(I) Catalyzed Reaction of Bromoalkynes.

Experimental mechanistic studies

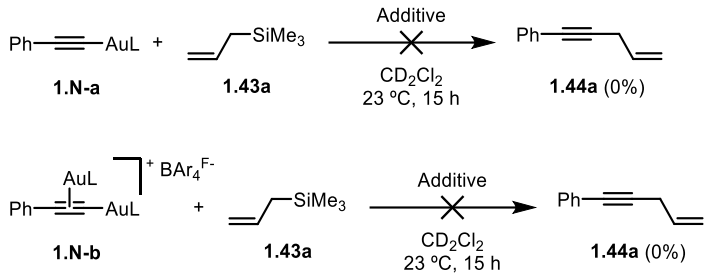
It has been proposed in some cases that gold(I)-catalyzed reactions of haloalkynes start with the displacement of the halogen by the gold complex to form a σ-gold acetylide complex, which is the species that initiates the reaction acting as a nucleophile.[84] In the same way, σ/π-digold(I) alkyne complexes could be formed and be competent in the reaction.[85] To prove if this is the case for either the cyclization of 1-bromo-1,6-enynes or for the intermolecular reactions of (bromoethynyl)benzene, we prepared σ-gold acetylide complexes **1.M**.[86] For practical reasons, IPr ligand was used in **1.M** instead of IMes, so we tested the reaction of **1.39n** catalyzed by the IPrAuCl/$AgNTf_2$ system and the desired product **1.40n** was obtained in 21% yield. (Scheme 1.21a). Stirring complex **1.M** at 75 °C overnight in presence or in the absence of **1.F** and $AgNTf_2$ did not lead to the formation of **1.40n** (Scheme 1.21).



Scheme 1.21 A) Reaction of **1.39n** to form **1.40n** using IPrAuCl as Precatalyst. B) Experiments with σ–gold acetylide **1.M.** L = IPr.

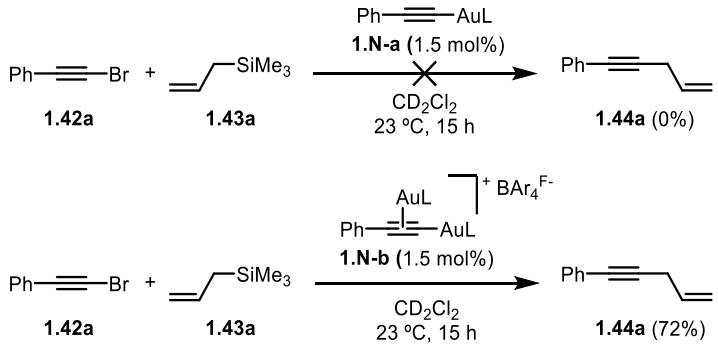
In the same way, stoichiometric experiments of complexes **1.N-a-b** with allylsilane **1.43a** with several additives revealed that 1,4-enyne **1.44a** is not formed starting from the σ-gold acetylide complex (Scheme 1.22). When **1.N-b** was used as catalyst in the reaction of **1.42a** and **1.43a**, the desired product was formed in 72% yield, probably because of a ligand exchanged occurring on **1.N-b** that initiate the reaction. As expected, **1.N-a** is not an active catalyst for the reaction (Scheme 1.23).

84 See as example Ref 77
85 P. Nösel, T. Lauterbach, M. Rudolph, F. Rominger, A. S. K. Hashmi, *Chem. Eur. J.* **2013**, *19*, 8634–8641.
86 Prepared adapting the procedure reported in S. Ferrer, A. M. Echavarren, *Organometallics* **2018**, *37*, 781–786.



Additive: **1.C** (5 mol%), or TMSBr (1 equiv), or TMSBr (1 equiv)/ **1.C** (5 mol%), or (nBu)$_4$NBr (1 equiv), or LiBr (1 equiv)

Scheme 1.22. Stoichiometric experiments with σ-gold acetylide complex **1.N-a** and σ/π-digold complex **1.N-b.** L = *t*BuXPhos.

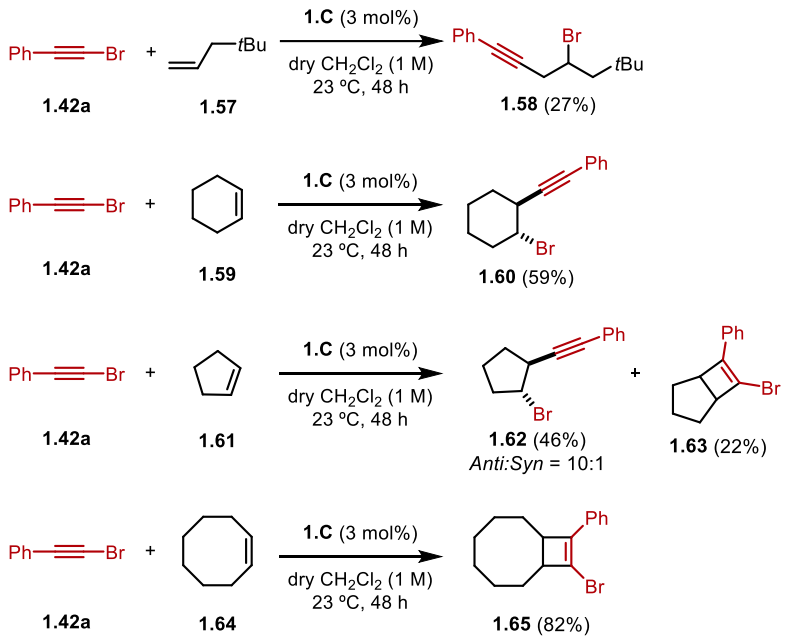


Scheme 1.23 Experiments with σ-gold acetylide complex **1.N-a** and σ/π-digold complex **1.N-b** as catalysts for the reaction of **1.42a** and **1.43a.** L = *t*BuXPhos.

In this way, we demonstrated that even if σ-gold complex or σ/π-digold complexes are formed in the reaction, they do not take part in the formation of the 1,4-enynes.

Reaction with simple alkenes

We decided to extend the reaction to simple alkenes by first replacing the trimethylsilyl group in **1.43** for a *tert*-butyl group. Surprisingly, in presence of catalyst **1.C**, alkene **1.57** undergoes 1,2-bromoalkynylation with **1.42a** to form **1.58** in moderate yield. No reaction was observed with $InBr_3$ (Scheme 1.24).



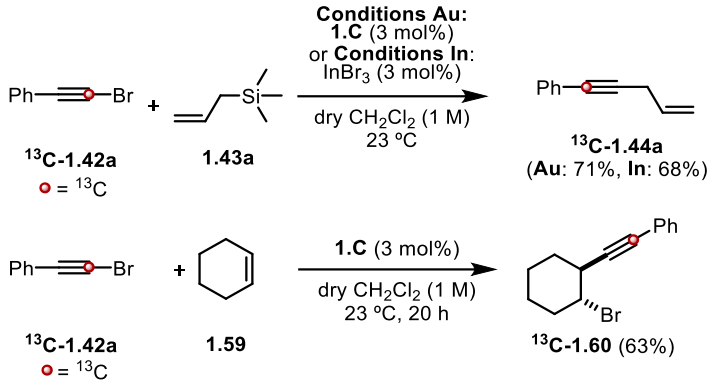
Scheme 1.24. Gold(I)-catalyzed 1,2-bromoalkynylation of alkenes.

Analogous homopropargyl bromides were formed when **1.42a** reacted with cyclohexene and cyclopentene (Scheme 1.24). The bromoalkynylation occurs diastereoselectively giving the *anti*-product exclusively in the case of **1.59**, while **1.61** led to 10:1 mixture of *anti*- and -*syn*-isomers **1.62**, along with the product of [2+2] cycloaddition **1.63** as minor product. Cyclooctene gave rise selectively to the product of [2+2] cycloaddition **1.65** in good yield.[87]

^{13}C-labelling experiments

To get additional insight into the reaction mechanism, we prepared ^{13}C-labelled bromoalkyne **^{13}C-1.42a**. Reaction of **^{13}C-1.42a** with **1.43a** under the standard reaction conditions with gold and indium led exclusively to 1,4-enyne **^{13}C-1.44**. Remarkably, the labelled carbon in the product is shifted from the β- to the α–position to the phenyl ring, which indicates that a 1,2-aryl migration has taken place during the reaction. The same shift was observed in the gold(I)-catalyzed formation of **^{13}C-1.60** from **^{13}C-1.42a** and cyclohexene, which demonstrates that the coupling of allylsilanes and the 1,2-bromoalkynylation take place through the same mechanistic scenario (Scheme 1.25).

87 A general gold(I)-catalyzed 1,2-haoalkynylation of was later reported: P. D. García-Fernández, C. Izquierdo, J. Iglesias-Sigüenza, E. Díez, R. Fernández, J. M. Lassaletta, *Chem. Eur. J.* **2020**, *26*, 629–633.

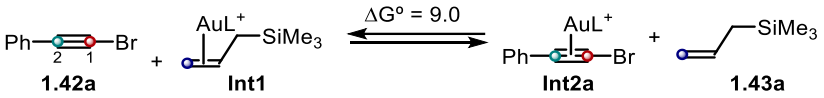


Scheme 1.25. ^{13}C-labelling experiments.

Computational mechanistic studies[88]

With these experiments in hand, we carried out DFT calculations[89] to have a better understanding of the mechanisms of formation of skipped enynes **1.44** from bromoalkynes **1.42** and allylsilanes **1.43** and the hydroarylation of **1.47** to form **1.49.** In addition to this, we aimed also to have a better insight into the mechanism of the cyclization of 1-bromo-1,6-enynes **1.39**.

As presented in the General Introduction, usually gold(I) catalyzed reaction of alkynes with alkenes start with the formation of a cyclopropyl gold(I) carbene intermediate. However, for haloalkynes, the 1,2-halogen migration to form a god(I)-vinylidenes could compete with this event. Both reactions will start with the formation of (η^2-alkyne)gold(I) complex **Int2a** by ligand exchange from the more stable **Int1** (Scheme 1.26).

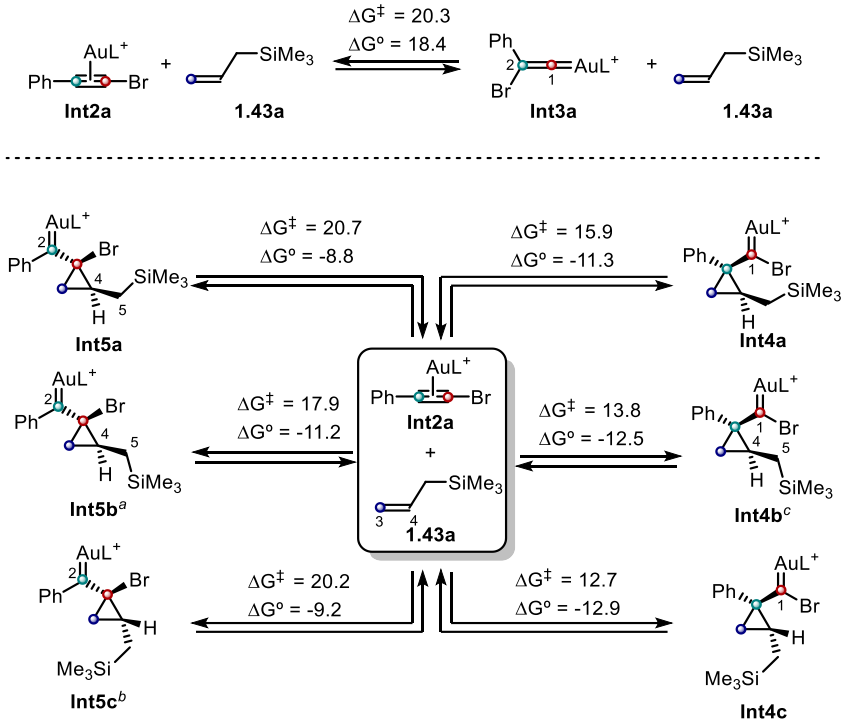


Scheme 1.26. Initial associative ligand exchange to form **Int2a** (L = PMe_3. Free energies in kcal/mol).

The direct isomerization of **Int2a** into the gold(I)-vinylidene **Int3a** requires a high activation energy ($\Delta G^{\ddagger}$ = 20.3, ΔG^{o} = 18.4 kcal/mol) (Scheme 1.27, top). On the other hand, the double bond of allylsilane **1.43a** can attack carbon C2 on the alkyne to form cyclopropyl gold(I) carbenes **Int.4a-c** with lower energy barriers ($\Delta G^{\ddagger}$ = 12.7-15.9 kcal/mol) (Scheme 1.27, bottom). As expected, the attack on carbon C1 to form **Int5a-c,** where the carbene is located close to the phenyl is less favored ($\Delta G^{\ddagger}$ = 17.9-20.7 kcal/mol). This is consistent with the general

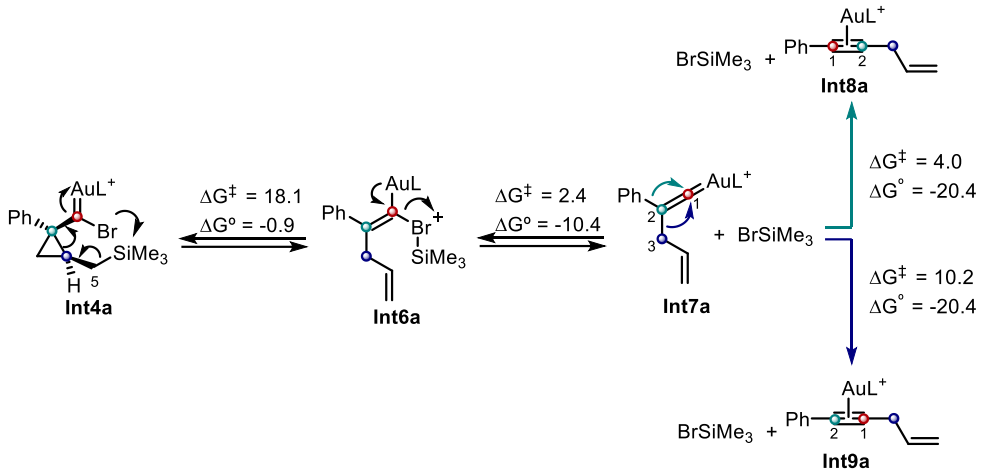
88 Study performed in collaboration with Dr. M. Elena de Orbe.
89 See the computational methods in the Experimental Part

trend observed in the intermolecular reaction of alkynes with alkenes, where the carbene is formed on the carbon bounded to the more electron-withdrawing substituent.



Scheme 1.27 Formation of gold(I) vinylidene **Int3a** (top) and formation of cyclopropyl gold(I) carbene **Int4a-c** and **Int5a-c** (bottom). (L = PMe3. Free energies in kcal/mol). [a] Transformation of **Int5b** into **Int5a** via C4−C5 bond rotation: $\Delta G^{\ddagger}$ = 5.1, ΔG^{o} = 2.4. [b] Transformation of **Int5c** into **Int5a** via C4−C5 bond rotation: $\Delta G^{\ddagger}$ = 6.2, ΔG^{o} = 0.2. [c] Transformation of **Int4b** into **Int4a** via C4−C5 bond rotation: $\Delta G^{\ddagger}$ = 8.7, ΔG^{o} = 1.2).

Intermediates **Int4a-c** are very similar in energy, so for the rest of the mechanistic analysis we will focus on the reaction pathways resulting from **Int4a**. In fact, this intermediate has the right conformation to undergo elimination of TMS-Br and consequent formation of gold(I) vinylidene **Int7a** passing through **Int6a** (Scheme 1.28). **Int7a** can then undergo exothermic 1,2-phenyl migration ($\Delta G^{\ddagger}$ = 4.0 kcal/mol) to form the skipped enyne coordinated to gold(I) through the alkyne (**Int8a**), while the alternative 1,2-alkyl migration of carbon C3 requires higher energy ($\Delta G^{\ddagger}$ = 10.20 kcal/mol). The two η^2 coordinate enynes (**Int8a** and **Int9a**) differ just for the relative position of C1 and C2 and the lower barrier to access **Int8a** is in line with the observed 1,2-shift in the ^{13}C-labelling experiments (Scheme 1.25). However, the preliminary elimination of TMS-Br will not allow the experimentally observed 1,2-bromoalkynylation of alkenes reported in Scheme 1.24. Therefore, despite being energetically feasible, the reaction must follow another pathway.



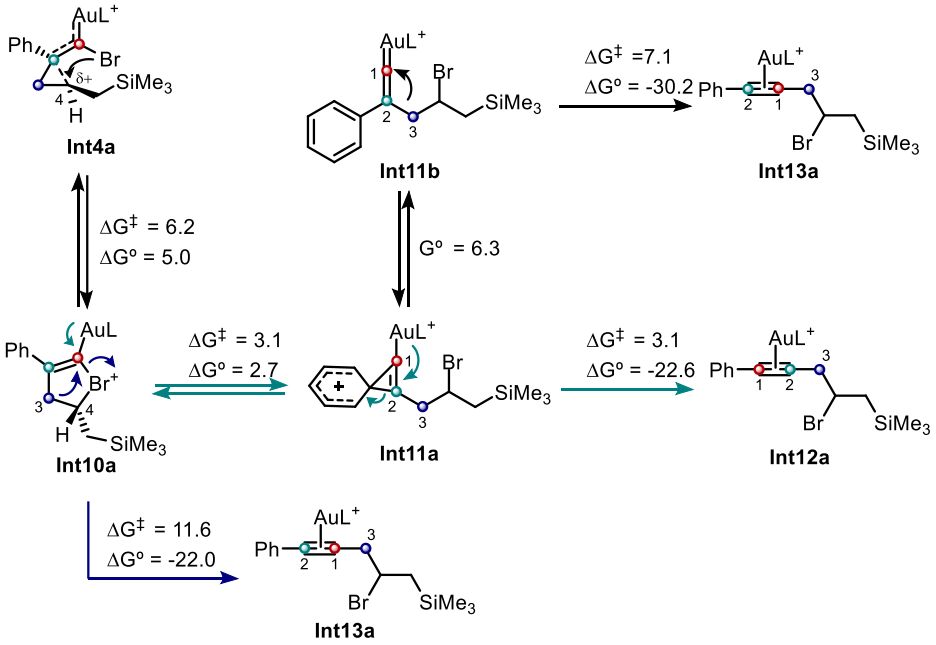
Scheme 1.28. Elimination of TMS-Br to form gold(I)-vinylidene **Int7a** and its evolution in skipped enynes **Int8a** and **Int9a** (L = PMe3. Free energies in kcal/mol).

The bromide substituent in **Int4a** can attack carbon C4, which has a partial positive charge stabilized by silicon, leading to the formation of an unprecedented bromonium cyclic intermediate **Int10a** with inversion of configuration at C4 ($\Delta G^{\ddagger}$ = 6.2, ΔG° = 5.0 kcal/mol) (Scheme 1.29).[90] The low energy barrier opening of the cyclic intermediate follows leading to **Int11a**, a vinylidenephenonium intermediate, which shows bond distances between the *ipso*-carbon an C2 and C1 of 1.51 Å and 1.67 Å, respectively. This intermediate can be converted into vinylidene **Int11b** upon rotation of the C2-Ph bond. However, **Int11b** lays 6.8 kcal/mol above **Int11a**.

Vinylidenearenium cations like **Int11a** are known to rearrange *via* 1,2-aryl migration.[91] Thus, in our case, the exothermic 1,2-phenylmigration from **Int11a** restores the triple bond ($\Delta G^{\ddagger}$ = 3.1, ΔG° = -22.6 kcal/mol) with the substituents on C1 and C2 inverted respect to the starting material. The alternative 1,2-alkylmigration of C3 through the less stable linear vinylidene **Int11b** requires a higher 13.4 kcal/mol barrier to form **Int13a.**

90 Five-membered-ring chloronium cations have been proposed in the Lewis acid-catalyzed opening of chloro vinyl epoxides: A. Shemet, D. Sarlah, E. M. Carreira, *Org. Lett.* **2015**, *17*, 1878–1881

91 Depending on the substituents the vinylidenearenium cation can be either an actual intermediate in the 1,2-migration of one of the aryl substituents or a transition state between the two regioisomer with the triple bond. See ref. 92a



Scheme 1.29. Rearrangement of cyclopropyl gold(I) carbene into cyclic bromonium cation **Int10a** and opening into vinylidenephenonium gold(I) cation **Int11a.** (L = PMe_3. Free energies in kcal/mol).

Cyclic bromonium intermediate **Int10a** can also undergo a concerted ring opening and 1,3-alkylmigration of carbon C3 to generate **Int13a** (Scheme 1.29). However, this transformation has a higher energy of activation and is inconsistent with the ^{13}C-labelling experiment.

We then studied the bonding situation for the two intermediates **Int11a** and **Int11b** by means of NBO analysis. To have a closer picture to the experimental system, we optimized these two structures with the complete ligand used in the reaction (*t*BuXPhos) and we found that two intermediates differs in only 0.4 kcal/mol (Scheme 1.30). For **Int11b'**, carbon C1 has carbene character with a filled *sp*-orbital (occupancy 1.55) and an empty *p*-orbital (occupancy 0.29) (Figure 1.4a). According to the analysis, the main contribution on the stabilization of the vinylidene is given by a relatively high π-backdonation with a d_{yz}(Au) to $2p^{\pi}$(C1) donor acceptor interaction (27.53 kcal/mol) and a 6.9% contribution of $2p^{\pi}$(C1) in the corresponding NLMO (Figure 1.4b). In addition, the substituents on C2 contribute to the stabilization *via* σ/π-hyperconjugation (6.4 kcal/mol from C2-C3 σ-bond and 11.40 kcal/mol from C2-C*ipso* σ-bond) (Figure 1.4c,d).

Scheme 1.30. Equilibrium of the two conformers **Int11a'** and **Int11b'.** (L = *t*BuXPhos. Free energies in kcal/mol).

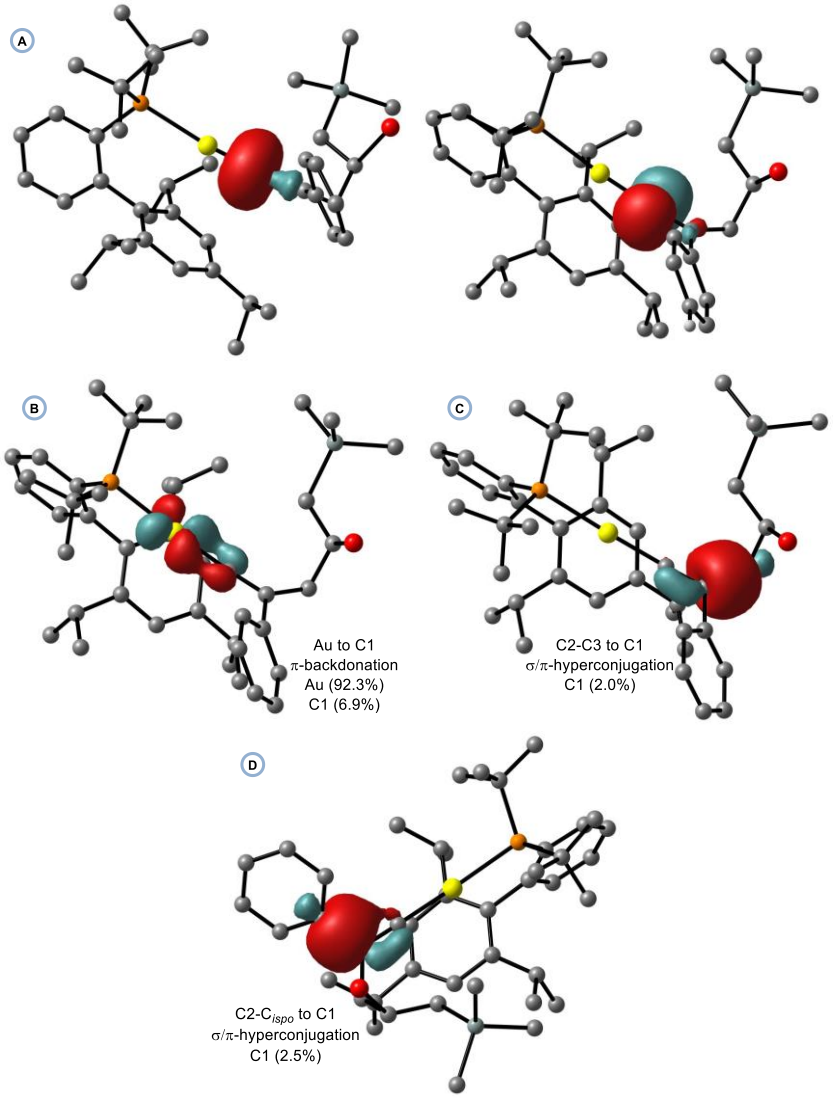


Figure 1.4. A) Plot for the NBO associated the orbitals of C1 of **Int11b'**. B) Plot for the NLMO associated to the π-backdonation from Au to C1 of **Int11b'**. C) Plot for the NLMO associated to the σ/π-hyperconjugation from C2-C3 σ-bond to C1 of **Int11b'**. D) Plot for the NLMO associated to the σ/π-hyperconjugation from C2-C_{ispo} σ-bond to C1 of **Int11b'**. Cutoff: 0.05. Hydrogen atoms removed for clarity.

For **Int11a'**, instead, C1 has not carbene character and no low valence *p*-orbital is located on this carbon. This is due to the fact that the six-membered ring is oriented in such a way that it can interact with the *p*-orbital of C1 that in this case is involved in an actual C-C bond with C_{ipso}. This bond has a strong p-character and is highly polarized on C_{ipso}. As additional prove that **Int11a'** has no vinylidene character, no NLMO associated with π-backdonation from gold to C1 was found. In contrast, a positive charge was found delocalized around the cyclohexadienyl cation. Overall, the structure of **Int11a'** corresponds to a gold(I)-vinylidenephenonium cation,[92] where the phenyl ring is stabilizing both the incipient positive charge on C2 generated by the 1,2-phenylmigration and on C1. The NLMO plots associated with the C1-C_{ispo} bond and the C2-C_{ispo} bond are shown in Figure 1.5 as an example of the extensive delocalization of the molecular orbitals of this species.

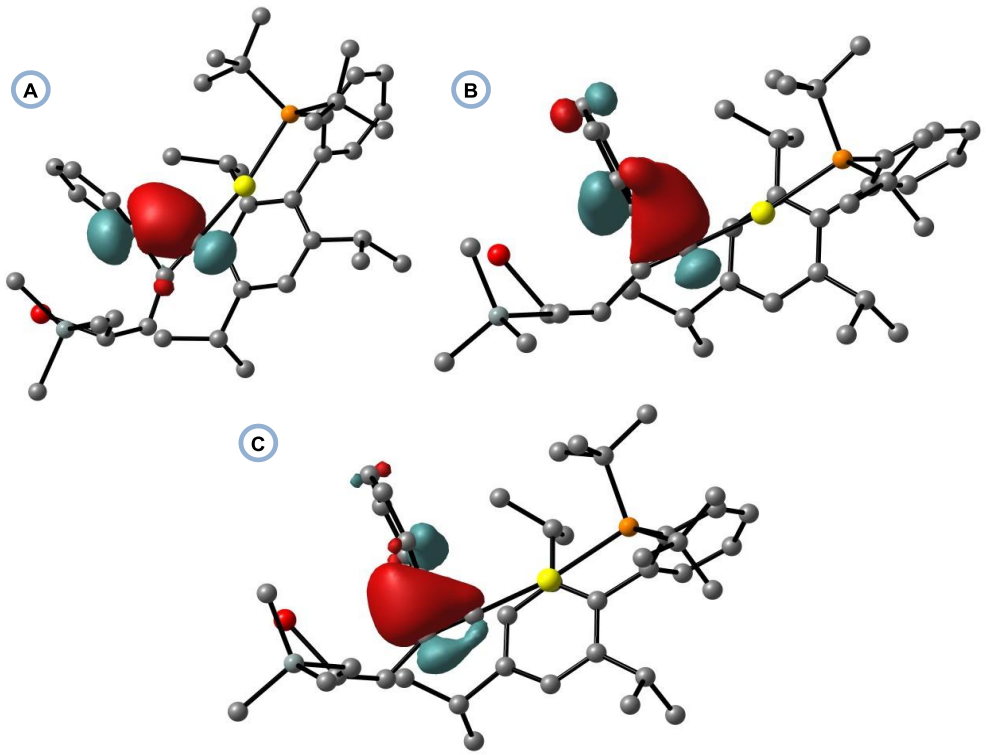
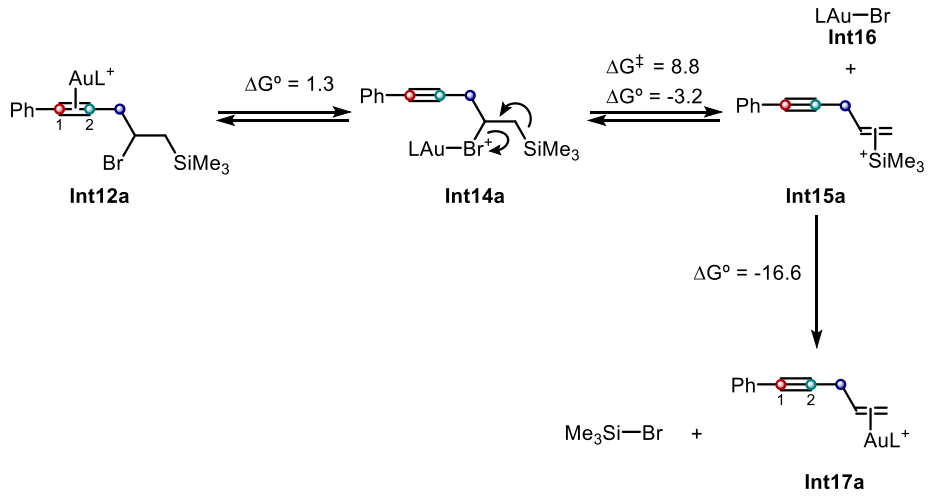


Figure 1.5. A) Plot for the NBO associated with the C1-C_{ipso} bond for **Int11a'**. B) Plot for the NLMO associated with the C1-C_{ipso} bond of **Int11a'**. C) Plot for the NLMO associated with the C2-C_{ipso} bond of **Int11a'**. Cutoff: 0.05. Hydrogen atoms removed for clarity.

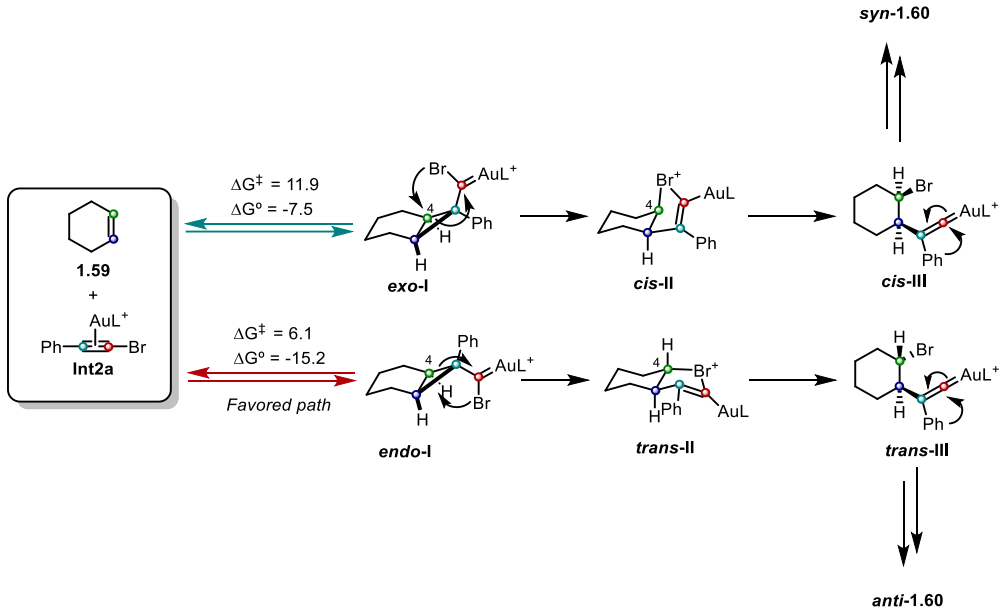
92 For generation and 1,2-arylmigration of diphenylvinylidenephenonium cations see: (a) H. Yamataka, S. E. Biali, Z. Rappoport, *J. Org. Chem.* **1998**, *63*, 9105–9108. (b) Z. Rappoport, S. Kobayashi, A. Stanger, R. Boese, *J. Org. Chem.* **1999**, *64*, 4370–4375. (c) R. Gronheid, H. Zuilhof, M. G. Hellings, J. Cornelisse, G. Lodder, *J. Org. Chem.* **2003**, *68*, 3205–3215.

Having defined the nature of the key **Int11a**, we studied the mechanism for the formal elimination of TMS-Br. According to calculations, **Int17a** is formed stepwise in an overall gold(I)-assisted TMS-Br elimination (Scheme 1.31). First, LAuBr is released from **Int14a** giving the enyne **Int15a** with the trimethylsilane still bounded to the double bond. Finally, gold(I) complex **Int16** reacts with **Int15a** forming (η^2-alkene)gold(I) complex **Int17a**.



Scheme 1.31. Mechanism of the gold(I)-assisted elimination of TMS-Br. (L = PMe_3. Free energies in kcal/mol).

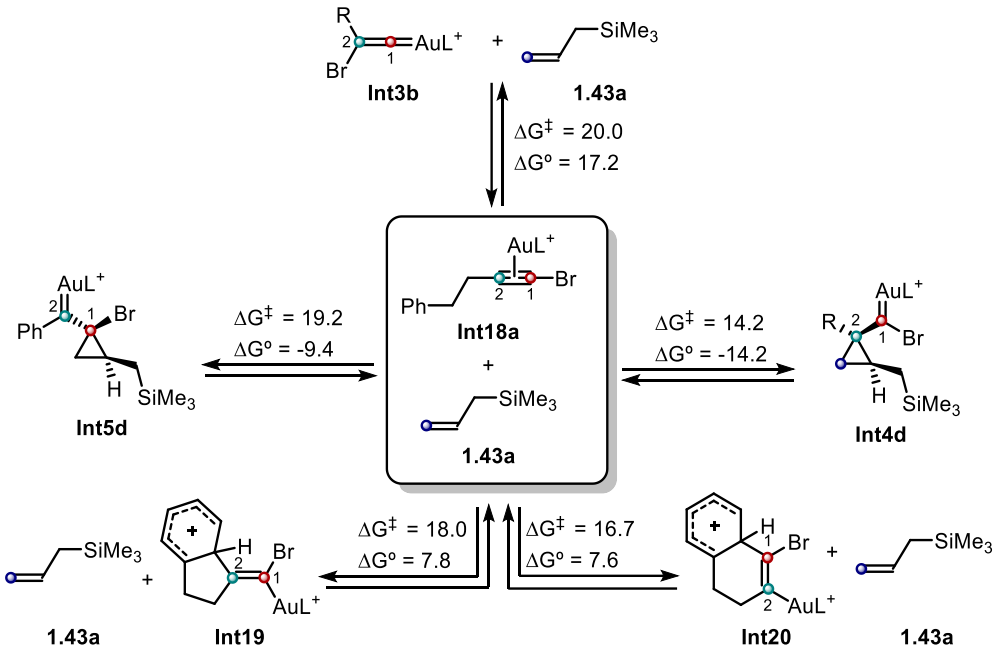
According to the ^{13}C-labelling experiments, it is reasonable to propose that the reaction of **1.42a** with simple alkenes (Scheme 1.24) occurs under an analogous mechanism. Even more, the diasteroselectivity observed in the formation of the *anti*-products **1.60** and **1.62** is an additional evidence that the bromide migration takes place through a cyclic intermediate. In fact, once the *endo*-cyclopropyl gold(I) carbene is formed (Scheme 1.32), the attack of the bromide on carbon C4 occurs by an S_N2-type mechanism with inversion of configuration (as observed in the formation of **Int10a**), forming the *trans*-fused bicyclic intermediate **trans-II.** The opening of the cation, followed by the 1,2-phenyl shift would lead to the formation of observed ***anti*-1.60**. The same principle can be applied for the reaction of **1.61**. However, in this case the selectivity towards the formation of the *endo*-cyclopropyl gold(I) carbene is lower and ***exo*-I** can also be formed delivering at the end a small amount of ***syn*-1.62**. Preliminary calculations performed on this system are in accordance with the hypothesis and the formation of ***endo*-I** is favored over ***exo*-I** both kinetically ($\Delta\Delta G^{\ddagger}$ = 5.8 kcal/mol) and thermodynamically ($\Delta\Delta G°$ = 7.7 kcal/mol).



Scheme 1.32. Proposed mechanism for the formation of ***anti*-1.60**.

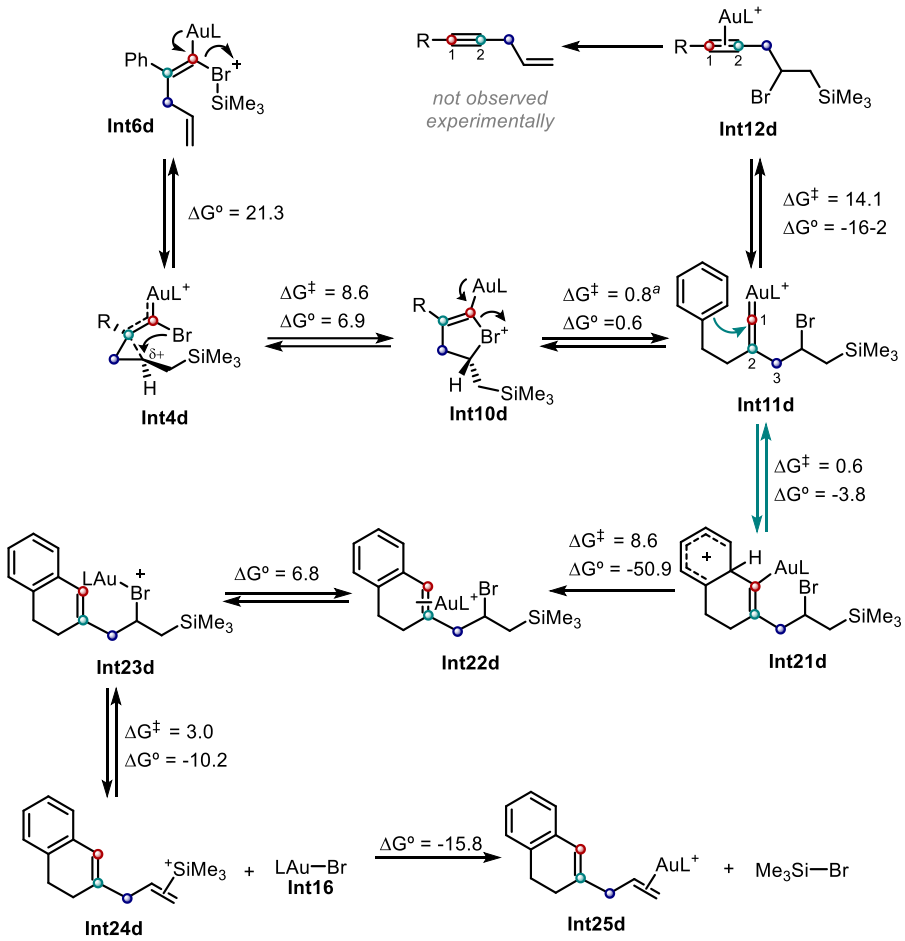
We then moved our attention to the allylation/hydroarylation sequence to form dienes such as **1.54** (see Table 1.15). We studied by means of DTF calculations the model reaction of **1.53a** with allyltrimethylsilane **1.43a** that forms efficiently diene **1.54a.**

Starting from **Int18a** three scenarios are possible for the first step (Scheme 1.33): as for the reaction of **1.42a,** the alkyne can undergo isomerization to form vinylidene **Int3b** or can form cyclopropyl gold(I) intermediates **Int4d** and **Int5d**. In addition, the triple bond can undergo intramolecular hydroarylation as observed experimentally. Again, the direct formation of the vinylidene requires a high energy barrier ($\Delta G^{\ddagger}$ = 20.0 kcal/mol). The formation of cyclopropyl gold(I)carbene **Int5d** ($\Delta G^{\ddagger}$ = 19.2 kcal/mol) and 5-*exo*-hydroarylation to form vinyl-gold(I) complex **Int19d** ($\Delta G^{\ddagger}$ = 18.0 kcal/mol) also have high energy barriers. On the other hand, the transition states leading to **Int4d** and **Int20d** are just 2.5 kcal/mol apart ($\Delta G^{\ddagger}$ = 14.2 kcal/mol and $\Delta G^{\ddagger}$ = 16.7 kcal/mol, respectively), although cyclopropyl gold(I) carbene is thermodynamically favored. This small difference explains the formation of **1.55a** in the model reaction, and also why the presence of slightly electron donating group such as the methyl in **1.53b** inverts the selectivity towards the 6-*exo*-hydroarylation path (Table 1.16).



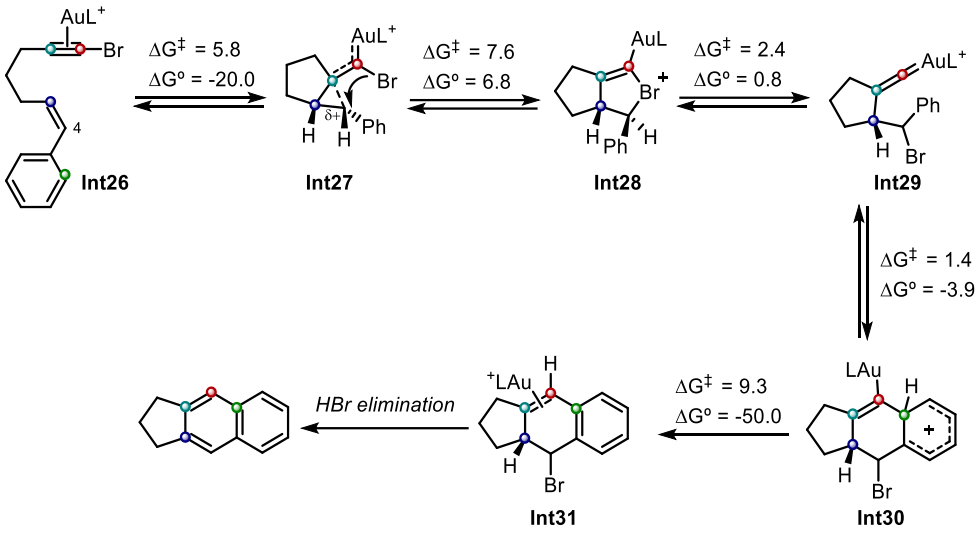
Scheme 1.33. Evolution of **Int18a.** (R = CH_2CH_2Ph, L = PMe_3. Free energies in kcal/mol).

The possible evolution of the cyclopropyl gold(I) carbene **Int4d** (Scheme 1.34) is analogous to the one of **Int4a** and, again, the formation of bromonium cation **Int10d** ($\Delta G^{\ddagger}$ = 8.6 kcal/mol) is more favored than the elimination of TMS-Br through **Int6d** ($\Delta G^{\ddagger}$ = 21.3 kcal/mol). The opening of the cyclic intermediate **Int10d** to form vinylidene **Int11d** is almost barrierless. The formation of Wheland-type intermediate **Int21d** requires very low energy and is followed by an highly exothermic 1,2-H shift yielding (η^2 -dehydronapthalene)gold(I) complex **Int22d.** The turnover of the catalytic cycle happens *via* gold(I)-promoted TMS-Br elimination and ligand exchange between product and substrates, in line with what we computed before for the formation of 1,4-enynes **1.44**. The 1,2-alkyl migration that would lead to **int12d** and, subsequently to the skipped enyne, is clearly disfavored ($\Delta G^{\ddagger}$ = 14.1 kcal/mol), in accordance with the experimental results in which the 1,4-enyne is not observed.



Scheme 1.34. Evolution of **Int4d** to form diene **Int25d.** (R = CH_2CH_2Ph, L = PMe_3. Free energies in kcal/mol). [a] The energy of this TS was calculated by freezing the distance of the bond C−Br which is cleaved in this step.

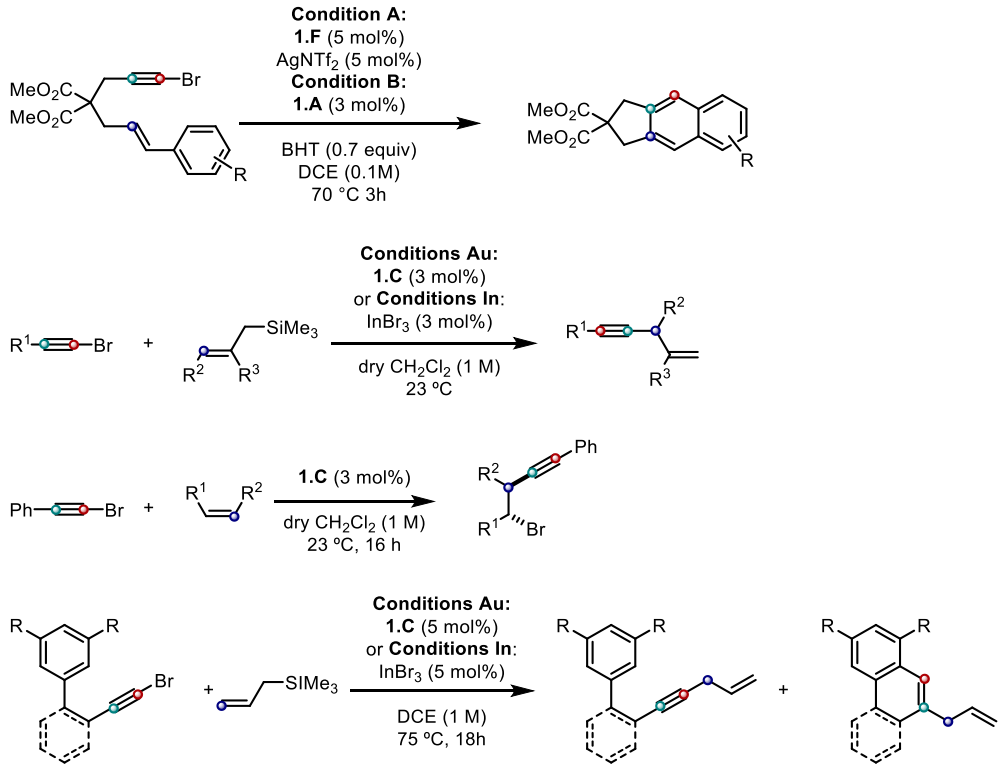
The cyclization of 1-bromo-1,6 enynes **1.39** leading to products of formal dehydro-Diels-Alder reaction occurs under an analogous mechanism. According to DFT calculations, model substrate **Int26** undergoes exothermic formation of cyclopropyl(I) gold carbene **Int27** via 5-*exo*-dig cyclization (Scheme 1.35). This time the partial positive charge on C4 of **Int27** is located on a stabilized benzylic position, thus favoring the attack of the bromide to form the bicyclic cation **Int28**, which evolves into the gold(I)-vinylidene **Int29** *via* low energy ring opening as seen before ($\Delta G^{\ddagger}$ = 2.4 kcal/mol). The tricyclic system is then formed by hydroarylation of the vinylidene to form more stable Int31. The final 2,3-dihydro-1*H*-cyclopenta[*b*]naphthalene product is obtained by loss of HBr driven by the aromatization of the second ring.



Scheme 1.35. Mechanism of the gold(I)-catalyzed cyclization of 1-bromo-1,6-enynes.

Conclusions

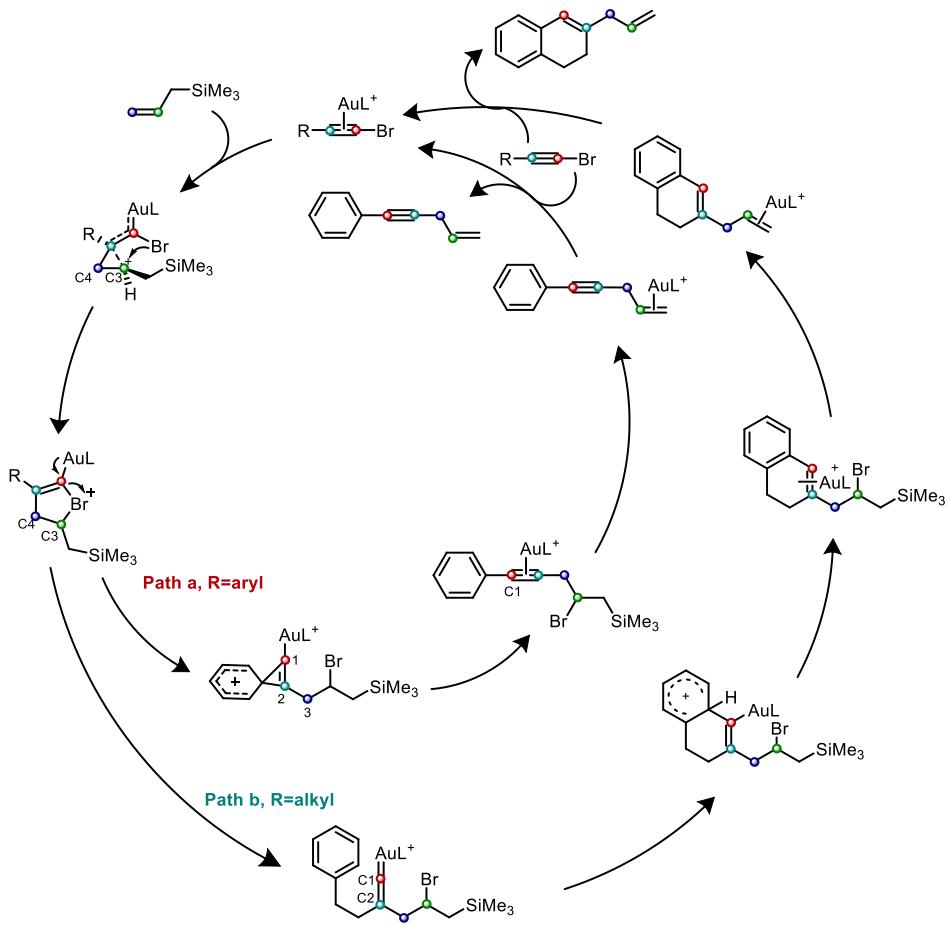
In this Chapter we disclosed a series of new reactions of bromoalkynes with electron rich alkenes. The cyclization of 1-bromo-1,6-enyes leads to the formation of cyclopenta[*b*]naphthalenes in a formal dehydro-Diels-Alder reaction with loss of HBr. In addition, the intermolecular reaction with allylsilanes delivers 1,4-enynes *via* a formal cross-coupling reaction or dehydronaphthalenes arising from an allylation/cyclization cascade. Moreover, the reaction was extended to simple alkenes to give homopropargyl bromides *via* 1,2-bromoalkynylation. Interestingly, $InBr_3$ is also able to catalyze the formal cross-coupling with allylsilanes.



Scheme 1.36 . Novel intra- and intermolecular reactions of haloalkynes catalyzed by gold(I) or indium(III).

By means of control experiments and DFT calculations we proved that all these reactions proceed *via* a cyclic bromonium cation as common intermediate. When an aryl alkyne is used, the cyclic bromonium cation undergoes aryl-assisted ring opening to generate gold(I)-vinylidenephenonium cation **Int11a**, which upon 1,2-phenyl migration restores the triple bond. In absence of a stabilizing group, such in the case of **Int10d**, the opening of the bromonium cyclic cation leads to the formation of a linear gold(I) vinylidenes such as **Int11d.** In this case,

an almost barrierless hydroarylation occurs selectively. According to ^{13}C-labelling experiments, the reaction catalyzed by $InBr_3$ follows an analogous path.



Scheme 1.37. Proposed mechanism for the reaction of haloalkynes with allylsilanes.

Experimental Part

General Information

Anhydrous reactions were performed under nitrogen or argon in solvents dried by passing through an activated alumina column on a PureSolv™ solvent purification system (Innovative Technologies, Inc., MA). Analytical thin layer chromatography was carried out using TLC-aluminium sheets with 0.2 mm of silica gel (Merck GF_{234}) using UV light as the visualizing agent and an acidic solution of vanillin in ethanol or potassium permanganate as the developing agent. Chromatographic purifications were carried out using flash grade silica gel (SDS Chromatogel 60 ACC, 40-60 µm) or automated flash chromatographer CombiFlash Companion. Preparative TLC was performed on 20 cm × 20 cm silica gel plates (2.0 mm or 1.0 mm thick, Analtech). Organic solutions were concentrated under reduced pressure on Büchi or IKA rotary evaporators. NMR spectra were recorded at 298 K on a Bruker Avance 300, Bruker Avance 400 Ultrashield and Bruker Avance 500 Ultrashield apparatuses. The signals are given as δ / ppm (multiplicity, coupling constant (Hertz), number of protons) downfield from tetramethylsilane, with calibration on the residual protio-solvent used (δ_H = 7.26 ppm and δ_C = 77.16 ppm for $CDCl_3$). Mass spectra were recorded on a Waters UPLC-QqTOF (Maxis Impact, Bruker Daltonics) with ESI and APCI, or a Waters Alliance HPLC-TOF (MicroTOF Focus, Bruker Daltonics) with ESI and APCI. Melting points were determined using a Büchi melting point apparatus.

All reagents were used as purchased, with no further purification, unless otherwise stated.

Complexes [(*t*BuXPhos)AuNCMe]BAr_4^F (**1.C**),[93] [(SPhos)AuNCMe]SbF_6 (**1.D**),[94] [(IPr)$AuNTf_2$] (**1.G**)[95], [(IPr)AuNCMe]SbF_6 (**1.H**)[96], **1.N-a and 1.N-b**[97], the cynnamil bromides[98], terminal alkynes, cinnamyltrimethylsilane,[99] (*E*)-trimethyl(pent-2-en-1-yl)silane[100] were prepared following literature procedures. The NMR data are in agreement with the ones reported in the literature.

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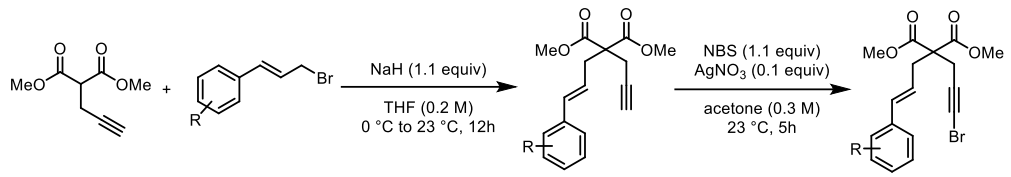
Synthetic Procedures and Characterization Data

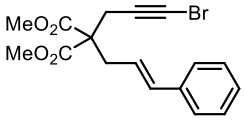
General procedure A for the synthesis of 1-bromo-1,6-enynes ***1.39***



Dimethyl 2-(prop-2-yn-1-yl) malonate (1 equiv) was added dropwise to a suspension of sodium hydride (1,1 equiv) in THF (0.4 M with respect of the limiting reagent) at 0ºC. The mixture was stirred at 23ºC until the evolution of hydrogen was completed, then cooled down again to 0ºC and the substituted cinnamyl bromide (1,2 equiv) dissolved in THF (0.4 M with respect of the limiting reagent) was added. The reaction was stirred overnight at 23ºC, then quenched with NH_4Cl and the two phases diluted with Et_2O and separated. The water phase was extracted with Et_2O and the collected organic phases washed with brine, dried over Na_2SO_4 and evaporated. The crude product was used directly in the following step without further purification considering quantitative the reaction.

The crude enyne (1 equiv) was dissolved in acetone (0,3 M). Silver nitrate (0.1 equiv) was added, followed by *N*-bromosuccinimide (1.1 equiv). The reaction mixture was stirred at 23 °C with exclusion of light for 5 h. Then, solvent was removed, and the crude redissolved in Et_2O and stirred for 5 minutes with Brine. The two phases were then separated, and the organic phase was washed three times with Brine, dried over Na_2SO_4 and evaporated. The product was purified by flash chromatography on silica gel (Eluent = Cyclohexane/Ethyl acetate= 10/1).

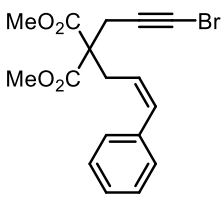
Methyl (*E*)-2-acetoxy-2-(3-bromoprop-2-yn-1-yl)-5-phenylpent-4-enoate (1.39a)



Bromoenyne **1.39a** was synthetized following general procedure A, from dimethyl 2-(prop-2-yn-1-yl) malonate (1.6 mL, 10 mmol) and (*E*)-cinnamyl bromide (2.4 g, 12 mmol). The crude was purified by silica gel chromatography to afford **1.39a** as a colorless oil (3.32 g 91%).

^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.35 – 7.27 (m, 5H), 7.25 – 7.20 (m, 1H), 6.51 (dt, *J* = 15.7 Hz, 1.3 Hz, 1H), 6.00 (dt, *J* = 15.5, 7.7 Hz, 1H), 3.76 (s, 6H), 2.95 (dd, *J* = 7.7, 1.3 Hz, 2H), 2.87 (s, 2H). **^{13}C-NMR (**126 MHz, $CDCl_3$) δ 170.18, 137.05, 134.90, 128.64, 127.69, 126.45, 126.43, 123.13, 75.01, 57.32, 53.02, 52.96, 41.77, 36.25, 24.33. **HRMS** (ESI) m/z calculated for $C_{17}H_{17}BrNaO_4$ $[M+Na]^+$: 387.0202, found: 387.0207.

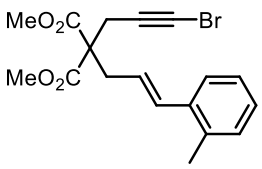
Methyl (*Z*)-2-acetoxy-2-(3-bromoprop-2-yn-1-yl)-5-phenylpent-4-enoate (1.39b)



Bromoenyne **1.39b** was synthetized following general procedure A, from dimethyl 2-(prop-2-yn-1-yl) malonate (480 μL, 3 mmol) and (*Z*)-cinnamyl bromide (709 mg, 3.6 mmol). The crude was purified by silica gel chromatography to afford **1.39b** as a yellow oil (*Z:E* = 3:1-937 mg, 87%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.41 – 7.18 (m, 5H), 6.61 (d, *J* = 11.7 Hz, 1H), 5.45 (dt, *J* = 11.7, 7.5 Hz, 1H), 3.68 (s, 6H), 3.10 (dd, *J* = 7.5, 1.8 Hz, 2H), 2.84 (s, 2H). **^{13}C-NMR (**126 MHz, $CDCl_3$) δ 170.2, 136.8, 133.4, 128.8, 128.4, 127.1, 126.4, 124.7, 74.7, 57.0, 53.0, 52.9, 30.8, 24.1. **HRMS** (ESI) m/z calculated for $C_{17}H_{17}BrNaO_4^+$ $[M+Na]^+$: 387.0201, found: 387.0199.

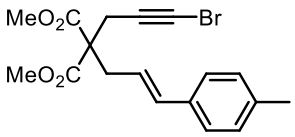
Methyl (*E*)-2-acetoxy-2-(3-bromoprop-2-yn-1-yl)-5-(*o*-tolyl)pent-4-enoate (1.39c)



Bromoenyne **1.39c** was synthetized following general procedure A, from dimethyl 2-(prop-2-yn-1-yl) malonate (430 μL, 2.9 mmol) and (*E*)-1-(3-bromoprop-1-en-1-yl)-2-methylbenzene (735 mg, 3.5 mmol). The crude was purified by silica gel chromatography to afford **1.39c** as a yellow oil (745 mg, 68%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.33 (m, 1H), 7.19 – 7.09 (m, 3H), 6.74 (dt, *J* = 15.6, 1.3 Hz, 1H), 5.86 (dt, *J* = 15.4, 7.7 Hz, 1H), 3.77 (s, 6H), 2.98 (dd, *J* = 7.7, 1.3 Hz, 2H), 2.89 (s, 2H), 2.33 (s, 3H). **^{13}C-NMR (**101 MHz, $CDCl_3$) δ 170.19, 136.36, 135.31, 133.13, 130.27, 127.61, 126.18, 126.00, 124.50, 75.01, 57.26, 53.01, 41.73, 36.45, 24.29, 19.84. **HRMS** (ESI) m/z calculated for $C_{18}H_{19}BrNaO_4$ $[M+Na]^+$: 401.0359, found: 401.0365

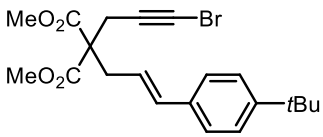
Methyl (*E*)-2-acetoxy-2-(3-bromoprop-2-yn-1-yl)-5-(*p*-tolyl)pent-4-enoate (1.39d)



Bromoenyne **1.39d** was synthetized following general procedure A, from dimethyl 2-(prop-2-yn-1-yl) malonate (254 μL, 1.7 mmol) and (*E*)-1-(3-bromoprop-1-en-1-yl)-4-methylbenzene (431 mg, 2 mmol). The crude was purified by silica gel chromatography to afford **1.39d** as a yellowish solid (547 mg, 85%).

M.p. 53-56 ºC. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.25 – 7.20 (m, 2H), 7.10 (m, 2H), 6.47 (d, *J* = 15.7 Hz, 1H), 5.94 (dt, *J* = 15.5, 7.6 Hz, 1H), 3.76 (s, 6H), 2.93 (dd, *J* = 7.6, 1.3 Hz, 2H), 2.86 (s, 2H), 2.33 (s, 3H). **^{13}C-NMR (**101 MHz, $CDCl_3$) δ 170.24, 137.52, 134.78, 134.31, 129.34, 126.37, 122.00, 75.08, 57.38, 53.01, 41.69, 36.27, 24.32, 21.31. **HRMS** (ESI) m/z calculated for $C_{18}H_{19}BrNaO_4^+$ $[M+Na]^+$: 401.0359, found: 401.0367

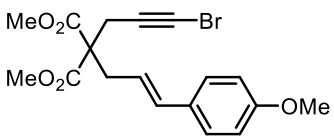
Methyl (*E*)-2-acetoxy-2-(3-bromoprop-2-yn-1-yl)-5-(4-(tert-butyl)phenyl)pent-4-enoate (1.39e)



Bromoenyne **1.39e** was synthetized following general procedure A, dimethyl 2-(prop-2-yn-1-yl) malonate (67 μL, 0.45 mmol) and from (*E*)-1-(3-bromoprop-1-en-1-yl)-4-(tert-butyl)benzene (137 mg, 0.54 mmol). The crude was purified by silica gel chromatography to afford **1.39e** as a yellow oil (139 mg, 73%).

^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.34 – 7.30 (m, 2H), 7.29 – 7.24 (m, 2H), 6.48 (d, J = 15.7 Hz, 1H), 5.94 (dt, J = 15.5, 7.6 Hz, 1H), 3.76 (s, 6H), 2.93 (dd, J = 7.7, 1.3 Hz, 2H), 2.86 (s, 2H), 1.31 (s, 9H).**^{13}C-NMR (**126 MHz, $CDCl_3$) δ 170.23, 150.82, 134.70, 134.32, 126.19, 125.57, 122.23, 75.07, 57.36, 53.02, 41.68, 36.24, 34.69, 31.42, 24.27. **HRMS** (ESI) m/z calculated for $C_{21}H_{25}BrNaO_4$ $[M+Na]^+$: 443.0828, found 443.0833.

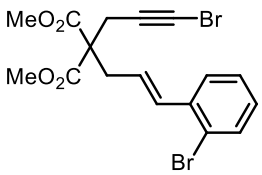
Methyl (*E*)-2-acetoxy-2-(3-bromoprop-2-yn-1-yl)-5-(4-methoxyphenyl)pent-4-enoate (1.39f)



Bromoenyne **1.39f** was synthetized following general procedure A, from dimethyl 2-(prop-2-yn-1-yl) malonate (245 mg, 1.4 mmol) and (*E*)-1-(3-bromoprop-1-en-1-yl)-4-methoxybenzene (381 mg, 1.7 mmol). The crude was purified by silica gel chromatography to afford **1.39f** as a yellow oil (111 mg, 24%).

^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.29 – 7.23 (m, 2H), 6.87 – 6.79 (m, 2H), 6.44 (d, J = 15.6 Hz, 1H), 5.84 (dt, J = 15.5, 7.6 Hz, 1H), 3.80 (s, 3H), 3.76 (s, 6H), 2.91 (dd, J = 7.7, 1.3 Hz, 2H), 2.86 (s, 2H). **^{13}C-NMR (**126 MHz, CDCl3) δ 170.27, 159.35, 134.30, 129.92, 127.62, 120.78, 114.07, 75.11, 57.40, 55.45, 53.01, 41.67, 36.26, 24.30. **HRMS (ESI)** m/z calculated for $C_{17}H_{17}BrNaO_4^+$ $[M+Na]^+$: 387.0202, found: 387.0207

Methyl (*E*)-2-acetoxy-5-(2-bromophenyl)-2-(3-bromoprop-2-yn-1-yl)pent-4-enoate (1-39g)

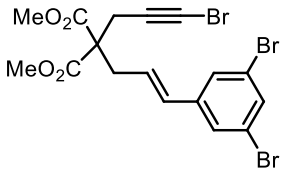


Bromoenyne **1.39g** was synthetized following general procedure A, from dimethyl 2-(prop-2-yn-1-yl) malonate (433 μl, 2.9 mmol) and (*E*)-1-bromo-2-(3-bromoprop-1-en-1-yl)benzene (960 mg, 3.5 mmol). The crude was purified by silica gel chromatography to afford **1.39g** as a yellow solid (904 mg, 70%).

M.p. 55-60 ºC. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.52 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.44 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.27 – 7.22 (m, 1H), 7.13 – 7.04 (m, 1H), 6.84 (d, *J* = 15.6 Hz, 1H), 5.96 (dt, *J* =

15.5, 7.7 Hz, 1H), 3.77 (s, 6H), 2.98 (dd, *J* = 7.7, 1.3 Hz, 2H), 2.89 (s, 2H). **^{13}C-NMR (**126 MHz, $CDCl_3$) δ 170.1 (2C), 137.1, 133.9, 132.9, 129.0, 127.6, 127.4, 126.4, 126.4, 123.4, 74.9, 57.3, 53.1, 53.0, 42.0, 36.3, 24.4. **HRMS (ESI)** m/z calculated for $C_{17}H_{16}Br_2NaO_4^+$ $[M+Na]^+$: 464.9308, found: 464.9307.

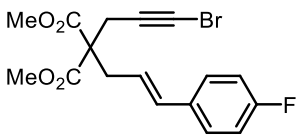
Methyl (*E*)-2-acetoxy-2-(3-bromoprop-2-yn-1-yl)-5-(3,5-dibromophenyl)pent-4-enoate (1.39h)



Bromoenyne **1.39h** was synthetized following general procedure A, from dimethyl 2-(prop-2-yn-1-yl) malonate (299 µl, 2 mmol) and (*E*)-1,3-dibromo-5-(3-bromoprop-1-en-1-yl)benzene (852 mg, 2.4 mmol). The crude was purified by silica gel chromatography to afford **1.39h** as a white solid (523 mg, 50%).

M.p. 103-106 ºC. **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.50 (t, *J* = 1.7 Hz, 1H), 7.38 (dd, *J* = 1.7, 0.5 Hz, 2H), 6.40 – 6.32 (m, 1H), 6.05 (dt, *J* = 15.5, 7.6 Hz, 1H), 3.76 (s, 6H), 2.93 (dd, *J* = 7.7, 1.3 Hz, 2H), 2.85 (s, 2H). **^{13}C-NMR (**126 MHz, $CDCl_3$) δ 169.97, 140.57, 132.90, 132.09, 128.13, 126.74, 123.23, 74.78, 57.14, 53.15, 42.17, 36.28, 24.50. **HRMS (ESI)** m/z calculated for $C_{17}H_{15}NaO_4Br_3^+$ $[M+Na]^+$: 542.8413, found: 542.8409.

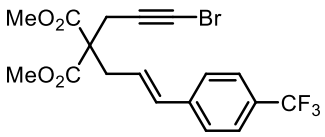
Methyl (*E*)-2-acetoxy-2-(3-bromoprop-2-yn-1-yl)-5-(4-fluorophenyl)pent-4-enoate (1.39i)



Bromoenyne **1.39i** was synthetized following general procedure A, from dimethyl 2-(prop-2-yn-1-yl) malonate (202 µl, 1.35 mmol) and (*E*)-1-(3-bromoprop-1-en-1-yl)-4-fluorobenzene (384 mg, 1.6 mmol). The crude was purified by silica gel chromatography to afford **1.39i** as a yellow solid (399 mg, 77%).

M.p. 68-71 ºC. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.33 – 7.24 (m, 2H), 7.03 – 6.93 (m, 2H), 6.46 (d, *J* = 15.7 Hz, 1H), 5.91 (dt, *J* = 15.5, 7.6 Hz, 1H), 3.76 (s, 6H), 2.92 (dd, *J* = 7.7, 1.3 Hz, 2H), 2.86 (s, 2H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -114.56 – -114.71 (m).**^{13}C-NMR (**101 MHz, $CDCl_3$) δ 170.18, 162.45 (d, *J* = 246.7 Hz), 133.24 (d, *J* = 3.3 Hz), 127.96 (d, *J* = 8.0 Hz), 122.95 (d, *J* = 2.3 Hz), 115.55 (d, *J* = 21.6 Hz), 74.98, 57.30, 53.05, 41.84, 36.24, 24.38. **HRMS (ESI)** m/z calculated for $C_{17}H_{16}BrFNaO_4^+$ $[M+Na]^+$: 405.0108, found: 405.0118.

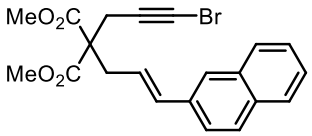
Methyl (*E*)-2-acetoxy-2-(3-bromoprop-2-yn-1-yl)-5-(4-(trifluoromethyl)phenyl)pent-4-enoate (1.39j)



Bromoenyne **1.39j** was synthetized following general procedure A, dimethyl 2-(prop-2-yn-1-yl) malonate (209 µl, 1.4 mmol) and from (*E*)-1-(3-bromoprop-1-en-1-yl)-4-(trifluoromethyl)benzene (445 mg, 1.7mmol). The crude was purified by silica gel chromatography to afford **1.39j** as a yellow solid (500 mg, 82%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.2 Hz, 2H), 7.42 (d, *J* = 8.1 Hz, 2H), 6.53 (d, *J* = 15.7 Hz, 1H), 6.13 (dt, *J* = 15.5, 7.6 Hz, 1H), 3.76 (s, 6H), 2.96 (dd, *J* = 7.6, 1.3 Hz, 2H), 2.87 (s, 2H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -62.62. **^{13}C-NMR (**126 MHz, $CDCl_3$) δ 170.03, 140.45, 133.48, 129.48 (q, *J* = 32.4 Hz), 126.59, 125.59 (q, *J* = 3.8 Hz), 124.28 (q, J = 271.8 Hz), 74.83, 57.19, 53.05, 42.01, 36.34, 24.47. **HRMS (ESI)** m/z calculated for $C_{18}H_{16}BrF_3NaO_4^+$ $[M+Na]^+$: 455.0076, found: 455.0080.

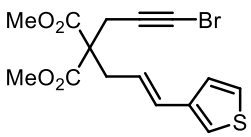
Methyl (*E*)-2-acetoxy-2-(3-bromoprop-2-yn-1-yl)-5-(naphthalen-2-yl)pent-4-enoate (1.39k)



Bromoenyne **1.39k** was synthetized following general procedure A, from dimethyl 2-(prop-2-yn-1-yl) malonate (373 µl, 2.5 mmol) and (*E*)-2-(3-bromoprop-1-en-1-yl)naphthalene (741 mg, 3 mmol). The crude was purified by silica gel chromatography to afford **1.39k** as a yellow oil (806 mg, 78%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.10 – 8.04 (m, 1H), 7.84 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.77 (d, *J* = 8.1 Hz, 1H), 7.50 (td, *J* = 7.7, 1.4 Hz, 3H), 7.43 (dd, *J* = 8.2, 7.1 Hz, 1H), 7.31 – 7.23 (m, 1H), 6.02 (dt, *J* = 15.4, 7.7 Hz, 1H), 3.78 (s, 6H), 3.08 (dd, *J* = 7.7, 1.3 Hz, 2H), 2.94 (s, 2H). **^{13}C-NMR (**126 MHz, $CDCl_3$) δ 170.24, 134.98, 133.66, 132.55, 131.19, 128.63, 128.09, 126.52, 126.23, 125.91, 125.73, 124.18, 123.91, 75.07, 57.34, 53.10, 41.89, 36.65, 31.06, 24.47. **HRMS (ESI)** m/z calculated for $C_{21}H_{19}BrNaO_4^+$ $[M+Na]^+$: 437.0359, found: 437.0354

Methyl (*E*)-2-acetoxy-2-(3-bromoprop-2-yn-1-yl)-5-(thiophen-3-yl)pent-4-enoate (1.39l)

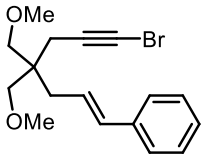


Bromoenyne **1.39l** was synthesized following general procedure A, from dimethyl 2-(prop-2-yn-1-yl) malonate (300 µl, 2.0 mmol) and (*E*)-2-(3-bromoprop-1-en-1-yl)naphthalene (487 mg, 2.4 mmol). The crude was purified by silica gel chromatography to afford **1.39l** as a yellow oil (365 g, 49%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.24 (dd, *J* = 4.9, 2.8 Hz, 1H), 7.16 (dd, *J* = 5.1, 1.2 Hz, 1H), 7.11 (dd, *J* = 2.8, 1.2 Hz, 1H), 6.50 (d, *J* = 15.8 Hz, 1H), 5.83 (dt, *J* = 15.5, 7.7 Hz, 1H), 3.76 (s, 5H), 2.90 (dd, *J* = 7.7, 1.2 Hz, 2H), 2.86 (s, 2H). **^{13}C-NMR (**126 MHz, $CDCl_3$) δ 170.0,

140.5, 132.9, 132.1, 128.1, 126.7, 123.2, 74.7, 57.1, 53.8, 42.2, 36.3, 24.5. **HRMS (ESI)** m/z calculated for $C_{15}H_{15}BrNaO_4S^+$ $[M+Na]^+$: 392.9772, found: 392.9770

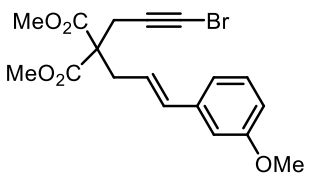
(*E*)-(7-bromo-4,4-bis(methoxymethyl)hept-1-en-6-yn-1-yl)benzene (1.39m)



Bromoenyne **1.39m** was synthesized following the bromination procedure used for the others enynes (second step of the general procedure A) starting from known (*E*)-(4,4-bis(methoxymethyl)hept-1-en-6-yn-1-yl)benzene[101] (312 mg, 1.2 mmol) The crude was purified by silica gel chromatography to afford **1.39m** as a yellow oil, 7:1 mixture of *E:Z* isomers (268 mg, 66% yield).

^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.33 (m, 2H), 7.32 – 7.26 (m, 2H), 7.22 – 7.17 (m, 1H), 6.43 (d, J = 15.7 Hz, 1H), 6.18 (dt, J = 15.6, 7.7 Hz, 1H), 3.33 (s, 6H), 3.26 (s, 2H), 3.26 (s, 2H), 2.29 (dd, J = 7.8, 1.3 Hz, 2H), 2.26 (s, 2H). **^{13}C-NMR (***major)* (101 MHz, CDCl3) 137.77, 133.32, 128.61, 127.19, 126.21, 125.70, 74.51, 59.46, 42.85, 39.34, 35.72, 23.66. **^{13}C-NMR (***minor)* (101 MHz, $CDCl_3$) δ 137.94, 132.94, 132.90, 127.10, 126.52, 126.16, 73.69, 59.36, 43.28, 39.81, 36.23, 23.38. **HRMS (ESI)** m/z calculated for $C_{17}H_{21}BrNaO_2^+$ $[M+Na]^+$: 359.0617, found: 359.0617.

Methyl (*E*)-2-acetoxy-2-(3-bromoprop-2-yn-1-yl)-5-(3-methoxyphenyl)pent-4-enoate (1.39n)

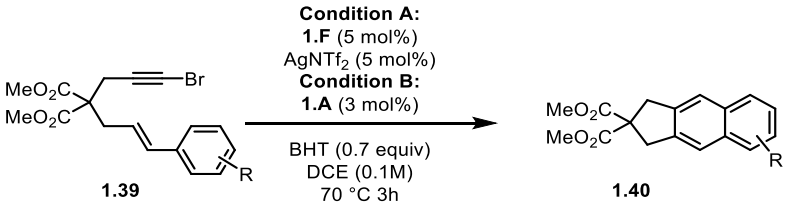


Bromoenyne **1.39g** was synthetized following general procedure A, from dimethyl 2-(prop-2-yn-1-yl) malonate (254 µl, 1.7 mmol) and (*E*)-1-(3-bromoprop-1-en-1-yl)-3-methoxybenzene (463 mg, 2.0 mmol). The crude was purified by silica gel chromatography to afford **1.39g** as a yellow oil (654 mg, 97%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.21 (t, *J* = 7.9 Hz, 1H), 6.93 (d, *J* = 7.7 Hz, 1H), 6.88 – 6.84 (m, 1H), 6.78 (ddd, *J* = 8.2, 2.7, 0.9 Hz, 1H), 6.47 (d, *J* = 15.6 Hz, 1H), 5.99 (dt, *J* = 15.5, 7.6 Hz, 1H), 3.81 (s, 3H), 3.76 (s, 6H), 2.93 (dd, *J* = 7.7, 1.3 Hz, 2H), 2.87 (s, 2H). **^{13}C-NMR (**101 MHz, $CDCl_3$) 170.13, 159.89, 138.48, 134.77, 129.60, 123.47, 119.08, 113.16, 111.96, 74.99, 57.30, 55.35, 53.01, 41.78, 36.23, 24.34. **HRMS (ESI)** m/z calculated for $C_{18}H_{19}BrNaO_5^+$ $[M+Na]^+$: 417.0308, found: 417.0302.

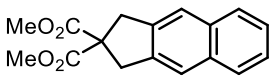
101 R. Miller, J. Carreras, M. E. Muratore, M. Gaydou, F. Camponovo, A. M. Echavarren, *J. Org. Chem.* **2016**, *81*, 1839–1849.

General procedure B for the gold(I) catalyzed intramolecular reaction of 1-bromo-1,6-enynes ***1.39***



The 1-bromo-1,6-enyne (0.1 mmol, 1 equiv) was dissolved in DCE (1 mL, 0.1M) in a screw cap vial. BHT (0.07 mmol, 0.7 equiv) was added followed by the gold(I) pre-catalyst IMesAuCl (5 mol%) and $AgNTf_2$ (5 mol%) in this order (**method A**) or catalyst $[(JohnPhos)AuNCMe]SbF_6$ (3 mol%) (**method B**). The resulting mixture was stirred at 75 ºC until complete conversion of the starting material monitored by TLC or ^{1}H-NMR. Once completed, the reaction was quenched with three drops of triethylamine and filtered through a plug of silica. The crude was evaporated and submitted to silica gel column chromatography (eluent = cyclohexane:ethyl acetate 20:1). The resulting solid was then washed carefully with small aliquots of Et_2O to obtain the pure tricyclic product.

