Title
Development of Gold-Catalyzed Insertions into Unactivated Aliphatic C-H Bonds

Author
Wang, Youliang

Publication Date
2016

Peer reviewed|Thesis/dissertation

UNIVERSITY OF CALIFORNIA

Santa Barbara

Development of Gold-Catalyzed Insertions into Unactivated Aliphatic C-H Bonds

A dissertation submitted in partial satisfaction of the

requirements for the degree Doctor of Philosophy

in Chemistry

by

Youliang Wang

Committee in charge:

Professor Liming Zhang, Chair

Professor Daniel Little

Professor Javier Read de Alaniz

Professor Trevor Hayton

September 2016

The dissertation of Youliang Wang is approved.

_____

Daniel Little

_____

Javier Read de Alaniz

_____

Trevor Hayton

_____

Liming Zhang, Committee Chair

August 2016

Development of Gold-Catalyzed Insertions into Unactivated Aliphatic C-H Bonds

by

Youliang Wang

ACKNOWLEDGEMENTS

First of all, I want to thank my advisor, Professor Liming Zhang. Liming's extreme enthusiasm and devotion to organic chemistry always motivates me to work harder and think deeper. I am really lucky to be Liming's Ph.D. student. After five years study with Liming, I have learned a lot not only knowledge and techniques but also the perseverance and pursuit for higher quality in academics.

I want to thank my Ph.D. committee members: Professor Daniel Little, Trevor Hayton and Javier Read de Alaniz. Their valuable advice and suggestions really helped me to improve during the following four years after my Ph.D. candidacy exam. I also want to express my gratitude to my undergraduate advisor, Professor Guan-Wu Wang. His directions really inspired my initial interest in organic chemistry.

I also want to thank my labmates, both former and current. It is really enjoyable to work together with them. Besides sharing knowledge and experience in organic chemistry, they have become my best friends and they really made my life in America more magnificent.

Finally, I want to thank my whole family for their love and support. I want to thank my grandparents: Tianbao Wang and Xiumei Yi for raising me up from a little baby. I want to thank my parents: Yongfu Wang and Jinfang Gao. They always encouraged me and supported me to pursue higher education and their life values really shaped me into the person I am. I want to thank my older sister, Zhenzhen Wang. I am really lucky to grow up with her and she really loved me and helped me with anything without any hesitation.

VITA OF YOULIANG WANG

August 2016

EDUCATION

Bachelor of Science, University of Science and Technology of China (USTC), July 2011

Doctor of Philosophy in Chemistry, University of California, Santa Barbara, August 2016 (expected)

PROFESSIONAL EMPLOYMENT

2012-2016: Teaching Assistant, Department of Chemistry and Biochemistry, University of California, Santa Barbara

2011-2016: Research Assistant, Department of Chemistry and Biochemistry, University of California, Santa Barbara

2010-2011: Undergraduate Student Researcher, School of Chemistry and Materials Science, University of Science and Technology of China

PUBLICATIONS

1. **Youliang Wang**, Maxence Zarca, Liu-Zhu Gong, Liming Zhang. "A C-H Insertion Approach to Functionalized Cyclopentenones." *J. Am. Chem. Soc.*, **2016,** *138*, 7516-7519.
2. **Youliang Wang**, Zhitong Zheng, Liming Zhang. "Intramolecular Insertions into Unactivated C(sp3)-H Bonds by Oxidatively Generated *β*-Diketone-*α*-Gold Carbenes: Synthesis of Cyclopentanones" *J. Am. Chem. Soc.*, **2015**, *137*, 5316-5319.

3. **Youliang Wang**, Zhitong Zheng, Liming Zhang. "Ruthenium-Catalyzed Oxidative Transformations of Terminal Alkynes to Ketenes by Using Tethered Sulfoxides: Access to β-Lactams and Cyclobutanones" *Angew. Chem. Int. Ed.* **2014**, *53*, 9572-9576.
4. **Youliang Wang**, Akop Yepremyan, Subir Ghorai, Robert Todd, Donald H. Aue, Liming Zhang. "Gold-Catalyzed Cyclizations of cis-Enediynes: Insights into the Nature of Gold–Aryne Interactions" *Angew. Chem. Int. Ed.* **2013**, *52*, 7795-7799.
5. **Youliang Wang**, Alexandre Genoux, Subir Ghorai, Hongyi Chen, Robert Todd, Liming Zhang. "Direct Conversion of Internal Alkynes into α-Iodoenones: One-Step Collaborative Iodination and Oxidation." *Adv. Synth. Catal.*, **2016**, *358*, 1417-1420.
6. **Youliang Wang**, Zhitong Zheng, Liming Zhang. "Facile Synthesis of Cyclobutanones via Gold Carbene Insertion into Unactivated C(sp3)-H Bonds." Manuscript in Preparation.
7. **Youliang Wang**, Liming Zhang. "Recent Developments in the Chemistry of Heteroaromatic *N*-Oxides" *Synthesis* **2015**, *47*, 289. (Invited Review)
8. Zhitong Zheng, Zhixun Wang, **Youliang Wang**, Liming Zhang "Au Catalyzed Oxidative Cyclisation." *Chem. Soc. Rev.* DOI: 10.1039/C5CS00887E.
9. Renhua Zheng, **Youliang Wang**, Liming Zhang "Ruthenium-catalyzed rearrangement of propargyl sulfoxides: formation of α,β-unsaturated thioesters" *Tetrahedron Lett.* **2015**, *56*, 3144-3146.
10. Biao Lu, Yuxue Li, **Youliang Wang**, Donald H. Aue, Yingdong Luo, Liming Zhang. "[3,3]-Sigmatropic Rearrangement versus Carbene Formation in Gold-Catalyzed Transformations of Alkynyl Aryl Sulfoxides: Mechanistic Studies and Expanded Reaction Scope" *J. Am. Chem. Soc.*, **2013**, *135*, 8512-8524.

11. Yi-Tan Su, **Youliang Wang**, Guan-Wu Wang. "Palladium-catalyzed heteroannulation of [60] fullerene with *N*-benzyl sulfonamides and subsequent functionalisation." *Chem. Commun.*, **2012**, *48*, 8132-8134.
12. Yi-Tan Su, **Youliang Wang**, Guan-Wu Wang. "Palladium-catalyzed heteroannulation of [60]fullerene with *N*-(2-arylethyl) sulfonamides *via* C–H bond activation." *Org. Chem. Front.*, **2014**, *1*, 689-693.

AWARDS

2015 Department of Chemistry and Biochemistry Chair's Fellowship, *UC Santa Barbara*

2013 Rickborn-Johnson Fellow, *UC Santa Barbara*

2012 Phi Lambda Upsilon Award, *UC Santa Barbara*

2010 Huang Minglong Scholarship, *Shanghai Institute of Organic Chemistry and USTC*

2009 National Scholarship, *Ministry of Education of China and USTC*

2008 Outstanding Student Scholarship (Grade 1), *USTC*

PRESENTATIONS

1. **Youliang Wang**, Liming, Zhang. "Gold-Catalyzed Cyclizations of *cis*-Enediynes: Insights into the Nature of Gold–Aryne Interactions." Division of Organic Chemistry, 249th American Chemical Society National Meeting, Denver, CO, March 22-26, 2015 (oral talk).
2. **Youliang Wang**, Liming, Zhang. "Gold Carbenes from Alkynes: Insertions into Unactivated C(sp3)-H Bonds." ACS Division of Organic Chemistry, 2015 Graduate Research Symposium, St. Edwards University, Austin, Texas, July 23-26, 2015 (oral talk).

ABSTRACT

Development of Gold-Catalyzed Insertions into Unactivated Aliphatic C-H Bonds

by

Youliang Wang

Despite the tremendous advance in homogeneous gold catalysis in the past decade or so, the functionalization of unactivated C(sp^3)-H bonds, a highly desirable and yet challenging streamlining synthetic strategy, has so far rarely been realized in this 'gold rush'. My graduate work was focused on the development of new strategies of gold catalysis to access highly reactive gold intermediates and harness their reactivities in insertion into unactivated C(sp^3)-H bonds. Three approaches are discussed in this dissertation: (1) via gold vinylidenes: fully functionalized gold vinylidenes generated from simple TMS-terminated alkynones facilely insert into unactivated alkyl groups to furnish versatile 2-bromocyclopentenones; (2) via 'gold benzyne': gold-catalyzed cycloisomerizations of enediynes provide access to hypothetical 'gold benzyne' species, which exhibit reactivities distinctively different from transition metal-free benzynes, including insertions into unactivated C(sp^3)-H bonds and regiospecific nucleophilic additions; (3) via oxidatively generated gold carbene: gold carbenes generated upon the oxidation of alkynones are demonstrated for the first time to be capable of inserting into unactivated C(sp^3)-H bonds to yield cylcopentanones and cyclobutanones.

TABLE OF CONTENTS

Chapter 1. Homogeneous Gold Catalysis……1

1.1 Introduction to Homogeneous Gold Catalysis……1

1.2 Gold-Catalyzed Organic Transformations……..3

1.2.1 Transformations Initiated by Alkene Activation……3

1.2.1.1 Simple Nucleophilic Additions to Alkenes……..3

1.2.1.2 Bisfuntionalization of Alkenes via Au(I)/Au(III) Catalysis……5

1.2.2 Transformations Initiated by Alkyne Activation……...9

1.2.2.1 Simple Nucleophilic Additions to Alkynes……9

1.2.2.2 Propargyl Esters Migration Reactions……12

1.2.2.3 Enyne Cylcoisomerization Reactions……16

1.2.3 Transformations Initiated by Allene Activation……19

1.2.3.1 Simple Nucleophilic Additions to Allenes……..19

1.2.3.2 Allene-Ene Cylcoisomerization Reactions……..20

1.3 Summary of Gold-Catalyzed C(sp^3)-H Functionalization Reactions ……...21

1.4 References……24

Chapter 2. C-H Functionalization via Insertion into Unactivated C(sp^3)-H Bonds by Intermolecularly Generated Gold Vinylidenes……..……29

2.1 Introduction to Gold Vinyidene Chemistry……...29

2.2 Our Strategy to Generate Fully Substituted Gold Vinylidenes and Reaction Discovery……22

2.3 Scope Study of Gold Vinylidene C(sp^3)-H Insertion Reactions…..……...36

2.4 Mechanistic Studies……..46

2.5 Conclusion……51

2.6 Experimental Details……51

2.7 References……..86

Chapter 3. C-H Functionalization via Insertion into Unactivated C(sp^3)-H Bonds by Hypothetical Gold Benzyne Intermediates……..……...……88

3.1 Initial 'Gold Benzyne' Chemistry Discovery with a Reassigned Structure……88

3.2 Conditions Optimization for 'Gold Benzyne' Chemistry……91

3.3 Reactivity Study of 'Gold Benzyne'……..93

3.4 Mechanistic Studies……99

3.5 Conclusion……..102

3.6 Experimental details……103

3.7 References……..130

Chapter 4. C-H Functionalization via Insertion into Unactivated C(sp^3)-H Bonds by Oxidatively Generated Gold Carbenes……132

4.1 Introduction to Oxidative Gold Carbene Chemistry……132

4.2 Challenge in Oxidative Gold Carbene Chemistry: C(sp^3)-H Insertion Reaction…135

4.3 Our Initial Approach to the Above Challenge: the Thorpe-Ingold Effect……..136

4.4 Our 2nd Generation Strategy: Reactions of Alkynones Facilitated by the Thorpe-Ingold Effect……..137

4.5 Substrate Scope Study for Cyclopentanone Synthesis……140

4.6 Proposed Mechanism for the Reaction of **T9-1**……..144

4.7 Mechanistic Studies for the Cyclopentanone Formation……145

4.8 Conclusion for Cyclopentanone Synthesis……..147

4.9 Experimental Details……...……147

4.10 References……178

Chapter 5. Appendix: Selected NMR Spectra……..180

LIST OF FIGURES

Figure 1. Representative Gold Catalysts……...2

Figure 2. DFT Calculation on Three Gold Complexes……..100

Figure 3. The Resonance Structures of **F2B**…….101

LIST OF SCHEMES

Scheme 1. Pioneer Work of Homogeneous Gold Catalysis……1

Scheme 2. Summary of Gold-Catalyzed Alkene, Alkyne, and Allene Reactions……..3

Scheme 3. Gold-Catalyzed Alkene Hydroalkoxylation Reactions…….4

Scheme 4. Gold-Catalyzed Alkene Hydroamination Reactions…….4

Scheme 5. Gold-Catalyzed C-H Bond Addition to Alkenes……...5

Scheme 6. Gold-Catalyzed 1,3-Diene Hydrothiolation Reactions……..5

Scheme 7. Gold-Catalyzed Alkene Bisamination Reaction……6

Scheme 8. Gold-Catalyzed Aminoarylation of Alkenes…….7

Scheme 9. Gold-Catalyzed Cross Coupling of Amide, Alkene, and $ArB(OH)_2$ (Zhang)……7

Scheme 10. Gold-Catalyzed Cross Coupling of Amide, Alkene, and $ArB(OH)_2$ (Toste)…...8

Scheme 11. Gold-Catalyzed Aminohydroxylation of Alkenes……...8

Scheme 12. Gold-Catalyzed Oxygen-Based Nucleophiles Addition to Alkynes……9

Scheme 13. Gold-Catalyzed Nitrogen-Based Nucleophiles Addition to Alkynes……..10

Scheme 14. Gold-Catalyzed Carbon-Based Nucleophiles Addition to Alkynes…….11

Scheme 15. Gold-Catalyzed Sulfur-Based and Halogens Nucleophiles Addition to Alkynes11

Scheme 16. Summary of the Reaction Pattern of Propargyl Esters……12

Scheme 17. Gold-Catalyzed [3,3]-Rearrangement of Propargyl Esters Followed by [2+2] Reaction……..13

Scheme 18. Gold-Catalyzed [3,3]-Rearrangement of Propargyl Esters Followed by Nucleophilic Addition Reaction……..14

Scheme 19. Gold-Catalyzed [3,3]-Rearrangement of Propargyl Esters Followed by Michael Addition……..14

Scheme 20. Gold-Catalyzed [1,2]-Acyloxy Migration of Propargyl Esters: Cyclopropanation Reaction ……14

Scheme 21. Gold-Catalyzed [1,2]-Acyloxy Migration of Propargyl Esters: [4+3] Reaction.15

Scheme 22. Gold-Catalyzed [1,2]-Acyloxy Migration of Propargyl Esters: 1,2-H Shift Reaction ……...15

Scheme 23. Hashmi Phenol Synthesis ……16

Scheme 24. 1,6-Enyne Cycloisomerization into Two Dienes……17

Scheme 25. Intermolecular Enyne Cycloisomerization……..18

Scheme 26. Interrupted Enyne Cycloisomerization……19

Scheme 27. Gold-Catalyzed Nucleophilic Additions to Allenes……19

Scheme 28. Allene/Ene [2+2] Reactions……20

Scheme 29. Allene/Diene [2+4] and [3+4] Reactions……20

Scheme 30. Conjugated Allene-Ene Cycloisomerization Reactions……...21

Scheme 31. C(sp^3)-H Functionalization via [1,5]-Hydride Shift……22

Scheme 32. C(sp^3)-H Functionalization via Gold Carbene C-H Insertion……..23

Scheme 33. C(sp^3)-H Functionalization via Gold Vinylidene C-H Insertion……..24

Scheme 34. Iodoalkyne Isomerization into Gold Vinylidene……..29

Scheme 35. Gold Vinylidene Formation via Dual Gold Catalysis……..30

Scheme 36. Widenhoefer and Hashmi's Intramolecular Approaches to Gold Vinylidenes…31

Scheme 37. Our Initial Intermolecular Approach to Fully Substituted Gold Vinylidenes and the C-H Insertion Reaction Design……32

Scheme 38. Our Terminal Alkynone Strategy to a Fully Substituted Gold Vinylidene and its C(sp^3)-H Insertion Reaction……33

Scheme 39. Unsuccessful Insertions into Linear Alkyl Groups by Gold Vinylidene……..38

Scheme 40. Diastereoselective Insertions into Linear Alkyl Groups by Gold Vinylidene….39

Scheme 41. Gold Vinylidene Chemoselective Insertions into Two Biased Alkyl Groups..…43

Scheme 42. Our Chemistry versus Dreiding's and Stang's ……45

Scheme 43. Our Initially Proposed Mechanism for Gold Vinylidene Formation……46

Scheme 44. Significant Role of Carbonyl Group for Gold Vinylidene Formation……..47

Scheme 45. Our Revised Mechanism for the Intermolecular Gold Vinylidene Formation….50

Scheme 46. Longwu's Extension with Enediyne after the Gold Vinylidene Chemistry…...88

Scheme 47. My Initial Discovery with Revised Structure……89

Scheme 48. Bifurcation Mechanism Proposed by Aue……90

Scheme 49. Rational for Our Enediyne Cycloisomerization……91

Scheme 50. 'Gold Benzyne' Reaction with Allyl Ether……...95

Scheme 51. 'Gold Benzyne' Cycloaddition Reactions……..98

Scheme 52. Regioselectivity Study with Properly Designed Substrate……99

Scheme 53. Deuterium Labeling Experiments……..101

Scheme 54. Our Group and Toste Group's Initial Discoveries of Alkyne Oxidation……...132

Scheme 55. Our Revised Mechanism for Alkynyl Sulfoxide Reaction……133

Scheme 56. First Intermolecular Generation of α-Oxo Gold Carbenes……134

Scheme 57. General Reactivities of Oxidatively Generated Gold Carbenes……135

Scheme 58. Unsuccessful C(sp^3)-H Insertions by Oxidatively Generated Gold Carbenes...136

Scheme 59. First Realization of C(sp^3)-H Insertions by Oxidatively Generated Gold Carbenes……137

Scheme 60. Other Types of Substrates for Oxidative Gold Carbene C(sp^3)-H Insertion Reactions……144

Scheme 61. Proposed Mechanism for Our Gold Carbene Chemistry……..145

Scheme 62. Control Experiment Between Ynone and Diazoketone……146

Scheme 63. Deuterium Labeling Experiment……...……146

LIST OF TABLES

Table 1. Initial Reaction Discovery and Conditions Optimization……..35

Table 2. Scope of Gold-Catalyzed Cyclopentenone Synthesis: Insertion into Linear Alkyl Groups…….37

Table 3. Synthesis of Carbocycle Fused Cyclopentenones…….41

Table 4. Gold Vinylidene Generation with Other Electrophilic Reagents……..44

Table 5. Significant Role of Lewis Acid for Gold Vinylidene Formation……...48

Table 6. Initial Reaction Discovery and Optimization……..92

Table 7. Scope of ‘Gold Benzyne’ C-H Insertion Reactions……94

Table 8. ‘Gold Benzyne’ Nucleophilic Addition Reactions……..96

Table 9. Initial Reaction Discovery and Conditions Optimization……138

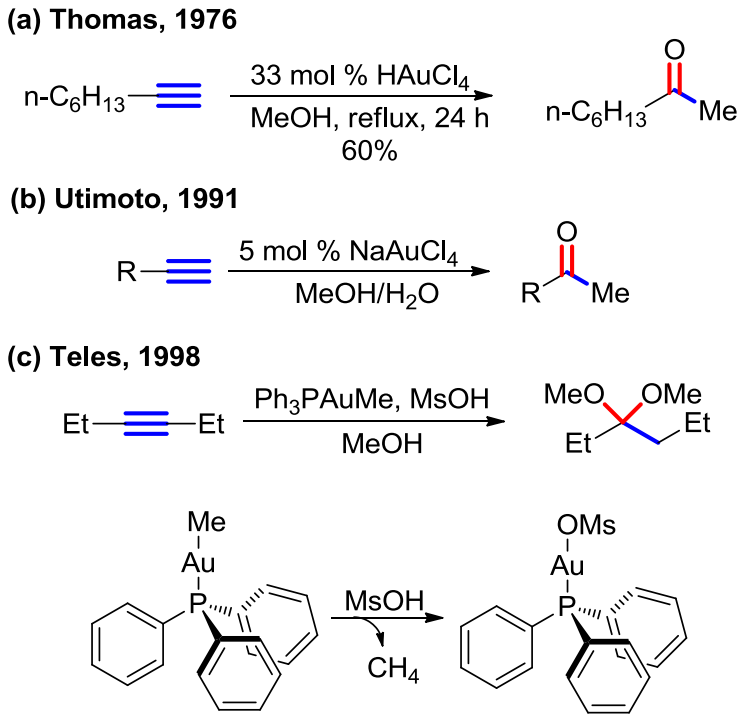
Table 10. C(sp^3)-H Insertion Reactions using Ynones with α-Carbon Fully Substituted….141