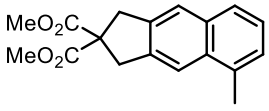
Dimethyl 1,3-dihydro-2H-cyclopenta[*b*]naphthalene-2,2-dicarboxylate (1.40a)



Compound **1.40a** was synthesized following general procedure **B** starting from **1.39a** or **1.39b** (36,5 mg, 0.1 mmol). The crude product was purified via flash chromatography followed by recrystallization from Et_2O affording **1.40a** as a white solid (method A: 19.6 mg, 69%).

M.p. 146-150 ºC. **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.75 (dd, *J* = 6.2, 3.3 Hz, 2H), 7.65 (s, 2H), 7.39 (dd, *J* = 6.3, 3.3 Hz, 2H), 3.75 (s, 6H), 3.73 (d, *J* = 1.1 Hz, 4H). **^{13}C-NMR (**126 MHz, $CDCl_3$) δ 171.9 (2C), 138.9 (2C), 133.2 (2C), 127.6 (2C), 125.3 (2C), 122.5 (2C), 60.9, 53.0 (2C), 40.2 (2C). The NMR data match with those reported in the literature[102].

Dimethyl 5-methyl-1,3-dihydro-2H-cyclopenta[*b*]naphthalene-2,2-dicarboxylate (1.40b)

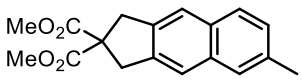


Compound **1.40b** was synthesized following general procedure **B** starting from **1.39c** (38 mg, 0.1 mmol) The crude product was purified via flash chromatography followed by recrystallization* from Et_2O affording **1.40b** as a white solid (method A: 18 mg, 60%, purity: 72%). *The crystallization did not increase the purity of the product.

102 J. C. Hsieh, C. H. Cheng, *Chem. Commun.* **2008**, 2992–2994.

M.p. 148-151 ºC. **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.80 (s, 1H), 7.64 (d, *J* = 6.7 Hz, 1H), 7.62 (d, *J* = 8.1 Hz, 1H), 7.32 – 7.27 (m, 1H), 7.24 (d, *J* = 6.9 Hz, 1H), 3.75 (bs, 8H), 3.72 (d, *J* = 9.0 Hz, 2H), 2.66 (s, 3H). **^{13}C-NMR (**101 MHz, $CDCl_3$) δ 172.1, 138.9, 138.5, 134.0, 133.4, 132.5, 126.3, 126.2, 125.2, 123.2, 119.0, 61.1, 53.1, 40.7, 40.3, 19.7. **HRMS (ESI)** m/z calculated for $C_{18}H_{18}NaO_4$ $[M+Na]^+$: 321.1097, found: 321.1099.

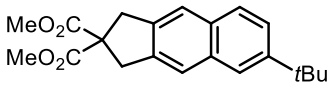
Dimethyl 6-methyl-1,3-dihydro-2H-cyclopenta[*b*]naphthalene-2,2-dicarboxylate (1.40c)



Compound **1.40c** was synthesized following general procedure **B** starting from **1.39d** (38 mg, 0.1 mmol). The crude product was purified via flash chromatography followed by recrystallization from Et_2O affording **1.40c** as a white solid (method A: 17 mg, 57%).

M.p. 153-156 ºC. **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.65 (d, *J* = 8.3 Hz, 1H), 7.59 (s, 1H), 7.55 (s, 1H), 7.52 (s, 1H), 7.23 (dd, *J* = 8.4, 1.8 Hz, 1H), 3.75 (s, 6H), 3.71 (bs, 4H), 2.48 (s, 3H). **^{13}C-NMR (**101 MHz, $CDCl_3$) δ 172.0 (2C), 138.9, 137.9, 134.9, 133.4, 131.4, 127.6, 127.4, 126.6, 122.2, 121.8, 60.9, 53.0 (2C), 40.3, 40.2, 21.6. **HRMS (ESI)** m/z calculated for $C_{18}H_{18}NaO_4$ $[M+Na]^+$: 321.1097, found: 321.1099.

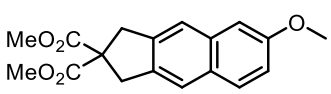
Dimethyl 6-(tert-butyl)-1,3-dihydro-2H-cyclopenta[*b*]naphthalene-2,2-dicarboxylate (1.40d)



Compound **1.40d** was synthesized following general procedure **B** starting from **1.39e** (42 mg, 0.1 mmol). The crude product was purified via flash chromatography followed by recrystallization from Et_2O affording **1.40d** as a white solid (Method A: 15 mg, 45%).

M.p. 129-131 ºC. **^{1}H-NMR** (500 MHz, CD_2Cl_2) δ 7.70 (m, 2H), 7.61 (s, 1H), 7.59 (s, 1H), 7.51 (dd, *J* = 8.8, 1.9 Hz, 1H), 3.73 (s, 6H), 3.69 (d, *J* = 0.8 Hz, 2H), 3.68 (bs, 2H), 1.39 (s, 9H). **^{13}C-NMR (**126 MHz, CD_2Cl_2) 172.4, 148.7, 139.5, 138.9, 133.7, 131.9, 127.6, 124.8, 123.2, 122.9, 122.3, 61.42, 53.4, 40.7, 40.6, 35.2, 31.5. **HRMS** (ESI) m/z calculated for $C_{21}H_{24}NaO_4^+$ $[M+Na]^+$: 363.1567, found: 363.1563.

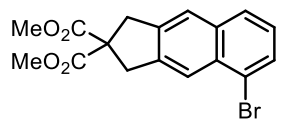
Dimethyl 6-methoxy-1,3-dihydro-2H-cyclopenta[*b*]naphthalene-2,2-dicarboxylate (1.40e)



Compound **1.40e** was synthesized following general procedure **B** starting from **1.39f** (39.5 mg, 0.1 mmol)). The crude product was purified via flash chromatography followed by recrystallization from Et_2O affording **1.40e** as a white solid (method A: 6.4 mg, 20%).

M.p: 162-164 ºC. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.64 (d, *J* = 9.7 Hz, 1H), 7.55 (d, *J* = 8.4 Hz, 2H), 7.25(m, 2H), 3.90 (s, 3H), 3.75 (s, *J* = 3.0 Hz, 6H), 3.70 (s, 2H), 3.69 (s, 2H). **^{13}C-NMR (**101 MHz, $CDCl_3$) δ 172.1, 157.5, 139.6, 136.6, 134.4, 129.1, 128.8, 122.5, 121.5, 118.1, 106.0, 61.1, 55.4, 53.1, 40.4, 40.2.

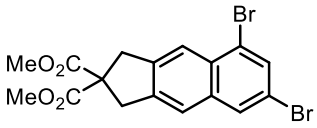
Dimethyl 5-bromo-1,3-dihydro-2H-cyclopenta[*b*]naphthalene-2,2-dicarboxylate (1.40f)



Compound **1.40f** was synthesized following general procedure **B** starting from **1.39g** (44.4 mg, 0.1 mmol). The crude product was purified via flash chromatography followed by recrystallization from Et_2O affording **1.40f** as a white solid (method B: 22 mg, 54%,).

M.p 159-162 ºC. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 8.06 (s, 1H), 7.71 (t, *J* = 7.6 Hz, 2H), 7.63 (s, 1H), 7.23 (t, *J* = 7.8 Hz, 1H), 3.77 (s, 2H), 3.76 (s, 6H), 3.74 (s, 2H). **^{13}C-NMR (**101 MHz, $CDCl_3$) δ 171.8 (2C), 140.7, 139.9, 134.5, 131.7, 129.4, 127.6, 125.7, 123.0, 122.5, 121.9, 60.9, 53.1 (2C), 40.4, 40.1. **HRMS** (ESI) m/z calculated for $C_{17}H_{15}BrNaO_4^+$ $[M+Na]^+$: 385.0046, found: 385.0051.

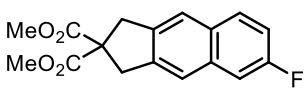
Dimethyl 5,7-dibromo-1,3-dihydro-2H-cyclopenta[*b*]naphthalene-2,2-dicarboxylate (1.40g)



Compound **1.40g** was synthesized following general procedure **B** starting from **1.39f** (52.3 mg, 0.1 mmol). The crude product was purified via flash chromatography followed by recrystallization from Et_2O affording **1.40g** as a white solid (method B: 22 mg, 49%).

M.p. 149-152 ºC. **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 8.00 (s, 1H), 7.87 (s, 1H), 7.80 (d, *J* = 1.8 Hz, 1H), 7.53 (s, 1H), 3.76 (s, 6H), 3.74 (d, *J* = 1.0 Hz, 2H), 3.73 (s, 2H). **^{13}C-NMR (**101 MHz, $CDCl_3$) 171.7, 141.4, 141.1, 135.2, 132.1, 130.5, 129.7, 123.3, 122.3, 122.2, 118.4, 60.9, 53.3, 40.5, 40.2. **HRMS** (ESI) m/z calculated for $C_{17}H_{14}Br_2NaO_4^+$ $[M+Na]^+$: 462.9151, found: 462.9158.

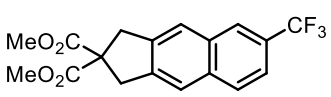
Dimethyl 6-fluoro-1,3-dihydro-2H-cyclopenta[*b*]naphthalene-2,2-dicarboxylate (1.40h)



Compound **1.40h** was synthesized following general procedure **B** starting from **1.39g** (38 mg, 0.10 mmol). The crude product was purified via flash chromatography followed by recrystallization from Et_2O affording **1.40h** as a white solid (method B: 11.8 mg, 39%).

M.p. 68-70 ºC. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.73 (dd, *J* = 9.0, 5.7 Hz, 1H), 7.63 (s, 1H), 7.59 (s, 1H), 7.36 (dd, *J* = 10.1, 2.5 Hz, 1H), 7.18 (td, *J* = 8.7, 2.6 Hz, 1H), 3.76 (s, 6H), 3.72 (s, 2H), 3.71 (s, 2H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ 116.07 (td, *J* = 9.2, 5.6 Hz).**^{13}C-NMR (**101 MHz, $CDCl_3$) δ 171.9, 160.6 (d, *J* = 244.8 Hz), 140.3, 138.4, 134.0 (d, *J* = 9.2 Hz), 130.3, 129.9 (d, *J* = 9.1 Hz), 122.7, 122.0 (d, *J* = 5.2 Hz), 115.7 (d, *J* = 25.3 Hz), 110.8 (d, *J* = 20.5 Hz), 61.0, 53.2, 40.3 (d, *J* = 12.9 Hz). **HRMS** (ESI) m/z calculated for $C_{17}H_{15}FNaO_4^+$ $[M+Na]^+$: 325.0847, found: 325.0844.

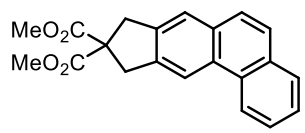
Dimethyl 6-(trifluoromethyl)-1,3-dihydro-2H-cyclopenta[*b*]naphthalene-2,2-dicarboxylate (1.40i)



Compound **1.40i** was synthesized following general procedure **B** starting from **1.39h** (43 mg, 0.1 mmol). The crude product was purified via flash chromatography followed by recrystallization from Et_2O affording **1.40i** as a white solid (method B: 14.8 mg, 42%).

M.p. the compound started to decompose at 131 °C. **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 8.05 (s, 1H), 7.85 (d, *J* = 8.6 Hz, 1H), 7.72 (d, *J* = 12.2 Hz, 2H), 7.56 (dd, *J* = 8.6, 1.7 Hz, 1H), 3.76 (s, 6H), 3.75 (d, *J* = 0.5 Hz, 4H). **^{13}C-NMR (**126 MHz, $CDCl_3$) δ z171.8, 141.6, 140.6, 134.5, 132.1, 128.7, 125.5 (q, J = 4.5 Hz), 123.6, 121.1 (q, J = 3.2 Hz), 61.0, 53.2 (q, J = 147.7 Hz), 53.2, 40.4, 40.3. **^{19}F NMR** (376 MHz, $CDCl_3$) -54.80.

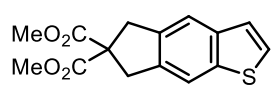
Dimethyl 8,10-dihydro-9H-cyclopenta[*b*]phenanthrene-9,9-dicarboxylate (1.40j)



Compound **1.40j** was synthesized following general procedure **B** starting from **1.39k**(42 mg, 0.1 mmol). The crude product was purified via flash chromatography followed by recrystallization from Et_2O affording **1.40j** as a white solid (method A: 13 mg, 39%).

M.p. 155-158 ºC. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 8.63 (d, *J* = 8.0 Hz, 1H), 8.51 (s, 1H), 7.86 (dd, *J* = 7.8, 1.1 Hz, 1H), 7.72 – 7.68 (m, 1H), 7.67 (s, 2H), 7.65 – 7.53 (m, 1H), 7.59 – 7.54 (m, 1H), 3.84 (s, 2H), 3.78 (d, *J* = 3.9 Hz, 2H), 3.77 (s, 6H). **^{13}C-NMR (**101 MHz, $CDCl_3$) 172.1, 139.5, 139.3, 132.1, 131.8, 130.4, 130.0, 128.6, 127.0, 126.5, 126.4, 123.7, 122.7, 118.0, 61.1, 5.18, 40.9, 40.5. **HRMS** (ESI) m/z calculated for $C_{21}H_{18}NaO_4^+$ $[M+Na]^+$: 367.1097, found: 357.1089.

Dimethyl 5,7-dihydro-6H-indeno[5,6-*b*]thiophene-6,6-dicarboxylate (1.40k)

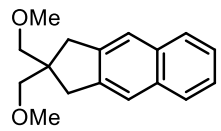


Compound **1.40k** was synthesized following general procedure **B** starting from **1.39j** (74.2 mg, 0.2 mmol), the reaction time was 14h. The crude product was purified via flash chromatography followed

by recrystallization from Et_2O affording **1.40k** as a white solid (method A: 13 mg, 0.044 mmol, 22%).

M.p. 110-112 ºC. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.68 (s, 1H), 7.62 (s, 1H), 7.35 (d, *J* = 5.4 Hz, 1H), 7.24 (d, *J* = 5.4 Hz, 1H), 3.75 (s, 5H), 3.68 (s, *J* = 3.3 Hz, 2H), 3.67 (s, 2H). **^{13}C-NMR (**101 MHz, $CDCl_3$) 172.9, 139.3, 139.1, 137.3, 137.2, 126.0, 123.6, 119.0, 117.9, 61.3, 53.1, 40.3, 40.2. **HRMS** (ESI) m/z calculated for $C_{15}H_{14}NaO_4S^+$ $[M+Na]^+$: 313.0505, found: 313.0511.

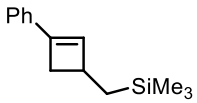
2,2-Bis(methoxymethyl)-2,3-dihydro-1H-cyclopenta[*b*]naphthalene (1.40l)



Compound **1.40l** was synthesized following general procedure **B** starting from **1.39m** (33.7 mg, 0.1 mmol). The crude product was purified via flash chromatography followed by recrystallization* from Et_2O affording **1.40l** as a white solid (method A: 11.4 mg, purity 90%, 0.04 mmol, 40%) * The crystallization did not increase the purity of the product.

M.p. 83-85 ºC. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.76 (dd, *J* = 6.2, 3.3 Hz, 2H), 7.63 (m, 2H), 7.40 (m, 2H), 3.42 (s, 4H), 3.38 (s, 6H), 3.00 (d, *J* = 1.1 Hz, 4H). **^{13}C-NMR (**101 MHz, $CDCl_3$) δ 141.7, 133.2, 127.5, 125.0, 123.0, 76.0, 59.5, 48.9, 38.6. **HRMS** (ESI) m/z calculated for $C_{17}H_{20}NaO_2^+$ $[M+Na]^+$: 279.1356, found: 279.1351.

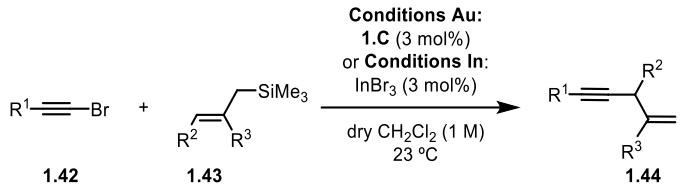
Synthesis of Cyclobutene 1.45



Ethynylbenzene (22 µL, 0.2 mmol, 1 equiv) was dissolved in dry CH_2Cl_2 (0.4 mL, 0.5 M). Allyltrimethylsilane (64 µL, 0.4 mmol, 2 equiv) was added, followed by [(*t*BuXPhos)AuNCMe]BAr_4^F (9 mg, 3 mol%). The resulting mixture was stirred at 50 ºC for 14 h in a sealed vial. The crude was directly subjected to silica gel column chromatography (eluent = pentane) to obtain the pure trimethyl((3-phenylcyclobut-2-en-1-yl)methyl)silane (colorless oil, 25 mg, 58%).

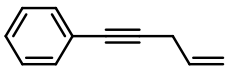
^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.43 – 7.31 (m, 4H), 7.29 – 7.24 (m, 1H), 6.41 (d, *J* = 1.2 Hz, 1H), 3.05 (dd, *J* = 12.6, 4.4 Hz, 1H), 3.00 – 2.86 (m, 1H), 2.33 (dd, *J* = 12.6, 1.7 Hz, 1H), 0.97 – 0.84 (m, 2H), 0.09 (s, 9H). **^{13}C-NMR (**75 MHz, $CDCl_3$) δ 143.7, 135.1, 133.5, 128.2 (2C), 127.4, 124.3 (2C), 37.8, 35.3, 22.4, -1.0 (3C). **HRMS** (APCI) *m/z* calculated for $C_{14}H_{21}Si^+$ $[M+H]^+$: 217.1407, found: 217.1406.

*General procedure C for the synthesis of 1,4-enynes **1.44***



The bromoalkyne (0.2 mmol, 1 equiv) was dissolved in dry CH_2Cl_2 (0.2 mL, 1 M). The allylsilane (0.4 mmol, 2 equiv) was added, followed by the catalyst (3 mol%, **method A**: 9 mg of [(*t*BuXPhos)AuNCMe]BAr_4^F (**1.C**) or **method B**: 2 mg of $InBr_3$). The resulting mixture was stirred at 23 ºC for 18 h (otherwise stated). The reaction was monitored by TLC or GC-MS. Once completed, the crude was directly subjected to silica gel column chromatography (eluent = pentane, otherwise stated) to obtain the pure 1,4-enyne.

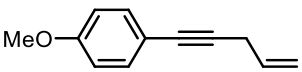
Pent-4-en-1-yn-1-ylbenzene (1.44a)



Enyne **1.44a** was synthesized following general procedure **C** starting from (bromoethynyl)benzene (36 mg, 0.2 mmol) and allyltrimethylsilane (64 µL, 0.4 mmol). The crude product was purified by flash chromatography affording **1.44a** as a colorless oil (method A: 22 mg, 77%; method B: 23 mg, 81%).

^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.47 – 7.38 (m, 2H), 7.32 – 7.23 (m, 3H), 5.98 – 5.81 (m, 1H), 5.46 – 5.35 (m, 1H), 5.22 – 5.12 (m, 1H), 3.24 – 3.15 (m, 1H). **^{13}C-NMR (**101 MHz, $CDCl_3$) δ 132.4, 131.6 (2C), 128.2 (2C), 127.7, 123.7, 116.2, 86.5, 82.9, 23.7. The NMR data match with those reported in the literature.[103]

1-Methoxy-4-(pent-4-en-1-yn-1-yl)benzene (1.44b)

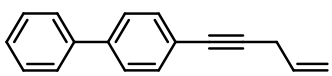


Enyne **1.44b** was synthesized following general procedure **C** starting from 1-(bromoethynyl)-4-methoxybenzene (42 mg, 0.2 mmol) and allyltrimethylsilane (64 µL, 0.4 mmol). The crude product was purified *via* flash chromatography affording **1.44b** as a yellow oil (method A: 23 mg, 67%; method B: 22 mg, 64%).

^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.40 – 7.33 (m, 2H), 6.87 – 6.79 (m, 2H), 5.95 – 5.85 (m, 1H), 5.40 (dq, *J* = 16.9, 1.8 Hz, 1H), 5.16 (dq, *J* = 10.0, 1.7 Hz, 1H), 3.80 (s, 3H), 3.18 (dt, *J* = 5.3, 1.8 Hz, 2H). **^{13}C-NMR (**126 MHz, $CDCl_3$) δ 159.2, 132.9 (2C), 132.7, 116.1, 115.8, 113.8 (2C), 84.9, 82.6, 55.2, 23.7. The NMR data match with those reported in the literature.[103]

103 J. Choe, Y. Yang, K. Park, T Palani, S. Lee, *Tetrahedron Lett.* **2012**, *53*, 6908–6912.

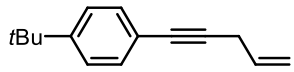
4-(Pent-4-en-1-yn-1-yl)-1,1'-biphenyl (1.44c)



Enyne **1.44c** was synthesized following general procedure **C** starting from 4-(bromoethynyl)-1,1'-biphenyl (51 mg, 0.2 mmol) and allyltrimethylsilane (64 µL, 0.4 mmol). The crude product was purified *via* flash chromatography affording **.144c** as a sticky yellow oil (method A: 27 mg, 62%; method B: 35 mg, 80%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.66 – 7.31 (m, 9H), 6.04 – 5.84 (m, 1H), 5.52 – 5.38 (m, 1H), 5.26 – 5.15 (m, 1H), 3.28 – 3.19 (m, 2H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 140.5, 140.4, 132.4, 132.0 (2C), 128.8 (2C), 127.5, 127.0 (2C), 126.9 (2C), 122.6, 116.3, 87.2, 82.7, 23.8. **HRMS** (APCI) m/z calculated for $C_{17}H_{15}^+$ $[M+H]^+$: 219.1168, found: 219.1160.

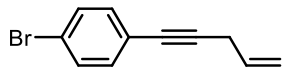
1-(*tert*-Butyl)-4-(pent-4-en-1-yn-1-yl)benzene (1.44d)



Enyne **1.44d** was synthesized following general procedure **C** starting from 1-(bromoethynyl)-4-(*tert*-butyl)benzene (47 mg, 0.2 mmol) and allyltrimethylsilane (64 µL, 0.4 mmol). The crude product was purified *via* flash chromatography affording **1.44d** as a yellow oil (method A: 28 mg, 71%; method B: 21 mg, 53%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.35 (m, 2H), 7.34 – 7.29 (m, 2H), 5.97 – 5.85 (m, 1H), 5.42 (dq, *J* = 17.0, 1.7 Hz, 1H), 5.17 (dq, *J* = 10.0, 1.7 Hz, 1H), 3.20 (dt, *J* = 5.2, 1.9 Hz, 2H), 1.32 (s, 9H). **^{13}C-NMR (**75 MHz, $CDCl_3$) δ 150.9, 132.6, 131.3 (2C), 125.2 (2C), 120.7, 116.1, 85.7, 82.9, 34.7, 31.2 (3C), 23.7. The NMR data match with those reported in the literature.[103]

1-Bromo-4-(pent-4-en-1-yn-1-yl)benzene (1.44e)

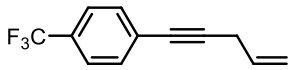


Enyne **1.44e** was synthesized following general procedure **C** starting from 1-bromo-4-(bromoethynyl)benzene (52 mg, 0.2 mmol) and allyltrimethylsilane (64 µL, 0.4 mmol). The reaction was carried out at 50 °C in a sealed vial for 16 h. The crude product was purified *via* flash chromatography affording **1.44e** as a yellow oil (method A: 27 mg, 60%; method B: 32 mg, 73%).

^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.45 – 7.39 (m, 2H), 7.31 – 7.25 (m, 2H), 5.89 (ddt, *J* = 17.0, 10.0, 5.3 Hz, 1H), 5.39 (dq, *J* = 17.0, 1.8 Hz, 1H), 5.17 (dq, *J* = 10.0, 1.7 Hz, 1H), 3.18 (dt, *J* = 5.3, 1.8 Hz, 2H). **^{13}C-NMR (**126 MHz, $CDCl_3$) δ 133.2 (2C), 132.3, 131.6 (2C), 122.8, 122.0, 116.6 (2C), 88.0, 82.0, 23.9. The NMR data match with those reported in the literature.[104]

104 A. R. Katritzky, A. A. A. Abdel-Fattah, M. Wang, *J. Org. Chem.* **2002**, *67*, 7526–7529.

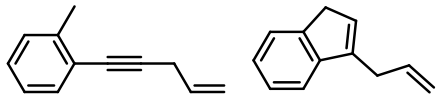
1-(Pent-4-en-1-yn-1-yl)-4-(trifluoromethyl)benzene (1.44f)



Enyne **1.44f** was synthesized following general procedure **C** starting from 1-(bromoethynyl)-4-(trifluoromethyl)benzene (49.8 mg, 0.2 mmol) and allyltrimethylsilane (64 µL, 0.4 mmol). The reaction was carried out at at 50 ºC for 40 h. The crude product was purified *via* flash chromatography affording **1.44f** as a yellow oil (method A: 26 mg, 62%; method B: 31 mg, 74%).

^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.5 Hz, 2H), 7.52 (d, *J* = 8.5 Hz, 2H), 5.90 (ddt, *J* = 17.0, 10.3, 5.3 Hz, 1H), 5.40 (dd, *J* = 17.0, 1.7 Hz, 1H), 5.19 (dq, *J* = 10.0, 1.6 Hz, 1H), 3.22 (dt, *J* = 5.3, 1.8 Hz, 2H). **^{13}C-NMR (**126 MHz, $CDCl_3$) δ 132.1, 132.0, 129.7 (q, *J* = 32.6 Hz), 127.7, 125.3 (q, *J* = 3.8 Hz), 124.1 (q, *J* = 272 Hz) 116.7, 89.6, 81.8, 23.9. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -62.88. **HRMS** (APCI) *m/z* calculated for $C_{12}H_{10}F_3^+$ $[M+H]^+$: 211.0729, found: 211.0724.

1-Methyl-2-(pent-4-en-1-yn-1-yl)benzene and 3-allyl-1H-indene (1.44g and 1.46a)



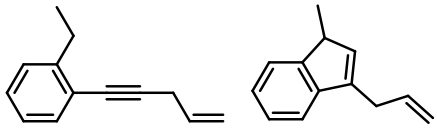
Enyne **1.44g** and indene **1.46a** were synthesized following general procedure **C** (methods A and B) starting from 1-(bromoethynyl)-2-methylbenzene (39 mg, 0.2 mmol) and allyltrimethylsilane (64 µL, 0.4 mmol).

1-Methyl-2-(pent-4-en-1-yn-1-yl)benzene **1.44a** was obtained as a yellow oil (method A: 24 mg, 77%; method B: 22 mg, 70%). **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.40 (dt, *J* = 7.4, 1.1 Hz, 1H), 7.23 – 7.16 (m, 2H), 7.15 – 7.08 (m, 1H), 5.93 (ddt, *J* = 16.9, 10.2, 5.2 Hz, 1H), 5.45 (dq, *J* = 17.0, 1.8 Hz, 1H), 5.18 (dq, *J* = 10.0, 1.7 Hz, 1H), 3.25 (dt, *J* = 5.2, 1.8 Hz, 2H), 2.44 (s, 3H). **^{13}C-NMR (**126 MHz, $CDCl_3$) δ 140.1, 132.8, 132.1, 129.5, 127.9, 125.6, 123.6, 116.3, 90.6, 82.0, 24.0, 20.9. The NMR data match with those reported in the literature.[103]

3-Allyl-1H-indene **1.46a** was obtained by method A. This product was isolated as a colorless oil in mixture 10:1 with 1-methyl-2-(pent-4-en-1-yn-1-yl)benzene (method A: 7.5 mg, 24% isolated yield, 20% yield according to ^{1}H-NMR using 2-bromomesitylene as internal standard). **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.46 (dt, J = 7.3, 1.0 Hz, 1H), 7.37 (dt, J = 7.5, 1.0 Hz, 1H), 7.29 (tdd, J = 7.5, 1.2, 0.6 Hz, 1H), 7.20 (td, J = 7.4, 1.2 Hz, 1H), 6.25 (t, J = 1.6 Hz, 1H), 6.05 (ddt, J = 16.6, 10.1, 6.5 Hz, 1H), 5.19 (dq, J = 17.1, 1.6 Hz, 1H), 5.14 – 5.09 (m, 1H), 3.38 – 3.30 (m, 4H). **^{13}C-NMR (**126 MHz, $CDCl_3$) δ 144.6, 142.6, 139.7, 135.8, 129.1, 126.1, 124.7, 123.9, 119.3, 116.4, 37.9, 32.6. The NMR data match with those reported in the literature.[105]

105 S. Silver, A.-S. Leppänen, R. Sjöholm, A. Penninkangas, R. Leino, R. *Eur. J. Org. Chem.* **2005**, 1058–1081.

Mixture of 1-ethyl-2-(pent-4-en-1-yn-1-yl)benzene and 3-allyl-1-methyl-1H-indene (1.5:1) (1.44h and 1.46b)

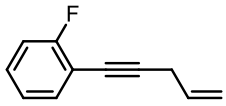


Enyne **1.44h** and indene **1.46b** were synthesized following the general procedure **C** (methods A and B) starting from1-(bromoethynyl)-2-ethylbenzene (23 mg, 0.1 mmol) and allyltrimethylsilane (64 µL, 0.4 mmol).**1.46b** was obtained just with method A and the products were obtained as an unseparable mixture after purification *via* flash chromatography. ^{1}H-NMR yields were determined using 2-bromomesitylene as internal standard.

1-Ethyl-2-(pent-4-en-1-yn-1-yl)benzene **1.44h** was obtained as a yellow oil (method A: 40% yield according to ^{1}H-NMR, method B: 18 mg, 53%) **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.43 – 7.37 (m, 1H), 7.26 – 7.20 (m, 1H), 7.23 – 7.17 (m, 1H), 7.12 (td, *J* = 7.3, 1.9 Hz, 1H), 5.92 (ddt, *J* = 17.0, 10.2, 5.2 Hz, 1H), 5.43 (dq, *J* = 17.0, 1.8 Hz, 1H), 5.21 – 5.14 (m, 1H), 3.24 (dt, *J* = 5.2, 1.9 Hz, 2H), 2.82 (q, *J* = 7.6 Hz, 2H), 1.25 (t, *J* = 7.6 Hz, 3H).**^{13}C-NMR (**126 MHz, $CDCl_3$) δ 146.4, 136.0, 133.0, 132.6, 128.3, 128.2, 125.9, 123.2, 116.5, 90.3, 81.9, 24.2, 15.2.

3-Allyl-1-methyl-1H-indene **1.46b** was obtained as a yellow oil (method A: 29% yield according to ^{1}H-NMR). **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.43 – 7.37 (m, 1H), 7.32 (dt, *J* = 7.3, 1.1 Hz, 1H), 7.29 – 7.25 (m, 2H), 6.17 (q, *J* = 1.7 Hz, 1H), 6.04 (ddt, *J* = 16.8, 10.1, 6.6 Hz, 1H), 5.19 (dq, *J* = 7.8, 1.7 Hz, 1H), 5.12 (dq, *J* = 10.1, 1.5 Hz, 1H), 3.44 (qd, *J* = 7.5, 2.0 Hz, 1H), 3.29 (dp, *J* = 6.6, 1.6 Hz, 2H), 1.30 (d, *J* = 7.6 Hz, 3H). **^{13}C-NMR (**126 MHz, $CDCl_3$) δ 150.3, 144.6, 141.0, 136.6 (2C), 126.5, 125.2, 122.9, 119.6, 116.6, 44.0, 32.6, 16.6.

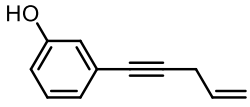
1-Fluoro-2-(pent-4-en-1-yn-1-yl)benzene (1.44i)



Enyne **1.44i** was synthesized following general procedure **C** starting from1-(bromoethynyl)-2-fluorobenzene (40 mg, 0.2 mmol) and allyltrimethylsilane (64 µL, 0.4 mmol). The reaction time was 72 h. The crude product was purified *via* flash chromatography affording **.144i** as a colorless oil (method A: 16 mg, 50%; method B: 25 mg, 78%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.38 (m, 1H), 7.33 – 7.20 (m, 1H), 7.11 – 6.99 (m, 2H), 5.91 (ddt, *J* = 17.0, 10.2, 5.2 Hz, 1H), 5.44 (dq, *J* = 17.0, 1.8 Hz, 1H), 5.19 (dq, *J* = 10.0, 1.7 Hz, 1H), 3.24 (dt, *J* = 5.1, 1.7 Hz, 2H). **^{13}C-NMR (**75 MHz, $CDCl_3$) δ 164.3 (d, *J* (^{13}C-^{19}F) = 250.6 Hz), 133.5 (d, *J* (^{13}C-^{19}F) = 1.6 Hz), 132.0, 129.3 (d, *J* (^{13}C-^{19}F) = 7.9 Hz), 123.8 (d, *J* (^{13}C-^{19}F) = 3.7 Hz), 116.4, 115.4 (d, *J* (^{13}C-^{19}F) = 21.0 Hz), 112.15 (d, *J* (^{13}C-^{19}F) = 15.8 Hz), 92.0 (d, *J* (^{13}C-^{19}F) = 3.3 Hz), 76.2, 23.8. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -110.93. **HRMS** (APCI) *m/z* calculated for $C_{11}H_{10}F^+$ $[M+H]^+$: 161.0761, found: 161.0755.

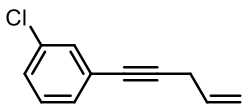
3-(Pent-4-en-1-yn-1-yl)phenol (1.44j)



Enyne **1.44j** was synthesized following general procedure **C** starting from 1-(bromoethynyl)-3-chlorobenzene (43 mg, 0.2 mmol) and allyltrimethylsilane (64 µL, 0.4 mmol). The reaction time was 72 h. In the purification pentane and then a 1:1 mixture of pentane:DCM were used. Only 13 mg (yellow oil, 42% yield) of the desired product **1.44j** were isolated due to a byproduct with almost identical R_f. (method A: 63%; method B: 56% yield according to ^{1}H-NMR).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.16 (t, *J* = 7.9 Hz, 1H), 7.01 (dt, *J* = 7.6, 1.2 Hz, 1H), 6.89 (dd, *J* = 2.6, 1.4 Hz, 1H), 6.77 (ddd, *J* = 8.2, 2.6, 1.0 Hz, 1H), 5.89 (ddt, *J* = 17.0, 10.0, 5.3 Hz, 1H), 5.40 (dq, *J* = 17.0, 1.8 Hz, 1H), 5.17 (dq, *J* = 10.0, 1.7 Hz, 1H), 4.86 – 4.73 (m, 1H), 3.19 (dt, *J* = 5.3, 1.8 Hz, 2H). **^{13}C-NMR (**75 MHz, $CDCl_3$) δ 155.2, 132.3, 129.5, 124.9, 124.3, 118.3, 116.3, 115.2, 86.7, 82.4, 23.7. **HRMS** (ESI-) *m/z* calculated for $C_{11}H_9O^-$ $[M-H]^-$: 157.0659, found: 157.0659.

1-Chloro-3-(pent-4-en-1-yn-1-yl)benzene (1.44k)

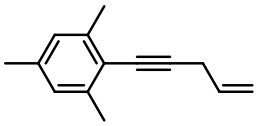


The title compound (yellow oil, was synthesized according to the general procedure starting from. The reaction was carried out at 50 ºC in a sealed vial.

Enyne **1.44k** was synthesized following general procedure **C** starting from 1-(bromoethynyl)-3-chlorobenzene (43 mg, 0.2 mmol) and allyltrimethylsilane (64 µL, 0.4 mmol). The reaction was carried out at 50 °C in a sealed vial. The crude product was purified *via* flash chromatography affording **1.44k** as a yellow oil (A: 16 mg, 45%; method B: 15 mg, 43%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.45 (m, 1H), 7.35 – 7.20 (m, 3H), 5.91 (ddt, *J* = 16.9, 10.3, 5.3 Hz, 1H), 5.41 (dq, *J* = 17.0, 1.8 Hz, 1H), 5.20 (dq, *J* = 10.0, 1.7 Hz, 1H), 3.21 (dt, *J* = 5.3, 1.8 Hz, 2H). **^{13}C-NMR (**126 MHz, $CDCl_3$) δ 134.0, 132.1, 131.5, 129.7, 129.4, 128.0, 125.4, 116.4, 88.0, 81.5, 23.6. **HRMS** (APCI) *m/z* calculated for $C_{11}H_8Cl^+$ $[M-H]^+$: 175.0309, found: 175.0309.

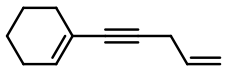
1,3,5-Trimethyl-2-(pent-4-en-1-yn-1-yl)benzene (1.44l)



Enyne **1.44l** was synthesized following general procedure **C** starting from 2-(bromoethynyl)-1,3,5-trimethylbenzene (45 mg, 0.2 mmol) and allyltrimethylsilane (64 µL, 0.4 mmol). The crude product was purified *via* flash chromatography using cyclohexane:triethylamine 99:1 as eluent affording **1.44l** as a yellow oil (method A: 36 mg, 98%; method B: 34 mg, 92%).

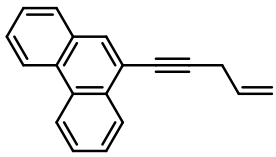
^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.93 – 6.79 (m, 2H), 6.04 – 5.85 (m, 1H), 5.46 (dq, *J* = 17.0, 1.9 Hz, 1H), 5.17 (dq, *J* = 10.0, 1.7 Hz, 1H), 3.29 (dt, *J* = 5.1, 1.9 Hz, 2H), 2.40 (s, 6H), 2.27 (s, 3H). **^{13}C-NMR (**75 MHz, $CDCl_3$) δ 140.0 (2C), 136.9, 132.9, 127.4 (2C), 120.4, 115.9, 93.9, 80.6, 24.0, 21.2, 21.0 (2C). **HRMS** (APCI) *m/z* calculated for $C_{14}H_{17}^+$ $[M+H]^+$: 185.1325, found: 185.1217.

1-(Pent-4-en-1-yn-1-yl)cyclohex-1-ene (1.44m)



Enyne **1.44m** was synthesized following general procedure **C** starting from 1-(bromoethynyl)cyclohex-1-ene (37 mg, 0.2 mmol) and allyltrimethylsilane (64 µL, 0.40 mmol). The crude product was purified *via* flash chromatography affording **1.44m** as a yellow oil (method A: 9 mg, 31%; method B: 6 mg, 21%). **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 6.08 – 6.02 (m, 1H), 5.84 (ddt, *J* = 17.0, 10.2, 5.3 Hz, 1H), 5.32 (dq, *J* = 16.9, 1.8 Hz, 1H), 5.11 (dq, *J* = 10.0, 1.7 Hz, 1H), 3.14 – 3.02 (m, 2H), 2.19 – 2.01 (m, 4H), 1.72 – 1.48 (m, 4H). **^{13}C-NMR (**126 MHz, $CDCl_3$) δ 133.7, 132.9, 120.8, 115.9, 84.7, 83.5, 29.5, 25.6, 23.6, 22.4, 21.6. **HRMS** (APCI) *m/z* calculated for $C_{11}H_{15}^+$ $[M+H]^+$: 147.1168, found: 141.1166.

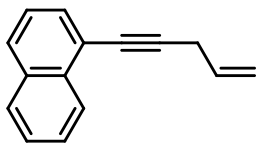
9-(Pent-4-en-1-yn-1-yl)phenanthrene (1.44n)



Enyne **1.44n** was synthesized following general procedure **C** starting from 9-(bromoethynyl)phenanthrene (42 mg, 0.15 mmol) and allyltrimethylsilane (48 µL, 0.30 mmol). The crude product was purified *via* flash chromatography affording **1.44n** as a sticky yellow oil (method A: 22 mg, 61%; method B: 20 mg, 55%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.72 – 8.62 (m, 2H), 8.57 – 8.42 (m, 1H), 7.99 (s, 1H), 7.90 – 7.78 (m, 1H), 7.74 – 7.51 (m, 4H), 6.03 (ddt, *J* = 17.0, 10.2, 5.3 Hz, 1H), 5.55 (dq, *J* = 17.0, 1.8 Hz, 1H), 5.27 (dq, *J* = 10.0, 1.7 Hz, 1H), 3.41 (dt, *J* = 5.4, 1.8 Hz, 2H). **^{13}C-NMR (**126 MHz, $CDCl_3$) δ 132.5, 131.5, 131.4, 131.3, 130.1, 130.0, 128.4, 127.2, 127.0, 126.9, 126.9, 126.8, 122.7, 122.5, 120.1, 116.5, 91.2, 81.0, 24.1. **HRMS** (APCI) *m/z* calculated for $C_{19}H_{15}^+$ $[M+H]^+$: 243.1168, found: 243.1167.

1-(Pent-4-en-1-yn-1-yl)naphthalene (1.44o)

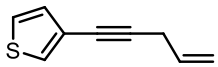


Enyne **1.44o** was synthesized following general procedure **C** starting from 1-(bromoethynyl)naphthalene (46 mg, 0.2 mmol) and allyltrimethylsilane (64 µL, 0.4 mmol). The crude product was purified *via* flash chromatography using pentane and then a

pentane:DCM 1:1 mixture as eluent affording **1.44o** as a yellow oil (method A: 21 mg, 55%; method B: 25 mg, 65%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.42 – 8.36 (m, 1H), 7.90 – 7.77 (m, 2H), 7.68 (dd, *J* = 7.2, 1.2 Hz, 1H), 7.55 (dddd, *J* = 22.9, 8.1, 6.8, 1.4 Hz, 2H), 7.43 (dd, *J* = 8.3, 7.1 Hz, 1H), 6.02 (ddt, *J* = 17.0, 10.2, 5.2 Hz, 1H), 5.54 (dq, *J* = 17.0, 1.8 Hz, 1H), 5.25 (dq, *J* = 10.0, 1.7 Hz, 1H), 3.39 (dt, *J* = 5.3, 1.8 Hz, 2H). **^{13}C-NMR (**101 MHz, $CDCl_3$) δ 133.5, 133.2, 132.5, 130.2, 128.2, 128.2, 126.5, 126.2 (2C), 125.2, 121.4, 116.4, 91.5, 80.9, 24.0. **HRMS** (APCI) *m/z* calculated for $C_{15}H_{13}^+$ $[M+H]^+$: 193.1012, found: 193.1012.

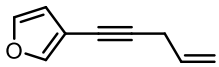
3-(Pent-4-en-1-yn-1-yl)thiophene (1.44p)



Enyne **1.44p** was synthesized following general procedure **C** starting from 3-(bromoethynyl)thiophene (37.4 mg, 0.2 mmol) and allyltrimethylsilane (64 µL, 0.4 mmol). The crude product was purified *via* flash chromatography affording **1.44p** as a yellow oil (method A: 14 mg, 48%; method B: 13 mg, 44%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.39 (dd, *J* = 3.0, 1.2 Hz, 1H), 7.24 (dd, *J* = 5.0, 3.0 Hz, 1H), 7.10 (dd, *J* = 5.0, 1.2 Hz, 1H), 5.90 (ddt, *J* = 17.0, 9.9, 5.3 Hz, 1H), 5.39 (dq, *J* = 17.0, 1.8 Hz, 1H), 5.17 (dq, *J* = 10.0, 1.7 Hz, 1H), 3.18 (dt, *J* = 5.3, 1.8 Hz, 2H). **^{13}C-NMR (**126 MHz, $CDCl_3$) δ 132.5, 130.1, 128.0, 125.2, 122.8, 116.4, 86.2, 78.0, 23.9. **HRMS** (APCI) *m/z* calculated for $C_9H_9S^+$ $[M+H]^+$: 149.0419, found: 149.0419.

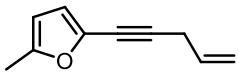
3-(Pent-4-en-1-yn-1-yl)furan (1.44q)



Enyne **1.44q** was synthesized following general procedure **C** starting from 3-(bromoethynyl)furan (25.6 mg, 0.15 mmol) and allyltrimethylsilane (48 µL, 0.3 mmol). The crude product was purified *via* flash chromatography affording **1.44q** as a yellow oil (method A: 6 mg, 23%; method B: 4 mg, 20%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.62 – 7.57 (m, 1H), 7.37 (t, *J* = 1.7 Hz, 1H), 6.45 (dd, *J* = 1.9, 0.8 Hz, 1H), 5.90 (ddt, *J* = 16.9, 9.9, 5.4 Hz, 1H), 5.39 (dq, *J* = 16.9, 1.8 Hz, 1H), 5.18 (dq, *J* = 10.0, 1.7 Hz, 1H), 3.18 (dt, *J* = 5.4, 1.8 Hz, 2H). **^{13}C-NMR (**126 MHz, $CDCl_3$) δ 145.2, 142.6, 132.4, 116.29, 112.7, 107.8, 88.3, 73.7, 23.8. **HRMS** (APCI) *m/z* calculated for $C_9H_9O^+$ $[M+H]^+$: 133.0648, found: 133.0649.

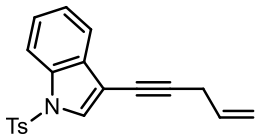
2-Methyl-5-(pent-4-en-1-yn-1-yl)furan (1.44r)



Enyne **1.44r** was synthesized following general procedure **C** starting from 2-(bromoethynyl)-5-methylfuran[106] (61.7 mg, 0.2 mmol) and allyltrimethylsilane (64 µL, 0.4 mmol). The crude product was purified *via* flash chromatography affording **1.44r** as a yellow oil (method A: 9 mg, 31%; method B: 7 mg, 22%).

^{1}H-NMR (500 MHz, Chloroform-d) δ 6.40 (d, J = 3.2 Hz, 1H), 5.94 (dq, J = 3.1, 1.0 Hz, 1H), 5.86 (ddt, J = 17.0, 10.0, 5.4 Hz, 1H), 5.37 (dq, J = 17.0, 1.7 Hz, 1H), 5.16 (dq, J = 10.0, 1.6 Hz, 1H), 3.21 (dt, J = 5.4, 1.8 Hz, 2H), 2.28 (t, J = 0.7 Hz, 3H). **^{13}C-NMR (**126 MHz, Chloroform-d) δ 153.3, 135.9, 132.1, 117.0, 115.6, 107.1, 90.9, 73.8, 24.2, 14.1. **HRMS** (APCI) *m/z* calculated for $C_{10}H_{11}O^+$ $[M+H]^+$: 147.0804, found: 147.0804.

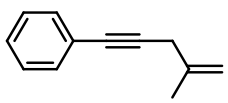
3-(Pent-4-en-1-yn-1-yl)-1-tosyl-1H-indole (1.44s)



Enyne **1.44s** was synthesized following general procedure **C** starting from 3-(bromoethynyl)-1-tosyl-1H-indole[107] (75 mg, 0.2 mmol) and allyltrimethylsilane (64 µL, 0.4 mmol). The crude product was purified *via* flash chromatography affording **1.44s** as a yellow oil (method A: 58 mg, 87%; method B: 13 mg, 19%).

^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.00 – 7.94 (m, 1H), 7.80 – 7.73 (m, 2H), 7.69 (s, 1H), 7.63 (dt, *J* = 7.7, 0.9 Hz, 1H), 7.34 (ddd, *J* = 8.4, 7.2, 1.3 Hz, 1H), 7.28 (td, *J* = 7.9, 1.3 Hz, 1H), 7.21 (d, *J* = 8.2 Hz, 2H), 5.92 (ddt, *J* = 17.0, 10.3, 5.3 Hz, 1H), 5.44 (dq, *J* = 16.9, 1.8 Hz, 1H), 5.19 (dq, *J* = 10.0, 1.7 Hz, 1H), 3.26 (dt, *J* = 5.3, 1.8 Hz, 2H), 2.33 (s, 3H). **^{13}C-NMR (**126 MHz, $CDCl_3$) δ 145.3, 135.1, 134.3, 132.4, 131.2, 130.1 (2C), 128.5, 127.0 (2C), 125.5, 123.8, 120.6, 116.6, 113.7, 105.8, 91.1, 73.8, 24.1, 21.7. **HRMS** (APCI) *m/z* calculated for $C_{20}H_{18}NO_2S^+$ $[M+H]^+$: 336.1053, found: 336.1065; *m/z* calculated for $C_{20}H_{17}NNaO_2S^+$ $[M+Na]^+$: 358.0872, found: 358.0887.

(4-Methylpent-4-en-1-yn-1-yl)benzene (1.44t)

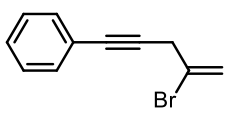


Enyne **1.44t** was synthesized following general procedure **C** starting from (bromoethynyl)benzene (36 mg, 0.2 mmol) and trimethyl(2-methylallyl)silane (70 µL, 0.4 mmol). The reaction time was 72h. The crude product was purified *via* flash chromatography affording **1.44t** as a colorless oil (method A and B: 17 mg, 54%).

106 S.K. Moodapelly, G. V. M. Sharma, V. K. Doddi, *Adv. Synth. Catal*. **2017**, *359*, 1535–1540.
107 C. D. Campbell, R. L. Greenaway, O. T. Holton, P. R. Walker, H. A. Chapman, C. A. Russell, G. Carr, A. L. Thomson, E. A. Anderson, *Chem. Eur. J*. **2015**, *21*, 12627–12639.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.47 – 7.39 (m, 2H), 7.34 – 7.25 (m, 3H), 5.14 – 5.06 (m, 1H), 4.94 – 4.85 (m, 1H), 3.14 (bs, 2H), 1.91 – 1.82 (m, 3H). **^{13}C-NMR (**75 MHz, $CDCl_3$) δ 140.5, 131.6 (2C), 128.2 (2C), 127.7, 123.8, 111.8, 87.1, 82.8, 28.1, 22.1. The NMR data match with those reported in the literature.[108]

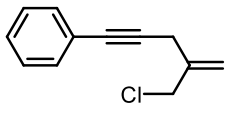
(4-Bromopent-4-en-1-yn-1-yl)benzene (1.44u)



Enyne **1.44u** was synthesized following general procedure **C** starting from (bromoethynyl)benzene (36 mg, 0.2 mmol) and (2-bromoallyl)trimethylsilane (69 µL, 0.4 mmol). The reaction was carried out at 50 ºC for 72 h in a sealed vial. The crude product was purified *via* flash chromatography affording **1.44u** as a yellow oil (method A: 28 mg, 64% - method B: 0%).

^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.48 – 7.41 (m, 2H), 7.35 – 7.28 (m, 3H), 6.10 – 6.05 (m, 1H), 5.62 – 5.58 (m, 1H), 3.58 (t, *J* = 1.5 Hz, 2H). **^{13}C-NMR (**126 MHz, $CDCl_3$) δ 131.6 (2C), 128.3 (2C), 128.2, 127.1, 123.0, 118.0, 84.6, 84.0, 32.4. **HRMS** (APCI) *m/z* calculated for $C_{11}H_{10}Br^+$ $[M+H]^+$: 220.9960, found: 220.9952.

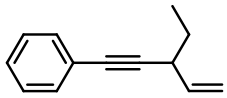
(4-(Chloromethyl)pent-4-en-1-yn-1-yl)benzene (1.44v)



Enyne **1.44v** was synthesized following general procedure **C** starting from(bromoethynyl)benzene (36 mg, 0.2 mmol) and (2-(chloromethyl)allyl)trimethylsilane (72 µL, 0.4 mmol). The reaction time was 48 h. The crude product was purified *via* flash chromatography affording **1.44v** as a green oil (method A: 18 mg, 48%; method B: 0%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.39 (m, 2H), 7.33 – 7.27 (m, 3H), 5.41 – 5.36 (m, 1H), 5.32 – 5.26 (m, 1H), 4.18 (bs, 2H), 3.34 (bs, 2H). **^{13}C-NMR (**101 MHz, $CDCl_3$) δ 140.3, 131.6 (2C), 128.2 (2C), 127.9, 123.4, 116.4, 85.6, 83.5, 47.4, 24.2. **HRMS** (APCI) *m/z* calculated for $C_{12}H_{12}Cl^+$ $[M+H]^+$: 191.0622, found: 191.0619.

(3-Ethylpent-4-en-1-yn-1-yl)benzene (1.44w)

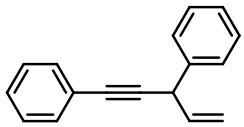


Enyne **1.44w** was synthesized following general procedure **C** starting from (bromoethynyl)benzene (36 mg, 0.2 mmol) and (*E*)-trimethyl(pent-2-en-1-yl)silane (40% solution in pentane, 157 mg, 0.44 mmol).The crude product was purified *via* flash chromatography affording **1.44w** as a yellow oil (method A (50ºC, 64 h): 16 mg, 47%; method B (50ºC, 16 h): 25 mg, 73%).

108 D.-M. Cui, N. Hashimoto, S. Ikeda, Y. Sato, *J. Org. Chem.* **1995**, *60*, 5752–5756.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.39 (m, 2H), 7.33 – 7.25 (m, 3H), 5.85 (ddd, *J* = 17.0, 10.0, 6.1 Hz, 1H), 5.38 (dt, *J* = 17.0, 1.6 Hz, 1H), 5.14 (dt, *J* = 10.1, 1.5 Hz, 1H), 3.23 (dtt, *J* = 7.5, 6.0, 1.5 Hz, 1H), 1.77 – 1.56 (m, 2H), 1.06 (t, *J* = 7.4 Hz, 3H). **^{13}C-NMR (**126 MHz, $CDCl_3$) δ 138.0, 131.8 (2C), 128.3 (2C), 127.8, 124.0, 115.3, 90.5, 83.8, 37.8, 28.6, 11.6. The NMR data match with those reported in the literature.[109]

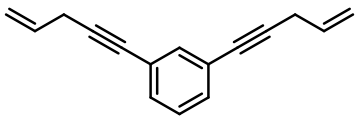
Pent-4-en-1-yne-1,3-diyldibenzene (1.44x)



Enyne **1.44x** was synthesized following general procedure **C** starting from(bromoethynyl)benzene (36 mg, 0.2 mmol) and cinnamyltrimethylsilane (76 mg, 0.4 mmol). The crude product was purified *via* flash chromatography affording **1.44x** as a yellow oil (method A (20ºC, 5 days): 15 mg, 35%; method B (20ºC, 20 h): 24 mg, 55%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.54 – 7.44 (m, 4H), 7.40 – 7.20 (m, 6H), 6.03 (ddd, *J* = 16.9, 9.9, 6.1 Hz, 1H), 5.48 (dt, *J* = 16.9, 1.5 Hz, 1H), 5.22 (dt, *J* = 9.9, 1.4 Hz, 1H), 4.61 (d, *J* = 6.1, 1H). **^{13}C-NMR (**75 MHz, $CDCl_3$) δ 140.1, 137.9, 131.7 (2C), 128.6 (2C), 128.2 (2C), 128.0, 127.7 (2C), 127.0, 123.5, 115.2, 88.6, 85.3, 42.0. The NMR data match with those reported in the literature.[110]

1,3-Di(pent-4-en-1-yn-1-yl)benzene (1.44y)

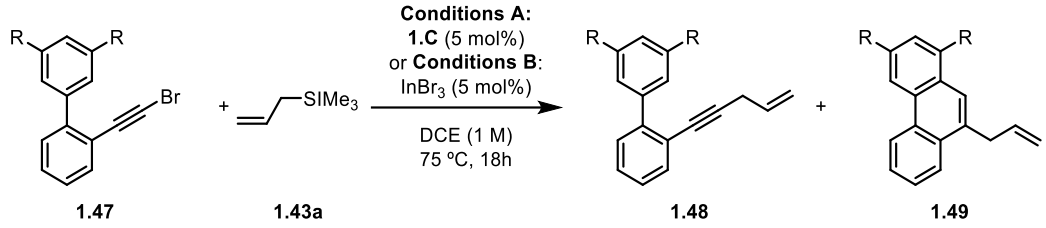


Enyne **1.44y** was synthesized following general procedure **C** starting from 1,3-bis(bromoethynyl)benzene (56.8 mg, 0.2 mmol) and allyltrimethylsilane (175 µL, 1.1 mmol). The crude product was purified *via* flash chromatography affording **1.44y** as a colorless oil (method A: 18 mg, 44%; method B: 26 mg, 63%).

^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.50 (t, *J* = 1.7 Hz, 1H), 7.34 (dd, *J* = 7.7, 1.6 Hz, 2H), 7.22 (t, *J* = 7.7 Hz, 1H), 5.89 (ddt, *J* = 17.0, 10.3, 5.3 Hz, 2H), 5.40 (dq, *J* = 17.0, 1.7 Hz, 3H), 5.17 (dq, *J* = 10.0, 1.6 Hz, 3H), 3.19 (dt, *J* = 5.3, 1.9 Hz, 4H). **^{13}C-NMR (**126 MHz, $CDCl_3$) δ 134.8, 132.4 (2C), 131.0 (2C), 128.3, 124.0 (2C), 116.5 (2C), 87.2 (2C), 82.3 (2C), 23.8 (2C). **HRMS** (APCI) *m/z* calculated for $C_6H_{15}^+$ $[M+H]^+$: 207.1168, found: 207.1160.

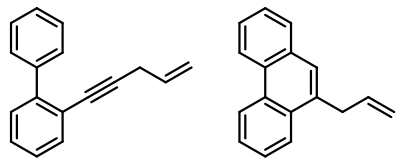
*General procedure D for Intermolecular reaction of bromoalkynes **1.47** with allylsilanes **1.43** by gold or indium catalysis*

109 H. Li, A. Alexakis,. *Angew. Chem. Int. Ed*, **2012**, 51, 1055–1058.
110 J. Y. Hamilton, D. Sarlah, E. M. Carreira, *Angew. Chem. Int. Ed.* **2013**, *52*, 7532–7535.



The bromoalkyne (0.2 mmol, 1 equiv) was dissolved in DCE (0.2 mL, 1 M). The allylsilane (0.4 mmol, 2 equiv) was added, followed by the catalyst (5 mol%; **method A**: 15 mg of [(*t*BuXPhos)AuNCMe]BAr_4^F (**1.C**) or **method B**: 3.5 mg of $InBr_3$). The resulting mixture was stirred at 75 ºC for 18 h (otherwise stated). The reaction was monitored by TLC or GC-MS. The crude was directly subjected to silica gel column chromatography (eluent = pentane, otherwise stated) to obtain the pure 1,4-enyne and 1,4-diene.

2-(Pent-4-en-1-yn-1-yl)-1,1'-biphenyl and 9-allylphenanthrene (1.48a and 1.49a)



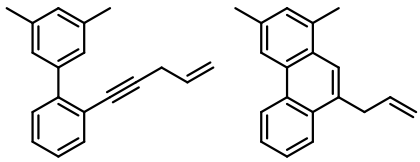
Enyne **1.48a** and phenanthrene **1.49a** were synthesized following the general procedure **D** (methods A and B) starting from 2-(bromoethynyl)-1,1'-biphenyl (51 mg, 0.2 mmol) and allyltrimethylsilane (64 µL, 0.4 mmol).**1.48a** and **1.49a** were separated by flash chromatography using pentane and then a 9:1 mixture of pentane.

2-(Pent-4-en-1-yn-1-yl)-1,1'-biphenyl **1.48a** was obtained as a colorless oil (method A: 23 mg, 53%, method B: 14 mg, 32%). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.64 – 7.58 (m, 2H), 7.58 – 7.53 (m, 1H), 7.46 – 7.32 (m, 5H), 7.31 – 7.25 (m, 1H), 5.78 (ddtd, *J* = 16.6, 10.2, 5.2, 1.3 Hz, 1H), 5.20 (dp, *J* = 17.0, 1.6 Hz, 1H), 5.06 (dp, *J* = 9.9, 1.6 Hz, 1H), 3.09 (dq, *J* = 5.1, 1.6 Hz, 2H). **^{13}C-NMR (**101 MHz, $CDCl_3$) δ 143.7, 140.7, 133.1, 132.1, 129.4, 129.3 (2C), 127.9, 127.8 (2C), 127.2, 126.9, 122.0, 116.1, 89.5, 82.4, 23.8. **HRMS** (APCI) *m/z* calculated for $C_{17}H_{15}^+$ $[M+H]^+$: 219.1168, found: 219.1168.

9-Allylphenanthrene **1.49a** was obtained as a colorless oil (method A: 10 mg, 23%, method B: 7 mg, 17%). **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 8.74 (dd, *J* = 7.9, 1.6 Hz, 1H), 8.67 (d, *J* = 8.1 Hz, 1H), 8.10 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.85 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.74 – 7.54 (m, 5H), 6.20 (ddt, *J* = 15.7, 11.2, 6.2 Hz, 1H), 5.19 (bs, 1H), 5.16 (dm, *J* = 7.1, 1H), 3.90 (bd, *J* = 6.3, 2H). **^{13}C-NMR (**126 MHz, $CDCl_3$) δ 136.7, 134.4, 131.9, 131.3, 130.7, 129.8, 128.1, 126.7, 126.6, 126.5, 126.2, 126.1, 124.7, 123.1, 122.5, 116.6, 37.6. The NMR data match with those reported in the literature.[111]

111 M.-B. Li, Y. Wang, S.-K. Tian, *Angew. Chem. Int. Ed.* **2012**, *51*, 2968–2971.

3',5'-Dimethyl-2-(pent-4-en-1-yn-1-yl)-1,1'-biphenyl and 9-allyl-1,3-dimethylphenanthrene (1.48b and 1.49b)

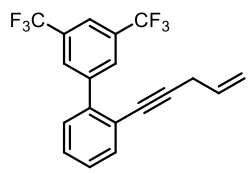


Enyne **1.48b** and phenanthrene **1.49b** were synthesized following the general procedure **D** (methods A and B) starting from 2-(bromoethynyl)-3',5'-dimethyl-1,1'-biphenyl (57 mg, 0.2 mmol) and allyltrimethylsilane (64 µL, 0.4 mmol). **1.48b** and **1.49b** were separated by flash chromatography using pentane as eluent.

3',5'-Dimethyl-2-(pent-4-en-1-yn-1-yl)-1,1'-biphenyl **1.48b** was obtained as a colorless oil (method A: 20 mg, 41%, method B: 11 mg, 21%). **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.54 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.40 – 7.30 (m, 2H), 7.29 – 7.24 (m, 1H), 7.24 (s, 2H), 7.00 (s, 1H), 5.80 (ddt, *J* = 17.0, 10.2, 5.2 Hz, 1H), 5.24 (dq, *J* = 17.0, 1.8 Hz, 1H), 5.08 (dq, *J* = 10.0, 1.7 Hz, 1H), 3.11 (dt, *J* = 5.3, 1.9 Hz, 2H), 2.37 (s, 6H). **^{13}C-NMR (**126 MHz, $CDCl_3$) δ 144.2, 140.9, 137.7 (2C), 133.5, 132.7, 129.78, 129.3, 128.3, 127.5 (2C), 127.1, 122.3, 116.5, 89.8, 82.9, 24.3, 21.7 (2C). **HRMS** (MALDI) m/z calculated for $C_{19}H_{18}^{+\cdot}$ $[M]^{+\cdot}$: 246.1403, found: 246.1415.

9-Allyl-1,3-dimethylphenanthrene **1.49b** was obtained as a colorless oil (method A: 13 mg, 26%). **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 8.73 (dd, *J* = 7.9, 1.8 Hz, 1H), 8.34 (s, 1H), 8.07 (dd, *J* = 7.5, 2.1 Hz, 1H), 7.76 (s, 1H), 7.65 – 7.55 (m, 2H), 7.27 (s, 1H), 6.24 – 6.08 (m, 1H), 5.15 (t, *J* = 1.6 Hz, 1H), 5.12 (dq, *J* = 7.7, 1.7 Hz, 1H), 3.89 (dd, *J* = 6.2, 1.2 Hz, 2H), 2.70 (s, 3H), 2.56 (s, 3H). **^{13}C-NMR (**126 MHz, $CDCl_3$) δ 137.4, 135.6, 134.6, 133.4, 131.4, 131.2, 130.4, 130.0, 128.9, 126.6, 126.3, 125.0, 123.8, 123.1, 120.7, 116.8, 38.4, 22.4, 20.1. **HRMS** (APCI) m/z calculated for $C_{19}H_{19}^{+}$ $[M+H]^{+}$: 247.1481, found: 247.1477.

2-(Pent-4-en-1-yn-1-yl)-3',5'-bis(trifluoromethyl)-1,1'-biphenyl (1.48c)

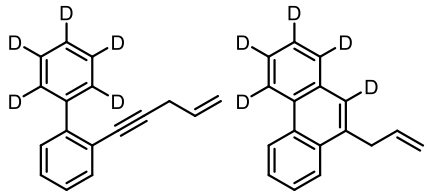


Enyne **1.48c** was synthesized following general procedure **D** starting from 2-(bromoethynyl)-3',5'-bis(trifluoromethyl)-1,1'-biphenyl (79 mg, 0.2 mmol) and allyltrimethylsilane (64 µL, 0.4 mmol). The crude product was purified *via* flash chromatography affording **1.48c** as a yellow oil (method A: 60 mg, 85%; method B: 64 mg, 90%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.10 (dd, *J* = 1.7, 0.9 Hz, 2H), 7.96 – 7.81 (m, 1H), 7.60 (dt, *J* = 7.1, 1.3 Hz, 1H), 7.45 – 7.32 (m, 3H), 5.76 (ddt, *J* = 17.0, 10.0, 5.4 Hz, 1H), 5.17 (dq, *J* = 17.0, 1.8 Hz, 1H), 5.07 (dq, *J* = 10.0, 1.6 Hz, 1H), 3.08 (dt, *J* = 5.5, 1.8 Hz, 2H). **^{13}C-NMR (**101 MHz, $CDCl_3$) δ 142.5, 140.5, 133.4, 131.7, 131.2 (q, *J* = 33.2 Hz, 2C), 129.6 (d, *J* = 3.0 Hz, 2C), 129.1, 128.4 (2C), 123.5 (q, *J* = 272.6 Hz, 2C), 122.2, 121.0 (p, *J* = 3.8 Hz), 116.4, 91.3,

81.1, 23.6. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -62.88. **HRMS** (APCI) m/z calculated for $C_{19}H_{11}F_6^+$ $[M-H]^+$: 353.0759, found: 353.0759.

2-(Pent-4-en-1-yn-1-yl)-1,1'-biphenyl-2',3',4',5',6'-*d*$_5$ and 9-allylphenanthrene-1,2,3,4,10-*d*$_5$ (1.48d and 1.49d)

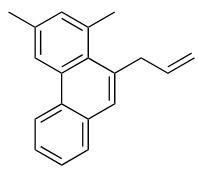


Enyne **1.48d** and phenanthrene **1.49d** were synthesized following the general procedure **D** (methods A and B) starting from 2-(bromoethynyl)-1,1'-biphenyl-2',3',4',5',6'-d_5 (53 mg, 0.2 mmol) and allyltrimethylsilane (64 µL, 0.40 mmol). **1.48d** and **1.49d** were separated by flash chromatography using pentane as eluent.

2-(Pent-4-en-1-yn-1-yl)-1,1'-biphenyl-2',3',4',5',6'-d_5 (65% deuterated) **1.48d** was obtained as a colorless oil (method A: 18 mg, 40%, method B: 16 mg, 36%). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.64 – 7.52 (m, 1H), 7.45 – 7.26 (m, 3H), 5.78 (ddt, J = 17.0, 10.2, 5.2 Hz, 1H), 5.20 (dq, J = 17.0, 1.8 Hz, 1H), 5.06 (dq, J = 10.0, 1.7 Hz, 1H), 3.09 (dt, J = 5.2, 1.8 Hz, 2H). **^{13}C-NMR (**101 MHz, $CDCl_3$) δ 143.70 (d, J = 4.8 Hz), 140.65 (d, J = 19.3 Hz), 133.2, 132.2, 129.5, 129.3 (2C), 128.0, 127.9 (2C), 127.3, 126.9, 122.1, 116.2, 89.5, 82.4, 23.8. **HRMS** (APCI) m/z calculated for $C_{17}H_{10}D_5^+$ $[M+H]^+$: 224.1482, found: 224.1471.

9-Allylphenanthrene-1,2,3,4,10-d_5 (65% deuterated) **1.48d** was obtained as a colorless oil (method C: 11 mg, 24%). The structure was assigned on basis of nOe experiments. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 8.77 – 8.71 (m, 1H), 8.13 – 8.08 (m, 1H), 7.71 – 7.57 (m, 2H), 6.29 – 6.12 (m, 1H), 5.20 (t, J = 1.5 Hz, 1H), 5.16 (dt, J = 6.5, 1.6 Hz, 1H), 3.90 (dt, J = 6.2, 1.5 Hz, 2H). **^{13}C-NMR (**126 MHz, $CDCl_3$) δ 136.8, 134.4, 131.9, 131.4, 130.8, 129.9, 128.3, 126.8, 126.8, 126.6, 126.4, 126.3, 124.9, 123.3, 122.6, 116.8, 37.7. **HRMS** (APCI) m/z calculated for $C_{17}H_9D_5^{+\cdot}$ $[M]^{+\cdot}$: 223.1404, found: 223.1414.

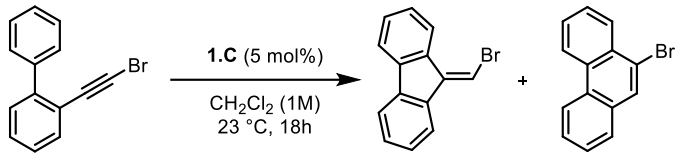
Synthesis of Allylphenanthrene 150b



The title compound (colorless oil, 6 mg, quant.) was synthesized by mixing (3',5'-dimethyl-2-(pent-4-en-1-yn-1-yl)-1,1'-biphenyl) (5.7 mg, 0.023 mmol) with [(*t*BuXPhos)AuNCMe]BAr_4^F (5 mol%, 1.8 mg) in DCE (0.46 mL, 0.05 M). The resulting mixture was stirred at 100 ºC for 18 h under argon. After this time, TLC indicated completion of the reaction and the crude was directly subjected to silica gel column chromatography (eluent = pentane) to obtain 10-allyl-1,3-dimethylphenanthrene (90% pure). The structure was assigned on basis of nOe experiments. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 8.64 (dd, *J* = 7.6, 1.7 Hz, 1H), 8.46 (s, 1H), 7.77 (dd, *J* = 7.6,

1.7 Hz, 1H), 7.60 – 7.52 (m, 2H), 7.51 (s, 1H), 7.25 (s, 1H), 6.18 (ddt, *J* = 17.2, 10.5, 5.4 Hz, 1H), 5.12 (dq, *J* = 10.3, 1.8 Hz, 1H), 4.89 (dq, *J* = 17.2, 1.9 Hz, 1H), 4.05 (d, *J* = 5.3 Hz, 2H), 2.92 (s, 3H), 2.56 (s, 3H). **^{13}C-NMR (**101 MHz, $CDCl_3$) δ 138.6, 135.3, 135.2, 134.9, 133.1, 132.6, 131.7, 130.2, 129.6, 129.1, 127.7, 126.5, 126.1, 123.1, 121.8, 116.2, 41.4, 25.6, 21.7. **HRMS** (APCI) m/z calculated for $C_{19}H_{19}^+$ $[M+H]^+$: 247.1481, found: 247.1474.

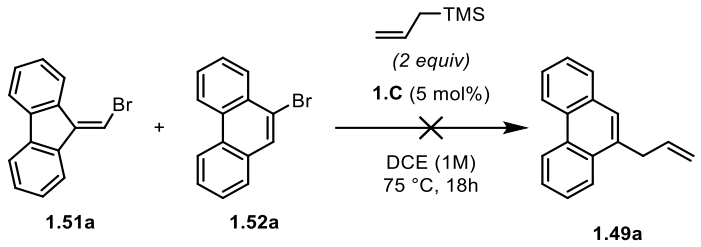
Synthesis of 9-(Bromomethylene)-9H-fluorene (1.51a)



2-(Bromoethynyl)-1,1'-biphenyl **1.47a** (5 mg, 20 µmol, 1 equiv) was dissolved in CH_2Cl_2 (40 µL). [(*t*BuXPhos)AuNCMe]BAr_4^F (1.5 mg, 1 µmol, 5 mol%) was added. The resulting mixture was stirred at 23 °C for 18 h. The crude was analyzed by NMR. A mixture of 9-(bromomethylene)-9H-fluorene and 9-bromophenanthrene was detected in a 95:5 ratio. The crude product was purified by flash chromatography affording just **1.51a**

9-(Bromomethylene)-9H-fluorene: **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 8.60 (dt, *J* = 7.6, 0.9 Hz, 1H), 7.73 (ddd, *J* = 7.5, 1.3, 0.6 Hz, 1H), 7.69 (ddd, *J* = 7.6, 1.3, 0.7 Hz, 1H), 7.59 (dt, *J* = 7.5, 0.9 Hz, 1H), 7.46 (td, *J* = 7.5, 1.2 Hz, 1H), 7.41 (s, 1H), 7.42 – 7.34 (m, 2H), 7.33 – 7.26 (m, 1H). **^{13}C-NMR (**101 MHz, $CDCl_3$) δ 141.4, 139.1, 138.8, 138.4, 136.6, 129.4, 128.6, 127.3, 127.2, 125.7, 120.1, 119.8, 119.8, 105.8. The NMR data were in agreement with the ones previously reported in the literature.[112]

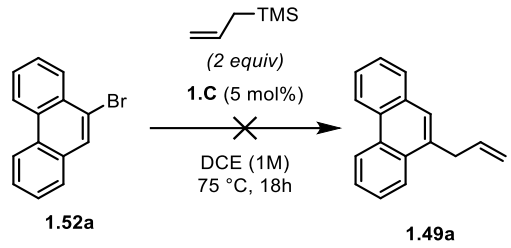
Attempted synthesis of 1.49a from 1.51a and **1.52a**



The crude 95:5 mixture of **1.51a** and **1.52a** obtained according to the previous conditions was filtered through a small plug of silica gel, concentrated under reduced pressure, and subjected to the following conditions without further purification. The crude was dissolved in DCE (0.1

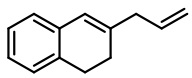
112 G. C. Paul, J. J. Gajewski, *Synthesis* **1997**, *5*, 524–526.

mL). Allyltrimethylsilane (6.2 µL, 40 µmol, 2 equiv) was added, followed by [(*t*BuXPhos)AuNCMe]BAr_4^F (1.5 mg, 1 µmol, 5 mol%). The reaction was stirred at 75 °C for 18 h. The crude was analyzed by NMR. No reaction was detected.



9-Bromophenanthrene (26 mg, 0.1 mmol, 1 equiv) was dissolved in DCE (0.1 mL). Allyltrimethylsilane (32 µL, 0.2 mmol, 2 equiv) was added, followed by [(*t*BuXPhos)AuNCMe]BAr_4^F (7.6 mg, 5 µmol, 5 mol%). The reaction was stirred at 75 °C for 18 h. The crude was allowed to cool to room temperature and analyzed by ^{1}H-NMR. No reaction was detected.

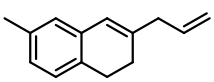
3-Allyl-1,2-dihydronaphthalene (1.54a)



Diene **1.54a** was synthesized following general procedure **D** starting from (4-bromobut-3-yn-1-yl)benzene (42 mg, 0.2 mmol) and allyltrimethylsilane (64 µL, 0.4 mmol). The crude product was purified by flash chromatography affording **1.54a** as a colorless oil (method A: 22 mg, 64%). The structure was assigned on basis of nOe experiments.

^{1}H-NMR (400 MHz, $CDCl_3$*d*) δ 7.17 – 7.06 (m, 3H), 7.03 – 6.95 (m, 1H), 6.25 (bs, 1H), 5.89 (ddtd, *J* = 16.8, 10.0, 6.8, 0.9 Hz, 1H), 5.41 – 4.95 (m, 2H), 2.94 (bd, *J* = 6.7, 2H), 2.82 (t, *J* = 8.2 Hz, 2H), 2.26 (bt, *J* = 8.9, 2H). **^{13}C-NMR (**126 MHz, $CDCl_3$) δ 140.1, 135.8, 134.8, 134.4, 127.2, 126.4, 126.2, 125.5, 123.1, 116.4, 41.8, 28.1, 27.2. **HRMS** (APCI) *m/z* calculated for $C_{13}H_{15}^+$ $[M+H]^+$: 171.1168, found: 171.1167.

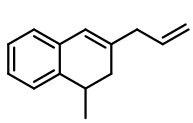
3-Allyl-6-methyl-1,2-dihydronaphthalene (1.54b)



Diene **1.54b** was synthesized following general procedure **D–method A** starting from 1-(4-bromobut-3-yn-1-yl)-3-methylbenzene (22 mg, 0.1 mmol) and allyltrimethylsilane (127 µL, 0.8 mmol). The crude mixture was analyzed by 1H-NMR using mesitylene as internal standard and product **1.54b** was detected in 20% yield.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.40 (s, 1H), 7.05 – 6.96(m, 2H), 6.23 (bs, 1H), 5,90 (ddt, *J* = 16.9, 10.0, 6.8 Hz, 1H), 5.19 – 5.08 (m, 2H), 2.96 (dd, *J* = 12.2, 6.3 Hz, 1H), 2.87 – 2.77 (m, 3H), 2.40 – 2.38 (m, 2H), 2.32 (s, 3H).

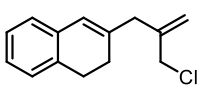
3-Allyl-1-methyl-1,2-dihydronaphthalene (1.54c)



Diene **1.54c** was synthesized following general procedure **D** starting from (5-bromopent-4-yn-2-yl)benzene (45 mg, 0.2 mmol) and allyltrimethylsilane (64 µL, 0.4 mmol). The crude product was purified by flash chromatography affording **1.54c** as a colorless oil (method A: 15 mg, 42%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.18 – 7.09 (m, 3H), 7.04 – 6.94 (m, 1H), 6.23 (p, *J* = 1.4 Hz, 1H), 5.87 (ddt, *J* = 16.9, 10.0, 6.8 Hz, 1H), 5.42 – 4.98 (m, 2H), 3.01 – 2.86 (m, 3H), 2.40 (dddt, *J* = 16.6, 6.7, 1.9, 1.0 Hz, 1H), 2.03 (ddq, *J* = 16.7, 7.5, 1.0 Hz, 1H), 1.22 (d, *J* = 7.0 Hz, 3H). **^{13}C-NMR (**101 MHz, $CDCl_3$) δ 139.4, 138.4, 135.7, 134.0, 126.5, 126.3, 125.8, 125.7, 122.5, 116.5, 41.9, 35.2, 32.3, 20.1. **HRMS** (APCI) m/z calculated for $C_{14}H_{17}^{+}$ $[M+H]^{+}$: 185.1325, found: 185.1323.

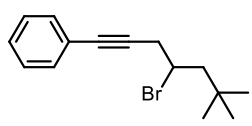
3-(2-(Chloromethyl)allyl)-1,2-dihydronaphthalene (1.54d)



Diene **1.54d** was synthesized following general procedure **D** starting from (4-bromobut-3-yn-1-yl)benzene (42 mg, 0.2 mmol) and (2-(chloromethyl)allyl)trimethylsilane (72 µL, 0.40 mmol). The crude product was purified by flash chromatography affording **1.54d** as a colorless oil (method A: 6 mg, 13%).