Table 11. Constructions of Fused Bicyclic Cyclopentanones……...143

Chapter 1. Homogeneous Gold Catalysis

1.1 Introduction to Homogeneous Gold Catalysis

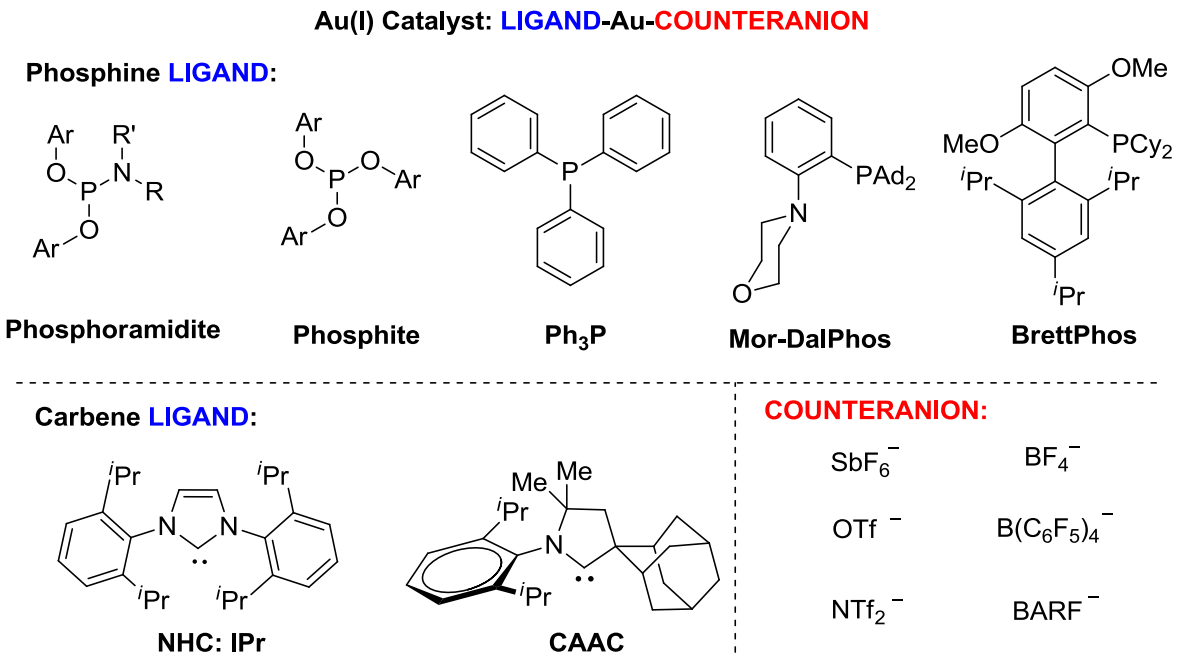
Scheme 1. Pioneer Work of Homogeneous Gold Catalysis



Gold as a precious metal has been known and used for thousands of years. However, in organic chemistry, gold catalysis has been seldomly studied until recently, which is surprising especially considering that so many other transition metals have been deeply investigated and widely applied to organic synthesis. The first gold reaction was an alkyne hydration reaction reported by the Thomas group in 1976 (Scheme 1a).[1] This type reaction was later improved by the Utimoto group in 1991 by using catalytic amount of $NaAuCl_4$ (Scheme 1b).[2] In 1998, Teles et al.[3] in-situ generated $Ph_3PAuOMs$ from Ph_3PAuMe (Scheme 1c) and successfully applied it to the alkyne nucleophilic addition reactions. The Teles's work is a breakthrough to homogeneous gold catalysis because it for the first time demonstrated that,

like other transition metal catalysis, ligands could be introduced to the cationic gold center to form ligand coordinated gold complexes. Ever since this pioneer work, many new gold catalysts applying various ligands have been synthesized (Figure 1). There are two major types of ligands for the common gold(I) catalysts: phosphine type and cabene type. For the phosphine ligand, besides the simplest Ph_3P, Buchwald type biaryl phosphine ligands and *P*,*N*-bidentate liagnds have been applied to homogeneous gold catalysis. Electronically deficient phosphite and phosphoramidite ligands are also effective for various transformations. The carbene ligands for gold(I) are mainly N-heterocyclic carbenes and cyclic alkyl amino carbenes. Non-coordinating or weakly coordinating counteranions are required for catalytically active gold catalysts. With the large collection of sterically and electronically divergent gold catalysts, numerous new reactions have been developed and many novel gold intermediates have been discovered. Gold catalysis has developed from a 'ugly duckling' into a 'beautiful swan' in the past 15 years.

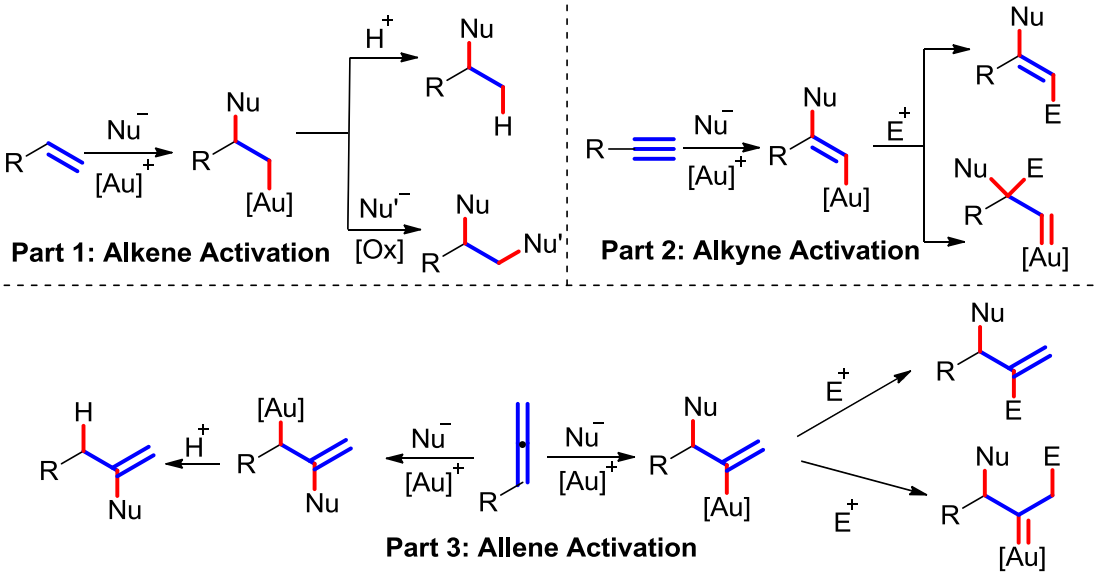
Figure 1. Representative Gold Catalysts



1.2 Gold-Catalyzed Organic Transformations

Gold(I) and gold(III) catalysts are soft and carbophilic Lewis acids favoring the activation of unsaturated bonds like alkynes, alkenes, and allenes. Most gold-catalyzed reactions were initiated by the gold activation of alkynes, allenes and alkenes and terminated by the attack of nucleophiles or electrophiles. The general reaction patterns are summerized in Scheme 2 and will be discussed in the following sections.

Scheme 2. Summary of Gold-Catalyzed Alkene, Alkyne, and Allene Reactions



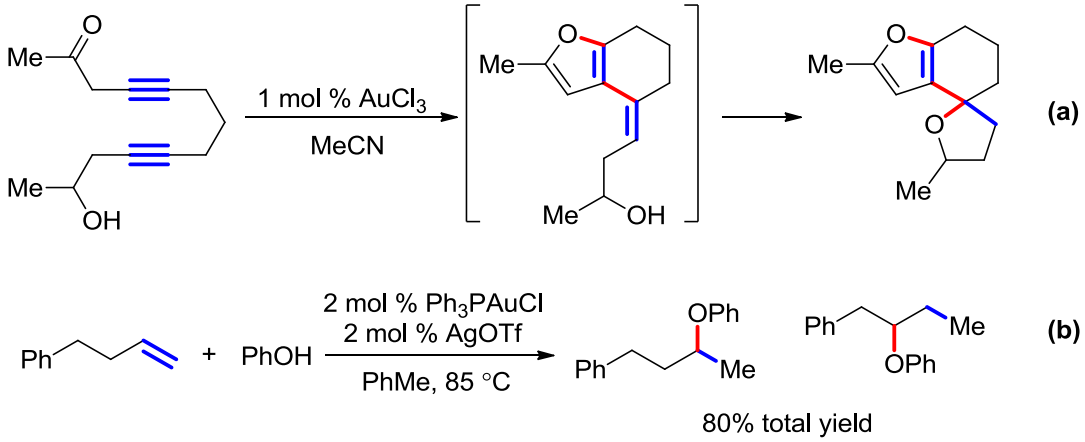
1.2.1 Transformations Initiated by Alkene Activation

1.2.1.1 Simple Nucleophilic Additions to Alkenes

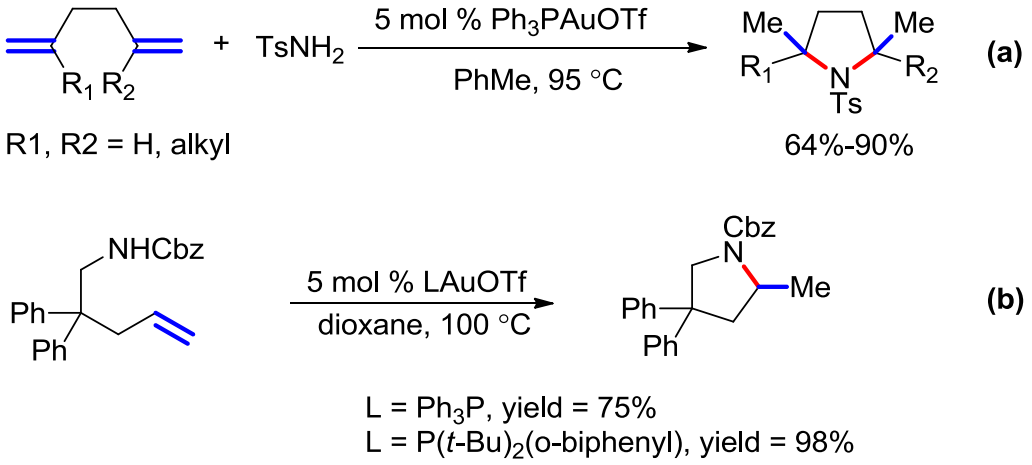
In 2000, Hashmi et al.[4] reported that the in-situ generated trisubstituted alkene could be further added by a tethered hydroxyl group, realizing the first gold-catalyzed alkene hydroalkoxylation reaction (Scheme 3a). He et al. later achieved the intermolecualr

hydroalkoxylation reaction using generally unactivated olefins with low gold catalyst loading (Scheme 3b).[5]

Scheme 3. Gold-Catalyzed Alkene Hydroalkoxylation Reactions



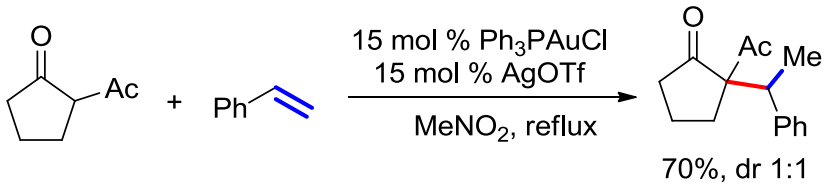
Scheme 4. Gold-Catalyzed Alkene Hydroamination Reactions



Using similar conditions, He et al. also accomplished the general alkene hydroamination reactions both inter and intramolecularly.[6] One synthetic application is the straightforward pyrrolidine synthesis from 1,5-diene and $TsNH_2$ in an atom economical manner (Scheme 4a).[6] Widenhoefer et al.[7] discovered that ligand on the gold(I) center could play a significant role on the gold-catalyzed intramolecular alkene hydroamination reactions (Scheme 4b).

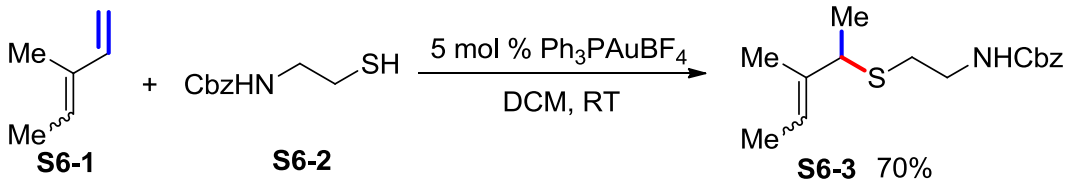
Compared to triphenylphosphine, sterically hindered and electron-rich JohnPhos was more compelling and permitted quantitative yield.

Scheme 5. Gold-Catalyzed C-H Bond Addition to Alkenes



Once activated by gold catalyst, olefins could also accept the addition of C-H bonds.[8] As shown in Scheme 5, homogeneous gold catalysis enabled efficient C(sp^3)-C(sp^3) bond construction, albeit both the two starting materials are somewhat activated and the diastereoselectivity was low. Conjugated dienes could be readily activated by cationic gold complexes for the nucleophilic additions.[9] For instance, great chemo- and regioselectivity were observed when aminothiol **S6-2** was added to 1,3-diene **S6-1** and only the thiol addition product was found in good yield (Scheme 6). It is possible that Bronsted acid catalysis may invole in all the above gold-catalyzed nucleophilic addition reactions due to the difficulty in protonating the C(sp^3)-Au bonds.[10]

Scheme 6. Gold-Catalyzed 1,3-Diene Hydrothiolation Reactions

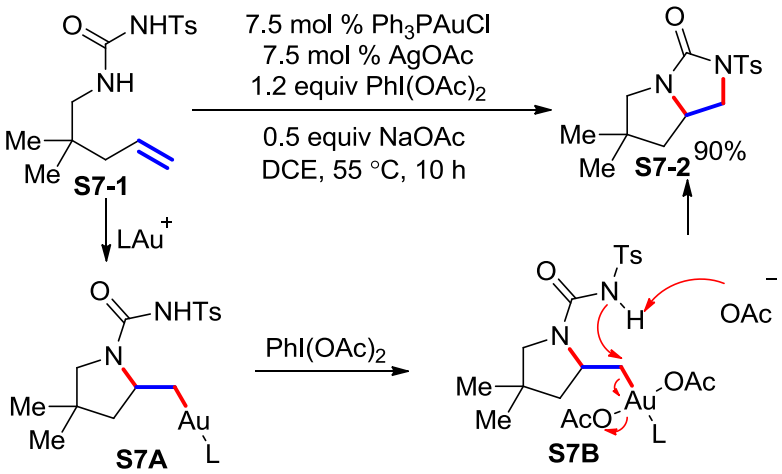


1.2.1.2 Bisfuntionalization of Alkenes via Au(I)/Au(III) Catalysis

During the 21st century gold rush, one of the most exciting discoveries is the redox gold catalysis via the Au(I)/Au(III) catalytic cycle.[11] As illustrated in Scheme 7,[12] gold activated

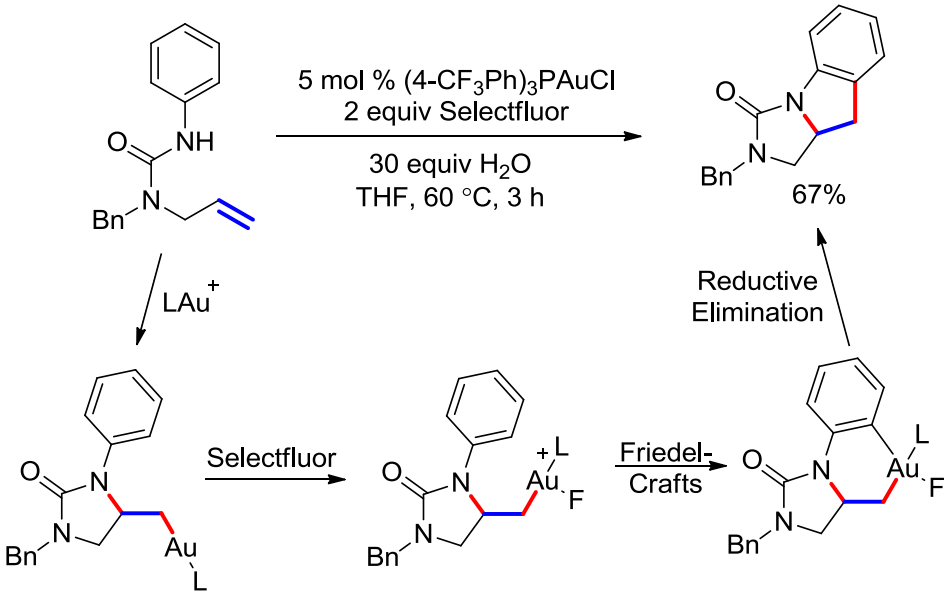
the terminal alkene **S7-1** and triggered the 5-exo-dig cyclization of the aminoalkene, leading to alkyl gold(I) intermediate **S7A**. Due to the covalent nature of the newly generated C(sp^3)-Au(I) bond, the protonation was slow and instead the oxidation occurred in presence of $PhI(OAc)_2$. The resulting C(sp^3)-Au(III) bond was rather polarized now and induced a S_N2 attack by the nearby imide nitrogen to build up a new C(sp^3)-N bond. At the meantime, the gold catalyst was released from the intermediate as a gold(I) salt. Instead of hydroamination, the olefin was eventually bisaminated in excellent yield.

Scheme 7. Gold-Catalyzed Alkene Bisamination Reaction

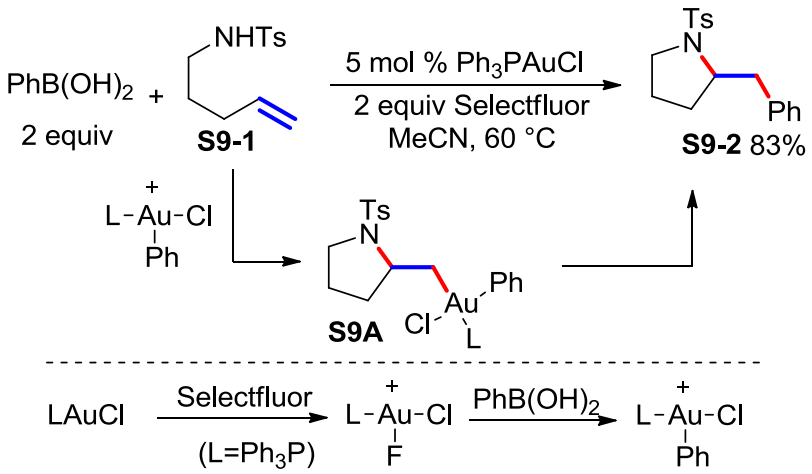


Our group[13] discovered that upon 5-exo-trig cyclization, the new C(sp^3)-Au(I) bond could be oxidized by Selectfluor into C(sp^3)-Au(III) one, which could undergo a Friedel-Crafts reaction with a tethered aromatic ring to form a new C(sp^2)-Au bond. Finally, reductive elimination from the C(sp^3)-Au(III)-C(sp^2) intermediate constructed a new C(sp^2)-C(sp^3) bond and regenerated the gold(I) catalyst (Scheme 8). This redox gold catalysis strategy provided an efficient approach to indoline type products from simple olefins and tethered anilines.

Scheme 8. Gold-Catalyzed Aminoarylation of Alkenes



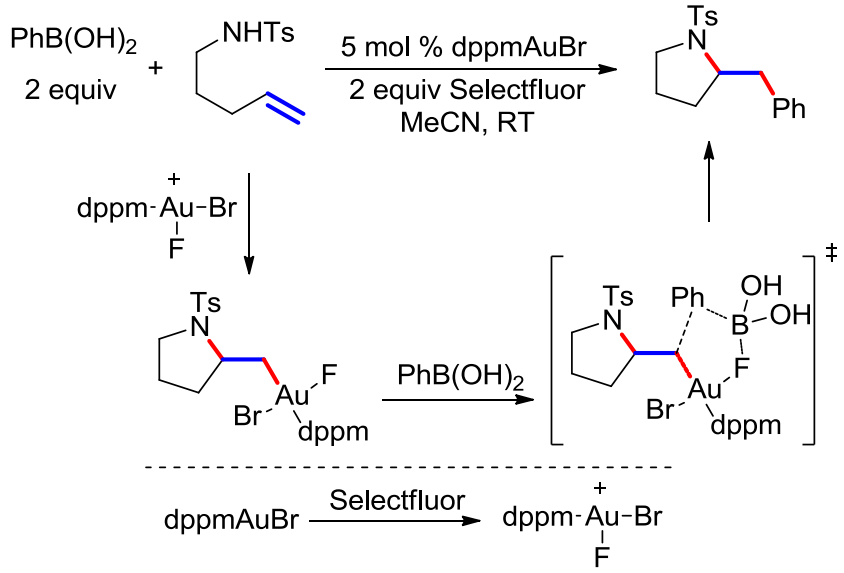
Scheme 9. Gold-Catalyzed Cross Coupling of Amide, Alkene, and ArB(OH)$_2$ (Zhang)



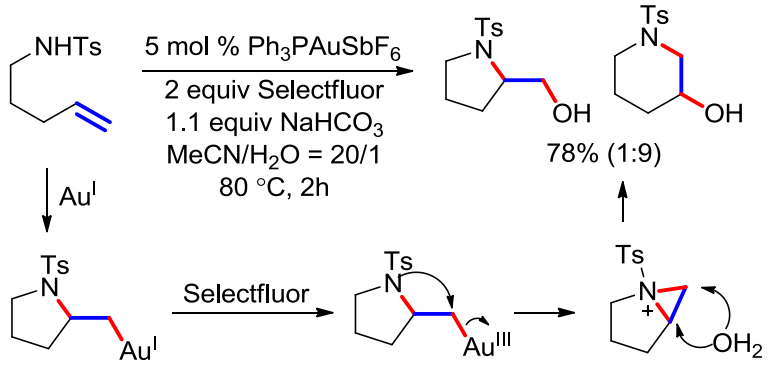
Furthermore, our group[14] for the first time successfully applied the in situ generated alkyl gold organometallic species in cross coupling reactions with aryl boronic acids (Scheme 9). In this work, the gold(I) precatalyst [LAuCl] was first oxidized into a cationic gold(III) species $[LAuClF]^+$ by Selectfluor. Then, transmetalation of phenyl boronic acid to the above species led to another cationic gold complex $[LAuClPh]^+$, which induced the *5-endo-dig*

cyclization of aminoalkene **S9-1** to generate a neutral gold(III) intermediate **S9A**. Finally, the cross coupling product arised from the inner sphere reductive elimination of the C(sp^3)-Au(III)-Ph intermediate (Scheme 9). In a later work by Toste et al.,[15] a different mechanism for the same cross coupling reaction was proposed (Scheme 10), which entailed the phenyl boronic acid participated in the final step via a five member ring transition state. Formally, the phenyl group was delivered via a S_N2 type process like the alkene bisamination reaction in Scheme 6.

Scheme 10. Gold-Catalyzed Cross Coupling of Amide, Alkene, and ArB(OH)$_2$ (Toste)



Scheme 11. Gold-Catalyzed Aminohydroxylation of Alkenes

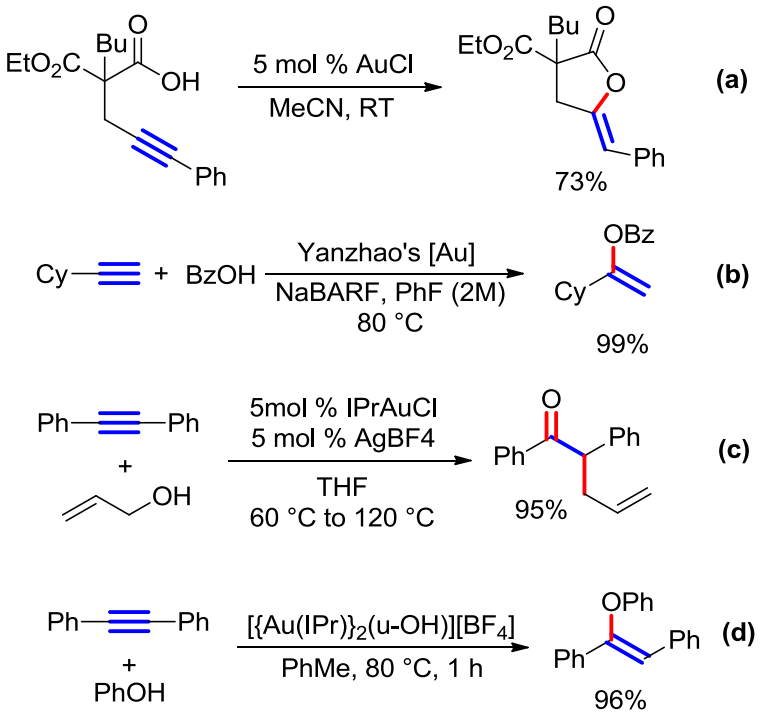


Interestingly, Nevado et al.[16] revealed that, without arylboronic acids for cross coupling, the Au(III) species generated from the gold-catalyzed aminoalkene cylization and oxidation process could undergo a intramolecular S_N2 reaction. The neighbouring tosyl amide attacked the C(sp^3)-Au(III) bond to form a aziridinium intermediate (Scheme 11). Then, regioselective ring opening of the aziridinium ring afforded the two final amino alcohol products.

1.2.2 Transformations Initiated by Alkyne Activation

1.2.2.1 Simple Nucleophilic Additions to Alkynes

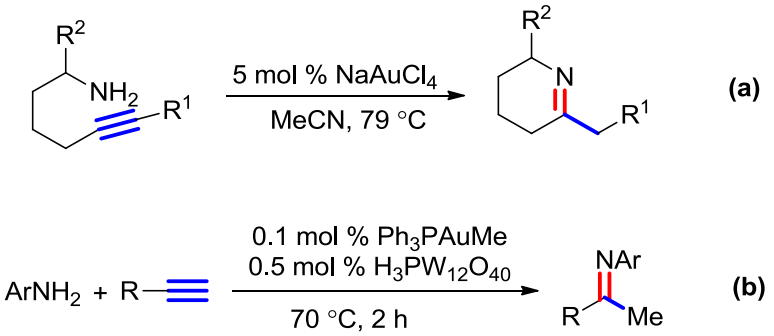
Scheme 12. Gold-Catalyzed Oxygen-Based Nucleophiles Addition to Alkynes



The first gold-catalyzed organic reaction is a characteristic and fundamental alkyne hydration reaction.[1] Later, many other oxygen-based nucleophiles have been efficiently added to alkynes in an *anti* addition manner (Scheme 12). For example, carboxylic acids

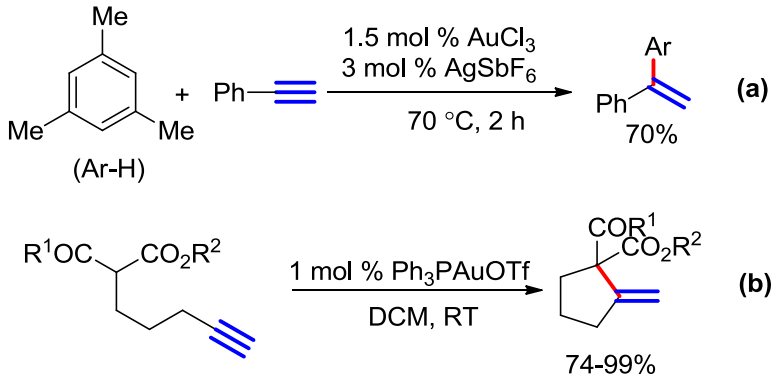
worked excellently for both internal and terminal alkynes both inter- and intramolecularly (Scheme 12a,b).[17,18] Compared to carboxylic acids, aliphatic alcohols are more reactive towards alkynes.[3,19] The reaction usually does not stop at the vinyl ether stage. Instead, another alcohol molecule will be added to the vinyl ether, leading to ketals or ketones. One exception is the gold-catalyzed allyl alcohols addition to alkynes.[20] After the initial addition recation, a subsequent Claisen rearrangement of the allyl vinyl ether inermediate furnished γ,δ-unsaturated ketones, making it an interesting and synthetically useful transformation (Scheme 12c). On the other hand, Nolan et al.[21] realized the efficient phenols addition to alkynes using a cooperative gold catalysis stragety (Scheme 12d).

Scheme 13. Gold-Catalyzed Nitrogen-Based Nucleophiles Addition to Alkynes

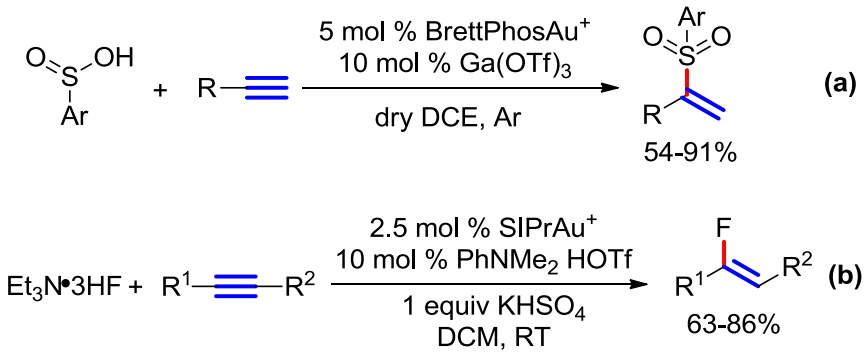


In 1991, Utimoto et al.[22] reported the first gold-catalyzed alkyne hydroamination reactions (Scheme 13a). The reaction conditions are mild and neutral and high 6-*exo*-*dig* selectivity was achieved with simple gold catalyst $NaAuCl_4$. Tanaka et al.[23] later realized the first intermolecular alkyne hydroamination reactions (Scheme 13b). The catalyst loading could be as low as 0.01 mol % and turn over number up to 9000. Unfortunately, only anilines worked due to the much stonger basicity of aliphatic amines.

Scheme 14. Gold-Catalyzed Carbon-Based Nucleophiles Addition to Alkynes



Scheme 15. Gold-Catalyzed Sulfur-Based and Halogens Nucleophiles Addition to Alkynes

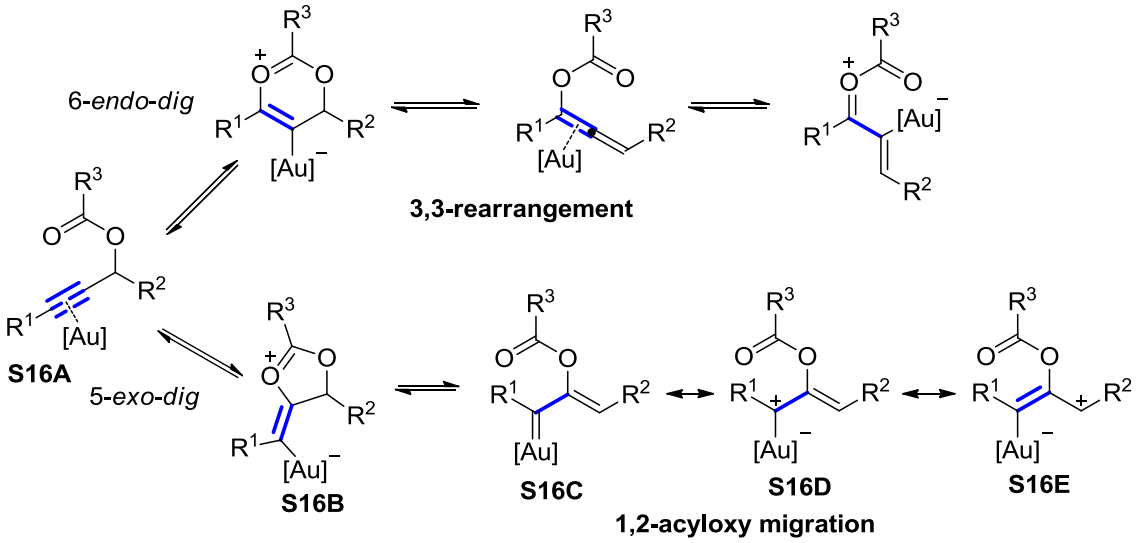


Two types of carbon nucleophiles could be added to alkynes in gold catalysis: electron-rich aromatics[24] (Scheme 14a) and enolizable 1,3-dicarbonyls[25] (Scheme 14b). Although a few intramolecualr reactions have been reported, thiols are generally not very compatible in gold catalysis because they may coordinate with the gold to deactivate it or even reduce it. In 2014, Shi et al.[26] presented an alternative approach to construct carbon-sulfur bond using sulfinic acids instead of thiols. Under their optimized conditions, various vinyl aryl sulfones were synthesized from simple terminal alkynes and sulfinic acids (Scheme 15a). However, internal alkynes showed poor reactivity in Shi's methodology. In 2007, Sadighi et al.[27] developed the first gold-catalyzed carbon-fluorine bond formation reactions (Scheme 15b).

They initially found that NHCAuF could be added to alkynes reversibly. Encouraged by this discovery, they then applied catalytic amount of cationic gold catalyst, stoicmetric amout of fluoride source, and slightly acidic additives and realized the catalytic synthesis of fluorinated alkenes from readily available alkynes.

1.2.2.2 Propargyl Esters Migration Reactions

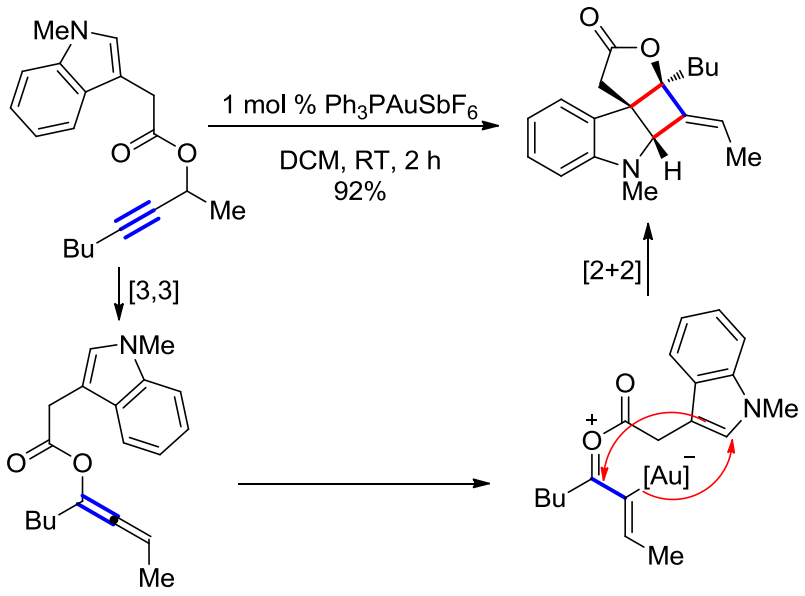
Scheme 16. Summary of the Reaction Pattern of Propargyl Esters



Another major type of gold-catalyzed alkyne reactions is the propargyl ester migration reaction (Scheme 16).[28] When the alkyne moiety was activated by gold, the nearby ester would attack it and both 6-*endo-dig* and 5-*exo-dig* cyclizations are allowed. The 6-membered intermediate from the 6-*endo-dig* cyclization could open up to generate the allenyl ester product, which could either be isolated as a valuable synthetic building block or be further functionalized. The alternative 5-*exo-dig* cyclization and fragmentation pathway led to a gold carbene intermediate **S16C**, which had resonance structures like gold stabilized allyl cation **S16D** or all carbon 1,3-dipole **S16E**. The selectivity between the two cyclization

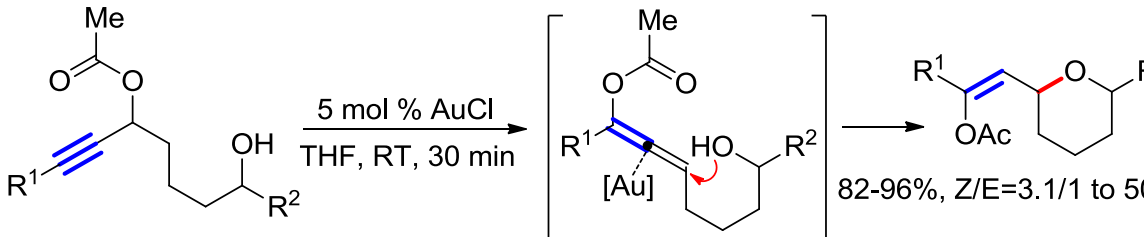
pathways is largely affected by both the substitutes on the propargyl ester and the electron property of the alkyne.

Scheme 17. Gold-Catalyzed [3,3]-Rearrangement of Propargyl Esters Followed by [2+2] Reaction

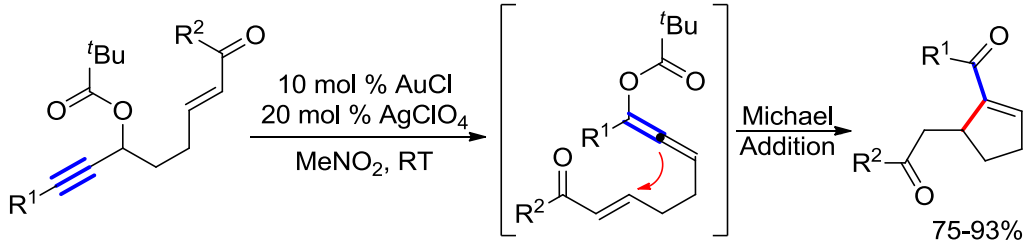


Three representative examples of gold-catalyzed [3,3]-rearrangement are depicted in Scheme 17-19. In 2005, our group[29] discovered an interesting cascade transformation (Scheme 17), where the in-situ formed allene underwent a stepwise [2+2] reaction with indole, leading to highly functionalized tetracyclic cyclobutanones. The reaction proceeded rapidly and high efficiently at room temperature with low catalyst loading. Brabander et al.[30] reported that the in-situ generated allenyl acetate from [3,3]-rearrangement could be trapped by a tethered alcohol efficiently and selectively (Scheme 18). Besides being an electronphile, the allenyl ester could also act as a nucleophile for Michael addition reactions (Scheme 19).[31]

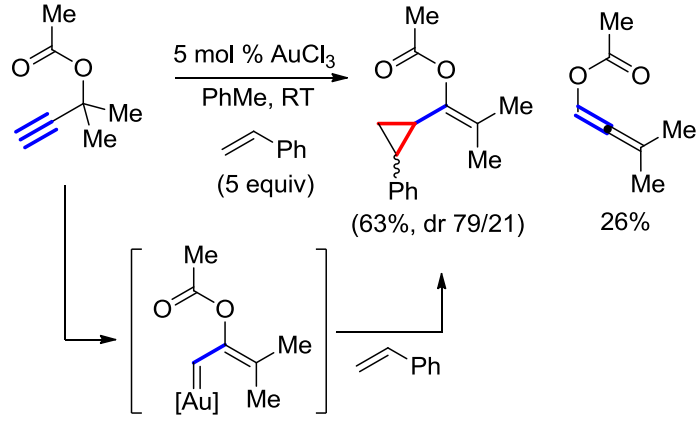
Scheme 18. Gold-Catalyzed [3,3]-Rearrangement of Propargyl Esters Followed by Nucleophilic Addition Reaction



Scheme 19. Gold-Catalyzed [3,3]-Rearrangement of Propargyl Esters Followed by Michael Addition

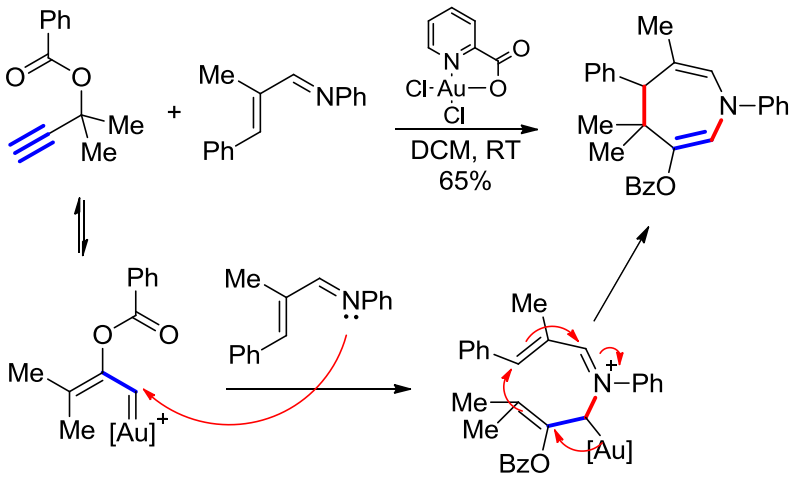


Scheme 20. Gold-Catalyzed [1,2]-Acyloxy Migration of Propargyl Esters: Cyclopropanation Reaction

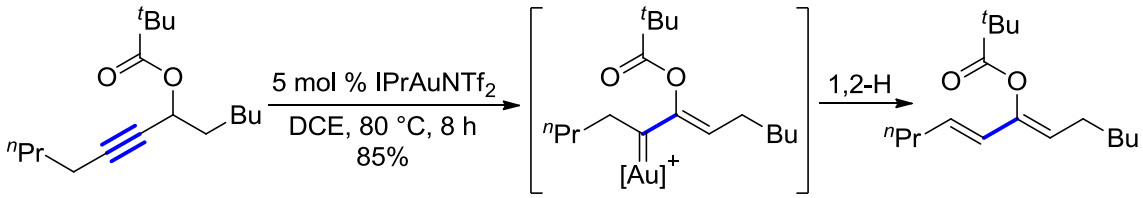


Ohe and Uemura et al.[32] first demonstrated that the [3,3]-rearrangement and 1,2-acyloxy migration could happen to 2-methylbut-3-yn-2-yl acetate simultaneously (Scheme 20). The latter pathway was evidenced by the cyclopropanation reaction. Toste et al.[33] later showed that the gold carbene from the 1,2-acyloxy migration could be trapped by α,β-unsaturated aldmines via a stepwise [4+3] process (Scheme 21). The imine nitrogen first attacked the gold carbene center to form the iminium ion, which then cyclized into the final dihydroazepine product.