^{1}H-NMR (500 MHz, CDCl3) δ 7.17 – 7.11 (m, 1H), 7.11 – 7.08 (m, 2H), 7.04 – 6.99 (m, 1H), 6.33 (bs, 1H), 5.25 (bs, 1H), 5.10 (q, *J* = 1.3 Hz, 1H), 4.05 (d, *J* = 0.9 Hz, 1H), 3.07 (s, 1H), 2.81 (t, *J* = 8.2 Hz, 1H), 2.22 (t, *J* = 7.9 Hz, 2H). **^{13}C-NMR (**101 MHz, CDCl3) δ 142.8, 138.0, 134.5, 134.5, 127.2, 126.6, 126.5, 125.7, 125.1, 116.6, 47.5, 41.5, 28.2, 26.7. **HRMS** (APCI) m/z calculated for $C_{14}H_{16}Cl^{+}$ $[M+H]^{+}$: 219.0935, found: 219.0935.

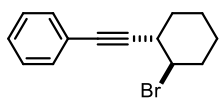
(4-Bromo-6,6-dimethylhept-1-yn-1-yl)benzene (1.58)



Compound **1.58** was synthesized following general procedure **C** starting from (bromoethynyl)benzene (36 mg, 0.2 mmol) and dimethylpent-1-ene (58 µL, 0.4 mmol). The reaction time was 48 h. The crude product was purified by flash chromatography affording **1.58** as a colorless oil (method A: 15 mg, 27%).

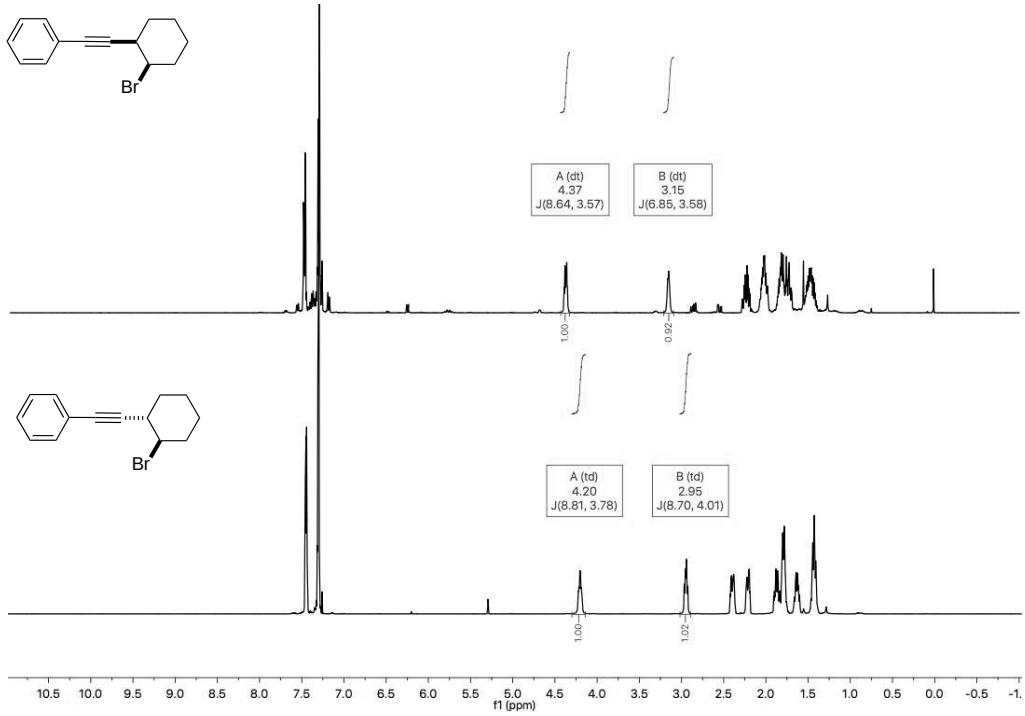
^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.40 (m, 2H), 7.35 – 7.30 (m, 3H), 4.20 (tdd, *J* = 7.3, 5.6, 3.6 Hz, 1H), 3.07 (dd, *J* = 17.1, 5.7 Hz, 1H), 2.99 (dd, *J* = 17.1, 7.3 Hz, 1H), 2.14 (dd, *J* = 15.5, 3.6 Hz, 1H), 2.06 (dd, *J* = 15.5, 7.4 Hz, 1H), 1.05 (s, 9H). **^{13}C-NMR (**101 MHz, $CDCl_3$) δ 131.6 (2C), 128.3 (2C), 128.0, 123.3, 86.6, 82.9, 51.6, 48.0, 32.4, 31.1, 29.7 (3C). **HRMS** (APCI) *m/z* calculated for $C_{15}H_{20}Br^{+}$ $[M+H]^{+}$: 279.0743, found: 279.0740.

(2-Bromocyclohexyl)ethynyl)benzene (1.60)

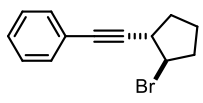


Compound **1.60** was synthesized following general procedure **C** starting from (bromoethynyl)benzene (36 mg, 0.2 mmol) and cyclohexene (20 µL, 0.4 mmol).The crude product was purified by flash chromatography affording **1.60** as a yellow oil (method A: 16 mg, 60%). The relative configuration has been assigned by comparison with the ^{1}H-NMR of the *syn* product.

^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.48 – 7.42 (m, 2H), 7.33 – 7.27 (m, 3H), 4.20 (td, *J* = 8.8, 3.8 Hz, 1H), 2.95 (td, *J* = 8.7, 4.0 Hz, 1H), 2.44 – 2.34 (m, 1H), 2.22 (dddd, *J* = 13.2, 5.4, 3.3, 1.6 Hz, 1H), 1.93 – 1.82 (m, 1H), 1.82 – 1.74 (m, 2H), 1.63 (dddd, *J* = 13.7, 10.1, 9.1, 3.2 Hz, 1H), 1.43 (ddq, *J* = 12.3, 8.1, 2.4 Hz, 2H). **^{13}C-NMR (**126 MHz, $CDCl_3$) δ 132.1, 132.0, 132.0, 128.6, 128.3, 123.8, 91.5, 83.1, 55.7, 39.5, 36.0, 31.9, 25.5, 24.2. **HRMS** (APCI) *m/z* calculated for $C_{14}H_{16}Br^{+}$ $[M+H]^{+}$: 249.0430, found: 279.0436.

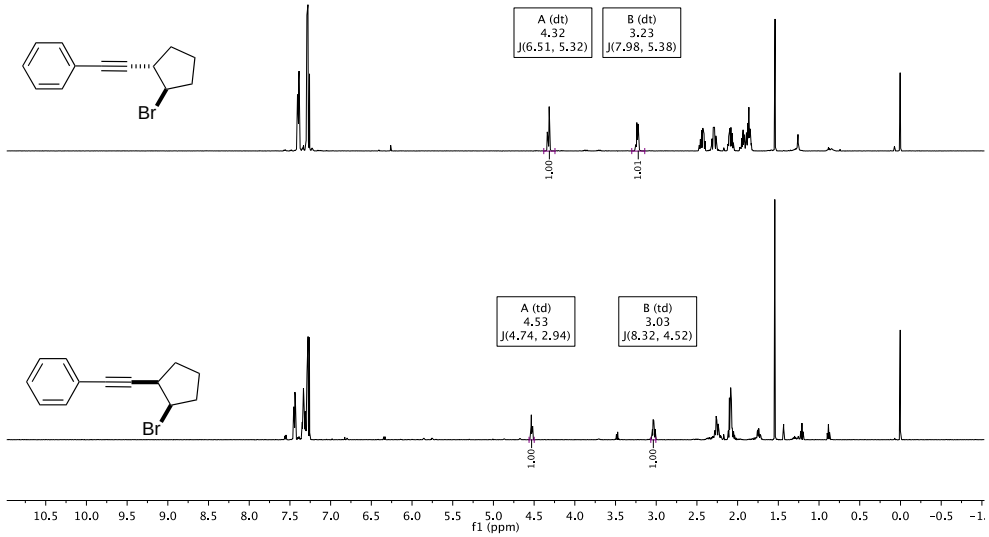


(2-Bromocyclopentyl)ethynyl)benzene (1.62)

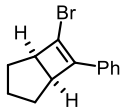


Compound **1.62** was synthesized following general procedure **C** starting from (bromoethynyl)benzene (36 mg, 0.2 mmol) and cyclopentene (18 µL, 0.4 mmol).The crude product was purified by flash chromatography affording **1.62** as a yellow oil (method A: 12 mg, 46%). The relative configuration has been assigned by comparison with the ^{1}H-NMR of the *syn* product.

^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.42 – 7.37 (m, 2H), 7.31 – 7.27 (m, 3H), 4.32 (dt, *J* = 6.5, 5.3 Hz, 1H), 3.23 (dt, *J* = 8.0, 5.4 Hz, 1H), 2.49 – 2.38 (m, 1H), 2.33 – 2.25 (m, 1H), 2.09 (ddt, *J* = 15.7, 8.6, 5.3 Hz, 1H), 1.98 – 1.80 (m, 3H). **^{13}C-NMR (**126 MHz, $CDCl_3$) δ 132.0 (2C), 128.6, 128.6, 128.3, 123.7, 90.7, 83.1, 55.8, 42.5, 36.8, 31.8, 23.1. **HRMS** (APCI) *m/z* calculated for $C_{13}H_{14}Br^+$ $[M+H]^+$: 249.0273, found: 249.0274.



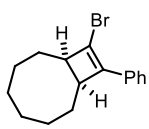
6-Bromo-7-phenylbicyclo[3.2.0]hept-6-ene (1.63)



Compound **1.63** was synthesized following general procedure **C** starting from (bromoethynyl)benzene (36 mg, 0.2 mmol) and cyclopentene (18 µL, 0.4 mmol).The crude product was purified by flash chromatography affording **1.63** as a yellow oil (method A: 6 mg, 22%).

^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.69 – 7.65 (m, 2H), 7.37 (tq, *J* = 8.2, 1.1 Hz, 2H), 7.33 – 7.28 (m, 1H), 3.57 (dd, *J* = 6.9, 3.5 Hz, 1H), 3.42 (dd, *J* = 7.2, 3.5 Hz, 1H), 1.82 (dd, *J* = 12.8, 6.0 Hz, 1H), 1.77 – 1.68 (m, 2H), 1.61 (qt, *J* = 12.5, 6.1 Hz, 1H), 1.39 – 1.21 (m, 2H). **^{13}C-NMR**δ 143.4, 132.4, 128.7 (2C), 128.5, 126.1 (2C), 111.1, 52.8, 46.7, 26.3, 24.9, 23.2. **HRMS** (APCI) *m/z* calculated for $C_{13}H_{14}Br^+$ $[M+H]^+$: 249.0273, found: 249.0267.

(2-Bromocyclopentyl)ethynyl)benzene (1.65)



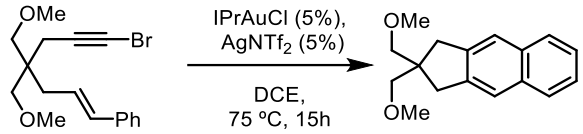
Compound **1.65** was synthesized following general procedure **C** starting from (bromoethynyl)benzene (36 mg, 0.2 mmol) and (*Z*)-cyclooctene (26 µL, 0.4

mmol).The crude product was purified by flash chromatography affording **1.65** as a yellow oil (method A: 24 mg, 82%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.66 – 7.51 (m, 2H), 7.40 – 7.34 (m, 2H), 7.32 – 7.27 (m, 1H), 3.22 – 3.08 (m, 1H), 2.99 (ddd, *J* = 12.0, 4.5, 2.1 Hz, 1H), 2.06 – 1.99 (m, 1H), 1.92 (dtd, *J* = 12.8, 3.3, 1.8 Hz, 1H), 1.80 – 1.70 (m, 1H), 1.70 – 1.61 (m, 1H), 1.61 – 1.34 (m, 8H).

Experimental mechanistic studies

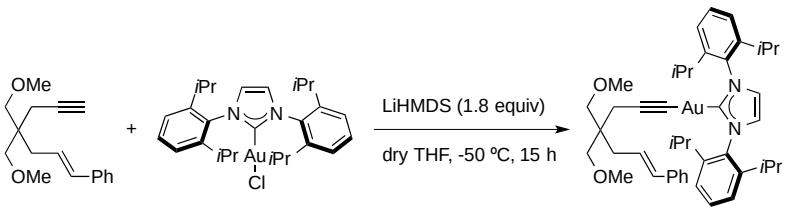
Experiments with σ-gold(I) acetylide complexes



1.39n **1.40n**

The reaction was carried out following the general procedure **B** starting from **1.39n** (33.7 mg, 0.1 mmol)**.,** and using IPrAuCl (5 mol%, 3.1 mg). The reaction was monitored by TLC and once completed the reaction was cooled down to room temperature, the solvent removed under reduced pressure and the crude analyzed by ^{1}H-NMR using trichloroethylene as internal standard indicating that **1.40n** was obtained in 21% yield.

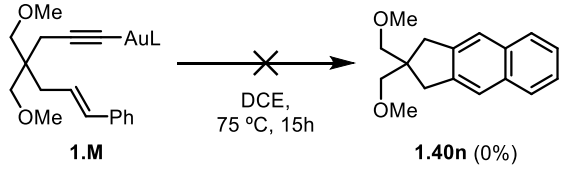
Synthesis of σ-(Phenylacetylene)gold(I) complex 1.M

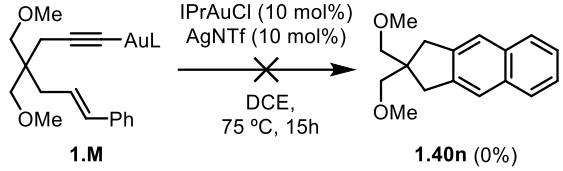


An oven dried schlenk tube was loaded with (*E*)-(4,4-bis(methoxymethyl)hept-1-en-6-yn-1-yl)benzene (38.8 mg, 0.15 mmol) and THF (1.3 ml), and the mixture was cooled down to -50 °C. A freshly prepared solution of lithium bis(trimethylsilyl)amide (75 µl, 0.18 mmol) in THF (2.4 M) was added dropwise and the reaction was stirred for 30 min at the same temperature. Then, (1,3-bis(2,6-diisopropylphenyl)-2,3-dihydro-1H-imidazol-2-yl)gold(I) chloride (62.2 mg, 0.1 mmol) dissolved in THF (2.7 ml) was added dropwise. After 15 min, the cooling bath was removed letting the reaction stirring for 10 h at 23 ºC. The crude was then concentrated and redissolved in CH_2Cl_2, filtered through cotton and teflon (0.22). The solvent was removed and

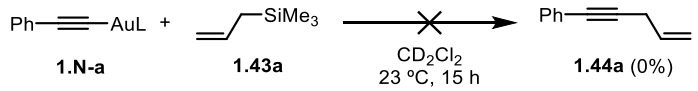
the solid washed several times with pentane affording the product as a pale-yellow solid in 73% yield.

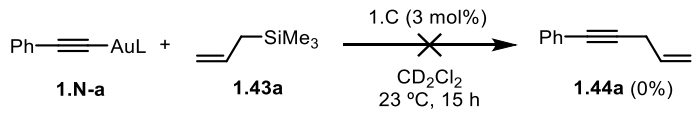
^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.46 (t, *J* = 7.8 Hz, 2H), 7.31 – 7.22 (m, 8H), 7.16 (ddt, *J* = 7.5, 6.3, 1.7 Hz, 1H), 7.11 (s, 2H), 6.34 (d, *J* = 15.8 Hz, 1H), 6.18 (dt, *J* = 15.6, 7.6 Hz, 1H), 3.23 (s, 6H), 3.23 – 3.17 (m, 4H), 2.60 (hept, *J* = 7.0 Hz, 4H), 2.21 (dd, *J* = 7.7, 1.2 Hz, 2H), 2.16 (s, 2H), 1.36 (d, *J* = 6.9 Hz, 12H), 1.21 (d, *J* = 6.9 Hz, 12H). **^{13}C-NMR (**101 MHz, $CDCl_3$) δ 192.0, 145.8 (4C), 138.4, 134.5 (2C), 132.2, 130.5 (2C), 128.4 (2C), 127.4, 126.7, 126.2 (2C), 124.2 (4C), 123.1 (2C), 118.7, 100.8, 75.0 (2C), 59.4 (2C), 42.9, 35.3, 28.9 (4C), 24.6 (4C), 24.2 (4C), 24.0. **HRMS** (ESI) *m/z* calculated for $C_{44}H_{57}AuN_2NaO_2^+$ $[M+Na]^+$: 865.3978, found: 865.3999.



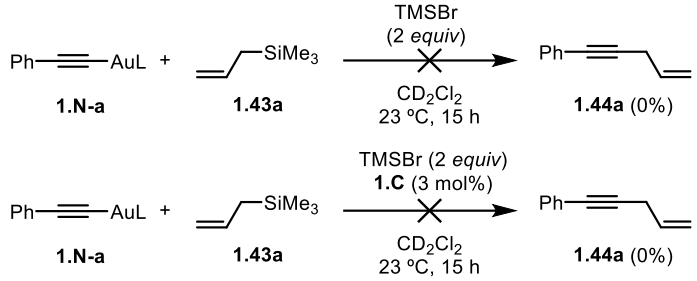


σ-(Phenylacetylene)gold(I) complex **1.M** (10 mg, 12 µmol, 1 equiv) was dissolved in DCE (0.1 mL). In the second reaction, IPrAuCl (0.7 mg, 1.2 µmol, 10 mol%) was added followed by $AgNTf_2$ (0.5 mg, 1.2 µmol, 10%). The mixture was stirred at 75 °C for 15 h. Then, the solvent was evaporated, 2-bromo-mesitylene (2.8 µL) was added as internal standard and the crude was analyzed by ^{1}H-NMR in CD_2Cl_2. No reaction was detected.

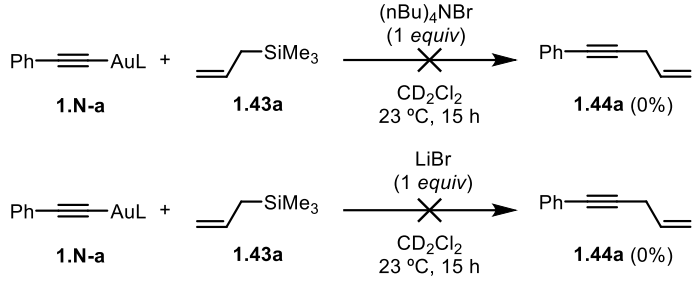




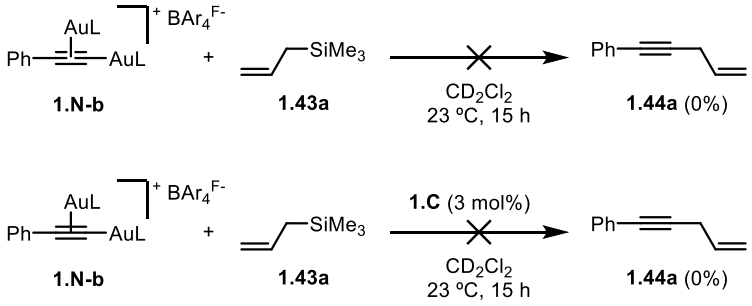
σ-(Phenylacetylene)gold(I) complex **1.N-a** (30 mg, 42 µmol, 1 equiv) was dissolved in CD_2Cl_2 (0.1 mL). Allyltrimethylsilane **1.43a** (13 µL, 83 µmol, 2 equiv) was added, followed (or not) by $[(t\text{BuXPhos})AuNCMe]BAr_4^F$ (1.9 mg, 1.2 µmol, 3 mol%). The mixture was stirred at 23 °C for 15 h. Mesitylene (5 µL) was added as internal standard and the crude was analyzed by ^{1}H and ^{31}P NMR. No reaction was detected.



σ-(Phenylacetylene)gold(I) complex **1.N-a** (20 mg, 28 µmol, 1 equiv) was dissolved in CD_2Cl_2 (0.06 mL). Allyltrimethylsilane **1.43a** (13 µL, 83 µmol, 3 equiv) was added, followed by TMS-Br (7 µL, 55 µmol, 2 equiv) The mixture was stirred at 23 °C for 15 h. 2-Bromo-mesitylene (4,2 µL) was added as internal standard and the crude was analysed by ^1H. No reaction was detected

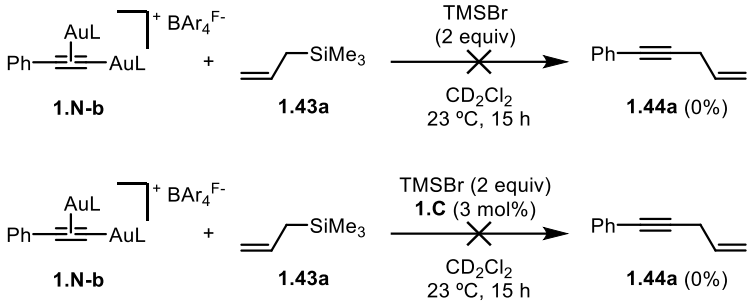


σ-(Phenylacetylene)gold(I) complex **1.N-a** (6 mg, 8.3 µmol, 1 equiv), allyltrimethylsilane **1.43a** (4 µL, 25 µmol, 3 equiv) and tetra-*n*-butylammonium bromide (3 mg, 8.3 µmol, 1 equiv) or LiBr (0.7 mg, 8.3 µmol, 1 equiv) were dissolved in CD_2Cl_2 or THF (0.1 mL), respectively. The mixture was stirred at 23 °C for 16 h. The crude was analyzed by NMR. No reaction was detected.

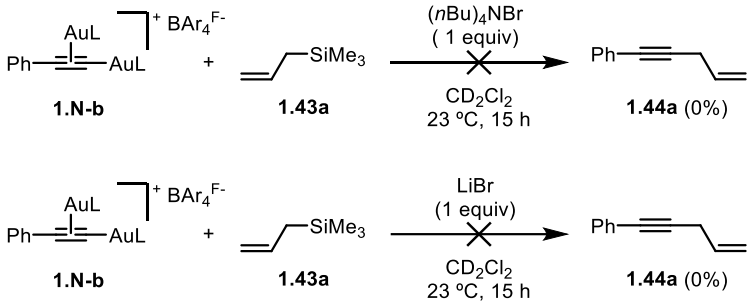


σ,π-(Phenylacetylene)digold(I) complex **1.N-b** (30 mg, 13 µmol, 1 equiv) was dissolved in CD_2Cl_2 (0.1 mL). Allyltrimethylsilane **1.43a** (4.3 µL, 27 µmol, 2 equiv) was added, followed (or not) by [(*t*BuXPhos)AuNCMe]BAr_4^F (0.6 mg, 0.4 µmol, 3 mol%). The mixture was stirred

at 23 ºC for 15 h. Mesitylene (5 µL) was added as internal standard and the crude was analyzed by ^{1}H and ^{31}P NMR. No reaction was detected.

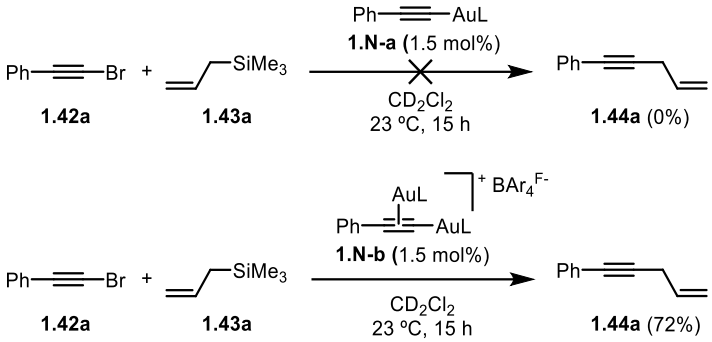


σ,π-(Phenylacetylene)digold(I) complex **1.N-b** (40 mg, 18 µmol, 1 equiv) was dissolved in CD_2Cl_2 (0.04 mL). Allyltrimethylsilane **1.43a** (9µL, 54 µmol, 3 equiv) was added, followed by TMS-Br (5,5 µL, 36 µmol, 2 equiv) The mixture was stirred at 23 °C for 15 h. 2-Bromo-mesitylene (2,8 µL) was added as internal standard and the crude was analysed by ^{1}H. No reaction was detected



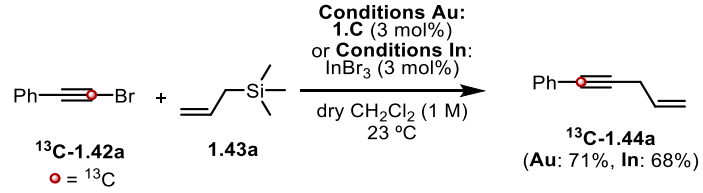
σ,π-(Phenylacetylene)digold(I) complex **1.N-b** (6 mg, 2.7 µmol, 1 equiv), allyltrimethylsilane **1.43a** (1.3 µL, 8.1 µmol, 3 equiv) and tetra-*n*-butylammonium bromide (1 mg, 2.7 µmol, 1 equiv) or LiBr (0.2 mg, 2.7 µmol, 1 equiv) were dissolved in CD_2Cl_2 or THF (5 µL), respectively. The mixture was stirred at 23 °C for 16 h. The crude was analyzed by NMR. No reaction was detected.

*Experiments with **1.N-a** or **1.N-b** as catalysts*



(Bromoethynyl)benzene **1.42a** (36 mg, 0.2 mmol, 1 equiv) was dissolved in CD_2Cl_2 (0.2 mL). Allyltrimethylsilane **1.43a** (64 µL, 0.4 mmol, 2 equiv) was added, followed by *σ*-(phenylacetylene)gold(I) complex **1.N-a** (4.34 mg, 6 µmol, 3 mol%) or *σ,π*-(phenylacetylene)digold(I) complex **1.N-b (**6.7 mg, 3 µmol, 1.5 mol%). The mixture was stirred at 23 °C for 15 h. Mesitylene (10 µL) was added as internal standard and the crude was analyzed by ^{1}H and ^{31}P NMR. Reaction was detected only in the case of using *σ,π*-(phenylacetylene)digold(I) complex **1.N-b**, in which the 1,4-enyne **1.44a** was formed in 72% yield.

^{13}C-labelling experiments

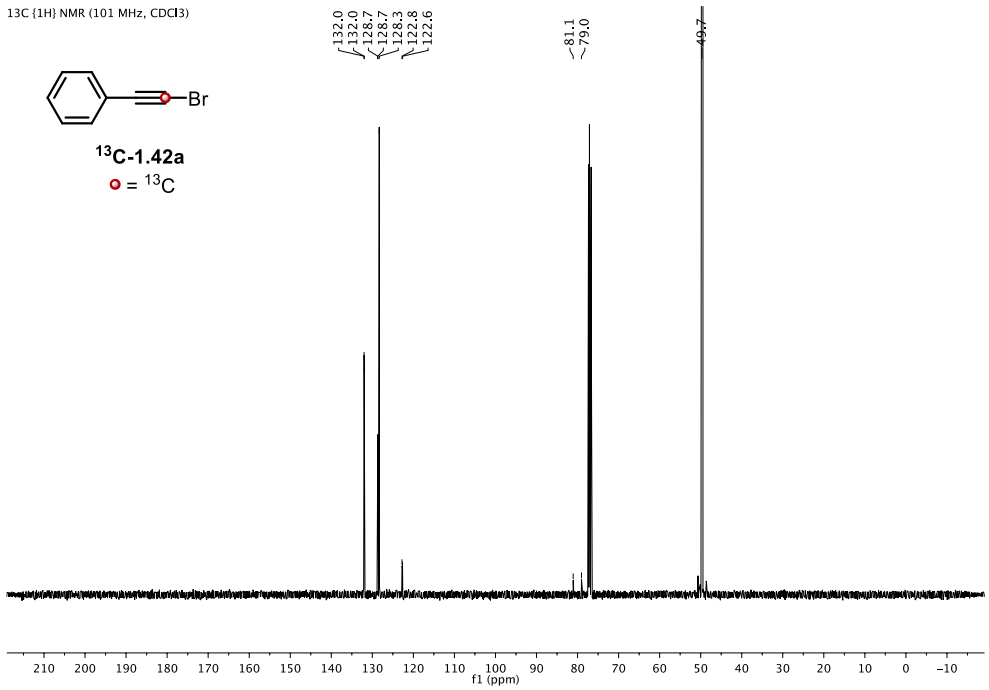


^{13}C-labeled (bromoethynyl)benzene (36 mg, 0.2 mmol, 1 equiv) was dissolved in dry dichloromethane (0.2 mL, 1 M). Allylsilane (64 µL, 0.4 mmol, 2 equiv) was added, followed by the catalyst (3 mol%, **method A**: 9 mg of [(*t*BuXPhos)AuNCMe]BAr_4^F or **method B**: 2 mg of $InBr_3$). The resulting mixture was stirred at 23 ºC for 16 h. The crude was directly submitted to silica gel column chromatography (eluent = pentane) to obtain the pure ^{13}C-labeled 1,4-enyne (colorless oil, **method A**: 20 mg, 71%; **method B**: 19 mg, 68%).

^{13}C-Labeled (bromoethynyl)benzene ^{13}C-1.42a: ^{13}C-NMR (101 MHz, $CDCl_3$) δ 132.0 (d, *J* = 3.5 Hz, 2C), 128.7 (d, *J* = 1.3 Hz), 128.3 (2C), 122.7 (d, *J* = 13.7 Hz), 80.1 (d, *J* = 203.0 Hz), 49.7.

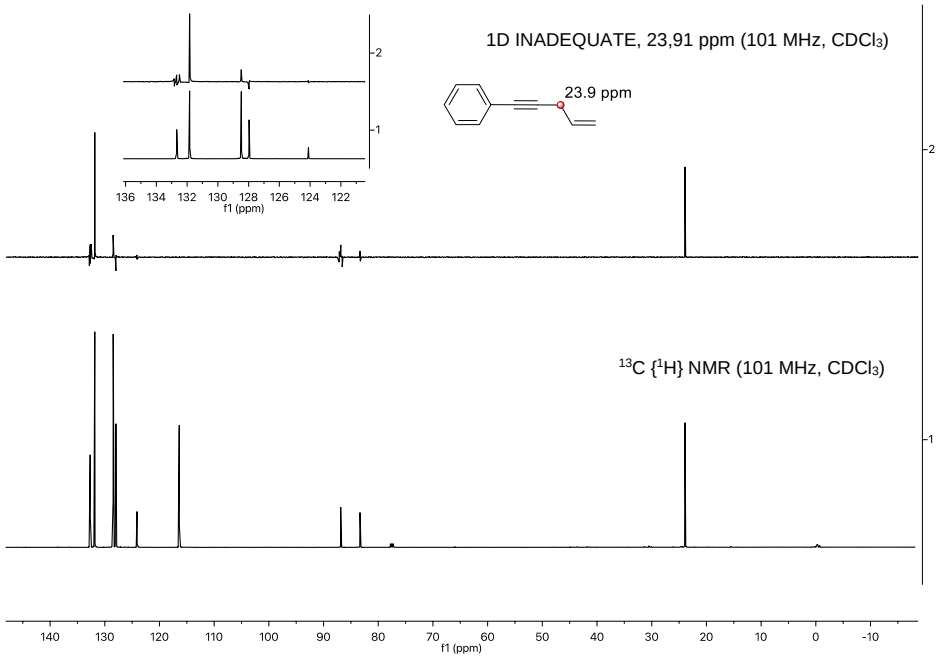
^{13}C-Labeled pent-4-en-1-yn-1-ylbenzene ^{13}C-1.44a: ^{13}C-NMR (101 MHz, $CDCl_3$) δ 132.4 (d, *J* = 2.1 Hz), 131.6 (d, *J* = 1.8 Hz, 2C), 128.2 (d, *J* = 5.5 Hz, 2C), 127.7 (d, *J* = 1.7 Hz), 123.7

(d, *J* = 90.7 Hz), 116.2, 86.2 (d, *J* = 71.7 Hz), 82.9, 23.7 (d, *J* = 11.2 Hz). The signal at 127.0 in the ^{13}C-NMRspectrum corresponds to a ^{13}C-labeled impurity.

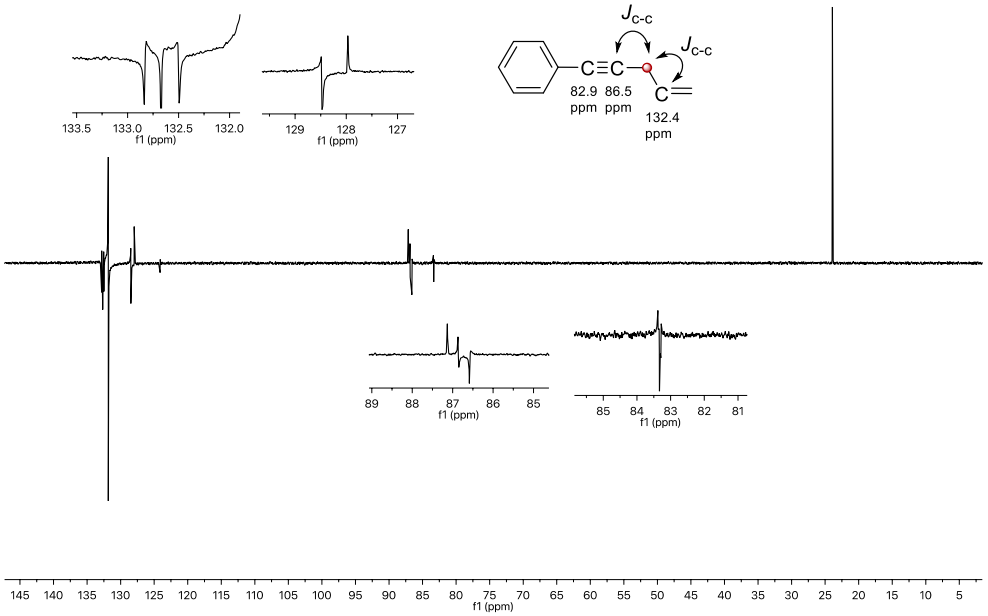


1D INADEQUATE (SELINQUATE) experiment

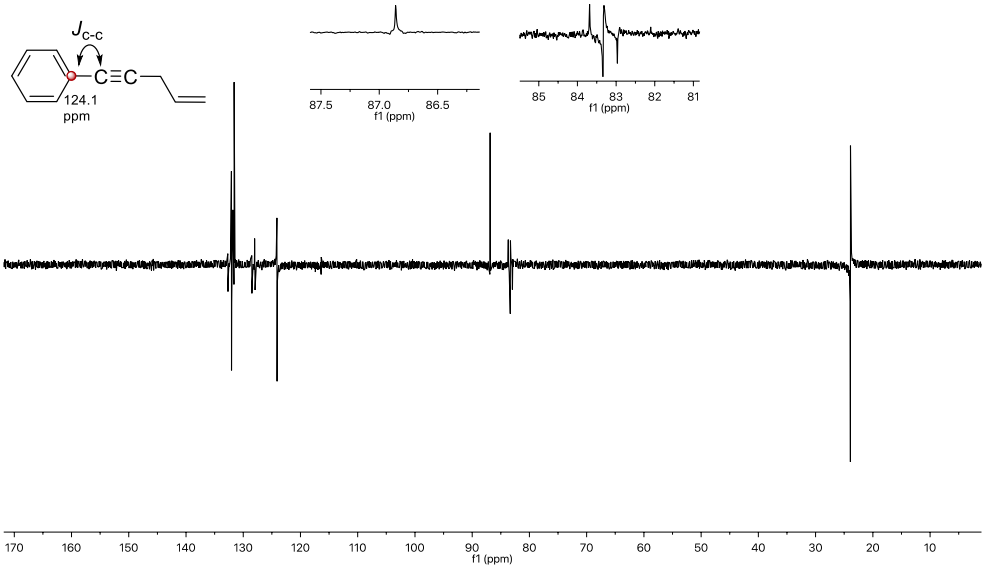
We performed a 1D INADEQUATE (SELINQUATE) experiment of compound **1.44a**, irradiating the C(sp^3), to assign each alkyne signal.

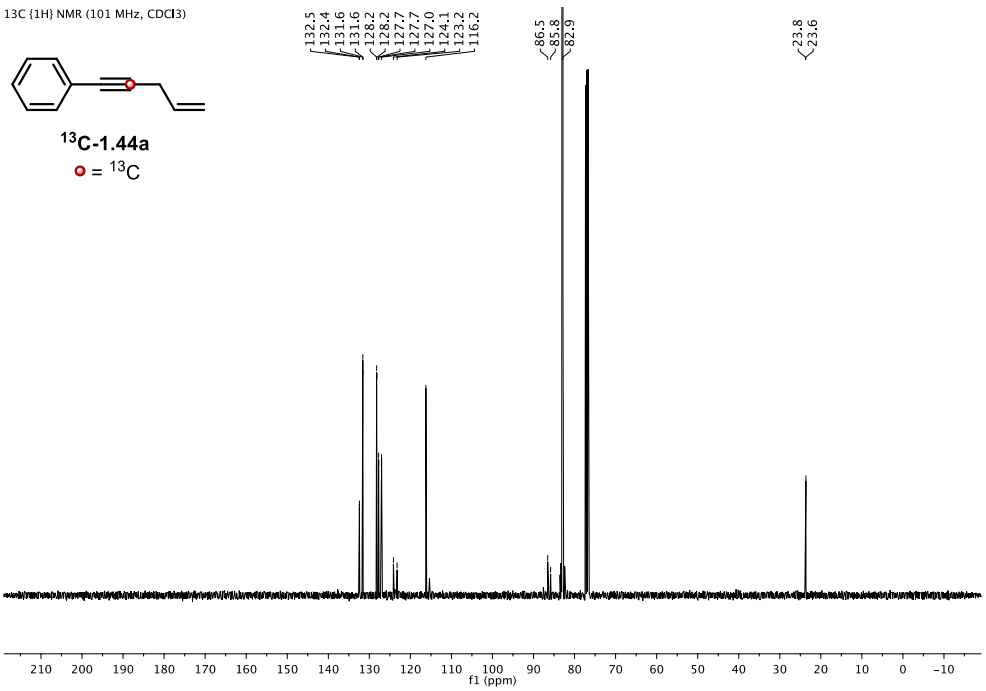


1D INADEQUATE, 23,91 ppm, 60 Hz (101 MHz, $CDCl_3$)

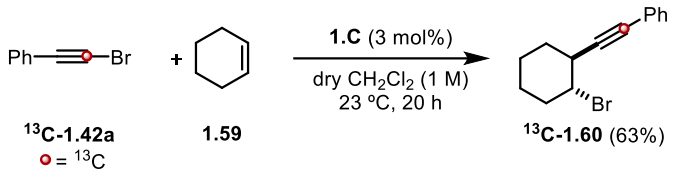


1D INADEQUATE, 124,11 ppm, 90 Hz (101 MHz, $CDCl_3$)



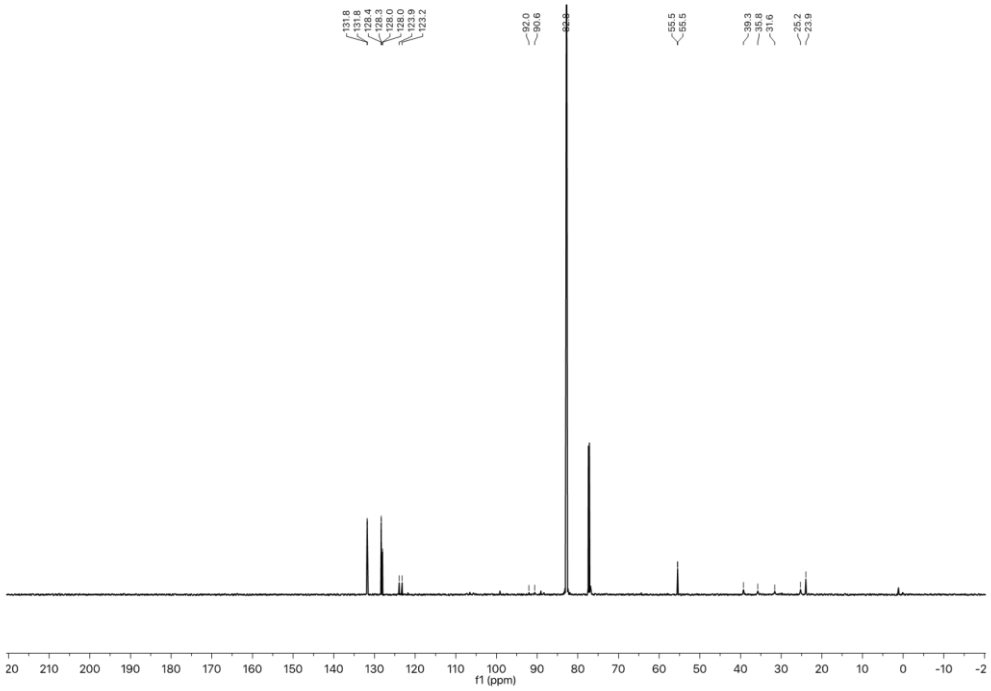


(2-Bromocyclohexyl)ethynyl-1-^{13}C)benzene



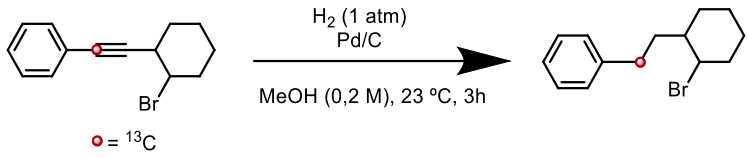
^{13}C-Labeled (bromoethynyl)benzene (18 mg, 0.1 mmol, 1 equiv) was dissolved in dry dichloromethane (0.1 mL, 1 M). Cyclohexene (20 µL, 0.2 mmol, 2 equiv) was added, followed by the catalyst (3 mol%, 4.5 mg of [(*t*BuXPhos)AuNCMe]BAr_4^F). The resulting mixture was stirred at 23 ºC for 16 h. The crude was directly submitted to silica gel column chromatography (eluent = pentane) to obtain the pure ^{13}C-labeled product (colorless oil, 17 mg, 64%).

^{13}C-NMR (126 MHz, $CDCl_3$) δ 131.8 (d, *J* = 2.1 Hz), 128.3 (d, *J* = 5.5 Hz), 128.0 (d, *J* = 1.9 Hz), 123.6 (d, *J* = 90.5 Hz), 91.3 (d, *J* = 178.2 Hz), 82.8, 55.5 (d, *J* = 2.4 Hz), 39.3, 35.8, 31.6, 25.2, 23.9.



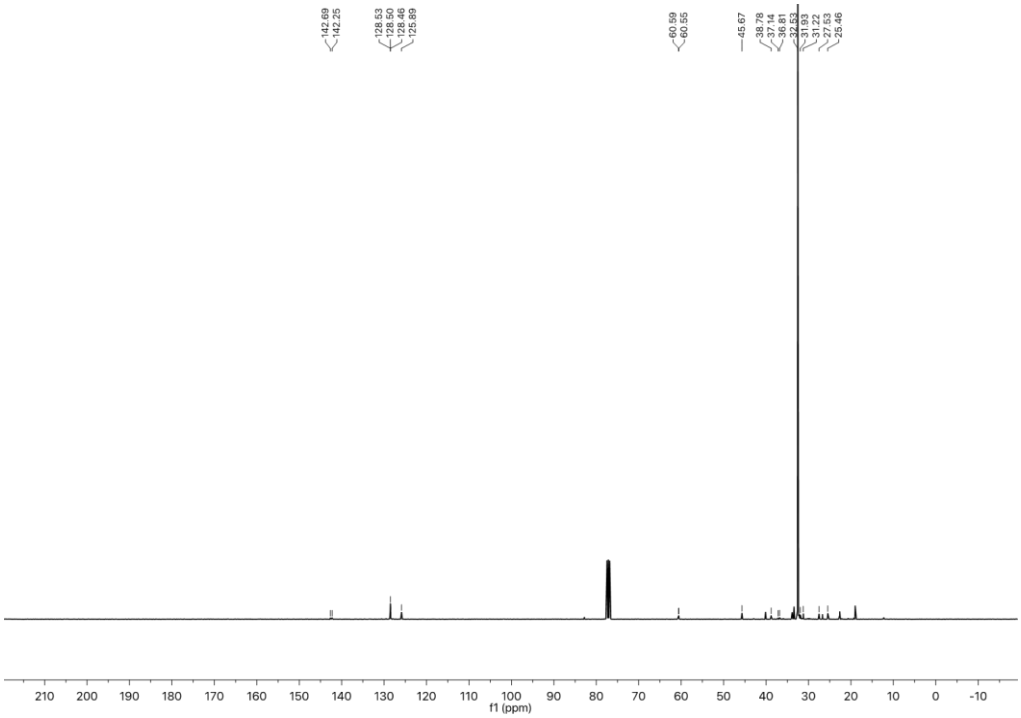
We hydrogenated **^{13}C-1.60** and **1.60** in order to be able to distinguish between the two carbon of the alkyne and then assign the position of the labelled carbon in **^{13}C-1.60**.

(2-(2-Bromocyclohexyl)-ethynyl-1-^{13}C)benzene (^{13}C-S1.1)**

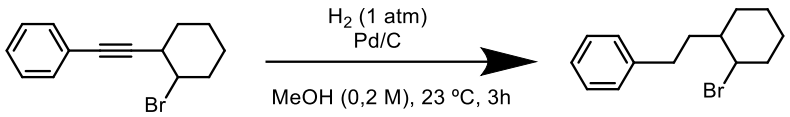


((2-Bromocyclohexyl)ethynyl-1-^{13}C)benzene (18 mg, 0.7 mmol, 1 equiv) and Pd/C (7 mg) were suspended in degassed MeOH (0.35 mL, 0.2 M) in a microwave vial, the vial closed and argon was bubbled inside for 10 min. Then, the vial was evacuated and backfilled three times with hydrogen using a balloon. The mixture was the stirred for 3 h at 23 ºC. Afterwards, the crude was filtered thought a pad of Celite® and the pad washed with Et_2O. The solvent was removed under vacuum to obtain the product (18 mg, 96% yield).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.26 (m, 2H), 7.24 – 7.16 (m, 3H), 3.90 (ddd, *J* = 11.2, 10.1, 4.2 Hz, 1H), 2.72 (dddd, *J* = 125.9, 13.5, 11.1, 5.0 Hz, 1H), 2.69 (ddd, *J* = 13.6, 10.7, 6.2 Hz*, 1H) 2.46 – 2.30 (m, 1H), 2.25 – 2.11 (m, 1H), 2.10 – 1.99 (m, 1H), 1.88 (dddd, *J* = 14.8, 12.9, 8.1, 3.5 Hz, 1H), 1.82 – 1.64 (m, 3H), 1.63 – 1.46 (m, 1H), 1.40 – 1.23 (m, 3H), 1.22 – 1.08 (m, 1H). * The signal overlaps with the multiplet at 2.46-2.30 ppm making not possible to establish the $^{1}J_{C\text{-}H}$. **^{13}C-NMR (**101 MHz, $CDCl_3$) δ 142.5 (d, *J* = 43.6 Hz), 128.5 (2C), 128.4 (2C), 125.9, 60.6 (d, *J* = 3.7 Hz), 45.7, 38.8, 37.0 (d, *J* = 34.1 Hz), 32.5, 31.9, 27.5, 25.5.



(2-(2-Bromocyclohexyl)ethyl)benzene (S1.1)

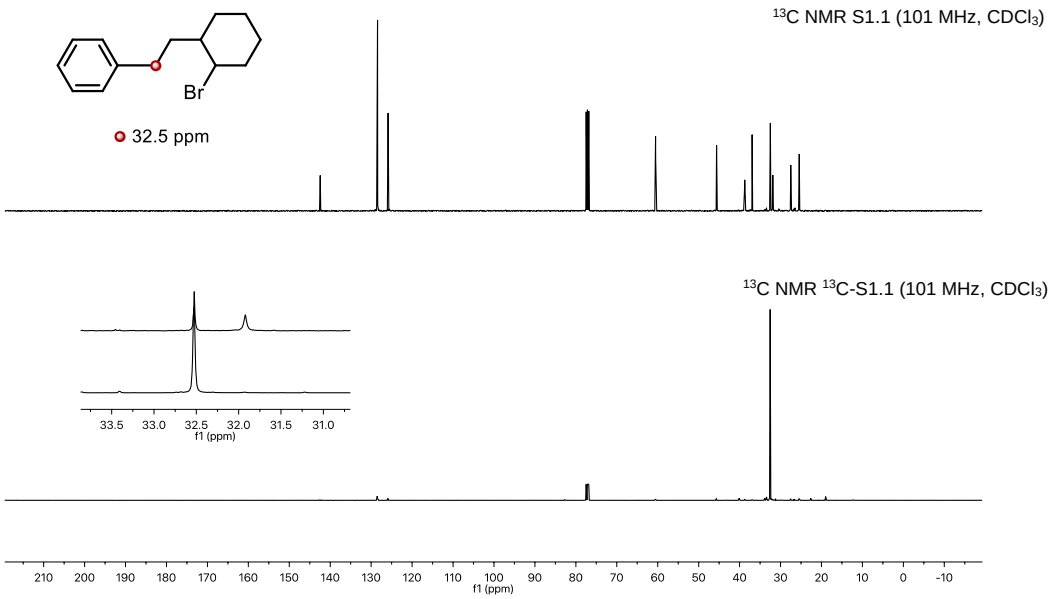


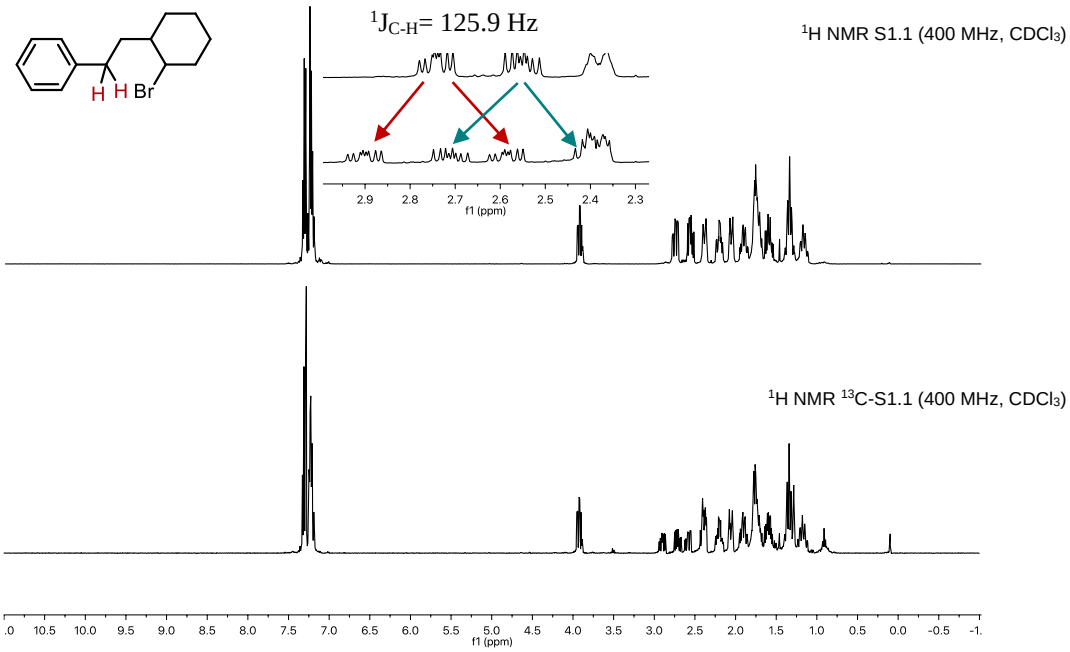
1.60 **S1**

((2-bromocyclohexyl)ethynyl)benzene (18 mg, 0.07 mmol, 1 equiv) and Pd/C (7 mg) were suspended in degassed MeOH (0,35 mL, 0,2 M) in a microwave vial, the vial closed and argon was bubbled inside for 10 minutes. Then the vial was evacuated and backfilled three times with hydrogen using a balloon. The mixture was the stirred for 3h at 23 ºC, then the crude was filtered thought a pad of Celite® and the pad washed with Et_2O. The solvent was removed under vacuum to obtain the product (18 mg, 96% yield).

^{1}H-NMR (400 MHz, Chloroform-*d*) δ 7.37 – 7.27 (m, 2H), 7.25 – 7.17 (m, 3H), 4.06 – 3.76 (m, 1H), 2.74 (ddd, *J* = 13.51, 11.13, 5.05 Hz, 1H), 2.55 (ddd, *J* = 13.52, 10.66, 6.17 Hz, 1H), 2.44 – 2.35 (m, 1H), 2.20 (dddd, *J* = 13.80, 11.14, 6.21, 2.84 Hz, 1H), 2.11 – 2.02 (m, 1H), 1.90 (tdd, *J* = 12.83, 11.18, 3.52 Hz, 1H), 1.74 (ddtd, *J* = 19.12, 10.31, 7.06, 6.37, 2.97 Hz, 3H), 1.59 (dddd, *J* = 13.64, 10.72, 8.67, 5.04 Hz, 1H), 1.43 – 1.26 (m, 2H), 1.16 (tdd, *J* = 13.87, 8.20, 3.10 Hz, 1H). **^{13}C-NMR (**101 MHz, $CDCl_3$) δ 142.4, 128.5 (2C), 128.4 (2C), 125.9, 60.5, 45.6, 38.8, 36.9, 32.5, 31.9, 27.5, 25.4.

Superimposition of the ^{13}C-labeled compound and the unlabeled compound





Theoretical DFT Calculations

Computational Methods

Calculations were performed by means of the Gaussian 09 suite of programs.[113] DFT was applied using M06.[114] The LANL2DZ basis set[115] was utilized to describe Au, In, and Br with ECP and additional polarization function (ζ_f = 1.050 for Au,[116] ζ_d = 0.143 for In,[117] and ζ_d = 0.428 for Br[117]). The 6-31G(d) basis set[118] was employed for all remaining atoms (C, H, P and

113 Gaussian 09, Revision B.1, Frisch, M. J., Trucks, G. W., Schlegel, H. B., Scuseria, G. E., Robb, M. A., Cheeseman, J. R., Scalmani, G., Barone, V., Mennucci, B., Petersson, G. A., Nakatsuji, H., Caricato, M., Li, X., Hratchian, H. P., Izmaylov, A. F., Bloino, J., Zheng, G., Sonnenberg, J. L., Hada, M., Ehara, M., Toyota, K., Fukuda, R., Hasegawa, J., Ishida, M., Nakajima, T., Honda, Y., Kitao, O., Nakai, H., Vreven, T., Montgomery, J. A., Peralta, Jr. J. E., Ogliaro, F., Bearpark, M., Heyd, J. J., Brothers, E., Kudin, K. N., Staroverov, V. N., Kobayashi, R., Normand, J., Raghavachari, K., Rendell, A., Burant, J. C., Iyengar, S. S., Tomasi, J., Cossi, M., Rega, N., Millam, J. M., Klene, M., Knox, J. E., Cross, J. B., Bakken, V., Adamo, C., Jaramillo, J., Gomperts, R., Stratmann, R. E., Yazyev, O., Austin, A. J., Cammi, R., Pomelli, C., Ochterski, J. W., Martin, R.L., Morokuma, K.,, Zakrzewski, V. G., Voth, G. A., Salvador, P., Dannenberg, J. J., Dapprich, S., Daniels, A. D., Farkas, Ö., Foresman, J. B., Ortiz, J. V., Cioslowski, J., Fox, D. J. Gaussian, Inc., Wallingford CT **2009**.

114 Y. Zhao, D. G. Truhlar, *Theor. Chem. Acc.* **2008**, *120*, 215–241.

115 a) P. J. Hay, W. R. J. Wadt, *Chem. Phys.* **1985**, *82*, 270−283. (b) P. J. Hay, W. R. J. Wadt, *Chem. Phys.* **1985**, *82*, 299−310.

116 A. Ehlers, M. Böhme, S. Dapprich, A. Gobbi, A. Höllwarth, V. Jonas, K. Köhler, R. Stegmann, A. Veldkamp, G. Frenking, *Chem. Phys. Lett.* **1993**, *208*, 111−114.

117 A. Höllwarth, M. Böhme, S. Dapprich, A. W. Ehlers, A. Gobbi, V. Jonas, K. F. Köhler, R. Stegmann, A. Veldkamp, G. Frenking, *Chem. Phys. Lett.* **1993**, *208*, 237–240.

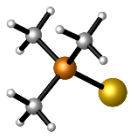
118 W. J. Hehre, R. Ditchfield, J. A. Pople, *J. Chem. Phys.* **1972**, *56*, 2257–2261.

Si). Full geometry optimizations were carried out in CH_2Cl_2, through an implicit solvent SMD.[119] The stationary points were characterized by vibrational analysis. Transition states were identified by the presence of one imaginary frequency while minima by a full set of real frequencies. The connectivity of the transition states was confirmed by relaxing each transition state towards both the reactant and the product. The energy for the optimized geometry of some specific non-critical structures, that could not be located, was estimated through constrained optimizations with distances at reasonable values. These cases are indicated in the main schemes. Reported energies are potential energies (E) and free energies (G) in solution, computed at 298 K and 1 atm.

The bonding situation was analyzed using Natural Bond Orbital analysis (NBO 6.0).[120] The Natural Localized Molecular Orbitals (NLMO) associated to the Au–C1 and C1–C2 interactions have been determined.[121] And the NLMOs isosurface were visualized using ChemCraft, with the surface contour set at 0.05.[122]

Computed Structures and Energies

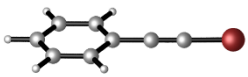
$AuOMe_3$



E = -596.285531 Hartrees

G = -596.206222 Hartrees

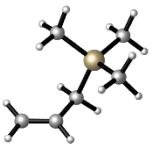
1.42a



E = -320.690177 Hartrees

G = -320.624009 Hartrees

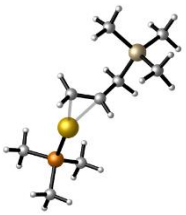
1.43a



E = -526.337057 Hartrees

G = -526.192697 Hartrees

Int1



E = -1122.666956 Hartrees

G = -1122.422385 Hartrees

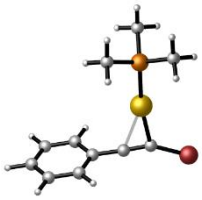
Int2a

119 A.V. Marenich, C. J. Cramer, D.G. Truhlar, *J. Phys. Chem. B*. **2009**, *113*, 6378–6396.

120 E. D. Glendening, J. K. Badenhoop, A. E. Reed, J. E. Carpenter, J. A. Bohmann, C. M. Morales, C. R. Landis, F. Weinhold, Theoretical Chemistry Institute, University of Wisconsin, Madison, **2013**.

121 A. E. Reed, F. Weinhold,. *J. Chem. Phys.* **1985**, *83*, 1736–1740.

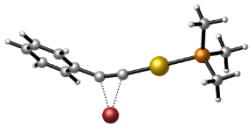
122 Chemcraft - graphical software for visualization of quantum chemistry computations. https://www.chemcraftprog.com.



E = -917.005188 Hartrees

G = -916.839399 Hartrees

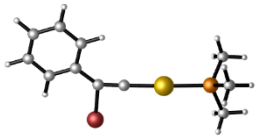
TS_{2a-3a}



E = -916.972001 Hartrees

G = -916.807066 Hartrees

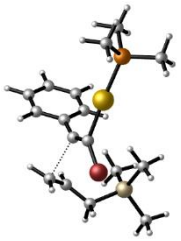
Int3a



E = -916.974224 Hartrees

G = -916.810155 Hartrees

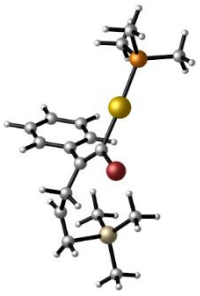
TS_{2a-4a}



E = -1443.341615 Hartrees

G = -1443.006714 Hartrees

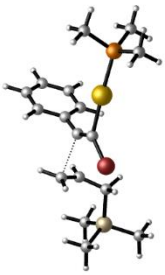
Int4a



E = -1443.388423 Hartrees

G = -1443.050093 Hartrees

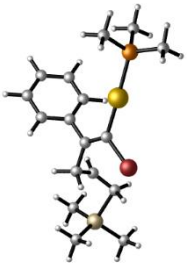
TS_{2a-4b}



E = -1443.341355 Hartrees

G = -1443.010038 Hartrees

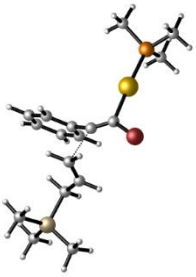
Int4b



E = -1443.389057 Hartrees

G = -1443.051952 Hartrees

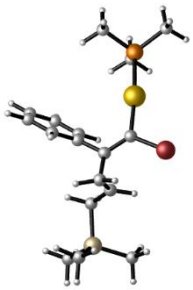
TS_{2a-4c}



E = -1443.345029 Hartrees

G = -1443.011914 Hartrees

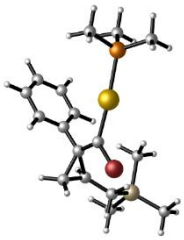
Int4c



E = -1443.392267 Hartrees

G = -1443.052591 Hartrees

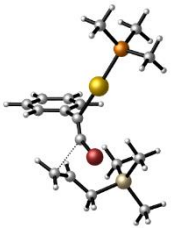
TS_{4a-4a}



E = -1443.378962 Hartrees

G = -1443.038141 Hartrees

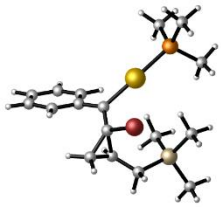
TS_{2a-5a}



E = -1443.332051 Hartrees

G = -1442.999147 Hartrees

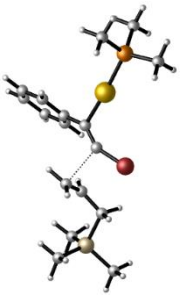
Int5a



E = -1443.388523 Hartrees

G = -1443.046143 Hartrees

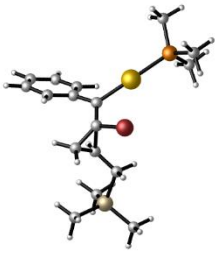
TS_{2a-5b}



E = -1443.332906 Hartrees

G = -1443.003499 Hartrees

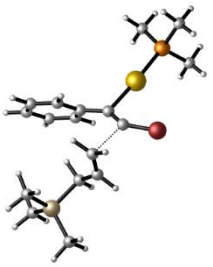
Int5b



E = -1443.385638 Hartrees

G = -1443.050019 Hartrees

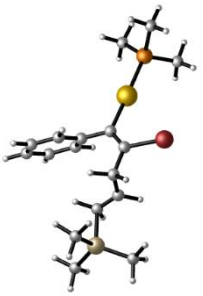
TS_{2a-5c}



E = -1443.332322 Hartrees

G = -1442.999974 Hartrees

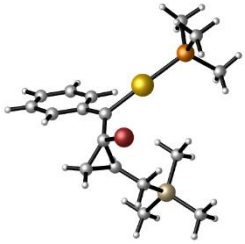
Int5c



E = -1443.383649 Hartrees

G = -1443.046384 Hartrees

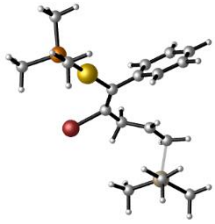
TS_{5b-5a}



E = -1443.381372 Hartrees

G = -1443.041744 Hartrees

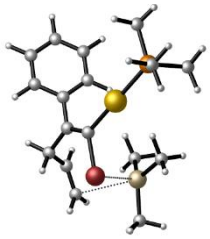
TS_{5c-5b}



E = -1443.377199 Hartrees

G = -1443.036555 Hartrees

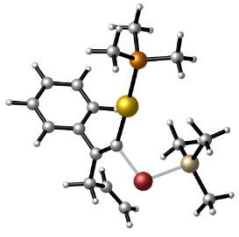
TS_{4a-6a}



E = -1443.360667 Hartrees

G = -1443.021300 Hartrees

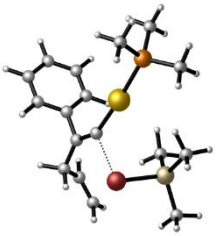
Int6a



E = -1443.387853 Hartrees

G = -1443.051538 Hartrees

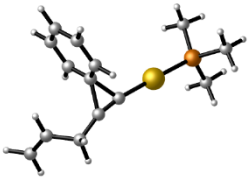
TS_{6a-7a}



E = -1443.386079 Hartrees

G = -1443.047769 Hartrees

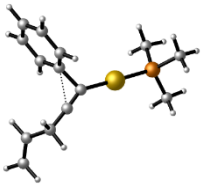
Int7a



E = -1021.052307 Hartrees

G = -1020.818080 Hartrees

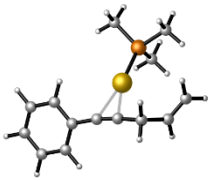
TS_{7a-8a}



E = -1021.044896 Hartrees

G = -1020.811813 Hartrees

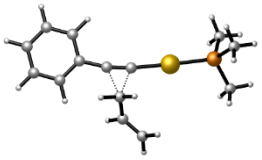
Int8a and Int9a



E = -1021.088724 Hartrees

G = -1020.854108 Hartrees

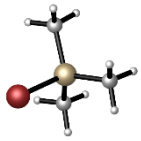
TS_{7a-9a}



E = -1021.038332 Hartrees

G = -1020.801922 Hartrees

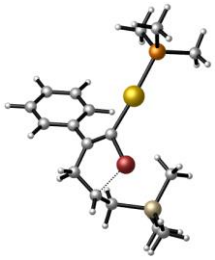
TMSBr



E = -422.327535 Hartrees

G = -422.249984 Hartrees

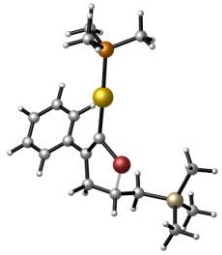
TS_{4a-10a}



E = -1443.380179 Hartrees

G = -1443.040235 Hartrees

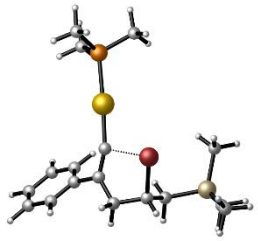
Int10a



E = -1443.383549 Hartrees

G = -1443.042177 Hartrees

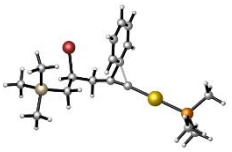
$TS_{10a-11a}$



E = -1443.377369 Hartrees

G = -1443.039483 Hartrees

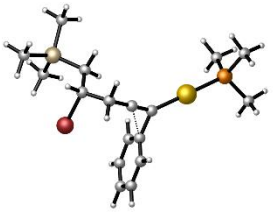
Int11a



E = -1443.376221 Hartrees

G = -1443.040214 Hartrees

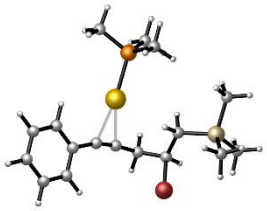
$TS_{11a-12a}$



E = -1443.370089 Hartrees

G = -1443.034948 Hartrees

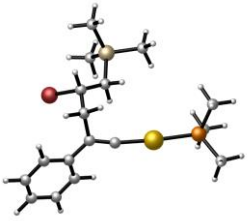
Int12a and Int13a



E = -1443.413467 Hartrees

G = -1443.07753 Hartrees

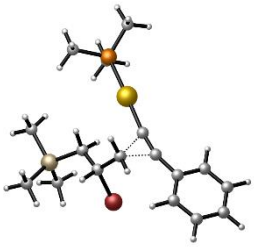
Int11b



E = -1443.368468 Hartrees

G = -1443.029359 Hartrees

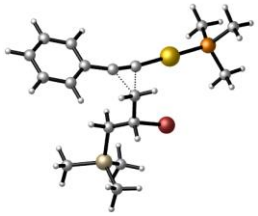
$TS_{11b-13a}$



E = -1443.359664 Hartrees

G = -1443.018041 Hartrees

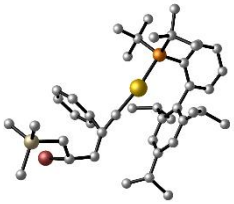
$TS_{10a\text{-}13a}$



E = -1443.360906 Hartrees

G = -1443.023592 Hartrees

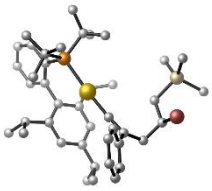
Int11a'



E = -2455.062317 Hartrees

G = -2454.189742 Hartrees

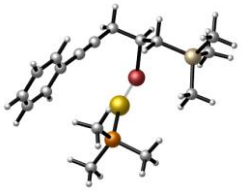
Int11b'



E = -2455.06141 Hartrees

G = -2454.190399 Hartrees

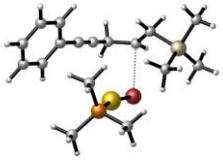
Int14a



E = -1443.414110 Hartrees

G = -1443.075077 Hartrees

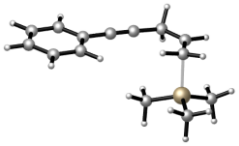
$TS_{14a\text{-}15a}$



E = -1443.400975 Hartrees

G = -1443.061044 Hartrees

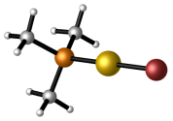
Int15a



E = -833.734326 Hartrees

G = -833.495116 Hartrees

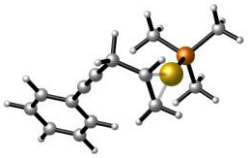
Int16



E = -609.661436 Hartrees

G = -609.585184 Hartrees

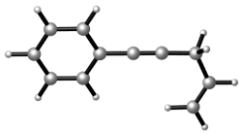
Int17a



E = -1021.094438 Hartrees

G = -1020.856693 Hartrees

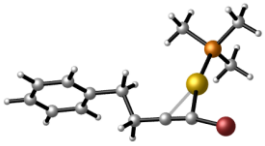
1.44



E = -424.766500 Hartrees

G = -424.631895 Hartrees

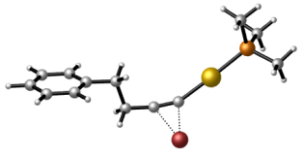
Int18a



E = -995.565187 Hartrees

G = -995.347107 Hartrees

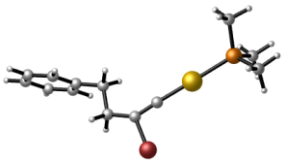
TS_{18a-3b}



E = -995.532868 Hartrees

G = -995.315255 Hartrees

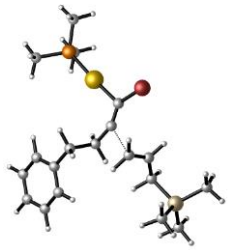
Int3b



E = -995.536834 Hartrees

G = -995.319683 Hartrees

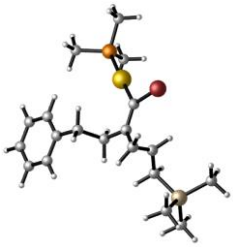
TS_{18a-4d}



E = -1521.902552 Hartrees

G = -1521.517107 Hartrees

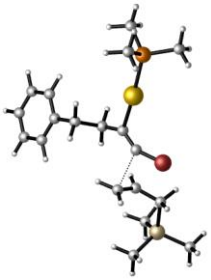
Int4d



E = -1521.954258 Hartrees

G = -1521.562363 Hartrees

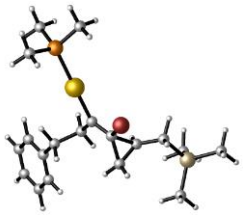
TS_{18a-5d}



E = -1521.894316 Hartrees

G = -1521.509162 Hartrees

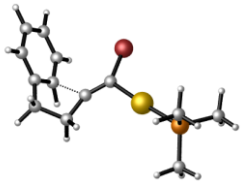
Int5d



E = -1521.946050 Hartrees

G = -1521.554744 Hartrees

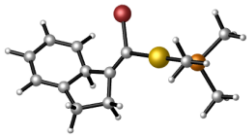
TS_{18a-19}



E = -995.538878 Hartrees

G = -995.318382 Hartrees

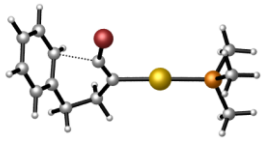
Int19



E = -995.557427 Hartrees

G = -995.334676 Hartrees

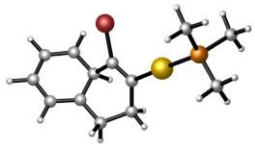
TS_{18a-20}



E = -995.542198 Hartrees

G = -995.320466 Hartrees

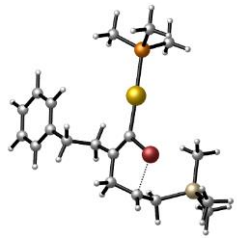
Int20



E = -995.557517 Hartrees

G = -995.335046 Hartrees

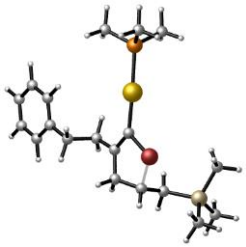
TS_{4d-10d}



E = -1521.941067 Hartrees

G = -1521.548723 Hartrees

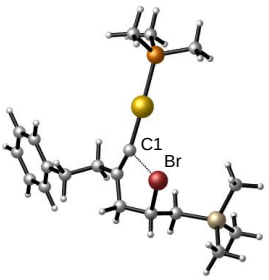
Int10d



E = -1521.944641 Hartrees

G = -1521.551452 Hartrees

$TS_{10d-11d}$

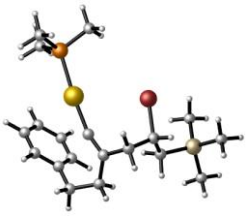


Frozen distance: d(C1−Br) = 2.56 Å.

E = -1521.940598 Hartrees

G = -1521.550227 Hartrees

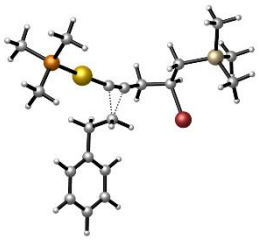
Int11d



E = -1521.943863 Hartrees

G = -1521.550433 Hartrees

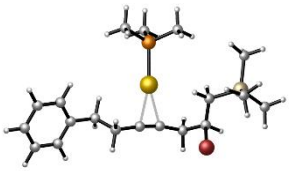
$TS_{11d-12d}$



E = -1.521,923545 Hartrees

G = -1.521,534073 Hartrees

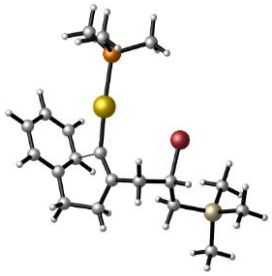
Int12d



E = -1.521,975481 Hartrees

G = -1.521,582368 Hartrees

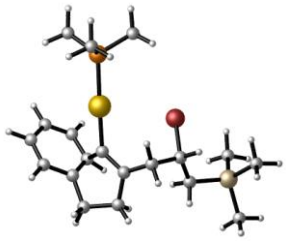
$TS_{11d-21d}$



E = -1521.942163 Hartrees

G = -1521.549526 Hartrees

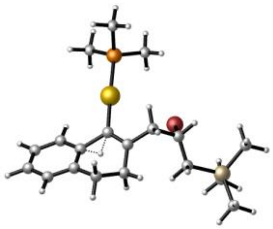
Int21d



E = -1521.951195 Hartrees

G = -1521.556609 Hartrees

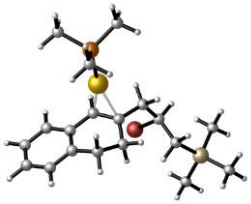
$TS_{21d\text{-}22d}$



E = -1521.936015 Hartrees

G = -1521.542864 Hartrees

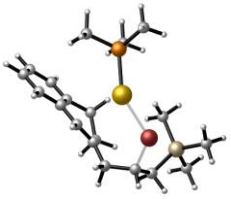
Int22d



E = -1522.034490 Hartrees

G = -1521.637645 Hartrees

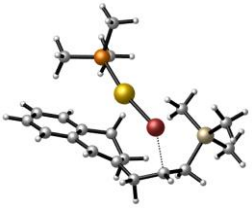
Int23d



E = -1522.029035 Hartrees

G = -1521.626855 Hartrees

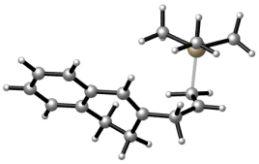
$TS_{23d\text{-}24d}$



E = -1522.022227 Hartrees

G = -1521.621962 Hartrees

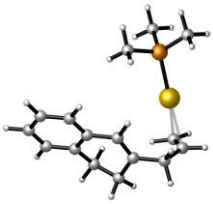
Int24d



E = -912.356970 Hartrees

G = -912.057942 Hartrees

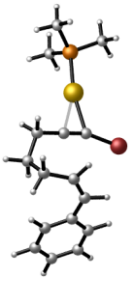
Int25d



E = -1099.715837 Hartrees

G = -1099.418224 Hartrees

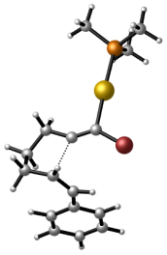
Int26



E = -1112.178583 Hartrees

G = -1111.900253 Hartrees

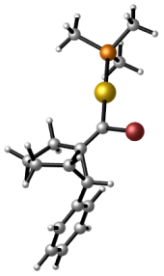
$TS_{26\text{-}27}$



E = -1112.169439 Hartrees

G = -1111.890997 Hartrees

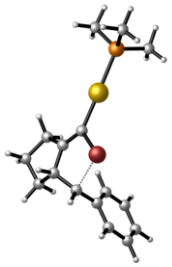
Int27



E = -1112.214437 Hartrees

G = -1111.932123 Hartrees

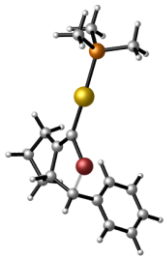
$TS_{27\text{-}28}$



E = -1112.203238 Hartrees

G = -1111.919938 Hartrees

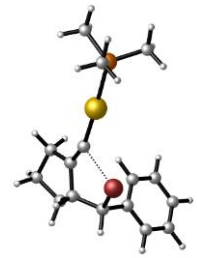
Int28



E = -1112.203418 Hartrees

G = -1111.921250 Hartrees

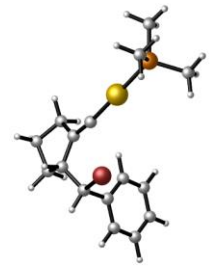
$TS_{28\text{-}29}$



E = -1112.200428 Hartrees

G = -1111.917490 Hartrees

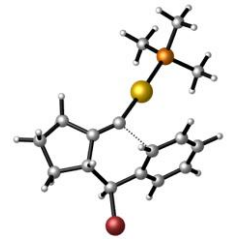
Int29



E = -1112.201022 Hartrees

G = -1111.920020 Hartrees

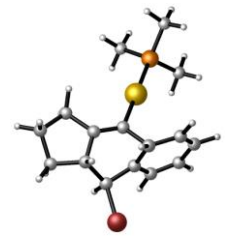
$TS_{29\text{-}30}$



E = -1112.200078 Hartrees

G = -1111.917848 Hartrees

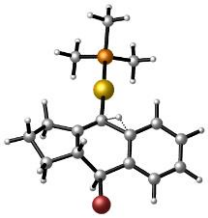
Int30



E = -1112.210068 Hartrees

G = -1111.926307 Hartrees

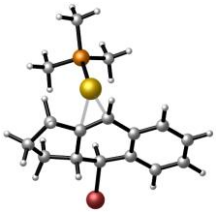
TS_{30-31}



E = -1112.193675 Hartrees

G = -1111.911351 Hartrees

Int31



E = -1112.293826 Hartrees

G = -1112.007327 Hartrees

Chapter 2

Gold(I)-Catalyzed Cycloaddition of Ynol Ethers with Alkenes

Introduction

Synthesis of Cyclobutanones via [2+2] Cycloaddition of Ketenes with Alkenes

Cyclobutanes, and cyclobutanones as their subclass, are of high interest due to their presence in the scaffold of natural products[123] as well as in pharmaceutical relevant compounds (Figure 2.1, top).[124] Their importance is not limited to their synthesis, but also as versatile intermediates. In fact, cyclobutyl derivatives are characterized for a high ring strain,[125] calculated to range from 18 to 27 kcal/mol depending on the substituents and the hybridization of the carbons of the four-membered ring. Therefore, the release of this strain is an excellent driving force for many transformations.[126] Favored by thermodynamics then, a variety of ring expansion can be performed accessing larger carbocycles[127], including lactones and lactams[128]. Acyclic compounds can be also obtained by ring opening reactions.