Scheme 21. Gold-Catalyzed [1,2]-Acyloxy Migration of Propargyl Esters: [4+3] Reaction



Scheme 22. Gold-Catalyzed [1,2]-Acyloxy Migration of Propargyl Esters: 1,2-H Shift Reaction

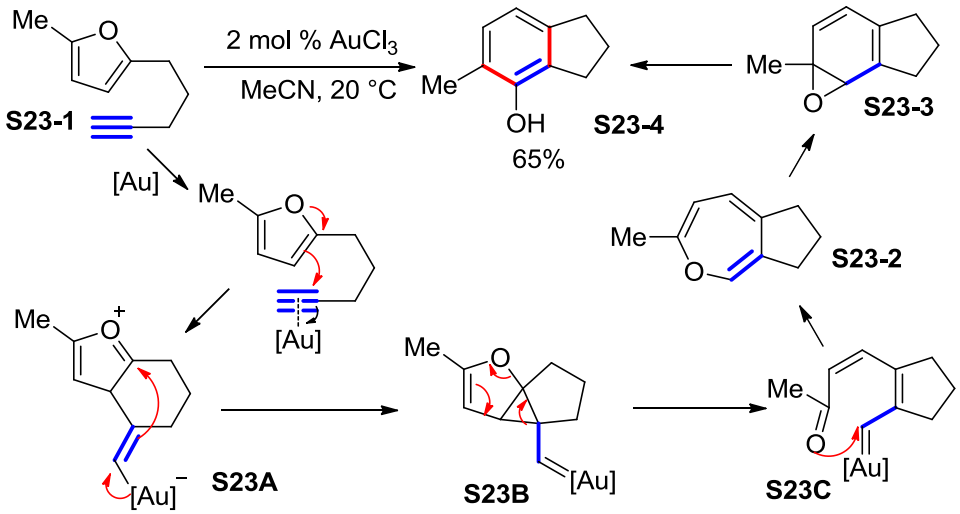


In 2008, our group[34] discovered that electronically unbiased internal propargyl pivalates could also undergo the 1,2-acyloxy migration pathway under properly optimized conditions (Scheme 22). Different from the terminal alkyne derived gold carbenes, this new type of gold carbene was directly bonded to alkyl chains, thus providing another reaction scenario: 1,2-H migration. As a result, 1,3-dienes were facilely generated in excellent diastereoselectivity. Notably, ligand played a critical role in this transformation. Only $IPrAuNTf_2$ or $IMesAuNTf_2$ permitted the 1,2-acyloxy migration. Others like $Ph_3PAuNTf_2$ and dichloro(pyridine-2-carboxylate)Au(III) only catalyzed the 3,3-rearrangement.

1.2.2.3 Enyne Cylcoisomerization Reactions

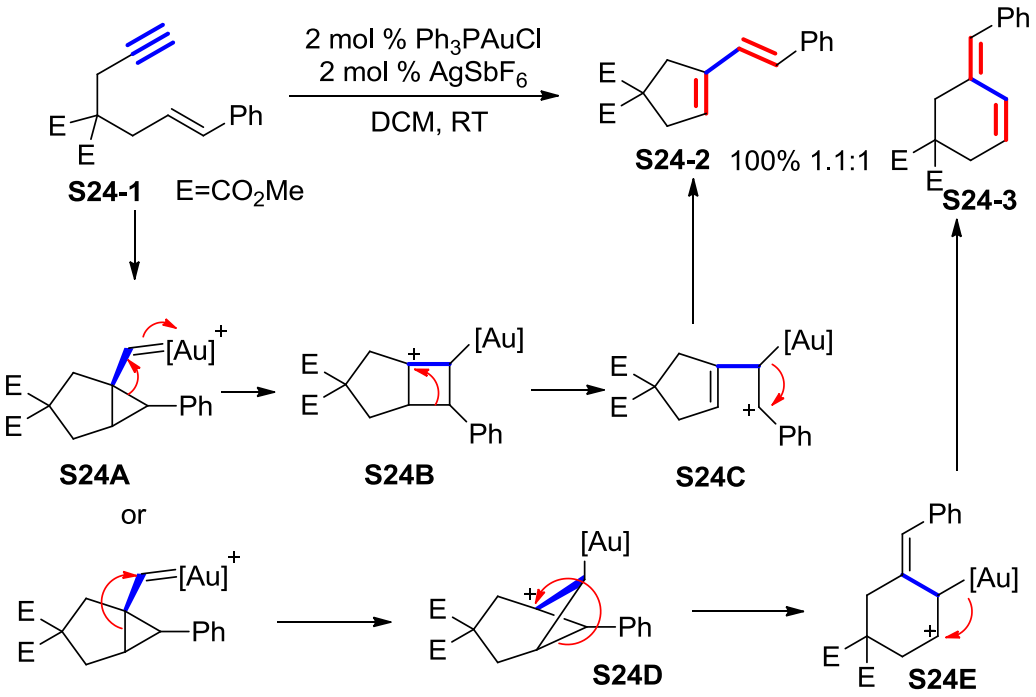
When alkene and alkyne are both present, gold catalyst usually activates the alkyne and alkene serves as the nucleophile for attack. There has been significant progress in gold-catalyzed enyne cycloisomerization reactions.[35] Unlike the simple nucleophilic alkyne additions, enyne cycloisomerization usually involves multiple bond cleavage and formation and thus enables rapid increase of molecular complexity.

Scheme 23. Hashmi Phenol Synthesis



One pioneer gold-catalyzed enyne isomerization reaction was reported by Hashmi et al.[36] in 2000 (Scheme 23). They proposed that the alkene from the furan ring attacked the gold activated alkyne to form a six member ring intermediate **S23A**. The vinyl gold then interacted with the oxycarbenium ion, leading to the cyclopropyl gold carbene intermediate **S23B**. The highly strained cyclopropane fused dihydrofuran opened up into dienone **S23C**. Then, gold carbene trapped the carbonyl group to form an oxepine intermediate **S23-2**. Eventually, the oxepine isomerized into benzene oxide **S23-3** through 6π electrocyclic reaction, which then aromatized into the final phenol product **S23-4**.

Scheme 24. 1,6-Enyne Cycloisomerization into Two Dienes

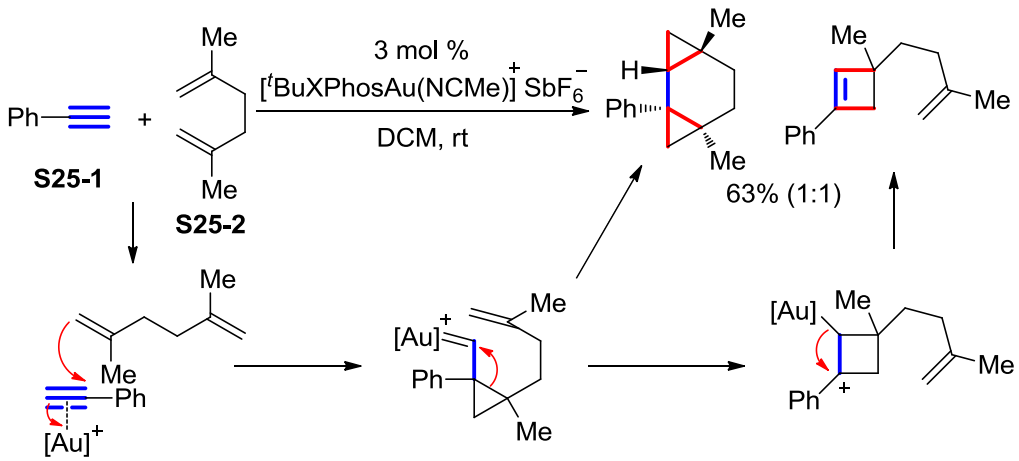


Another representative enyne cycloisomerization reaction involving skeleton rearrangement was reported by Echavarren et al.[37] (Scheme 23). The characteristic

cyclopropyl gold carbene intermediate **S24A** was formed via the gold-catalyzed 1,6-enyne cycloisomerization. The electrophilic gold carbene center induced the enlargement of the cyclopropane ring into cyclobutane one. Depending on which bond of the cyclopropane ring to migrate, two possible cyclobutane intermediates **S24B** and **S24D** could be formed. The carbon cation in **S24B** induced the α-C-C sigma bond cleavage and thus released the cyclobutane ring strain. The product **S24-2** was then generated via the gold elimination from **S24C**. The other cyclobutane cation **S24D** is a constitutional isomer of **S24B**. The bridge head carbo cation in **S24D** was extremely unstable and caused the fragmentation of the neighbouring C-C bond leading to form **S24E**. Finally, the C-Au bond elimination released the other product **S24-3**.

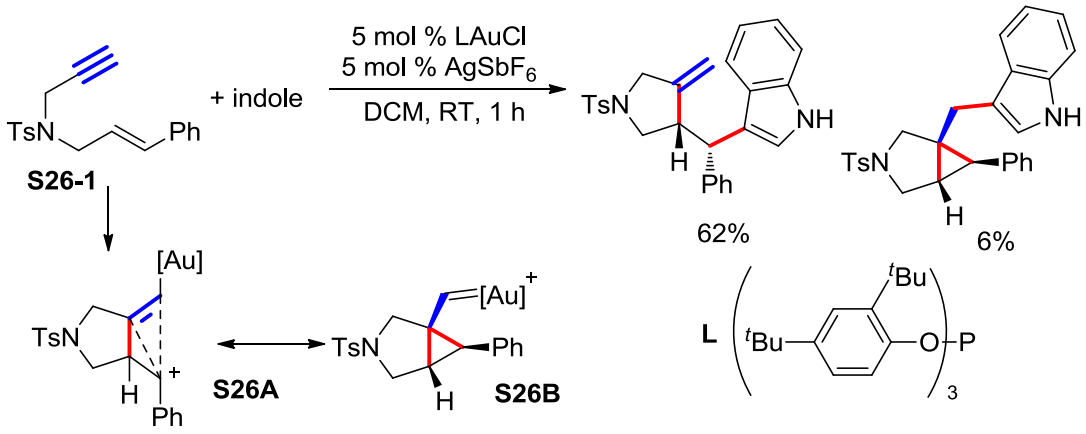
The first gold-catalyzed intermolecular enyne cycloisomerization was also demonstrated by Echavarren et al.[38] (Scheme 25), although the reaction substrates are restricted to aryl alkynes and 1,1-disubstitued olefins. The intermolecular reaction shared the same mechanism as the intramolecular one, which was evidenced by the two products formed from the reaction between **S25-1** and **S25-2**.

Scheme 25. Intermolecular Enyne Cycloisomerization



Various nucleophiles could be involved in the gold-catalyzed enyne cycloisomerization reactions.[35] As shown in Scheme 26,[39] indole could interrupt the cycloisomerization of **S26-1**. Two different constitutional isomers formed as a result of regioselective indole addition to cyclopropyl gold carbene **S26B**.

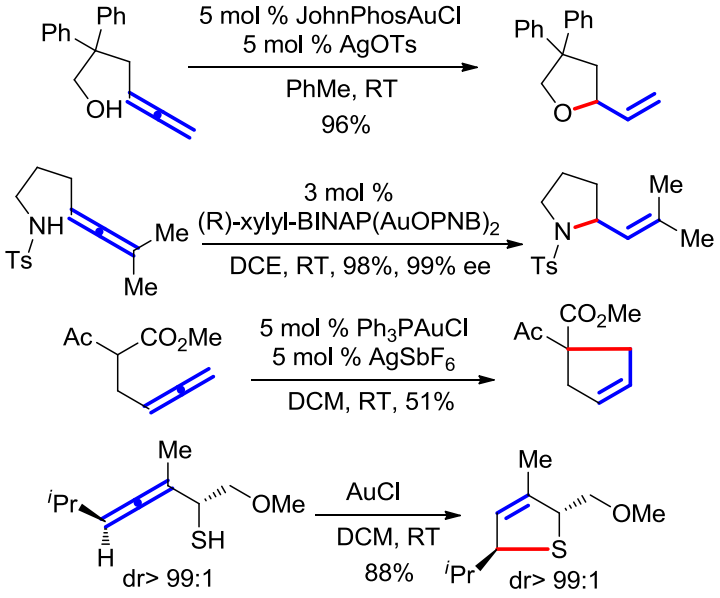
Scheme 26. Interrupted Enyne Cycloisomerization



1.2.3 Transformations Initiated by Allene Activation

1.2.3.1 Simple Nucleophilic Additions to Allenes

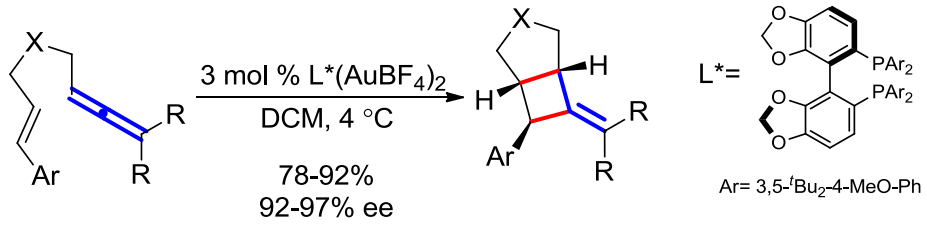
Scheme 27. Gold-Catalyzed Nucleophilic Additions to Allenes



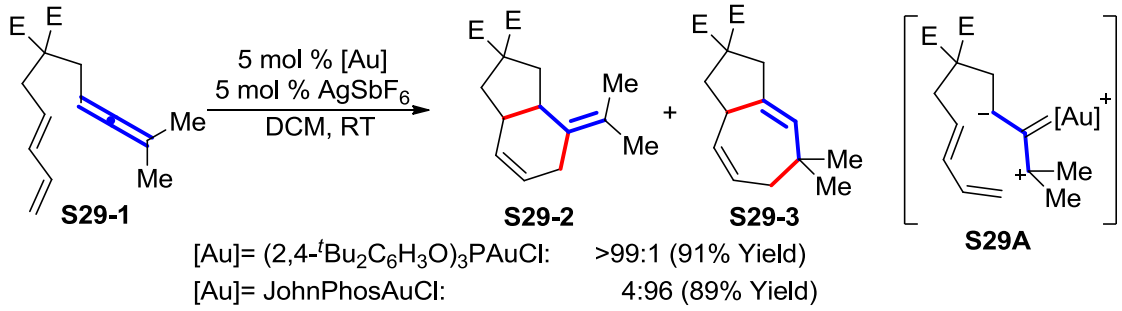
Like alkenes and alkynes, allenes can also be easily activated by cationic gold catalysts. The activated allenes could be attacked by various nucleophiles.[40] As shown in Scheme 27, alcohol,[41] amide,[42] 1,3-dicarbonyls,[43] even thiols[44] have been added to allenes highly enantioselectively, regioselectively, and diastereoselectively.

1.2.3.2 Allene-Ene Cylcoisomerization Reactions

Scheme 28. Allene/Ene [2+2] Reactions



Scheme 29. Allene/Diene [2+4] and [3+4] Reactions

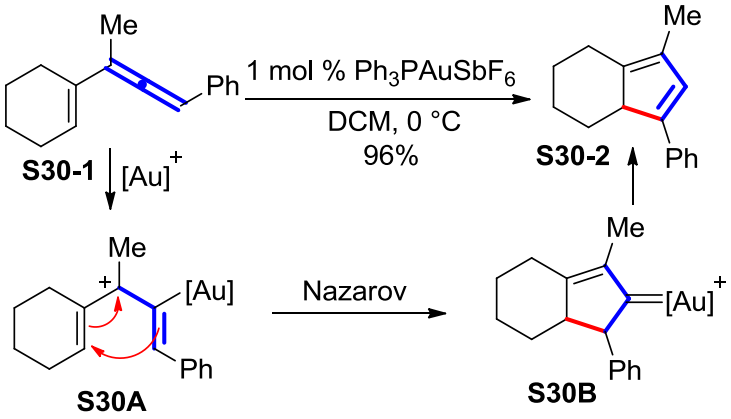


When activated by gold catalyst, allenes could be attacked by tethered olefins (Scheme 28).[45] A formal [2+2] reaction occurred between the olefin and one olefinic bond of the allene. Highly enantioselective transformation has been achieved by Toste et al. using chiral gold catalyst. They also observed significant ligand effect on the chemoselectivity of cycloisomerization reactions of dieneallene **S29-1** (Scheme 29).[46] When the dieneallene **S29-1** was treated with electron deficient phosphite gold catalyst, the Diels-Alder product **S29-2**

predominated. Simply swithching the ligand to sterically hindered and electron-rich JohnPhos, they observed the opposite selectivity with the cycloheptadiene product **S29-3** favored more than twenty times. Notably, in the above allene/diene [3+4] reaction, the allene was formaly an equivalent of gold containing all carbon 1,3-dipole **S29A**.

Toste et al.[47] also developed the cycloisomerization reactions of conjugated allene-enes (Scheme 30). The reaction presumably proceeded through a Nazarov type cyclization of the dienyl cation **S30A** but not a concerted mechanism because enantiomeric rich substrates resulted in totally racemic products.

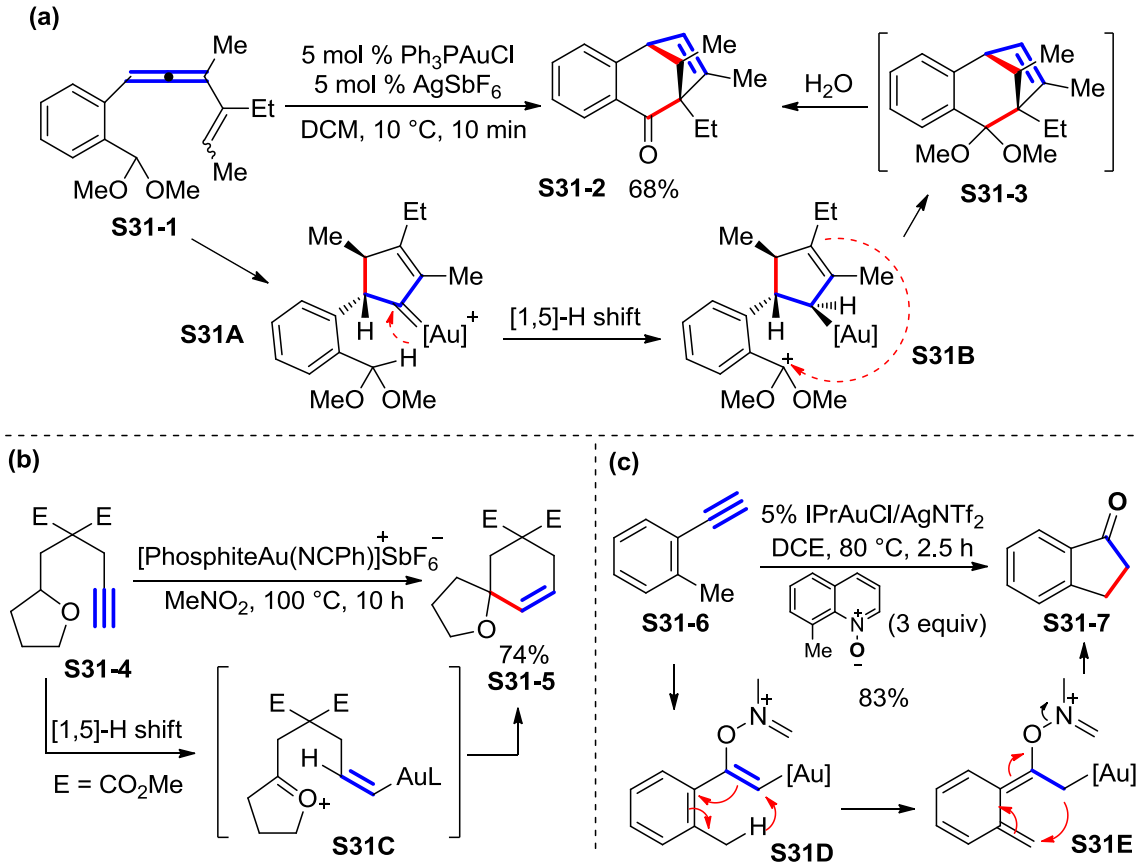
Scheme 30. Conjugated Allene-Ene Cycloisomerization Reactions



1.3 Summary of Gold-Catalyzed C(sp^3)-H Functionalization Reactions

Ever since the 21st century gold rush, tremendous new gold-catalyzed reactions have been discovered with thousands papers published. However, the reactions involving unactivated C(sp^3)-H are rare and limited to certain types of reactions. Since my graduate research was focused on developing new reactions to directly functionalize C(sp^3)-H bonds via gold catalysis. I hereby summary all the gold-catalyzed C(sp^3)-H functionaliztion reactions that have been published prior to my own research work.

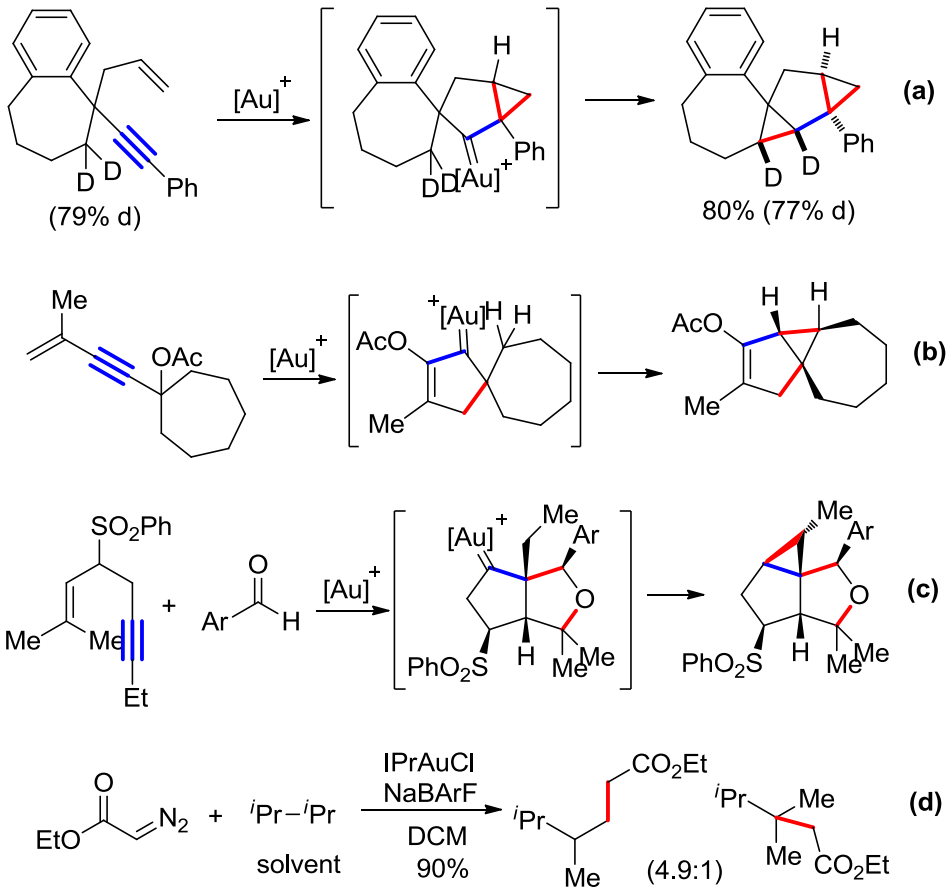
Scheme 31. C(sp^3)-H Functionalization via [1,5]-Hydride Shift



C(sp^3)-H bonds α to heteroatoms or aromatic rings successfully participated in gold-catalyzed reactions through 1,5-hydride migration (Scheme 31). Liu et al.[48] discovered that the gold carbene **S31A** from the cycloisomerization of vinyl allene **S31-1** could induce the 1,5-hydride migration from the benzylic position to gold carbene center (Scheme 31a). The resulting carbocation then reacted with the allyl gold moiety to form **S31-3**, which was then hydrolyzed into final product **S31-2**. Gagosz et al.[49] demonstrated that a simple terminal alkyne **S31-4**, once activated by electron deficient gold catalyst, could directly abstract a hydride from a tethered tetrahydrofuran ring to form the oxocarbenium ion intermediate **S31C** (Scheme 31b). Then, intramolecular cylization between the vinyl gold moiety and the

oxocarbenium ion furnished the final product **S31-5**. Another example of gold-catalyzed 1,5-hydride migration was shown in Liu's indanone synthesis (Scheme 31c).[50] Their mechanistic studies suggested that after 8-methylquinoline *N*-oxide was added to the alkyne, the gold/alkyne/*N*-oxide adduct **S31-D** didn't fragment into α-oxo gold carbene, instead 1,5-hydride migration happened. The resulting intermediate **S31E** then aromatized into indanone product by ring closing and N-O bond cleavage.

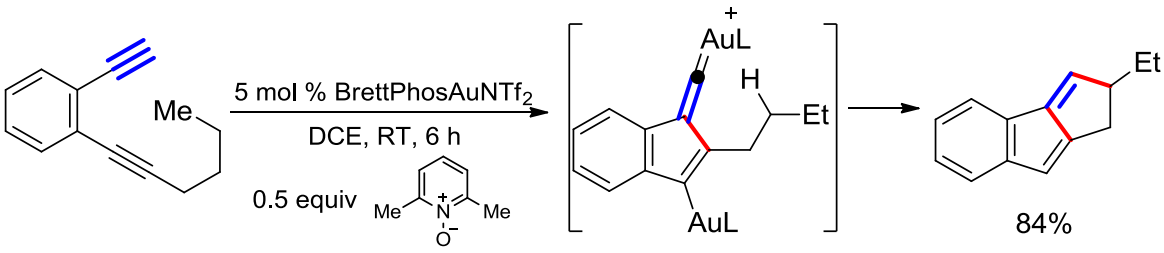
Scheme 32. C(sp^3)-H Functionalization via Gold Carbene C-H Insertion



While all the above studies involve slightly activated C(sp^3)-H bonds, in the year 2009, the Toste,[51] Malacria,[52] and Echavarren[53] groups independently reported insertions into unactivated C(sp^3)-H bonds by gold carbenes generated from enyne cycloisomerizations

(Scheme 32a,b,c). In all the above three reports, gold carbenes inserted into neighbouring C(sp^3)-H bonds to make cyclopropane rings. Nolan and Perez and coworkers demonstrated that gold carbenes from the decomposition of ethyl diazo acetate could efficiently insert into alkanes (Scheme 32d).[54] Unfortunately, they had to use large excess of alkanes and the chemoselectivity between methyl and methine was poor. In 2011, our group[55] and Hashmi group[56] independently discovered that gold vinylidenes are also capable of C(sp^3)-H insertion reactions (Scheme 33). The mechanistic details will be discussed in the following related chapters.

Scheme 33. C(sp^3)-H Functionalization via Gold Vinylidene C-H Insertion



1.4 References

(1) Norman, R. O. C.; Parr, W. J. E.; Thomas, C. B. *Journal of the Chemical Society, Perkin Transactions 1* **1976**, 1983.

(2) Fukuda, Y.; Utimoto, K. *The Journal of Organic Chemistry* **1991**, *56*, 3729.

(3) Teles, J. H.; Brode, S.; Chabanas, M. *Angewandte Chemie International Edition* **1998**, *37*, 1415.

(4) Hashmi, A. S. K.; Schwarz, L.; Choi, J.-H.; Frost, T. M. *Angewandte Chemie International Edition* **2000**, *39*, 2285.

(5) Yang, C.-G.; He, C. *Journal of the American Chemical Society* **2005**, *127*, 6966.

(6) Zhang, J.; Yang, C.-G.; He, C. *Journal of the American Chemical Society* **2006**, *128*, 1798.

(7) Han, X.; Widenhoefer, R. A. *Angewandte Chemie International Edition* **2006**, *45*, 1747.

(8) Yao, X.; Li, C.-J. *Journal of the American Chemical Society* **2004**, *126*, 6884.

(9) Brouwer, C.; Rahaman, R.; He, C. *Synlett* **2007**, *2007*, 1785.

(10) Li, Z.; Zhang, J.; Brouwer, C.; Yang, C.-G.; Reich, N. W.; He, C. *Organic Letters* **2006**, *8*, 4175.

(11) Zheng, Z.; Wang, Z.; Wang, Y.; Zhang, L. *Chemical Society Reviews* **2016**.

(12) Iglesias, A.; Muñiz, K. *Chemistry – A European Journal* **2009**, *15*, 10563.

(13) Zhang, G.; Luo, Y.; Wang, Y.; Zhang, L. *Angewandte Chemie International Edition* **2011**, *50*, 4450.

(14) Zhang, G.; Cui, L.; Wang, Y.; Zhang, L. *Journal of the American Chemical Society* **2010**, *132*, 1474.

(15) Brenzovich, W. E.; Benitez, D.; Lackner, A. D.; Shunatona, H. P.; Tkatchouk, E.; Goddard, W. A.; Toste, F. D. *Angewandte Chemie International Edition* **2010**, *49*, 5519.

(16) de Haro, T.; Nevado, C. *Angewandte Chemie International Edition* **2011**, *50*, 906.

(17) Genin, E.; Toullec, P. Y.; Antoniotti, S.; Brancour, C.; Genêt, J.-P.; Michelet, V. *Journal of the American Chemical Society* **2006**, *128*, 3112.

(18) Wang, Y.; Wang, Z.; Li, Y.; Wu, G.; Cao, Z.; Zhang, L. *Nat Commun* **2014**, *5*.

(19) Belting, V.; Krause, N. *Organic Letters* **2006**, *8*, 4489.

(20) Ketcham, J. M.; Biannic, B.; Aponick, A. *Chemical Communications* **2013**, *49*, 4157.

(21) Oonishi, Y.; Gómez-Suárez, A.; Martin, A. R.; Nolan, S. P. *Angewandte Chemie International Edition* **2013**, *52*, 9767.

(22) Fukuda, Y.; Utimoto, K. *Synthesis* **1991**, *1991*, 975.

(23) Mizushima, E.; Hayashi, T.; Tanaka, M. *Organic Letters* **2003**, *5*, 3349.

(24) Reetz, Manfred T.; Sommer, K. *European Journal of Organic Chemistry* **2003**, *2003*, 3485.

(25) Kennedy-Smith, J. J.; Staben, S. T.; Toste, F. D. *Journal of the American Chemical Society* **2004**, *126*, 4526.

(26) Xi, Y.; Dong, B.; McClain, E. J.; Wang, Q.; Gregg, T. L.; Akhmedov, N. G.; Petersen, J. L.; Shi, X. *Angewandte Chemie International Edition* **2014**, *53*, 4657.

(27) Akana, J. A.; Bhattacharyya, K. X.; Müller, P.; Sadighi, J. P. *Journal of the American Chemical Society* **2007**, *129*, 7736.

(28) Dorel, R.; Echavarren, A. M. *Chemical Reviews* **2015**, *115*, 9028.

(29) Zhang, L. *Journal of the American Chemical Society* **2005**, *127*, 16804.

(30) Brabander, J. K. D.; Liu, B.; Qian, M. *Organic Letters* **2008**, *10*, 2533.

(31) Cran, J. W.; Krafft, M. E. *Angewandte Chemie International Edition* **2012**, *51*, 9398.

(32) Miki, K.; Ohe, K.; Uemura, S. *The Journal of Organic Chemistry* **2003**, *68*, 8505.

(33) Shapiro, N. D.; Toste, F. D. *Journal of the American Chemical Society* **2008**, *130*, 9244.

(34) Li, G.; Zhang, G.; Zhang, L. *Journal of the American Chemical Society* **2008**, *130*, 3740.

(35) Jiménez-Núñez, E.; Echavarren, A. M. *Chemical Reviews* **2008**, *108*, 3326.

(36) Hashmi, A. S. K.; Frost, T. M.; Bats, J. W. *Journal of the American Chemical Society* **2000**, *122*, 11553.

(37) Nieto-Oberhuber, C.; Muñoz, M. P.; López, S.; Jiménez-Núñez, E.; Nevado, C.; Herrero-Gómez, E.; Raducan, M.; Echavarren, A. M. *Chemistry – A European Journal* **2006**, *12*, 1677.

(38) López-Carrillo, V.; Echavarren, A. M. *Journal of the American Chemical Society* **2010**, *132*, 9292.

(39) Amijs, C. H. M.; Ferrer, C.; Echavarren, A. M. *Chemical Communications* **2007**, 698.

(40) Krause, N.; Winter, C. *Chemical Reviews* **2011**, *111*, 1994.

(41) Zhang, Z.; Liu, C.; Kinder, R. E.; Han, X.; Qian, H.; Widenhoefer, R. A. *Journal of the American Chemical Society* **2006**, *128*, 9066.

(42) LaLonde, R. L.; Sherry, B. D.; Kang, E. J.; Toste, F. D. *Journal of the American Chemical Society* **2007**, *129*, 2452.

(43) Jiang, X.; Ma, X.; Zheng, Z.; Ma, S. *Chemistry – A European Journal* **2008**, *14*, 8572.

(44) Morita, N.; Krause, N. *Angewandte Chemie International Edition* **2006**, *45*, 1897.

(45) Luzung, M. R.; Maulón, P.; Toste, F. D. *Journal of the American Chemical Society* **2007**, *129*, 12402.

(46) Maulón, P.; Zeldin, R. M.; González, A. Z.; Toste, F. D. *Journal of the American Chemical Society* **2009**, *131*, 6348.

(47) Lee, J. H.; Toste, F. D. *Angewandte Chemie* **2007**, *119*, 930.

(48) Bhunia, S.; Liu, R.-S. *Journal of the American Chemical Society* **2008**, *130*, 16488.

(49) Jurberg, I. D.; Odabachian, Y.; Gagosz, F. *Journal of the American Chemical Society* **2010**, *132*, 3543.

(50) Bhunia, S.; Ghorpade, S.; Huple, D. B.; Liu, R.-S. *Angewandte Chemie International Edition* **2012**, *51*, 2939.

(51) Horino, Y.; Yamamoto, T.; Ueda, K.; Kuroda, S.; Toste, F. D. *Journal of the American Chemical Society* **2009**, *131*, 2809.

(52) Lemière, G.; Gandon, V.; Cariou, K.; Hours, A.; Fukuyama, T.; Dhimane, A.-L.; Fensterbank, L.; Malacria, M. *Journal of the American Chemical Society* **2009**, *131*, 2993.

(53) Escribano-Cuesta, A.; López-Carrillo, V.; Janssen, D.; Echavarren, A. M. *Chemistry – A European Journal* **2009**, *15*, 5646.

(54) Fructos, M. R.; de Frémont, P.; Nolan, S. P.; Díaz-Requejo, M. M.; Pérez, P. J. *Organometallics* **2006**, *25*, 2237.

(55) Ye, L.; Wang, Y.; Aue, D. H.; Zhang, L. *Journal of the American Chemical Society* **2012**, *134*, 31.

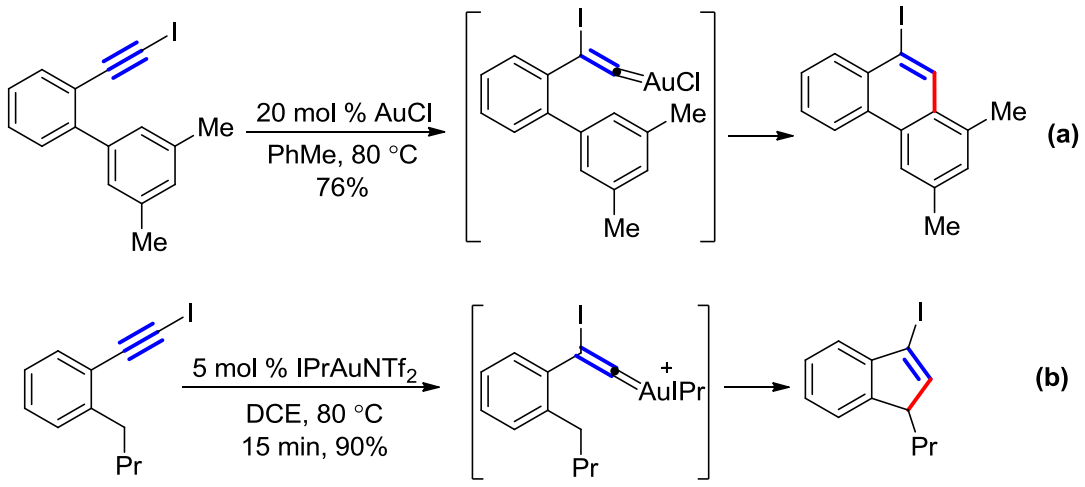
(56) Hashmi, A. S. K.; Braun, I.; Nösel, P.; Schädlich, J.; Wieteck, M.; Rudolph, M.; Rominger, F. *Angewandte Chemie International Edition* **2012**, *51*, 4456.

Chapter 2. C-H Functionalization via Insertion into Unactivated C(sp^3)-H Bonds by Intermolecularly Generated Gold Vinylidenes

2.1 Introduction to Gold Vinyidene Chemistry

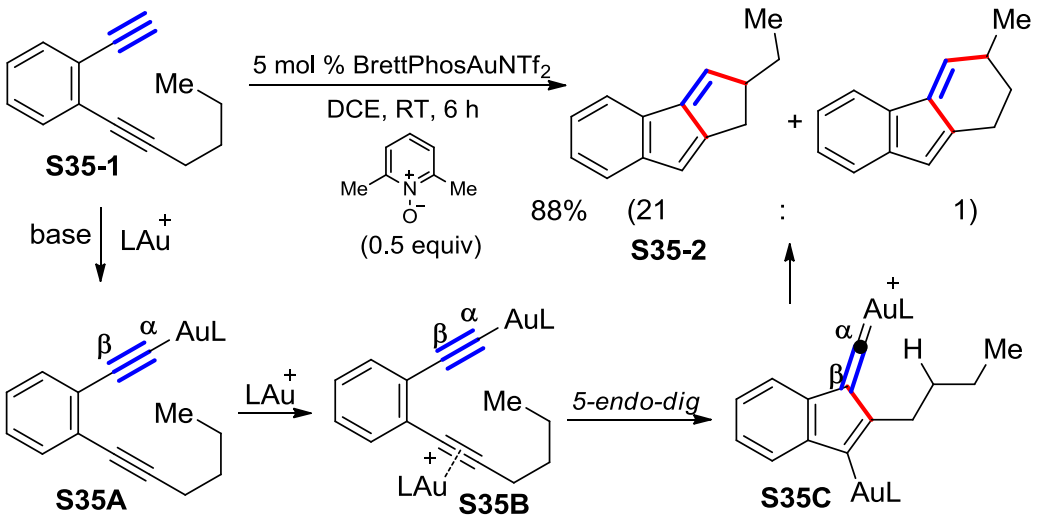
Various transition metals (Cu, Ru, Rh etc) could form metal vinylidene complexes, some of which are even stable and isolable.[1] The transition metal vinylidene chemistry is rich and has contributed various valuable synthetic methods to organic chemists.[1] In the early years of homogeneous gold catalysis, gold vinylidene has already been proposed as a reactive species. Furstner et al.[2] published a pioneer work on the direct isomerization of simple iodoarylalkynes into gold vinylidenes, which then reacted with aromatic rings (Scheme 34a). As a result, the iodide migrated in the final product. The Furstner's vinylidene mechanism was later supported by DFT calculation.[3] In 2015, Gonzalez et al.[4] demonstrated that the Furstner type of gold vinylidenes could facilely insert into benzylic C(sp^3)-H bonds (Scheme 34b).

Scheme 34. Iodoalkyne Isomerization into Gold Vinylidene



In the diyne cycloisomerization chemistry (Scheme 35), our group[5] for the first time established by DFT calculations that gold vinylidenes indeed can be generated and moreover by experiments that they can readily insert into unactivated C(sp^3)-H bonds, which is the first demonstration of such type and also unique as other transition metal vinylidenes do not possess this type of reactivity. As shown in Scheme 35, the terminal alkyne reacted with one cationic gold complex to form the alkynyl gold species **S35A**, which could be facilitated by an external weak base. The internal alkyne was activated by another cationic gold catalyst via coordination **S35B**. Thus the diyne substrate was dually activated. Then the β-carbon of the gold acetylide moiety attacked the activated internal alkyne and this *5-endo-dig* cyclization afforded the gold vinylidene intermediate **S35C**. The gold vinylidene then inserted into unactivated aliphatic C(sp^3)-H bonds. The Hashmi group later independently reported similar reactions using similar substrates.[6]

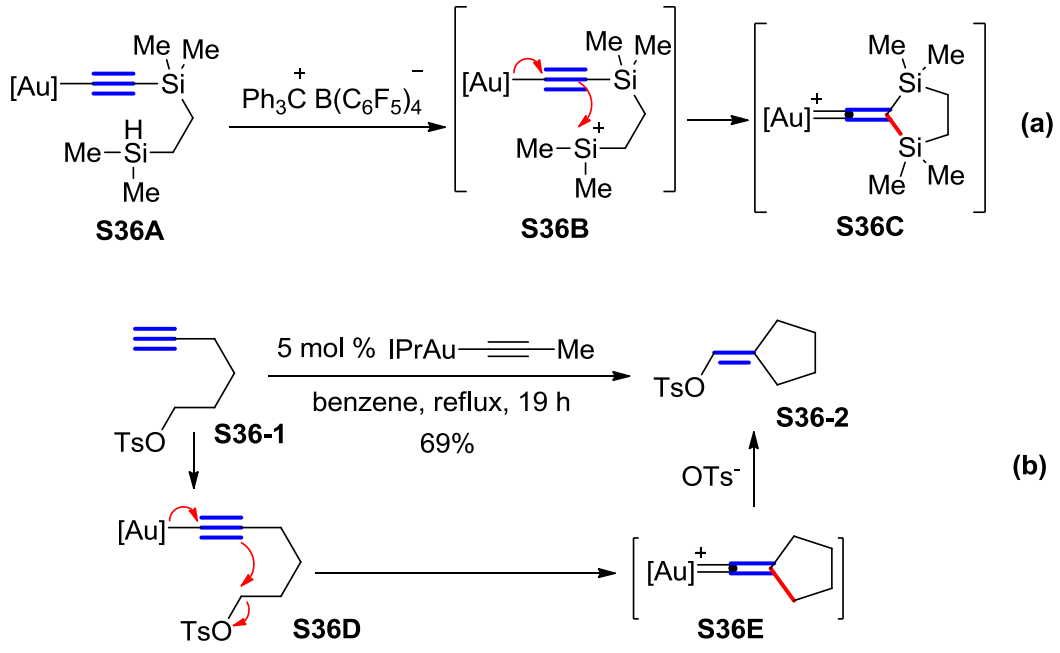
Scheme 35. Gold Vinylidene Formation via Dual Gold Catalysis



Besides the above diyne approach, the Hashmi group[7] and Widenhoefer group[8] provided other interesting intramolecular entries to gold vinylidenes (Scheme 36). In Widenhoefer's

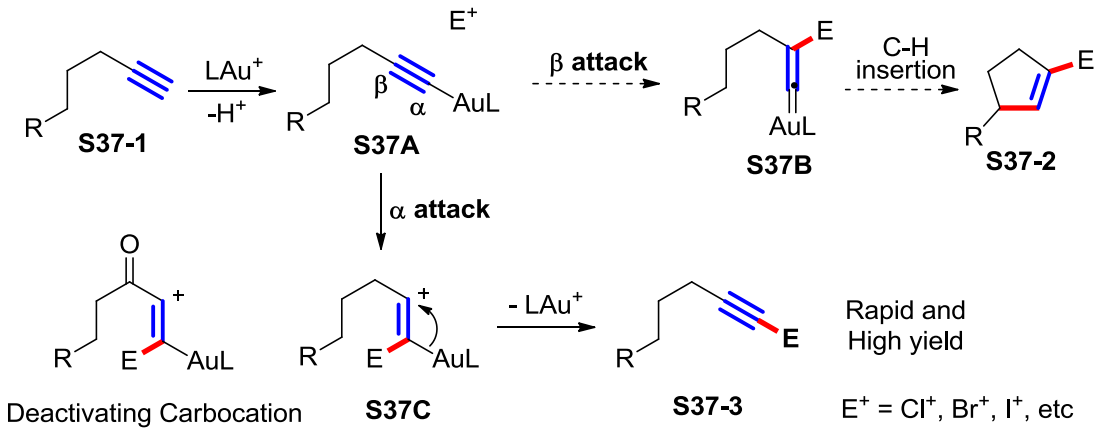
work (Scheme 36a), they synthesized the gold acetylide organometallic complex with a silane moiety properly tethered to the alkyne **S36A**. The addition of hydride abstraction reagent resulted in a silyl cation **S36B**, which then reacted with the gold acetylide moiety. They observed the β-carbon attack from the gold acetylide to generate gold vinylidene **S36C**. In Hashmi's work (Scheme 36b), alkynyl tosylate **S36-1** was cyclized into cyclic vinyl tosylate **S36-2** through gold catalysis. They proposed that gold acetylide **S36D** was first formed then its β-carbon did an intramolecular S_N2 reaction to kick out tosylate anion. Gold vinylidene **S36E** was generated as a result and then trapped by the nearby tosylate anion. This work clearly showed that the β-carbon of gold aetylide possessed significant nucleophilicity and could react with proper electrophiles.