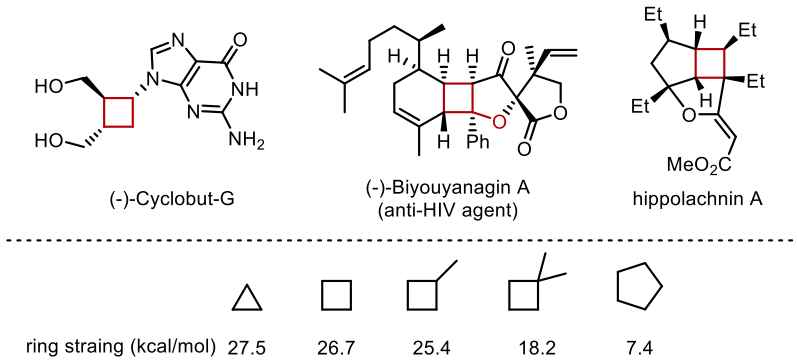


Figure 2.1. Selected examples of cyclobutyl derivatives in natural occurring products and pharmaceuticals (top). Ring strain in kcal mol $^{-1}$ for small carbocycles (bottom).

Cyclobutanones present an even higher synthetic value due to the high electrophilicity of the carbonyl group that represents an additional handle for functionalization. Especially relevant in

123 a) F. Secci, A. Frongia, P. P. Piras, *Molecules* **2013**, *18*, 15541–15572. b) J. Li, K. Gao, M. Bian, H. Ding, *Org. Chem. Front.* **2019**, *7*, 136–154. c) J. P. Deprés, P. Delair, J. F. Poisson, A. Kanazawa, A. E. Greene, *Acc. Chem. Res.* **2016**, *49*, 252–261. d) A. Sergeiko, V. V Poroikov, L. O. Hanus, V. M. Dembitsky, *Open Med. Chem. J.* **2008**, *2*, 26–37.

124 a) G. S. Bisacchi, A. Braitman, C. W. Cianci, J. M. Clark, *J. Med. Chem.* **1991**, *34*, 1415–1421. b) E. D. Deeks, *Drugs* **2019**, *79*, 463–468. c) M. D. Tricklebank, *Idrugs* **2000**, *3*, 228–231.

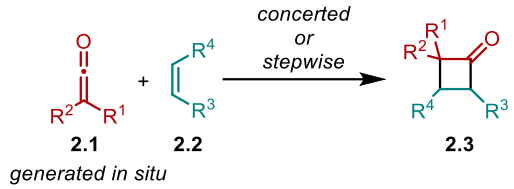
125 For an overview on ring strain: a) J. F. Liebman, A. Greenberg, *Chem. Rev.* **1976**, *76*, 311–365. b) K. B. Wiberg, *Angew. Chem Int. Ed.* **1986**, *25*, 312–322.

126 For two reviews on the topic: a) T. Seiser, T. Saget, D. N. Tran, N. Cramer, *Angew. Chem. Int. Ed.* **2011**, *50*, 7740–7752. b) E. Lee-Ruff, G. Mladenova, *Chem. Rev.* **2003**, *103*, 1449–1483.

127 For selected examples see: a) J. A. Dabrowski, D.C. Moebius, A.J. Wommack, A.F. Kornahrens, J.S. Kingsbury, *Org. Lett.* **2010**, *12*, 3598–3601. b) E. Leemans, M. D'Hooghe, N. De Kimpe, *Chem. Rev.* **2011**, *111*, 3268–3333. c) T. Seiser, N. Cramer, *Chem. Eur. J.* **2010**, *16*, 3383–3391. d) S. A. Miller, R. C. Gadwood, *J. Org. Chem.* **1988**, *53*, 2214–2220. e) M. H. Shaw, J. F. Bower, *Chem. Commun.* **2016**, *52*, 10817–10829.

128 K. S. Petersen, B. M. Stoltz, *Tetrahedron* **2011**, *67*, 4352–4357.

this context is their use as reactive center for desymmetrization.[129] Therefore, several transformations have been developed for the synthesis of cyclobutanones, among which the [2+2] cycloaddition alkenes **2.2** with ketenes **2.1** is the most direct and atom economical strategy[130] (Scheme 2.1).



Scheme 2.1. [2+2] Cycloaddition of ketenes with alkenes to form cyclobutanones.

Diphenylketene **2.5**, a stable and isolable compound described by Herman Staudinger in 1905, is formed by dehalogenation of chlorodiphenylacetyl chloride **2.4**, and is the first reported representative of these reactive intermediates (Figure 2.2a).[131] Nowadays, ketenes can be generated thermally and photochemically, but probably the most popular method is the dehydrohalogenation of acid chlorides with tertiary amines or under reductive conditions in analogy with the Staudinger experiment.

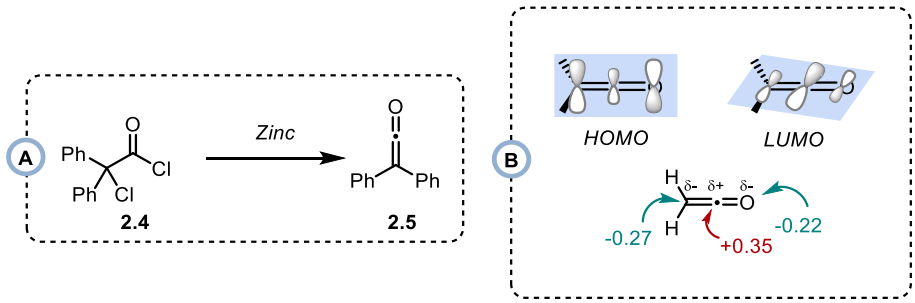


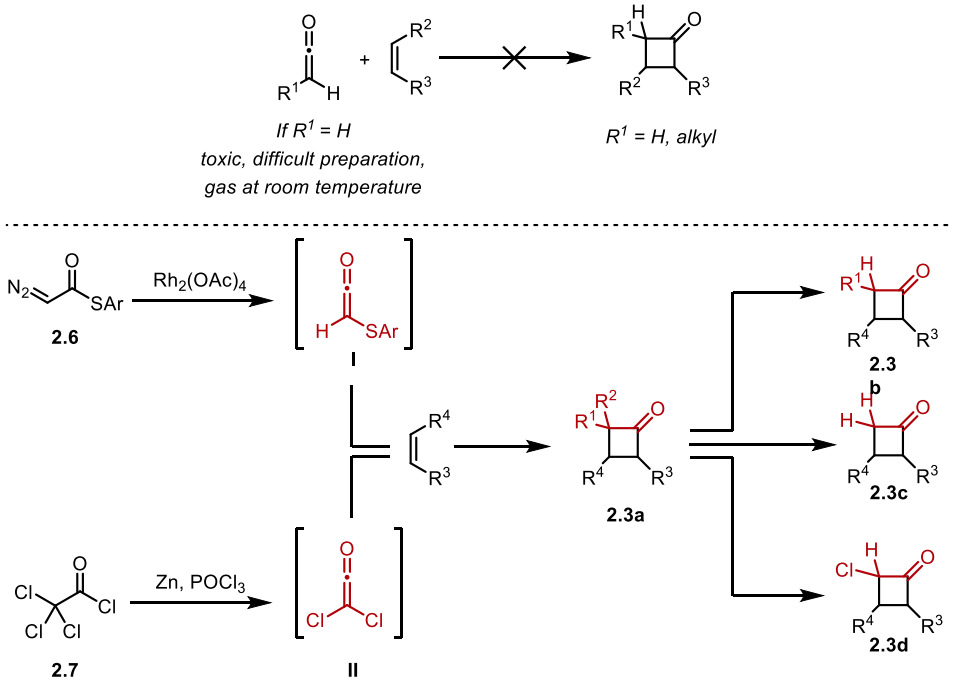
Figure 2.2. A) First ketene synthesis from Staudinger. B) frontier orbital structure and partial charges on the heteroallene moiety of a ketene.

Structurally, ketenes are characterized for a linear "heteroallenic" moiety where the reactions take place. NMR and computational studies revealed that the HOMO of the ketene is located perpendicular to the plane and mainly on the oxygen and the β-carbon, while the LUMO lays on the plane of the double bond and is mainly located on the α-carbon. Therefore, a significant partial negative charge is located on β-carbon making this prone to react with electrophiles,

129 J. Sietmann, J. M. Wiest, *Angew. Chem. Int. Ed.* **2020**, *59*, 6964–6974.
130 a) T. T. Tidwell, *Acc. Chem. Res.* **1990**, *23*, 273–279. b) C. M. Rasik, M. K. Brown, *Synlett* **2014**, *25*, 760–765.c) A. D. Allen, T. T. Tidwell, *Chem. Rev.* **2013**, *113*, 7287–7342. d) A. D. Allen, T. T. Tidwell, *Eur. J. Org. Chem.* **2012**, 1081–1096.
131 a) Staudinger, H. *Ber. Dtsch. Chem. Ges.* **1905**, *38*, 1735. b) Staudinger, H. *Justus Liebigs Ann. Chem.* **1907**, *356*, 51. c) (b) Staudinger, H. *Ber. Dtsch. Chem. Ges.* **1907**, *40*, 1145.

while a partial positive charge is located on the α-carbon that is easily attacked by nucleophiles (Figure 2.2b).

Due to the high polarization of ketenes, their stability is also highly influenced by the attached substituents: substituents donating electron density through s-p conjugation as well as π-acceptors stabilize the ketene that can eventually be isolated, while π-donors and electronegative substituents lead to species more reactive towards [2+2] cycloaddition, and more difficult to handle. Considering the limited number of isolable ketenes, the general approach in their [2+2] cycloaddition with alkene is the generation of these reactive intermediates and their trapping *in situ*. It is important to note that, in general, unsubstituted ketene or mono-substituted ketenes are poorly reactive even with activated alkenes and can undergo decomposition or polymerization. In addition to this, the parent ketene is a highly toxic species with a bp of -56 °C and whose preparation requires high temperatures (>500 °C) and a specific equipment[132].



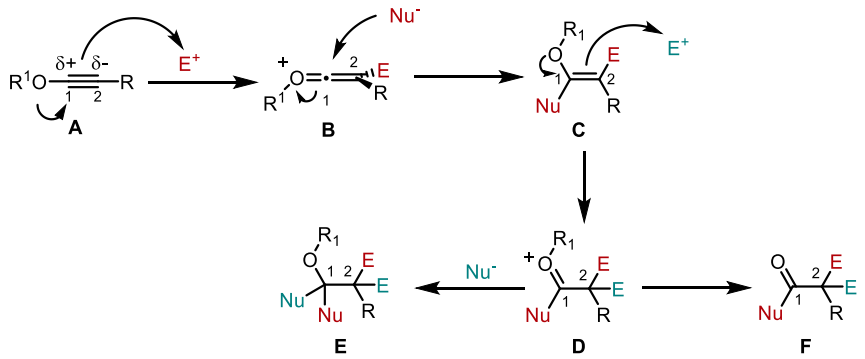
Scheme 2.2. Limitation of the [2+2] cycloaddition of ketenes with alkenes (top). Use of chloro- and thioketenes as ketene surrogates (bottom).

132 Mitzel, T.M. and Pigza, J.A. (2009). Ketene. In Encyclopedia of Reagents for Organic Synthesis, (Ed.). doi:10.1002/047084289X.rk000.pub2

An expedient way to access α-unsubstituted or α-monosubstituted cyclobutanones is to use the more reactive chloro-[133] or thioketenes[134] as ketene surrogate (**2.6** and **2.7** in Scheme 2.2). Once the corresponding cyclobutanone is formed, the α-substituents can be then removed under reductive conditions with Zn(0) or Bu_3SnH to form the unsubstituted cyclobutanone **2.3c**. In alternative, the substituents can be used as reactive centers for the insertion of other functional groups in α–position.

Ynol Ethers: A General Introduction

Alkynes directly bounded to a heteroatom, namely ynamides, ynamines, alkynyl thioethers and ynol ethers (also known as ynol ethers) are valuable building blocks especially for reactions of carbon-carbon bond formation. All these species are characterized for a low steric hindrance due to the linear geometry and a highly polarized triple bond. In this sense ynol ethers like **A** resemble ketenes, since a partial positive charge is located on the carbon attached to the oxygen (C1 in Scheme 2.3) and a partial negative charge is located on the other carbon of the alkyne (C2 in Scheme 2.3). For this reasons ynol ethers can react both as nucleophiles (at C2) and as electrophiles (at C1) and up to 4 new bonds can be forged in a single transformation[135] (Scheme 2.3). Upon their reaction with an electrophile followed by addition of a nucleophile enol ether **C** is formed, which can further react with a new electrophile to generate intermediate **D.** Intermediate **D** can evolve into the highly substituted carbonyl compound **F** or undergo final nucleophilic attack to form ether **E.**



Scheme 2.3. General reactivity of ynol ethers.

133 Fieser, L.F., Fieser, M., Ho, T., Ho, T.-L., Fieser, M., Fieser, L., Danheiser, R., Roush, W. and Smith, J. (2006). Dichloroketene. In Fieser and Fieser's Reagents for Organic Synthesis (eds L.F. Fieser, M. Fieser and T. Ho). doi:10.1002/9780471264194.fos03663

134 M. D. Lawlor, T. W. Lee, R. L. Danheiser, *J. Org. Chem.* **2000**, *65*, 4375–4384.

135 For a review on synthesis and applications of alkynyl ethers see: V. J. Gray, J. D. Wilden, *Org. Biomol. Chem.* **2016**, *14*, 9695–9711.

Despite the potential of these compounds, their use in synthesis is more limited compared to their nitrogen- or sulfur- analogous, mainly because of a general difficulty in their preparation and isolation. However, this lack of stability confers to ynol ethers unique reactive features. In fact, *O*-ethyl or *O*-*tert*-butyl ynol ethers **2.8a-b** can easily undergo retro-ene reaction upon thermal treatment forming an ketene and extruding one molecule of ethylene or isobutylene, respectively. The reactive ketene can be then trapped intramolecularly by an appended alcohol or amine to generate lactones **2.9** or lactams **2.3**[135,136] (Scheme 2.4, blue). When the reaction is performed in a sealed tube the transient ketene can be trapped with a molecules of substrate in a [2+2] cycloaddition to form cyclobutenone **2.11** which can lead to symmetric diketone **2.12** after hydrolysis (Scheme 2.4, green).[137]

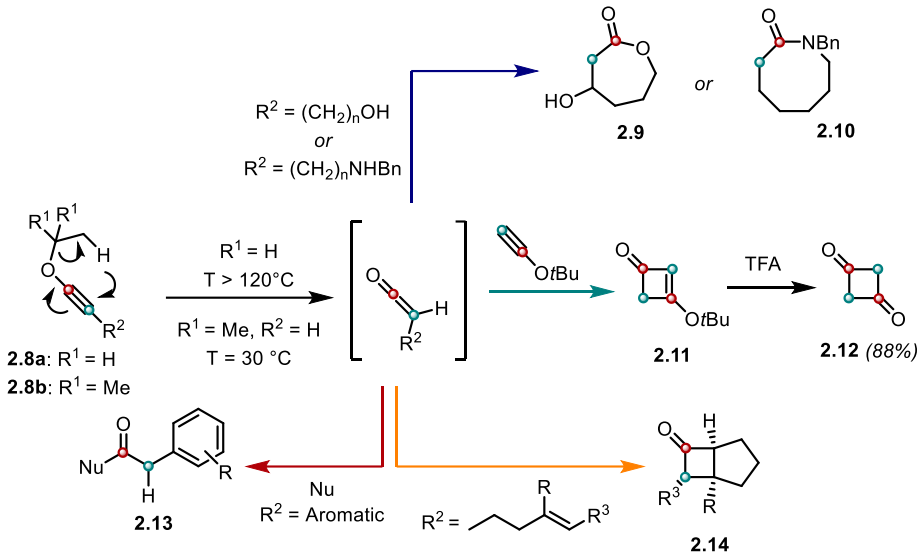
For aryl substituted *O*-*tert*-butyl ynol ethers the thermal retro-ene reaction occurs at 75 °C and the more stable ketene has been trapped with different external nucleophiles to form ketones, amides, esters, cyclobutanones, quinolines or allenes (Scheme 2.4, red). [138] Ketenes generated from 1-*tert*-butoxy-1,6-enyne undergo intramolecular [2+2] cycloaddition forming *cis*-fused cyclobunanones **2.14** (Scheme 2.4, orange). [139]

136 See as example: a) T. G. Minehan, *Acc. Chem. Res.* **2016**, *49*, 1168–1181. b) X. Y. Mak, R. P. Ciccolini, J. M. Robinson, J. W. Tester, R. L. Danheiser, *J. Org. Chem.* **2009**, *74*, 9381–9387. c) L. Liang, M. Ramaseshan, D. I. MaGee, *Tetrahedron* **1993**, *49*, 2159–2168. d) For the application of the reaction in total synthesis see: R. M. Moslin, T. F. Jamison, *J. Am. Chem. Soc.* **2006**, *128*, 15106–15107.

137 M. A. Pericàs, F. Serratosa and E. Valentí, *Synthesis*, **1985**, 1118-1120.

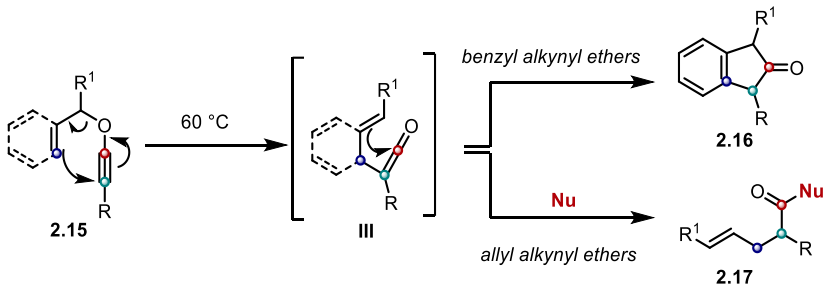
138 W. Zhang, J. M. Ready, *Angew. Chem. Int. Ed.* **2014**, *53*, 8980–8984.

139 V. Tran, T. G. Minehan, *Org. Lett.* **2011**, *13*, 6588–6591.



Scheme 2.4. Thermal retro-ene reaction of O-alkyl ynol ethers to form transient ketenes and trapping with different reagents.

The scope of possible ketene precursors has also been expanded to allyl or benzyl ynol ethers **2.15**, which upon [3,3] sigmatropic rearrangement form the corresponding allyl ketenes **III** (Scheme 2.5). For benzyl ynol ethers, the intermediate ketene undergoes a cyclization to form 2-indanones **2.16**.[140] In case of allyl ynol ethers, the corresponding ketene is then trapped by alcohols or amines to form γ,δ-unsaturated esters and amides **2.17**.[141]



Scheme 2.5. [3,3]-Sigmatropic of allyl or benzyl ynol ethers rearrangement to generate ketenes.

Compared to the aliphatic ynol ethers, silyloxy- and aromatic ynol ethers are generally more stable since they cannot undergo neither retro-ene reaction or sigmatropic rearrangement. For example, aryl ynol ethers have been used as directing groups in transition metal catalyzed C-H

140 a) H. Olsman, A. Graveland, J. F. Arens, Chemistry of acetylenic ethers *71*. *Rec. Trav. Chim. Pays-Bas* **1964**, *83*, 301−306. b) A. Wunderli, J. Zsindely, H.J. Hansen, H. Schmid, *Chimia*, **1972**, *26*, 643−645. c) A. A. Tudjarian, T. G. Minehan, *J. Org. Chem.* **2011**, *76*, 3576–3581.

141 a) A. Christopher, D. Brandes, S. Kelly, T. Minehan, *Org. Lett.* **2006**, *8*, 451–454. b) J. R. Sosa, A. A. Tudjarian, T. G. Minehan, *Org. Lett.* **2008**, *10*, 5091–5094.

functionalization[142] and, due to the polarized nature of the triple bond, are suitable substrates to undergo migratory insertion in presence of a transition metal.[143] Of particular relevance for the following discussion is the reactivity of ynol ethers in presence of either a Brønsted or Lewis acid that will presented in the next section.

Brønsted and Lewis Acid Mediated Reaction of Ynol ethers

As for the other alkynes, ynol ethers can be converted into electrophiles with of both Brønsted and Lewis acids.

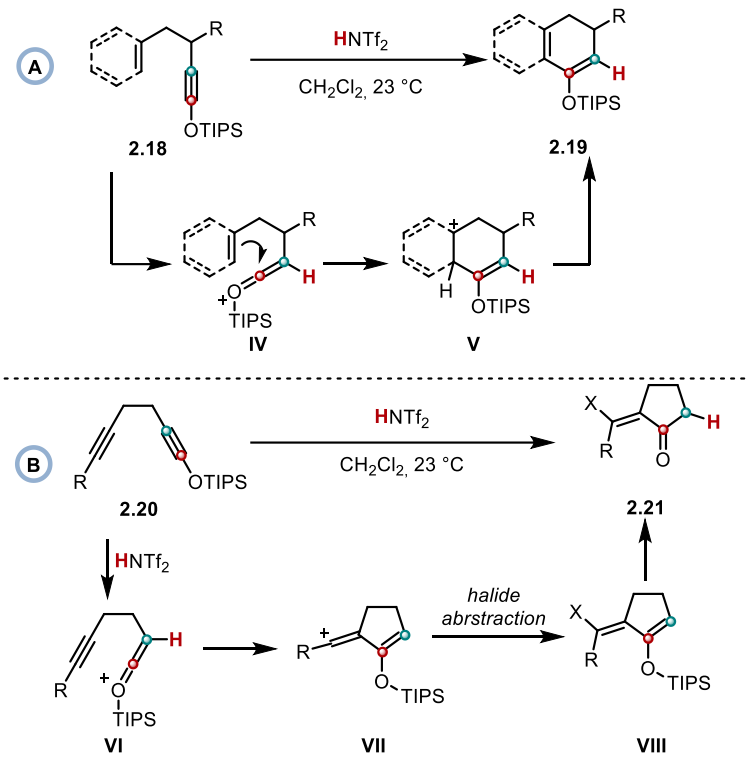
In presence of $HNTf_2$ silyloxyalkynes **2.18** are protonated forming ketenium ion **IV** which can be intercepted by an aromatic ring or an alkene in a *6-exo-trig* cyclization delivering a tetralone or a cyclohexanone, derivative respectively (Scheme 2.6a).[144] The same concept has been applied applied for the Brønsted acid initiated cyclization of 1-siloxy-1,5-diynes **2.20**(Scheme 2.6b). Interestingly, in this case *5-exo-dig* cyclization is favored over the *6-exo-trig* cyclization and the reaction occurs with the concomitant incorporation of a halogen extracted from the solvent.[145] The reaction is proposed to start in the same way as the previous cases with the formation of the ketenium ion **VI** followed by cyclization to form alkenyl cation **VII** that then abstract the halide from the solvent. A final hydrolysis of the silyl dienol ether **VIII** delivers the α,β-unsaturated ketone **2.21**.

142 a) Y. Minami, Y. Shiraishi, K. Yamada, T. Hiyama, *J. Am. Chem. Soc.* **2012**, *134*, 6124–6127. b) Y. Minami, K. Yamada, T. Hiyama, *Angew. Chem. Int. Ed.* **2013**, *52*, 10611–10615. c) T. Mitsui, Y. Tokoro, R. Haraguchi, K. Sugita, M. Harada, S. I. Fukuzawa, Y. Minami, T. Hiyama, *Bull. Chem. Soc. Jpn.* **2018**, *91*, 839–845.

143 B. L. Coles-Taylor, M. S. McCallum, J. S. Lee, B. W. Michel, *Org. Biomol. Chem.* **2018**, *16*, 8639–8646

144 L. Zhang, S. A. Kozmin, *J. Am. Chem. Soc.* **2004**, *126*, 10204–10205.

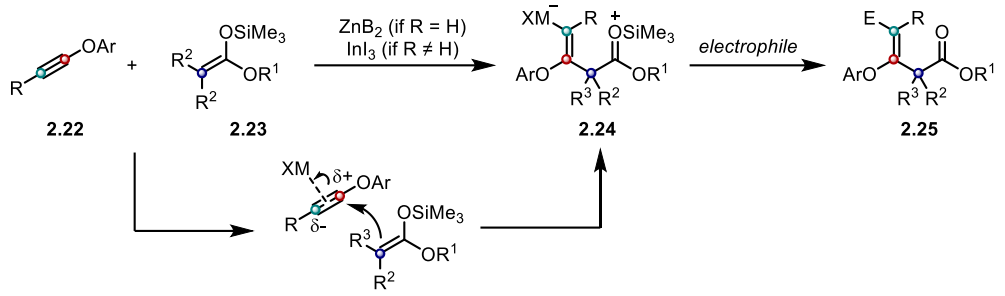
145 L. Zhang, J. Sun, S. A. Kozmin, *Tetrahedron* **2006**, *62*, 11371–11380.



Scheme 2.6. Bronsted acid catalyzed cyclization of silyloxyenynes and diyenes.

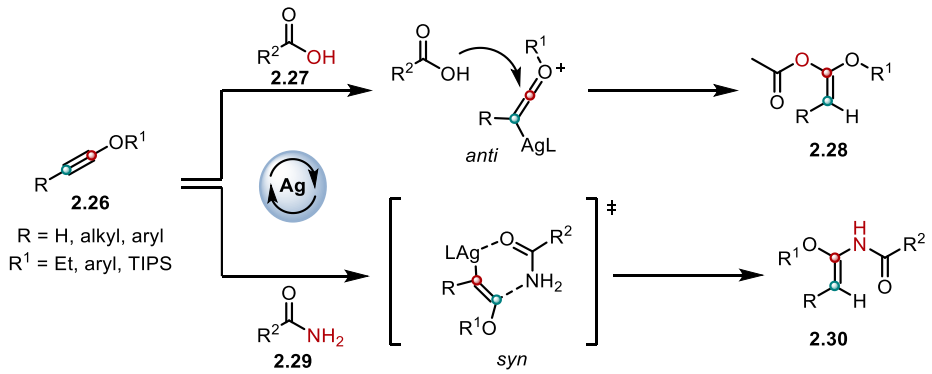
Lewis acids like $ZnBr_2$ and InI_3 have been used for the carbometallation of terminal and internal ynol ethers **2.22**, using silyl ketene acetals **2.23** as nucleophiles Scheme 2.7).[146] According to calculations, the coordination of the metal to the π-system of the ynol ether enhances the partial positive charge on C1 which is attacked by the nucleophile in an *anti*-fashion generating the corresponding β-*anti*-metalated enol ether **2.24**. Upon quenching with a proton source or other electrophiles a series of highly substituted enol ethers **2.25** were synthesized with excellent regio- and stereocontrol.

146 a) Y. Nishimoto, K. Kang, M. Yasuda, *Org. Lett.* **2017**, *19*, 3927–3930. b) K. Kang, Y. Nishimoto, M. Yasuda, *J. Org. Chem.* **2019**, *84*, 13345–13363.



Scheme 2.7. Lewis acid mediated regio- and stereoselective *anti*-carbometallation of ynol ethers.

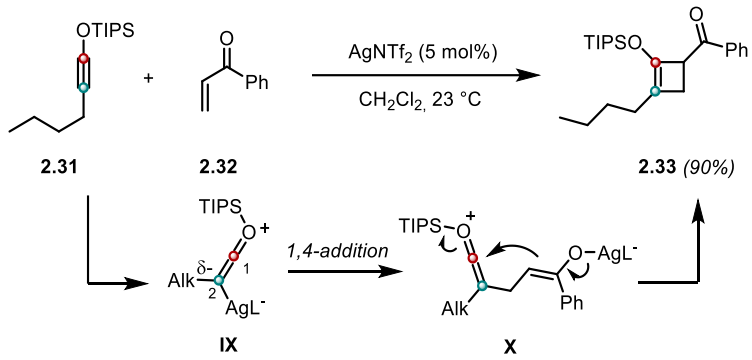
Furthermore α-acyloxy enol ethers like **2.28** can be prepared using Ag_2O as catalyst, through the formation of β-*anti*-metalated enol ether (Scheme 2.8, top).[147] On the other hand, the silver(I)-catalyzed hydroamination of silyloxy ynol ethers proceeds with *syn*-selectivity to form **2.30** (Scheme 2.8, bottom). [148] The nucleophilic attack on the activated alkyne in this case takes place through a six-membered chelated transition state with the oxygen of the nucleophile coordinated to silver.



Scheme 2.8. Silver catalyzed hydrofunctionalization of ynol ethers.

The [2+2] cycloaddition of silyloxy ynol ethers **2.31** with unsaturated carbonyl compound **2.32** to form silyloxy cyclobutene derivatives **2.33** can be catalyzed by $AgNTf_2$.[149] The reaction was proposed to start with the activation of the alkyne by coordination with silver forming the zwitterionic species **IX**, which undergo 1,4-addition with the Michael-acceptor generating ketenium ion **X**, followed by ring closure to form the product (Scheme 2.9).

147 a) L. Zeng, Z. Lai, S. Cui, *J. Org. Chem.* **2018**, *83*, 14834–14841. b) L. Zeng, B. Huang, Y. Shen, S. Cui, *Org. Lett.* **2018**, *20*, 3460–3464.
148 J. Sun, S. A. Kozmin, *Angew. Chem. Int. Ed.* **2006**, *45*, 4991–4993.
149 R. F. Sweis, M. P. Schramm, S. A. Kozmin, *J. Am. Chem. Soc.* **2004**, *126*, 7442–7443



Scheme 2.9. Silver catalyzed [2+2] cycloaddition of silyloxyalkynes with α,β-unsaturated carbonyl compounds.

Based on this fist report on the reaction of ynol ethers as nucleophiles, the reaction was expanded towards different electrophiles such phthalazines[150], aldehydes[151], and Lewis acid activated acetals[152].

Gold(I)-Catalyzed Reaction of Ynol ethers

Compare to other alkynes, the number of transformations of alkynyl enol ether catalyzed by gold are rather limited[153].The first example, reported in 2004 by Kozmin[154], was the reaction of silyloxy enynes like **2.18** in presence of AuCl to form cyclohexadienes **2.34a** and **2.34b** (Scheme 2.10). Once the cyclopropyl-gold(I) carbene **XI** is formed a series of 1,2-alkyl shifts via **XII** and **XIII** leads to gold(I) carbene **XIV**, which gives the final products that *via* 1,2-H-shift. It is interesting to note that the same substrate cyclizes in presence of a Brønsted acid to form cyclohexyl enol ether **2.19** (see Scheme 2.6).

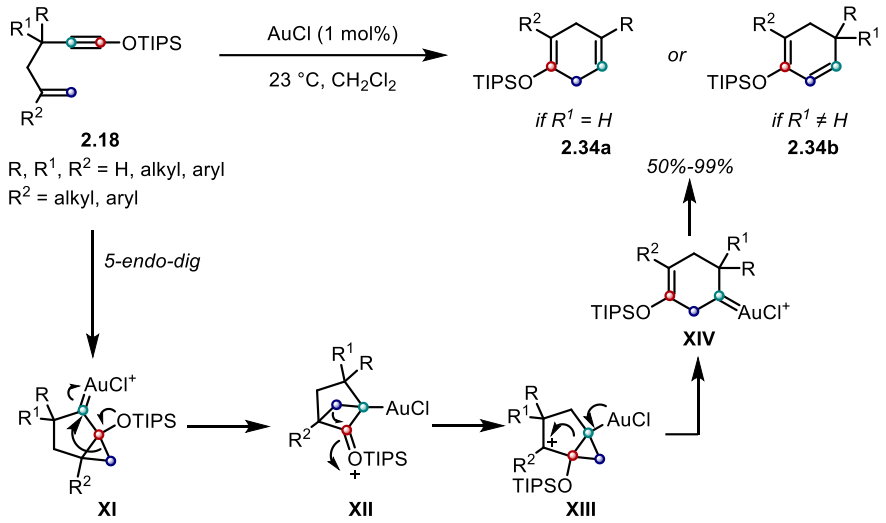
150 a) Y. E. Türkmen, T. J. Montavon, S. A. Kozmin, V. H. Rawal, *J. Am. Chem. Soc.* **2012**, *134*, 9062–9065. b) Few years later the same authors reported that the silver catalyst can be replaces either by copper or nickel salts: C. S. Sumaria, Y. E. Türkmen, V. H. Rawal, *Org. Lett.* **2014**, *16*, 3236–3239.

151 Sun, V. A. Keller, S. T. Meyer, S. A. Kozmin, *Adv. Synth. Catal.* **2010**, *352*, 839–842.

152 a) V. Tran, T. G. Minehan, *Org. Lett.* **2012**, *14*, 6100–6103. b) W. Zhao, Z. Li, J. Sun, *J. Am. Chem. Soc.* **2013**, *135*, 4680–4683.

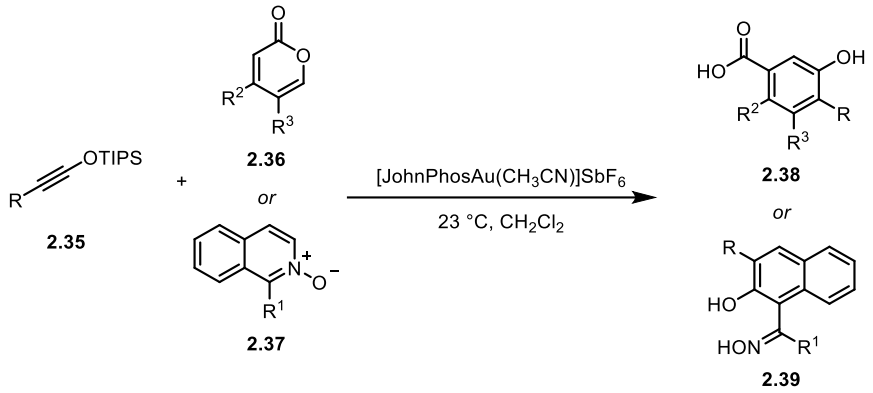
153 Alkyl alkynyl ethers that are reported to undergo retro-ene reaction at around 80 °C in our hands decomposed into the ketene in presence of catalytic amount of gold(I) complexes already at room temperature.

154 L. Zhang, S. A. Kozmin, *J. Am. Chem. Soc.* **2004**, *126*, 11806–11807.



Scheme 2.10. Gold(I)-catalyzed cyclization of 1-silyloxy-1,5-enynes.

Silyloxy alkynes activated by gold(I) complexes react in [4+2] cycloadditions 2-pyrones **2.36** or isoquinoline *N*-oxides **2.37**to form functionalized salicylic acids **2.38** and naphthols **2.39**, respectively, upon fragmentation and TIPS-removal (Scheme 2.11).[155]

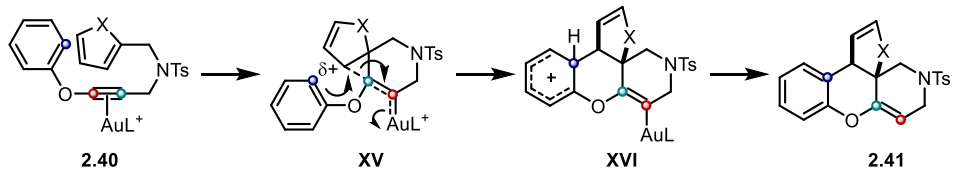


Scheme 2.11. Gold(I)-catalyzed [4+2] cycloaddition of silyl alkynyl enol ethers.

Furans tethered with an ynol ether moiety form dihydrobenzofurans and chromanes in the presence of $AuCl_3$ as catalyst.[156] Noteworthy, For substrates of type **2.40** tetracyclic systems such as **2.41** are formed (Scheme 2.12).[157] The *6-endo-dig* cyclization is favored for these substrates leading to the formation of cyclopropyl gold(I) carbene **2.XV** that undergoes a

155 J. R. Cabrera-Pardo, D. I. Chai, S. Liu, M. Mrksich, S. A. Kozmin, *Nat. Chem.* **2013**, *5*, 423–427.
156 A. Stephen, K. Hashmi, M. Rudolph, J. W. Bats, W. Frey, F. Rominger, T. Oeser, *Chem. Eur. J.* **2008**, *14*, 6672–6678.
157 A. S. K. Hashmi, M. Rudolph, J. Huck, W. Frey, J. W. Bats, M. Hamzić, *Angew. Chem Int. Ed.* **2009**, *48*, 5848–5852.

Friedel-Crafts-type leading to **XVI**, which gives the final product by re-aromatization and protodemetalation.



Scheme 2.12. Gold(I) catalyzed furan-yne cyclization.

Objectives

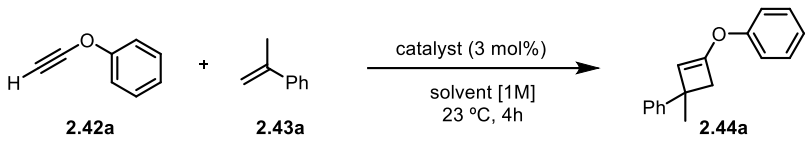
We aimed to extend our previous studies on gold(I)-catalyzed intermolecular [2+2] cycloaddition between alkynes and alkenes to the reaction of terminal and internal ynol ethers with alkenes with the objective to develop a general method for the synthesis of cyclobutanones.

Results and Discussion

Gold(I)-Catalyzed [2+2] Cycloaddition of Terminal Ynol ethers with Alkenes

To start our study on the gold(I)-catalyzed reaction of ynol ethers with alkenes we selected phenoxyacetylene **2.42a** and α-methyl styrene **2.43a** as model substrates. Substrates of type **2.42a** can be prepared in just two steps from commercially available compounds and can be stored neat in the freezer for months with minimal decomposition. The reaction under the optimal conditions developed for the gold(I)-catalyzed [2+2] cycloaddition of terminal alkynes with alkenes[38] led regioselectively to phenoxycyclobutene **2.44a** in 54% yield a (Table 2.1).

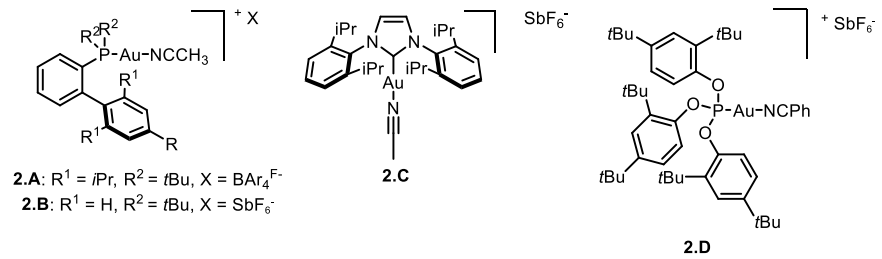
Table 2.1. Optimization of the gold(I)-catalyzed [2+2] cycloaddition of **2.42a** with **2.43a** to form **2.44a**.



2.42a **2.43a** **2.44a**

Entry	Catalyst	solvent	**2.42:2.43a**	Yield (%)[a]
1	**2.A**	CH_2Cl_2	1:2	54
2	**2.B**	CH_2Cl_2	1:2	71
3	**2.C**	CH_2Cl_2	1:2	46
4	**2.D**	CH_2Cl_2	1:2	15
5	**2.A**	$PhCH_3$	1:2	50
6	**2.A**	1,4-Dioxane	1:2	37
7	**2.A**	CH_2Cl_2	1:3	64
8	**2.A**	CH_2Cl_2	2:1	14[c]
9	**2.A**	CH_2Cl_2[b]	1:2	54
10	**2.B**	CH_2Cl_2	1:3	87 (85)

[a] Yields determined by ^{1}H-NMR using trichloroethylene as internal standard, isolated yields in parenthesis. [b] Reaction performed in 0.25 M concentration. [c] 22% conversion of limiting starting material.



2.A: R^1 = *i*Pr, R^2 = *t*Bu, X = BAr_4^{F-}
2.B: R^1 = H, R^2 = *t*Bu, X = SbF_6^-

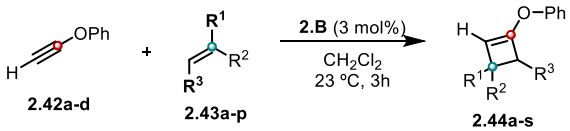
2.C

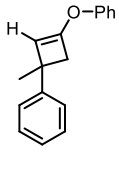
2.D

Changing the catalyst from **2.A** to the more active **2.B** increases the yield of the reaction up to 71%, while using NHC-ligand based gold(I) complex (**2.C**) and phosphite-gold(I) complex (**2.D)** led to lower yields (Table 2.1, entries 2-4). Solvents different from CH_2Cl_2 gave the same or lower yields using **2.A** as catalyst (Table 2.1, entries 5 and 6). A larger excess of alkene (**2.42a:2.43a** = 1:3) gave **2.44a** in 64% yield, while and excess of the alkyne caused a drastic drop in yield and conversion (Table 2.1, entries 7 and 8). Finally, using **2.B** as catalyst in CH_2Cl_2 and with a 1:3 ratio of **2.42a**/**2.43a** gave **2.42a** in 85% isolated yield (Table 2.1, entry 10).

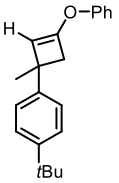
Having in hand a good set of conditions for [2+2] cycloaddition of terminal ynol ethers, we explored the scope and limitation of the reaction (Table 2.2). The reaction can accommodate differently substituted α-methyl styrene derivatives with good to very good yields (**2.44a-d**). However, increasing the size of the α-substituent on the styrene the yield starts to drop and **2.44e** was obtained in 40% of yield and larger substituents such in **2.43q** or **2.43r** failed to give the expected products (Figure 2.3). Simple styrenes are suitable substrates for the reaction although an electron rich substituent is necessary and **2.44f** was obtained in 37% yield. The reaction could also be performed with aliphatic alkenes, and a series of 1,1-disubstituted, 1,2-disubstituted, trisubstituted and tetrasubstituted alkenes successfully yielded the desired products **2.44g-k** in yields ranging from 45 to 77%. Terminal, monosubstituted alkenes instead are inert towards the desired cycloaddition and in the rection of **2.42a** with isoprene, **2.44l** was obtained selectively in 34% yield. In an analogous way, in the reaction with β-caryophyllene only the most reactive trisubstituted double bond undergoes the cycloaddition and product **2.44m** is obtained in 57% yield as a 3:1 mixture of regioisomers. In this case, the enol ether suffers partial hydrolysis to form ketone **2.45a**. The highly activated allyltrimethylsilane is the only monosubstituted aliphatic alkene that led to the desired product **2.4p**, although in only 24% yield. Sterically hindered enol ethers are also suitable substrates for the reaction giving rise to substituted cyclobutyl enol ethers **2.44n** and **2.44o** in 79% and 92% yield, respectively.

Table 2.2. Scope of the gold(I)-catalyzed [2+2] cycloaddition of ynol ethers with alkenes. [a]

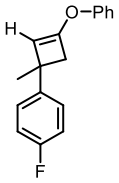




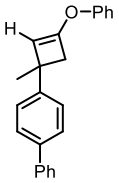
2.44a: 85%



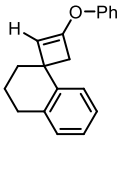
2.44b: 89%



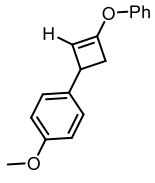
2.44c: 67%



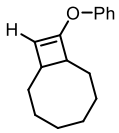
2.44d: 90%



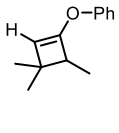
2.44e: 40%



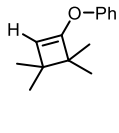
2.44f:37%



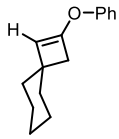
2.44g: 45%



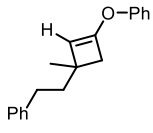
2.44h: 77%
(r.r. = 7:1)



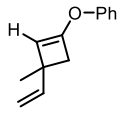
2.44i: 59%



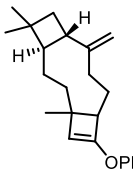
2.44j: 74%



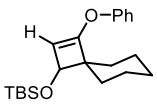
2.44k: 54%



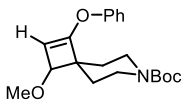
2.44l: 34%



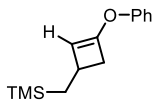
2.44m:57%[b]
(r.r. = 3:1)



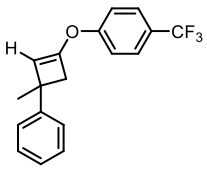
2.44n:79%



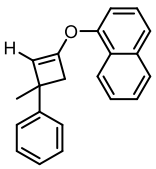
2.44o:92%



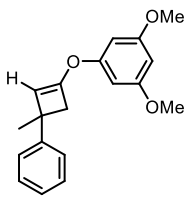
2.44p: 24%



2.44q: 72%

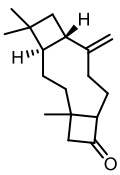


2.44r: 58%



2.44s: 22%

[a] Isolated yield; [b] yield determined by ^{1}H-NMR using trichloroethylene as internal standard, during time decomposed in **2.45a**



2.45a
(r.r. = 3:1)

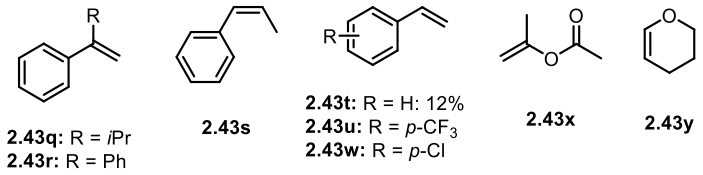
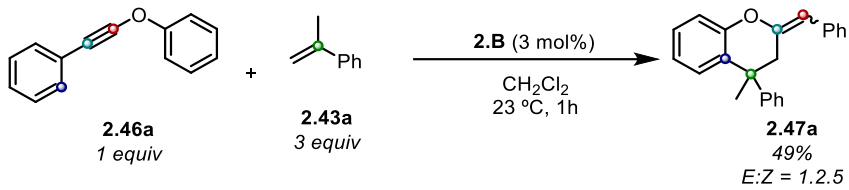


Figure 2.3. Selected examples alkenes that failed in the reaction.

In contrast smaller enol ethers (**2.43x** and **2.43y** in Figure 2.3) underwent decomposition in presence of the gold(I) catalyst. Interestingly, although the products of the [2+2] cycloaddition contain an enol ether, further addition of the enol ether to the starting ynol ether was never observed during the reaction. We also tested few other aromatic substituents on the ynol ether (**2.42b-d**): while **2.44q** and **2.44r** where obtained in 58% and 78% of yield respectively, **2.44s** was obtained in only 22% yield even if with complete conversion of the starting ynol ether. It is important to note that even in presence of the highly activated phenolic ring in **2.42d** the product of (4+2) cycloaddition was never observed.

Gold(I)-Catalyzed Reaction of Internal Ynol ethers with Alkenes

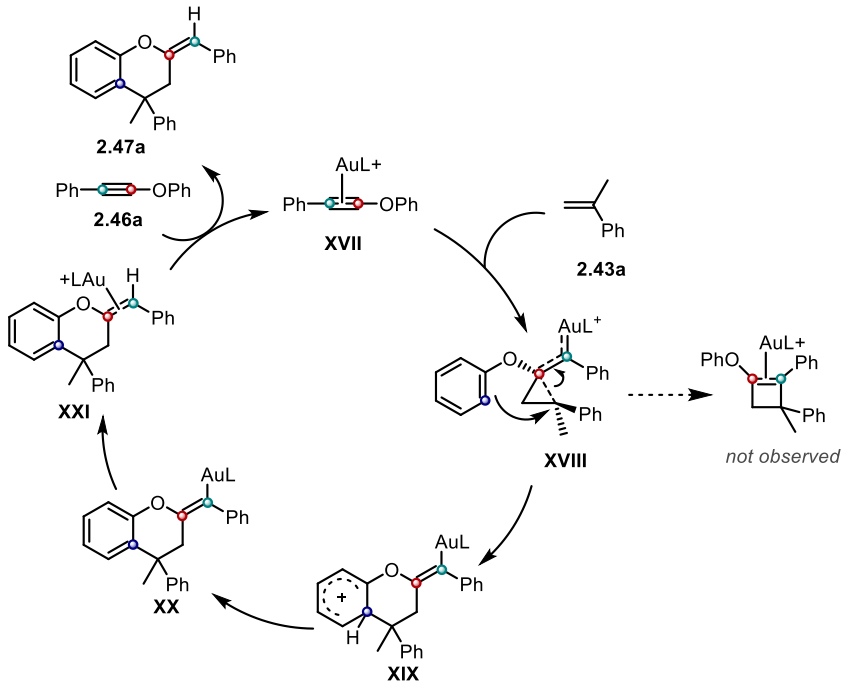
In an intent to expand the scope of the [2+2] cycloaddition using internal ynol ethers, chromane **2.47a** was obtained in 49% yield as a 1:2.5 mixture of *E:Z* isomers from phenyl acetylene derivative **2.46a**, while the expected cyclobutene was not detected (**Scheme 2.13**).



Scheme 2.13. Gold(I) catalyzed (4+2) cycloaddition of internal ynol ether with alkenes.

This outcome can be explained according to the mechanistic hypothesis presented in Scheme 2.14[158]. In analogy with the other gold(I)-catalyzed reaction of alkynes with alkenes, the reaction could start with the formation of cyclopropyl gold(I) carbene **XVIII**, evolves into Wheland intermediate **XIX** *via* Friedel-Crafts-type reaction with the more electron rich aromatic ring. The catalytic cycle is then closed by re-aromatization and protodeauration. This mechanism resembles the one already proposed by Hashmi in the intramolecular reaction of furanyne.[Errore. Il segnalibro non è definito.]

158 The mechanism of this reaction will be discussed in more detail in the following section.



Scheme 2.14. Proposed mechanism for the (4+2) cycloaddition of internal ynol ethers with alkenes.

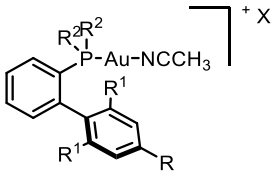
In this case, using just 2 equiv of alkene resulted in slightly better yield (55%) of **2.47a** and no substantial changes in the stereoselectivity (Table 2.3, entry 1). Several phosphine supported complexes where then tested and among them **2.A** outperformed above the others delivering the product in 76% isolated yield, as a 1:1 *E/Z* mixture (Table 2.3, entry 2). Using complexes **2.E-2.G** as catalysts the product was obtained in yields ranging from 30 up to 57%, but slightly better stereoselectivity (Table 2.3, entries 3-5). Analogous results were obtained when NHC- and phosphite-based ligands were used (Table 2.3, entries 6 and7). Based on our experience with bromoalkynes, we evaluated also different ndium salts as catalyst (Table 2.3, entries 8-10). However, $InOTf_3$ and $InCl_3$ caused the complete decomposition of **2.46a** without formation of the desired product, while using $InBr_3$ **2.47a** was obtained in moderate yield (40%), but remarkably just the Z-isomer was detected in the crude mixture. However, in this last case, quite surprisingly, only the *Z*-isomer was detected in the crude mixture. We also tested TFA as a potential catalyst (Table 2.3, entry 11), although the starting material was recovered unchanged.

Table 2.3: Catalyst screening for the intermolecular reaction of **2.46a** with **2.43a**. [a]

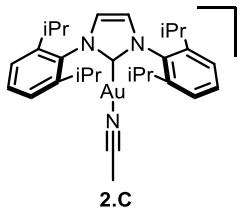
2.46a + **2.43a** → **2.47a**

Entry	Catalyst	Yield (%)[b]	E:Z[b]
1	**2.B**	55	1:3
2	**2.A**	79 (76)	1:1
3	**2.E**	30	1:2
4	**2.F**	44	1:1.7
5	**2.G**	57	1:4
6	**2.C**	49	1:1.2
7	**2.D**	45	1:3
8	$InBr_3$	40	>1:20
9	$InOTf_3$	-[c]	-[c]
10	$InCl_3$	-[c]	-[c]
11	TFA	-[d]	-[d]

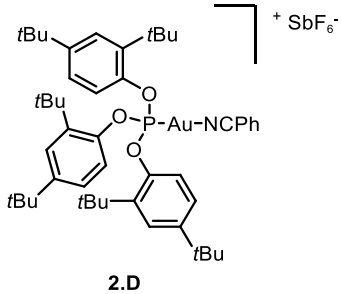
[a] Substrates **2.46a**:**2.43a** in a 1:2 ratio. [b] Yields determined by ^{1}H-NMR using trichloroethylene as internal standard. Isolated yields in parentheses. [c] decomposition of **2.46a.** [d] No reaction



2.A R^1 = *i*Pr, R^2 = *t*Bu, X = BAr_4^{F-}
2.B: R^1 = H, R^2 = *t*Bu, X = SbF_6^-
2.E: R^1 = *i*Pr, R^2 = *t*Bu, X = SbF_6^-
2.F: R^1 = H, R^2 = Cy, X = SbF_6^-
2.G: R^1 = H, R^2 = *t*Bu, X = BAr_4^{F-}



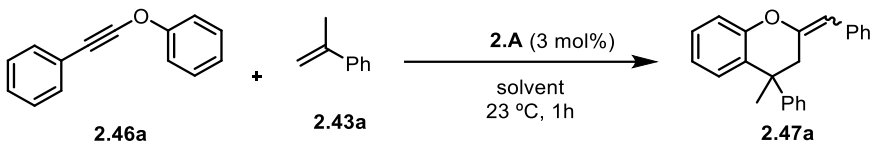
2.C



2.D

Different solvents were also evaluated with **2.A** as the best catalyst (Table 2.4). As a general trend the solvent does not have a remarkable effect on both yield and stereoselectivity and **2.47a** is obtained with yields ranging from 47% in THF (Table **2.4**, entry 4) up to 79% in both CH_2Cl_2 or 1,4-dioxane (Table 2.4, entries 1 and 9). Interestingly, the reaction can also be performed in absence of solvent (Table 2.4. entry 10) and **2.47a** is obtained in 60% yield with a 1.3:1 *E/Z* ratio.

Table 2.4. Solvent screening for the intermolecular reaction of **2.46a** with **2.43a**. [a]



2.46a **2.43a** **2.47a**

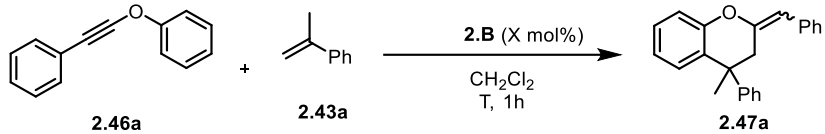
Entry	Solvent	Yield (%)[b]	E:Z[b]
1	CH_2Cl_2	79 (76)	1:1
2	DCE	67	1:1
3	$PhCH_3$	77	1.3:1
4	THF	47	1:2
5	$PhCF_3$	77	1:1
6	CH_3NO_2	77	1:1
7	EtOAc	69	1:1
8	Hexane	62	1.5:1
9	1,4-Dioxane	79	1.4:1
10	Neat	60	1.3:1

[a] Substrates **2.46a**:**2.43a** in a 1:2 ratio. [b] Yields determined by ^{1}H-NMR using trichloroethylene as internal standard. Isolated yields in parentheses.

We finally evaluated the role of other parameters such as catalyst loading, temperature, and ratio between the reagents. We found that decreasing the catalyst loading to 1%, as well as increasing

it to 5% led to lower yield (Table 2.5, entries 1 and 2) delivering **2.47a** in 36% and 48% yield, respectively. In the first case, **2.46a** was partially recovered, while an excess of catalyst probably favors side reactions leading to the decomposition of the starting ynol ether. Increasing the temperature to 45 °C allowed the reaction to reach complete conversion in 20 min, but with a decrease of yield (60%, Table 2.5, entry 3). While at lower temperatures (0 °C and -20 °C) **2.47a** was obtained in analogous yields and stereoselectivity, but with longer reaction times (Table 2.5, entries 4 and 5). The ratio between **2.46a** and **2.43a** was found to be crucial to achieve good yields as demonstrated in entries 6-8 of Table 2.5 where the product was obtained in moderate to good yields when higher or lower amounts of **2.43a** were used.

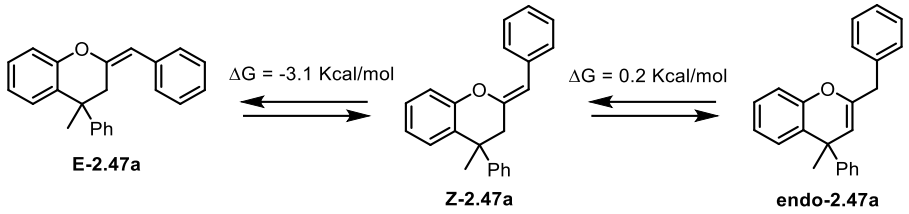
Table 2.5. Screening of conditions for the gold(I) catalyzed (4+2) cycloaddition of **2.46a** with **2.43a**.



Entry	Cat. loading (%)	**2.46a:2.43a**	T (°C)	Yield (%)[a]	E:Z[a]
1	**1**	1:2	23	36	1.2:1
2	**5**	1:2	23	48	1.1:1
3	3	1:2	**45**	60	1:1
4	3	1:2	**0**[c]	75	1.2:1
5	3	1:2	**-20**[d]	71	1.4:1
6	3	**1:3**	23	58	1:1
7	3	**1:1**	23	62	1:1
8	3	**3:1**	23	42	1.5:1

[a] Yields determined by ^{1}H-NMR using trichloroethylene as internal standard.
[b] reaction time 20 minutes. [c] Reaction time 4 h. [d] Reaction time 14h.

We observed that the *E*/Z ratio changed during the purification of **2.47a** by column chromatography, leading to also to the formation of third product identified as ***endo*-2.47a** (Scheme 2.16).

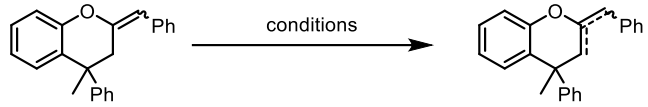


Scheme 2.15. equilibrium and energy barriers for the three stereoisomers of **2.47a.**

According to DFT calculations[159] **Z-2.47a** is slightly the most stable of the three isomers (by just 0.2 kcal mol^{-1}).

Treatment of a 1:1 mixture of ***E*-2.47a** and ***Z*-2.47a** with silica gel led to 1:2 mixture of **Z.2.47a** and ***endo*-2.47a** (Table 2.6, entries 1 and 2). The same result was obtained when the mixture was treated with 1 equiv of acetic acid for 1 h (Table 2.6, entry 4). Using HCl or citric acid led to a 1:1 and 3:1 *Z/endo* mixture, respectively (Table 2.6, entry 3,5). Finally, when the mixture was treated for 1 h with one equiv of *p*-TSA·H_2O ***endo*-2.47a** was formed selectively, albeit in only in 40% yield (Table 2.6, entry 6). Probably, the enol ether suffers hydrolysis to form open ketone under these conditions.

Table 2.6. Attempts towards the isomerization of the double bond in **2.47a**.



2.47a *E:Z* = 1:1 — **2.47a** *E:Z:endo*

Entry	Conditions [c]	*E*:*Z*:endo[a]
1	Silica gel - 40 minutes	-:1:2
2	Silica gel - 4 h	-:1:2
3	2 M HCl in water (1 equiv) - 15h[d]	-:1.3:1
4	Acetic acid (1 equiv) - 1h	-:1:2
5	Citric acid (1 equiv) - 1h	-:3:1

159 Calculations were performed with B3LYP/6-31G(d,p) (C,H,O) in CH_2Cl_2 (SMD). See experimental section for full details.

6	(1 equiv) - 1h		-:-:1[b]

[a] ratio between the isomers determined by ^{1}H-NMR using trichloroethylene as internal standard. [b] **endo-2.47a** was obtained in 40% yield determined by ^{1}H-NMR using trichloroethylene as internal standard. [c] Reaction performed at 23 °C. [d] Reaction performed at 40 °C.

Exploring the scope of the reaction, we found that depending on the alkene involved in the reaction internal ynol ethers can undergo exclusively (4+2) cycloaddition (Table 2.7, section A), exclusively [2+2] cycloaddition (Table 2.7, section B), or a mixture of the two products can be obtained (Table 2.7, section C).

The reaction of substrate **2.46a** with differently substituted α-methyl styrenes led to the selective formation of the (4+2) product (**2.47a,b,d**) in good yields (70-84%) but with no stereoselectivity. In the same way **2.47e** was isolated in 78% yield with a 1.6:1 *E/Z* ratio, starting from the *o*-MeO substituted **2.46b**. On the other hand, the more electron rich *p*-MeO-styrene led to **2.47c** in 74% yield with 1:10 *E/Z* ratio. Complete stereoselection was achieved in **2.47f** which was obtained as single *Z*-isomer and 92% yield.

Substrate **2.46a** undergoes selectively [2+2] cycloaddition with cycloalkenes allowing the access to a series for bicyclic products in yields from moderate (**2.44t**, 43% yield) to good (**2.44u**, 85% yield). In addition, the reaction can accommodate different aromatic rings on the alkynyl part of the ynol ether giving **2.44v** and **2.44w** in 72% and 70% yield, respectively.

In the presence of alkenes with electronic properties intermediate between the electron rich styrenes and cycloalkenes, **2.46a** can undergo both (4+2) and [2+2] cycloadditions leading to a mixture of the two products (Table 2.7, section C)

Interestingly an analogous behavior is observed when electron-donating substituents are introduced on the alkynyl aromatic ring: **2.47j** and **2.44bb** were obtained in fact as a separable mixture in 17% and 43% yield, respectively. It is important to note that **2.44bb** was obtained as a single regioisomer which is the opposite of the one obtained with the other alkynes. The structure of **2.44bb** has been confirmed by GOESY correlation.[160] Finally, **2.46e** reacted with **2.43a** under the standard conditions resulting in an inseparable mixture of **2.47k** and **2.44bb** in 75% overall yield.

160 More details regarding the unusual regioselectivity observed in the formation of **2.44aa** will be given in the computational study section of this chapter.

Table 2.7. Scope of the gold(I)-catalyzed reactions of internal ynol ethers **2.46a-e** with alkenes **2.43** to form either **2.47a-k** or **2.44s-cc**.

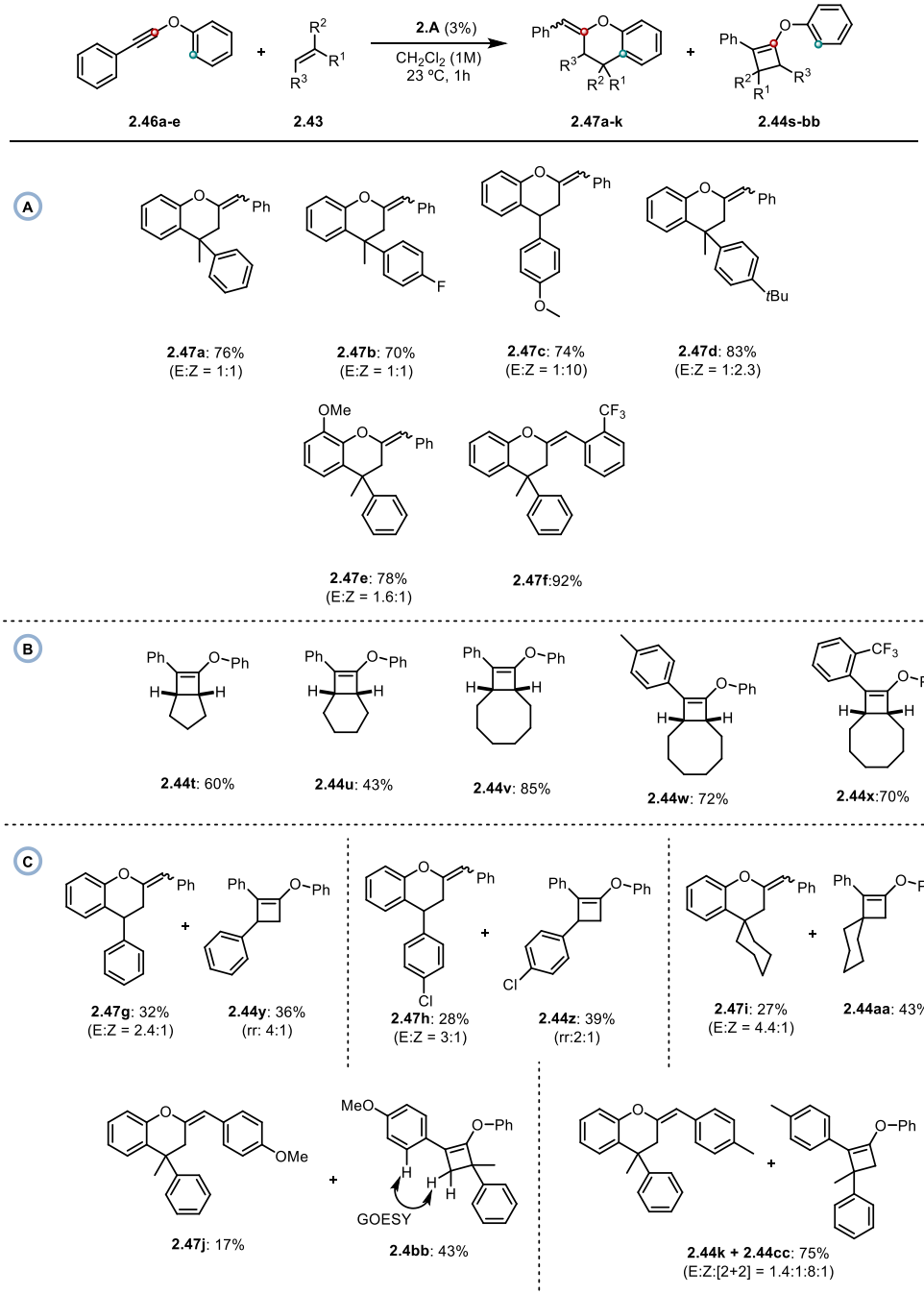
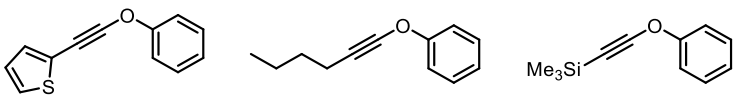


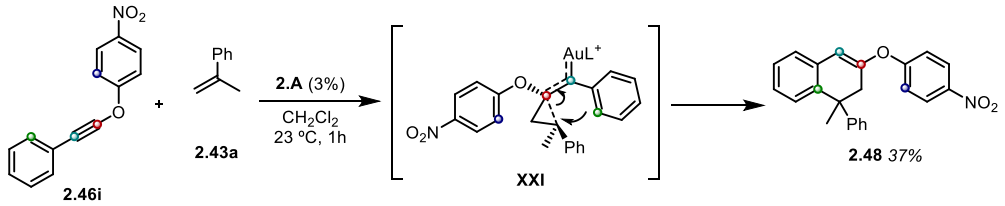
Figure 2.4 shows the ynol ether that failed under the developed conditions. Thus **2.46f** was highly unstable and just traces of product where detected in the crude ^{1}H-NMR of the reaction. On the other hand, **2.46g** and **2.46h** were recovered unchanged after 24h at 23 °C or 60 °C.



2.46f **2.46g** **2.46h**

Figure 2.4. Unsuccessful ynol ethers.

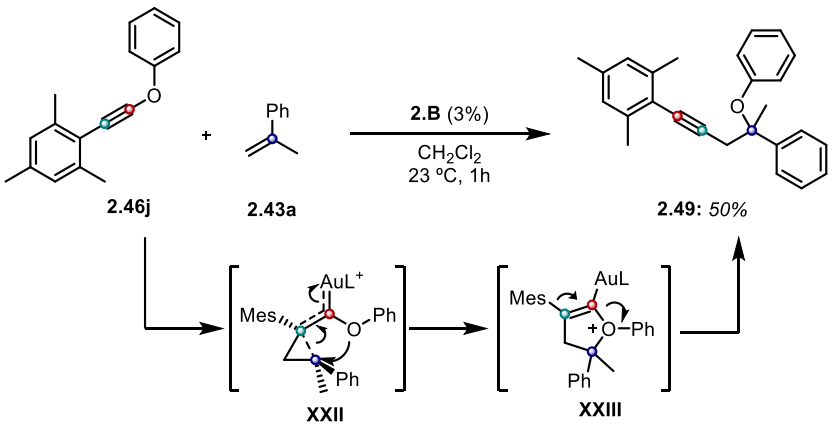
When a highly electron withdrawing substituent is appended to the phenol ring of the alkyne in **2.46i**, dihydronapthalene derivative **2.48** was obtained in 37% yield (Scheme 2.16). This product is most likely formed by Friedel-Crafts-like rection between the phenyl ring attacked to the alkyne and the cyclopropyl ring



2.46i **2.43a** **XXI** **2.48** *37%*

Scheme 2.16. Gold(I)-catalyzed reaction of **2.46i** with **2.43a** to form **2.48**.

Completely different behavior was displayed by **2.46j** which underwent oxoalkynylation of **2.43a** forming **2.49** in 50% yield under the standard reaction conditions (Scheme 2.17). This product can be formed by a mechanism resembling the one followed by bromoalkynes in the reaction with allylsilanes presented in Chapter 1. Thus, we propose the initial cyclopropyl gold(I) carbene **XXII** is converted into oxonium cation **XXIII** (analogous of the bromonium cation reported in Chapter 1). Finally, aromatic ring-assisted ring opening, and phenyl migration gives the final product.



2.46j **2.43a** **2.49:** *50%*

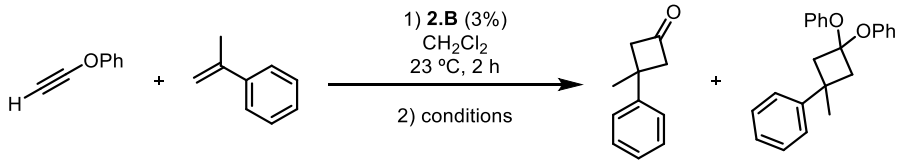
XXII **XXIII**

Scheme 2.17. Gold(I)-catalyzed reaction of **2.46j** and **2.43a** to form **2.49**.

One-pot Synthesis of Cyclobutanones Starting from Ynol ethers

With the exception of **2.44m**, the isolation and characterization of enol ethers **2.44** did not presented any problem due to their eventual hydrolysis. However, we expected that under the proper conditions it would be possible to access directly to the corresponding cyclobutanones. To do so, we pursued a one pot- two step approach starting with the already optimized conditions for the [2+2] cycloaddition followed by acidic hydrolysis of the enol ether moiety and we selected again **2.42a** and **2.43a** as model substrates (Table 2.8).

Table 2.8. Optimization of the one pot-two steps synthesis of cyclobutanone **2.45b**.[a]



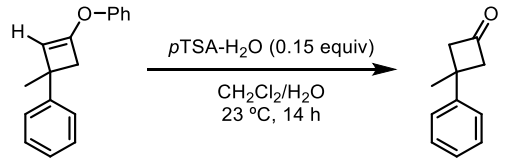
2.42a **2.43a** **2.45b** **2.50**

Entry	Conditions[b]	**2.45b** (%)[c]	**2.50** (%)[c]
1	H_2O (100 equiv)	-[d]	-[d]
2	*p*-TSA·H_2O (0.15 equiv), water	37	31
3	*p*-TSA·H_2O (1 equiv), water	73 (69)	-
4	*p*-TSA·H_2O (2 equiv), water	68	11
5	10% HCl in water (HCl 1 equiv)	43	43
6	1M TFA in water (TFA 1 equiv)	44	35
7	1M H_2SO_4 in water (H_2SO_4 1 equiv)	-[d]	-[d]
8	1M AcOH in water (AcOH 1 equiv)	-[d]	-[d]

[a] **2.42a:2.43a** = 1:3. [b] reaction time 14 h, temperature = 23 °C. [c] yield determined by ^{1}H-NMR using trichloroethylene as internal standard. Isolated yield in parenthesis. [d] **2.44a** fully recovered.

By simple addition of water after to the reaction and stirring overnight at 23 °C, **2.44a** was recovered in 83% yield and no hydrolysis was observed (Table 2.8, entry 1). Using *p*-TSA·H_2O as catalyst together with water as cosolvent, the enol ether was completely consumed, however

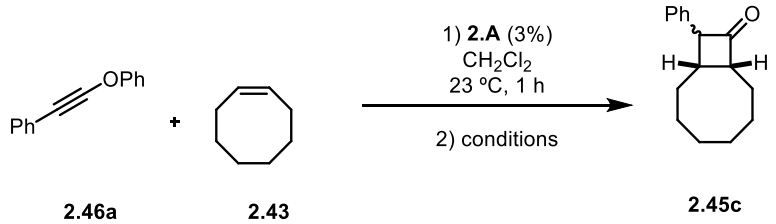
a 1:1 mixture of the desired ketone and the acetal **2.50** was obtained (Table 2.8, entry 2). Nevertheless, treatment of pure **2.44a** under the same acidic conditions leads instead to the complete hydrolysis of the enol ether into the ketone in almost quantitative yield (Scheme 2.18). Increasing the amount of acid up to 1 equiv gave ketone **2.45b** in 69% yield and no formation of the acetal **2.50** was detected (Table 2.8, entry 3). With a larger excess of acid, small amounts of the undesired acetal was detected in the crude ^{1}H-NMR (Table 2.8, entry 4). By addition of an aqueous solution of HCl or TFA, a mixture of the ketone and the acetal was obtained (Table 2.8, entry 5 and 6). Interestingly, the enol ether formed in the first step was completely recovered after stirring for 14 h at 23 °C in presence of H_2SO_4 or acetic acid. (Table 2.8, entry 7 and 8). In the first case, the reaction failed most likely due to solubility issues, while acetic acid is probably not acidic enough to promote the reaction.



Scheme 2.18. Hydrolysis of enol ether **2.44a** to form **2.45b**.

With this approach, 2-monosubstituted cyclobutanones could be accessed starting from the internal ynol ether **2.46a** and an aliphatic alkene, giving the product of [2+2] cycloaddition. Using the best conditions we found for the hydrolysis of the unsubstituted substrates the desired cyclobutanone was obtained in 49% yield and a 2.5.1 *dr*, although 38% of the enol ether intermediate **2.44u** remained unreacted (Table 2.9, entry 1). By increasing the temperature to 40 °C during the hydrolysis step, full conversion was achieved and **2.45c** obtained in 75% yield and a 2:1 *dr* (Table 2.9, entry 2). Interestingly, when the reaction was conducted at 65 °C and using toluene as solvent the diastereoselectivity increased up to 4:1, but the yield was lower (Table 2.9, entry 3). Finally, HCl turned out to give better results and the desired product was isolated in 75% yield as a 4.5 :1 mixture of diastereoisomers (Table 2.9, entry 4).

Table 2.9. Optimization of the one pot-two steps synthesis of cyclobutanone **2.45c**.[a]

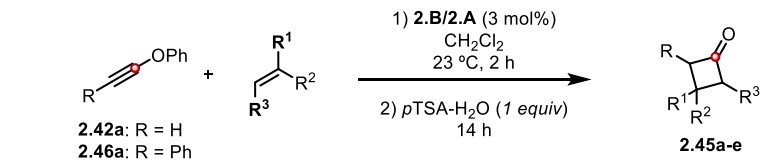


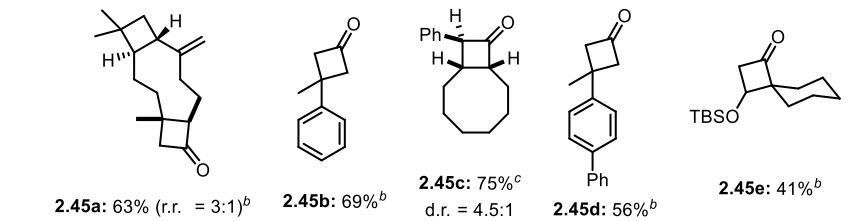
Entry	Conditions [b]	T (°C)	**2.45e** (%)[c]	**d.r.**[c]
1	*p*-TSA·H_2O (1 equiv), water	23	49[d]	2.5:1
2	*p*-TSA·H_2O (1 equiv), water	40	75	2:1
3	*p*-TSA·H_2O (1 equiv), water[e]	65	50	4:1
4	2M HCl in water (HCl 2 equiv)	40	(75%)	4.5:1
5	2M HCl in water (HCl 2 equiv)[e]	65	55	3:1

[a] **2.46a:2.43** = 1:2. [b] reaction time 14 h. [c] yield determined by ^{1}H-NMR using trichloroethylene as internal standard. Isolated yield in parenthesis. [d] **2.44u** was also obtained in 38% yield. [e] Reaction performed in toluene.

Table 2.10 shows the cyclobutanones that we obtained in the one pot-two steps process starting from the ynol ether and the alkene. Interestingly, the cyclobutanone **2.45a** generated from the reaction of **2.42a** and β-caryophyllene was obtained in 63% yield, and the -OTBS group of **2.45e** remained in place after the hydrolysis of the enol ether, although the product was obtained in moderate yield. In general, the one-pot approach for the generation of the cyclobutanone requires less time and product manipulation, although performing the two steps separately led to better overall yields.

Table 2.10. Scope of the one-pot two-steps synthesis of cyclobutanones **2.45a-e**.[a]





[a] Isolated yield; [b] **2.42a**:alkene = 1:3, **2.B** used as catalyst; [c] **2.46a**:alkene = 1:2, **2.A** used as catalyst, the hydrolysis was performed according to the best conditions reported in Table 2.9

Mechanism of the Gold(I) Catalyzed Reactions of Ynol ethers

According to our previous studies,[39] it was reasonable to propose that both the mechanism of the [2+2] and the formal (4+2) cyclization start with the formation of the cyclopropyl gold(I) carbenes **XXIV** and/or its regioisomer **XXV** (Figure 2.5). Therefore, we performed DFT calculations to elucidate the role of the different parts towards the observed selectivity.[161]

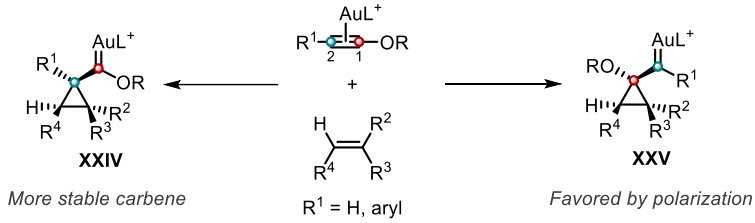


Figure 2.5. Different driving forces for the formation of the cyclopropyl gold(I) carbene.