Scheme 36. Widenhoefer and Hashmi's Intramolecular Approaches to Gold Vinylidenes



2.2 Our Strategy to Generate Fully Substituted Gold Vinylidenes and Reaction Discovery

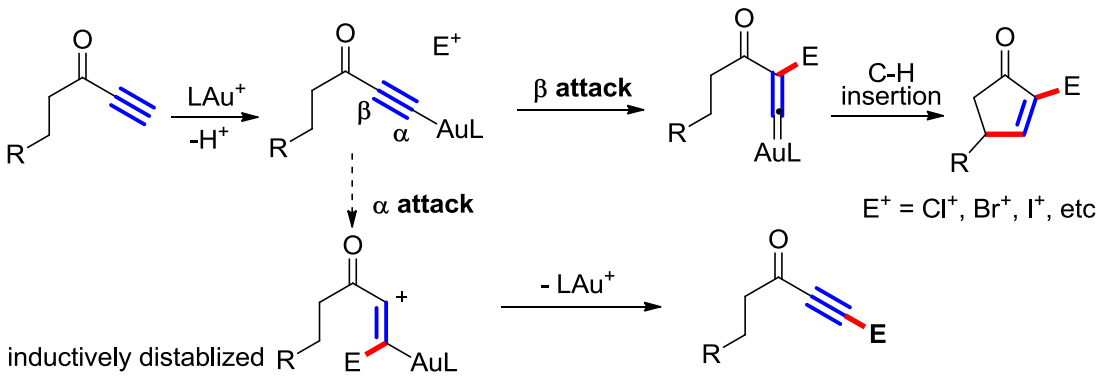
Scheme 37. Our Initial Intermolecular Approach to Fully Substituted Gold Vinylidenes and the C-H Insertion Reaction Design



As shown above, there are several approaches to gold vinylidenes and certain reactions to utilize them including the C(sp^3)-H insertion reactions. However, such C(sp^3)-H insertions relied on very special benzene fused 1,2-diyne substrates and the C(sp^3)-H insertion products lacked general interest for the whole areas of organic chemistry. We wanted to realize a most straightforward and meaningful reaction: to convert a simple and readily available aliphatic terminal alkyne **S37-1** like 1-dodecyne into a substituted cyclopentene **S37-2** via a gold vinylidene formation and C-H insertion process (Scheme 37). Somewhat similar to Widenhoefer and Hashmi's approaches (Scheme 36), our initial attempt was based on the nucleophilicity of the β-carbon of the alkynyl gold complex **S37A**. We expected that this in-situ generated alkynyl gold complex would react with external electrophiles like NBS leading to the gold vinylidene intermediate **S37B** via the β-carbon attack. Then the vinylidene insertion into alkyl group would afford us functionalized cyclopentene **S37-2**.

Much to our disappointment, no desired product was ever detected and the α-carbon attack occurred rapidly and efficiently, leading to product **S37-3** with the terminus carbon functionalized. We envisoned that the α-carbon attack could happen because the carbon cation in **S37C** could be partially stabilized by the two neighbouring C-H bonds via hyperconjugation. If we replace the propargylic methylene group with a carbonyl group, the α-attack will be disfavored not only because the hyperconjugation doesn't exist but also because the carbonyl group will inductively destabilize the carbon cation (Scheme 38). Although this is slightly off our initial design, the whole transformation is still very attractive because we start with readily available alkynones and end up with highly valuable functionalized cyclopentenones.

Scheme 38. Our Terminal Alkynone Strategy to a Fully Substituted Gold Vinylidene and its C(sp^3)-H Insertion Reaction

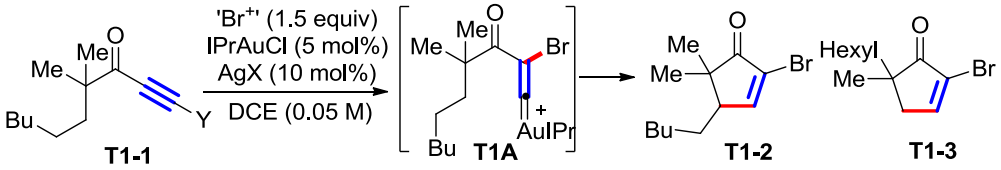


We examined the possibility of the above alkynone stragety for gold vinylidene C-H insertion reactions by using ynone **T1-1** as the substrate and brominating reagent as the electrophile (Table 1). Two gem-dimethyl groups were installed to facilitate the intramolecular C-H insertion reactions through the Thorpe-Ingold effect. Unfortunately, no matter what phosphine ligand we used, only trace amount of desired procuct was ever

detected and the starting material **T1-1** decomposed into unknown mixtures in a short while. To our delight, the N-heterocyclic carbene ligand IPr provided us 5% desired product (entry 1). Although in a small amount, it really motivated me to continue with this project. In the conditions optimization process, I tried to improve every single detail in my reaction. First of all, chloride scavenger was varied for our gold catalyst. The counteranion turned out to be critical for this transformation (entry 1-3). The less coordinating OTf^- was much better than NTf_2^- and improved the yield dramatically from 5% to 49%. SbF_6^- turned out to be the most effective one leading to a total 61% yield of cyclopentenone products even at room temperature (entry 3). Other counteranions like PF_6^-, BF_4^-, $BARF^-$ were not as effective. Interestingly, the amount of $AgSbF_6$ also affected the reaction outcome (entries 3-5). Extra $AgSbF_6$ accelerated the whole reaction, indicating that the catalytic reaction occurred in an acidic environment. With the gold catalyst and the chloride scavenger settled down, we then tested other commercially available brominating reagents. Compared to NBS, the more reactive NBP (*N*-bromophthalimide) didn't improve the reaction (entry 6). To the opposite, the less reactive brominating reagent NBA (*N*-bromoacetamide) was better and an outstanding 86% yield was achieved (entry 7). Since TMS protected alkyne has also been demonstrated to form alkynyl gold species with cationic gold complex, we then synthesized and tested the TMS alkynone **T1-1-TMS**. The reaction proceeded at a similar rate and **T1-2** was afforded in an excellent 93% yield without noticeable formation of bromoalkynone side product **T1-4** (entry 8). Compared to TMS group, TES retarded the reaction, resulting in low conversion after 48 hours (entries 9). This result is reasonable according to our proposed mechanism becaused TES is much bigger that TMS and thus slowed down the first gold acetylide formation step. Under the best conditions, the bromoalkynone **T1-4** led to no desired product and only decomposed gradually (entry 10), which rules out its potential

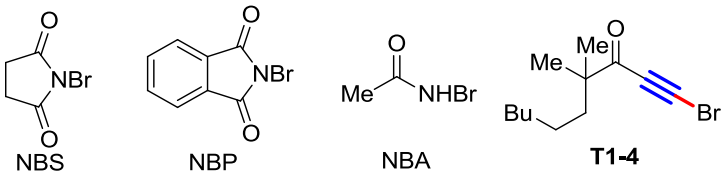
intermediacy in the C-H insertion catalytic cycle. The silver salt alone led to 60% bromoalkynone **T1-4** and no C-H insertion product (entry 11). The residual H_2O from undried vial was beneficial to the reaction. The reaction became much less efficient with molecular sieves in flame dried vial (entry 12). On the other hand, adding H_2O (4 equiv) accelerated the reaction but slightly diminished the yield (entry 13). The water's accelerating effect could be attributed to the gold acetylide formation step by helping remove the TMS group. Finally, the DCM was as effective as DCE, and the α-bromo cyclopentenone product was isolated in excellent 95% yield with excellent chemoselectivity. The methylene C-H bonds are preferred over the methyl ones by a ratio of >40/1.

Table 1. Initial Reaction Discovery and Conditions Optimization



entry	Y	AgX	'Br+'	Temp./time	conv.	Yield[a]	
						T1-2/T1-3	**T1-4**
1	H	$AgNTf_2$	NBS	60 ℃/12 h	88%	5% (NA)	<2%
2	H	AgOTf	NBS	60 ℃/4 h	100%	49% (>12/1)	10%
3	H	$AgSbF_6$	NBS	rt/18 h	100%	61% (>17/1)	<2%
4	H	$AgSbF_6$ (5 mol%)	NBS	rt/18 h	84%	24%	<2%
5	H	$AgSbF_6$ (20 mol%)	NBS	rt/5 h	100%	48%	<2%
6	H	$AgSbF_6$	NBP	rt/18 h	100%	47% (>32/1)	<2%
7	H	$AgSbF_6$	NBA	rt/7 h	100%	86% (>20/1)	12%
8	TMS	$AgSbF_6$	NBA	rt/7 h	100%	95% (>40/1)	<2%
9	TES	$AgSbF_6$	NBA	rt/48 h	19%	16% (5/1)	<2%
10	Br	$AgSbF_6$	--	rt/48 h	22%	0	78%
11	TMS	$AgSbF_6$[b]	NBA	rt/7 h	62%	0	60%
12[c]	TMS	$AgSbF_6$	NBA	rt/7 h	51%	20%(>20/1)	12%
13[d]	TMS	$AgSbF_6$	NBA	rt/3.5 h	100%	87%(>20/1)	<2%

[a] Reaction run in regular vial. The yields estimated by ^{1}H NMR using diethyl phthalate as the internal reference. [b] No gold used. [c] 4 Å MS added. [d] H_2O (4 equiv to **T1-1**) added.



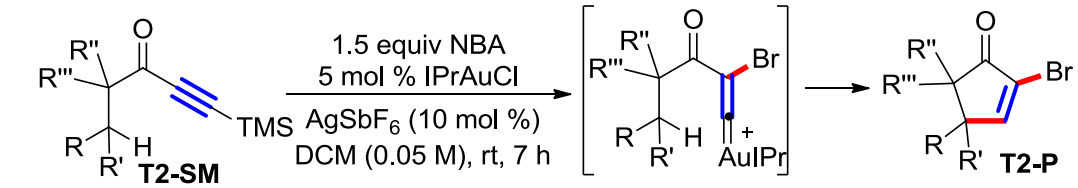
2.3 Scope Study of Gold Vinylidene C(sp^3)-H Insertion Reactions

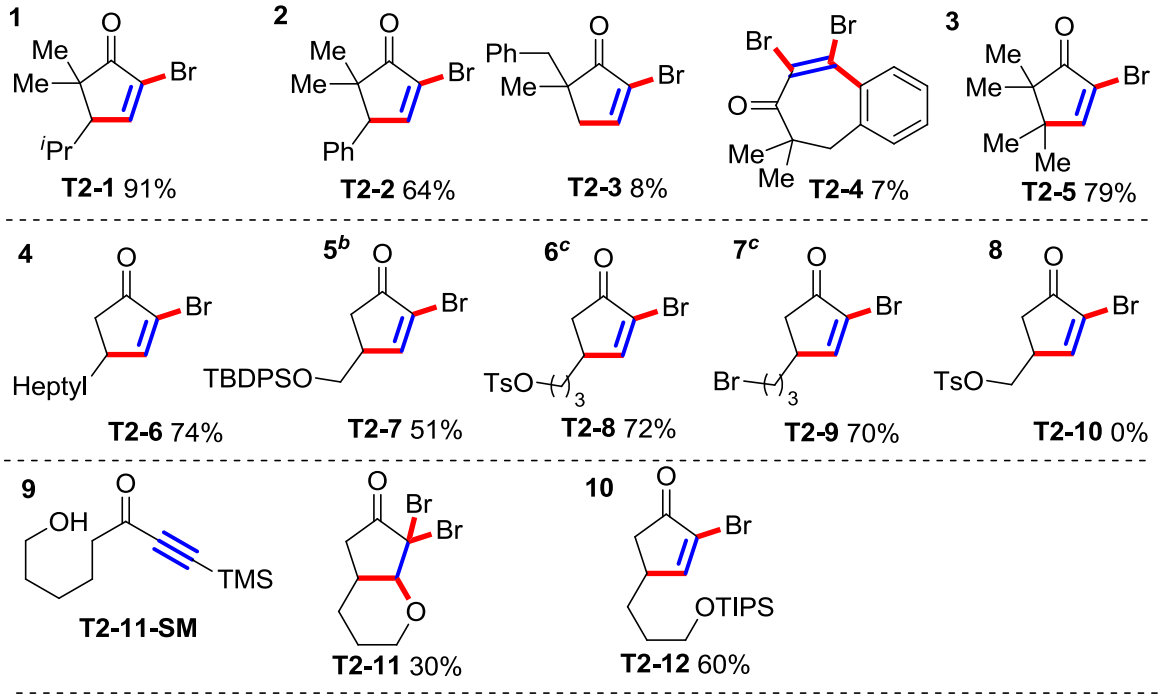
Cyclopentenones are exceptionally useful in organic synthesis, and the products via our streamlining C-H insertion strategy are more synthetically valuable because they possess extra α-bromination,[9-11] which could be additionally functionalized, and also the starting materials can be easily synthesized from cheap and readily available carboxylic acid derivatives. This rapid access to highly versatile α-bromocyclopentenone prompted us to extensively explore the reaction scope.

We first probed the general reactivity of our gold vinylidene towards various types of C(sp^3)-H bonds. Slightly hindered C(sp^3)-H bond was still inserted smoothly (entry 1). Our gold vinylidene favored tertiary C(sp^3)-H bond over primary ones (entry 3). We actually got some problem for the benzylic C-H insertion reaction. Although the desired **T2-2** product was formed as the major one, we got small amount of benzene insertion and methyl insertion products. We are very delighted to find that our reaction is not limited to substrates bearing α-quaternary carbons. Simple linear TMS-terminated ynone (entry 4) worked efficiently under the optimized conditions, affording **T2-6** in a good 74% yield. The alkyl groups for C(sp^3)-H insertion could be decorated with various valuable functional groups such as OTs, OTBDPS and Br (entry 5-7). Moreover, we found that the closer an inductively deactivating group was installed to the C-H insertion carbon, the more sluggish the reaction was. For instance, the insertion into a γ'-OTBDPS group led to 51% yield with more catalyst loading and in longer time (entry 5). If the siloxyl group was replaced with a more inductive OTs

group, no desired C-H insertion product was detected. To the opposite, the OTs three carbons away from the insertion carbon didn't affect the reaction at all (entry 6).

Table 2. Scope of Gold-Catalyzed Cyclopentenone Synthesis: Insertion into Linear Alkyl Groups[a]



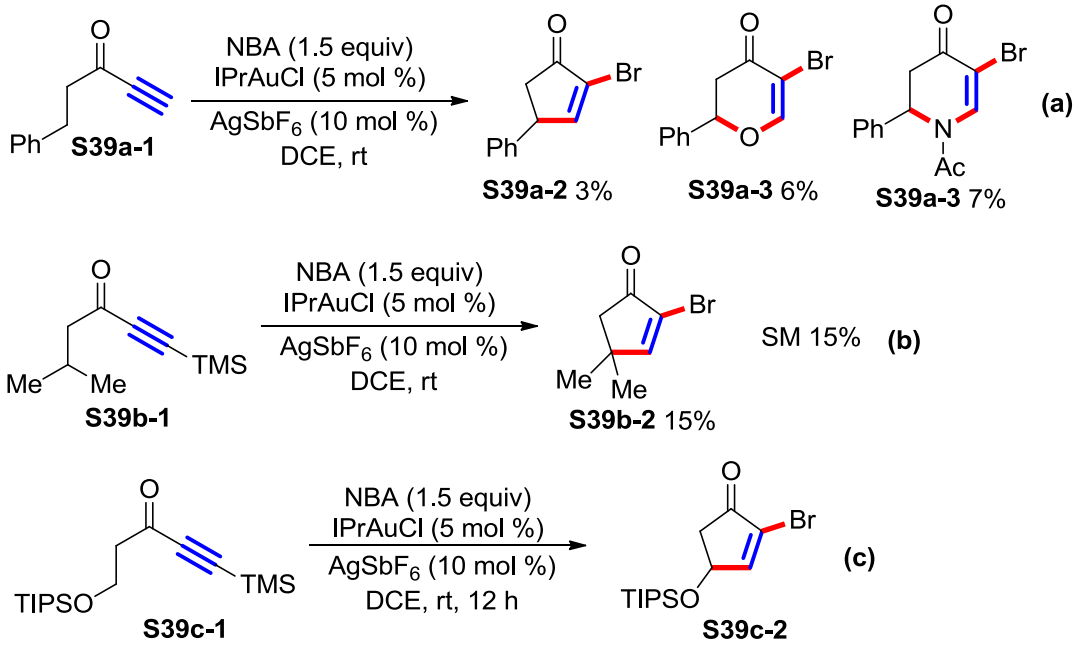


[a]Typical reaction conditions: 1 (0.05 M in DCM), IPrAuCl (5 mol%), $AgSbF_6$ (10 mol%), NBA (1.5 equiv), rt, 7 h. [b]IPrAuCl (10 mol%), $AgSbF_6$ (20 mol%), NBA (3 equiv), rt, 24 h. [c]IPrAuCl (7.5 mol%), $AgSbF_6$ (15 mol%), NBA (2 equiv), rt, 7 h.

Interestingly, when there is a free hydroxyl group not too far from the C-H insertion center (**T2-11-SM**), the gold vinylidene C-H insertion still worked but the α-bromo

cyclopentenone product was consumed in-situ via a bromoalkoxylation reaction, leading to the final 6,5-fused cyclopentanone **T2-11** (entry 9). Once the free hydroxyl group was masked by a TIPS group, α-bromo cyclopentenone T2-12 was isolated in moderated yield with 20% starting material left and no further cyclization from the oxygen atom occurred (entry 10).