We started our study with the [2+2] cycloaddition of terminal ynol ether **2.42a** and **2.43a**. The computed structure of **2.42a** displays a short C(sp)-O distance (1.30 A) and, as expected, a partial charge separation on the alkyne (Figure 2.6). The η^2 complex with gold(I) (**Int2a)** is highly distorted and gold is located at 2.1Å from C2 and 2.8 Å from C1. The coordination also causes an elongation of the C-C triple bond and the shortening of the C-O bond and the two bonds now have almost the same length (1.25 Å and 1.26 Å, respectively). Hence the resulting structure resemble a metalated ketene similar to the zwitterionic intermediate **IX** proposed by Kozmin[149]. Also, by coordination of gold(I) the separation of the partial charges on the triple bond increases and C1 results even more electrophilic.

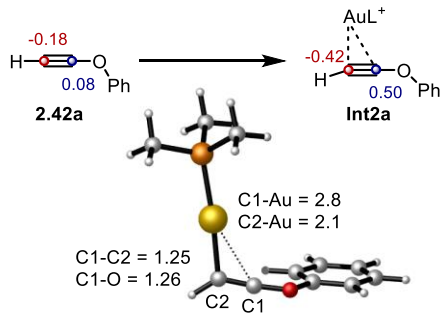
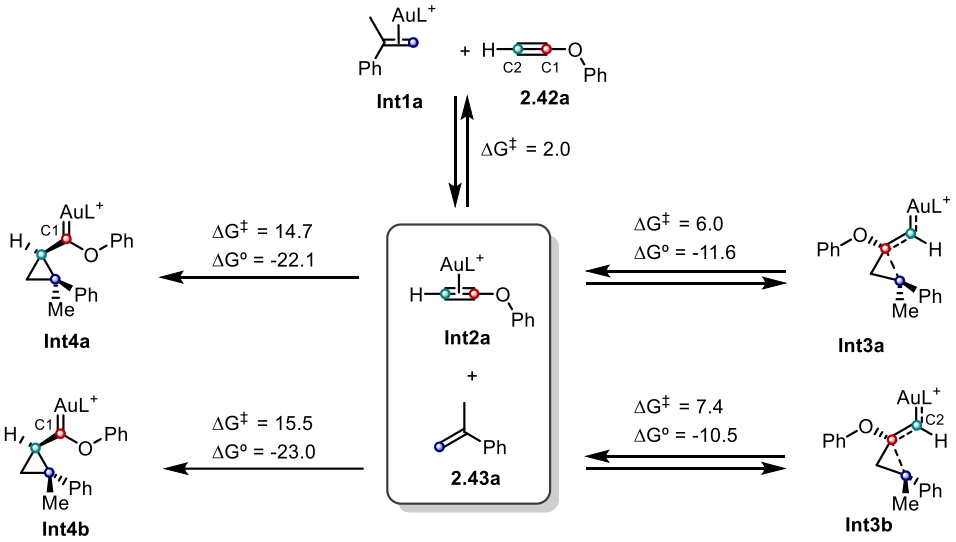


Figure 2.6. Computed structures of **2.42a** and **Int2a** with charge distribution expressed. Positive charges in blue and negative charges in red. (L = PMe_3).

The associative ligand exchange between **Int1a** and the ynol ether gives (η^2-alkyne)gold(I) complex **Int2a**. Interestingly, in this case the (η^2-alkene)gold(I) complex **Int1a** is less stable

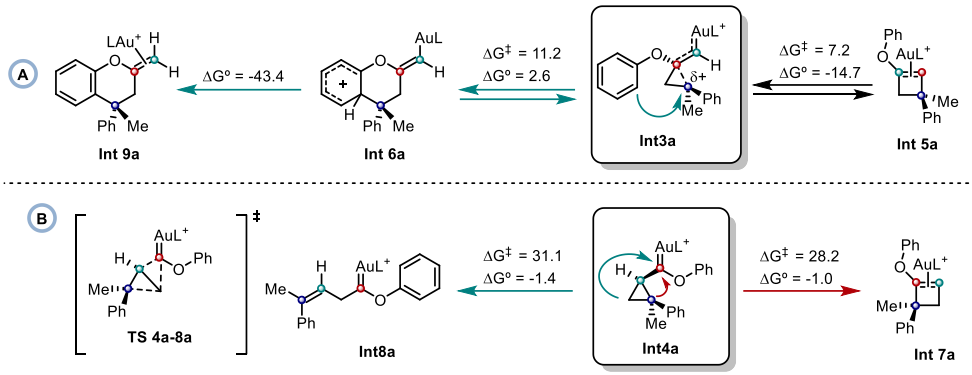
161 See the computational methods in the Experimental part

than **Int2a.** Comparing the energy barriers for the formation of the four possible cyclopropyl gold(I) carbenes **Int3a-b** and **Int4a-b**, the attack of the styrene on carbon C2 to form cyclopropyl gold(I) carbenes **Int4a-b** ($\Delta G^{\ddagger}$ = 14.7 - 15.5 kcal/mol) is highly exothermic due to the stabilization of the oxygen (ΔG° = -22.8 - -23.0 kcal/mol). However, the formation of **Int3a-b** ($\Delta G^{\ddagger}$ = 6.0 - 7.4 kcal/mol) is favored kinetically by *ca* 7-9 kcal/mol (Scheme 2.19). Interestingly, **Int4a-b** present a highly carbenic character due to the stabilization of the oxygen on C1, while in **Int3a-b** the cyclopropyl ring is more open and the intermediate is closer to a homoallylic gold(I)-stabilized cation with the benzylic carbon positively charged.



Scheme 2.19. Formation of cyclopropyl gold(I) carbene **Int3a-b** and **Int4a-b** (L = PMe_3. Free energies in kcal/mol).

We then continued our study following the evolution of both **Int3a** and **Int4a** (Scheme 2.20), considering that **Int3a/Int3b** and **Int4a/Int4b** have almost the same energies, the choice of one of these diastereoisomers over the other has no influence on the final conclusions of this study.

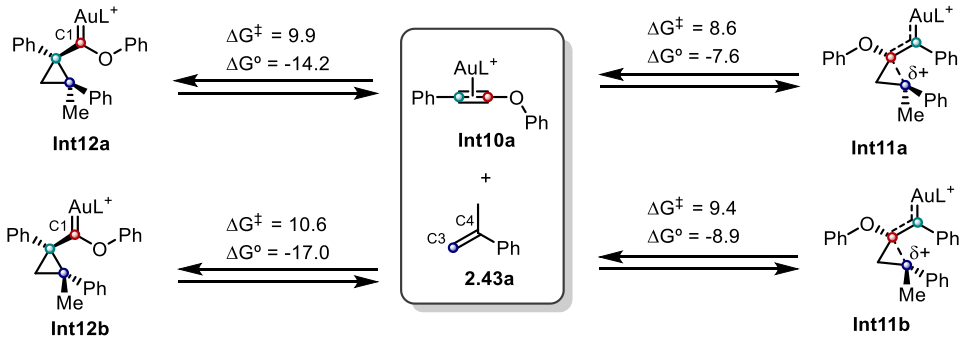


Scheme 2.20. Evolution of **Int3a** and **Int4a.** (L = PMe_3. Free energies in kcal/mol).

Starting from **Int3a**, **Int5a** can be formed upon exothermic ring expansion ($\Delta G^{\ddagger}$ = 7.2 kcal/mol), which will lead to the observed product **2.44a** upon ligand exchange with another molecule of substrate. Alternatively, the aromatic ring can attack the benzylic carbon on the cyclopropyl ring in a Friedel-Craft-type reaction forming Wheland intermediate **Int6a** ($\Delta G^{\ddagger}$ = 11.2 kcal/mol). Thus, for terminal alkynes this second pathway is disfavored both kinetically and thermodynamically.

In the case of **Int4a,** the attack of the aromatic ring is disfavored because of the increased carbenic nature of the intermediate. Instead **Int7a** can be formed via ring expansion ($\Delta G^{\ddagger}$ = 28.2 kcal/mol) or **Int8a** can be generated upon migration of carbon C3 on the gold(I) carbene($\Delta G^{\ddagger}$ = 31.1 kcal/mol). The energy barriers for these two transformations are too high to compete at room temperature with the formation of **Int5a** from **Int3a**, in full agreement with the experimentally observed regioselective formation of the cyclobutene derived from **Int5a**.

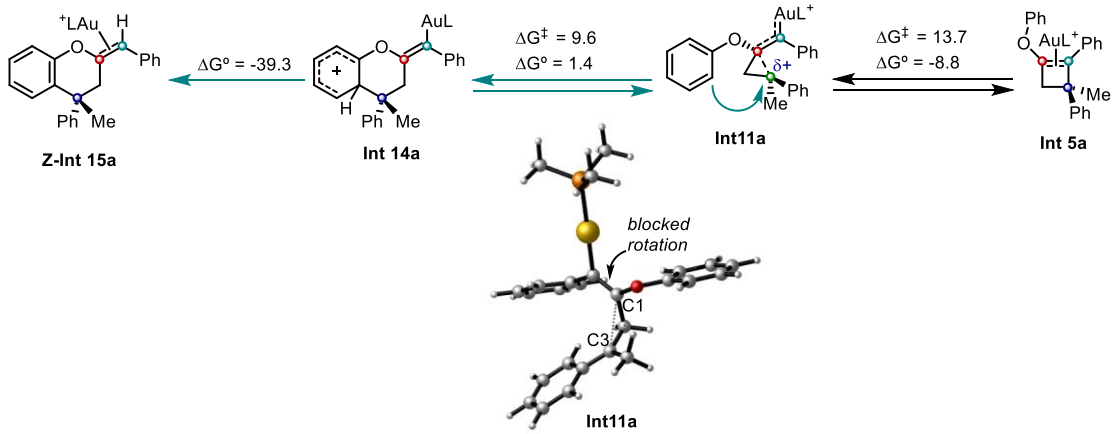
We then moved to the study of the reaction of internal alkyne **2.46a** with alkene **2.43a.** The reaction starts as before with the formation of four possible cyclopropyl gold(I) carbenes **Int11a-b** and **Int12a-b**, two diastereoisomers for each of the regioisomers (Scheme 2.21).



Scheme 2.21. Formation of cyclopropyl gold(I) carbene **Int11a-b** and **Int12a-b** (L = PMe_3. Free energies in kcal/mol).

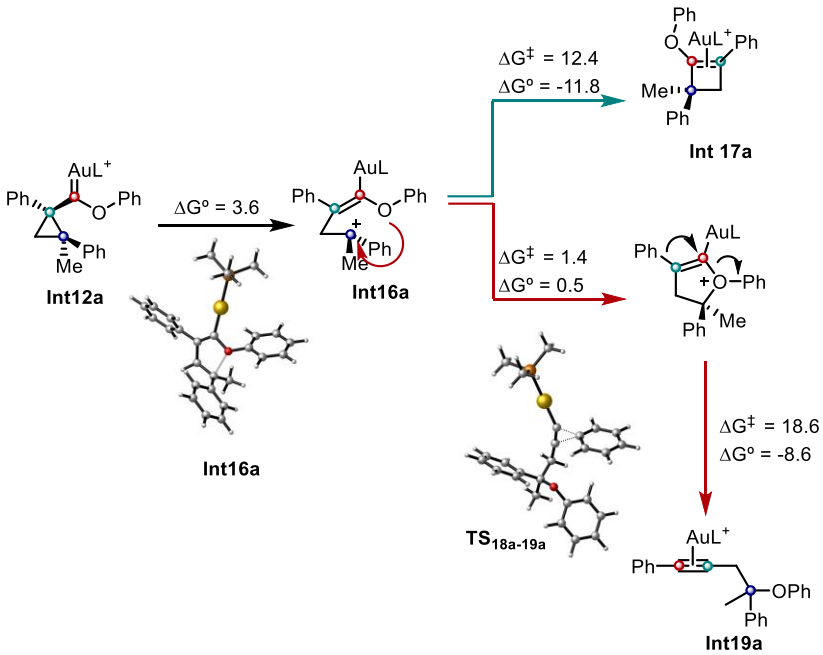
Compared to the previous case, the difference in activation energy for the formation of the two regioisomers is smaller: for **Int11a** we found $\Delta G^{\ddagger}$ = 8.6 kcal/mol and for **Int12a** $\Delta G^{\ddagger}$ = 9.9 kcal/mol, but still the attack of the alkene on carbon C1 remains favored. As we did before, we selected **Int11a** and **Int12a** to continue our investigation.

In **Scheme 2.22** are represented the possible evolutions of **Int11a**, analogous of the one calculated for **Int3a**. However, in this case the attack of the aromatic ring to form **Int14a** is favored over the ring expansion towards **Int13a** ($\Delta G^{\ddagger}$ = 9.6 kcal/mol vs $\Delta G^{\ddagger}$ = 13.7 kcal/mol). Wheland intermediate **Int14a** then undergoes deprotonation and protodeauration in highly an exergonic sequence (ΔG° = -39.3 kcal/mol) delivering the observed product. This model agreed with the observed selectivity towards the (4+2) cycloaddition for the internal ynol ethers and suggests that the product initially formed has the *E*-configuration.



Scheme 2.22. Evolution of **Int11a.** (L = PMe_3. Free energies in kcal/mol). and computed structure of structure of **Int11a**.

On the other hand, **Int12a** evolves to the open carbocation **Int16a** (ΔG° = 3.6 kcal/mol) stabilized by the oxygen. Starting from this intermediate two paths are possible. First, it can undergo ring expansion to form **Int17a**, regioisomer of **Int13a**, with an energy barrier of 12.4 kcal/mol. In alternative, the attack of the oxygen on the open carbocation to form the 5-membered oxonium cation **Int18a** is almost barrierless ($\Delta G^{\ddagger}$ = 1.4 kcal/mol). This species is analogous of the bromonium cation presented in Chapter 1 and, in the same way, can undergo aryl-assisted ring-opening via a vinylidenephenonium gold(I) cation, which in this case is not a minimum, but a transition state connecting **Int18a** and the (η^2-alkyne)gold(I) complex **Int19a**.[92]



Scheme 2.23. Evolution of **Int12a.** (L = PMe_3. Free energies in kcal/mol).

In the case of **2.46a**, the formation of **Int11a** is favored over **Int12a** accounting for the formation of **2.47** and **2.44.** However, experimentally we observed that the formation of the cyclobutene **2.44u** and **2.49** are possible in presence of electron rich substituents. So, we decided to investigate computationally the step of formation of the cyclopropyl gold(I) carbene between **2.46d** and **2.43a**. Interestingly, we found that two geometries that differs only by 0.4 kcal/mol are possible for the (η^2-alkyne)gold(I) complex. The first one is analogous of **Int2a** with the gold atom closer to C2 (C2-Au = 2.20Å Vs C1-Au = 2.58 Å) and activating C1 as electrophile. In the second one, the gold atom stays closer to C1 (C1-Au = 2.15Å Vs C2-Au = 2.63 Å) due to the electron density provided by the electron rich aromatic ring to the alkyne. In this second coordination mode, the distribution of the partial charges is inverted and C2 is more electrophilic of C1. Starting from **Int20a**, the formation of **Int22a** ($\Delta G^{\ddagger}$ = 8.0 kcal/mol - ΔG° = -13.0

kcal/mol) was found to be favored over **Int21a** ($\Delta G^{\ddagger}$ = 10.5 kcal/mol, ΔG° = -6.4 kcal/mol) in line with the experimental result. The same findings can be extended also for the electron rich alkyne **2.46j**, even if in this case the corresponding cyclopropyl gold(I) carbene will undergo migration of the phenoxy group to form finally **2.49.**

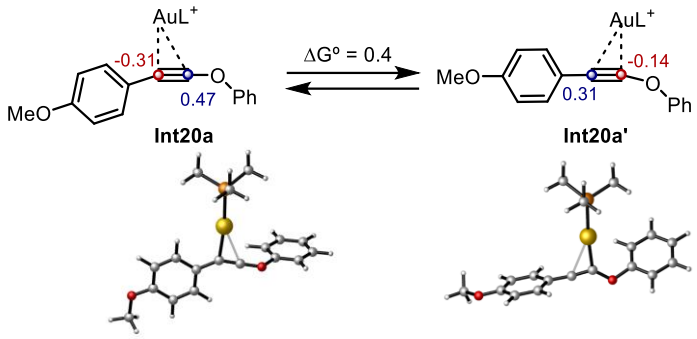
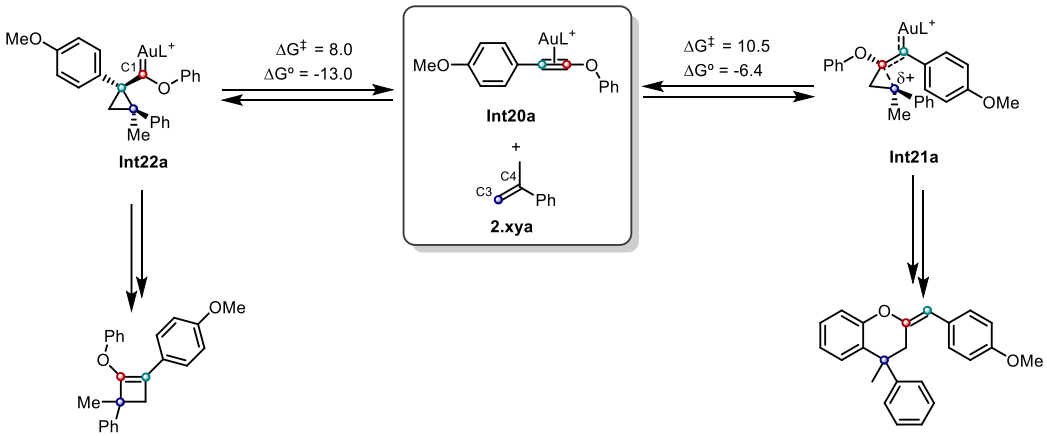


Figure 2.7. Computed structures of the two possible (η^2-alkyne)gold(I) complex with **2.46d**, with charge distribution on the alkyne expressed. Positive charges in blue and negative charges in red. (L = PMe_3. Free energies in kcal/mol).

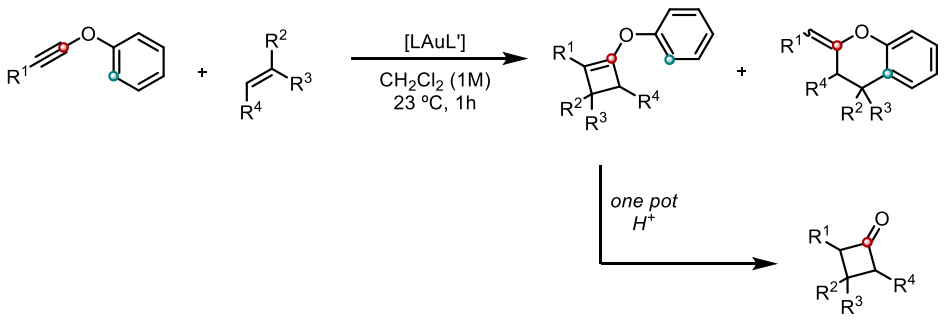


Scheme 2.24: Formation of cyclopropyl gold(I) carbene **Int21a** and **Int22a.** (L = PMe_3. Free energies in kcal/mol).

Conclusions

In this Chapter we summarize our study on the gold(I)-catalyzed intermolecular reaction of ynol ethers with alkenes. We found first that terminal ynol ethers undergo [2+2] cycloaddition with electron rich alkenes to form the corresponding phenoxycyclobutenes. In addition, we found that cyclobutanones can be accessed in a one pot process with a gold(I) catalyzed [2+2] cycloaddition/hydrolysis sequence. The cyclobutanones obtained in this way are the products of formal [2+2] cycloaddition of the parent ketene with an alkene. Hence, terminal ynol ether can be seen as practical ketene surrogate for the synthesis of cyclobutanones.

Internal aryl ynol ethers undergo either formal (4+2) cycloaddition with electron rich styrenes or [2+2] cycloaddition with cycloalkenes. The outcome of the reaction is highly substrate-dependent and in many cases a mixture of the two possible products is obtained.



Mechanistically, the [2+2] and the (4+2) cycloaddition branch from the same cyclopropyl gold(I) carbene intermediate. Depending on the substitution pattern on the reagents, either ring expansion to form the cyclobutene or a Friedel-Crafts like reaction take place.

Experimental Part

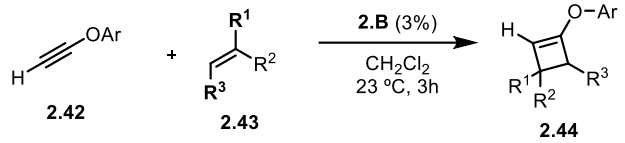
General Information

The general information is provided in the Experimental Part of **Chapter 1.** All reagents were used as purchased, with no further purification.

Ynol ethers **1.42a-d**[162] **and 2.46h**[163],1-(tert-butyl)-4-(prop-1-en-2-yl)benzene, 4-(prop-1-en-2-yl)-1,1'-biphenyl, 1-methylene-1,2,3,4-tetrahydronaphthalene, (3-methylbut-3-en-1-yl)benzene[164], tert-butyl(cyclohexylidenemethoxy)dimethylsilane, tert-butyl 4-(methoxymethylene)piperidine-1-carboxylate[165] were synthesized according to previously reported procedures. The NMR data are in agreement with the ones reported in the literature.

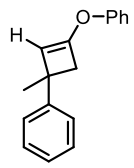
Synthetic Procedures and Characterization Data

*General procedure A: Gold(I)-catalyzed reaction of **2.42** with **2.43.***



The needed ynol ether (0.2 mmol, 1 equiv) was dissolved in CH_2Cl_2 (0.2 mL, 1 M). The needed alkene (0.6 mmol, 3 equiv) was added followed by [(JohnPhos)AuNCMe]SbF_6 (**2.B**, 3 mol%, 4.6 mg). The resulting mixture was stirred at 23 °C for 3 h. The reaction was monitored by GC-MS or UHPLC-MSD. Once completed, the reaction was quenched with few drops of triethylamine and the solvent evaporated. The crude product was purified by flash chromatography on silica gel (eluent = pentane:Et2O gradient from 100:0 to 50:1, otherwise stated) to obtain the pure oxy-cyclobutene.

(1-Methyl-3-phenoxycyclobut-2-en-1-yl)benzene (2.44a)

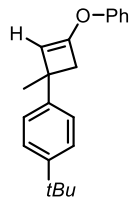


Cyclobutene **2.44a** was synthesized following general procedure **A** starting from (ethynyloxy)benzene (23.6 mg, 0.2 mmol) and α-methylstyrene (78 µL, 0.6 mmol). The crude product was purified by flash chromatography affording **2.44a** as a colorless oil (40 mg, 85%).

162 K. Graf, C. L. Rühl, M. Rudolph, F. Rominger, A. S. K. Hashmi, *Angew. Chemie - Int. Ed.* **2013**, *52*, 12727–12731.
163 T. Aechtner, D. A. Barry, E. David, C. Ghellamallah, D. F. Harvey, A. De La Houpliere, M. Knopp, M. J. Malaska, D. Pérez, K. A. Schärer, et al., *Synth.* **2018**, *50*, 1053–1089.
164 C. García-Morales, B. Ranieri, I. Escofet, L. López-Suarez, C. Obradors, A. I. Konovalov, A. M. Echavarren, *J. Am. Chem. Soc.* **2017**, *139*, 13628–13631.
165 M. Mato, C. García-Morales, A. M. Echavarren, *ACS Catal.* **2020**, *10*, 3564–3570.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.30 (m, 6H), 7.25 – 7.11 (m, 4H), 5.19 (s, 1H), 2.91 (d, *J* = 12.6 Hz, 1H), 2.87 (d, *J* = 12.6 Hz, 1H), 1.61 (s, 3H). **^{13}C-NMR (**101 MHz, $CDCl_3$) δ 155.0, 149.5, 148.0, 129.7, 128.2, 126.1, 125.9, 124.2, 119.5, 109.1, 47.3, 41.4, 28.4. **HRMS** (APCI) *m/z* calculated for $C_{17}H_{17}O^+$ $[M+H]^+$: 237.1274, found: 237.1273.

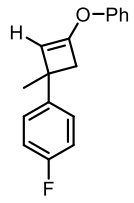
1-(tert-Butyl)-4-(1-methyl-3-phenoxycyclobut-2-en-1-yl)benzene (2.44b)



Cyclobutene **2.44a** was synthesized following general procedure **A** starting from (ethynyloxy)benzene (23.6 mg, 0.2 mmol) and 1-(tert-butyl)-4-(prop-1-en-2-yl)benzene (105 mg, 0.6 mmol). The crude product was purified by flash chromatography affording **2.44b** as a colorless oil (52 mg, 89%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.30 (m, 6H), 7.20 (m, 3H), 7.18 – 7.12 (m, 1H), 5.18 (s, 1H), 2.91 (d, *J* = 12.6 Hz, 1H), 2.85 (d, *J* = 12.6 Hz, 1H), 1.61 (s, 3H), 1.35 (s, 9H). **^{13}C-NMR (**101 MHz, $CDCl_3$) δ 155.1, 149.4, 148.6, 144.9, 129.7, 125.8, 125.1, 124.2, 119.5, 109.3, 47.3, 41.0, 34.5, 31.6, 28.3. **HRMS** (ESI) *m/z* calculated for $C_{21}H_{25}O^+$ $[M+H]^+$: 293.1900, found: 293.1898.

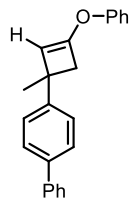
1-Fluoro-4-(1-methyl-3-phenoxycyclobut-2-en-1-yl)benzene (2.44c)



Cyclobutene **2.44c** was synthesized following general procedure **A** starting from (ethynyloxy)benzene (23.6 mg, 0.2 mmol) and 1-fluoro-4-(prop-1-en-2-yl)benzene (82 mg, 0.6 mmol). The crude product was purified by flash chromatography affording **2.44c** as a colorless oil (34 mg, 67%).

^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.35 (tt, *J* = 6.8, 1.0 Hz, 2H), 7.32 – 7.28 (m, 2H), 7.19 – 7.14 (m, 2H), 7.14 – 7.11 (m, 1H), 7.02 – 6.92 (m, 2H), 5.13 (d, *J* = 0.7 Hz, 1H), 2.87 – 2.80 (m, 2H), 1.57 (s, 3H). **^{13}C-NMR (**126 MHz, $CDCl_3$) δ 162.3 (d, *J* = 243.7 Hz), 155.0, 149.6, 143.7, 143.7, 129.7, 127.6 (d, *J* = 7.8 Hz), 124.3, 119.5, 114.9 (d, *J* = 21.0 Hz), 108.9, 47.4, 40.9, 28.4. **^{19}F-NMR** (376 MHz, $CDCl_3$) δ -117.87.

4-(1-Methyl-3-phenoxycyclobut-2-en-1-yl)-1,1'-biphenyl (2.44d)

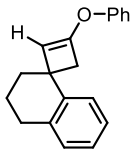


Cyclobutene **2.44d** was synthesized following general procedure **A** starting from (ethynyloxy)benzene (23.6 mg, 0.2 mmol) and 4-(prop-1-en-2-yl)-1,1'-biphenyl (117 mg, 0.6 mmol). The crude product was purified by flash chromatography affording **2.44d** as a white solid (56 mg, 90%).

^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.66 – 7.61 (m, 2H), 7.61 – 7.55 (m, 2H), 7.50 – 7.44 (m, 4H), 7.42 – 7.33 (m, 3H), 7.24 – 7.21 (m, 2H), 7.17 (td, *J* = 7.3, 1.2 Hz, 1H), 5.23 (s, 1H), 2.97 (d, *J* = 12.7 Hz, 1H), 2.92 (d, *J* = 12.7 Hz, 1H), 1.67 (s, 3H). **^{13}C-NMR (**126 MHz, $CDCl_3$) δ 155.0, 149.6, 147.1, 141.2, 138.9, 129.7, 128.9, 127.2, 127.2, 127.0, 126.6, 124.3,

119.5, 109.1, 47.4, 41.2, 28.3. **HRMS** (APCI) *m/z* calculated for $C_{23}H_{21}O^+$ $[M+H]^+$: 313.1587, found: 313.1568.

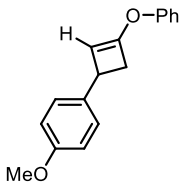
3-Phenoxy-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-naphthalen]-2-ene (2.44e)



Cyclobutene **2.44e** was synthesized following general procedure **A** starting from (ethynyloxy)benzene (23.6 mg, 0.2 mmol) and 1-methylene-1,2,3,4-tetrahydronaphthalene (87 mg, 0.6 mmol). The crude product was purified by flash chromatography affording **2.44e** as a brownish oil (21 mg, 40%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.57 (dd, *J* = 7.5, 1.6 Hz, 1H), 7.42 – 7.34 (m, 2H), 7.28 – 7.23 (m, 2H), 7.21 – 7.06 (m, 4H), 5.00 (s, 1H), 2.84 (dd, *J* = 7.8, 4.3 Hz, 2zH), 2.01 – 1.90 (m, 3H), 1.82 (dddd, *J* = 18.7, 9.1, 7.5, 4.0 Hz, 1H). **^{13}C-NMR (**126 MHz, $CDCl_3$) δ 155.1, 150.5, 141.8, 137.4, 129.7, 129.0, 126.2, 126.2, 125.7, 124.2, 119.3, 110.6, 49.6, 40.6, 36.0, 30.4, 22.1. **HRMS** (APCI) *m/z* calculated for $C_{19}H_{19}O^+$ $[M+H]^+$: 263.1430, found: 263.1429.

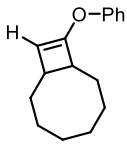
1-Methoxy-4-(3-phenoxycyclobut-2-en-1-yl)benzene (2.44f)



Cyclobutene **2.44f** was synthesized following general procedure **A** starting from (ethynyloxy)benzene (23.6 mg, 0.2 mmol) and 1-methoxy-4-vinylbenzene (81 mg, 0.6 mmol). The crude product was purified by flash chromatography affording **2.44f** as a yellow oil (19 mg, 37%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.34 (m, 2H), 7.28 – 7.19 (m, 4H), 7.15 (ddt, *J* = 8.5, 7.0, 1.2 Hz, 1H), 6.90 – 6.84 (m, 2H), 4.97 (d, *J* = 1.0 Hz, 1H), 3.81 (s, 3H), 3.66 (dt, *J* = 4.6, 1.3 Hz, 1H), 3.24 (dd, *J* = 13.0, 4.6 Hz, 1H), 2.52 (dd, *J* = 13.0, 1.6 Hz, 1H). **^{13}C-NMR (**101 MHz, $CDCl_3$) δ 158.4, 155.0, 150.1, 136.2, 129.7, 127.7, 124.2, 119.4, 113.9, 105.3, 55.5, 41.9, 36.8. **HRMS** (ESI) *m/z* calculated for $C_{17}H_{17}O_2^+$ $[M+H]^+$: 253.1223, found: 253.1221

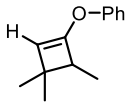
9-Phenoxybicyclo[6.2.0]dec-9-ene (2.44g)



Cyclobutene **2.44g** was synthesized following general procedure **A** starting from (ethynyloxy)benzene (23.6 mg, 0.2 mmol) and (Z)-cyclooctene (78 μL, 0.6 mmol). The crude product was purified by flash chromatography affording **2.44g** as a yellow oil (21 mg, 45%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.32 (tt, *J* = 7.5, 2.2 Hz, 2H), 7.18 – 7.12 (m, 2H), 7.12 – 7.06 (m, 1H), 4.60 (d, *J* = 1.0 Hz, 1H), 2.96 (ddd, *J* = 12.0, 4.2, 2.0 Hz, 1H), 2.48 – 2.37 (m, 1H), 1.91 (dtd, *J* = 14.4, 3.9, 1.9 Hz, 1H), 1.76 – 1.68 (m, 1H), 1.68 – 1.57 (m, 2H), 1.53 – 1.23 (m, 8H). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 155.3, 152.0, 129.6, 123.8, 119.2, 104.5, 48.5, 39.2, 30.6, 30.0, 28.3, 26.4, 26.3, 24.5. **HRMS** (ESI) *m/z* calculated for $C_{16}H_{21}O^+$ $[M+H]^+$: 229.1587, found: 229.1586.

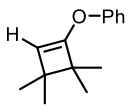
((3,3,4-Trimethylcyclobut-1-en-1-yl)oxy)benzene (2.44h)



Cyclobutene **2.44h** was synthesized following general procedure **A** starting from (ethynyloxy)benzene (23.6 mg, 0.2 mmol) and 2-methylbut-2-ene (64 μL, 0.6 mmol). The crude product was purified by flash chromatography affording **2.44h** as a yellow oil 7:1 mixture of regioisomers (29 mg, 77%). Major regiosomer (Mr), minor regioisomer (mr).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.29 (m, 3H, Mr + mr), 7.19 – 7.12 (m, 2H, Mr + mr), 7.09 (td, *J* = 7.3, 1.2 Hz, 1H, Mr), 7.06 – 6.96 (m, 0.15H, mr), 4.73 (s, 1H, Mr), 4.56 (d, *J* = 1.0 Hz, 0.15H, mr), 2.69 (q, *J* = 7.1 Hz, 1H, Mr), 2.21 – 2.14 (m, 0.15H, mr), 1.19 (s, 3H, Mr), 1.18 (s, 0.7H, mr), 1.12 (s, 0.7H, mr), 1.09 (d, *J* = 7.2 Hz, 3H, Mr), 1.07 (s, 3H, Mr), 1.03 (d, *J* = 6.8 Hz, 1H, mr). **^{13}C-NMR (**101 MHz, $CDCl_3$) δ 155.4 (mr), 152.6 (Mr), 129.5 (Mr), 129.5 (Mr), 123.8 (Mr), 122.7 (mr), 119.4 (mr), 119.2 (Mr), 117.9 (mr), 110.0 (Mr), 102.2 (mr), 48.8 (Mr), 45.1 (mr), 40.4 (mr), 37.3 (mr), 28.1 (Mr), 24.8 (Mr), 22.7 (Mr), 19.6 (mr), 15.6 (mr), 12.6 (Mr). **HRMS** (ESI) *m/z* calculated for $C_{13}H_{17}O^+$ $[M+H]^+$: 189.1274, found: 189.1273.

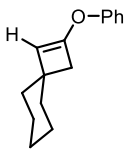
((3,3,4,4-Tetramethylcyclobut-1-en-1-yl)oxy)benzene (2.44i)



Cyclobutene **2.44i** was synthesized following general procedure **A** starting from (ethynyloxy)benzene (23.6 mg, 0.2 mmol) and 2,3-dimethylbut-2-ene (72 μL, 0.6 mmol). The crude product was purified by flash chromatography affording **2.44i** as a colorless oil (24 mg, 59%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.28 (m, 2H), 7.19 – 7.14 (m, 2H), 7.09 (ddt, *J* = 7.7, 7.0, 1.2 Hz, 1H), 4.60 (s, 1H), 1.19 (s, 7H), 1.10 (s, 7H). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 156.5, 155.5, 129.5, 123.8, 119.4, 107.4, 48.8, 40.5, 24.3, 21.5. **HRMS** (ESI) *m/z* calculated for $C_{14}H_{19}O^+$ $[M+H]^+$: 203.1430, found: 203.14.32.

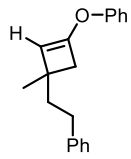
2-Phenoxyspiro[3.5]non-1-ene (2.44j)



Cyclobutene **2.44i** was synthesized following general procedure **A** starting from (ethynyloxy)benzene (23.6 mg, 0.2 mmol) and methylenecyclohexane (58 mg, 0.6 mmol). The crude product was purified by flash chromatography affording **2.44j** as a colorless oil (32 mg, 74%).

^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.36 – 7.29 (m, 2H), 7.16 – 7.13 (m, 2H), 7.11 (tt, *J* = 7.3, 1.2 Hz, 1H), 4.98 (s, 1H), 2.37 (s, 2H), 1.62 – 1.38 (m, 10H). **^{13}C-NMR** (126 MHz, $CDCl_3$) δ 155.3, 149.9, 129.6, 123.9, 119.3, 110.8, 43.4, 39.5, 37.3, 26.0, 25.1. **HRMS** (APCI) *m/z* calculated for $C_{15}H_{19}O^+$ $[M+H]^+$: 215.1430, found: 215.1428.

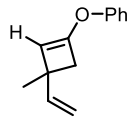
((3-Methyl-3-phenethylcyclobut-1-en-1-yl)oxy)benzene (2.44k)



Cyclobutene **2.44k** was synthesized following general procedure **A** starting from (ethynyloxy)benzene (23.6 mg, 0.2 mmol) and (3-methylbut-3-en-1-yl)benzene (87.6 mg, 0.6 mmol). The crude product was purified by flash chromatography affording **2.44k** as a colorless oil (29 mg, 59%).

^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.39 – 7.32 (m, 2H), 7.29 (t, *J* = 7.5 Hz, 2H), 7.24 – 7.18 (m, 3H), 7.18 – 7.10 (m, 3H), 4.88 (s, 1H), 2.73 – 2.61 (m, 2H), 2.54 (d, *J* = 12.7 Hz, 1H), 2.44 (d, *J* = 12.7 Hz, 1H), 1.90 – 1.78 (m, 2H), 1.31 (s, 3H). **^{13}C-NMR** (126 MHz, $CDCl_3$) δ 155.2, 148.7, 143.1, 129.6, 128.4, 125.8, 123.9, 119.3, 110.7, 44.3, 42.7, 37.9, 32.8, 24.8. **HRMS** (APCI) *m/z* calculated for $C_{19}H_{21}O^+$ $[M+H]^+$: 265.1587, found: 265.1585.

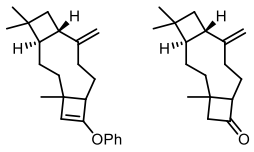
((3-Methyl-3-vinylcyclobut-1-en-1-yl)oxy)benzene (2.44l)



Cyclobutene **2.44l** was synthesized following general procedure **A** starting from (ethynyloxy)benzene (23.6 mg, 0.2 mmol) and isoprene (60 μl, 0.6 mmol). The crude product was purified by flash chromatography affording **2.44l** as a colorless oil (13 mg, 34%).

^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.38 – 7.29 (m, 2H), 7.17 – 7.14 (m, 2H), 7.14 – 7.10 (m, 1H), 6.06 (dd, *J* = 17.2, 10.4 Hz, 1H), 5.06 (dd, *J* = 17.2, 1.6 Hz, 1H), 4.94 (dd, *J* = 10.4, 1.6 Hz, 1H), 4.84 (s, 1H), 2.61 (d, *J* = 12.7 Hz, 1H), 2.55 (d, *J* = 12.7 Hz, 1H), 1.34 (s, 3H). **^{13}C-NMR** (126 MHz, $CDCl_3$) δ 155.1, 148.9, 145.8, 129.7, 129.6, 124.1, 119.3, 111.2, 109.4, 45.5, 39.8, 24.1. **HRMS** (ESI) *m/z* calculated for $C_{13}H_{15}O^+$ $[M+H]^+$: 187.1117, found: 187.1122.

(1R,11S)-4,13,13-Trimethyl-10-methylene-6-phenoxytricyclo[9.2.0.04,7]tridec-5-ene (2.44m) and (1R,11S)-4,13,13-trimethyl-10-methylenetricyclo[9.2.0.04,7]tridecan-6-one (2.45a)



The cyclobutene **2.44m** and the cyclobutanone **2.45m** were synthesized following general produced **A** starting from (ethynyloxy)benzene (23.6 mg, 0.2 mmol) and β-Caryophyllene (170 μl, 0.6 mmol). The crude product was purified by flash chromatography affording a mixture of **2.44m** and **2.45a** in a ratio changing during time. Few fractions of pure **2.44m** as 1:1 mixture of regioisomers were separated (8 mg, 10%) and used to assign the structure by ^{1}H-NMR and ^{13}C-NMR, however **2.44m** was fully converted into **2.45a** overnight, and no HRMS was measured. A second purification by flash chromatography afforded **2.45a** as a yellow oil, 3:1 mixture of regioisomers (21 mg, 43%).

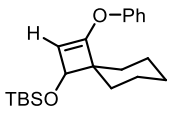
(1R,11S)-4,13,13-Trimethyl-10-methylene-6-phenoxytricyclo[9.2.0.04,7]tridec-5-ene (2.44m) (Mr = major regioisomer, mr = minor regioisomer)

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.30 (m, 4H, Mr + mr), 7.16 (dq, *J* = 7.9, 1.3 Hz, 4H, Mr + mr), 7.13 – 7.08 (m, 2H, Mr + mr), 4.95 (t, *J* = 1.3 Hz, 1H, mr), 4.93 (s, 1H, Mr), 4.86 (d, *J* = 1.5 Hz, 1H, mr), 4.85 (s, 1H, Mr), 4.66 (s, 1H, Mr), 4.48 (d, *J* = 1.1 Hz, 1H, mr), 2.86 (dd, *J* = 12.9, 2.7 Hz, 1H, Mr), 2.54 – 2.38 (m, 6H, Mr + mr), 2.09 – 2.00 (m, 1H, mr), 1.95 – 1.86 (m, 3H, Mr + mr), 1.86 – 1.69 (m, 5H, Mr + mr), 1.63 (m, 6H, Mr + mr), 1.56 – 1.40 (m, 3H, Mr + mr), 1.41 – 1.25 (m, 2H, Mr + mr), 1.23 (s, 3H, mr), 1.14 (s, 3H, Mr), 1.04 (s, 3H, mr), 1.02 (s, 3H, Mr), 1.00 (s, 6H, Mr + mr). **^{13}C-NMR (**101 MHz, $CDCl_3$) δ 155.3, 153.2, 152.6, 151.7, 129.5, 123.8, 119.3, 119.2, 110.4, 109.5, 101.0, 54.8, 50.2, 49.3, 49.2, 43.1, 41.9, 40.6, 39.7, 36.9, 34.4, 34.0, 34.0, 33.9, 32.9, 30.1, 30.1, 29.2, 26.9, 26.3, 25.7, 24.8, 24.5, 21.8, 19.3.

(1R,11S)-4,13,13-Trimethyl-10-methylenetricyclo[9.2.0.04,7]tridecan-6-one (2.45a) (Mr = major regioisomer, mr = minor regioisomer)

^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.95 (d, *J* = 1.2 Hz, 1H, Mr), 4.92 (t, *J* = 1.3 Hz, 0.3H, mr), 4.85 (d, *J* = 1.6 Hz, 0.3H, mr), 4.84 (q, *J* = 1.1 Hz, 1H, Mr), 3.15 – 3.07 (m, 0.3H, mr), 3.06 – 2.99 (m, 1H, Mr), 2.78 (dd, *J* = 16.8, 2.9 Hz, 1H, Mr), 2.69 (dd, *J* = 18.0, 8.1 Hz, 0.3H, mr), 2.55 (dd, *J* = 16.8, 2.1 Hz, 1H, Mr), 2.49 – 2.33 (m, 2H, Mr + mr), 2.33 – 2.22 (m, 1H, Mr), 2.05 – 1.97 (m, 1H, Mr), 1.96 – 1.80 (m, 3H, Mr + mr), 1.69 – 1.51 (m, 8H, Mr + mr), 1.51 – 1.33 (m, 2H, Mr + mr), 1.12 (s, 1H, mr), 1.12 (s, 3H, Mr), 1.00 (s, 6H, Mr), 0.99 (s, 1H, mr), 0.98 (s, 1H, mr). **^{13}C-NMR (**126 MHz, $CDCl_3$) δ 216.3(mr), 211.6 (Mr), 152.6 (mr), 152.2 (Mr), 110.6 (Mr), 109.3 (mr), 63.9 (mr), 62.9 (Mr), 60.1 (Mr), 55.6 (Mr), 54.9 (mr), 49.6, 48.2, 45.5, 44.8, 38.1, 37.0, 36.9, 34.4, 34.3 (mr), 34.2, 33.9, 33.5, 32.9, 32.4, 30.1 (mr), 30.1 (Mr), 25.7, 24.8 (mr), 24.5 (Mr), 21.9 (Mr), 21.7 (mr), 20.1 (Mr), 14.1 (mr).

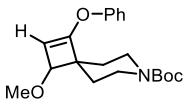
tert-Butyldimethyl((3-phenoxyspiro[3.5]non-2-en-1-yl)oxy)silane (2.44n)



Cyclobutene **2.44n** was synthesized following general procedure **A** starting from (ethynyloxy)benzene (23.6 mg, 0.2 mmol) and tert-butyl(cyclohexylidenemethoxy)dimethylsilane (136 mg, 0.6 mmol). The crude product was purified by flash chromatography affording **2.44n** as a yellow oil (54 mg, 79%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.28 (m, 2H), 7.18 – 7.09 (m, 3H), 4.58 (d, *J* = 0.8 Hz, 1H), 4.12 (d, *J* = 0.8 Hz, 1H), 1.82 – 1.70 (m, 2H), 1.70 – 1.61 (m, 2H), 1.61 – 1.45 (m, 2H), 1.44 – 1.32 (m, 2H), 1.32 – 1.12 (m, 2H), 0.90 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H). **^{13}C-NMR (**101 MHz, $CDCl_3$) δ 162.0, 155.2, 129.6, 124.4, 119.8, 100.8, 72.8, 55.5, 33.8, 30.4, 26.1, 26.1, 24.4, 23.5, 18.4, -4.2, -4.5.

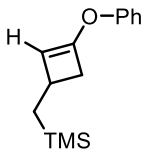
tert-Butyl 3-methoxy-1-phenoxy-7-azaspiro[3.5]non-1-ene-7-carboxylate (2.44o)



Cyclobutene **2.44o** was synthesized following general procedure **A** starting from (ethynyloxy)benzene (23.6 mg, 0.2 mmol) and tert-butyl 4-(methoxymethylene)piperidine-1-carboxylate (136 mg, 0.6 mmol). The crude product was purified by flash chromatography affording **2.44o** as a colorless oil (64 mg, 92%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.30 (m, 2H), 7.20 – 7.11 (m, 3H), 4.78 (d, *J* = 0.8 Hz, 1H), 3.77 (d, *J* = 0.8 Hz, 1H), 3.70 – 3.47 (m, 4H), 3.33 (s, 3H), 1.93 – 1.79 (m, 3H), 1.72 (ddd, *J* = 12.7, 7.8, 3.9 Hz, 1H), 1.47 (s, 9H). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 161.8, 155.2, 154.7, 129.7, 124.8, 119.7, 98.7, 80.1, 79.4, 56.9, 53.2, 28.6, 28.6.

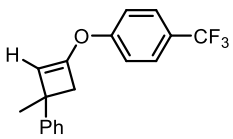
Trimethyl((3-phenoxycyclobut-2-en-1-yl)methyl)silane (2.44p)



Cyclobutene **2.44o** was synthesized following general procedure **A** starting from (ethynyloxy)benzene (23.6 mg, 0.2 mmol) and allyltrimethylsilane (95 µl, 0.6 mmol). The crude product was purified by flash chromatography affording **2.44p** as a colorless oil (11.6 mg, 25%).

^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.40 – 7.25 (m, 3H), 7.15 – 7.11 (m, 2H), 7.10 (dt, *J* = 7.3, 1.2 Hz, 1H), 4.80 (d, *J* = 0.9 Hz, 1H), 2.94 (dd, *J* = 12.9, 4.2 Hz, 1H), 2.57 (tdt, *J* = 7.5, 4.2, 1.3 Hz, 1H), 2.22 (dd, *J* = 12.8, 1.5 Hz, 1H), 0.79 (d, *J* = 7.6 Hz, 2H), 0.01 (s, 9H). **^{13}C-NMR** (126 MHz, $CDCl_3$) δ 155.2, 148.3, 129.6, 123.9, 119.3, 108.7, 40.9, 29.8, 23.3, -0.9.

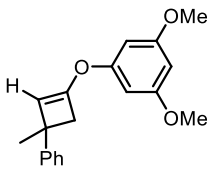
1-((3-Methyl-3-phenylcyclobut-1-en-1-yl)oxy)-4-(trifluoromethyl)benzene (2.44q)



Cyclobutene **2.44q** was synthesized following general procedure **A** starting from 1-(ethynyloxy)-4-(trifluoromethyl)benzene (37.2 mg, 0.2 mmol) and α-methylstyrene (78 µL, 0.6 mmol). The crude product was purified by flash chromatography affording **2.44q** as a colorless oil (44 mg, 72%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.72 – 7.54 (m, 2H), 7.47 – 7.33 (m,4H), 7.31 – 7.14 (m, 3H), 5.32 (s, 1H), 2.94 (d, *J* = 12.7 Hz, 1H), 2.89 (d, *J* = 12.7 Hz, 1H), 1.63 (s, 3H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -62.0. **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 157.7, 148.4, 147.5, 128.3, 127.1 (q, J = 3.7 Hz), 126.1, 124.2 (q, J = 271.6 Hz), 119.2, 111.2, 47.3, 41.7, 28.3.

1,3-Dimethoxy-5-((3-methyl-3-phenylcyclobut-1-en-1-yl)oxy)benzene (2.44r)

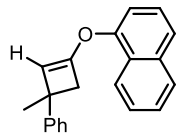


Cyclobutene **2.44r** was synthesized following general procedure **A** starting from 1-(ethynyloxy)-3,5-dimethoxybenzene (35.6 mg, 0.2 mmol) and α-methylstyrene (78 µL, 0.6 mmol). The crude product was

purified by flash chromatography affording **2.44r** as a colorless oil (13 mg, 22%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.42 – 7.29 (m, 4H), 7.21 (ddt, *J* = 8.5, 6.4, 1.6 Hz, 1H), 6.36 (d, *J* = 2.2 Hz, 2H), 6.26 (t, *J* = 2.2 Hz, 1H), 5.27 (s, 1H), 3.79 (s, 6H), 2.88 (d, *J* = 12.8 Hz, 1H), 2.87 (d, *J* = 12.8 Hz, 1H), 1.60 (s, 3H). **^{13}C-NMR (**101 MHz, $CDCl_3$) δ 161.5, 156.7, 148.9, 147.9, 128.2, 126.1, 125.9, 109.9, 97.9, 96.3, 55.6, 47.3, 41.5, 28.4.

1-((3-Methyl-3-phenylcyclobut-1-en-1-yl)oxy)naphthalene (2.44s)



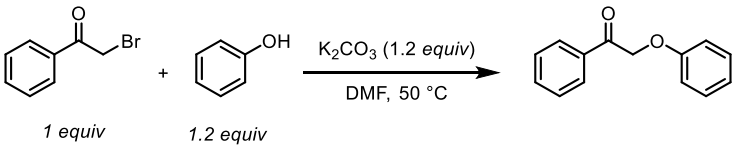
Cyclobutene **2.44s** was synthesized following general procedure **A** starting from 1-(ethynyloxy)naphthalene (34 mg, 0.2 mmol) and α-methylstyrene (78 µL, 0.6 mmol). The crude product was purified by flash chromatography affording **2.44s** as a colorless oil z (34 mg, 58%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.18 (ddt, *J* = 6.4, 3.6, 0.8 Hz, 1H), 7.91 – 7.83 (m, 1H), 7.65 (dt, *J* = 8.2, 1.0 Hz, 1H), 7.57 – 7.49 (m, 3H), 7.44 (dd, *J* = 8.2, 7.6 Hz, 1H), 7.41 – 7.36 (m, 2H), 7.36 – 7.29 (m, 3H), 7.25 – 7.19 (m, 1H), 5.20 (s, 1H), 2.99 (d, *J* = 12.7 Hz, 1H), 2.95 (d, *J* = 12.7 Hz, 1H), 1.62 (s, 3H). **^{13}C-NMR (**101 MHz, $CDCl_3$) δ 150.8, 149.7, 148.0, 135.0, 128.2, 127.9, 126.6, 126.2, 126.1, 125.9, 125.6, 124.2, 122.1, 114.4, 109.6, 47.3, 41.4, 28.4.

Synthesis of Internal Ynol ethers

Internal ynol ethers **2.46a-d,i** were synthesized following a modified reported procedure[166]:

General procedure B: Synthesis of internal ynol ethers



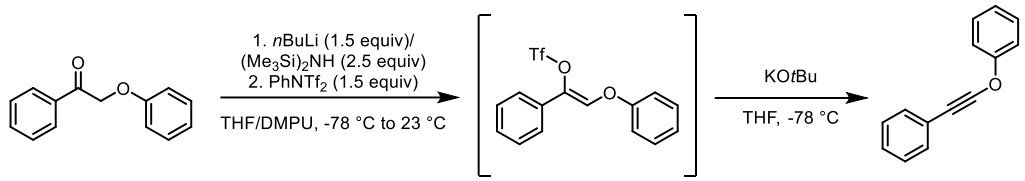
The phenol (1.2 equiv) and K_2CO_3 (1.2 equiv) were suspended in dry DMF (0.3 M) and stirred for 30 minutes, then the needed 2-bromoketone (1 equiv) was added and the mixture was stirred at 50 °C until complete conversion monitored by GC-MS.

The reaction was then quenched with water and the crude product was extracted three times with EtOAc. The collected organic phases were washed several times with KOH 2M in H_2O and Brine, dried over Na_2SO_4 and the solvent evaporated. The crude product was filtered through a plug of silica gel and used in the following step without further purifications.

Note: In some case larger excess of phenol was necessary and after the filtration through silica gel the product was obtained as a mixture with residual phenol. The presence of the phenol does

166 J. R. Sosa, A. A. Tudjarian, T. G. Minehan, *Org. Lett.* **2008**, *10*, 5091–5094.

not affect the following step as far as its amount remains less than the 20% of the total. In case of a larger excess a second washing with KOH 2M in H_2O it will be necessary.



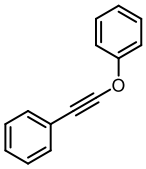
Bis(trimethylsilyl)amine (2.5 equiv) dissolved in THF (1 M with respect of the limiting reagent) under argon was cooled to 0 °C in an ice bath and butyllithium (2.5 M in hexane, 1.5 equiv) was added dropwise. After 10 minutes, the mixture was cooled to -78 °C and a solution of the crude mixture from the previous step (1 equiv) in THF (1 M) was added dropwise. The reaction mixture was stirred for 1 h at -78 °C, and then a solution of 1,1,1-trifluoro-N-phenyl-N-((trifluoromethyl)sulfonyl)methanesulfonamide (1.5 equiv) in 1:1 mixture DMPU:THF (total volume: 1 M with respect of the limiting reagent) was added rapidly (1s). The mixture was allowed to warm to room temperature and then was stirred for 1 h. The reaction mixture was quenched with ice-cold saturated $NaHCO_3$ solution and was then diluted with ether. The phases were separated, and the aqueous layer was back-extracted with ether. The combined organic phases were then dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude triflate was dissolved in THF (1 M) under argon and cooled to -78 °C. A solution of KO*t*Bu in THF (1 molar, 2.5 equiv) was added dropwise, and the reaction mixture darkened in color. After 20 minutes, a saturated solution $NaHCO_3$ was added and the mixture was allowed to warm to room temperature with stirring. Et_2O was added, and the phases were separated. The aqueous layer was back-extracted with Et_2O and the combined organic phases were then dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification of the residue by flash chromatography silica gel afforded the ynol ether.

Notes: 1) The crude triflate can be stored without solvent and under argon for up to three days in the freezer and then used in the second step without erosion of the final yield.

2) Highly electron-rich ynol ethers are generally unstable, and the final purification has to be carried on quickly and eventually using neutral alumina instead of silica gel.

3) The reported procedure can be followed without modifications for amounts of starting material up to 1g. On larger scale the overall yield dropped drastically.

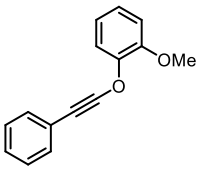
(Phenoxyethynyl)benzene (2.46a)



Ynol ether **2.46a** was synthesized following general procedure **B** starting from 2-bromo-1-phenylethan-1-one and phenol. The second step of the synthesis was carried out on 1g of crude and after purification by flash chromatography on silica gel **2.46a** was obtained as an orange oil (609 mg, 67%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.51 – 7.44 (m, 2H), 7.44 – 7.28 (m, 7H), 7.22 – 7.14 (m, 1H). Data in agreement with the one reported in literature[166.]

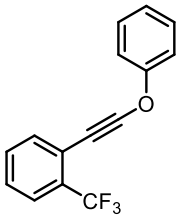
1-Methoxy-2-((phenylethynyl)oxy)benzene (2.46b)



Ynol ether **2.46b** was synthesized following general procedure **B** starting from 2-bromo-1-phenylethan-1-one and 2-methoxyphenol. The second step of the synthesis was carried out on 340 mg of crude and after purification by flash chromatography on silica gel **2.46b** was obtained as an orange oil (239 mg, 76%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.56 (dd, *J* = 8.1, 1.6 Hz, 1H), 7.46 – 7.40 (m, 2H), 7.31 – 7.23 (m, 3H), 7.09 (ddd, *J* = 8.0, 7.6, 1.6 Hz, 1H), 6.96 (ddd, *J* = 8.1, 7.6, 1.5 Hz, 1H), 6.92 (dd, *J* = 8.0, 1.5 Hz, 1H), 3.87 (s, 3H). **^{13}C-NMR (**101 MHz, $CDCl_3$) δ 148.3, 145.5, 131.9, 128.4, 127.5, 125.1, 123.1, 120.9, 115.1, 112.7, 92.7, 56.2, 46.3.

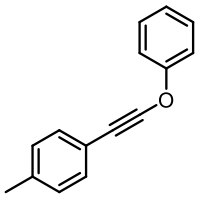
1-(Phenoxyethynyl)-2-(trifluoromethyl)benzene (2.46c)



Ynol ether **2.46c** was synthesized following general procedure **B** starting from 2-bromo-1-(2-(trifluoromethyl)phenyl)ethan-1-one and phenol. The second step of the synthesis was carried out on 390 mg of crude and after purification by flash chromatography on silica gel **2.46c** was obtained as an orange oil (179 mg, 49%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.67 (ddd, *J* = 7.9, 1.4, 0.7 Hz, 1H), 7.61 (ddt, *J* = 7.7, 1.4, 0.7 Hz, 1H), 7.49 (tdd, *J* = 7.6, 1.4, 0.7 Hz, 1H), 7.45 – 7.34 (m, 5H), 7.21 (tt, *J* = 6.6, 1.5 Hz, 1H). **^{19}F-NMR** (376 MHz, $CDCl_3$) δ -62.5. **^{13}C-NMR (**101 MHz, $CDCl_3$) δ 156.1, 134.1, 131.5, 130.0, 127.1, 126.0 (q, J = 5.1 Hz) , 124.9, 124.0 (q, J = 273.2 Hz), 122.6, 121.7 (q, J = 2.3 Hz), 115.2, 97.4, 43.2.

1-Methyl-4-(phenoxyethynyl)benzene (2.46d)

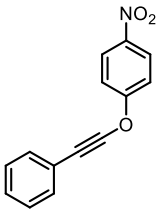


Ynol ether **2.46d** was synthesized following general procedure **B** starting from 2-bromo-1-(p-tolyl)ethan-1-one and phenol. The second step of the synthesis was carried out on 340 mg (assumed 1.5 mmol) of crude and after

purification by flash chromatography on silica gel **2.46d** was obtained as an orange oil (219 mg, 70%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.31 (m, 7H), 7.22 – 7.11 (m, 3H), 2.37 (s, 3H). **^{13}C-NMR (**101 MHz, $CDCl_3$) δ 156.3, 137.6, 131.8, 129.8, 129.2, 124.5, 119.8, 115.2, 92.0, 46.4, 21.5.

1-Nitro-4-((phenylethynyl)oxy)benzene (2.46i)

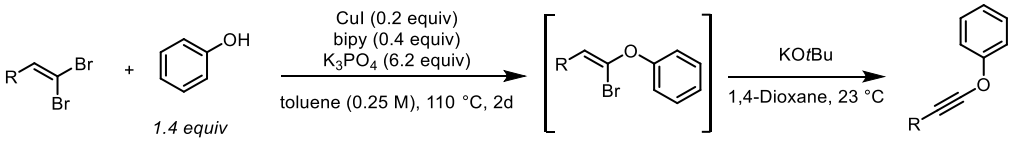


Ynol ether **2.46i** was synthesized following general procedure **B** starting from 2-bromo-1-(p-tolyl)ethan-1-one and 4-nitrophenol. The second step of the synthesis was carried out on 1 g (assumed 3.9 mmol) of crude and after purification by flash chromatography on silica gel **2.46i** was obtained as an orange oil (507 mg, 55%).

^{1}H-NMR (400 MHz, CDCl3) δ 8.36 – 8.28 (m, 2H), 7.53 – 7.46 (m, 4H), 7.35 (tt, *J* = 3.7, 2.6 Hz, 3H). **^{13}C-NMR (**101 MHz, $CDCl_3$) δ 160.5, 144.6, 132.0, 128.6, 128.3, 126.1, 121.9, 115.9, 90.8, 48.6.

Internal ynol ethers **2.46e,g,j** were synthesized following a modified reported procedure[167]:

General procedure C: Synthesis of internal ynol ethers



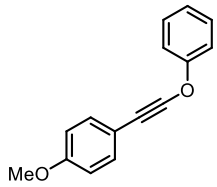
15 mL pressure tube was charged with the phenol (1.4 equiv), 2,2'-bipyridine (0.4 equiv), K_3PO_4 (6.2 equiv), and copper(I) iodide (0.2 equiv). The tube was fitted with a rubber septum, evacuated under high vacuum and backfilled with argon. Dry and degassed toluene (0.25 M) was next added followed by the needed 1,1-dibromo-1-alkene (1 equiv) The rubber septum was replaced by teflon-coated screw cap and the heterogeneous suspension heated at 110 °C for 2 days, cooled to room temperature, filtered through a plug of silica gel and concentrated under reduced pressure.

The crude product was then dissolved in dry dioxane (0.4 M) and treated with potassium tert-butoxide (2 equiv). The resulting mixture was stirred overnight at room temperature, filtered

167 K. Jouvin, A. Coste, A. Bayle, F. Legrand, G. Karthikeyan, K. Tadiparthi, G. Evano, *Organometallics* **2012**, *31*, 7933–7947.

through a plug of silica gel (washed with EtOAc), and concentrated in vacuo. The crude residue was purified by flash column chromatography eluting with hexane.

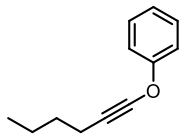
1-Methoxy-4-(phenoxyethynyl)benzene (2.46e)



Ynol ether **2.46e** was synthesized following general procedure **C** starting from 1-(2,2-dibromovinyl)-4-methoxybenzene (672 mg, 2.3 mmol) and phenol. After purification by flash chromatography on neutral alumina **2.46e** was obtained as an orange oil (162 mg, 31%).

^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.43 – 7.37 (m, 2H), 7.38 (m, 1H), 7.37 – 7.31 (m, 2H), 7.19 – 7.12 (m, 1H), 6.89 – 6.82 (m, 2H), 3.81 (s, 3H). **^{13}C-NMR (**126 MHz, $CDCl_3$) δ 159.2, 156.4, 133.3, 129.8, 124.5, 115.2, 114.1, 91.4, 55.4, 46.1, 27.3. **HRMS** (APCI) *m/z* calculated for $C_{15}H_{13}O_2^+$ $[M+H]^+$: 225.0910, found: 225.0909. *m/z* calculated for $C_{15}H_{13}O_2^+$ $[M+CH_3OH+H]^+$: 257.1172, found: 257.1171.

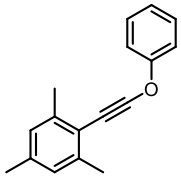
(Hex-1-yn-1-yloxy)benzene (2.46g)



Ynol ether **2.46g** was synthesized following general procedure **C** starting from 1,1-dibromohex-1-ene (726 mg, 3.0 mmol) and phenol. After purification by flash chromatography on silica gel **2.46g** was obtained as colorless oil (236 mg, 45%).

^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.31 (m, 2H), 7.25 (dtd, *J* = 7.7, 2.1, 0.9 Hz, 2H), 7.14 – 7.07 (m, 1H), 2.28 (t, *J* = 6.9 Hz, 2H), 1.60 – 1.51 (m, 2H), 1.51 – 1.42 (m, 2H), 0.94 (t, *J* = 7.3 Hz, 3H). **^{13}C-NMR (**126 MHz, $CDCl_3$) δ 156.6, 129.8, 129.7, 124.0, 116.7, 115.0, 83.4, 44.8, 31.6, 22.1, 17.1, 13.8. Data in agreement with the one reported in literature[167]

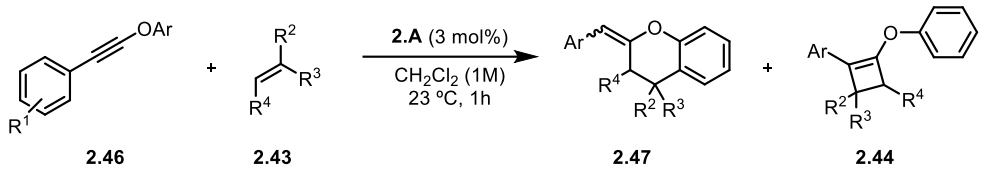
1,3,5-trimethyl-2-(phenoxyethynyl)benzene (2.46j)



Ynol ether **2.46j** was synthesized following general procedure **C** starting from 2-(2,2-dibromovinyl)-1,3,5-trimethylbenzene (720 mg, 2.4 mmol) and phenol. After purification by flash chromatography on neutral alumina **2.46j** was obtained as a red oil (194 mg, 33%). The product is highly unstable and decomposed within three days stored under argon in the freezer.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.35 (m, 4H), 7.21 – 7.14 (m, 1H), 6.90 (s, 2H), 2.45 (s, 6H), 2.30 (s, 3H). **^{13}C-NMR (**126 MHz, $CDCl_3$) δ 156.5, 140.0, 136.8, 129.9, 127.9, 127.7, 124.4, 119.6, 115.1, 100.0, 44.1, 21.4, 21.4. **HRMS** (APCI) *m/z* calculated for $C_{17}H_{17}O^+$ $[M+H]^+$: 273.1274, found: 273.1275.

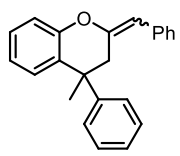
*General procedure D: Gold(I)-catalyzed reaction of **2.46** with **2.43**.*



2.46 **2.43** **2.47** **2.44**

The needed ynol ether (0.2 mmol, 1 equiv) was dissolved in CH_2Cl_2 (0.2 mL, 1 M). The alkene (0.4 mmol, 2 equiv) was added followed by [(*t*BuXPhos)AuNCMe]BAr_4^F (**2.A**, 3 mol%, 9.2 mg). The resulting mixture was stirred at 23 °C for 1 h. The reaction was monitored by GC-MS or UHPLC-MSD. Once completed, the reaction was quenched with few drops of triethylamine and the solvent evaporated. The crude product was purified by flash chromatography on neutral alumina (eluent = pentane:Et_2O gradient from 100:0 to 20:1) to obtain the pure product.

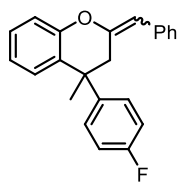
2-Benzylidene-4-methyl-4-phenylchromane (2.47a)



chromane **2.47a** was synthesized following general procedure **D** starting from (phenoxyethynyl)benzene (38 mg, 0.2 mmol) and α-methylstyrene (52 µL, 0.4 mmol). The crude product was purified by flash chromatography affording **2.47a** as a greenish oil (*E:Z* = 1:1, 47 mg, 76%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.17 (m, 13H, E+Z), 7.17 – 7.09 (m, 4H, E+Z), 7.09 – 7.00 (m, 6H, E+Z), 6.98 – 6.88 (m, 4H, E+Z), 6.30 (s, 1H, E), 5.56 (d, *J* = 1.1 Hz, 1H, Z), 3.21 (dd, *J* = 14.5, 0.9 Hz, 1H, E), 3.06 (d, *J* = 16.7 Hz, 1H, Z), 2.83 (dd, *J* = 14.5, 1.2 Hz, 1H, E), 2.71 (dd, *J* = 16.7, 1.2 Hz, 1H, Z), 1.75 (s, 3H), 1.69 (s, 3H). **^{13}C-NMR (**101 MHz, $CDCl_3$) δ 156.9, 154.9, 152.5, 150.1, 147.9, 146.6, 139.9, 135.8, 134.7, 131.1, 129.7, 129.1, 128.3, 128.3, 128.2, 128.1, 127.6, 127.2, 127.0, 127.0, 126.6, 126.4, 126.3, 126.1, 125.9, 124.3, 121.7, 120.8, 116.6, 108.7, 104.4, 44.4, 42.1, 40.3, 38.1, 27.8, 27.8.

2-Benzylidene-4-(4-fluorophenyl)-4-methylchromane (2.47b)

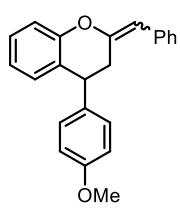


chromane **2.47b** was synthesized following general procedure **D** starting from (phenoxyethynyl)benzene (38 mg, 0.2 mmol) and 1-fluoro-4-(prop-1-en-2-yl)benzene (54 µL, 0.4 mmol). The crude product was purified by flash chromatography affording **2.47b** as a colorless oil (*E:Z* = 1:1, 46 mg, 70%).

^{1}H-NMR (500 MHz, CD_2Cl_2) δ 7.38 – 7.32 (m, 2H, E+Z), 7.31 – 7.26 (m, 2H, E+Z), 7.26 – 7.21 (m, 3H, E+Z), 7.21 – 7.15 (m, 1H, E+Z), 7.15 – 7.11 (m, 2H, E+Z), 7.10 – 7.08 (m, 2H, E+Z), 7.08 – 7.05 (m, 2H, E+Z), 7.05 – 6.94 (m, 8H, E+Z), 6.93 – 6.88 (m, 3H, E+Z), 6.25 (s, 1H, E), 5.52 (d, *J* = 1.3 Hz, 1H, Z), 3.25 (dd, *J* = 14.6, 0.7 Hz, 1H, E), 2.98 (d, *J* = 16.6 Hz, 1H, Z), 2.80 (dd, *J* = 14.6, 1.4 Hz, 1H, E), 2.74 (dd, *J* = 16.6, 1.4 Hz, 1H, Z), 1.73

(s, 3H), 1.67 (s, 3H). **^{19}F NMR** (471 MHz, CD_2Cl_2) δ -117.8, -118.2. **^{13}C-NMR (**126 MHz, CD_2Cl_2) δ 162.9, 161.0, 157.5, 155.2, 152.8, 150.5, 144.1, 144.1, 143.0, 140.0, 136.1, 135.1, 131.4, 130.6, 130.2, 129.4, 129.2, 129.2, 129.1, 129.1, 129.0, 128.8, 128.8, 127.7, 127.5, 126.6, 126.6, 126.5, 126.3, 125.0, 122.2, 121.2, 117.0, 115.4, 115.2, 115.1, 115.0, 109.0, 104.4, 44.2, 42.4, 40.3, 38.3, 28.4, 28.3.

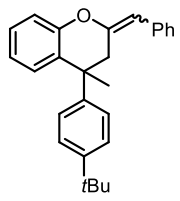
2-Benzylidene-4-(4-methoxyphenyl)chromane (2.47c)



chromane **2.47c** was synthesized following general procedure **D** starting from (phenoxyethynyl)benzene (38 mg, 0.2 mmol) and 1-methoxy-4-vinylbenzene (54 µL, 0.4 mmol). The crude product was purified by flash chromatography affording **2.47c** as a yellow oil (*E:Z* = 1:10, 48 mg, 73%).

^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.38 – 7.32 (m, 2H, E+Z), 7.25 – 7.22 (m, 0.2H, E), 7.22 – 7.15 (m, 3H, E+Z), 7.15 – 7.10 (m, 1H,Z), 7.10 – 7.06 (m, 0.2H, E), 6.94 (dd, *J* = 7.5, 1.3 Hz, 1H, Z), 6.92 – 6.87 (m, 2H, Z), 6.85 (dq, *J* = 7.7, 0.9 Hz, 1H, E+Z), 6.38 (s, 0.1H, E), 5.69 (d, *J* = 1.0 Hz, 1H, Z), 4.36 – 4.18 (m, 1H, Z), 4.10 (dd, *J* = 7.9, 5.2 Hz, 0.1H, E), 3.82 (s, 3H, Z), 3.80 (s, 0.3H, E), 3.12 (ddd, *J* = 14.3, 5.1, 0.9 Hz, 0.1H, E), 2.97 (ddd, *J* = 14.3, 7.9, 1.1 Hz, 0.1H, E), 2.90 (ddd, *J* = 16.6, 7.4, 0.9 Hz, 1H, Z), 2.84 (ddd, *J* = 16.6, 9.3, 1.1 Hz, 1H, Z). **^{13}C-NMR (**126 MHz, $CDCl_3$) δ 158.5, 157.0, 155.0, 135.8, 135.3, 134.9, 129.8, 129.4, 127.7, 127.0, 125.8, 125.6, 124.3, 120.6, 114.1, 104.9, 55.4, 44.5, 35.0.Here just the signal of the major isomer are reported.

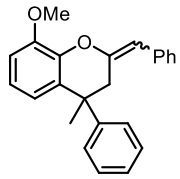
2-Benzylidene-4-(4-(tert-butyl)phenyl)-4-methylchromane (2.47d)



Chromane **2.47d** was synthesized following general procedure **D** starting from (phenoxyethynyl)benzene (39 mg, 0.2 mmol) and 1-(tert-butyl)-4-(prop-1-en-2-yl)benzene (70 mg, 0.4 mmol). The crude product was purified by flash chromatography affording **2.47d** as a yellow oil (*E:Z* = 1:2.3, 61 mg, 83%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.38 – 6.99 (m, 16H, E+Z), 6.98 – 6.89 (m, 4H, E+Z), 6.34 (s, 0.4H, E), 5.71 – 5.55 (m, 1H, Z), 3.18 (dd, *J* = 14.4, 1.0 Hz, 0.4H, E), 3.06 (d, *J* = 16.6 Hz, 1H, Z), 2.85 (dd, *J* = 14.4, 1.1 Hz, 0,4H, E), 2.72 (dd, *J* = 16.6, 1.3 Hz, 1H, Z), 1.78 (s, 3H, Z), 1.71 (s, 1.2H, E), 1.36 (s, 9H, Z), 1.33 (d, *J* = 1.1 Hz, 4H, E). **^{13}C-NMR (**126 MHz, $CDCl_3$) δ 156.7, 155.1, 150.5, 149.0, 148.7, 147.5, 147.3, 144.7, 140.1, 137.9, 134.6, 129.7, 129.0, 128.9, 128.5, 127.1, 127.0, 126.9, 126.8, 126.6, 126.4, 126.1, 125.9, 125.1, 125.0, 124.2, 123.2, 120.6, 116.4, 108.4, 105.0, 44.0, 42.2, 39.9, 34.5, 31.5, 31.5, 31.5, 30.9, 27.8.

2-Benzylidene-8-methoxy-4-methyl-4-phenylchromane (2.47e)



chromane **2.47e** was synthesized following general procedure **D** starting from 1-methoxy-2-((phenylethynyl)oxy)benzene (45 mg, 0.2 mmol) and α-methylstyrene (52 µL, 0.4 mmol). The crude product was purified by flash chromatography affording and the two isomers were separated affording **(E)-2.47e** as a yellow oil (33 mg, 48%) and **(Z)-2.47e** as a yellow oil (20 mg, 29%).

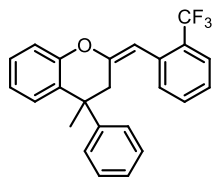
(E)-2-benzylidene-8-methoxy-4-methyl-4-phenylchromane

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.19 (m, 5H), 7.18 – 7.08 (m, 2H), 7.08 – 6.99 (m, 2H), 6.99 – 6.93 (m, 2H), 6.92 (dd, *J* = 7.1, 1.4 Hz, 1H), 6.90 – 6.85 (m, 1H), 5.40 (s, 1H), 3.76 (s, 3H), 3.14 (d, *J* = 16.6 Hz, 1H), 2.75 (dd, *J* = 16.6, 1.1 Hz, 1H), 1.76 (s, 3H). **^{13}C-NMR (**101 MHz, $CDCl_3$) δ 157.2, 151.7, 148.1, 143.3, 139.9, 134.9, 128.7, 128.1, 127.3, 126.8, 126.4, 126.2, 125.9, 125.7, 125.5, 122.8, 121.1, 113.0, 102.0, 56.0, 44.4, 42.0, 27.7.

(Z)-2-benzylidene-8-methoxy-4-methyl-4-phenylchromane

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.21 (m, 4H), 7.22 – 7.15 (m, 2H), 7.14 – 7.09 (m, 2H), 7.05 – 6.98 (m, 2H), 6.90 (dd, *J* = 8.1, 7.4 Hz, 1H), 6.86 (dd, *J* = 8.1, 2.0 Hz, 1H), 6.64 (dd, *J* = 7.4, 1.9 Hz, 1H), 6.45 (s, 1H), 3.95 (s, 3H), 3.18 (dd, *J* = 14.4, 0.9 Hz, 1H), 2.84 (dd, *J* = 14.4, 1.1 Hz, 1H), 1.69 (s, 3H). **^{13}C-NMR (**101 MHz, CDCl3) δ 149.6, 147.9, 146.6, 142.0, 135.7, 131.9, 129.0, 128.3, 127.0, 126.5, 126.1, 121.1, 119.4, 110.3, 109.4, 56.2, 40.5, 38.0, 27.8.

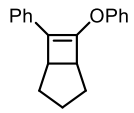
(*E*)-4-Methyl-4-phenyl-2-(2-(trifluoromethyl)benzylidene)chromane (2.47f)



chromane **2.47f** was synthesized following general procedure **D** starting from 1-(phenoxyethynyl)-2-(trifluoromethyl)benzene (54.2 mg, 0.2 mmol) and α-methylstyrene (52 µL, 0.4 mmol). The crude product was purified by flash chromatography affording **2.47f** as a colorless oil (70 mg, 92%).

^{1}H-NMR (500 MHz, CD_2Cl_2) δ 7.66 – 7.61 (m, 1H), 7.43 (tdt, *J* = 7.6, 1.4, 0.7 Hz, 1H), 7.37 – 7.30 (m, 1H), 7.28 – 7.22 (m, 3H), 7.22 – 7.17 (m, 1H), 7.10 – 7.06 (m, 2H), 7.06 – 7.02 (m, 1H), 6.98 (td, *J* = 7.5, 1.3 Hz, 1H), 6.95 – 6.89 (m, 1H), 6.39 (d, *J* = 2.8 Hz, 1H), 3.05 (dd, *J* = 14.6, 0.9 Hz, 1H), 2.70 (dd, *J* = 14.5, 1.3 Hz, 1H), 1.67 (s, 3H). **^{19}F NMR** (471 MHz, CD_2Cl_2) δ -61.3. z**^{13}C-NMR (**126 MHz, CD_2Cl_2) δ 152.8, 151.9, 147.0, 134.7, 132.3, 132.1, 131.5, 128.8, 128.8, 128.0, 127.4, 127.1(d, J = 3.9 Hz), 126.3 (q, J = 5.4 Hz),124.9 (q, J = 273.8 Hz), 122.4, 116.9, 105.5, 40.6, 38.8, 30.3, 28.0. **HRMS** (APCI) *m/z* calculated for $C_{24}H_{20}F_3O^+$ $[M+H]^+$: 381.1461, found: 381.1464.