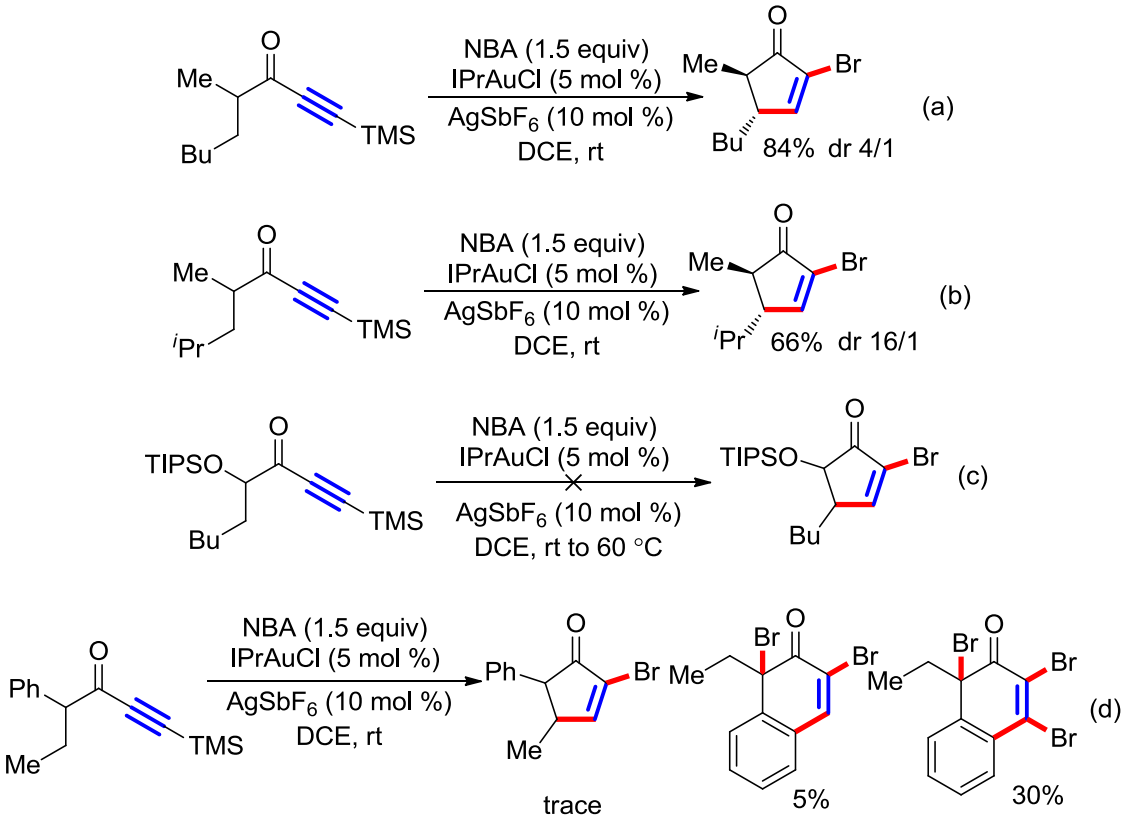
Scheme 39. Unsuccessful Insertions into Linear Alkyl Groups by Gold Vinylidene



However, we got some problems with certain types of linear substrates without the gem-dimethyl groups (Scheme 39). For example, under optimized conditions, the reaction of ynone **S39a-1** resulted in only 3% desired cyclopentenone product **S39a-2** and two unexpected side products **S39a-3 and S39a-4**, which indicated the possible competitive 1,5-hydride migration reaction (Scheme 39a). Without the Thorpe-Ingold effect, the gold vinylidene insertion into tertiary C-H bond was much more difficult, only 15%

cyclopentenone product was generated with 15% starting material left (Scheme 39b). Moreover, almost no reaction happened for ynone **S39c-1**, presumably because the facile 1,5-hydride migration from the ethereal position trapped the gold catalyst and thus shut down the whole catalytic cycle (Scheme 39c).

Scheme 40. Diastereoselective Insertions into Linear Alkyl Groups by Gold Vinylidene

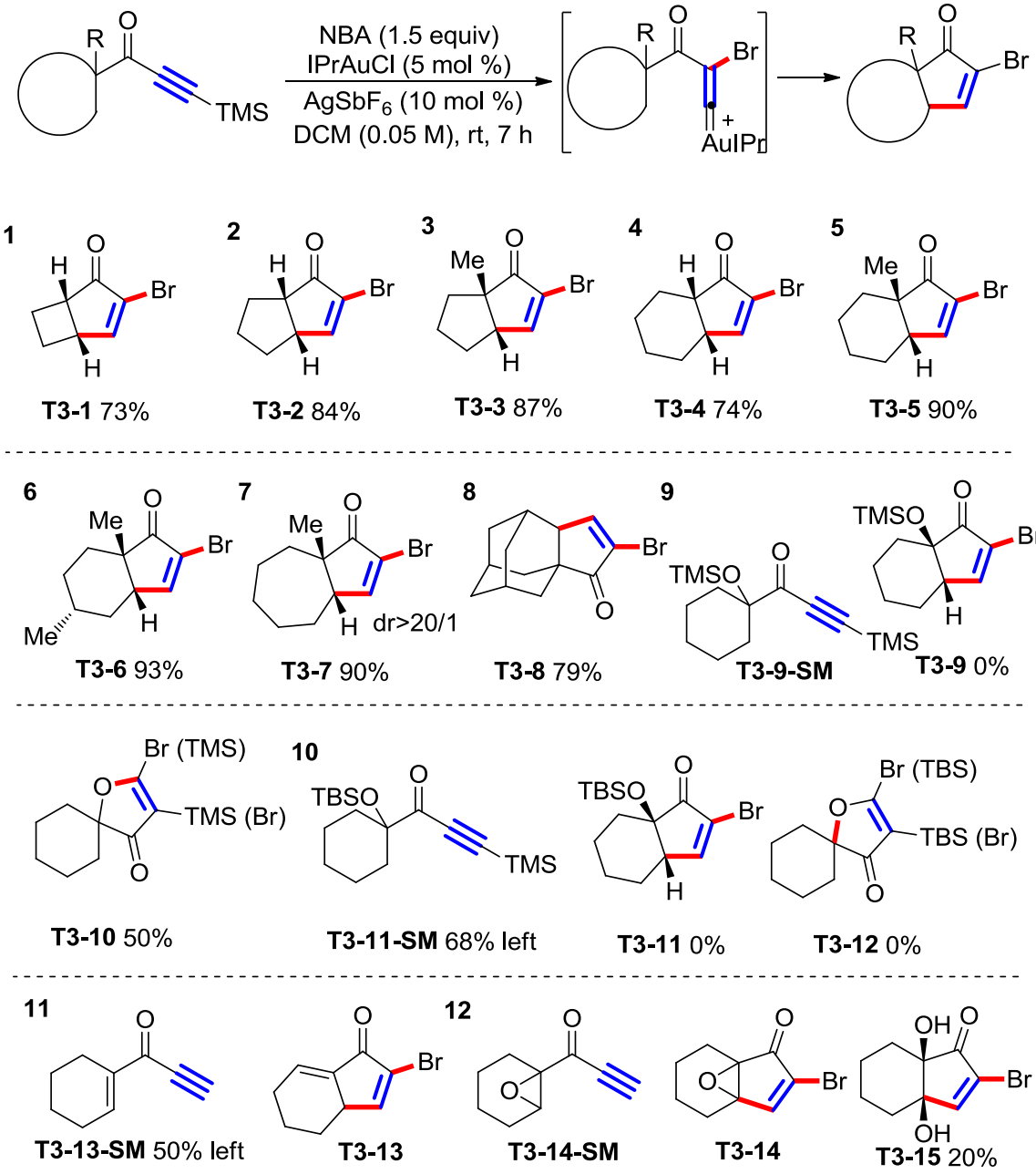


I then studied the diastereoselectivity issue for the substrates with one asymmetric carbon center (Scheme 40). As shown in Scheme 40a, the steric difference between a methyl group and primary butyl group induced a serviceable 4/1 diastereoselectivity favoring the *trans* one. Compared to the above butyl group, an isopropyl group substantially improved the diastereoselectivity (Scheme 40b). I then synthesized the linear TMS alkynone with a α-

TIPSO group in order to test whether a bulky group at ketone's α position could control the diasteroselectivity (Scheme 40c). However, the reaction was very slow and no C-H insertion product was ever detected. A phenyl group at α position also didn't help control the diastereoselectivity. On the contrary, the phenyl group reacted with the gold vinylidene more favorably than the ethyl group (Scheme 40d).

Our synthetic strategy was then applied to synthesize fused bicyclic cyclopentenones by the vinylidene insertions into carbocycles of different sizes (Table 3) including the strained cyclobutane one (entry 1). These reactions from entry 1 to entry 8 are all highly productive, with yield up to 93%. Moreover, excellent *cis*-selective C-H insertion reactions were observed including the cyclohexane-fused ones (entry 4-6) and the cycloheptane-fused one (entry 7). No competitive insertion into the nearby methyl group occurred even for the cylcopentane ring insertion case (entry 3). Our gold vinylidene was also able to insert into the conformationally fixed adamantane skeleton and the adamantane-fused 2-bromocyclopentenone **T3-8** was isolated in 79% yield (entry 8). However, for the cyclohexyl ynone **T3-9-SM** with a α-TMSO group, no C-H insertion product **T3-9** was formed (entry 9). Instead, the nearby oxygen atom participated in the reaction but the product **T3-10**'s structure was not completely determined. Due to this issue, TBS was applied as the protecting group to mask the oxygen atom (entry 10). Indeed, the TBSO group was not involved any more but no C-H insertion product was detected. The alkynyl enone **T3-13-SM** was not suitable for our gold vinylidene C-H insertion reaction (entry 11), probably due to the fixed conformation and also the deactivating effect from the alkynyl carbonyl group. Interestingly, when the double bond was converted to epoxide, cyclopentenone diol **T3-15** was isolated in 20% yield, which most possibly came from the hydrolysis of the initial C-H insertion product **T3-14**.

Table 3. Synthesis of Carbocycle Fused Cyclopentenones



With the general gold vinylidene C-H insertion reactivity investigated, we then turned our effort to the chemoselective C-H insertion issue when there are two different alkyl groups present for insertion (Scheme 41). From the previous results, we know that secondary

and tertiary C-H bonds are preferred to methyl groups usually with more than 20/1 selectivity, such as the case of Scheme 41a. However, if the butyl group from Scheme 41a was replaced by a $TBDPSOCH_2$ group, significant amount of methyl insertion was observed (Scheme 41b), indicating the strong deactivating effect of the oxygen atom on the alkyl chain. Comparing a propyl group and $TBDPSOCH_2CH_2$ group (Scheme 41c), the gold vinylidene prefered the regular nonsubstituted alkyl chain by a serviceable 4/1 ratio, highlighting the potential of electronic control of chemoselectivity. Surprisingly, the C-H bonds at the α,β-unsaturated ester's allylic position were sufficiently deactivated to avoid the insertion, and insertion only happened to the propyl group (Scheme 41d). Such electronic control could also be applied for the selective C-H insertion of TBDPSO substituted cyclohexanes (Scheme 41f, g). Besides the electronic effect, we also checked whether steric difference could be applied to control the chemoselective C-H bond. The reaction of ynone with two electronically similar but sterically different alkyl chains was highly efficient (Scheme 41e). Much to our surprise, the chemoselectivity was 1.5/1 favoring insertion into the sterically more hindered methylene group. This unexpected result supported the proposed gold vinylidene intermediate, which had an extended linear structure thus nonsentitive to steric factors. Instead, subtle electronic difference took control and our gold vinylidene inserted into the inductively more electron-rich C-H bond.

Scheme 41. Gold Vinylidene Chemoselective Insertions into Two Biased Alkyl Groups

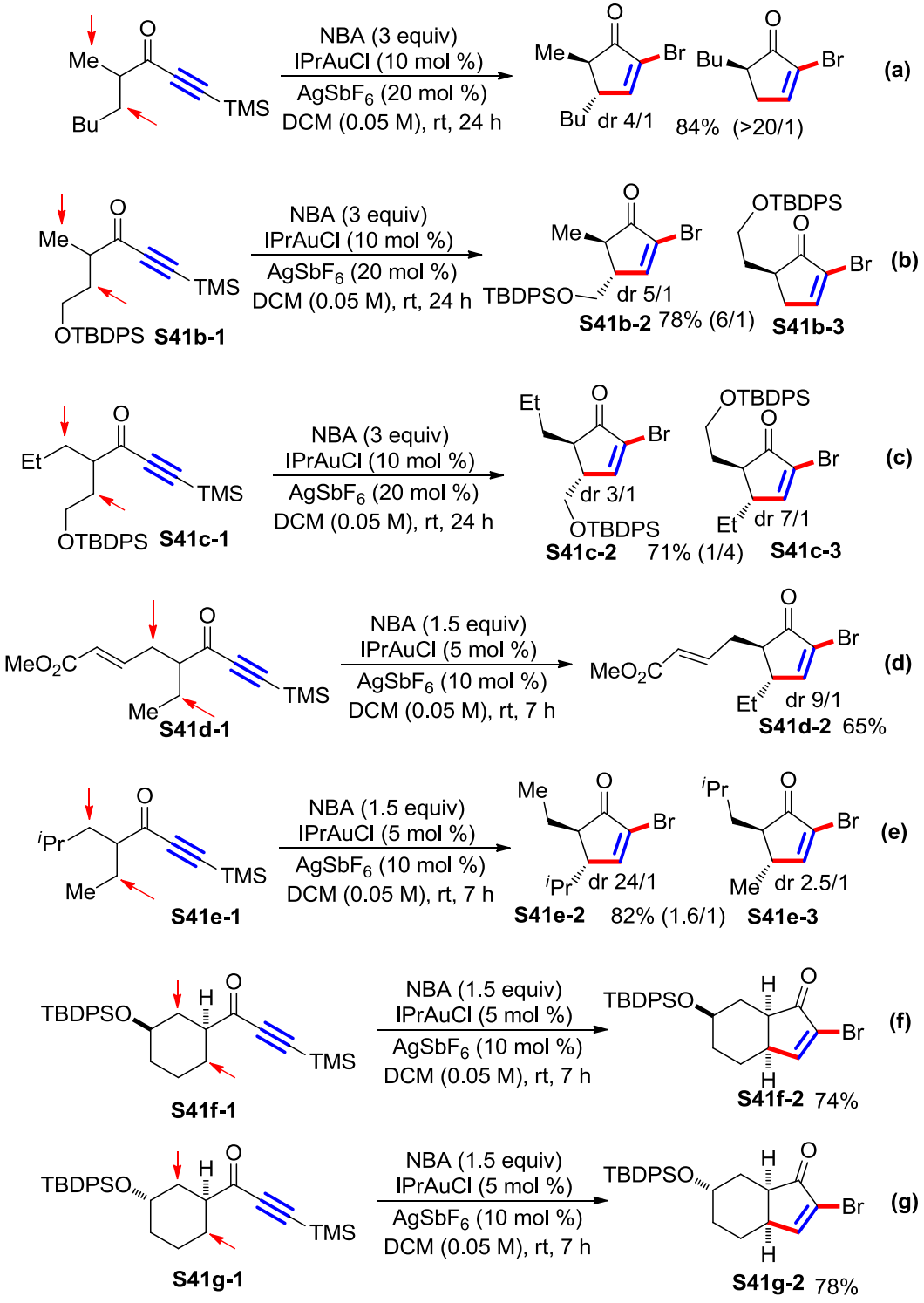
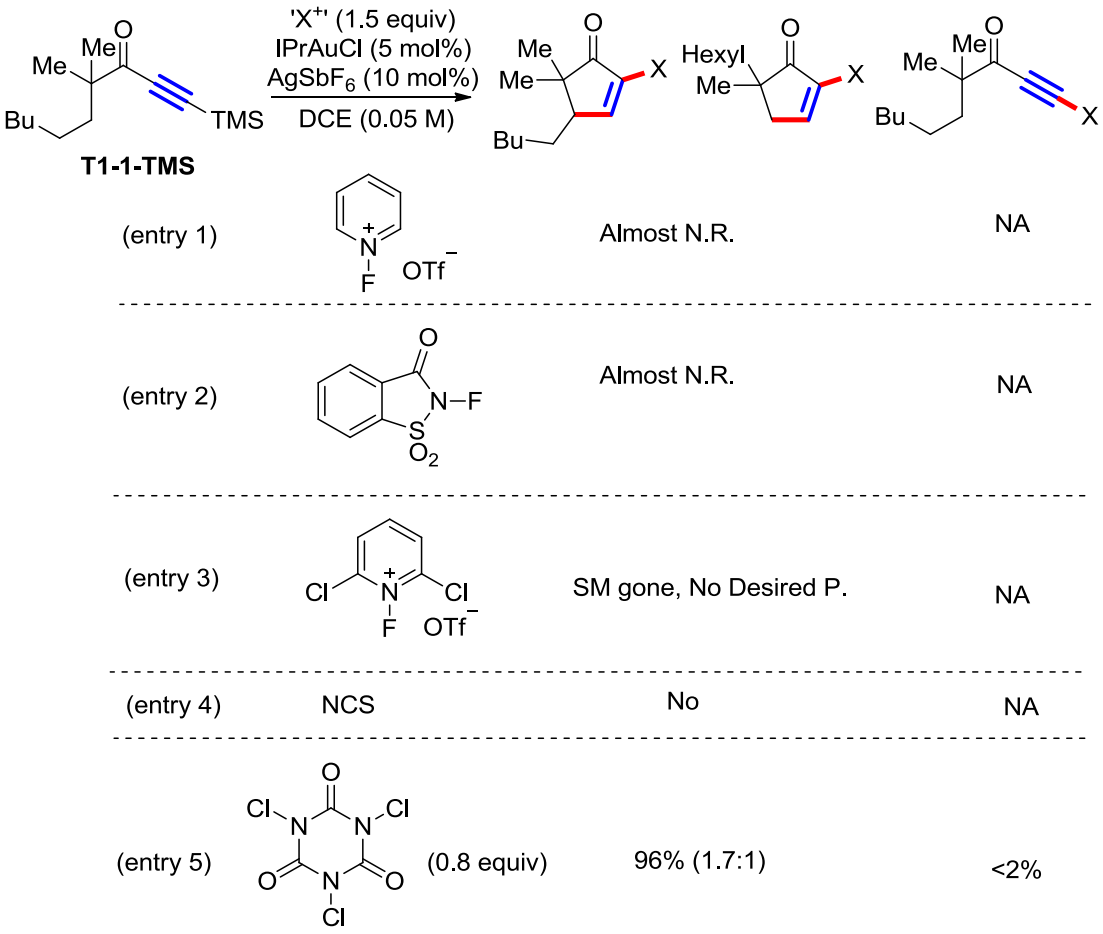


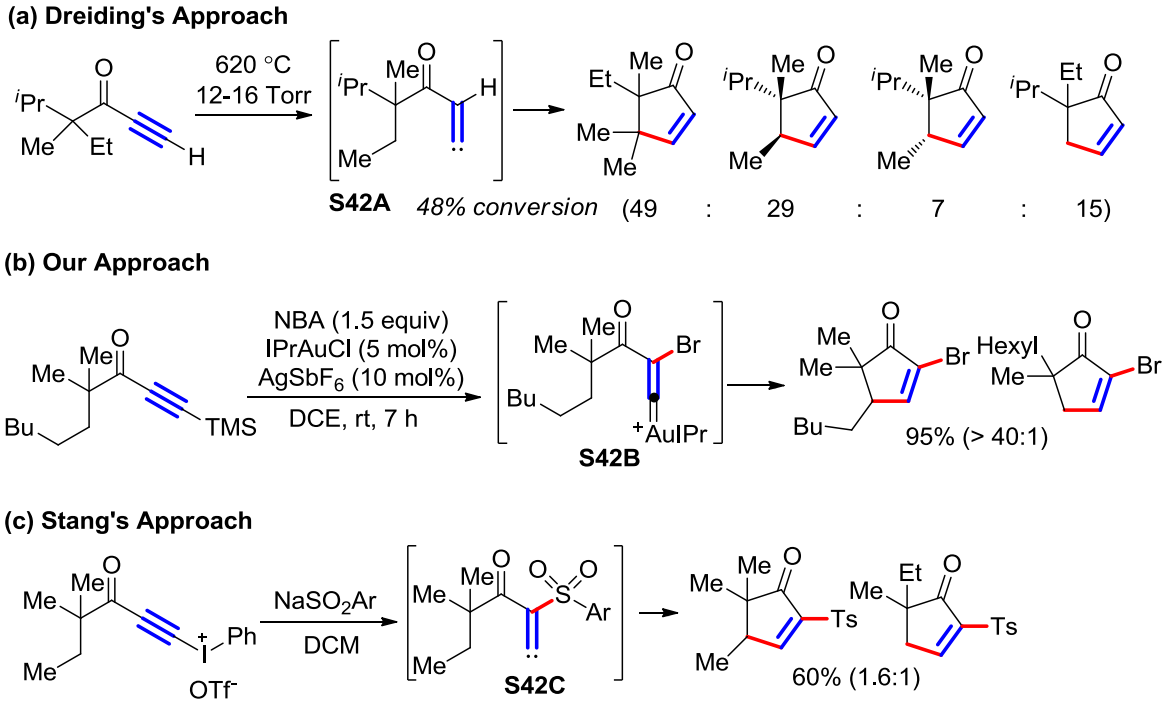
Table 4. Gold Vinylidene Generation with Other Electrophilic Reagents



With the successful generation of gold vinylidenes from TMS alkynones and brominating reagents, I then tried to extend our reaction scope with other electrophilc halogenating reagents. Several commercially available electrophilc F^+ reagents were first examined. No reaction happened for entry 1 and 2 even at elevated temperature. More reactive fluorinating reagent completely consumed the ynone **T1-1-TMS** but led to no desired product (entry 3). While NCS was not reactive enough, the use of more electrophilic TCCA (trichloroisocyanuric acid) resulted in quantitative yield of α-chlorocyclopentenone (entry 5). Although the efficiency of TCCA was similar to NBA working as the electrophile for gold

vinylidene formation and subsequent C-H insertion, the chemoselectivity for methyl insertion and methylene group insertion was lost. This is probably because the stronger inductively effect of chlorine atom made the gold vinylidene center more reactive and thus less selective.