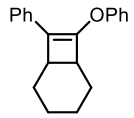
6-Phenoxy-7-phenylbicyclo[3.2.0]hept-6-ene (2.44t)



Cyclobutene **2.44t** was synthesized following general procedure **D** starting from (phenoxyethynyl)benzene (38 mg, 0.2 mmol) and cyclopentene (37 µL, 0.4 mmol). The crude product was purified by flash chromatography affording **2.44t** as a colorless oil (24 mg, 46%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.51 – 7.45 (m, 2H), 7.38 – 7.28 (m, 4H), 7.21 – 7.15 (m, 1H), 7.15 – 7.08 (m, 3H), 3.52 (dd, *J* = 7.3, 3.6 Hz, 1H), 3.21 (dd, *J* = 6.7, 3.6 Hz, 1H), 1.87 (dd, *J* = 12.6, 5.8 Hz, 1H), 1.80 – 1.63 (m, 2H), 1.57 – 1.48 (m, 1H), 1.32 (tt, *J* = 12.3, 6.8 Hz, 1H), 1.11 (ddt, *J* = 13.0, 12.2, 7.2 Hz, 1H). **^{13}C-NMR (**101 MHz, $CDCl_3$) δ 155.1, 143.0, 133.1, 129.6, 128.5, 126.4, 126.3, 123.6, 119.4, 119.0, 47.9, 38.6, 26.1, 24.6, 23.3.

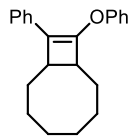
7-Phenoxy-8-phenylbicyclo[4.2.0]oct-7-ene (2.44u)



Cyclobutene **2.44u** was synthesized following general procedure **D** starting from (phenoxyethynyl)benzene (38 mg, 0.2 mmol) and cyclohexene (42 µL, 0.4 mmol). The crude product was purified by flash chromatography affording **2.44u** as a colorless oil (24 mg, 43%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.50 – 7.45 (m, 2H), 7.32 (qd, *J* = 6.7, 1.8 Hz, 4H), 7.20 – 7.15 (m, 1H), 7.14 – 7.07 (m, 3H), 3.23 (q, *J* = 5.1 Hz, 1H), 2.94 (q, *J* = 5.1 Hz, 1H), 1.89 (ddt, *J* = 14.1, 9.6, 4.4 Hz, 1H), 1.83 – 1.72 (m, 1H), 1.67 – 1.55 (m, 2H), 1.52 – 1.24 (m, 4H). **^{13}C-NMR (**101 MHz, $CDCl_3$) δ 155.2, 146.3, 134.0, 129.6, 128.5, 126.3, 126.2, 123.7, 121.4, 119.1, 41.5, 32.4, 23.7, 22.4, 18.6, 18.2.

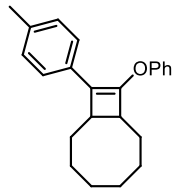
9-Phenoxy-10-phenylbicyclo[6.2.0]dec-9-ene (2.44v)



Cyclobutene **2.44v** was synthesized following general procedure **D** starting from (phenoxyethynyl)benzene (38 mg, 0.2 mmol) and (Z)-cyclooctene (52 µL, 0.4 mmol). The crude product was purified by flash chromatography affording **2.44v** as a colorless oil (52 mg, 85%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.41 (dt, *J* = 8.3, 1.3 Hz, 2H), 7.30 (qd, *J* = 6.8, 1.7 Hz, 4H), 7.21 – 7.12 (m, 1H), 7.12 – 7.05 (m, 3H), 3.16 (ddd, *J* = 11.4, 4.6, 2.4 Hz, 1H), 2.88 (dd, *J* = 10.5, 4.3 Hz, 1H), 2.23 – 2.04 (m, 1H), 1.75 – 1.63 (m, 1H), 1.61 – 1.43 (m, 7H), 1.42 – 1.30 (m, 1H), 1.25 – 1.13 (m, 1H). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 155.3, 145.2, 132.9, 129.6, 128.4, 126.6, 126.3, 123.2, 123.0, 118.0, 48.0, 39.4, 30.4, 30.1, 26.3, 26.1, 25.4, 24.4.

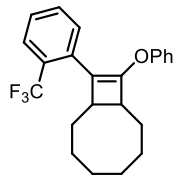
9-Phenoxy-10-(p-tolyl)bicyclo[6.2.0]dec-9-ene (2.44w)



Cyclobutene **2.44w** was synthesized following general procedure **D** starting from 1-methyl-4-(phenoxyethynyl)benzene (41.7 mg, 0.2 mmol) and (Z)-cyclooctene (52 µL, 0.4 mmol). The crude product was purified by flash chromatography affording **2.44w** as a white oil (46 mg, 72%).

^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.35 – 7.29 (m, 4H), 7.15 – 7.10 (m, 4H), 7.08 (dt, *J* = 7.3, 1.2 Hz, 1H), 3.17 (ddd, *J* = 11.7, 4.5, 2.0 Hz, 1H), 2.97 – 2.76 (m, 1H), 2.34 (s, 2H), 2.22 – 2.04 (m, 1H), 1.71 (dtt, *J* = 8.2, 4.5, 2.1 Hz, 1H), 1.64 – 1.44 (m, 5H), 1.39 (dtd, *J* = 10.0, 7.2, 3.4 Hz, 1H), 1.27 – 1.15 (m, 1H). **^{13}C-NMR (**126 MHz, $CDCl_3$) δ 155.5, 144.1, 136.0, 130.1, 129.6, 129.1, 126.6, 123.3, 123.0, 117.9, 47.9, 39.3, 30.5, 30.1, 26.4, 26.1, 25.5, 24.4, 21.4.

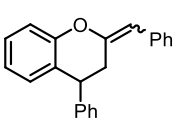
9-Phenoxy-10-(2-(trifluoromethyl)phenyl)bicyclo[6.2.0]dec-9-ene (2.44x)

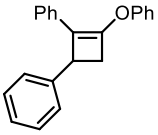


Cyclobutene **2.44x** was synthesized following general procedure **D** starting from 1-(phenoxyethynyl)-2-(trifluoromethyl)benzene (52 mg, 0.2 mmol) and (Z)-cyclooctene (52 µL, 0.4 mmol). The crude product was purified by flash chromatography affording **2.44x** as a yellow oil (52 mg, 70%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.63 – 7.56 (m, 1H), 7.44 – 7.33 (m, 2H), 7.29 – 7.17 (m, 3H), 7.06 – 6.96 (m, 3H), 3.15 (ddd, *J* = 11.7, 4.4, 2.0 Hz, 1H), 3.07 – 2.88 (m, 1H), 1.77 – 1.63 (m, 2H), 1.59 (ddd, *J* = 12.3, 8.7, 3.3 Hz, 1H), 1.46 (dddd, *J* = 28.3, 16.9, 13.5, 5.1 Hz, 5H), 1.34 – 1.13 (m, 2H). **^{19}F-NMR** (376 MHz, $CDCl_3$) δ -60.4. **^{13}C-NMR (**101 MHz, $CDCl_3$) δ 155.1, 147.2, 132.3, 131.8, 131.3, 129.4, 126.7, 125.9 (q, J = 5.6 Hz), 124.4 (q, J = 273.3), 123.3, 120.3, 118.4, 47.4, 43.0, 42.9, 30.2, 30.1, 26.3, 26.3, 25.9, 24.3.

2-Benzylidene-4-phenylchromane (2.47g) and (3-phenoxycyclobut-2-ene-1,2-diyl)dibenzene (2.44y)





The two products were synthesized following general procedure **D** starting from (phenoxyethynyl)benzene (39 mg, 0.2 mmol) and styrene (42 mg, 0.4 mmol). The two products were partially separated by flash chromatography affording **2.47g** as a yellow oil, *E:Z* = 2.6:1 (32% assigned by ^{1}H-NMR using trichloroethylene as internal standard) and **2.44y** as yellow oil, 4:1 mixture of regioisomers (38% assigned by ^{1}H-NMR using trichloroethylene as internal standard)

2-Benzylidene-4-phenylchromane (2.47g)

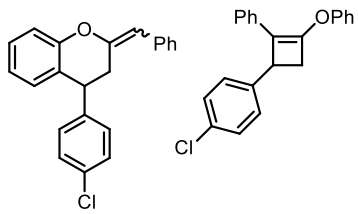
^{1}H-NMR (400 MHz, CD_2Cl_2) δ 7.38 – 7.27 (m, 4H, E+Z), 7.27 – 7.19 (m, 5H, E+Z), 7.18 – 7.08 (m, 4H, E+Z), 7.06 – 6.96 (m, 5H, E+Z), 6.96 – 6.80 (m, 4H, E+Z), 6.34 (s, 1H, E), 5.67

(s, 0.4H, Z), 4.32 (t, *J* = 7.9 Hz, 0.4H, Z), 4.21 – 4.14 (t, J = 6.6 Hz, 1H, E), 3.11 (ddd, *J* = 14.4, 5.4, 1.1 Hz, 1H, E), 3.03 (ddd, *J* = 14.4, 6.9, 0.9 Hz, 1H, E), 2.95 (ddd, *J* = 16.6, 7.4, 1.1 Hz, 0.4H, Z), 2.82 (dd, *J* = 16.6, 8.5 Hz, 0.4H, Z), 1.53 (s, 3H, E), 1.40 – 1.13 (m, 1.2H, Z).

(3-Phenoxycyclobut-2-ene-1,2-diyl)dibenzene (2.44y)

^{1}H-NMR (400 MHz, CD_2Cl_2) δ 7.42 – 7.27 (m, 10H, Mr+mr), 7.28 – 7.09 (m, 10H, Mr+mr), 7.07 – 6.96 (m, 1H, Mr), 4.33 (dd, *J* = 4.9, 1.7 Hz, 0.3H, mr), 3.97 (dd, *J* = 4.9, 1.7 Hz, 1H, Mr), 3.23 (dd, *J* = 13.7, 4.8 Hz, 1H, Mr), 3.00 (dd, *J* = 10.5, 4.9 Hz, 0.3H, mr), 2.51 (dd, *J* = 13.7, 1.7 Hz, 1H, Mr), 2.32 (dd, *J* = 10.5, 1.7 Hz, 0.3H, mr), 1.53 (s, 3H, Mr), 1.27 (s, 0.9H, mr).

2-Benzylidene-4-(4-chlorophenyl)chromane (2.47h) and 1-chloro-4-(3-phenoxy-2-phenylcyclobut-2-en-1-yl)benzene (2.44z)



The two products were synthesized following general procedure **D** starting from (phenoxyethynyl)benzene (39 mg, 0.2 mmol) and 1-chloro-4-vinylbenzene (55 mg, 0.4 mmol). The two products were separated by flash chromatography affording **2.47h** as a yellow oil, *E:Z* = 4:1 (19 mg, 28%) and **2.44z** as yellow oil, 2.6:1 mixture of regioisomers (25.4 mg, 38%).

2-Benzylidene-4-phenylchromane (2.47h)

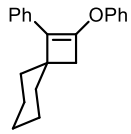
^{1}H-NMR (500 MHz, CD_2Cl_2) δ 7.42 – 7.21 (m, 8H, E+Z), 7.21 – 7.10 (m, 3H, E+Z), 7.10 – 7.06 (m, 2H, E), 7.02 – 6.98 (m, 3H, E+Z), 6.96 – 6.82 (m, 3H, E+Z), 6.35 (s, 1H, E), 5.65 (s, 0.25H, Z), 4.30 (t, *J* = 7.7 Hz, 0.25H, Z), 4.16 (t, *J* = 6.0 Hz, 1H, E), 3.08 (ddd, *J* = 14.4, 5.4, 1.2 Hz, 1H, E), 3.01 (ddd, *J* = 14.5, 6.7, 0.9 Hz, 1H, E), 3.00 – 2.91 (m, 0.25H, Z), 2.82 – 2.74 (m, 0.25H, Z). **^{13}C-NMR (**126 MHz, CD_2Cl_2) δ 153.5, 150.2, 142.3, 135.9, 133.1, 130.3, 130.2, 130.1, 130.1, 129.5, 129.3, 129.2, 129.1, 129.0, 128.8, 126.6, 125.8, 124.9, 122.2, 121.1, 116.8, 109.5, 40.9, 31.1. for the ^{13}C-NMR just the signals of the major isomer are reported.

(3-Phenoxycyclobut-2-ene-1,2-diyl)dibenzene (2.44z)

^{1}H-NMR (500 MHz, CD_2Cl_2) δ 7.50 – 7.42 (m, 1H), 7.43 – 7.35 (m, 3H, Mr+mr), 7.34 – 7.26 (m, 7H, Mr+mr), 7.26 – 7.20 (m, 3H, Mr+mr), 7.21 – 7.10 (m, 6H, Mr+mr), 4.29 (dd, *J* = 4.9, 1.6 Hz, 0.36H, mr), 3.95 (dd, *J* = 4.9, 1.6 Hz, 1H, Mr), 3.22 (dd, *J* = 13.7, 4.8 Hz, 1H, Mr), 3.00 (dd, *J* = 10.6, 4.8 Hz, 0.36H, mr), 2.47 (dd, *J* = 13.7, 1.6 Hz, 1H, Mr), 2.35 – 2.16 (m, 0.36H, mr). **^{13}C-NMR (**126 MHz, CD_2Cl_2) δ 155.2, 154.3 144.4, 142.0, 133.3, 130.6, 130.3, 130.0, 129.2, 129.2, 129.0, 128.9, 128.9, 128.9, 127.4l, 126.9, 126.8, 126.7, 126.6, 124.6, 124.2, 121.0,

119.5, 119.2, 117.3, 46.9, 41.2, 38.3, 32.0. The signals of ^{13}C-NMR were not assigned to each regioisomer.

2-Phenoxy-1-phenylspiro[3.5]non-1-ene (2.44aa)

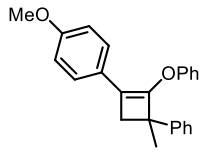


Cyclobutene **2.44aa** was synthesized following general procedure **D** starting from (phenoxyethynyl)benzene (39 mg, 0.2 mmol) and methylenecyclohexane (48 µl, 0.4 mmol). The crude product was purified by flash chromatography affording **2.44aa** as yellow solid, (25 mg, 43%). In the crude product also chromene **2.47i** was identified and quantified by 1H-NMR using trichloroethylene as internal standard (27%, *E:Z* = 4.4:1).

(3-Phenoxycyclobut-2-ene-1,2-diyl)dibenzene (2.44aa)

^{1}H-NMR (500 MHz, CDCl3) δ 7.60 – 7.52 (m, 2H), 7.38 – 7.28 (m, 4H), 7.18 – 7.14 (m, 1H), 7.13 – 7.08 (m, 3H), 2.46 (s, 2H), 2.06 (td, *J* = 13.1, 3.7 Hz, 2H), 1.77 (dt, *J* = 12.8, 3.2 Hz, 2H), 1.72 (dtt, *J* = 12.4, 3.2, 1.5 Hz, 1H), 1.65 (dq, *J* = 13.7, 2.0 Hz, 2H), 1.36 (qt, *J* = 12.7, 3.3 Hz, 2H), 1.29 – 1.21 (m, 1H). **^{13}C-NMR (**126 MHz, $CDCl_3$) δ 155.1, 143.9, 133.4, 129.6, 128.5, 126.8, 126.6, 125.9, 123.7, 119.1, 42.9, 41.6, 35.4, 25.9, 24.9.

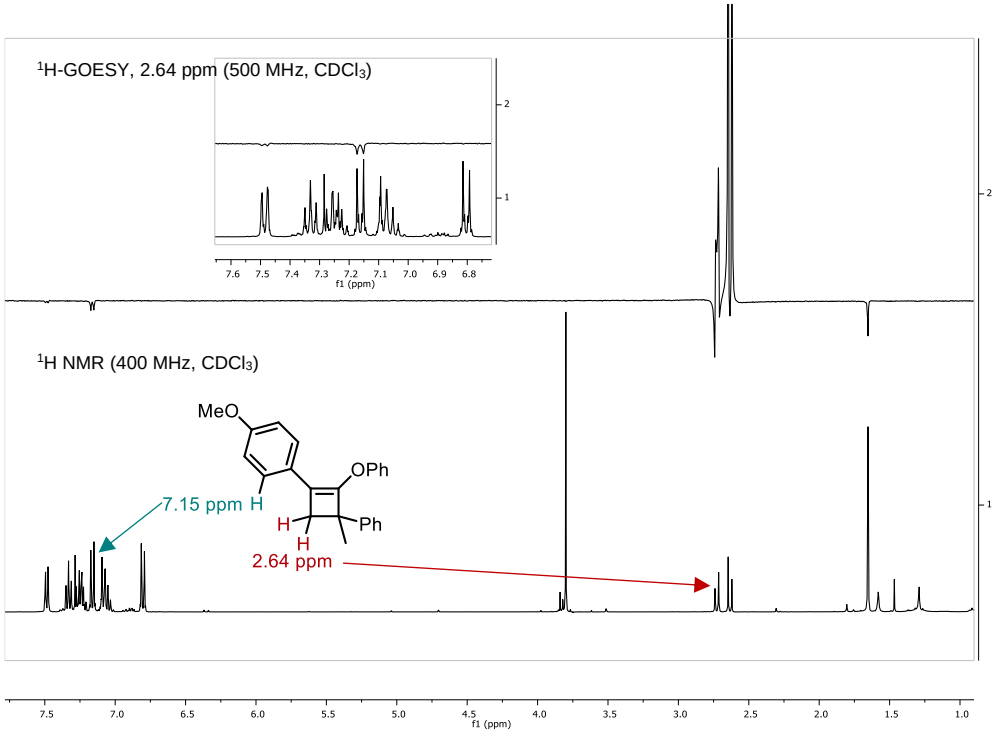
1-Methoxy-4-(3-methyl-2-phenoxy-3-phenylcyclobut-1-en-1-yl)benzene (2.44bb)



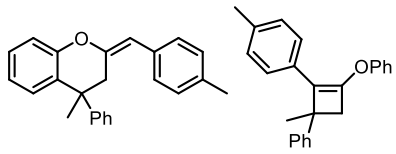
Cyclobutene **2.44bb** was synthesized following general procedure **D** starting from 1-methoxy-4-(phenoxyethynyl)benzene (44.8 mg, 0.2 mmol) and α-methylstyrene (52 µL, 0.4 mmol). The crude product was purified by flash chromatography affording **2.44bb** as colorless oil, (29.4 mg, 43%). In the crude product also chromene **2.47j** was identified and quantified by ^{1}H-NMR using trichloroethylene as internal standard (17%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.50 – 7.43 (m, 2H), 7.34 – 7.28 (m, 2H), 7.26 – 7.17 (m, 3H), 7.16 – 7.10 (m, 2H), 7.10 – 7.00 (m, 3H), 6.81 – 6.74 (m, 2H), 3.78 (s, 3H), 2.70 (d, *J* = 10.4 Hz, 1H), 2.61 (d, *J* = 10.4 Hz, 1H),1.63 (s, 3H). **^{13}C-NMR (**101 MHz, $CDCl_3$) δ 158.7, 155.5, 145.5, 145.2, 129.5, 128.4, 128.1, 126.3, 126.2, 123.1, 119.4, 118.1, 113.8, 55.4, 51.4, 39.2, 25.2. **HRMS** (APCI) *m/z* calculated for $C_{24}H_{22}O_2^+$ $[M+H]^+$: 343.1693, found: 343.1695.

We performed ^{1}H-GOESY experiment on **2.44bb** irradiating one of the cyclobutene protons to assign the structure of the compound.



2-Benzylidene-4-(4-chlorophenyl)chromane (2.47k) and 1-chloro-4-(3-phenoxy-2-phenylcyclobut-2-en-1-yl)benzene (2.44cc)



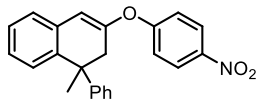
The two products were synthesized following general procedure **D** starting from 1-methyl-4-(phenoxyethynyl)benzene (41.7 mg, 0.2 mmol) and 1-α-methylstyrene (52 µL, 0.4 mmol). The two products coelute in column and it was not possible to separate them, the yield of the process was determined by ^{1}H-NMR using trichloroethylene as internal standard. The recorded NMRs are are reported below as they were registered without assigning the signals.

(*E*)-2.47k : (*Z*)2.47k : 2.44cc (1.4 : 1.8k : 1)

^{1}H-NMR (400 MHz, CD_2Cl_2) δ 7.50 – 7.44 (m, 2H), 7.36 – 7.28 (m, 6H), 7.28 – 7.17 (m, 12H), 7.17 – 7.03 (m, 13H), 7.02 – 6.90 (m, 11H), 6.81 (d, *J* = 7.5 Hz, 1H), 6.23 (s, 1H), 5.55 (d, *J* = 1.3 Hz, 1H), 3.28 (dd, *J* = 14.5, 0.8 Hz, 1H), 2.99 (d, *J* = 16.6 Hz, 1H), 2.82 (dd, *J* = 14.6, 1.3 Hz, 1H), 2.75 – 2.68 (m, 2H), 2.64 (d, *J* = 10.4 Hz, 1H), 2.33 (s, 4H), 2.30 (s, 2H), 2.28 (s, 4H), 1.73 (s, 4H), 1.68 (s, 3H), 1.63 (s, 2H). **^{13}C-NMR (**101 MHz, CD_2Cl_2) δ 156.5, 155.9, 155.5, 153.0, 150.3, 148.5, 147.2, 146.8, 145.8, 140.2, 137.4, 136.3, 136.0, 133.1, 132.3, 131.7, 131.0,

130.2, 130.0, 129.4, 129.4, 129.3, 128.8, 128.7, 128.6, 128.5, 128.4, 127.9, 127.9, 127.5, 127.5, 127.4, 127.1, 126.9, 126.7, 126.6, 126.4, 124.6, 123.7, 122.1, 121.0, 120.3, 118.5, 116.9, 108.7, 104.9, 51.8, 44.6, 42.4, 40.7, 39.5, 38.3, 32.2, 30.7, 30.3, 28.3, 28.3, 25.3, 23.2, 21.7, 21.6, 21.4, 14.5.

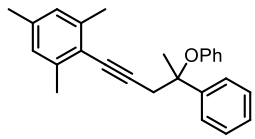
1-Methyl-3-(4-nitrophenoxy)-1-phenyl-1,2-dihydronaphthalene (2.48)



Dihydronaphthalene **2.48** was synthesized following general procedure **D** starting from 11-nitro-4-((phenylethynyl)oxy)benzene (48 mg, 0.2 mmol) and α-methylstyrene (52 µL, 0.4 mmol). The crude product was purified by flash chromatography affording **2.48** as yellow sticky oil, (26 mg, 37%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.14 – 8.05 (m, 2H), 7.32 – 7.25 (m, 3H), 7.22 (ddd, *J* = 7.0, 6.2, 1.8 Hz, 2H), 7.16 (tdd, *J* = 6.7, 3.1, 1.8 Hz, 4H), 7.05 (dd, *J* = 7.2, 1.7 Hz, 1H), 6.86 – 6.76 (m, 2H), 5.98 (d, *J* = 1.6 Hz, 1H), 2.90 (d, *J* = 16.9 Hz, 1H), 2.76 (dd, *J* = 16.8, 1.7 Hz, 1H), 1.80 (s, 3H). **^{13}C-NMR (**101 MHz, $CDCl_3$) δ 161.3, 153.5, 147.7, 143.4, 139.9, 133.7, 128.4, 127.4, 127.4, 127.2, 126.9, 126.8, 126.7, 126.0, 118.9, 111.1, 44.5, 42.1, 28.0.

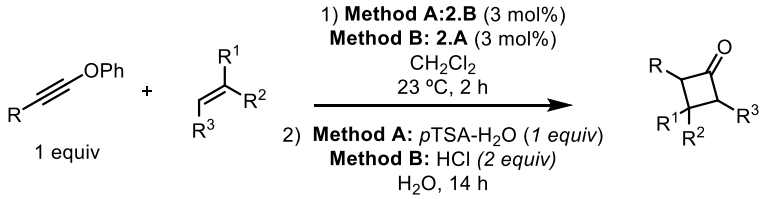
1,3,5-Trimethyl-2-(4-phenoxy-4-phenylpent-1-yn-1-yl)benzene (2.49)



Homopropargyl ether was synthesized following general procedure **D** starting from 1,3,5-trimethyl-2-(phenoxyethynyl)benzene (71 mg, 0.3 mmol) and α-methylstyrene (78 µL, 0.6 mmol). The crude product was purified by flash chromatography affording **2.49** as yellow oil, (54 mg, 50%).

^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.60 – 7.54 (m, 2H), 7.41 – 7.34 (m, 2H), 7.33 – 7.28 (m, 1H), 7.19 – 7.07 (m, 2H), 6.95 – 6.88 (m, 1H), 6.86 – 6.80 (m, 2H), 6.78 – 6.67 (m, 2H), 3.22 (d, *J* = 16.6 Hz, 1H), 3.13 (d, *J* = 16.6 Hz, 1H), 2.29 (s, 6H), 2.26 (s, 3H), 1.91 (s, 3H). **^{13}C-NMR (**126 MHz, $CDCl_3$) δ 155.8, 144.6, 140.3, 137.1, 129.0, 128.5, 127.6, 127.5, 126.2, 121.9, 120.6, 120.5, 93.6, 81.6, 80.9, 36.4, 24.0, 21.4, 21.1.

*General procedure E: one-pot synthesis of cyclobutanones **2.45** starting from ynol ethers **2.42** or **2.46.***



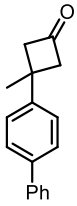
The ynol ether (0.2 mmol, 1 equiv) was dissolved in CH_2Cl_2 (0.2 mL, 1 M). The needed alkene (**Method A:** 0.6 mmol, 3 equiv, **Method B:** 0.4 mmol, 2 equiv) was added followed by the catalyst (**Method A:** [(JohnPhos)AuNCMe]SbF_6 (**2.B**, 3 mol%, 4.6 mg); **Method B:** by [(*t*BuXPhos)AuNCMe]BAr_4^F (**2.A**, 3 mol%, 9.2 mg). The resulting mixture was stirred at 23 °C for 3 h. The reaction was monitored by GC-MS or UHPLC-MSD. Once completed the acid was added (**Method A:** p-TSA·H_2O (38 mg, 0. 2 mmol, 1 equiv); **Method B:** 2M HCl in H_2O (200 µl, 0.4 mmol, 2 equiv), followed by 0.1 mL of H_2O. The reaction was stirred overnight and then diluted with CH_2Cl_2 and the organic phases was washed three times with H_2O. The collected organic phase was dried over Na_2SO_4 and the solvent removed under reduced pressure. The crude product was purified by flash chromatography on silica gel using a pentante:Et_2O 20:1 as eluent and affording cyclobutanone **2.45**

3-Methyl-3-phenylcyclobutan-1-one (2.45b)

Cyclobutanone **2.45b** was obtained synthesized following general procedure **E – Method A** starting from (ethynyloxy)benzene (23.6 mg, 0.2 mmol) and α-methylstyrene (78 µL, 0.6 mmol). The crude product was purified by flash chromatography affording **2.45b** as a colorless oil (22 mg, 69%). The same reaction was performed also on 1.0 mmol scale starting from (ethynyloxy)benzene (118 mg, 1 mmol) and α-methylstyrene (390 µL, 3 mmol) and using p-TSA·H_2O (323 mg, 1.7 mmol, 1.7 equiv). and 106 mg of **2.45b** were obtained (66% yield).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.42 – 7.29 (m, 4H), 7.29 – 7.21 (m, 2H), 3.58 – 3.39 (m, 2H), 3.25 – 3.00 (m, 2H), 1.61 (s, 3H). **^{13}C-NMR (**101 MHz, $CDCl_3$) δ 206.9, 148.4, 128.7, 126.4, 125.8, 59.4, 34.1, 31.2. Data in agreement with the one reported in literature[168]

3-([1,1'-Biphenyl]-4-yl)-3-methylcyclobutan-1-one (2.45c)

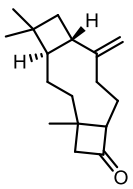


Cyclobutanone **2.45c** was obtained synthesized following general procedure **E – Method A** starting from (ethynyloxy)benzene (23.6 mg, 0.2 mmol) and 4-(prop-1-en-2-yl)-1,1'-biphenyl (117 mg, 0.6 mmol). The crude product was purified by flash chromatography affording **2.45c** as a white solid (26 mg, 56%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.65 – 7.56 (m, 4H), 7.50 – 7.43 (m, 2H), 7.43 – 7.39 (m, 2H), 7.39 – 7.32 (m, 1H), 3.62 – 3.39 (m, 2H), 3.26 – 3.04 (m, 2H), 1.67 (s, 3H). **^{13}C-NMR (**101 MHz, $CDCl_3$) δ 206.7, 147.4, 140.8, 139.4, 128.9, 127.4, 127.2, 126.3, 59.5, 33.9, 31.1.

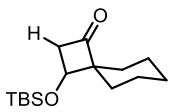
(1R,11S)-4,13,13-Trimethyl-10-methylenetricyclo[9.2.0.04,7]tridecan-6-one (2.45a)

168 K. S. Petersen, B. M. Stoltz, *Tetrahedron* **2011**, *67*, 4352–4357.



Cyclobutanone **2.45a** was obtained synthesized following general procedure **E – Method A** starting from(ethynyloxy)benzene (23.6 mg, 0.2 mmol) and β-Caryophyllene (170 μl, 0.6 mmol) The crude product was purified by flash chromatography affording **2.45a** as a yellow oil 3:1 mixture of regioisomers (34 mg, 68%). See above for the characterization.

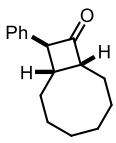
3-((tert-Butyldimethylsilyl)oxy)spiro[3.5]nonan-1-one (2.45e)



Cyclobutanone **2.45e** was obtained synthesized following general procedure **E – Method A** starting from (ethynyloxy)benzene (12 mg, 0.1 mmol) and tert-butyl(cyclohexylidenemethoxy)dimethylsilane (68 mg, 0.3 mmol). The crude product was purified by flash chromatography affording **2.45e** as a brown oil (11 mg, 41%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.14 (dd, *J* = 6.9, 4.7 Hz, 1H), 3.22 (dd, *J* = 17.8, 6.9 Hz, 1H), 2.86 (dd, *J* = 17.8, 4.7 Hz, 1H), 1.76 – 1.58 (m, 5H), 1.58 – 1.48 (m, 1H), 1.44 (dt, *J* = 9.1, 2.0 Hz, 2H), 1.34 – 1.21 (m, 2H), 0.90 (s, 9H), 0.09 (s, 3H), 0.07 (s, 3H). **^{13}C-NMR (**101 MHz, $CDCl_3$) δ 214.4, 68.2, 67.5, 52.8, 31.7, 26.5, 25.9, 25.8, 22.8, 22.6, 18.2, -4.6, -4.9. **HRMS** (ESI) *m/z* calculated for $C_{15}H_{28}NaO_2Si^+$ $[M+Na]^+$: 291.1751, found: 291.1744.

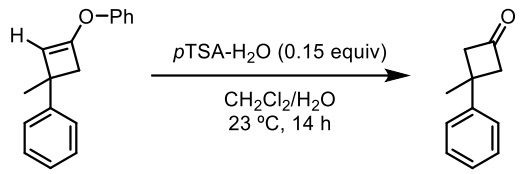
10-Phenylbicyclo[6.2.0]decan-9-one (2.45c)



Cyclobutanone **2.45c** was obtained synthesized following general procedure **E – Method B** starting from (phenoxyethynyl)benzene (39 mg, 0.2 mmol) and (Z)-cyclooctene (52 μl, 0.4 mmol). The crude product was purified by flash chromatography affording **2.45a** as a yellow oil 4:1 mixture of diastereoisomer (34 mg, 75%). The major diastereoisomer have been assigned by NOESY correlation. M = major diastereoisomer; m = minor diastereoisomer.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.27 (m, 2H, M+m), 7.27 – 7.19 (m, 3H, M+m), 7.18 – 7.11 (m, 0.4H, m), 4.74 (dd, *J* = 10.9, 2.6 Hz, 0.25H, m), 3.98 (dd, *J* = 7.9, 2.7 Hz, 1H, M), 3.30 (ddt, *J* = 12.4, 9.8, 2.6 Hz, 0.25H, m), 3.19 (ddt, *J* = 11.9, 9.5, 2.4 Hz, 1H, M), 2.89 – 2.75 (m, 0.25H, m), 2.57 (dddd, *J* = 11.9, 10.0, 7.9, 2.4 Hz, 1H, M), 2.11 – 1.91 (m, 2H, M+m), 1.90 – 1.80 (m, 1H, M), 1.80 – 1.54 (m, 3H, M+m), 1.52 – 1.44 (m, 0.4H, m), 1.44 – 1.33 (m, 2H, M+m), 1.33 – 1.09 (m, 2H, M+m). **^{13}C-NMR (**101 MHz, $CDCl_3$) δ 212.4 (M), 211.2 (m) 136.7 (M), 134.1 (m), 129.2 (M), 128.8 (M), 128.5 (M), 127.2 (m), 127.1 (M), 69.3 (M), 66.3 (m), 61.6 (M), 60.4 (m), 38.0 (M), 36.7 (m), 30.7 (m), 29.9 (M), 29.8 (m), 29.6 (M), 28.4 (M), 27.9 (m), 26.2 (m), 26.1 (M), 25.9 (m), 25.8 (m), 25.3 (M), 24.1 (M), 20.7 (m).

Hydrolysis of 2.44a o form cyclobutanone 2.45b



Cyclobutene **2.44a** (47 mg, 0.2 mmol) was dissolved in CH_2Cl_2 (0.2 mL) and water (0.1 mL). *p*-toluenesulfonic acid monohydrate (5.7 mg, 0.03 mmol) was then added and the biphasic mixture was vigorously stirred at 23°C until complete conversion was observed by monitoring the reaction by TLC. The reaction was then diluted with CH_2Cl_2 and the organic phases was washed three times with H_2O. The collected organic phase was dried over Na_2SO_4 and the solvent removed under reduced pressure. The crude product was purified by flash chromatography on silica gel using a pentane:Et_2O 20:1 as eluent and affording **2.45b** as a colorless oil (30 mg, 94%).

Theoretical DFT Calculations

Computational Methods

Calculations were performed by means of the Gaussian 09 suite of programs.[169] DFT was applied using B3LYP[170]. The LANL2DZ basis set[171] was utilized to describe Au with ECP and additional polarization function (ζ_f = 1.050 for Au,[172]). The 6-31G(d,p) basis set[173] was employed for all remaining atoms (C, H, O and P). Full geometry optimizations were carried out in CH_2Cl_2, through an implicit solvent SMD.[174] The stationary points were characterized by vibrational analysis.

169 Gaussian 09, Revision B.1, Frisch, M. J., Trucks, G. W., Schlegel, H. B., Scuseria, G. E., Robb, M. A., Cheeseman, J. R., Scalmani, G., Barone, V., Mennucci, B., Petersson, G. A., Nakatsuji, H., Caricato, M., Li, X., Hratchian, H. P., Izmaylov, A. F., Bloino, J., Zheng, G., Sonnenberg, J. L., Hada, M., Ehara, M., Toyota, K., Fukuda, R., Hasegawa, J., Ishida, M., Nakajima, T., Honda, Y., Kitao, O., Nakai, H., Vreven, T., Montgomery, J. A., Peralta, Jr. J. E., Ogliaro, F., Bearpark, M., Heyd, J. J., Brothers, E., Kudin, K. N., Staroverov, V. N., Kobayashi, R., Normand, J., Raghavachari, K., Rendell, A., Burant, J. C., Iyengar, S. S., Tomasi, J., Cossi, M., Rega, N., Millam, J. M., Klene, M., Knox, J. E., Cross, J. B., Bakken, V., Adamo, C., Jaramillo, J., Gomperts, R., Stratmann, R. E., Yazyev, O., Austin, A. J., Cammi, R., Pomelli, C., Ochterski, J. W., Martin, R.L., Morokuma, K.,, Zakrzewski, V. G., Voth, G. A., Salvador, P., Dannenberg, J. J., Dapprich, S., Daniels, A. D., Farkas, Ö., Foresman, J. B., Ortiz, J. V., Cioslowski, J., Fox, D. J. Gaussian, Inc., Wallingford CT **2009**.

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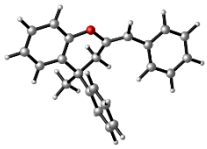
174 A. V. Marenich, C. J. Cramer, D. G. Truhlar, *J. Phys. Chem. B.* **2009**, *113*, 6378–6396.

Transition states were identified by the presence of one imaginary frequency while minima by a full set of real frequencies. The connectivity of the transition states was confirmed by relaxing each transition state towards both the reactant and the product. Reported energies are potential energies (E) and free energies (G) in solution, computed at 298 K and 1 atm.

Computed Structures and Energies

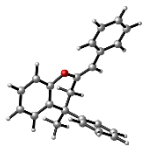
E-2.47a



E = -963.742061 Hartrees

G = -963.426467 Hartrees

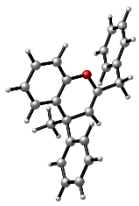
Z-2.47a



E = -963.747967 Hartrees

G = -963.431486 Hartrees

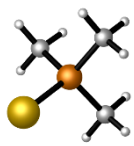
Endo-2.47a



E = -963.746057 Hartrees

G = -963.431189 Hartrees

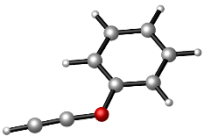
AuPMe3



E = -596.467300 Hartrees

G = -596.386432 Hartrees

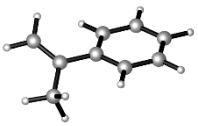
2.42a



E = -383.595111 Hartrees

G = -383.514415 Hartrees

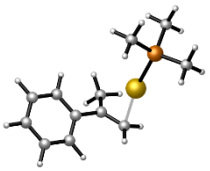
2.43a



E = -348.983441 Hartrees

G = -348.854198Hartrees

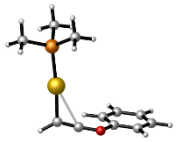
Int1a



E = -945.485454 Hartrees

G = -945.257300 Hartrees

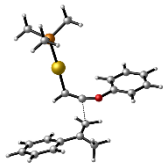
Int2a



E = -980.101491 Hartrees

G = -979. 920683 Hartrees

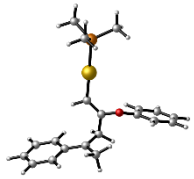
TS2a-3a



E = -1329.082841 Hartrees

G = -1328.750289 Hartrees

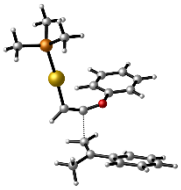
Int3a



E = -1329,116422 Hartrees

G = -1328.778309 Hartrees

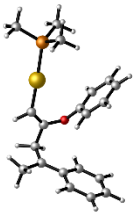
TS2a-3b



E = -1329.081996 Hartrees

G = -1328.748126 Hartrees

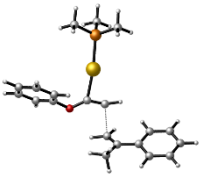
Int3b



E = -1329.114499 Hartrees

G = -1328.776556 Hartrees

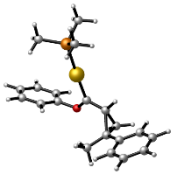
TS2a-4a



E = -1329.066469 Hartrees

G = -1328.73645 Hartrees

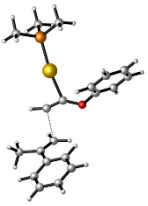
Int4a



E = -1329.134230 Hartrees

G = -1328.795054 Hartrees

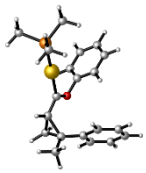
TS2a-4b



E = -1329.066219 Hartrees

G = -1328.735176 Hartrees

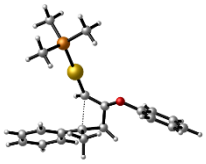
Int4b



E = -1329.136242 Hartrees

G = -1328.796505 Hartrees

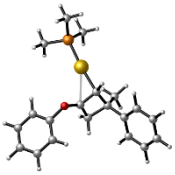
TS3a-5a



E = -1329.105228 Hartrees

G = -1328.766771Hartrees

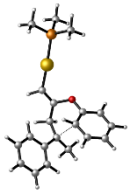
Int5a



E = -1329.140088 Hartrees

G = -1328.801754 Hartrees

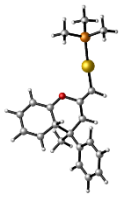
TS3a-6a



E = -1329.101443 Hartrees

G = -1328.774201 Hartrees

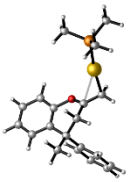
Int6a



E = -1329.115970 Hartrees

G = -1328.774201 Hartrees

Int9a



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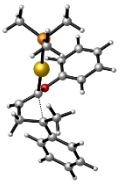
G = -1328.843406 Hartrees

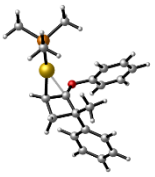
TS4a-7a



E = -1329.086200 Hartrees

G = -1328.750022 Hartrees

Int7a



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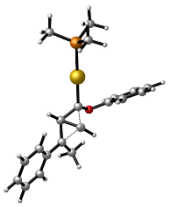
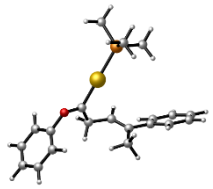
TS4a-8a



E = -1329.084923 Hartrees

G = -1328.745549 Hartrees

Int8a



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G = -1328.797298 Hartrees

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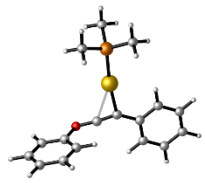

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G = -1210.912826 Hartrees

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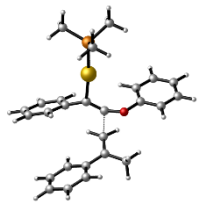

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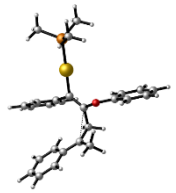
G = -1559.738133 Hartrees

Int11a



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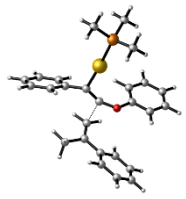
G = -1559.7764342 Hartrees

TS10a-11b



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G = -1559.736920 Hartrees

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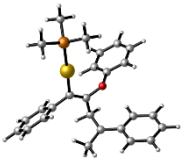
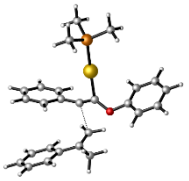


E = -1560.175714 Hartrees

G = -1559.765577 Hartrees

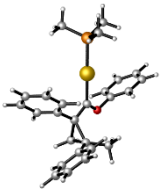
TS10a-12a



E = -1560.142362 Hartrees

G = -1559.736200 Hartrees

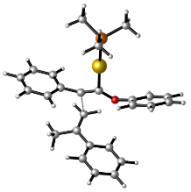
Int12a



E = -1560.187043 Hartrees

G = -1559.774520 Hartrees

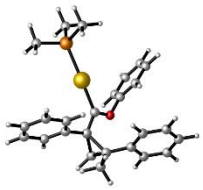
TS10a-12b



E = -1560.141184 Hartrees

G = -1559.735026 Hartrees

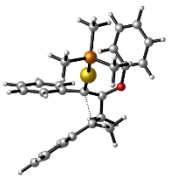
Int12b



E = -1560.190329 Hartrees

G = -1559.779063 Hartrees

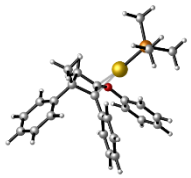
TS11a-13a



E = -1560.156474 Hartrees

G = -1559.742500 Hartrees

Int13a



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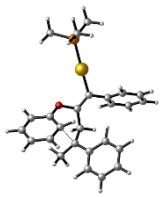
G = -1559.778369 Hartrees

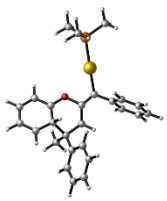
TS11a-14a



E = -1560.164042 Hartrees

G = -1559.748998 Hartrees

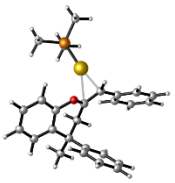
Int14a



E = -1560.178410 Hartrees

G = -1559.762132 Hartrees

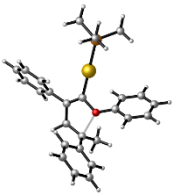
(E)-Int15a



E = -1560.242023 Hartrees

G = -1559.824770 Hartrees

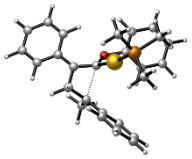
Int16a



E = -1560.182048 Hartrees

G = -1559.768789 Hartrees

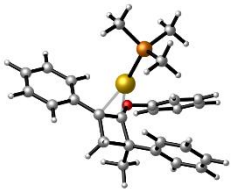
TS16a-17a



E = -1560.162576 Hartrees

G = -1559.749074 Hartrees

Int17a



E = -1560.203229 Hartrees

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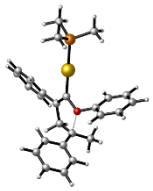
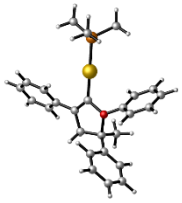
TS16a-18a



E = -1560.181746 Hartrees

G = -1559.766609 Hartrees

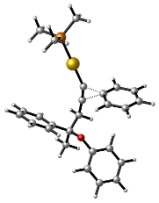
Int18a



E = -1560.182487 Hartrees

G = -1559.767991 Hartrees

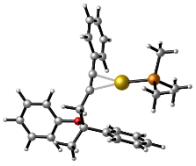
TS18a-19a



E = -1560.148883 Hartrees

G = -1559.738315 Hartrees

Int19a



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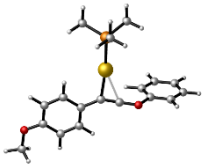
G = -1559.781765 Hartrees

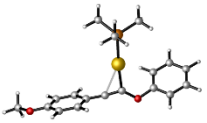
Int20a



E = -1674.680629 Hartrees

G = 1674.249155 Hartrees

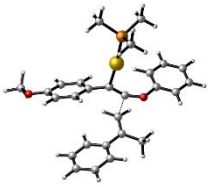
Int20a'



E = -1674.678613 Hartrees

G = 1674.248496 Hartrees

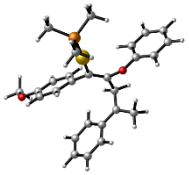
TS20a-21a



E = -1674.668192 Hartrees

G = 1674.232423 Hartrees

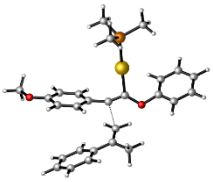
Int21a



E = -1674.700136 Hartrees

G = 1674.259394 Hartrees

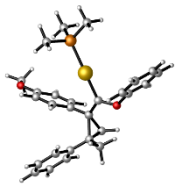
TS20a-22a



E = -1674.672595 Hartrees

G = 1674.236355 Hartrees

Int22a



E = -1674.712284 Hartrees

G = 1674.269795 Hartrees

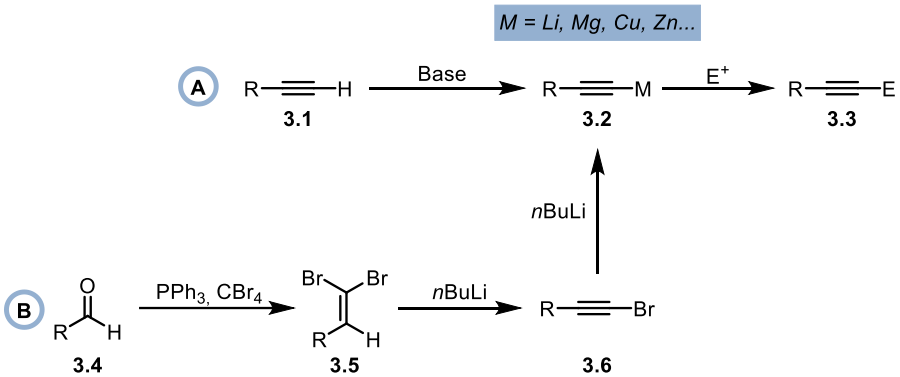
Chapter 3

Iridium (III)-Catalyzed β-Alkynylation of Aliphatic Oximes

Introduction

Classical Methods for the Alkynylation Reaction

Classically, the transfer of an alkyne unit to form internal alkynes relies on the relatively low pKa of the terminal proton (pKa = 24-26). By treatment with a strong base the alkyne can be metalated and then react with an electrophile -usually alkyl halides, ketones or imines - allowing the synthesis of a wide variety of product also in asymmetric fashion (Scheme 3.1a).

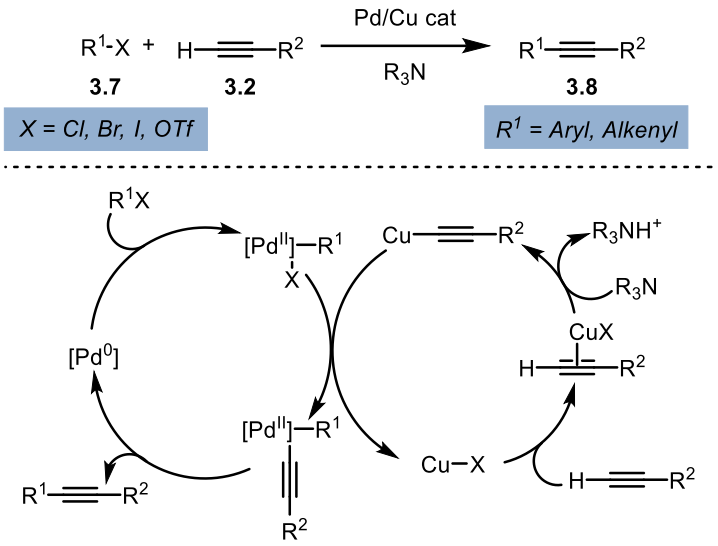


Scheme 3.1. Generation of metal-acetylides via (a) deprotonation or (b) Corey-Fuchs homologation and its trapping with electrophiles.

Alkynyl lithium compounds **3.2** can be also obtained starting from aldehydes in the two steps Corey-Fuchs homologation[175] (Scheme 3.1b). The aldehyde first undergoes alkenylation to form the 1,1-dibromoalkene **3.5**, which upon treatment with one equiv of *n*BuLi, gives bromoalkyne **3.6**. Reaction of **3.6** with a second equiv of *n*BuLi forms **3.2** by lithium-halogen exchange.

Besides these stoichiometric methods, the catalytic formation of metal-acetylides is central in cross-coupling reaction[176], being the most prominent example the Sonogashira coupling[177] (Scheme 3.2). This reaction allows the formation of a C(sp^2)-C(sp) bond between an aryl or alkenyl-(pseudo)halide and a terminal alkyne. Mechanistically this reaction occurs under the general cross-coupling mechanistic scheme with the main Pd-catalytic cycle passing through an oxidative addition/transmetalation/reductive elimination sequence. The transmetalating partner is provided by a second catalytic cycle in which the Cu-acetylide is formed.

175 E. J. Corey, P. L. Fuchs, *Tetrahedron Lett.*, 1972, 3769-3772.
176 E. I. Negishi, L. Anastasia, *Chem. Rev.* **2003**, *103*, 1979–2017.
177 R. Chinchilla, C. Nájera, *Chem. Soc. Rev.* **2011**, *40*, 5084–5121.



Scheme 3.2. Mechanism of the Sonogashira coupling.

Alkynylation *via* C-H Activation

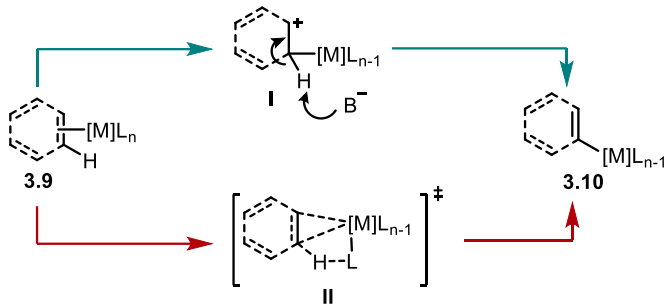
Despite their wide application and versatility, the alkynylation methods just presented highlight two major drawbacks: 1) catalytic methods of metalation of the terminal alkyne are limited mainly to copper. 2) The target carbon on the coupling partner needs to be pre-functionalized. On one side the pre-functionalization guarantees high selectivity in the coupling reaction, but at the same time presents intrinsic limitations on the range of accessible substrates.

In this sense is highly desirable to develop catalytic methods that directly transform C-H bonds into the desired products, and since the pioneering stoichiometric examples of C-H activation mediate by transition metals back in the '60s the repertoire of catalytic C-H functionalization is continuously growing[178]. The presentation of a complete picture of the C-H activation and functionalization field is out of the scope of this introduction, so just some mechanistic details relevant for the following discussion will be provided.

Generally, the mechanism of the transition metal-catalyzed C-H functionalization reaction, and in this sense, C-H alkynylation is not an exception, can be divided in two section: 1) the C-H activation step in which the C-H bond is metalated. 2) The functionalization of the C-M bond to form the final C-C or C-X bond.

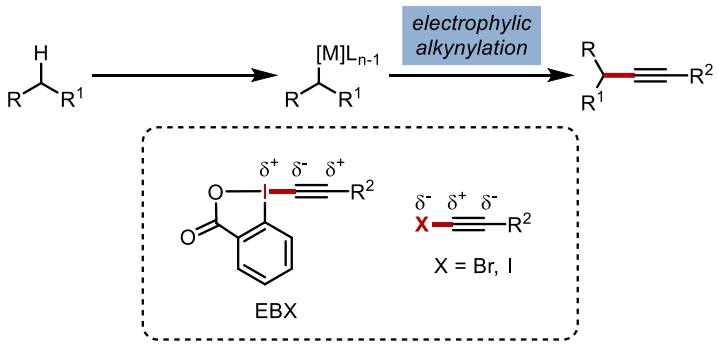
178 For selected reviews on C-H functionalization: a) F. Kakiuchi, N. Chatani, *Adv. Synth. Catal.* **2003**, *345*, 1077–1101. b) J. Yamaguchi, A. D. Yamaguchi, K. Itami, *Angew. Chem. Int. Ed.* **2012**, *51*, 8960–9009. c) T. Cernak, K. D. Dykstra, S. Tyagarajan, P. Vachal, S. W. Krska, Chem. Soc. Rev. 2016, 45, 546–576.

Regarding the C-H activation step with late transition metals in high oxidation state, two paths are usually followed. Firstly, after pre-coordination of the catalyst to the π-system of a C(sp^2)-H bond, this can be metalated in a S_EAr-like process where σ-complex **3.I** is formed first (Scheme 3.3, red path), which is followed by abstraction of the proton by an external base to form **3.10**. Alternatively, the metalation and the deprotonation can occur in a concerted manner with a ligand on the metal center acting as internal base passing through a cyclic 4-membered transition state **3.II** (Scheme 3.3, green path).



Scheme 3.3. Mechanism of the C-H metalation with late transition metals.

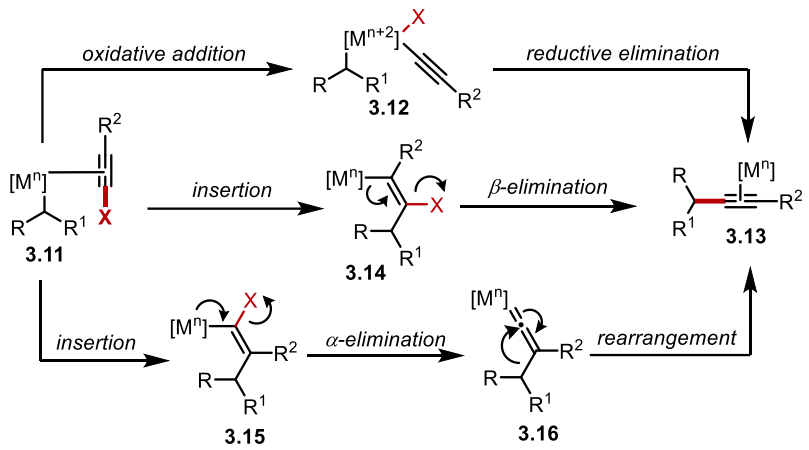
The most common approach to form the final C(sp)-C bond is by an electrophilic alkynylation with a pre-functionalized alkynyl derivative such as ethynylbenziodoxolones (EBX) or a haloalkyne. This approach is usually denominated "inverse Sonogashira coupling" because compared to the original reaction, in this transformation the pre-activated site is switched from the sp^2 carbon to the alkyne. Despite the inevitable drawback of the stoichiometric generation of byproducts due to the elimination of the living group, the use of a pre-oxidized alkyne prevents both alkyne-homocoupling and the use of external oxidants to close the redox neutral cycle, and consequently allows a wide functional group tolerance.



Scheme 3.4.electrophylic alkynylation and alkynylating agents.

After coordination to the metal center, three possible mechanism for the electrophilic alkynylation branch out.

Product **3.13** can be formed in an oxidative addition/reductive elimination sequence (Scheme 3.5, top). This path seems to be more feasible for EBX alkynes because of their oxidative character, although the occurrence of this mechanism for haloalkynes has not conclusively ruled out yet. Considering the polarization of the C-X bond, haloalkynes more commonly undergo insertion reaction into the C-M bond of **3.11** to form **3.14** that delivers the alkynylated product *via* β-halide elimination[179] (Scheme 3.5, middle). The 3-center-4-electron bond in EBX reagents causes an inversion of charge distribution compared to haloalkynes, thus a third possible path opens up where the initial insertion on the C-M bond occurs with inverted regiochemistry (Scheme 3.5, bottom), to achieve the final product by an α-elimination of iodobenzoate to generate the metal-vinylidene **3.16** that upon Fritsch-Butenberg-Wiechell-type rearrangement forms **3.13**.



Scheme 3.5. Possible mechanisms for the transition metal catalyzed C-H alkynylation with haloalkynes or EBX reagents.

Besides the inverse Sonogashira approach, that requires the functionalization of the alkyne partner prior to the reaction, the direct coupling of a C-H bond and a terminal alkyne was achieved in presence of a stoichiometric oxidant to activate the alkyne and/or close the catalytic cycle. This process is normally termed cross-dehydrogenative-coupling and ideally can be the most atom economical and environmentally sustainable option when just oxygen or air itself is used as oxidant.[180]

Probably the main challenge in C-H functionalization is the discrimination of the different C-H bond on the substrate. In some cases, the intrinsic reactivity of a specific C-H bond above the

179 For a detailed study on the effect of the metal in the β-elimination: B. E. Haines, R. Sarpong, D. G. Musaev, *J. Am. Chem. Soc.* **2018**, *140*, 10612–10618.
180 For a review see: S.A.Girard, T. Knauber, C.-J. Li, *Angew.Chem.Int. Ed*. **2014**, *53*,74–100

others in the molecule can be exploited for this purpose, but this limits the substrate scope to a specific group of substrates. In addition, relying on the higher reactivity of one position intrinsically restricts the number of positions of a given substrate that can be functionalized.

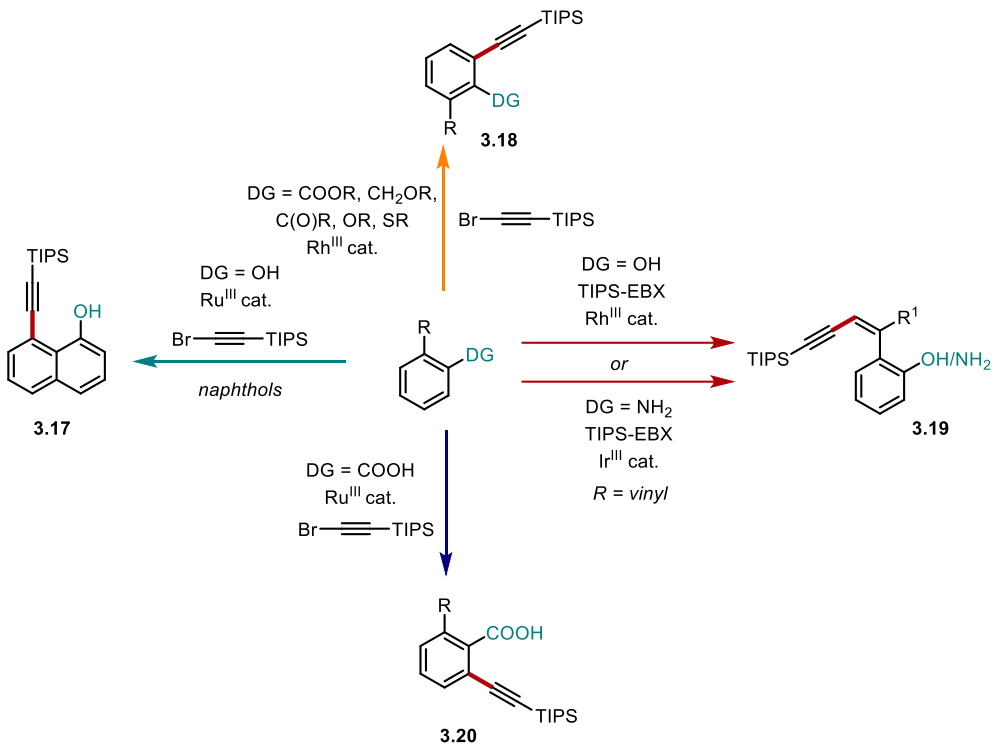
For transition metal catalyzed C-H activation, the introduction of a Lewis basic directing group in proximity of the target C-H bond is a valuable and widely successful option.

The first chelation-assisted C-H alkynylation was reported by Chatani and Tobisu in 2009 using a simple acetamide as directing group for the palladium-catalyzed *ortho*-functionalization of arenes[181]. Since then, the number of directing groups, transition metal catalysts and substrates has enormously grown for C(sp^2)-H alkynylation[182]. Due to general compatibility of nitrogen-containing groups with late transition metals and their mild basic character, amides or *N*-heterocycles are probably the most abundant directing groups used in C-H activation, but also derivatives such as nitrones, and oximes have been used in this context.[183]

Ideally, the directing group has to be easily removed or transformed in a suitable handle for further transformation. Thus, the use of common functional groups such as free amines, alcohols or carbonyl compounds bypasses the two step sequence of installation/removal of the directing group and gains consequently in step economy.

In this sense, significant progresses have been made in the context of C(sp^2)-H alkynylation (Scheme 3. ***6***). For example, ortho-vinylphenols can direct the alkynylation on the vinylic group using a modified EBX reagent and Ru(III) as catalyst[184] (Scheme 3. ***6***, red path). Free anilines are much more challenging directing groups compared to phenols. Nevertheless, an analogous vinyl alkynylation of *ortho*-vinylanilines **3.19** was achieved with an Ir(III) catalyst and a catalytic amount of pyridine to avoid product inhibition[185] (Scheme 3. ***6***, red path). Phenols cannot direct the ortho alkynylation on the aromatic ring because this would imply the unlikely formation of a 4-membered metallacycle. However 1-naphtols are efficient substrates for the Ru(III)-catalyzed peri-alkynylation using a bromoalkyne[186] (Scheme 3. ***6***, green path). Replacing the hydroxyl group for a carboxylic acid the alkynylation occurs under similar conditions, but this time selectively at the *ortho*-position (Scheme 3. ***6***, blue path).

181 M. Tobisu, Y. Ano, N. Chatani, *Org. Lett.* **2009**, *11*, 3250–3252.
182 For a recent review on directed transition metal-catalyzed C-H alkynylation: L. D. Caspers, B. J. Nachtsheim, *Chem.: Asian J.* **2018**, *13*, 1231–1247.
183 For the application of different nitrogen containing directing group in C(sp2)-H alkynylation see: F. Xie, Z. Qi, S. Yu, X. Li, *J. Am. Chem. Soc.* **2014**, *136*, 4780–4787.
184 P. Finkbeiner, U. Kloeckner, B. J. Nachtsheim, *Angew. Chem. Int. Ed.* **2015**, *54*, 4949–4952.
185 L. D. Caspers, P. Finkbeiner, B. J. Nachtsheim, *Chem. Eur. J.* **2017**, *23*, 2748–2752.
186 E. Tan, A. I. Konovalov, G. A. Fernández, R. Dorel, A. M. Echavarren, *Org. Lett.* **2017**, *19*, 5561–5564.



Scheme 3. 6. Examples of transitions metal catalyzed directed C(sp2)-H alkynylation.

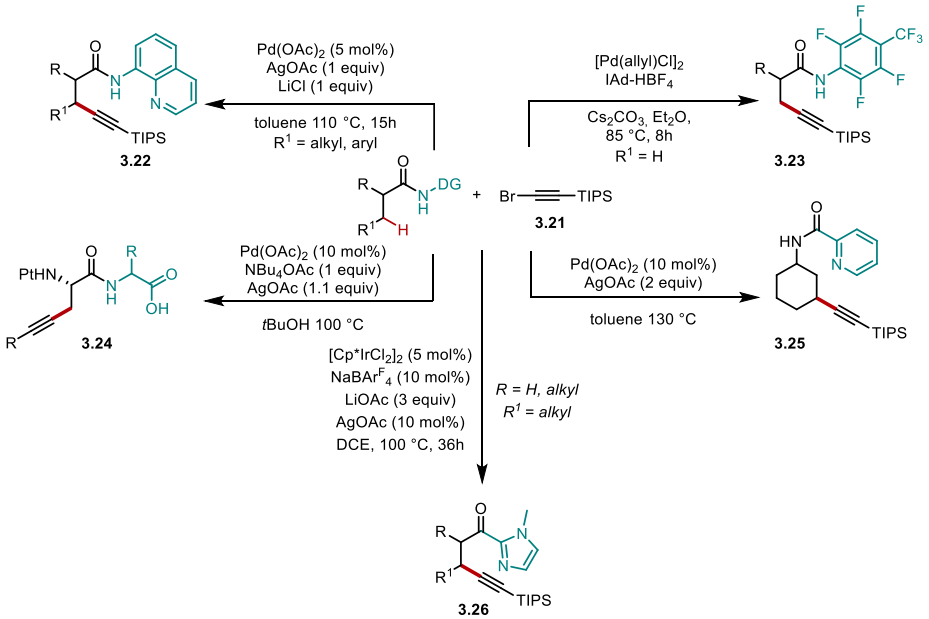
To further expand the scope towards synthetic useful directing group, our group recently reported the rhodium(III)-catalyzed alkynylation of C(sp^2)-H bond using TIPS-protected bromoacetylene directed by ethers, esters, ketones and sulfur containing functional groups[187] (Scheme 3. ***6***, orange path). Mechanistic studies on this reaction suggested that the C-H activation occurs in a concerted manner and it is followed by an electrophilic alkynylation occurring via insertion/β-elimination sequence.

Despite the lower bond dissociation energy,[188] the metalation of aliphatic C(sp^3)-H bonds is more challenging compared to the one of C(sp^2)-H bonds. In addition, C(sp^3)-H bonds are ubiquitous in organic molecules and the selective activation of the target C-H bond is hence more difficult. Consequently, the number of C(sp^3)-H alkynylation reactions is very limited compared to the significant advances achieved in the C(sp^2)-H counterpart.

The first example of a transition metal catalyzed C-H alkynylation on aliphatic carbons, reported by Chatani in 2011, was the Pd(II)-catalyzed β-functionalization of amides directed by 8-aminoquinoline to form **3.22** (Scheme 3.7).[189] The reaction allows the functionalization of a

187 E. Tan, O. Quinonero, M. Elena De Orbe, A. M. Echavarren, *ACS Catal.* **2018**, *8*, 2166–2172.
188 S. J. Blanksby, G. B. Ellison, *Acc. Chem. Res.* **2003**, *36*, 255–263.
189 Y. Ano, M. Tobisu, N. Chatani, *J. Am. Chem. Soc.* **2011**, *133*, 12984–12986.

series of masked carboxylic acids selectively on secondary β-C(sp^3)-H bonds. Additionally, the directing group can be efficiently recovered upon treatment of the product under acidic conditions. The selective targeting of primary C-H bonds in β-position of amides (**3.23**) was then achieved by switching the catalyst from a Pd(II) to Pd(0) catalyst coupled with a specific NHC or phosphine ligand (Scheme 3.7)[190]. Also, the bidentate directing group was replaced by perfluoroarylamide. In these examples the alkynylation step is probably occurring through an oxidative addition/reductive elimination sequence with the bromoalkyne (see Scheme 3.5).



Scheme 3.7. Transition metal catalyzed β- or γ-alkynylation of C(sp^3)-H carbons with haloalkynes.

The same perfluorotolylamine can be used as directing group for the β-alkynylation on the side chain of protected amino acids with different bromoalkynes using $Pd(OAc)_2$ and a pyridine based ligand.[191]

A series of natural and unnatural α -amino acids have been used to build dipeptides of general structure RHN-Ala-aa-OH (where aa is a general amino acid) and have been used as directing group in the Pd(II)-catalyzed alkynylation of the side chain of the alanine fragment[192]. The reaction is not just limited to TIPS-protected bromoalkyne and can accommodate instead

190 J. He, M. Wasa, K. S. L. Chan, J. Q. Yu, *J. Am. Chem. Soc.* **2013**, *135*, 3387–3390.
191 a) H. Fu, P. X. Shen, J. He, F. Zhang, S. Li, P. Wang, T. Liu, J. Q. Yu, *Angew. Chem. Int. Ed.* **2017**, *56*, 1873–1876. b) Q. F. Wu, P. X. Shen, J. He, X. B. Wang, F. Zhang, Q. Shao, R. Y. Zhu, C. Mapelli, J. X. Qiao, M. A. Poss, J. Q. Yu, *Science.* **2017**, *355*, 499–503.
192 T. Liu, J. X. Qiao, M. A. Poss, J. Q. Yu, *Angew. Chem. Int. Ed.* **2017**, *56*, 10924–10927.

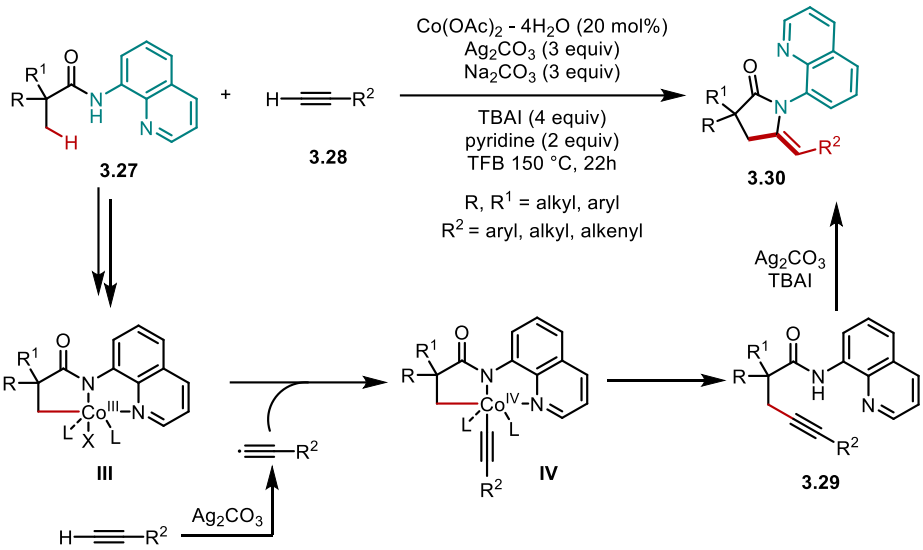
different bulky propargyl silyl ethers derived in some cases from natural occurring carbonyl compounds delivering a wide variety of compounds of general structure **3.24** (Scheme 3.7).

The uncommon γ-alkynylation of alkylamines can be achieved, by generation of the corresponding picolinamide derivative and treatment with bromoalkyne **3.21** and $Pd(OAc)_2$ to form **3.25** (Scheme 3.7). [193]

Very recently, the Ir(III)-catalyzed β-alkynylation of 2-acylimidazoles as masked esters or amides has been developed. The reaction proved to be efficient for the functionalization of secondary $C(sp^3)$-H bonds with **3.21**, however the use of other bulky bromoalkynes seems to be limited to the functionalization of $C(sp^2)$-H positions[194] (Scheme 3.7). The authors propose also in this case that the alkynylation step occurs through an oxidative addition/reductive elimination sequence.

The products of β-alkynylation of amides are in principle a suitable substrate for 5-exo-dig cyclization to form pyrrolidinones. However, in the palladium catalyzed reaction this cyclization was observed just as side reaction with generally low yields, even when silver salts were involved in stoichiometric amount. In contrast, in the C-H alkynylation of 8-aminoquinoline amides **3.27** with terminal alkynes the cyclized products **3.30** are the only one formed (Scheme 3.8). [195] According to mechanistic studies, the reaction occurs by cross-dehydrogenative-coupling via cobaltacycle **III** and **3.28** is oxidized by silver forming an alkyne radical that is intercepted by **III** to from a Co(IV) species **IV**, which upon reductive elimination releases the alkynylated amide **3.29**. A similar reaction has been developed using nickel or copper catalysts.[196]

193 V. G. Landge, A. Parveen, A. Nandakumar, E. Balaraman, *Chem. Commun.* **2018**, *54*, 7483–7486.
194 S. K. Mahato, N. Chatani, *ACS Catal.* **2020**, *9, 10*, 5173-5178.
195 J. Zhang, H. Chen, C. Lin, Z. Liu, C. Wang, Y. Zhang, *J. Am. Chem. Soc.* **2015**, *137*, 12990–12996.
196 (a) C. Lin, J. Zhang, Z. Chen, Y. Liu, Z. Liu, Y. Zhang, *Adv. Synth. Catal.* **2016**, *358*, 1778–1793. (b) J. Zhang, D. Li, H. Chen, B. Wang, Z. Liu, Y. Zhang, *Adv. Synth. Catal.* **2016**, *358*, 792–807.

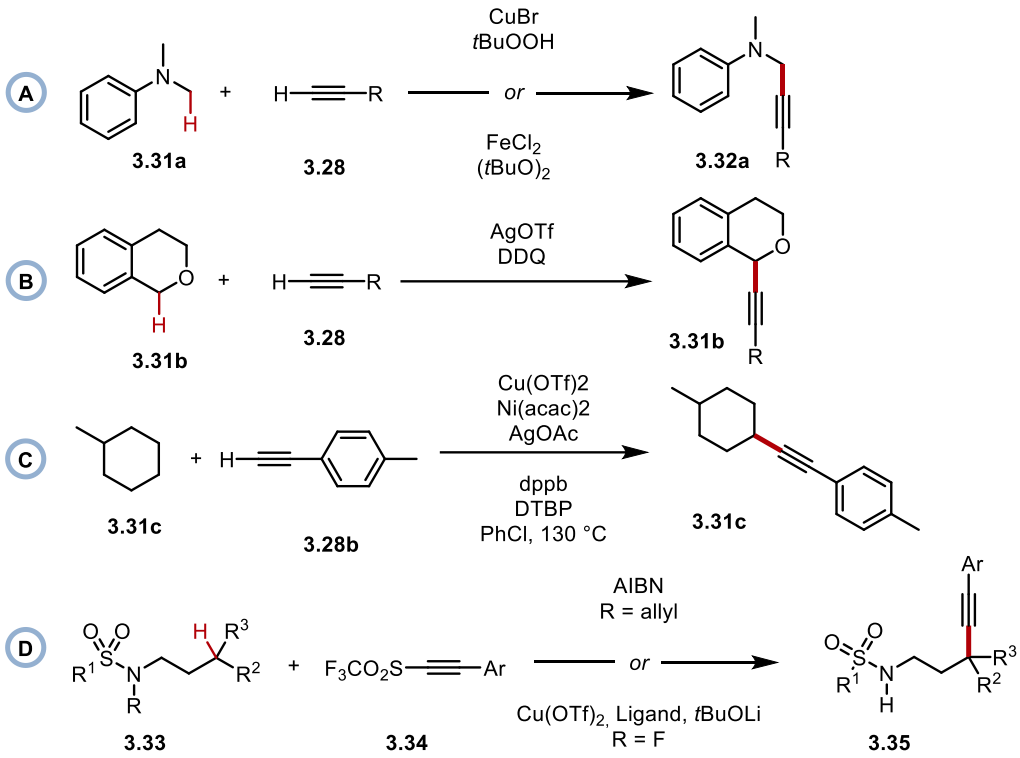


Scheme 3.8. Co(II)-catalyzed C-H alkynylation/cyclization for the synthesis of pyrrolidinones

Although the cross-dehydrogenative-coupling does not require the functionalization of the C-H bonds, the presence of a directing group or a heteroatom α- to de carbon to be coupled is necessary to facilitate its activation. In this sense, the C(sp^3)-H bond next to a nitrogen can be easily oxidized either to form the corresponding propargyl amine **3.32a** with CuBr/*t*BuOOH[197] or $FeCl_2$/(*t*BuO)$_2$[198] (Scheme 3.9a). An analogous coupling between isochromanes **3.31b** and terminal arylalkynes can be catalyzed by AgOTf and using DDQ as oxidant (Scheme 3.9b). [199]

The role of the heteroatom next to the target C-H bond is not limited to the assistance in the activation but can also be crucial to achieve good regioselectivity. An interesting example is the Cu/Ni/Ag co-catalyzed coupling of simple alkanes leading to **3.31c** (Scheme 3.9c), where the remarkable activation of C-H bond without the assistance of any heteroatom is achieved.[200] However, when the reaction is performed on asymmetric alkanes, the product is obtained as mixture of all the possible regioisomers.

197 Z. Li, C. J. Li, *J. Am. Chem. Soc.* **2004**, *126*, 11810–11811.
198 C. M. R. Volla, P. Vogel, *Org. Lett.* **2009**, *11*, 1701–1704.
199 C.-J. Li, C. A. Correia, *Heterocycles* **2010**, *82*, 555.
200 S. Tang, P. Wang, H. Li, A. Lei, *Nat. Commun.* **2016**, *7*, 1–8.



Scheme 3.9. radical oxidative alkynylation of alkenes.

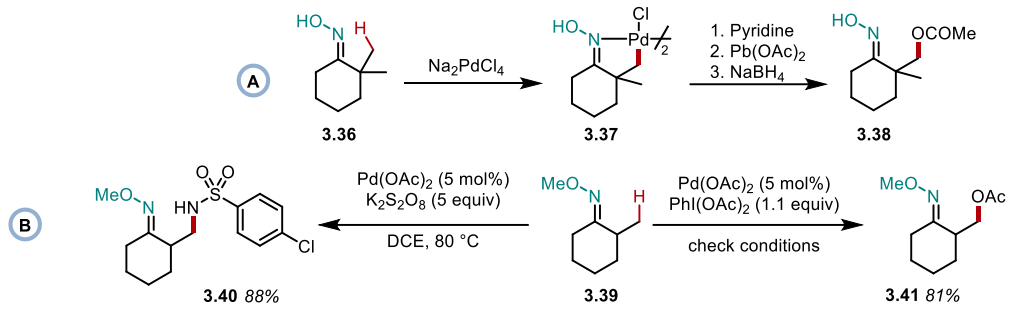
Site specific radical C(sp^3)-H alkynylation can be remotely directed by allyl or fluoro-sulfonamides with perfect regioselectivity, leading to **3.35** (Scheme 3.9d). [201]

Oximes as Directing Groups in C(sp^3)-H Functionalization

Oximes have been identified as efficient directing group in transition metal catalyzed C-H functionalization of masked ketones and alcohols. Initial experiments on stoichiometric cyclopalladiation/oxidation reaction revealed an exquisite selectivity toward the formation of the 5-membered palladacycle **3.37** via C-H activation on aliphatic carbons[202] (Scheme 3.10a). The first oxime-directed catalytic oxidation of C(sp^3)-H bonds was reported in 2004 by Sanford[203] (Scheme 3.10b). The oxime in this case acts as carbonyl equivalent allowing the selective Pd(II)-catalyzed oxidation of primary C-H bonds in β-position on the nitrogen side of the oxime in **3.39** (for the rest of the manuscript we will refer to the carbonyl side of the oxime as "*N*-side"). The high selectivity is guaranteed by the formation of the highly favored 5-

201 (a) L. Wang, Y. Xia, K. Bergander, A. Studer, *Org. Lett.* **2018**, *20*, 5817–5820. (b) Z. Yin, Y. Zhang, S. Zhang, X. F. Wu, *Adv. Synth. Catal.* **2019**, *361*, 5478–5482.
202 J. E. Baldwin, C. Nájera, M. Yus *J. Chem. Soc., Chem. Commun*., **1985**, 126-127
203 L. V. Desai, K. L. Hull, M. S. Sanford, *J. Am. Chem. Soc.* **2004**, *126*, 9542–9543.

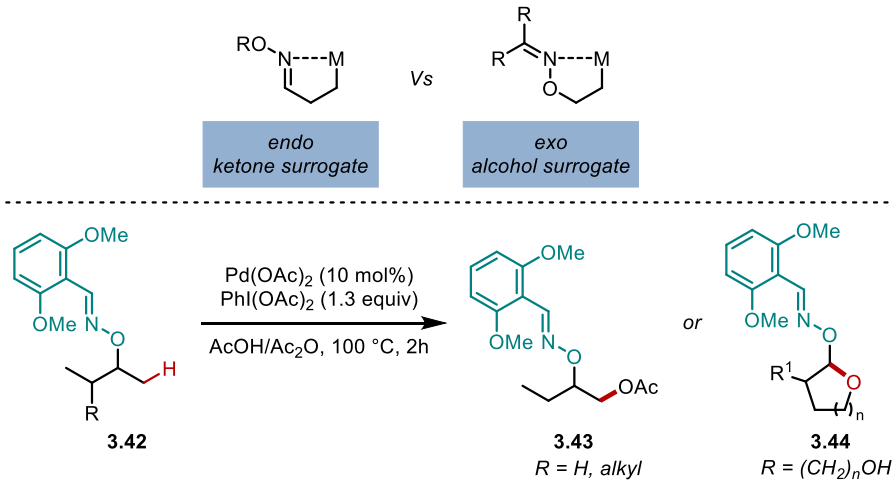
membered *endo*-palladacycle.[204] The same activation principle was then applied for the amidation of this very same position using sulfonamides and $K_2S_2O_8$ ad stoichiometric oxidant to close the catalytic cycle delivering **3.40**[205].



Scheme 3.10. A) stoichiometric cyclopalladation and subsequent oxidation. B) catalytic oxygenation and amidation of primary C(sp^3)-H bonds.

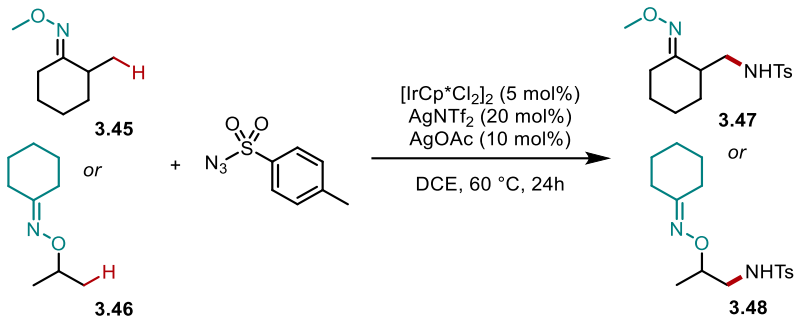
In principle, oximes can act also as alcohol surrogates and direct the C-H metalation on their oxygen side (from now "*O*-side"). The main challenge in the metalation on the *O*-side resides in the necessary formation of an *exo*-metallacycle (with the double bond of the oxime outside of the ring) less favored compared to the *endo*- one (Scheme 3.11). In order to avoid the competition between the two sides it is necessary to block the reactive β-positions on the *N*-side. Thus, Dong reported in 2012 the use of 2,6-dimethoxybenzyl oxime (**3.42**) as optimal directing group for the Pd(II)-catalyzed oxidation of masked aliphatic alcohols to generate protected 1,2-diols **3.43** (Scheme 3.11).[206] Remarkably, the reaction is not limited just to methyl C-H bonds but, under proper steric and electronic conditions, also secondary and tertiary aliphatic C-H bond can be oxidized. The authors then extended the use of this oxime for the β-selective intramolecular C-H functionalization using a free alcohol as nucleophiles, leading to the synthesis cyclic ethers **3.44**

204 The regioselectivity in cyclopalladation have been studied for several directing groups revealing that usually the endo-palladacycle is favored, see as example: R. Y. Mawo, S. Mustakim, V. G. Young, M. R. Hoffmann, I. P. Smoliakova, *Organometallics* **2007**, *26*, 1801–1810.
205 H. Y. Thu, W. Y. Yu, C. M. Che, *J. Am. Chem. Soc.* **2006**, *128*, 9048–9049.
206 Z. Ren, F. Mo, G. Dong, *J. Am. Chem. Soc.* **2012**, *134*, 16991–16994.



Scheme 3.11. Use of the oximes as alcohol surrogate.

Oximes can also be used as directing groups for the β-amidation of C(sp^3)-H bonds with sulphonyl or aryl-azides under Ir(III) catalysis.[207],[208] Also in this case either the N-side or the O-side of the oxime can be involved in the reaction by proper design of the substrate. (Scheme 3. 12).

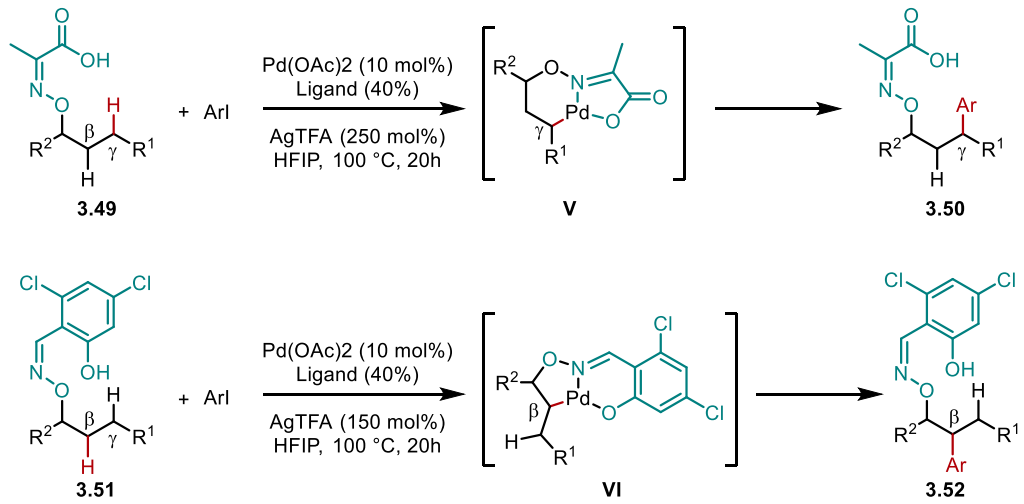


Scheme 3. 12. Use of oximes as directing groups for the Ir(III)-catalyzed amidation of C(sp^3)-H bonds.

A careful directing group design is not just crucial for the selective formation of the *exo*-metalacycle over the *endo*-one but can be also the key to access more distal position on the aliphatic chain. A very elegant example was reported recently by Yu in the context of Pd(II)-catalyzed C-H arylation of aliphatic alcohols (Scheme 3. ***13***). [209] The use of a pivalic acid derivative as directing group in **3.49** first inhibits the activation of the C-H bonds on the N-side, and more importantly, confers enough geometry constrain to the system to form the rare 6-memebered palladacycle **V**. Key for this uncommon selectivity was the introduction of the

207 T. Kang, Y. Kim, D. Lee, Z. Wang, S. Chang, *J. Am. Chem. Soc.* **2014**, *136*, 4141–4144.
208 T. Kang, H. Kim, J. G. Kim, S. Chang, *Chem. Commun.* **2014**, *50*, 12073–12075.
209 G. Xia, J. Weng, L. Liu, P. Verma, Z. Li, J. Q. Yu, *Nat. Chem.* **2019**, *11*, 571–577.

double bond in the bicyclic skeleton of **V**. In this way it is possible to selective arylate the γ-position of the O-side[210]. An analogous approach was applied to the challenging β-methylene C-H arylation of alcohols, leading to the formation of **3.52**.[211] This methods relies on the use of a salicylic aldehyde derivative as a bidentate directing group (**3.51**), together with an electron deficient pyridinone ligand. The potential of bidentate oximes derivatives was finally demonstrated in the palladium-catalyzed oxidation/iodination sequence of C(sp^3)-H bonds β- to a masked carbonyl, since the reaction was not possible with the use of the simple methoxime as directing group.[212]



Scheme 3. 13. Directing group effect for the selective C(sp^3)-H arylation of masked alcohols.

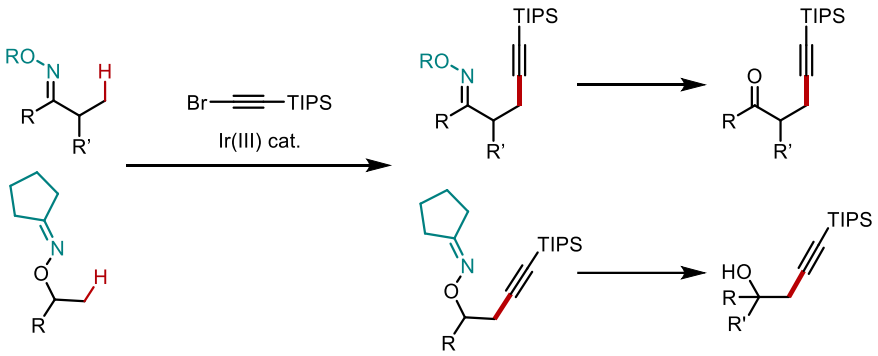
210 The selective β-arylation of aliphatic ketone directed by oximes was already reported in: (a) P. Gao, W. Guo, J. Xue, Y. Zhao, Y. Yuan, Y. Xia, Z. Shi, *J. Am. Chem. Soc.* **2015**, *137*, 12231–12240. (b) J. Peng, C. Chen, C. Xi, *Chem. Sci.* **2016**, *7*, 1383–1387.

211 G. Xia, Z. Zhuang, L. Y. Liu, S. L. Schreiber, B. Melillo, J. Q. Yu, *Angew. Chem. Int. Ed.* **2020**, *59*, 7783-7787.

212 R. Y. Zhu, L. Y. Liu, J. Q. Yu, *J. Am. Chem. Soc.* **2017**, *139*, 12394–12397.

Objectives

Our first objective was to develop new broad-scope method for the C(sp^3)-H alkynylation directing by oximes readily prepared from carbonyl compounds. A second objective was to extend this reaction to the alkynylation of alcohols derivatized as the corresponding oximes.

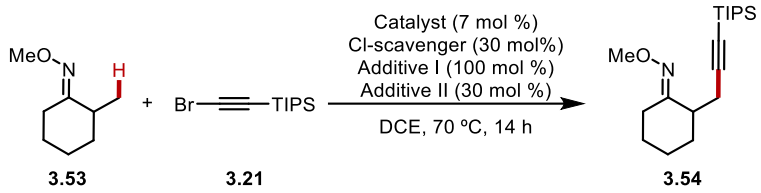


Results and Discussion

β-Alkynylation of Ketoximes

We initially centered our attention to the alkynylation of ketoximes, selecting **3.53** as model substrate and, based on our previous experience on C(sp^2)-H alkynylation,[186,187] we aimed to use bromoalkyne **3.21** as alkynylating agent(Table 3.1).[213] After screening a series of metal complexes, we found that Ir(III) complex $[Cp^*IrCl_2]_2$ in combination with Ag_2CO_3 and LiOAc gave the expected product **3.54** in 80% yield (Table 3.1, entry 3). Ru and Rh complexes known to catalyze the alkynylation of C(sp^2)-H bonds were ineffective for the C(sp^3)-H alkynylation (Table 3.1, entries 1 and 2). Similarly, $Pd(OAc)_2$ failed also as catalyst for this reaction (Table 3.1, entry 4). To proof that all the components in the reaction are necessary we tested the model reaction in absence of Ir(III) complex, silver salts or LiOAc (Table 3.1, entries 5-7 and 10) and in all the cases **3.54** was not formed. We additionally tested different silver salts instead of Ag_2CO_3 (Table 3.1, entries 8 and 9), but none of them proved to be efficient in the reaction.

Table 3.1. Optimization of the Ir(III) catalyzed β-alkynylation of ketoximes.[a]



3.53 **3.21** **3.54**

Entry	Catalyst	Cl-Scavenger	Additive I	Additive II	Yield (%)[b]
1	$[Cp^*RhCl_2]_2$	$AgSbF_6$	Ag_2CO_3	LiOAc	-
2	$[RuCl_2(p\text{-cymene})]_2$	$AgSbF_6$	Ag_2CO_3	LiOAc	-
3	$[Cp^*IrCl_2]_2$	$AgSbF_6$	Ag_2CO_3	LiOAc	80 (78)
4	$Pd(OAc)_2$	-	Ag_2CO_3	LiOAc	-
5	-	$AgSbF_6$	Ag_2CO_3	LiOAc	-
6	$[Cp^*IrCl_2]_2$	-	Ag_2CO_3	LiOAc	-

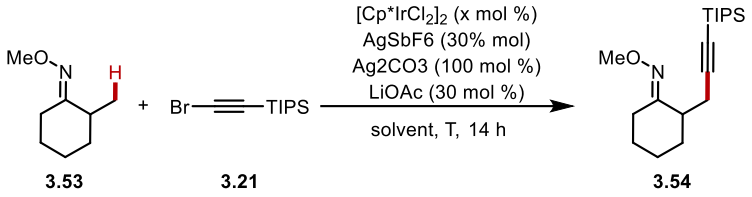
213 The optimization of the reaction was performed by Dr. E. Tan

7	$[Cp^*IrCl_2]_2$	$AgSbF_6$	-	LiOAc	-
8	$[Cp^*IrCl_2]_2$	$AgSbF_6$	$AgNO_3$	LiOAc	-
9	$[Cp^*IrCl_2]_2$	$AgSbF_6$	Ag_2O	LiOAc	-
10	$[Cp^*IrCl_2]_2$	$AgSbF_6$	Ag_2CO_3	-	-

[a] Substrates **3.53** and **3.21** in 1:1.2 ratio. [b] yield determined by ^{1}H-NMR using biphenyl as internal standard. Isolated yields in parenthesis.

Defined the components to obtain **3.54** in satisfactory yield, we tested different modifications on these conditions (Table 3.2). Lower catalyst loading resulted in a decreased yield (Table 3.2, entries 1 and 2), and higher or lower reaction temperatures caused a slight decrease of yield (Table 3.2, entries 7 and 8). Solvents different from DCE, as well the use of co-solvents (Table 3.2, entries 3-6) were also less efficient.

Table 3.2. Optimization of the Ir(III) catalyzed β-alkynylation of ketoximes.[a]



3.53 **3.21** **3.54**

Entry	$[Cp^*IrCl_2]_2$ (mol%)	solvent	T (°C)	Yield (%)[b]
1	3%	DCE	70	25
2	5%	DCE	70	50
3	7%	THF	70	50
4	7%	*tert*-amyl alcohol	70	20
5	7%	DCE:TFE (1/1)	70	50
6	7%	DCE:HFIP (1/1)	70	40
7	7%	DCE	25	60

8	7%	DCE	80	60

[a] Substrates **3.53** and **3.28** in 1:1.2 ratio. [b] yield determined by ^{1}H-NMR using biphenyl as internal standard.

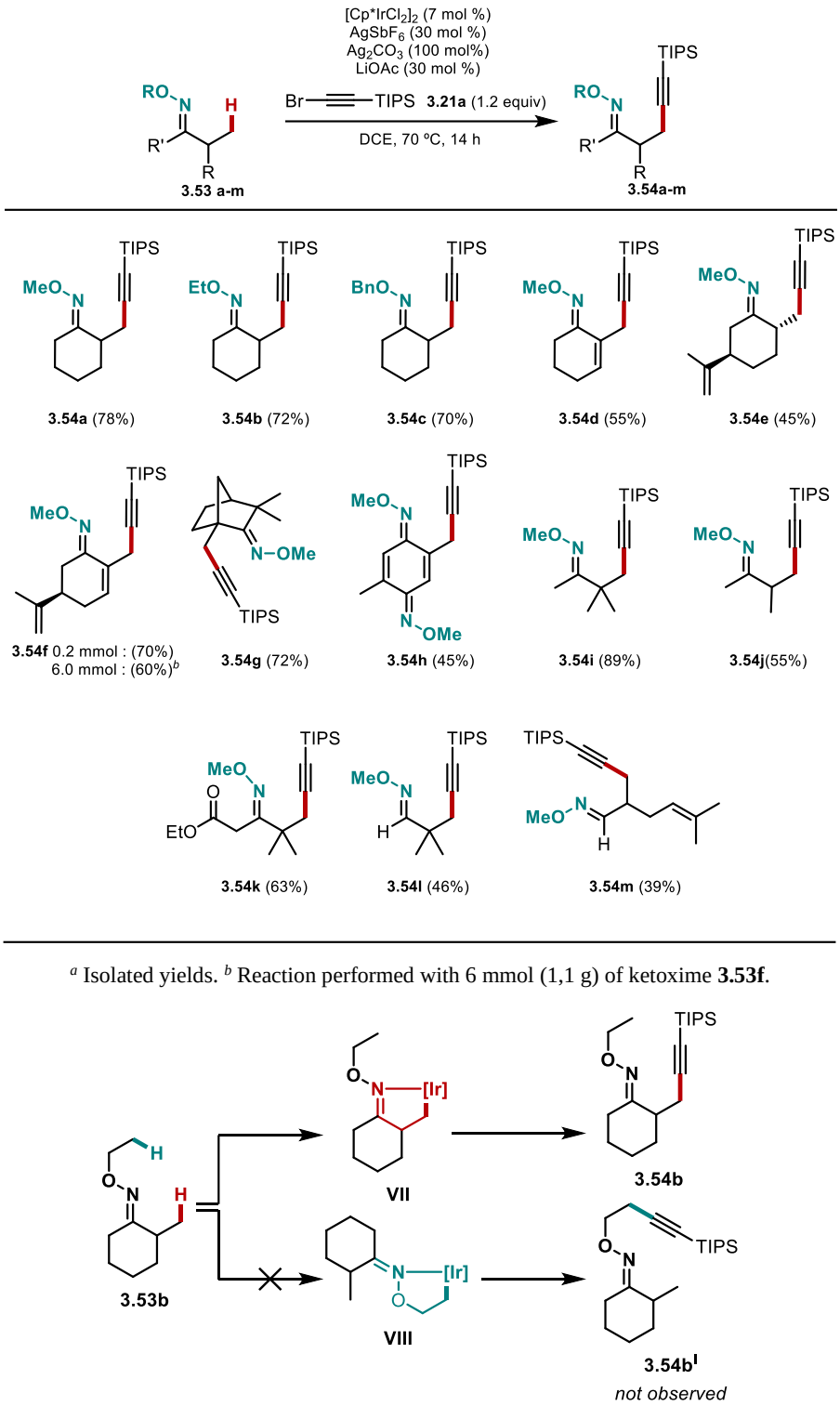
Having found the conditions for the iridium(III)-catalyzed β-alkynylation of **3.53**, we explored the substrate scope (Table 3.3)[214]. Thus, the ethoxime (**3.53b**) or benzyloxime (**3.53c**) of 2-methyl-cyclohexanone were also satisfactory substrates leading to products **3.54c** and **3.54b** in 72% and 70% yields, respectively. In the case of **3.53b**, the C-H activation step can occur in principle on either the *N*-side or the *O*-side via *endo*- or *exo*-iridacycles (Scheme 3.14). However, the latter is less favored and as expected, the product of alkynylation of the *O*-side was not observed.

Differently functionalized methoxime derivatives (**3.53d-f**) were successfully alkynylated in good yields (45-72%) even in presence of the more labile C(sp^2)-H bonds. The di-methoxime **3.53h** was mono-alkynylated to give **3.54h** in 45% yield. Interestingly, the (*E*)-isomer of the oxime derivative of (*L*)-fenchone was exclusively alkynylated on the bridgehead methyl to form **3.54g** in 72% yield despite the presence of other two possible reactive sites. In contrast the (*Z*)-isomer of (*L*)-fenchone was unreactive under the optimized reaction conditions, probably because of steric reasons that disfavor the C-H activation step. Additionally, acyclic substrates such as pinacolone derivative **3.53i** was alkynylated in 89% yields, whereas **3.54j** was formed in 45% yield. β-Ketoesthers derivative **3.53k** and aldoximes **3.53l,m** were be also alkynylated in good yields (39-63%).

Oxime **3.53n**, as well as the acetoxime **3.53o** and *O*-allyloxime **3.53p** did not provide the desired products (Figure 3.1). We tested also other haloalkynes in the reaction **3.21b-d** although none of them was affective as alkynylating reagent.

214 Experiments mainly performed by Dr. E. Tan.

Table 3.3. Ir(III) catalyzed β-alkynylation of ketoximes **3.53a-m** with **3.28**[a].



[a] Isolated yields. [b] Reaction performed with 6 mmol (1,1 g) of ketoxime **3.53f**.

Scheme 3.14. Selective alkynylation of the *N*-side oxime **3.53b**.

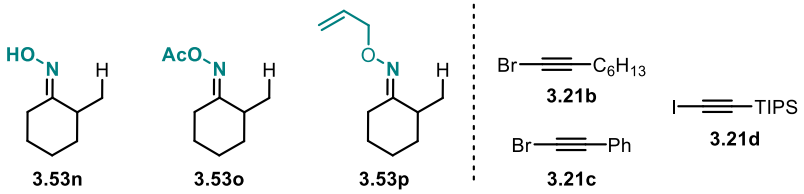
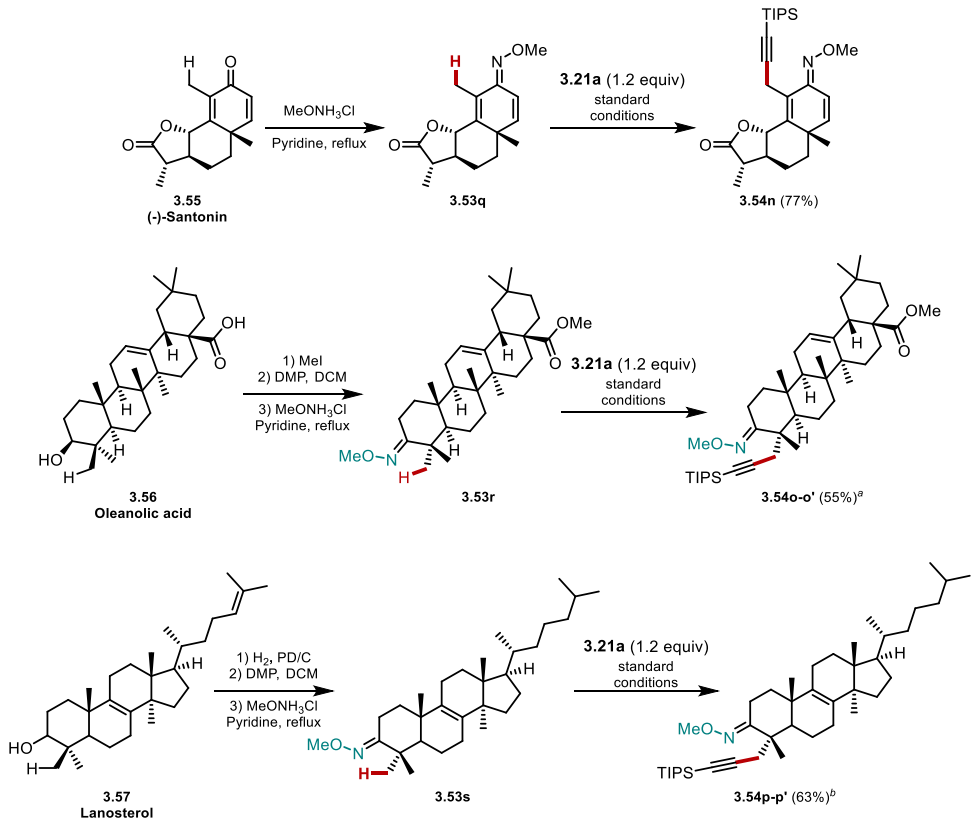


Figure 3.1. Other oximes and alkynes tested in the reaction.

The relatively mild conditions of the rection make this methodology suitable also for the functionalization of more complex molecules. Thus, (-)-santonine **3.55** was β-alkynylated via the methoxime **3.53q** giving rise to **3.54n** in 77% yield. In the same way, the carboxylic acid of oleanolic acid (**3.56**) was protected and the alcohol oxidized to form the corresponding ketone, whose oxime was β-alkynylated to form a 1.7:1 mixture **3.54o** and **3.54o'** in 55% yield. Lanosterol derivative **3.53s** was alkynylated to give a 4:1 mixture of diastereoisomers **3.54p** and **3.54p'** in 63% yield. In both cases the two isomers were separated, and their configurations were assigned based on previously reported C-H functionalization of the same oxime derivatives.[215]

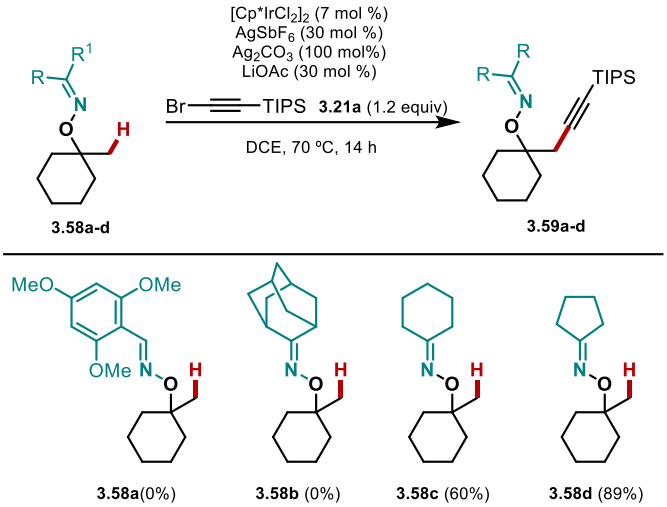
215 The assignment of the configuration of **3.54o, 3.54o', 3.54p** and **3.54p'** based just on NMR was not conclusive, see the experimental part for details.



Scheme 3.15. Functionalization of natural products.

β-Alkynylation of Oximes Derived from Alcohols

Although oxime **3.53b** selective reacts on the *N*-side of the oxime, we anticipated that by removal of reactive methyls from the ketone part, the alkynylation of oximes as alcohols surrogates would be possible with our catalytic system. First, we derivatized 1-methyl-cyclohexanol with different oximes lacking reactive sites (Scheme 3.16). 2,4,6-Trimethoxybenzaldehyde derivative **3.58a** was fully recovered under our standard conditions. Similar negative results were obtained with adamantanone derivative **3.58b**. Reducing the steric bulk of the directing group, allowed to achieve the alkynylation of product **3.58c** in 60% yield. Finally, the smaller cyclopentanone derivative **3.58d** led to the alkynylation of the methyl group in 89% yield.

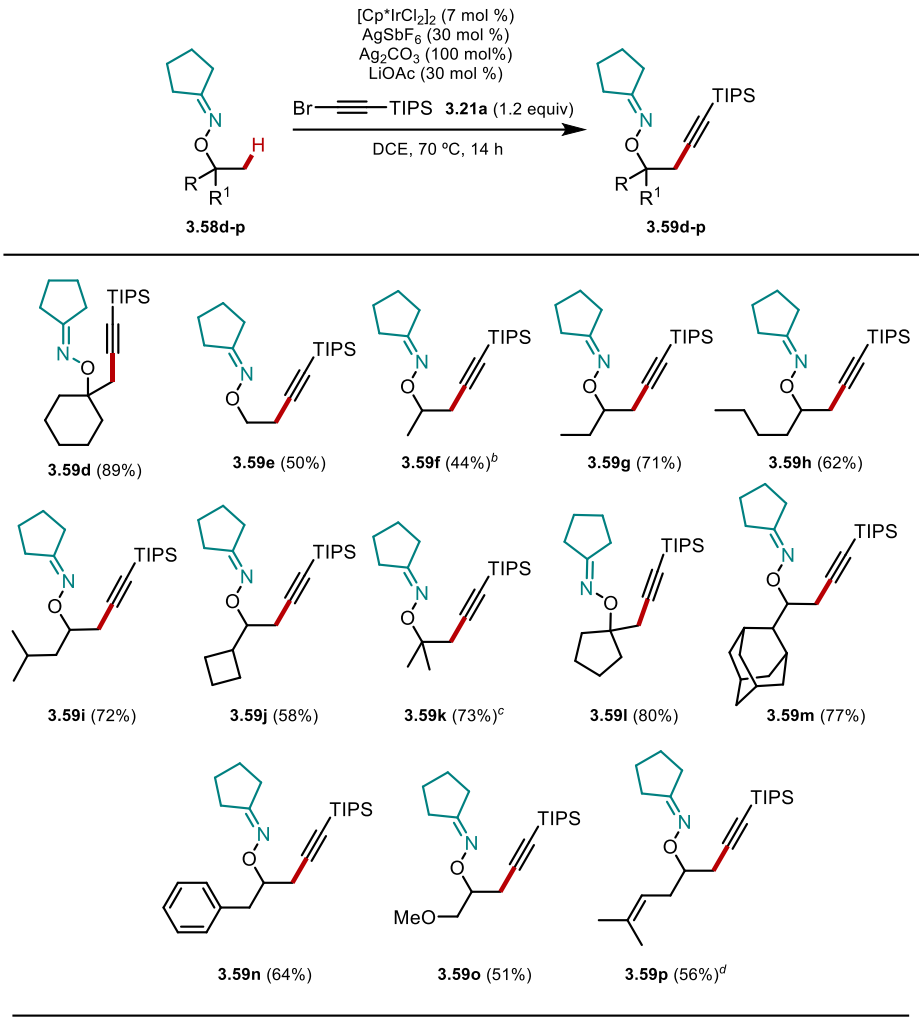


Scheme 3.16.Screening of different directing group for the β-alkynylation of alchoximes **3.58** with **3.21a**.

Table 3.4 reports the scope of the iridium(III)-catalyzed β-alkynylation of masked alcohols. The alkynylation of ethanol derivative **3.58e** occurred in 50% yield, while for isopropanol derivative **3.58f**, the mono-alkynylation product was obtained in 44% yield together with 21% of the di-alkynylated derivative **3.59f'**. Also, for *tert*-butanol derivative **3.58k** we obtained **3.59k** and **3.59k'** in 73% yield as a 7:1 inseparable mixture.

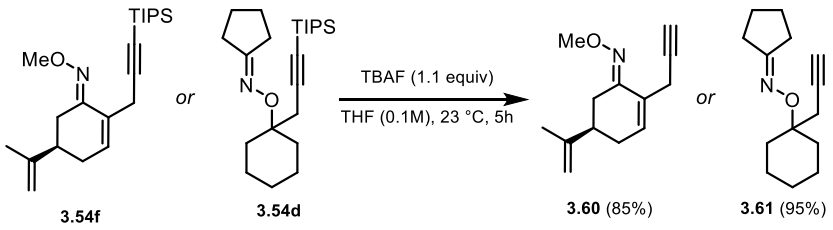
With this methodology a series of β-alkynylated secondary alcohol derivatives (**3.59f-j,m,p**) could be efficiently prepared (44-77% yield) with very good selectivity. In all the cases the reaction occurred on the methyl whose activation would generate a 5-membered metallacycle intermediate, while the γ-position, which requires the formation of a 6-membered ring, was not activated as shown in **3.59g-j**. The selective activation of methyl groups was also observed in presence of more reactive C(sp^3)-H bonds of methylene groups (belzylic, allylic or activated by a MeO group) such in the cases of **3.59n-p**. Masked tertiary alcohols are also alkynylated in very good yields (**3.59d,k,l**).

Table 3.4. Ir(III) catalyzed β-alkynylation of ketoximes **3.58d-p** with **3.21a**.[a]



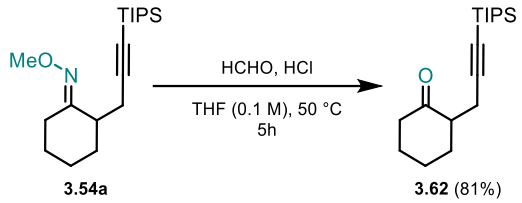
[a] Isolated yields. [b] Dialkynylated product also isolated in 21% yield. [c] Obtained as a mixture 3:1 of mono-:di-alkynylated products. [d] Yield corrected for conversion (57%).

The alkyne could be easily deprotected both in the ketone and alcohol derivatives by treatment with TBAF, forming **3.60** and **3.61** in excellent yields (Scheme 3.17).



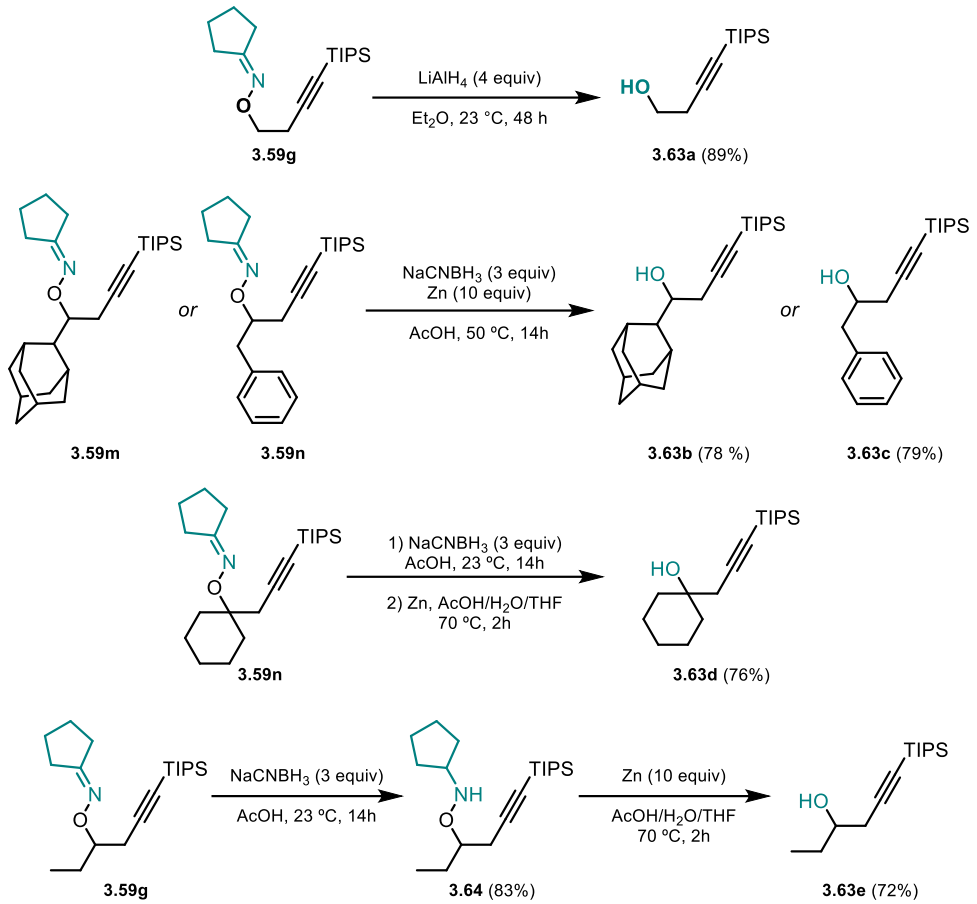
Scheme 3.17. TIPS removal from **3.54f** and **3.59d**.

Removal of methoxime from **3.54a** occurred smoothly in presence of formaldehyde and HCl to form **3.62** in good yield (Scheme 3.18).



Scheme 3.18. Deprotection of oxime **3.54a** to form β-alkynylated ketone **3.80**.

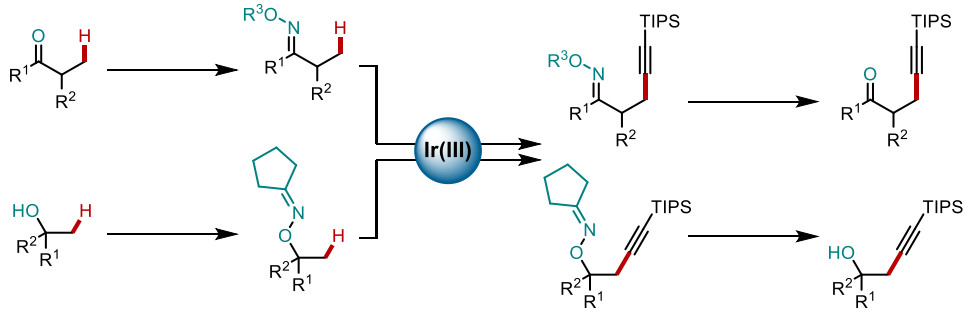
However, the generation of the free alcohol from alkylated products **3.59** was more challenging (Scheme 3.19). Alkynylated ethanol **3.63a** was obtained in 89% yield from **3.59g** by treatment with an excess of $LiAlH_4$, but the same reaction conditions failed for the deprotection of more complex substrates, even increasing the temperature. After screening different conditions, we found that secondary alcohols **3.63b,c** can be obtained from the corresponding oxime in good yields (78% and 79%, respectively) under reductive conditions using $NaBH_3CN$ and Zn powder in acetic acid. Also, tertiary alcohol **3.63d** was deprotected under the same reaction conditions, although a cleaner reaction mixture was obtained reducing first the oxime to the corresponding hydroxylamine with $NaBH_3CN$, followed by the addition of Zn powder in a one-pot procedure. Under these conditions, **3.63d** was isolated in 76% yield. In the case of **3.59g**, the intermediate hydroxylamine **3.64** could also be isolated in 83% yield. The reductive cleavage of the N-O bond gave free alcohol **3.63e** in 72% yield.



Scheme 3.19. Deprotection of oximes alkynylated oximes to form the corresponding alcohol or hydroxylamine.

Conclusions

In this Chapter we have presented the iridium(III)-catalyzed β-alkynylation of carbonyl derivatives and alcohols masked as oxime derivatives. The oxime acts as directing group for the selective alkynylation of primary C(sp^3)-H bonds and it can be removed either under acidic or reductive conditions, restoring then the initial functionality. This methodology tolerates the presence of aromatic or alkenyl C-H bonds that can potentially compete with the desired reaction. This methodology has also been extended to the alkynylation of oxime derivatives of natural products.



Experimental Part

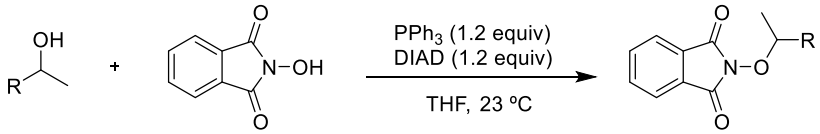
General Information

The general information is provided in the Experimental Part of **Chapter 1.** All reagents were used as purchased, with no further purification.

Haloalkynes **3.71a-d** and oxime ether substrates **3.70a-s** are synthesized according to previously reported procedures[216]. The NMR data are in agreement with the ones reported in the literature.

Synthetic Procedures and Characterization Data

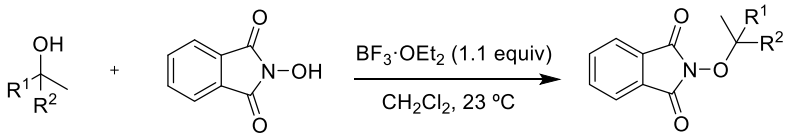
General procedure A: Synthesis of N-alkoxyphthalimide from primary and secondary alcohols.



s 3.1e-m

To a stirred solution of the alcohol (1 equiv), 2-hydroxyisoindoline-1,3-dione (1.2 equiv) and triphenylphosphane (1.2 equiv) in THF (0.25 M) at 0 ºC, diisopropyl (*E*)-diazene-1,2-dicarboxylate (1.2 equiv) was added dropwise over 1 h, the reaction was then warmed up at 23 ºC and stirred until no starting material was detected by TLC. The solvent was then removed under reduced pressure and the resulting residue was purified by column chromatography on silica gel to give the corresponding *N*-alkoxyphthalimide.

General Procedure B: Synthesis of N-alkoxyphthalimide from tertiary alcohols



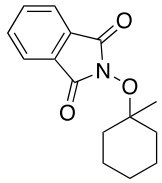
s 3.1a,n,o

A suspension of *N*-hydroxyphthalimide (2 equiv) and tertiary alcohol (1 equiv) in 30 mL of CH_2Cl_2, was stirred at 23 ºC for 3h, then cooled down to 0 ºC and $BF_3{\cdot}OEt_2$ (1.1 equiv) was added dropwise. The reaction mixture was stirred for at room temperature until no starting

216 For bromo- and iodo-alkynes: a) E. Tan, A. I. Konovalov, G. A. Fernandez, R. Dorel, A. M. Echavarren, *Org. Lett.* **2017**, *19*, 5561-5564. b) E. M. de Orbe, M. Zanini, O. Quinonero, A. M. Echavarren *ACS Catal.* **2019**, *9*, 7817- 7822. For oxime ether substrates: c) T. Kang, Y. Kim, D. Lee, Z. Wang, S. Chang, *J. Am. Chem. Soc.* **2014**, *136*, 4141-4144. d) P. Gao, W. Guo, J. Xue, Y. Zhao, Y. Yuan, Y. Xia, Z. Shi, *J. Am. Chem. Soc*. **2015**,*137*, 12231-12240. e) J. Peng, C. Chen, C. Xi, *Chem. Sci*, **2016**, *7*, 1383-1387.

material was detected by TLC and then a saturated solution of $NaHCO_3$ solution in H_2O was added. The aqueous layer was extracted three times with CH_2Cl_2, the combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to give desired *N*-alkoxyphthalimide.

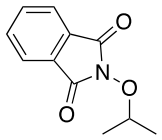
2-((1-Methylcyclohexyl)oxy)isoindoline-1,3-dione (S3.1a)



N-Alkoxyphthalimide **S3.1a** was synthesized following general procedure **B** starting from 1-methylcyclohexanol (10 mmol, 1,14 g). The crude product was purified by flash chromatography affording **S3.1a** as white solid (567 mg, 22%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.9 – 7.8 (m, 1H), 7.8 – 7.7 (m, 1H), 1.9 (tdt, J = 12.4, 9.0, 3.9 Hz, 2H), 1.7 (ddt, J = 12.0, 7.2, 3.7 Hz, 1H), 1.5 – 1.4 (m, 2H), 1.4 (s, 2H). **^{13}C-NMR (**101 MHz, $CDCl_3$) δ 166.0, 134.5, 129.5, 123.5, 88.5, 36.4, 25.6, 23.7, 23.2. Characterization data are in agreement with the literature[217]

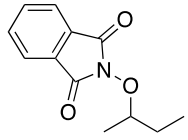
2-Isopropoxyisoindoline-1,3-dione (S3.1f)



N-Alkoxyphthalimide **S3.1f** was synthesized following general procedure **A** starting from isopropanol (180 mg, 3 mmol). The crude product was purified by flash chromatography affording **S3.1f** as white solid (538 mg, 89%).

^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.8 (m, 2H), 7.8 – 7.7 (m, 2H), 4.5 (m, 1H), 1.4 (dt, J = 6.3, 2.2 Hz, 6H). **^{13}C-NMR (**126 MHz, $CDCl_3$) δ 164.4, 134.5, 129.1, 123.5, 80.7, 20.9. **HRMS** (ESI) *m/z* calculated for $C_{11}H_{11}NNaO_3^+$ $[M+Na]^+$: 228.0631, found: 228.0632. Characterization data are in agreement with the literature.[218]

2-(*sec*-Butoxy)isoindoline-1,3-dione (S3.1g)



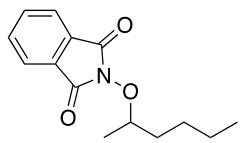
N-Alkoxyphthalimide **S3.1g** was synthesized following general procedure **A** starting from 2-butanol (1.0 g, 13.5 mmol). The crude product was purified by flash chromatography affording **S3.1f** as white solid (2.42g, 82%).

M.p. 59-61 ºC. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.8 (td, J = 5.2, 2.1 Hz, 2H), 7.8 – 7.7 (m, 2H), 4.3 (h, J = 6.3 Hz, 1H), 1.8 (dqd, J = 13.3, 7.5, 5.7 Hz, 1H), 1.7 – 1.6 (m, 1H), 1.3 (d, J = 6.3 Hz, 3H), 1.0 (t, J = 7.5 Hz, 3H). **^{13}C-NMR (**101 MHz, $CDCl_3$) δ 164.5, 134.5, 129.1, 123.5,

217 J. R. Harris, M. T. Haynes, A. M. Thomas, K. A. Woerpel, *J. Org. Chem.* **2010**, *75*, 5083–5091.
218 Z. Ren, F. Mo, G. Dong, *J. Am. Chem. Soc.* **2012**, *134*, 16991–16994.

85.8, 27.8, 18.3, 9.7. **HRMS** (ESI) *m/z* calculated for $C_{12}H_{13}NNaO_3^+$ $[M+Na]^+$: 242.0788, found: 242.0789.

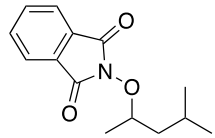
2-(Hexan-2-yloxy)isoindoline-1,3-dione (S3.1h)



N-Alkoxyphthalimide **S3.1h** was synthesized following general procedure **A** starting from 2-hexanol (307 mg, 3 mmol). The crude product was purified by flash chromatography affording **S3.1h** as yellow oil (719 mg, 97%).

^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.8 – 7.8 (m, 2H), 7.7 (dt, *J* = 5.4, 2.6 Hz, 2H), 4.4 (pq, *J* = 4.8, 3.0, 1.9 Hz, 1H), 1.8 (ddtt, *J* = 11.7, 9.9, 6.0, 1.9 Hz, 1H), 1.6 (ddddd, *J* = 13.5, 10.0, 6.2, 3.8, 1.8 Hz, 1H), 1.4 (qdd, *J* = 8.9, 5.5, 2.2 Hz, 2H), 1.4 (ddd, *J* = 9.9, 5.1, 2.7 Hz, 2H), 1.3 (ddd, *J* = 6.1, 3.7, 1.6 Hz, 3H), 0.9 – 0.9 (m, 3H). **^{13}C-NMR (**126 MHz, $CDCl_3$) δ 164.5, 134.5, 129.1, 123.5, 84.6, 34.7, 27.5, 22.8, 18.9, 14.1. Characterization data are in agreement with the literature[219]

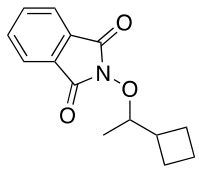
2-((4-Methylpentan-2-yl)oxy)isoindoline-1,3-dione (S3.1i)



N-Alkoxyphthalimide **S3.1i** was synthesized following general procedure **A** starting from 4-methyl-2-pentanol (409 mg, 4.0 mmol). The crude product was purified by flash chromatography affording **S3.1i** as white solid (837 mg, 85%).

M.p. 68-71ºC. **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.9 – 7.8 (m, 2H), 7.8 – 7.7 (m, 2H), 4.5 (dq, *J* = 7.6, 6.0 Hz, 1H), 2.0 – 1.9 (m, 1H), 1.8 (ddd, *J* = 13.3, 7.6, 6.6 Hz, 1H), 1.4 – 1.4 (m, 1H), 1.3 (d, *J* = 6.1 Hz, 3H), 1.0 (d, *J* = 6.5 Hz, 3H), 0.9 (d, *J* = 6.6 Hz, 3H). **^{13}C-NMR (**126 MHz, $CDCl_3$) δ 164.5, 134.5, 129.2, 123.5, 83.0, 44.4, 24.9, 22.9, 22.7, 19.6. **HRMS** (ESI) *m/z* calculated for $C_{14}H_{17}NNaO_3^+$ $[M+Na]^+$: 270.1101, found: 270.1098

2-(1-Cyclobutylethoxy)isoindoline-1,3-dione (S3.1j)



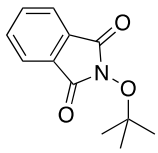
N-Alkoxyphthalimide **S3.1j** was synthesized following general procedure **A** starting from 1-cyclobutylethan-1-ol (300 mg, 3.0 mmol). The crude product was purified by flash chromatography affording **S3.1j** as yellow oil (538 mg, 73%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.8 (dddd, *J* = 6.9, 5.0, 3.0, 1.3 Hz, 2H), 7.8 – 7.6 (m, 2H), 4.4 – 4.2 (m, 1H), 2.7 – 2.5 (m, 1H), 2.1 – 2.0 (m, 3H), 2.0 – 1.7 (m, 3H), 1.2 (dt, *J* = 6.3, 1.0 Hz,

219 Wang, B. Stefane, D. Jaber, J. A. I. Smith, C. Vickery, M. Diop, H. O. Sintim, *Angew. Chem. Int. Ed.* **2010**, *49*, 3964–3968.

3H). **^{13}C-NMR (**101 MHz, $CDCl_3$) δ 164.4, 134.5, 134.4, 129.2, 123.5, 88.0, 39.7, 25.9, 24.7, 18.5, 16.3. HRMS (ECI) *m/z* calculated for $C_{14}H_{15}NNaO_3^+$ $[M+Na]^+$: 268.0944 found: 268.0952.

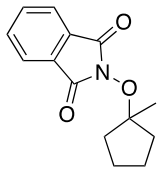
2-(*tert*-Butoxy)isoindoline-1,3-dione (S3.1k)



N-Alkoxyphthalimide **S3.1k** was synthesized following general procedure **B** starting from *tert*-butanol (383 mg, 4.0 mmol). The crude product was purified by flash chromatography affording **S3.1k** as white solid (516 mg, 58%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.9 – 7.8 (m, 1H), 7.8 – 7.7 (m, 1H), 1.4 (s, 5H). **^{13}C-NMR (**101 MHz, $CDCl_3$) δ 165.8, 134.5, 129.5, 123.6, 86.7, 27.5. Characterization data are in agreement with the literature[220]

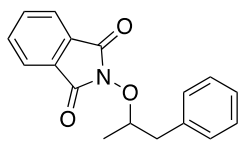
2-((1-Methylcyclopentyl)oxy)isoindoline-1,3-dione (S3.1l)



N-Alkoxyphthalimide **S3.1l** was synthesized following general procedure **B** starting from 1-methylcyclopentan-1-ol (401 mg, 4.0 mmol). The crude product was purified by flash chromatography affording **S3.1l** as white solid (516 mg, 53%).

M.p. 112-115 ºC. **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.8 – 7.8 (m, 1H), 7.7 – 7.7 (m, 1H), 2.1 – 2.0 (m, 1H), 2.0 – 1.9 (m, 1H), 1.6 (qdd, *J* = 8.1, 6.6, 4.7 Hz, 1H), 1.6 – 1.5 (m, 1H), 1.4 (s, 2H). **^{13}C-NMR (**126 MHz, $CDCl_3$) δ 165.9, 134.5, 134.5, 129.4, 123.4, 123.4, 97.9, 38.0, 24.5, 24.4. **HRMS** (ESI) *m/z* calculated for $C_{14}H_{15}NNaO_3^+$ $[M+Na]^+$: 268.0944, found: 268.0950

2-((1-Phenylpropan-2-yl)oxy)isoindoline-1,3-dione (S3.1n)

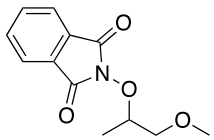


N-Alkoxyphthalimide **S3.1n** was synthesized following general procedure **A** starting from 1-phenylpropan-2-ol (545 mg, 4.0 mmol). The crude product was purified by flash chromatography affording **S3.1n** as white solid (765 mg, 68%).

M.p. 90-93 ºC. **^{1}H-NMR (**500 MHz, $CDCl_3$) δ 7.8 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.8 – 7.7 (m, 2H), 7.3 – 7.2 (m, 3H), 7.2 (ddt, *J* = 7.5, 6.0, 2.0 Hz, 1H), 4.7 – 4.6 (m, 1H), 3.2 (dd, *J* = 13.8, 5.6 Hz, 1H), 2.9 (dd, *J* = 13.8, 7.8 Hz, 1H), 1.3 (d, *J* = 6.2 Hz, 3H). **^{13}C-NMR (**126 MHz, $CDCl_3$) δ 164.4, 137.3, 134.6, 129.4, 129.1, 128.6, 126.6, 123.6, 84.8, 41.5, 18.5. **HRMS** (ESI) *m/z* calculated for $C_{17}H_{16}NO_3^+$ $[M+H]^+$: 282.1125, found: 282.1116

220 S. G. Davies, C. J. Goodwin, D. Hepworth, P. M. Roberts, J. E. Thomson, *J. Org. Chem.* **2010**, *75*, 1214–1227.

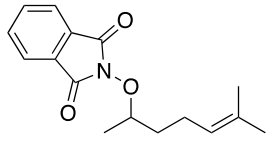
2-((1-Methoxypropan-2-yl)oxy)isoindoline-1,3-dione (S 3.1p)



N-Alkoxyphthalimide **S3.1p** was synthesized following general procedure **A** starting from 1 1-methoxypropan-2-ol (294 µl, 3.0 mmol). The crude product was purified by flash chromatography affording **S3.1p** as yellow oil (139 mg, 20%).

^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.7 – 7.7 (m, 2H), 7.7 – 7.6 (m, 2H), 4.5 – 4.4 (m, 1H), 3.6 (dd, *J* = 10.9, 6.1 Hz, 1H), 3.4 (dd, *J* = 10.8, 3.5 Hz, 1H), 3.2 (s, 3H), 1.3 (d, *J* = 6.5 Hz, 3H). **^{13}C-NMR (**126 MHz, $CDCl_3$) δ 163.7, 134.3, 128.8, 123.3, 82.4, 74.9, 59.0, 15.8. **HRMS** (ESI) *m/z* calculated for $C_{12}H_{14}NO4^+$ $[M+H]^+$: 236.0917, found: 236.0922.

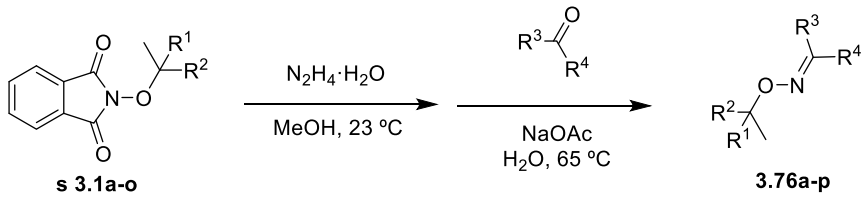
2-((6-Methylhept-5-en-2-yl)oxy)isoindoline-1,3-dione (S3.1p)



N-Alkoxyphthalimide **S3.1p** was synthesized following general procedure **A** starting from 6-methylhept-5-en-2-ol (385 mg, 3 mmol). The crude product was purified by flash chromatography affording **S3.1p** as yellow oil (755 mg, 92%).

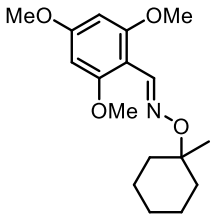
^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.8 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.8 – 7.7 (m, 2H), 5.1 (ddq, *J* = 8.6, 5.8, 1.5 Hz, 1H), 4.4 (h, *J* = 6.3 Hz, 1H), 2.2 (q, *J* = 7.7 Hz, 2H), 1.9 (ddt, *J* = 13.4, 8.6, 6.5 Hz, 1H), 1.7 (d, *J* = 1.4 Hz, 3H), 1.6 (m, 4H), 1.6 (d, *J* = 1.5 Hz, 1H), 1.3 (d, *J* = 6.3 Hz, 3H). **^{13}C-NMR (**101 MHz, $CDCl_3$) δ 164.4, 134.5, 132.3, 129.1, 123.6, 123.5, 84.2, 35.1, 25.8, 24.0, 18.9, 17.8. **HRMS** (ECI) *m/z* calculated for $C_{16}H_{19}NNaO_3^+$ $[M+Na]^+$: 296.1257 found: 296.1266.

General Procedure C: Synthesis of the oximes



To a solution of N-alkoxyphthalimide (1 equiv) in MeOH (0,55 M), hydrazine monohydrate (1 equiv) was added slowly at 23 ºC. After stirring for 30 minutes, the desired ketone (3 equiv), sodium acetate (5 equiv), and water (1,4 M) were added to the reaction mixture. The resulting mixture was heated to 65 °C and stirred for 5 h. The mixture was then cooled to room temperature, filtered to remove the precipitate and the liquid phase was washed three times with Et_2O, the collected organic phases were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel.

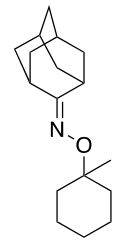
(E)-2,4,6-trimethoxybenzaldehyde *O*-(1-methylcyclohexyl) oxime (3.58a)



Oxime **3.76a** was synthesized following general procedure **C** starting from 2-((1-Methylcyclohexyl)oxy)isoindoline-1,3-dione **(S3.1a)** (200 mg, 0.771 mmol) and 2,4,6-trimethoxybenzaldehyde (151 mg mg, 0.771 mmol) The crude product was purified by flash chromatography affording **3.76a** as a yellow oil (206 mg, 68%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.35 (s, 1H), 6.12 (s, 2H), 3.81 (s, 3H), 3.81 (s, 6H), 1.97 – 1.87 (m, 2H), 1.70 – 1.58 (m, 2H), 1.56 – 1.37 (m, 6H), 1.32 (s, 3H). **^{13}C-NMR (**101 MHz, $CDCl_3$) δ 161.9, 160.1, 142.6, 104.3, 91.4, 78.9, 56.2, 55.5, 36.4, 26.0, 26.0, 22.5.

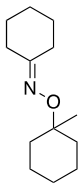
Adamantan-2-one *O*-(1-methylcyclohexyl) oxime (3.58b)



Oxime **3.76b** was synthesized following general procedure **C** starting from 2-((1-Methylcyclohexyl)oxy)isoindoline-1,3-dione **(S3.1a)** (200 mg, 0.771 mmol) and 2-adamantanone (348 mg, 2,31 mmol). The crude product was purified by flash chromatography affording **3.76b** as a yellow oil (137 mg, 68%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.58 (t, *J* = 3.3 Hz, 1H), 2.59 – 2.51 (m, 1H), 2.01 – 1.97 (m, 1H), 1.93 (ddd, *J* = 13.5, 8.2, 2.9 Hz, 4H), 1.88 – 1.75 (m, 10H), 1.59 – 1.18 (m, 12H). **^{13}C-NMR (**101 MHz, $CDCl_3$) δ 165.7, 77.2, 39.3, 37.9, 36.8, 36.6, 36.4, 29.7, 28.2, 26.0, 25.9, 22.4. **HRMS (ESI)** *m/z* calculated for $C_{17}H_{28}NO^+$ $[M+H]^+$: 262.2165, found: 262.2164.

Cyclohexanone *O*-(1-methylcyclohexyl) oxime (3.58c)

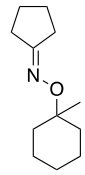


Oxime **3.58c** was synthesized following general procedure **C** starting from 2-((1-methylcyclohexyl)oxy)isoindoline-1,3-dione **(S3.1a)** (70 mg, 0.27 mmol) and cyclohexanone (82 µl, 0.8 mmol). The crude product was purified by flash chromatography affording **3.58c** as a yellow oil (86 mg, 81%).

^{1}H-NMR (500 MHz, $CDCl_3$) δ 2.53 – 2.47 (m, 2H), 2.23 – 2.17 (m, 2H), 1.83 (ddt, *J* = 13.1, 4.9, 2.5 Hz, 2H), 1.68 – 1.61 (m, 2H), 1.58 (p, *J* = 2.9 Hz, 4H), 1.56 – 1.45 (m, 3H), 1.45 – 1.37 (m, 2H), 1.37 – 1.28 (m, 2H), 1.24 (s, 3H). **^{13}C-NMR (**126 MHz, $CDCl_3$) δ 159.2, 77.5, 36.3, 32.7, 27.4, 26.2, 26.2, 26.0, 25.9, 25.4, 22.4, 15.4. Characterization data are in agreement with the literature[221].

221 T. Kang, H. Kim, J. G. Kim, S. Chang, *Chem. Commun.* **2014**, *50*, 12073–12075.

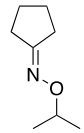
Cyclopentanone *O*-(1-methylcyclohexyl) oxime (3.58d)



Oxime **3.58d** was synthesized following general procedure **C** starting from 2-((1-methylcyclohexyl)oxy)isoindoline-1,3-dione **(S3.1a)** (317 mg, 1.22 mmol) and cyclopentanone (324 µl, 2,31 mmol). The crude product was purified by flash chromatography affording **3.58d** as a yellow oil (204 mg, 85%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.41 (tdd, *J* = 7.6, 2.4, 1.1 Hz, 2H), 2.34 (tt, *J* = 5.2, 1.5 Hz, 2H), 1.87 – 1.78 (m, 2H), 1.76 – 1.67 (m, 4H), 1.50 (ddt, *J* = 12.5, 6.9, 3.5 Hz, 3H), 1.46 – 1.25 (m, 5H), 1.23 (s, 3H). **^{13}C-NMR (**101 MHz, $CDCl_3$) δ 165.5, 78.0, 36.5, 31.2, 27.7, 26.3, 26.0, 25.4, 24.9, 22.5. **HRMS** (ESI) *m/z* calculated for $C_{12}H_{22}NO^+$ $[M+H]^+$: 196.1696, found: 196.1695.

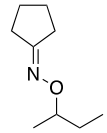
Cyclopentanone *O*-isopropyl oxime (3.58f)



Oxime **3.58f** was synthesized following general procedure **C** starting from 2-((1- 2-isopropoxyisoindoline-1,3-dione **(S3.1f)** (190 mg, 093 mmol) and cyclopentanone (246 µl, 2.8 mmol). The crude product was purified by flash chromatography affording **3.58f** as a colorless oil (104 mg, 80%).

^{1}H-NMR (500 MHz, $CDCl_3$) δ 4.27 (hept, *J* = 6.2 Hz, 1H), 2.52 – 2.27 (m, 4H), 1.88 – 1.66 (m, 4H), 1.21 (d, *J* = 6.2 Hz, 6H). **^{13}C-NMR (**126 MHz, $CDCl_3$) δ 165.8, 74.8, 31.1, 27.8, 25.3, 24.8, 22.0. **HRMS (**ESI) *m/z* calculated for $C_8H_{16}NO^+$ $[M+H]^+$: 142.1226, found: 142.1223

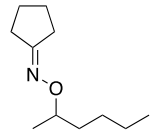
Cyclopentanone *O*-(*sec*-butyl) oxime (3.58g)



Oxime **3.58g** was synthesized following general procedure **C** starting from 2-(sec-butoxy)isoindoline-1,3-dione **(S3.1g)** (219 mg, 1 mmol) and cyclopentanone (265 µl, 3.0 mmol). The crude product was purified by flash chromatography affording **3.58g** as a yellow oil (132 mg, 85%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.04 (h, *J* = 6.2 Hz, 1H), 2.42 – 2.31 (m, 4H), 1.76 – 1.68 (m, 4H), 1.68 – 1.57 (m, 1H), 1.54 – 1.39 (m, 1H), 1.18 (d, *J* = 6.3 Hz, 3H), 0.89 (t, *J* = 7.5 Hz, 3H). **^{13}C-NMR (**101 MHz, $CDCl_3$) δ 165.7, 79.8, 31.1, 28.7, 27.7, 25.3, 24.8, 19.5, 9.8. **HRMS (**ESI) *m/z* calculated for $C_9H_{18}NO^+$ $[M+H]^+$: 156.1383, found: 156.1382.

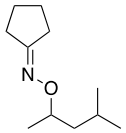
Cyclopentanone *O*-hexan-2-yl oxime (3.58h)



Oxime **3.58h** was synthesized following general procedure **C** starting from 2-(sec-butoxy)isoindoline-1,3-dione **(S3.1h)** (340 mg, 1.37 mmol) and cyclopentanone (365 µl, 4.12 mmol). The crude product was purified by flash chromatography affording **3.58h** as a yellow oil (203 mg, 81%).

^{1}H-NMR (500 MHz, $CDCl_3$) δ 4.08 (h, *J* = 6.2 Hz, 1H), 2.34 (dddd, *J* = 13.5, 7.3, 5.1, 1.1 Hz, 4H), 1.77 – 1.65 (m, 4H), 1.66 – 1.55 (m, 1H), 1.47 – 1.36 (m, 1H), 1.36 – 1.23 (m, 4H), 1.17 (d, *J* = 6.3 Hz, 3H), 0.91 – 0.84 (m, 3H). **^{13}C-NMR (**126 MHz, $CDCl_3$) δ 165.5, 78.6, 35.7, 31.1, 27.9, 27.7, 25.3, 24.8, 22.9, 20.1, 14.2. **HRMS** (ESI) *m/z* calculated for $C_{11}H_{22}NO^+$ $[M+H]^+$: 184.1696, found: 184.1696.

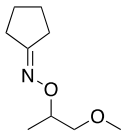
Cyclopentanone *O*-(4-methylpentan-2-yl) oxime (3.58i)



Oxime **3.58i** was synthesized following general procedure **C** starting from 2-((4-methylpentan-2-yl)oxy)isoindoline-1,3-dione **(S3.1i)** (312 mg, 1.26 mmol) and cyclopentanone (335 μl, 3.78 mmol). The crude product was purified by flash chromatography affording **3.58i** as a yellow oil (191 mg, 83%).

^{1}H-NMR (500 MHz, $CDCl_3$) δ 4.24 – 4.12 (m, 1H), 2.40 – 2.29 (m, 4H), 1.78 – 1.66 (m, 5H), 1.60 – 1.50 (m, 1H), 1.27 – 1.21 (m, 1H), 1.19 (d, *J* = 6.2 Hz, 3H), 0.89 (dd, *J* = 6.7, 5.9 Hz, 6H). **^{13}C-NMR (**126 MHz, $CDCl_3$) δ 165.6, 77.0, 45.1, 31.1, 27.8, 25.3, 25.0, 24.8, 23.1, 23.0, 20.7. **HRMS** (ESI) *m/z* calculated for $C_{11}H_{22}NO^+$ $[M+H]^+$: 184.1696, found: 184.1695.

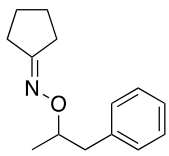
Cyclopentanone *O*-(1-methoxypropan-2-yl) oxime (3.58o)



Oxime **3.58o** was synthesized following general procedure **C** starting from 2-((1-methoxypropan-2-yl)oxy)isoindoline-1,3-dione **(S3.1o)** (286 mg, 1.2 mmol) and cyclopentanone (323 μl, 3.6 mmol). The crude product was purified by flash chromatography affording **3.58o** as a yellow oil (160 mg, 77%).

^{1}H-NMR (500 MHz, $CDCl_3$) δ 4.28 – 4.19 (m, 1H), 3.45 (dd, *J* = 10.2, 5.7 Hz, 1H), 3.34 (dd, *J* = 10.3, 4.6 Hz, 1H), 3.31 (s, 3H), 2.38 – 2.31 (m, 2H), 2.31 – 2.26 (m, 2H), 1.72 – 1.59 (m, 4H), 1.16 (d, *J* = 6.4 Hz, 3H). **^{13}C-NMR (**126 MHz, $CDCl_3$) δ 166.2, 77.4, 75.3, 59.2, 30.9, 27.7, 25.1, 24.6, 16.9. **HRMS (**ESI) *m/z* calculated for $C_9H_{17}NNaO_2^+$ $[M+Na]^+$: 194.1151, found: 194.1149

Cyclopentanone *O*-(1-phenylpropan-2-yl) oxime (3.76n)

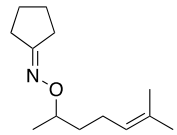


Oxime **3.76n** was synthesized following general procedure **C** starting from 2-((1-phenylpropan-2-yl)oxy)isoindoline-1,3-dione **(S3.1n)** (338 mg, 1.2 mmol) and cyclopentanone (319 μl, 3.9 mmol). The crude product was purified by flash chromatography affording **3.76n** as a yellow oil (303 mg, 74%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.29 (m, 2H), 7.28 – 7.21 (m, 3H), 4.55 – 4.31 (m, 1H), 3.06 (dd, *J* = 13.5, 5.9 Hz, 1H), 2.78 (dd, *J* = 13.5, 6.8 Hz, 1H), 2.54 – 2.32 (m, 4H), 1.88 – 1.65

(m, 4H), 1.24 (d, *J* = 6.3 Hz, 3H). **^{13}C-NMR (**101 MHz, $CDCl_3$) δ 166.2, 139.0, 129.8, 128.2, 126.1, 79.2, 42.3, 31.1, 28.0, 25.3, 24.8, 19.4. **HRMS** (ESI) *m/z* calculated for $C_{14}H_{20}NO^+$ $[M+H]^+$: 218.1535, found: 218.1539

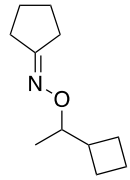
Cyclopentanone *O*-(6-methylhept-5-en-2-yl) oxime (3.58p)



Oxime **3.76p** was synthesized following general procedure **C** starting from 2-((6-Methylhept-5-en-2-yl)oxy)isoindoline-1,3-dione **(S3.1p)** (362 mg, 1.32 mmol) and cyclopentanone (334 mg, 3.9 mmol). The crude product was purified by flash chromatography affording **3.76p** as a pale-yellow oil (258 mg, 93%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.10 (ddq, *J* = 8.6, 5.7, 1.3 Hz, 1H), 4.09 (h, *J* = 6.3 Hz, 1H), 2.41 – 2.29 (m, 4H), 2.02 (q, *J* = 7.8 Hz, 2H), 1.75 – 1.67 (m, 4H), 1.65 (t, *J* = 1.3 Hz, 3H), 1.67 – 1.58 (m, 4H), 1.57 (s, 3H), 1.50 – 1.38 (m, 1H), 1.19 (dd, *J* = 6.2, 0.9 Hz, 3H). **^{13}C-NMR (**101 MHz, $CDCl_3$) δ 165.5, 131.5, 124.5, 78.1, 36.0, 31.0, 27.7, 25.8, 25.3, 24.8, 24.2, 20.1, 17.6. **HRMS** (ESI) *m/z* calculated for $C_{13}H_{24}NO^+$ $[M+H]^+$: 210.1852, found: 210.1855

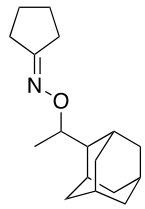
Cyclopentanone *O*-(1-cyclobutylethyl) oxime (3.58j)



Oxime **3.58j** was obtained following the general procedure **C** starting from 2-(1-Cyclobutylethoxy)isoindoline-1,3-dione **(S3.1j)** (300 mg, 1.223 mmol) and cyclopentanone (325 µl, 3.67 mmol). The crude product was purified by flash chromatography affording **3.58j** as a colorless oil (195 mg, 88%).

^{1}H-NMR (500 MHz, $CDCl_3$) δ 4.03 (dq, *J* = 7.6, 6.2 Hz, 1H), 2.42 – 2.30 (m, 5H), 2.01 – 1.75 (m, 6H), 1.74 – 1.68 (m, 4H), 1.09 (d, *J* = 6.2 Hz, 3H). **^{13}C-NMR (**126 MHz, $CDCl_3$) δ 165.7, 82.1, 40.6, 31.1, 27.7, 25.3, 25.2, 24.8, 24.6, 18.4, 17.5. **HRMS** (ESI) *m/z* calculated for $C_{11}H_{20}NO^+$ $[M+H]^+$: 182.1539, found: 182.1527

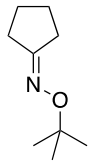
Cyclopentanone *O*-(1-((1*R*,3*S*,5*r*,7*r*)-adamantan-2-yl)ethyl) oxime (3.76m)



Oxime **3.76m** was synthesized following general procedure **C** starting from 2-(1-((1s,3s)-adamantan-1-yl)ethoxy)isoindoline-1,3-dione (139 mg, 0,427 mmol) and cyclopentanone (108 mg, 3 mmol). The crude product was purified by flash chromatography affording **3.76k** as a yellow oil (83 mg, 74%).

^{1}H-NMR (500 MHz, $CDCl_3$) δ 3.65 (q, *J* = 6.4 Hz, 1H), 2.40 (dddq, *J* = 7.2, 3.5, 2.2, 1.1 Hz, 2H), 2.38 – 2.32 (m, 2H), 1.96 (p, *J* = 3.2 Hz, 3H), 1.78 – 1.68 (m, 7H), 1.65 (m, 6H), 1.53 (m, 3H), 1.11 (d, *J* = 6.5 Hz, 3H). **^{13}C-NMR (**126 MHz, $CDCl_3$) δ 165.3, 86.4, 38.5, 37.5, 36.5, 31.1, 28.6, 27.8, 25.3, 24.8, 13.8. **HRMS** (ESI) *m/z* calculated for $C_{17}H_{28}NO^+$ $[M+H]^+$: 262.2174, found: 262.2165

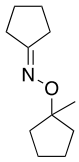
Cyclopentanone *O*-(*tert*-butyl) oxime (3.76k)



Oxime **3.76k** was synthesized following general procedure **C** starting from 2-(*tert*-Butoxy)isoindoline-1,3-dione (**S3.1k**) (438 mg, 2.0 mmol) and cyclopentanone (505 mg, 6 mmol). The crude product was purified by flash chromatography affording **3.76k** as a yellow oil (223 mg, 72%).

^{1}H-NMR (500 MHz, $CDCl_3$) δ 2.48 – 2.25 (m, 4H), 1.83 – 1.65 (m, 4H), 1.25 (s, 7H). **^{13}C-NMR (**126 MHz, $CDCl_3$) δ 165.1, 77.3, 31.1, 27.8, 27.6, 25.3, 24.8. **HRMS** (APCI) *m/z* calculated for $C_9H_{18}NO^+$ $[M+H]^+$: 156.1383, found: 156.1381.

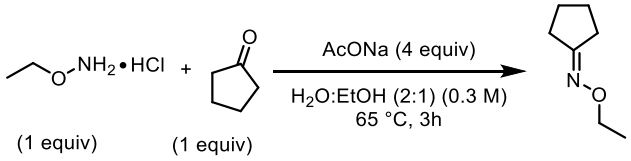
Cyclopentanone *O*-(1-methylcyclopentyl) oxime (3.58l)



Oxime **3.58l** was synthesized following general procedure **C** starting from 2-((1-methylcyclopentyl)oxy)isoindoline-1,3-dione (**S3.1l**) (82 mg, 0.33 mmol) and cyclopentanone (89 µl, 1 mmol). The crude product was purified by flash chromatography affording **3.76l** as a yellow oil (47 mg, 77%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.39 – 2.31 (m, 4H), 1.94 (dddd, *J* = 13.1, 7.2, 3.1, 1.3 Hz, 2H), 1.70 (m, 6H), 1.58 (m, 2H), 1.52 – 1.41 (m, 2H), 1.37 (s, 3H). **^{13}C-NMR (**101 MHz, $CDCl_3$) δ 165.5, 88.5, 38.1, 31.0, 27.5, 25.2, 25.0, 24.7, 24.5. **HRMS** (ESI) *m/z* calculated for $C_{11}H_{20}NO^+$ $[M+H]^+$: 182.1544, found: 182.1539.

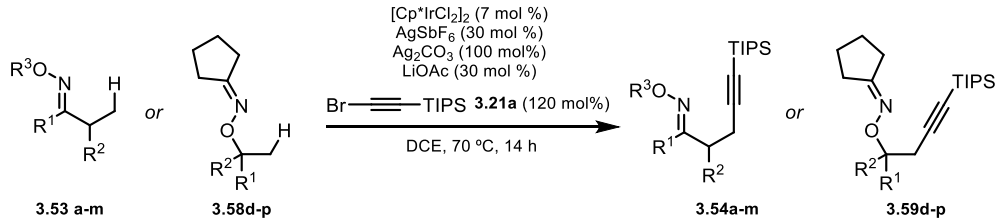
Cyclopentanone *O*-ethyl oxime (3.58e)



Ethoxyamine hydrochloride (585 mg, 6,00 mmol, 3 equiv) and sodium acetate (656 mg, 8,00 mmol, 4 equiv) were added to a stirred solution of cyclopentanone (177 µl, 2 mmol, 1 equiv) in Water (4 mL) and EtOH (2 mL) and the mixture was stirred at 65 ºC for 3h. After cooling to room temperature, the aqueous layer was extracted with EtOAc and the extracted organic phase dried over Na_2SO_4 filtered and dried under reduced pressure. The residue was purified by column chromatography on silica gel with pentane as eluent to give the pure oxime in 40% yield.

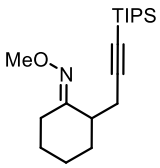
^{1}H-NMR (500 MHz, $CDCl_3$) δ 4.05 (q, *J* = 7.1 Hz, 1H), 2.43 – 2.24 (m, 2H), 1.81 – 1.65 (m, 2H), 1.22 (t, *J* = 7.0 Hz, 1H). **^{13}C-NMR (**126 MHz, $CDCl_3$) δ 166.1, 69.0, 31.1, 27.7, 25.2, 24.8, 14.9. **HRMS** (ESI) *m/z* calculated for $C_7H_{14}NO^+$ $[M+H]^+$: 128.1070, found: 128.1073.

General Procedure D: Iridium(III) catalyzed C(sp^3)-H alkynylation of oximes



In a glovebox, a microwave vial was charged with $[Cp^*IrCl_2]_2$ (7 mol %, 0.014 mmol, 11.2 mg), $AgSbF_6$ (30 mol %, 0.06 mol, 20.6 mg), LiOAc (30 mol %, 0.06 mmol, 4 mg), Ag_2CO_3 (100 mol%, 0.2 mmol, 55 mg) and filled with DCE (1.5 mL). The vial was sealed with and taken out of the glovebox. Substrate (0.2 mmol) and (bromoethynyl)triisopropylsilane (**3.28a**, 120 mol%, 2.4 mmol, 63 mg) were then added. The reaction was then stirred at 70 °C outside of the glovebox overnight. The reaction mixture was then cooled to room temperature and filtered through a pad of Celite, washed with CH_2Cl_2, and the solvent removed under reduced pressure. The crude mixture was purified by column chromatography on silica gel.

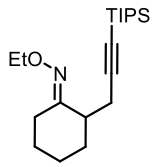
(*E*)-2-(3-(Triisopropylsilyl)prop-2-yn-1-yl)cyclohexan-1-one *O*-methyl oxime (3.54a)



Alkynylaed oxime **3.54a** was synthesized following general procedure **D** starting from (E)-2-methylcyclohexan-1-one O-methyl oxime (28.2 mg, 0.2 mmol). The crude product was purified by flash chromatography affording **3.54a** as a colorless oil (50 mg, 78%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 3.79 (s, 3H), 2.81 (ddd, *J* = 14.1, 5.6, 3.6 Hz, 1H), 2.73 – 2.59 (m, 1H), 2.44 – 2.30 (m, 2H), 2.20 – 1.95 (m, 2H), 1.81 – 1.62 (m, 2H), 1.56 – 1.41 (m, 3H), 1.05 (s, 21H). **^{13}C-NMR (**75 MHz, $CDCl_3$) δ 160.3, 107.7, 81.4, 61.2, 41.6, 32.3, 26.2, 24.2, 24.1, 22.2, 18.8, 11.4. **HRMS** (ESI) *m/z* calculated for $C_{19}H_{36}NOSi^+$ $[M+H]^+$: 322.2561, found: 322.2560.

(*E*)-2-(3-(Triisopropylsilyl)prop-2-yn-1-yl)cyclohexan-1-one *O*-ethyl oxime (3.54b)

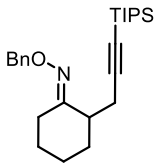


Alkynylaed oxime **3.54b** was synthesized following general procedure **D** starting from (E)-2-methylcyclohexan-1-one O-ethyl oxime (31.0 mg, 0.2 mmol). The crude product was purified by flash chromatography affording **3.54b** as a colorless oil (55 mg, 72%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 4.03 (q, *J* = 7.0 Hz, 2H), 2.91 – 2.79 (m, 1H), 2.74 – 2.60 (m, 1H), 2.43 – 2.31 (m, 2H), 2.19 – 1.96 (m, 2H), 1.79 – 1.64 (m, 2H), 1.48 (qt, *J* = 5.4, 1.7 Hz, 3H), 1.22 (t, *J* = 7.0 Hz, 3H), 1.09 – 1.03 (m, 21H). **^{13}C-NMR (**75 MHz, $CDCl_3$)

δ 159.9, 108.0, 81.3, 68.9, 41.7, 32.3, 26.1, 24.4, 24.2, 22.2, 18.8, 14.7, 11.4. **HRMS** (ESI) *m/z* calculated for $C_{20}H_{38}NOSi^+$ $[M+H]^+$: 336.2717, found: 336.2704.

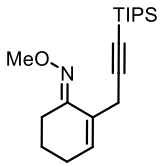
(*E*)-2-(3-(Triisopropylsilyl)prop-2-yn-1-yl)cyclohexan-1-one *O*-benzyl oxime (3.54c)



Alkynylaed oxime **3.54c** was synthesized following general procedure **D** starting from (E)-2-methylcyclohexan-1-one O-benzyl oxime (31.0 mg, 0.2 mmol). The crude product was purified by flash chromatography affording **3.54c** as a colorless oil (55 mg, 69%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.39 – 7.23 (m, 5H), 5.05 (s, 2H), 2.95 (dt, *J* = 14.0, 4.6 Hz, 1H), 2.78 – 2.60 (m, 1H), 2.38 (q, *J* = 3.8 Hz, 2H), 2.25 – 2.10 (m, 1H), 2.02 (ddd, *J* = 14.7, 9.9, 4.6 Hz, 1H), 1.70 (t, *J* = 6.1 Hz, 2H), 1.52 – 1.42 (m, 3H), 1.12 – 0.95 (m, 21H). **^{13}C-NMR (**75 MHz, $CDCl_3$) δ 160.9, 138.5, 128.4, 128.2, 127.7, 107.8, 81.4, 75.5, 41.8, 32.4, 26.2, 24.7, 24.3, 22.2, 18.8, 11.4. **HRMS** (ESI) *m/z* calculated for $C_{25}H_{40}NOSi^+$ $[M+H]^+$: 398.2874, found: 398.2871.

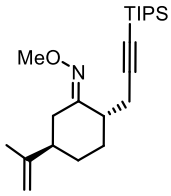
(*E*)-2-(3-(Triisopropylsilyl)prop-2-yn-1-yl)cyclohex-2-en-1-one *O*-methyl oxime (3.54d)



Alkynylated oxime **3.54d** was synthesized following general procedure **D** starting from (E)-2- (E)-2-methylcyclohex-2-en-1-one O-methyl oxime (27.8 mg, 0.2 mmol). The crude product was purified by flash chromatography affording **3.54d** as a colorless oil (35 mg, 55%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.53 (tt, *J* = 4.4, 1.7 Hz, 1H), 3.85 (s, 3H), 3.28 (m, 2H), 2.53 (m, 2H), 2.20 (m, 2H), 1.70 (m, 2H), 1.10 – 1. 05 (m, 21H). **^{13}C-NMR (**126 MHz, $CDCl_3$) δ 154.4, 133.1, 129.7, 105.9, 83.5, 61.9, 25.2, 23.1, 21.9, 21.3, 18.8, 11.5. **HRMS** (ESI) *m/z* calculated for $C_{19}H_{34}NOSi^+$ $[M+H]^+$: 320.2404, found: 320.2409.

(*E*)-5-(Prop-1-en-2-yl)-2-(3-(triisopropylsilyl)prop-2-yn-1-yl)cyclohexan-1-one *O*-methyl oxime (3.54e)

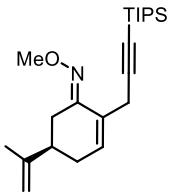


Alkynylated oxime **3.54e** was synthesized following general procedure **D** starting from(E)-2-methyl-5-(prop-1-en-2-yl)cyclohexan-1-one O-methyl oxime (36.3 mg, 0.2 mmol). The crude product was purified by flash chromatography affording **3.54e** as a colorless oil (30 mg, 42%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 4.74 (q, *J* = 1.4 Hz, 2H), 3.80 (s, 3H), 3.31 (ddd, *J* = 13.6, 3.9, 2.1 Hz, 1H), 2.83 – 2.72 (m, 1H), 2.41 – 2.22 (m, 3H), 2.05 (tt, *J* = 12.1, 3.6 Hz, 1H), 1.92 (ddd, *J* = 12.8, 3.4, 2.2 Hz, 1H), 1.74 (t, *J* = 1.1 Hz, 3H), 1.62 – 1.52 (m, 1H), 1.46 – 1.24 (m, 2H), 1.06 (d, *J* = 3.9 Hz, 21H). **^{13}C-NMR (**75 MHz, $CDCl_3$) δ 159.2, 148.6,

109.5, 108.1, 81.2, 61.4, 45.0, 42.6, 32.4, 30.8, 29.9, 21.7, 20.9, 18.8, 11.4. **HRMS** (ESI) *m/z* calculated for $C_{22}H_{40}NOSi^+$ $[M+H]^+$: 362.2874, found: 362.2873. α_D^{589}= -23.9 deg.cm^2.g^{-1}($CHCl_3$, c 0.1, 298 K).

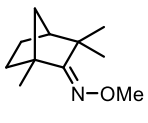
(*E*)-5-(Prop-1-en-2-yl)-2-(3-(triisopropylsilyl)prop-2-yn-1-yl)cyclohex-2-en-1-one *O*-methyl oxime (3.54f)



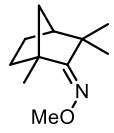
Alkynylated oxime **3.54f** was synthesized following general procedure **D** starting from(E)-2-methyl-5-(prop-1-en-2-yl)cyclohex-2-en-1-one O-methyl oxime (35.8 mg, 0.2 mmol). The crude product was purified by flash chromatography affording **3.54f** as a colorless oil (50 mg, 70%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.56 – 6.49 (m, 1H), 4.80 – 4.75 (m, 2H), 3.87 (s, 3H), 3.29 (dt, *J* = 3.3, 1.6 Hz, 2H), 3.13 (ddd, *J* = 16.4, 3.8, 1.7 Hz, 1H), 2.34 (dddd, *J* = 13.8, 12.6, 6.5, 2.8 Hz, 2H), 2.13 (dddd, *J* = 15.4, 12.4, 5.8, 3.0 Hz, 1H), 2.01 (dd, *J* = 16.4, 12.5 Hz, 1H), 1.75 (t, *J* = 1.1 Hz, 3H), 1.10 – 1.05 (m, 21H). **^{13}C-NMR (**75 MHz, $CDCl_3$) δ 154.5, 153.9, 148.0, 132.4, 129.5, 110.1, 105.8, 83.6, 61.9, 40.3, 30.5, 28.0, 21.7, 20.8, 18.8, 11.5. **HRMS** (ESI+) *m/z* calculated for $C_{24}H_{36}NOSi^+$ $[M+H]^+$: 382.2561, found: 382.2547. α_D^{589}= -19.6 deg.cm^2.g^{-1}($CHCl_3$, c 0.1, 298 K).

(1*S*,4*S*,*Z*)-1,3,3-Trimethylbicyclo[2.2.1]heptan-2-one *O*-methyl oxime (Z-3.53g) and **(1*S*,4*S*,*E*)-1,3,3-Trimethylbicyclo[2.2.1]heptan-2-one *O*-methyl oxime (E-3.53g)**



(Z)-3.53g



(E)-3.53g

The title compounds were synthesized according to a reported procedure in a separable mixture of isomers (Z:E = 2:1). The isomers have been assigned according to the same literature precedents[222]. The two geometrical isomers have been isolated and tested separately in the reaction.

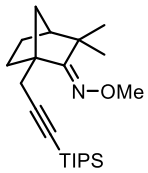
(Z-3.53g): **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 3.74 (s, 3H), 1.83 – 1.73 (m, 2H), 1.69 (dq, *J* = 10.04, 2.21 Hz, 1H), 1.60 – 1.46 (m, 2H), 1.45 – 1.37 (m, 1H), 1.31 (dd, *J* = 10.02, 1.52 Hz, 1H), 1.25 (s, 3H), 1.22 (s, 3H), 1.21 (s, 3H). **^{13}C-NMR (**101 MHz, $CDCl_3$) δ 172.9, 61.2, 50.1, 48.7, 44.7, 43.5, 34.6, 25.4, 23.5, 22.7, 17.3.

(E-3.53g): **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 3.70 (s, 3H), 1.83 (tt, *J* = 4.26, 2.10 Hz, 2H), 1.76 (dddd, *J* = 12.15, 9.40, 5.20, 2.85 Hz, 1H), 1.56 (tddd, *J* = 11.71, 6.68, 5.07, 3.51 Hz, 2H), 1.50 (s, 3H), 1.46 – 1.36 (m, 1H), 1.13 (s, 3H), 1.11 (s, 4H)*. **^{13}C-NMR (**101 MHz, $CDCl_3$) δ 171.1, 61.3, 52.1, 47.3, 45.3, 45.1, 34.2, 27.2, 25.3, 25.0, 20.2.

222 G. C. Dickmu, I. P. Smoliakova, *J. Organomet. Chem.* **2014**, *772*, 42–48.

*The methyl signal overlap with the one of a methylene proton.

(*Z*)-1,3-Dimethyl-3-(3-(triisopropylsilyl)prop-2-yn-1-yl)bicyclo[2.2.1]heptan-2-one *O*-methyl oxime (3.54g)

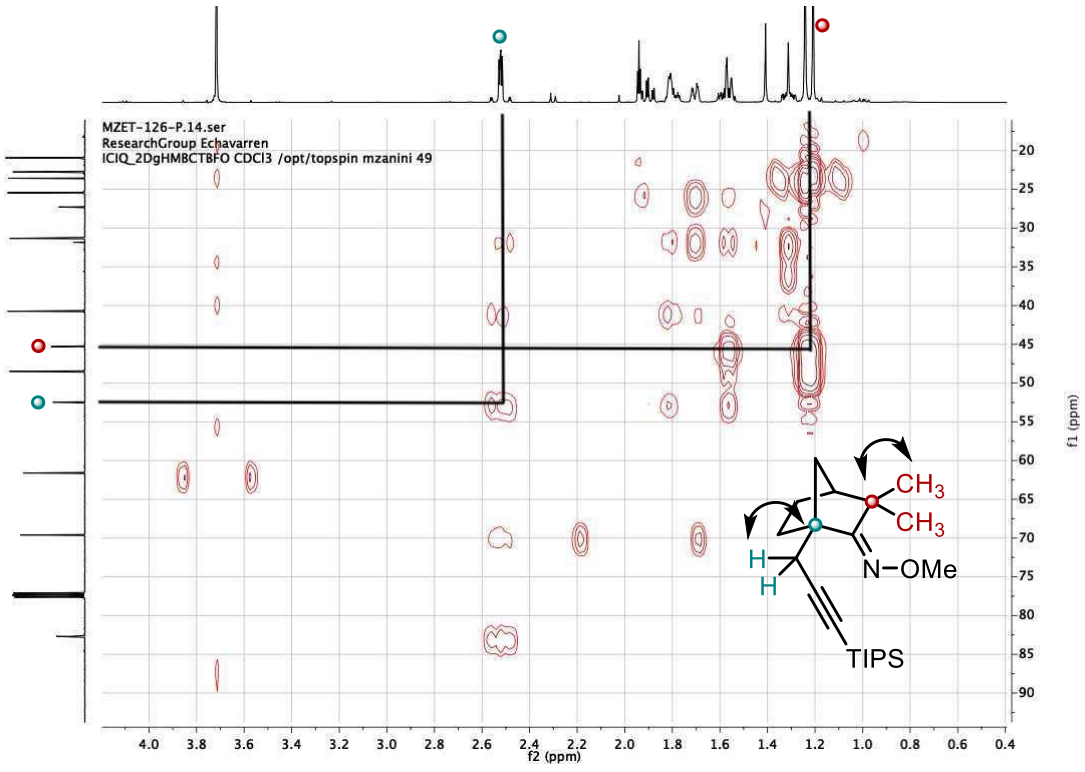


Alkynylated oxime **3.54g** was synthesized following general procedure **D** starting from (*Z*)-1,3,3-trimethylbicyclo[2.2.1]heptan-2-one O-methyl oxime (36.3 mg, 0.2 mmol). The crude product was purified by flash chromatography affording **3.54g** as a yellow oil (52 mg, 72%).*

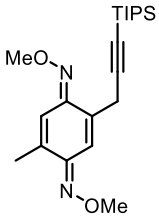
***(*E*-3.53g)** was recovered in 86% yield when submitted to the reaction conditions. No product of alkynylation was detected.

^{1}H-NMR (400 MHz, CDCl3) δ 3.75 (s, 3H), 2.64 (d, J = 17.4 Hz, 1H), 2.58 (d, J = 17.4 Hz, 1H), 1.95 (td, J = 12.3, 3.6 Hz, 1H), 1.89 – 1.77 (m, 3H), 1.65 – 1.53 (m, 2H), 1.35 (dddd, J = 14.3, 11.9, 5.4, 3.2 Hz, 1H), 1.28 (s, 3H), 1.24 (s, 3H), 1.14 – 0.99 (m, 21H). **^{13}C-NMR (**101 MHz, $CDCl_3$) δ 170.4, 106.9, 81.2, 61.3, 52.8, 48.3, 45.1, 40.7, 31.4, 25.4, 23.3, 22.6, 22.3, 18.8, 11.5. **HRMS** (ESI) *m/z* calculated for $C_{22}H_{40}NOSi^+$ $[M+H]^+$: 362.2874, found: 362.2866. α_D^{589}= +55.1 deg.cm^2.g^{-1}($CHCl_3$, c 0.1, 298 K).

The structure of the oxime was confirmed by HMBC correlation.



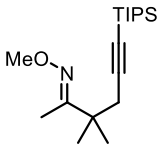
(1*E*,4*E*)-2-Methyl-5-(3-(triisopropylsilyl)prop-2-yn-1-yl)cyclohexa-2,5-diene-1,4-dione *O*,*O*-dimethyl dioxime (3.54h)



Monoakynylated oxime **3.54h** was synthesized following general procedure **D** starting from (*1E,4E*)-2,5-dimethylcyclohexa-2,5-diene-1,4-dione *O*,*O*-dimethyl dioxime (39 mg, 0.2 mmol). The crude product was purified by flash chromatography affording **3.54h** as a colorless oil (34 mg, 45%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.60 (t, *J* = 1.8 Hz, 1H), 6.94 (q, *J* = 1.3 Hz, 1H), 4.01 (s, 3H), 3.99 (s, 3H), 3.52 (d, *J* = 1.8 Hz, 2H), 2.10 (d, *J* = 1.4 Hz, 3H), 1.13 – 1.06 (m, 21H). **^{13}C-NMR (**75 MHz, $CDCl_3$) δ 151.2, 149.1, 138.1, 136.1, 116.5, 116.2, 104.2, 84.9, 62.9, 62.7, 21.7, 18.8, 17.5, 11.5. **HRMS** (ESI) *m/z* calculated for $C_{21}H_{35}N_2O_2Si^+$ $[M+H]^+$: 382.2561, found: 382.2547.

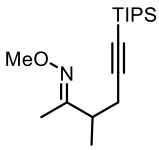
(*E*)-3,3-Dimethyl-6-(triisopropylsilyl)hex-5-yn-2-one *O*-methyl oxime (3.54i)



Akynylated oxime **3.54i** was synthesized following general procedure **D** starting from (*E*)-3,3-dimethylbutan-2-one *O*-methyl oxime (25.8 mg, 0.2 mmol). The crude product was purified by flash chromatography affording **3.54h** as a colorless oil (55 mg, 89%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 3.81 (s, 3H), 2.41 (s, 2H), 1.80 (s, 3H), 1.19 (s, 6H), 1.10 – 1.05 (m, 21H). **^{13}C-NMR (**75 MHz, $CDCl_3$) δ 161.0, 106.2, 82.5, 61.3, 40.4, 31.5, 25.2, 18.8, 11.4, 10.6. **HRMS** (APCI) *m/z* calculated for $C_{18}H_{36}NOSi$ $[M+H]^+$: 310.2561, found: 310.2571.

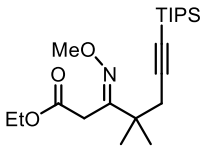
(*E*)-3-Methyl-6-(triisopropylsilyl)hex-5-yn-2-one *O*-methyl oxime (3.54j)



Akynylated oxime **3.54j** was synthesized following general procedure **D** starting from (*E*)-3-methylbutan-2-one *O*-methyl oxime (23 mg, 0.2 mmol). The crude product was purified by flash chromatography affording **3.54j** as a colorless oil (32 mg, 55%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 3.81 (d, *J* = 0.8 Hz, 3H), 2.63 – 2.53 (m, 1H), 2.50 – 2.27 (m, 2H), 1.79 (d, *J* = 0.8 Hz, 3H), 1.18 (d, *J* = 6.9 Hz, 3H), 1.12 – 1.06 (m, 21H). **^{13}C-NMR (**75 MHz, $CDCl_3$) δ 159.5, 106.5, 82.1, 61.3, 39.4, 29.8, 25.1, 18.7, 17.6, 11.4. **HRMS** (ESI) *m/z* calculated for $C_{17}H_{34}NOSi^+$ $[M+H]^+$: 296.2404, found: 296.2407.

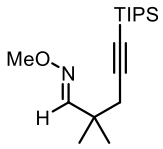
Ethyl (*E*)-3-(methoxyimino)-4,4-dimethyl-7-(triisopropylsilyl)hept-6-ynoate (3.54k)



Akynylated oxime **3.54k** was synthesized following general procedure **D** starting from ethyl (*E*)-3-(methoxyimino)-4,4-dimethylpentanoate (40 mg, 0.2 mmol). The crude product was purified by flash chromatography affording **3.54k** as a colorless oil (48 mg, 63%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.13 (q, *J* = 7.1 Hz, 2H), 3.80 (s, 3H), 3.24 (s, 2H), 2.45 (s, 2H), 1.28 – 1.14 (m, 9H), 1.10 – 0.95 (m, 22H). **^{13}C-NMR (**75 MHz, $CDCl_3$) δ 169.4, 157.8, 105.8, 82.9, 61.6, 60.9, 40.1, 32.1, 31.4, 24.9, 18.8, 14.2, 11.4. **HRMS** (ESI) *m/z* calculated for $C_{21}H_{39}NNaO_3Si^+$ $[M+Na]^+$: 404.2591, found: 404.2592.

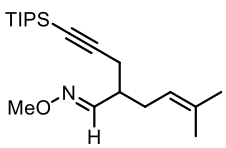
(*E*)-2,2-Dimethyl-5-(triisopropylsilyl)pent-4-ynal *O*-methyl oxime (3.54l)



Akynylated oxime **3.54l** was synthesized following general procedure **D** starting from (*E*)-pivalaldehyde *O*-methyl oxime (23 mg, 0.2 mmol). The crude product was purified by flash chromatography affording **3.54l** as a colorless oil (27 mg, 46%).

^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.36 (s, 1H), 3.80 (s, 3H), 2.35 (s, 2H), 1.19 (s, 6H), 1.17 – 0.98 (m, 21H). **^{13}C-NMR (**126 MHz, $CDCl_3$) δ 156.3, 105.2, 83.1, 61.4, 36.7, 32.1, 25.2, 18.8, 11.4. **HRMS** (APCI) *m/z* calculated for $C_{17}H_{34}NOSi^+$ $[M+H]^+$: 296.2404, found: 296.2412.

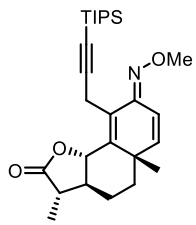
(*E*)-6-Methyl-2-(3-(triisopropylsilyl)prop-2-yn-1-yl)hept-5-enal *O*-methyl oxime (3.54m)



Alkynylated oxime **3.54m** was synthesized following general procedure **D** starting from (*E*)-2,5-dimethylhex-4-enal *O*-methyl oxime (31 mg, 0.2 mmol). The crude product was purified by flash chromatography affording **3.54m** as a colorless oil (27 mg, 39%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.22 (d, *J* = 7.3 Hz, 1H), 5.43 (tq, *J* = 7.2, 1.5 Hz, 1H), 3.81 (s, 3H), 2.95 – 2.92 (m, 2H), 2.36 (dt, *J* = 14.0, 7.2 Hz, 1H), 2.05 (dt, *J* = 8.8, 7.1 Hz, 2H), 1.67 – 1.66 (m, 3H), 1.55 (s, 3H), 1.46 – 1.36 (m, 2H), 1.12 – 1.05 (m, 21H). **^{13}C-NMR (**101 MHz, $CDCl_3$) δ 155.2, 130.7, 125.3, 106.2, 82.7, 61.3, 34.7, 34.0, 30.1, 25.6, 18.8, 18.3, 16.3, 11.5. **HRMS** (APCI) *m/z* calculated for $C_{21}H_{40}NOSi^+$ $[M+H]^+$: 350.2874, found: 350.2863.

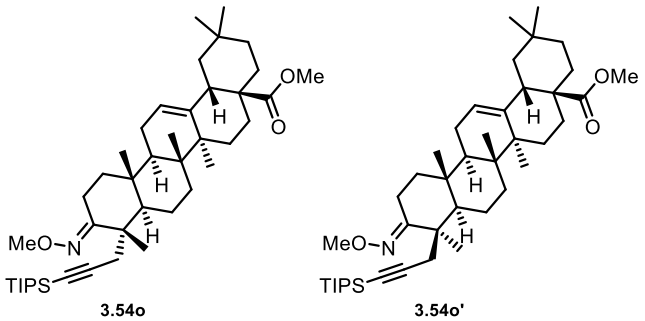
(3*S*,3a*S*,5a*S*,9b*S*,*E*)-8-(Methoxyimino)-3,5a-dimethyl-9-(3-(triisopropylsilyl)prop-2-yn-1-yl)-3a,4,5,5a,8,9b-hexahydronaphtho[1,2-*b*]furan-2(3*H*)-one (3.54n)



Akynylated oxime **3.54n** was synthesized following general procedure **D** starting from (3S,3aS,5aS,9bS,E)-8-(methoxyimino)-3,5a,9-trimethyl-3a,4,5,5a,8,9b-hexahydronaphtho[1,2-b]furan-2(3H)-one (55 mg, 0.2 mmol). The crude product was purified by flash chromatography affording **3.54n** as a white oil (75 mg, 82%).

M. p.: 97 -100 ºC. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 6.78 (d, *J* = 10.2 Hz, 1H), 5.93 (d, *J* = 10.2 Hz, 1H), 4.74 (d, *J* = 11.2 Hz, 1H), 3.91 (s, 3H), 3.78 – 3.62 (m, 2H), 2.32 (dq, *J* = 12.2, 6.9 Hz, 1H), 2.02 – 1.92 (m, 1H), 1.90 – 1.79 (m, 1H), 1.74 (ddd, *J* = 13.1, 3.7, 2.2 Hz, 1H), 1.69 – 1.57 (m, 1H), 1.47 (td, *J* = 13.0, 4.4 Hz, 1H), 1.32 – 1.15 (m, 6H), 1.00 – 0.75 (m, 21H). **^{13}C-NMR (**75 MHz, $CDCl_3$) δ 177.7, 147.4, 144.7, 139.2, 123.3, 113.1, 108.6, 81.9, 78.4, 62.2, 53.2, 41.1, 41.0, 38.6, 25.7, 23.8, 18.7, 16.9, 12.4, 11.4. **HRMS** (ESI) *m/z* calculated for $C_{27}H_{41}NNaO_3Si^+$ $[M+Na]^+$: 478.2748, found: 478.2751. $\boldsymbol{\alpha_D^{589}}$= -138.8 deg.cm^2.g^{-1}($CHCl_3$, c 0.1, 298 K).

Methyl (4aS,6aS,6bR,8aR,9S,12aR,12bR,14bS,E)-10-(methoxyimino)-2,2,6a,6b,9,12a-hexamethyl-9-(3-(triisopropylsilyl)prop-2-yn-1-yl)-1,3,4,5,6,6a,6b,7,8,8a,9,10,11,12,12a,12b,13,14b-octadecahydropicene-4a(2H)-carboxylate and Methyl(4a*S*,6a*S*,6b*R*,8a*R*,9*R*,12a*R*,12b*R*,14b*S*,*E*)-10-(methoxyimino)-2,2,6a,6b,9,12a-hexamethyl-9-(3-(triisopropylsilyl)prop-2-yn-1-yl)1,3,4,5,6,6a,6b,7,8,8a,9,10,11,12,12a, 12b,13,14b-octadecahydropicene-4a(2*H*)-carboxylate (3.54o and 3.54o')



3.54o 3.54o'

The two compounds **3.54o and 3.54o'** were synthesized following general procedure **D** starting from methyl (4aS,6aS,6bR,8aR,12aR,12bR,14bS,*E*)-10-(methoxyimino)-2,2,6a,6b,9,9,12a-heptamethyl-1,3,4,5,6,6a,6b,7,8,8a,9,10,11,12,12a,12b,13,14b-octadecahydropicene-4a(2H)-carboxylate **(3.53r)** (99 mg, 0.2 mmol). The crude product was purified by flash chromatography and the two diasteroisomer could be separated affording overall 74 mg of product (55% yield, d.r. = 1.7:1). The major diastereoisomer was assigned according to previously reported directed C-H functionalization of the oxime derivative of **3.53r**.[216c,d.]

Methyl (4aS,6aS,6bR,8aR,9S,12aR,12bR,14bS,E)-10-(methoxyimino)-2,2,6a,6b,9,12a-hexamethyl-9-(3-(triisopropylsilyl)prop-2-yn-1-yl)-1,3,4,5,6,6a,6b,7,8,8a,9,10,11,12,12a,12b,13,14b-octadecahydropicene-4a(2H)-carboxylate (3.54o)

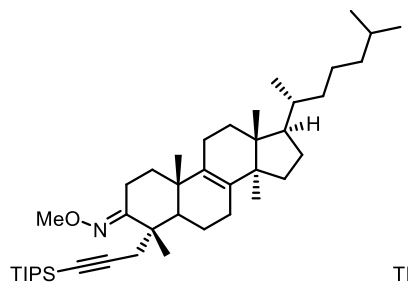
White solid. **M.p.** 217 -219 ºC **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 5.30 (t, *J* = 3.7 Hz, 1H), 3.81 (d, *J* = 1.5 Hz, 3H), 3.63 (d, *J* = 1.0 Hz, 3H), 2.95 (ddd, *J* = 17.2, 5.8, 2.4 Hz, 1H), 2.87 (dd, *J* = 14.0, 4.6 Hz, 1H), 2.79 (d, *J* = 16.6 Hz, 1H), 2.35 (d, *J* = 16.6 Hz, 1H), 2.15 – 2.04 (m, 1H), 2.02 – 1.89 (m, 3H), 1.78 (dd, *J* = 11.8, 2.1 Hz, 1H), 1.74 – 1.65 (m, 2H), 1.65 – 1.59 (m, 4H),

1.59 – 1.45 (m, 4H), 1.44 – 1.28 (m, 4H), 1.10 (s, 3H), 1.09 – 0.98 (m, 26H), 0.99 – 0.97 (m, 3H), 0.93 (s, 3H), 0.90 (s, 3H), 0.76 (s, 3H). **^{13}C-NMR (**126 MHz, $CDCl_3$) δ 178.4, 162.1, 144.0, 122.5, 107.8, 81.3, 61.3, 51.7, 50.0, 46.9, 46.7, 46.0, 43.3, 41.9, 41.5, 39.5, 36.7, 34.0, 33.3, 32.5, 32.3, 31.1, 30.9, 27.8, 25.9, 24.5, 23.8, 23.6, 23.2, 19.3, 18.9, 18.9, 18.7, 17.0, 14.7, 11.5. **HRMS** (ESI) *m/z* calculated for $C_{43}H_{72}NOSi^+$ $[M+H]^+$: 678.5276, found: 678.5277. **α_D^{589}**= +25.6 deg.cm^2.g^{-1}($CHCl_3$, c 0.3, 298 K).

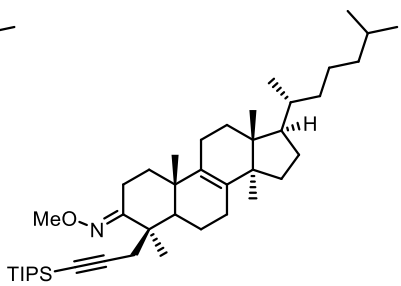
Methyl(4a*S*,6a*S*,6b*R*,8a*R*,9*R*,12a*R*,12b*R*,14b*S*,*E*)-10-(methoxyimino)-2,2,6a,6b,9,12a-hexamethyl-9-(3-(triisopropylsilyl)prop-2-yn-1-yl)1,3,4,5,6,6a,6b,7,8,8a,9,10,11,12,12a, 12b,13,14b-octadecahydropicene-4a(2*H*)-carboxylate (3.54o')

Amorphous solid. **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 5.27 (t, *J* = 3.6 Hz, 1H), 3.81 (s, 3H), 3.62 (s, 3H), 3.12 (ddd, *J* = 14.7, 4.4, 2.9 Hz, 1H), 2.85 (dd, *J* = 13.9, 4.6 Hz, 1H), 2.64 (d, *J* = 17.0 Hz, 1H), 2.38 (d, *J* = 17.0 Hz, 1H), 2.02 – 1.81 (m, 4H), 1.75 – 1.58 (m, 6H), 1.56 – 1.44 (m, 3H), 1.35 – 1.24 (m, 6H), 1.09 (s, 3H), 1.08 – 0.96 (m, 27H), 0.92 (s, 3H), 0.89 (s, 3H), 0.73 (s, 3H). **^{13}C-NMR (**126 MHz, $CDCl_3$) δ 178.4, 163.0, 144.0, 122.2, 106.0, 82.7, 61.2, 57.8, 51.7, 47.8, 46.9, 46.0, 43.7, 41.8, 41.4, 39.5, 37.4, 34.0, 33.2, 32.9, 32.5, 30.8, 30.5, 27.8, 26.8, 26.0, 23.8, 23.6, 23.3, 23.2, 19.4, 18.9, 18.8, 17.5, 16.9, 15.4, 11.5. **HRMS** (ESI) *m/z* calculated for $C_{43}H_{72}NOSi^+$ $[M+H]^+$: 678.5276, found: 678.5273. **α_D^{589}**= +30.7 deg.cm^2.g^{-1}($CHCl_3$, c 0.1, 298 K).

4*S*,10*S*,13*R*,14*R*,17*R*,*E*)-4,10,13,14-Tetramethyl-17-((*R*)-6-methylheptan-2-yl)-4-(3-(triisopropylsilyl)prop-2-yn-1-yl)-1,2,4,5,6,7,10,11,12,13,14,15,16,17-tetradecahydro-3*H*-cyclopenta[*a*]phenanthren-3-one *O*-methyl oxime and (4*R*,5*R*,10*S*,13*R*,14*R*,17*R*,*E*)-4,10,13,14-Tetramethyl-17-((*R*)-6-methvylheptan-2-yl)-4-(3-(triisopropylsilyl)prop-2-yn-1-yl)-1,2,4,5,6,7,10,11,12,13,14,15,16,17-tetradecahydro-3*H*-cyclopenta[*a*]phenanthren-3-one *O*-methyl oxime (3.54p and 3.54p')



3.54p



3.5p'

The two compounds **3.54p** and **3.54p'** were synthesized following general procedure **D** starting from (10S,13R,14R,17R,E)-4,4,10,13,14-pentamethyl-17-((R)-6-methylheptan-2-yl)-1,2,4,5,6,7,10,11,12,13,14,15,16,17-tetradecahydro-3H-cyclopenta[a]phenanthren-3-one O-methyl oxime **(3.53s)** (91 mg, 0.2 mmol). The crude product was purified by flash

chromatography and the two diasteroisomer could be separated affording overall 80 mg of product (63% yield, d.r. = 4:1). The major diastereoisomer was assigned according to previously reported directed C-H functionalization of the oxime derivative of **3.53s**. [216c,d,.]

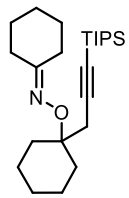
(4*S*,10*S*,13*R*,14*R*,17*R*,*E*)-4,10,13,14-Tetramethyl-17-((*R*)-6-methylheptan-2-yl)-4-(3-(triisopropylsilyl)prop-2-yn-1-yl)-1,2,4,5,6,7,10,11,12,13,14,15,16,17-tetradecahydro-3*H*-cyclopenta[*a*]phenanthren-3-one *O*-methyl oxime (3p)

Amorphous yellow solid. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 3.82 (s, 3H), 3.04 (ddd, *J* = 16.6, 5.6, 2.6 Hz, 1H), 2.80 (d, *J* = 16.6 Hz, 1H), 2.36 (d, *J* = 16.6 Hz, 1H), 2.13 – 2.07 (m, 4H), 2.04 – 2.00 (m, 2H), 1.95 – 1.90 (m, 2H), 1.81 (ddd, *J* = 12.8, 6.1, 2.5 Hz, 1H), 1.71 (d, *J* = 5.6 Hz, 1H), 1.54 – 1.47 (m, 3H), 1.35 (m, 2H), 1.26 (m, 5H), 1.11 (m, 2H), 1.06 (m, 5H), 1.03 (m, 21H), 0.98 (s, 1H), 0.89 – 0.86 (m, 15H), 0.70 (s, 3H). **^{13}C-NMR (**101 MHz, $CDCl_3$) δ 162.0, 135.1, 133.5, 107.6, 81.4, 61.2, 50.5, 50.0, 45.9, 44.5, 43.3, 39.5, 36.7, 36.5, 36.5, 34.1, 31.0, 31.0, 30.4, 29.7, 28.2, 28.0, 26.25, 24.1, 23.8, 22.8, 22.6, 21.0, 19.0, 18.8, 18.7, 18.5, 18.3, 15.9, 11.4. **HRMS** (ESI) *m/z* calculated for $C_{42}H_{73}NNaOSi^+$ $[M+Na]^+$: 658.5354, found: 658.5340 α_D^{589}= +42.4 deg.cm^2.g^{-1}($CHCl_3$, c 0.15, 298 K).

(4*R*,5*R*,10*S*,13*R*,14*R*,17*R*,*E*)-4,10,13,14-Tetramethyl-17-((*R*)-6-methvylheptan-2-yl)-4-(3-(triisopropylsilyl)prop-2-yn-1-yl)-1,2,4,5,6,7,10,11,12,13,14,15,16,17-tetradecahydro-3*H*-cyclopenta[*a*]phenanthren-3-one *O*-methyl oxime (3p')

Amorphous white solid. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 3.81 (s, 3H), 3.22 – 3.13 (m, 1H), 2.74 (d, *J* = 17.0 Hz, 1H), 2.34 (d, *J* = 17.0 Hz, 1H), 2.07 – 1.96 (m, 4H), 1.94 – 1.88 (m, 2H), 1.82 (ddd, *J* = 11.7, 8.0, 3.5 Hz, 2H), 1.70 (q, *J* = 6.5, 4.9 Hz, 1H), 1.61 – 1.55 (m, 1H), 1.48 – 1.41 (m, 2H), 1.38 – 1.29 (m, 6H), 1.25 (m, 2H), 1.11 (dd, *J* = 2.6, 1.4 Hz, 7H), 1.07 – 1.04 (m, 21H), 1.03 – 0.99 (m, 1H), 0.90 – 0.83 (m, 15H), 0.69 (s, 3H). **^{13}C-NMR (**101 MHz, $CDCl_3$) δ 162.7, 134.8, 134.0, 105.7, 82.5, 61.0, 52.8, 50.5, 49.8, 44.4, 43.7, 39.5, 37.2, 36.5, 36.5, 30.9, 30.8, 28.2, 28.0, 26.4, 26.14, 24.2, 24.1, 22.8, 22.5, 21.0, 19.2, 19.0, 18.7, 18.0, 15.8, 11.3. **HRMS** (ESI) *m/z* calculated for $C_{42}H_{73}NNaOSi^+$ $[M+Na]^+$: 658.5354, found: 658.5342 α_D^{589}= +1.6 deg.cm^2.g^{-1}($CHCl_3$, c 0.1, 298 K).

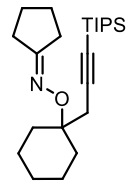
Cyclohexanone *O*-(1-(3-(triisopropylsilyl)prop-2-yn-1-yl)cyclohexyl) oxime (3.59c)



Alkynylated oxime **3.59c** was synthesized following general procedure **D** starting from cyclohexanone *O*-(1-methylcyclohexyl) oxime (40 mg, 0.19 mmol). The crude product was purified by flash chromatography affording **3.59c** as a pale-yellow oil (44 mg, 59%).

^{1}H-NMR (500 MHz, $CDCl_3$) δ 2.59 (s, 2H), 2.48 (td, *J* = 5.7, 4.9, 2.2 Hz, 2H), 2.20 – 2.13 (m, 2H), 1.94 – 1.86 (m, 2H), 1.64 (ddd, *J* = 13.5, 10.8, 6.3 Hz, 4H), 1.58 (dq, *J* = 6.5, 3.9, 3.0 Hz, 5H), 1.52 – 1.43 (m, 4H), 1.25 – 1.15 (m, 1H), 1.10 – 0.95 (m, 21H). **^{13}C-NMR (**126 MHz, $CDCl_3$) δ 159.5, 106.7, 81.7, 79.0, 33.3, 32.6, 30.7, 27.4, 26.2, 26.2, 25.8, 25.5, 22.0, 18.8, 11.5. **HRMS** (ESI) *m/z* calculated for $C_{24}H_{44}NOSi^+$ $[M+H]^+$: 390.3187, found: 364.3189.

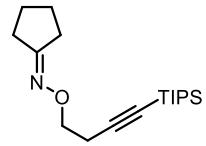
Cyclopentanone *O*-(1-(3-(triisopropylsilyl)prop-2-yn-1-yl)cyclohexyl) oxime (3.59d)



Alkynylated oxime **3.59d** was synthesized following general procedure **D** starting from cyclopentanone *O*-(1-methylcyclohexyl) oxime (39.1 mg, 0.2 mmol). The crude product was purified by flash chromatography affording **3.59d** as a pale yellow oil (67 mg,89%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.57 (s, 2H), 2.42 (ddd, *J* = 7.4, 5.1, 2.8 Hz, 2H), 2.36 – 2.30 (m, 2H), 1.94 – 1.85 (m, 2H), 1.75 – 1.68 (m, 4H), 1.68 – 1.56 (m, 4H), 1.54 – 1.43 (m, 4H), 1.10 – 1.03 (m, 21H).**^{13}C-NMR (**126 MHz, $CDCl_3$) δ 165.8, 106.5, 81.7, 79.2, 33.5, 31.1, 31.0, 27.6, 25.8, 25.4, 24.8, 22.0, 18.8, 11.5. **HRMS** (ESI) *m/z* calculated for $C_{23}H_{42}NOSi^+$ $[M+H]^+$: 376.3030, found: 376.3044.

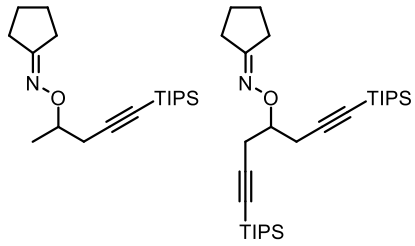
Cyclopentanone *O*-(4-(triisopropylsilyl)but-3-yn-1-yl) oxime (3.59e)



Alkynylated oxime **3.59e**was synthesized following general procedure **D** starting from cyclopentanone *O*-ethyl oxime (25.4 mg, 0.2 mmol). The crude product was purified by flash chromatography affording **3.59e** as a colorless oil (31 mg,50%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.13 (t, *J* = 7.1 Hz, 2H), 2.59 (t, *J* = 7.1 Hz, 2H), 2.45 – 2.31 (m, 4H), 1.80 – 1.66 (m, 4H), 1.12 – 0.97 (m, 21H). **^{13}C-NMR (**101 MHz, $CDCl_3$) δ 167.1, 105.5, 81.6, 71.8, 31.1, 27.8, 25.3, 24.8, 21.2, 18.7, 11.4. **HRMS** (ESI) *m/z* calculated for $C_{18}H_{34}NOSi^+$ $[M+H]^+$: 308.2404, found: 308.2403.

Cyclopentanone *O*-(5-(triisopropylsilyl)pent-4-yn-2-yl) oxime (3.59f) and cyclopentanone *O*-(1,7-bis(triisopropylsilyl)hepta-1,6-diyn-4-yl) oxime (3.59f')



Alkynylated oxime **3.59f** and **3.59f'** were synthesized following general procedure **D** starting from cyclopentanone *O*-isopropyl oxime (25.4 mg, 0.2 mmol). The two product were separated by flash chromatography affording **3.59f** as a colorless oil (24 mg, 44%) and **3.59f'** as a colorless oil (18 mg, 21%).

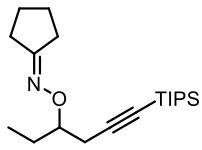
Cyclopentanone *O*-(5-(triisopropylsilyl)pent-4-yn-2-yl) oxime (3.59f)

^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.35 – 4.21 (m, 1H), 2.64 (dd, *J* = 16.6, 4.1 Hz, 1H), 2.47 – 2.41 (dd, *J* = 16.6, 7.6 Hz, 1H), 2.41 (m, 4H), 1.72 (ddp, *J* = 5.8, 3.8, 1.9 Hz, 4H), 1.35 (d, *J* = 6.3 Hz, 3H), 1.12 – 0.96 (m, 21H). **^{13}C-NMR (**101 MHz, $CDCl_3$) δ 166.7, 105.5, 82.0, 76.9, 31.1, 27.9, 27.1, 25.3, 24.8, 19.0, 18.8, 11.4. **HRMS** (ESI) *m/z* calculated for $C_{19}H_{36}NOSi^+$ $[M+H]^+$: 322.2561, found: 322.2564.

Cyclopentanone *O*-(1,7-bis(triisopropylsilyl)hepta-1,6-diyn-4-yl) oxime (3.59f')

^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.28 (p, *J* = 5.7 Hz, 1H), 2.73 (dd, *J* = 5.8, 1.0 Hz, 4H), 2.46 – 2.30 (m, 4H), 1.76 – 1.67 (m, 4H), 1.17 – 0.94 (m, 42H). **^{13}C-NMR (**101 MHz, $CDCl_3$) δ 167.4, 104.8, 82.4, 79.0, 31.1, 27.9, 25.3, 24.8, 24.1, 18.8, 18.7, 18.7, 11.4. **HRMS** (ESI) *m/z* calculated for $C_{30}H_{56}NOSi_2^+$ $[M+H]^+$: 502.3895, found: 502.3896.

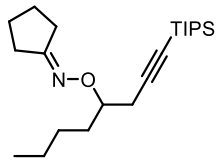
Cyclopentanone *O*-(6-(triisopropylsilyl)hex-5-yn-3-yl) oxime (3.59g)



Alkynylated oxime **3.59g**was synthesized following general procedure **D** starting from cyclopentanone *O*-(sec-butyl) oxime (31 mg, 0.2 mmol). The crude product was purified by flash chromatography affording **3.59g** as a colorless oil (48 mg, 72%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.06 (tt, *J* = 7.3, 4.7 Hz, 1H), 2.62 (dd, *J* = 16.8, 4.4 Hz, 1H), 2.48 (dd, *J* = 16.8, 7.2 Hz, 1H), 2.44 – 2.30 (m, 4H), 1.87 – 1.75 (m, 1H), 1.72 (tq, *J* = 5.6, 2.1 Hz, 5H), 1.10 – 1.02 (m, 21H). **^{13}C-NMR (**101 MHz, $CDCl_3$) δ 166.7, 105.7, 81.9, 81.8, 31.1, 27.8, 25.8, 25.3, 25.0, 24.8, 18.8, 11.4, 9.9. **HRMS** (ESI) *m/z* calculated for $C_{20}H_{38}NOSi^+$ $[M+H]^+$: 336.2717, found: 336.2719.

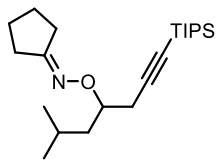
Cyclopentanone *O*-(1-(triisopropylsilyl)oct-1-yn-4-yl) oxime (3.59h)



Alkynylated oxime **3.59h**was synthesized following general procedure **D** starting from cyclopentanone *O*-hexan-2-yl oxime (37 mg, 0.2 mmol). The crude product was purified by flash chromatography affording **3.59h** as a colorless oil (45 mg, 62%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.11 (tt, *J* = 7.5, 4.7 Hz, 1H), 2.62 (dd, *J* = 16.8, 4.1 Hz, 1H), 2.47 (dd, *J* = 16.8, 7.3 Hz, 1H), 2.42 – 2.31 (m, 4H), 1.87 – 1.60 (m, 6H), 1.50 – 1.27 (m, 4H), 1.15 – 0.94 (m, 21H), 0.90 (t, *J* = 7.1 Hz, 3H). **^{13}C-NMR (**101 MHz, $CDCl_3$) δ 166.7, 105.8, 82.0, 80.9, 32.6, 31.2, 28.0, 27.9, 25.6, 25.4, 24.9, 23.0, 18.9, 14.2, 11.6. **HRMS (ESI)** *m/z* calculated for $C_{22}H_{42}NOSi^+$ $[M+H]^+$: 364.3030, found: 364,3031

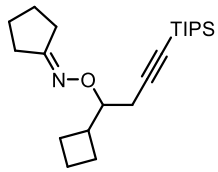
Cyclopentanone *O*-(6-methyl-1-(triisopropylsilyl)hept-1-yn-4-yl) oxime (3.59i)



Alkynylated oxime **3.59i** was synthesized following general procedure **D** starting from cyclopentanone *O*-(4-methylpentan-2-yl) oxime (37 mg, 0.2 mmol). The crude product was purified by flash chromatography affording **3.59i** as a colorless oil (52 mg, 72%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.19 (tdd, *J* = 7.4, 5.9, 3.8 Hz, 1H), 2.64 (dd, *J* = 16.7, 3.8 Hz, 1H), 2.45 (dd, *J* = 16.7, 7.6 Hz, 1H), 2.41 – 2.32 (m, 4H), 1.81 (dq, *J* = 13.4, 6.7 Hz, 1H), 1.76 – 1.69 (m, 4H), 1.64 – 1.57 (m, 2H), 1.10 – 1.02 (m, 21H), 0.92 (d, *J* = 6.7 Hz, 6H). **^{13}C-NMR (**126 MHz, $CDCl_3$) δ 166.6, 105.8, 81.9, 79.2, 41.9, 31.1, 27.9, 26.0, 25.3, 24.9, 24.8, 23.5, 22.6, 18.8, 11.4. **HRMS** (ESI) *m/z* calculated for $C_{22}H_{42}NOSi^+$ $[M+H]^+$: 364.3030, found: 364.3037.

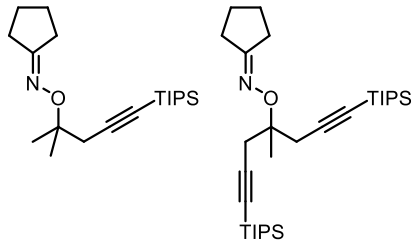
Cyclopentanone *O*-(1-cyclobutyl-4-(triisopropylsilyl)but-3-yn-1-yl) oxime (3.59j)



Alkynylated oxime **3.59j** was synthesized following general procedure **D** starting from cyclopentanone *O*-(1-cyclobutylethyl) oxime (36.3 mg, 0.2 mmol). The crude product was purified by flash chromatography affording **3.59j** as a colorless oil (42 mg, 58%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.06 (td, *J* = 6.9, 4.4 Hz, 1H), 2.81 – 2.68 (m, 1H), 2.54 (dd, *J* = 16.9, 4.4 Hz, 1H), 2.48 – 2.38 (m, 3H), 2.34 (td, *J* = 7.1, 3.7 Hz, 2H), 2.04 – 1.96 (m, 2H), 1.95 – 1.82 (m, 3H), 1.82 – 1.75 (m, 1H), 1.72 (ddp, *J* = 5.7, 3.9, 2.0 Hz, 4H), 1.09 – 0.98 (m, 21H). **^{13}C-NMR (**101 MHz, $CDCl_3$) δ 166.7, 105.7, 83.7, 81.5, 38.2, 31.1, 27.9, 25.3, 24.9, 24.8, 24.8, 23.4, 18.8, 18.6, 11.5. **HRMS** (ESI) *m/z* calculated for $C_{22}H_{40}NOSi^+$ $[M+H]^+$: 362.2874, found: 364.2861.

Cyclopentanone *O*-(2-methyl-5-(triisopropylsilyl)pent-4-yn-2-yl) oxime (3.59k) and cyclopentanone *O*-(4-methyl-1,7-bis(triisopropylsilyl)hepta-1,6-diyn-4-yl) oxime (3.59k')



Alkynylated oxime **3.59k** and **3.59k'** were synthesized following general procedure **D** starting from cyclopentanone *O*-(tert-butyl) oxime (31 mg, 0.2 mmol). The crude product was purified by flash chromatography affording **3.59k** and **3.59k'** as a inseparable mixture (monoalk : bisalk = 3:1) (56 mg, 73%).

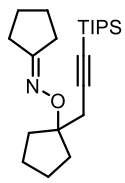
Cyclopentanone *O*-(2-methyl-5-(triisopropylsilyl)pent-4-yn-2-yl) oxime (3.59k)

^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.55 (s, 2H), 2.42 – 2.29* (m, 4H), 1.70* (tdd, *J* = 7.6, 3.6, 2.1 Hz, 4H), 1.36 (s, 6H), 1.09 – 1.02* (m, 21H). **^{13}C-NMR (**101 MHz, $CDCl_3$) δ 166.4, 106.5, 82.1, 78.9, 32.0, 31.1, 29.7, 27.7, 25.5, 25.3, 24.8, 18.8, 11.5. **HRMS** (ESI) *m/z* calculated for $C_{20}H_{38}NOSi^+$ $[M+H]^+$: 336.2717, found: 336.2716.

Cyclopentanone *O*-(4-methyl-1,7-bis(triisopropylsilyl)hepta-1,6-diyn-4-yl) oxime (3.59k')

^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.75 (d, *J* = 16.7 Hz, 2H), 2.64 (d, *J* = 16.7 Hz, 2H), 2.42 – 2.28* (m, 4H), 1.70* (tdd, *J* = 7.6, 3.6, 2.1 Hz, 4H), 1.44 (d, *J* = 3.6 Hz, 3H), 1.10 – 1.02* (m, 42H). **^{13}C-NMR (**101 MHz, $CDCl_3$) δ 165.8, 105.6, 81.7, 80.1, 32.0, 31.1, 29.7, 27.7, 25.5, 25.3, 24.8, 18.8, 11.5. **HRMS** (ESI) *m/z* calculated for $C_{31}H_{58}NOSi_2^+$ $[M+H]^+$: 516.4051, found: 516.4050.

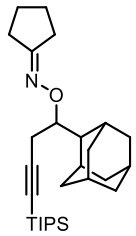
Cyclopentanone *O*-(1-(3-(triisopropylsilyl)prop-2-yn-1-yl)cyclopentyl) oxime (3.59l)



Alkynylated oxime **3.59d** was synthesized following general procedure **D** starting from cyclopentanone O-(1-methylcyclopentyl) oxime (36.3 mg, 0.2 mmol). The crude product was purified by flash chromatography affording **3.59d** as a pale-yellow oil (58 mg,80%).

^{1}H-NMR (500 MHz, $CDCl_3$) δ 2.71 (s, 2H), 2.40 – 2.30 (m, 4H), 1.97 – 1.89 (m, 2H), 1.88 – 1.79 (m, 2H), 1.76 – 1.66 (m, 6H), 1.65 – 1.57 (m, 2H), 1.09 – 1.00 (m, 21H). **^{13}C-NMR (**126 MHz, $CDCl_3$) δ 166.4, 106.9, 90.1, 80.9, 35.9, 31.2, 29.4, 27.8, 25.3, 25.1, 24.8, 18.8, 11.5. **HRMS** (ESI) *m/z* calculated for $C_{22}H_{40}NOSi^+$ $[M+H]^+$: 362.2874, found: 362.2871.

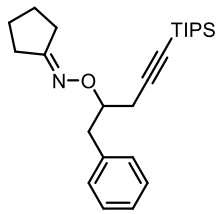
Cyclopentanone *O*-(1-((1*R*,3*S*,5*r*,7*r*)-adamantan-2-yl)-4-(triisopropylsilyl)but-3-yn-1-yl) oxime (3.59m)



Alkynylated oxime **3.59m** was synthesized following general procedure **D** starting from cyclopentanone *O*-(1-((3r,5r,7r)-adamantan-1-yl)ethyl) oxime (52.3 mg, 0.2 mmol). The crude product was purified by flash chromatography affording **3.59m** as a yellow oil (68 mg, 77%).

^{1}H-NMR (500 MHz, $CDCl_3$) δ 3.75 (t, *J* = 5.9 Hz, 1H), 2.57 (dd, *J* = 17.2, 5.9 Hz, 1H), 2.51 (dd, *J* = 17.2, 6.1 Hz, 1H), 2.47 – 2.38 (m, 2H), 2.33 (tt, *J* = 6.3, 2.3 Hz, 2H), 1.96 (p, *J* = 3.1 Hz, 3H), 1.71 (m, 10H), 1.64 (m, 6H), 1.16 – 0.92 (m, 21H). **^{13}C-NMR (**126 MHz, $CDCl_3$) δ 165.2, 107.4, 88.7, 81.3, 38.9, 37.4, 37.4, 31.0, 28.5, 27.9, 25.4, 24.8, 20.4, 18.8, 11.5. **HRMS** (ESI) *m/z* calculated for $C_{28}H_{48}NOSi^+$ $[M+H]^+$: 442.3500, found: 442.3503.

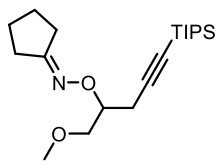
Cyclopentanone *O*-(1-phenyl-5-(triisopropylsilyl)pent-4-yn-2-yl) oxime (3.59n)



Alkynylated oxime **3.59n** was synthesized following general procedure **D** starting from cyclopentanone *O*-(1-phenylpropan-2-yl) oxime (43.5 mg, 0.2 mmol). The crude product was purified by flash chromatography affording **3.59n** as a yellow oil (51 mg, 64%).

^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.26 (h, *J* = 2.7 Hz, 4H), 7.23 – 7.17 (m, 1H), 4.34 (tdd, *J* = 7.1, 5.57, 4.1 Hz, 1H), 3.11 (dd, *J* = 13.8, 5.6 Hz, 1H), 3.01 (dd, *J* = 13.8, 6.9 Hz, 1H), 2.58 (dd, *J* = 16.8, 4.1 Hz, 1H), 2.48 (dd, *J* = 16.8, 7.3 Hz, 1H), 2.44 – 2.29 (m, 4H), 1.72 (ddp, *J* = 5.9, 3.8, 1.9 Hz, 4H), 1.14 – 1.03 (m, 21H). **^{13}C-NMR (**126 MHz, $CDCl_3$) δ 167.1, 138.5, 129.9, 128.3, 126.3, 105.4, 82.6, 81.3, 38.8, 31.1, 28.1, 25.3, 24.8, 24.7, 18.8, 11.5. **HRMS** (ESI) *m/z* calculated for $C_{25}H_{40}NOSi^+$ $[M+H]^+$: 398.2874, found: 398.2874.

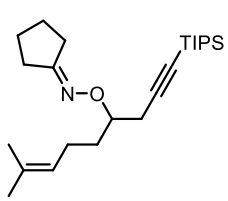
Cyclopentanone *O*-(1-methoxy-5-(triisopropylsilyl)pent-4-yn-2-yl) oxime (3.59o)



Alkynylated oxime **3.59o** was synthesized following general procedure **D** starting from cyclopentanone *O*-(1-methoxypropan-2-yl) oxime (34.2 mg, 0.2 mmol). The crude product was purified by flash chromatography affording **3.59o** as a yellow oil (36 mg, 51%).

^{1}H-NMR (500 MHz, $CDCl_3$) δ 4.35 – 4.28 (m, 1H), 3.68 – 3.65 (m, 2H), 3.39 (s, 3H), 2.63 (dd, *J* = 16.8, 4.9 Hz, 1H), 2.57 (dd, *J* = 16.8, 7.4 Hz, 1H), 2.45 – 2.40 (m, 2H), 2.37 – 2.32 (m, 2H), 1.71 (m, 4H), 1.09 – 0.99 (m, 21H). **^{13}C-NMR (**126 MHz, $CDCl_3$) δ 167.4, 104.9, 82.1, 79.9, 72.8, 59.5, 31.1, 28.0, 25.3, 24.8, 22.5, 18.7, 11.4. **HRMS** (ESI) *m/z* calculated for $C_{20}H_{38}NO_2Si^+$ $[M+H]^+$: 352.2666, found: 352.2661.

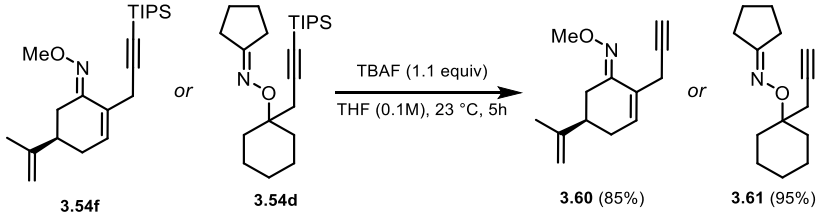
Cyclopentanone *O*-(8-methyl-1-(triisopropylsilyl)non-7-en-1-yn-4-yl) oxime (3.59p).



Alkynylated oxime **3.59p** was synthesized following general procedure **D** starting from cyclopentanone *O*-(6-methylhept-5-en-2-yl) oxime (42 mg, 0.2 mmol). The crude product was purified by flash chromatography affording **3.59p** as a yellow oil (25 mg, 32%). In addition, the starting oxime **3.58p** was recovered (18 mg, 43%).

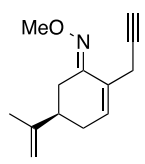
^{1}H-NMR (500 MHz, $CDCl_3$) δ 5.13 (tdq, *J* = 7.2, 2.9, 1.4 Hz, 1H), 4.11 (tt, *J* = 7.6, 4.3 Hz, 1H), 2.64 (dd, *J* = 16.8, 4.1 Hz, 1H), 2.48 (dd, *J* = 16.8, 7.5 Hz, 1H), 2.43 – 2.37 (m, 2H), 2.34 (m, 2H), 2.09 (q, *J* = 7.3, 6.8 Hz, 2H), 1.84 – 1.69 (m, 7H), 1.67 (d, *J* = 1.3 Hz, 3H), 1.59 (d, *J* = 1.3 Hz, 3H), 1.10 – 1.00 (m, 23H). **^{13}C-NMR (**126 MHz, $CDCl_3$) δ 166.6, 131.9, 124.3, 105.7, 81.9, 80.2, 32.9, 31.1, 27.9, 25.8, 25.5, 25.3, 24.8, 24.1, 18.8, 17.7, 11.4. **HRMS (ESI)** *m/z* calculated for $C_{24}H_{44}NOSi^+$ $[M+H]^+$: 390.3187, found: 390.3187.

Deprotection of TIPS-protecting group



TIPS-protected alkyne **3.54f** or **3.54d** (0.2 mmol, 1 equiv) was dissolved in dry THF under argon and TBAF (1.0M in THF, 1.1 equiv) was added dropwise at room temperature. The reaction mixture was stirred for 1 h and then quenched with $NaHCO_3$, diluted with Et_2O and the two phases separated. The organic phase was washed two times with water and once with brine, dried over Na_2SO_4 and concentrated and reduced pressure. The crude was then purified by flash chromatography on silica gel to yield the terminal alkyne **3.60** or **3.61**.

(*E*)-5-(Prop-1-en-2-yl)-2-(prop-2-yn-1-yl)cyclohex-2-en-1-one *O*-methyl oxime (3.60)

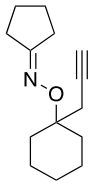


Alkyne **3.60** was synthesized starting from **3.54f** following the procedure above. The product was obtained as a pale-yellow oil in 85% yield.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.48 (ddq, *J* = 4.6, 3.2, 1.6 Hz, 1H), 4.81 – 4.73 (m, 2H), 3.88 (s, 3H), 3.21 (tt, *J* = 3.0, 1.5 Hz, 2H), 3.13 (ddd, *J* = 16.5, 3.9, 1.6

Hz, 1H), 2.41 – 2.28 (m, 2H), 2.13 (dt, *J* = 7.9, 2.9 Hz, 1H), 2.08 – 1.95 (m, 1H), 1.75 (d, *J* = 1.2 Hz, 3H). **^{13}C-NMR (**75 MHz, $CDCl_3$) δ 154.4, 147.8, 132.6, 129.0, 110.2, 81.8, 71.1, 62.0, 40.2, 30.4, 27.9, 20.8, 20.2. **HRMS** (ESI) *m/z* calculated for $C_{13}H_{18}NO^+$ $[M+H]^+$: 204.1383, found: 204.1381. $\boldsymbol{\alpha_D^{589}}$=-27.7 deg.cm^2.g^{-1}($CHCl_3$, c 0.1, 298 K).

Cyclopentanone *O*-(1-(prop-2-yn-1-yl)cyclohexyl) oxime (3.61)

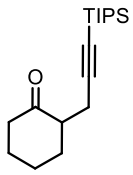


Alkyne **3.61** was synthesized starting from **3.58d** following the procedure above. The product was obtained as a colorles oil (42 mg, 95%).

^{1}H-NMR (500 MHz, $CDCl_3$) δ 2.52 (d, *J* = 2.7 Hz, 2H), 2.48 – 2.41 (m, 2H), 2.34 (tdd, *J* = 5.9, 2.3, 1.1 Hz, 2H), 1.95 (t, *J* = 2.7 Hz, 1H), 1.94 – 1.87 (m, 2H), 1.78 – 1.67 (m, 4H), 1.61 – 1.51 (m, 4H), 1.47 (m, 3H), 1.23 (dddd, *J* = 12.1, 10.6, 8.4, 4.4 Hz, 1H). **^{13}C-NMR (**126 MHz, $CDCl_3$) δ 166.4, 82.1, 78.8, 69.8, 33.5, 31.1, 29.3, 27.7, 25.7, 25.3, 24.8, 21.9. **HRMS** (ESI+) *m/z* calculated for $C_{14}H_{22}NO^+$ $[M+H]^+$: 220.1696, found: 220.1688.

Cleavage of the oxime direct group

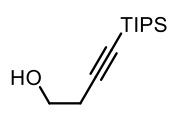
2-(3-(Triisopropylsilyl)prop-2-yn-1-yl)cyclohexan-1-one (3.62)



(*E*)-2-(3-(Triisopropylsilyl)prop-2-yn-1-yl)cyclohexan-1-one *O*-methyl oxime **(3.54a)** (32 mg, 0.1 mmol) was dissolved in THF (1 mL) and a 35% aqueous formaldehyde solution (1 mL) and a 10% aqueous HCl solution (0.5 mL) were then added. The mixture was stirred at 50 °C for 5h, and the mixture was diluted with ethyl acetate and neutralized with $NaHCO_3$ aq. The organic layer was dried over $MgSO_4$. Evaporation of the solvent and purification by column chromatography on silica gel yielded **9a** as a corlorless oil in 81% yield.

^{1}H-NMR (500 MHz, $CDCl_3$) δ 2.69 (dd, *J* = 17.3, 3.9 Hz, 1H), 2.53 – 2.37 (m, 3H), 2.35 – 2.21 (m, 2H), 2.15 – 2.03 (m, 1H), 1.93 (dtt, *J* = 11.3, 3.1, 1.6 Hz, 1H), 1.75 – 1.60 (m, 2H), 1.50 – 1.38 (m, 1H), 1.08 – 0.98 (m, 21H). **^{13}C-NMR (**126 MHz, $CDCl_3$) δ 211.0, 107.0, 81.8, 50.1, 42.0, 33.3, 27.9, 25.2, 20.4, 18.8, 11.4. **HRMS** (ESI) *m/z* calculated for $C_{18}H_{32}NaOSi^+$ $[M+H]^+$: 315.2115, found: 315.2118.

4-(Triisopropylsilyl)but-3-yn-1-ol (3.63a)

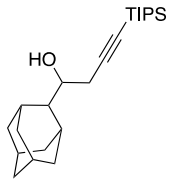


Cyclopentanone *O*-(4-(triisopropylsilyl)but-3-yn-1-yl) oxime **(3.59g)** (31 mg, 0.1 mmol) was dissolved in dry diethyl ether. $LiAlH_4$ (190 mg, 5 equiv) was added and the reaction mixture was stirred for 48h at room temperature. The reaction was then quenched with water, the two phases separated, and the aqueous phase

was extracted two other times with Et_2O, dried over $MgSO_4$ and purified by flash chromatography to yield **3.63a** in 89% yield.

^{1}H-NMR (500 MHz, $CDCl_3$) δ 3.72 (q, *J* = 6.0 Hz, 2H), 2.54 (t, *J* = 6.2 Hz, 2H), 1.79 (t, *J* = 6.6 Hz, 1H), 1.15 – 0.99 (m, 21H). **^{13}C-NMR (**126 MHz, $CDCl_3$) δ 105.1, 83.2, 61.3, 24.5, 18.7, 11.3. **HRMS** (ESI) *m/z* calculated for $C_{13}H_{27}OSi^+$ $[M+H]^+$: 227.1826, found: 227.1825.

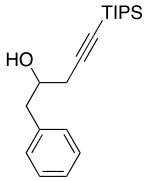
Adamantan-2-yl)-4-(triisopropylsilyl)but-3-yn-1-ol (3.63b)



Sodium cyanoborohydride (9,43 mg, 0,150 mmol) was added to a solution of cyclopentanone **3.59m** (22,09 mg, 0,050 mmol) in Acetic Acid (250 µl). The suspension was stirred at 50 °C overnight and then cooled down to room temperature. The mixture was filtered through a plug of Celite with K_2CO_3 on top. The volatiles were evaporated, and the crude mixture was purified by flash chromatography to yield compound **3.63b** as a colorless oil (14 mg, 78%).

^{1}H-NMR (500 MHz, $CDCl_3$) δ 3.25 (dt, J = 9.6, 3.1 Hz, 1H), 2.49 (dd, J = 16.7, 3.4 Hz, 1H), 2.37 (dd, J = 16.7, 9.6 Hz, 1H), 2.13 (d, J = 3.15 Hz, 1H), 1.99 (p, J = 3.2 Hz, 3H), 1.71 (dq, J = 9.9, 2.51 Hz, 3H), 1.69 – 1.60 (m, 6H), 1.53 (dq, J = 12.0, 2.5 Hz, 3H), 1.11 – 1.01 (m, 21H). **^{13}C-NMR (**126 MHz, $CDCl_3$) δ 106.5, 83.7, 77.6, 38.2, 37.3, 36.5, 28.5, 23.0, 18.8, 11.5, 11.4. **HRMS** (APCI) *m/z* calculated for $C_{23}H_{41}OSi^+$ $[M+H]^+$: 361.2921, found: 361.2924.

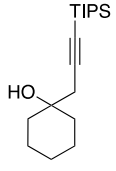
1-Phenyl-5-(triisopropylsilyl)pent-4-yn-2-ol (3.63c)



The alkynylated alcohol **3.63c** was obtained following the same procedure as for **3.63b** starting from **3.59n** (20 mg, 0.05 mmol). The crude product was purified by flash chromatography affording **3.63c** as a colorless oil (12.5 mg, 79%).

^{1}H-NMR (400 MHz, CDCl3) δ 7.35 – 7.29 (m, 2H), 7.27 – 7.22 (m, 3H), 3.98 (dq, J = 7.4, 5.7 Hz, 1H), 2.96 (dd, J = 13.5, 5.6 Hz, 1H), 2.85 (dd, J = 13.5, 7.3 Hz, 1H), 2.54 – 2.48 (m, 1H), 2.47 – 2.41 (m, 1H), 1.13 – 1.02 (m, 21H). **^{13}C-NMR (**101 MHz, $CDCl_3$) δ 138.1, 129.6, 128.7, 126.7, 104.6, 84.2, 71.2, 42.6, 28.2, 18.8, 11.4. **HRMS** (ESI) *m/z* calculated for $C_{20}H_{32}NaOSi^+$ $[M+Na]^+$: 339.2115, found:339.2131.

1-(3-(Triisopropylsilyl)prop-2-yn-1-yl)cyclohexan-1-ol (3.63d)

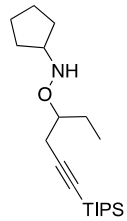


Sodium cyanoborohydride (9,43 mg, 0,150 mmol) was added to a solution of cyclopentanone *O*-(1-(3-(triisopropylsilyl)prop-2-yn-1-yl)cyclohexyl) oxime (**3.59n**) (18,78 mg, 0,050 mmol) in Acetic Acid (250 µl). The suspension was stirred at 23 °C overnight and then zinc powder (32,7 mg, 0,500 mmol) was added

together with Water (50,0 µl) and THF (50,0 µl). The mixture was then stirred at 70 ºC for 2 h. After that time, the reaction was cooled down to room temperature and filtered through a plug of Celite with K_2CO_3 and $MgSO_4$ on top. The volatiles were evaporated, and the crude mixture was purified by flash chromatography to yield compound **3.63d** as colorless oil (11 mg, 76%).

^{1}H-NMR (500 MHz, $CDCl_3$) δ 2.42 (s, 2H), 1.85 (bs, 1H, -OH), 1.64 (m, 4H), 1.58 – 1.51 (m, 2H), 1.51 – 1.44 (m, 2H), 1.31 – 1.21 (m, 2H), 1.10 – 1.00 (m, 21H). **^{13}C-NMR (**126 MHz, $CDCl_3$) δ 104.8, 84.3, 70.6, 37.0, 25.8, 22.4, 18.8, 11.4. **HRMS** (APCI) *m/z* calculated for $C_{18}H_{35}OSi^+$ $[M+H]^+$: 295.2452, found: 295.2451.

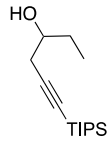
_N_-Cyclopentyl-_O_-(6-(triisopropylsilyl)hex-5-yn-3-yl)hydroxylamine (3.64)



Sodium cyanoborohydride (9,43 mg, 0,150 mmol) was added to a solution of cyclopentanone *O*-(6-(triisopropylsilyl)hex-5-yn-3-yl) oxime **(3.59g)** (16,78 mg, 0,050 mmol) in Acetic Acid (250 µl). The suspension was stirred at 23 °C overnight. The mixture was filtered through a plug of Celite with K_2CO_3 on top and the volatiles evaporated. The crude mixture was purified by flash chromatography to yield compound **3.64** as a colorless oil (14 mg, 83%).

^{1}H-NMR (500 MHz, $CDCl_3$) δ 3.61 (td, *J* = 6.9, 3.5 Hz, 1H), 3.51 (tt, *J* = 6.9, 5.0 Hz, 1H), 2.60 (dd, *J* = 16.8, 4.5 Hz, 1H), 2.45 (dd, *J* = 16.8, 7.0 Hz, 1H), 1.80 – 1.69 (m, 3H), 1.69 – 1.61 (m, 2H), 1.62 – 1.48 (m, 3H), 1.44 (m, 2H), 1.11 – 0.98 (m, 21H), 0.95 (t, *J* = 7.4 Hz, 3H). **^{13}C-NMR (**126 MHz, $CDCl_3$) δ 106.0, 82.5, 81.9, 62.0, 30.6, 30.5, 25.6, 24.5, 24.4, 24.3, 18.8, 18.7, 11.5, 10.1. **HRMS** (ESI) *m/z* calculated for $C_{20}H_{40}NOSi^+$ $[M+H]^+$: 338.2874, found:338.2869.

6-(Triisopropylsilyl)hex-5-yn-3-ol (3.63e)



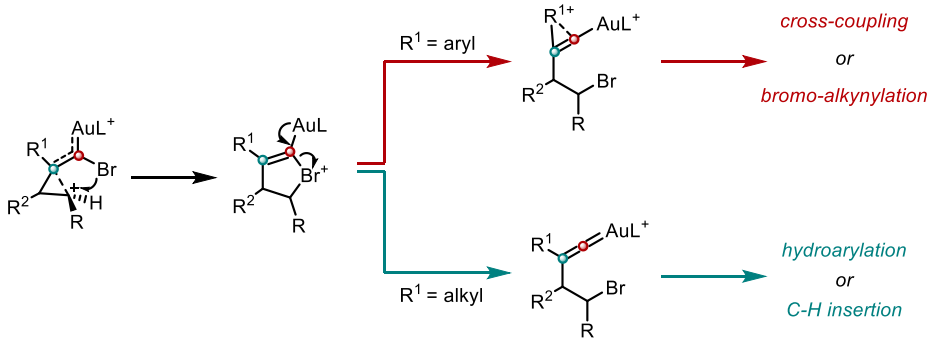
Zinc powder (19,36 mg, 0,296 mmol) was added to a solution of *N*-cyclopentyl-*O*-(6-(triisopropylsilyl)hex-5-yn-3-yl)hydroxylamine **(3.64)** (10 mg, 0,030 mmol) in Acetic Acid (118 µl),water (39,5 µl) and THF (39,5 µl). The mixture was then stirred at 70 ºC for 2 h. After that time the reaction was cooled down to room temperature and filtered through a plug of Celite with K_2CO_3 and $MgSO_4$ on top. The volatiles were evaporated, and the crude mixture was purified by flash chromatography to yield compound **3.63e** as a colorless oil (5.5 mg, 73%).

^{1}H-NMR (500 MHz, $CDCl_3$) δ 3.68 (tt, *J* = 6.8, 5.2 Hz, 1H), 2.51 (dd, *J* = 16.8, 4.8 Hz, 1H), 2.39 (dd, *J* = 16.8, 6.7 Hz, 1H), 1.88 (brs, 1H, -OH), 1.64 – 1.54 (m, 2H), 1.10 – 1.01 (m, 21H), 0.97 (t, *J* = 7.5 Hz, 3H). **^{13}C-NMR (**126 MHz, $CDCl_3$) δ 104.9, 83.7, 71.5, 29.2, 28.6, 18.8, 11.4, 10.1. **HRMS** (APCI) *m/z* calculated for $C_{15}H_{31}OSi^+$ $[M+H]^+$: 255.2139, found: 255.2140.

General Conclusions

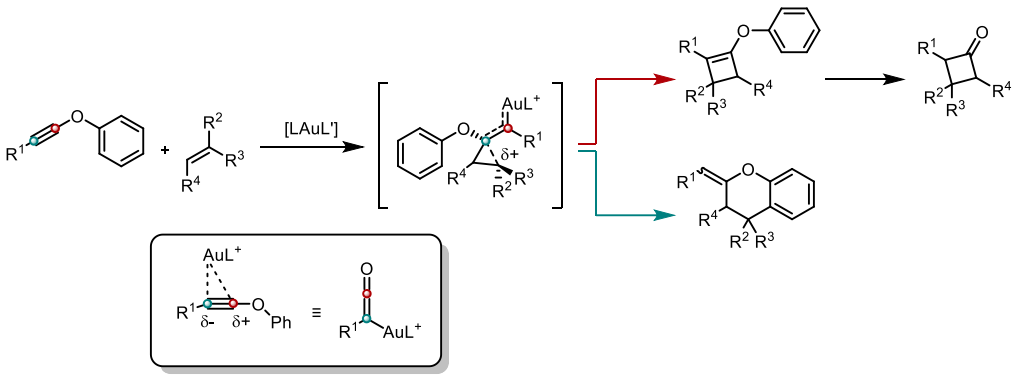
This Doctoral Thesis discusses the study of the reactivity of heteroatom-substituted alkynes in presence of different transition metals. The main conclusions for this work are the following.

In the study of the gold(I) catalyzed reactions of bromoalkynes with alkenes we discovered that 1-bromo-cyclopropyl gold(I) carbenes rearrange into gold(I) vinylidenes and vinylidenephenonium gold(I) cations passing through a cyclic bromonium intermediate (Scheme 1). Gold(I) vinylidenes can undergo hydroarylation or C-H insertion, while vinylidenephenonium gold(I) cations easily undergo 1,2-aryl shift forming a triple bond. After our pioneering mechanistic work, which is summarized in this PhD Thesis, new transformations that involve the formation of vinylidenephenonium gold(I) cations as intermediates have been uncovered by other authors.[80,81,87]



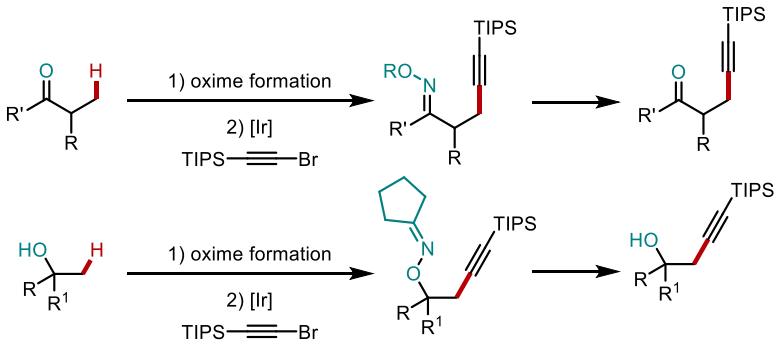
Scheme 1. Evolution of the cyclopropyl gold(I) carbene into vinylidenephenonium gold(I) cation or gold(I)-vinylidene and their reactivity.

We have discovered that phenoxycyclobutenes and cyclobutanones can be accessed *via* gold(I)-catalyzed [2+2] cycloaddition of ynol ethers with alkenes (Scheme 2). This reaction corresponds to the formal [2+2] cycloaddition of the parent ketene or a monosubstituted ketene to an alkene. Additionally, internal ynol ethers can undergo (4+2) cycloaddition with electron rich alkenes. Computational studies revealed that the (η^2-alkyne)gold(I) complex with ynol ethers is highly distorted and resemble a metalated ketene



Scheme 2. intermolecular gold(I)-catalyzed reaction of ynol ethers.

Finally, we have developed the iridium(III)-catalyzed β-alkynylation of primary C(sp^3)-H bonds in oximes (Scheme 3). The reaction can take place both on the *O*-side or the *N*-side of the oxime and after directing group removal the β-alkynylated ketone or alcohol are obtained.



Scheme 3. Ir(III)-catalyzed β-alkynylation of aliphatic oximes.