Scheme 42. Our Chemistry versus Dreiding's and Stang's

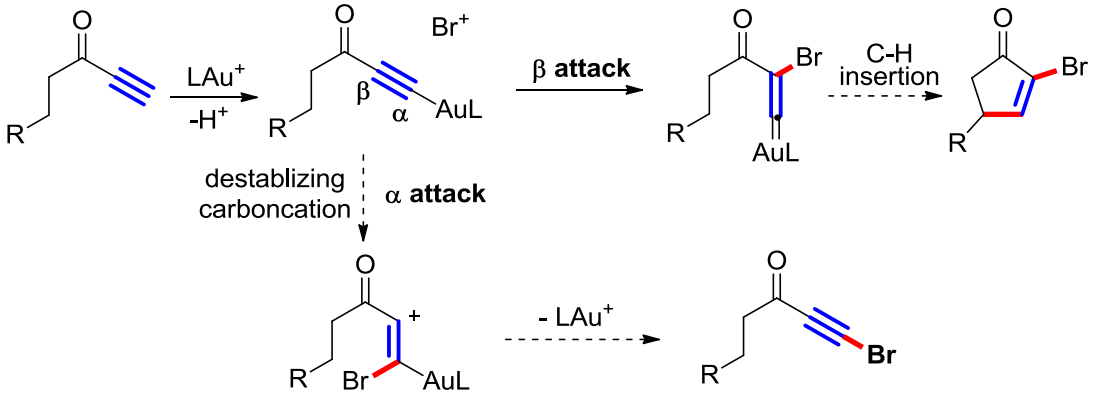


Interestingly, the concept of cyclopentenone synthesis via alkynone cyclization has been realized by the Dreiding group[12,13] and the Stang group[14] independently (Scheme 42). Compared to the above two transition metal free versions, our gold-catalyzed α-alkynone cyclization approach showed several advantages. First of all, in order to generate vinylidene **S42A**, the Dreiding's approach (Scheme 42a) requested very harsh flash vacuum pyrolysis conditions. Moreover, their conversion was low and the chemoselectivity between methyl, methylene, and methine groups was poor, while our gold-catalyzed reaction (Scheme 42b)

proceeded smoothly and efficiently at room temperature and most importantly, the reactivity of vinylidene **S42B** was attenuated by the gold catalyst ($IPrAu^+$), favoring secondary and tertiary C-H bonds over primary ones. Although Stang's reaction worked at room temperature (Scheme 42c), they had to use hazardous ketoethynyl(phenyl)iodonium salts as vinylidene precusors instead of our readily available and safe TMS alkynones. Additionally, their vinylidene **S42C** was much more reactive due to the extra sulfonyl group, causing very poor chemoselectivity. Although such poor chemoselectivity was also observed in our gold vinylidene C-H insertion reaction using TCCA as the electrophile (Table 4, entry 5), we could easily tune down our gold vinylidene's reactivity for chemoselective C-H insertion reactions by using NBA as the electrophile. Such flexibility is another significant advantage of our intermolecular approach to gold vinylidenes.

2.4 Mechanistic Studies

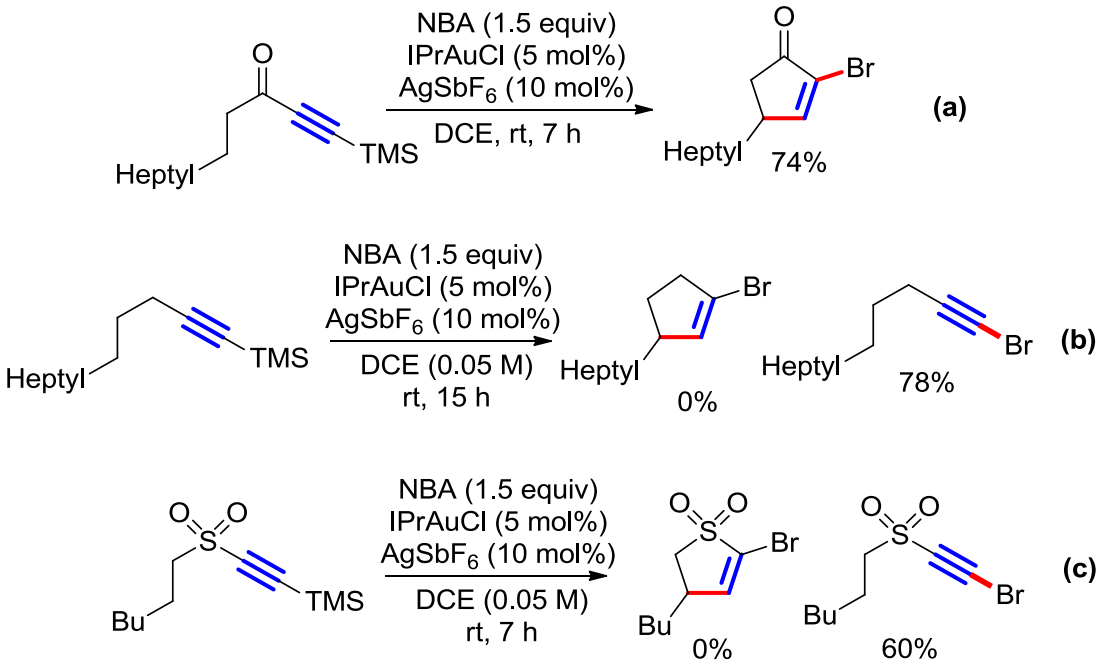
Scheme 43. Our Initially Proposed Mechanism for Gold Vinylidene Formation



With all the cases finished, I then studied the reaction mechanism. First of all, I compared three different types of TMS protected terminal alkynes (Scheme 44). According to our previously proposed mechanism, the carbonyl group in our alkynone substrate disfavored the bromoalkyne formation via inductively deactivating effect (Scheme 43). This

assumption was supported by the first two experiments in Scheme 44, where alkynone worked but 1-TMS-dodecyne only offered bromoalkyne. However, when I tried to extend the reaction scope with alkynyl alkyl sulfone (Scheme 44c), only bromoalkyne was formed, which didn't match our proposed mechanism because sulfonyl group should be more effective to disfavor such bromoalkyne formation through inductive effect. These three control experiments demonstrated the significant role of carbonyl group, but it is not simply the deactivating effect.

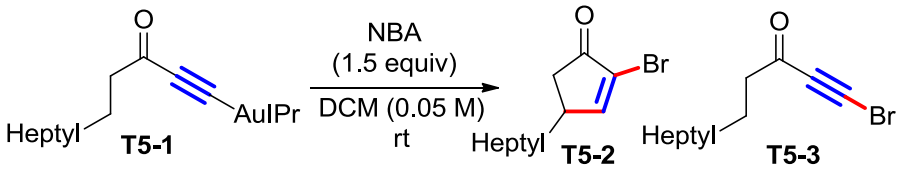
Scheme 44. Significant Role of Carbonyl Group for Gold Vinylidene Formation



In order to support our proposed direct β-carbon attack mechanism for gold vinylidene formation (Scheme 43), we synthesized the proposed alkynyl gold intermediate **T5-1** and treated it with NBA (Table 5, entry 1). The reaction of **T5-1** with NBA took 36 hours. Much to our astonishment, no desired product **T5-2** was detected by TLC, NMR, or GCMS.

Instead, we isolated the bromoalkynone **T5-3** in 70% yield. This is a confusing result for us. According to our previously proposed mechanism, the β-carbon of gold acetylide **T5-1** should attack NBA and consequently gold vinylidene was generated for C-H insertion. This piece of data, however, disproved it. I am lucky to start with a logical but wrong mechanism and set up the right experiments and get the right reaction going.

Table 5. Significant Role of Lewis Acid for Gold Vinylidene Formation



entry	additive	time	Yield[a]	
			T5-2	**T5-3**
1	none	36 h	0	70%
2	$AgSbF_6$ (0.05 equiv)	1 h	trace	decomp.
3	$IPrAuNTf_2$ (0.05 equiv)	1 h	trace	decomp.
4	$AgSbF_6$ (1.5 equiv)	1 h	55%	decomp.
5	$BF_3{\cdot}Et_2O$ (1.5 equiv)	1 h	24%	decomp.
6	TMSOTf (1.5 equiv)	1 h	16%	decomp.
7	NBS instead of NBA	50 min	0	85%
8	NBP instead of NBA	5 min	0	72%

[a] Reaction run in regular vial. The yields estimated by ^1H NMR using diethyl phthalate as the internal reference.

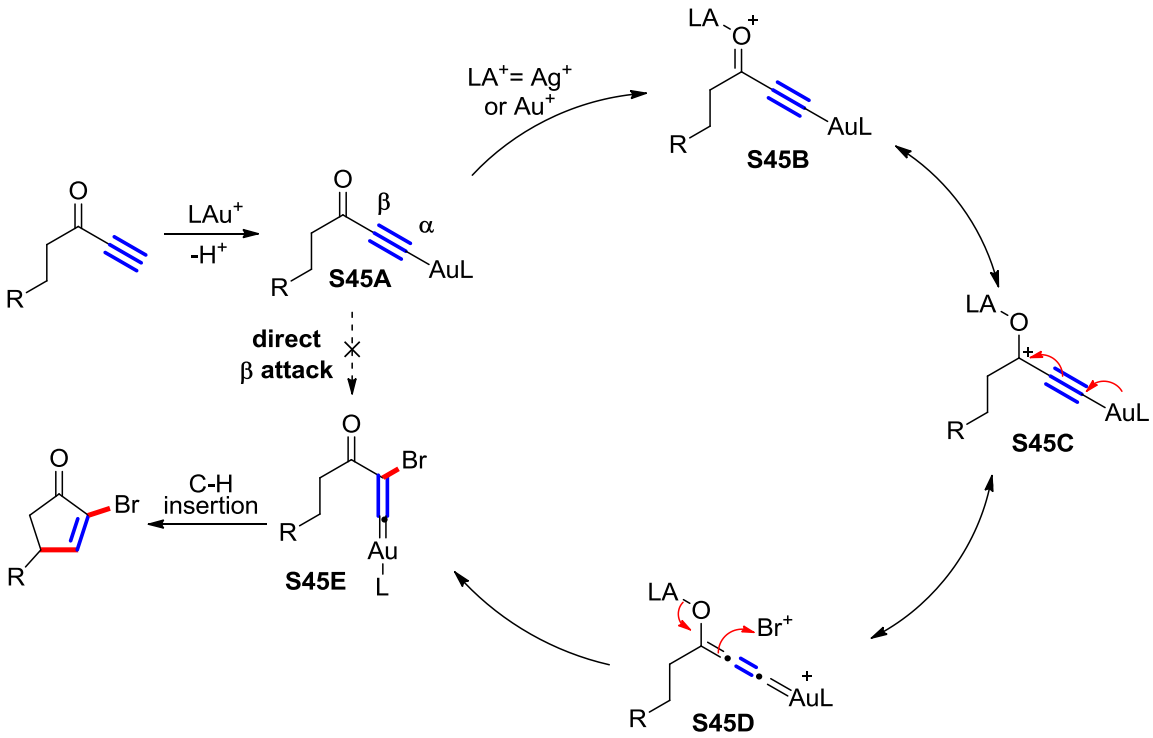
I then carefully compared the entry 1 reaction with our gold-catalyzed reactions and realized that our gold catalysis condition was acidic with 5 mol % $AgSbF_6$ and 5 mol %

$IPrAuSbF_6$ and in every single moment there's 5 mol % $AgSbF_6$ available. However, the reaction environment for the entry 1 reaction was neutral or even slightly basic. Maybe such acidic condition was the key for our gold vinylidene chemistry. Indeed, the addition of 5 mol % $AgSbF_6$ or $IPrAuNTf_2$ restored the vinylidene chemistry, although I only observed less than 5% desired product. Probably, the problem was that after the gold vinylidene C-H insertion, the gold part was released as IPrAu-acetamide, which then made the whole environment basic again and shut down the vinylidene reaction pathway. Addition of 1.5 equivalent of $AgSbF_6$ could largely push the vinylidene chemistry forward and cyclopentenone product was isolated in 55% yield. The vinylidene chemistry happened as the main reaction pathway because there was enough $AgSbF_6$ to keep the whole reaction acidic even if there was basic gold amide formation all the time. Other Lewis acid [e.g., $BF_3{\cdot}Et_2O$ (entry 5) or TMSOTf (entry 6)] also helped, albeit with lower yields. For entry 2-6, **T5-3** was detected by TLC but subsequently decomposed during the reaction. These results confirmed the intermediacy of **T5-1** and the importance of Lewis acid. There are two functions of Lewis acids in the reaction system: (1) to activate the NBA to make it more electrophilic, and (2) to activate carbonyl group. Further experiments were performed to figure out which activation was more critical for restoring the vinylidene chemistry. To test the first hypothesis, we tried more reactive NBS and NBP. Indeed, the reactions were much faster and gold acetylide **T5-1** was consumed in only 50 min by NBS (entry 7) and in 5 minutes by NBP (entry 8). However, only **T5-3** was isolated for the above two cases and no cyclopentenone **T5-2** was ever detected. These results clearly indicated that Lewis acid activation of the carbonyl group was more critical.

Based on the critical role of both the Lewis acid and carbonyl group, we revised our mechanism (Scheme 45). First of all, cationic gold catalyst reacted with alkynone to form the

gold acetylide **S45A**.[15] Lewis acid then activated the carbonyl group of the gold ynone intermediate. The activated carbonyl group **S45B** had a carbocation resonace structure **S45C**, which could be partially stabilized the nearby electron-rich gold acetylide moiety. As a result of such carboncation stablization, gold allenylidene complex **S45D** was formed. Interestingly, similar generation of gold allenylidene was also proposed by Hashmi,[16] Bertand,[17] and Che[18] et al. The gold allenylidene complex contained a Lewis acid coordinated enolate, which was extremely reactive towards brominating reagent. As a result, the β-carbon of the gold acetylide was selectively brominated to generate the gold vinylidene **S45E**.

Scheme 45. Our Revised Mechanism for the Intermolecular Gold Vinylidene Formation



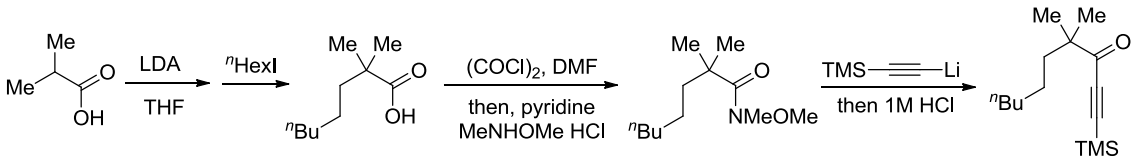
2.5 Conclusion

In summary, we have for the first time developed metal-catalyzed alkynone cyclization, which enables facile access to synthetically highly versatile cyclopentenones. The non-catalyzed reactions involved bare and reactive vinylidene intermediates, leading to poor selectivities. The gold catalysis we developed here permits the use of readily available substrates at ambient temperature and most important, owing to the modulation by gold, enable C(sp^3)-H insertion by gold vinylidenes with good chemo- and diastereoselectivities.[19]

2.6 Experimental Details

General. Ethyl acetate (ACS grade), hexanes (ACS grade), diethyl ether (ACS grade), were purchased from Fisher Scientific and used without further purification. Anhydrous toluene and 1,2-dichloroethane were bought from Acros and used directly. Commercially available reagents were used without further purification. Reactions were monitored by thin layer chromatography (TLC) using Silicycle precoated silica gel plates. Flash column chromatography was performed over Silicycle silica gel (230-400 mesh). ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian 400 MHz spectrometer, a Varian 500 MHz Unity plus spectrometer, and a Varian 600 MHz Unity plus spectrometer, using residue solvent peaks as internal standards ($CDCl_3$, ^{1}H: 7.26 ppm; ^{13}C: 77.00 ppm). Infrared spectra were recorded with a Perkin Elmer FT-IR spectrum 2000 spectrometer and are reported in reciprocal centimeter (cm^{-1}). Mass spectra were recorded with Waters micromass ZQ detector using electrospray method (MeCN as solvent).

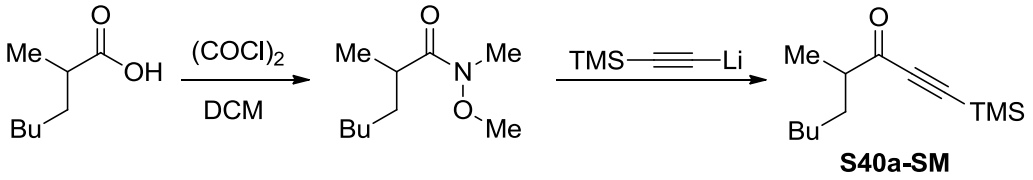
Procedure A: preparation of ynone T1-1-TMS



LDA (110 mmol) was added dropwise to a mixture of isobutyric acid (4.05 mL, 44 mmol) and THF (100 mL) at -78 ℃, and the mixture was allowed to warm up to room temperature and stirred for 1 h. Then the reaction mixture was recooled to -78 ℃ and hexyl iodide (6.5 mL, 44 mmol) was added dropwise. The resulting solution was allowed to warm up to room temperature and stirred overnight. After the reaction finished, the reaction mixture was quenched with 10% HCl solution and extracted with DCM. The combined organic extract was washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to give 2,2-dimethyloctanoic acid (6.2 g, crude)**,** which, without purification, was dissolved in DCM (60 mL). One drop of DMF was added to the above solution, followed by the dropwise addition of $(COCl)_2$ (3 mL). The resulting mixture was stirred for 1 h at room temperature and then concentrated under reduced pressure to give 2,2-dimethyloctanoyl chloride, which, without purification, was dissolved in DCM (100 mL). To the above mixture was added *N*,*O*-dimethylhydroxylamine hydrochloride (3.3 g), pyridine (7.3 mL), and catalytic amout of DMAP at 0 ℃. The resulting solution was allowed to warm up to room temperature and stirred overnight. After the reaction finished, the reaction mixture was quenched with 10% HCl solution and extracted with DCM. The combined organic extract was washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to give N-methoxy-N,2,2-trimethyloctanamide (6.3 g, crude)**.** 1.29 g (6 mmol) of the above crude product was dissolved in THF (10 mL). To the above solution was added a THF (20 mL) solution of ((trimethylsilyl)ethynyl)lithium (9 mmol) at -78 ℃. The resulting solution was allowed to warm up to room temperature within 2 hours. After the reaction

finished, the reaction mixture was quenched with 1M HCl solution (12 mL) and extracted with Et_2O. The combined organic extract was washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by chromatography on silica gel to afford the desired product **T1-1-TMS** (1.36 g, 5.4 mmol, 60% yield from isobutyric acid in three steps).

Procedure B: preparation of ynone S40a-SM

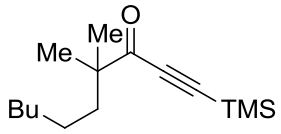


S40a-SM

2-Methylheptanoic acid (1.44 g, 10 mmol) was dissolved in DCM (30 mL). One drop of DMF was added to the above solution, followed by the dropwise addition of $(COCl)_2$ (1.3 mL). The resulting mixture was stirred for 1 h at room temperature and then concentrated under reduced pressure to give the corresponding acid chloride, which, without purification, was dissolved in DCM (30 mL). To the above mixture was added *N*,*O*-dimethylhydroxylamine hydrochloride (1.05 g), pyridine (2.4 mL), and catalytic amout of DMAP at 0 ℃. The resulting solution was allowed to warm up to room temperature and stirred overnight. After the reaction finished, the reaction mixture was quenched with 10% HCl solution and extracted with DCM. The combined organic extract was washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to give the corresponding weinreb amide**.** 374 mg (2 mmol) of the above crude product was dissolved in THF (4 mL). To the above solution was added dropwise ((trimethylsilyl)ethynyl)lithium (3 mmol, in 5 mL THF) at -78 ℃. The resulting solution was allowed to warm up to room temperature within 2 hours. After the reaction finished, the reaction mixture was quenched with 1M HCl solution (12 mL) and extracted with Et_2O. The combined organic extract was

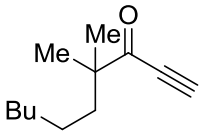
washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by chromatography on silica gel to afford the desired product **S40a-SM**.

4,4-dimethyl-1-(trimethylsilyl)dec-1-yn-3-one (T1-1-TMS)



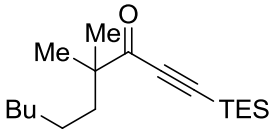
This compound was prepared following the procedure **A**. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 1.61 – 1.56 (m, 2H), 1.33 – 1.15 (m, 8H), 1.14 (s, 6H), 0.90 – 0.84 (m, 3H), 0.24 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 194.07, 100.46, 98.82, 48.00, 39.74, 31.56, 29.81, 24.49, 23.79, 22.55, 14.02, -0.74; IR (neat): 2962, 2932, 2859, 2149, 1673, 1470, 1253, 1096, 846; ESI$^+$ calculated for $[C_{15}H_{28}NaOSi]^+$: 275.18, found 275.11.

4,4-dimethyldec-1-yn-3-one (T1-1-H)



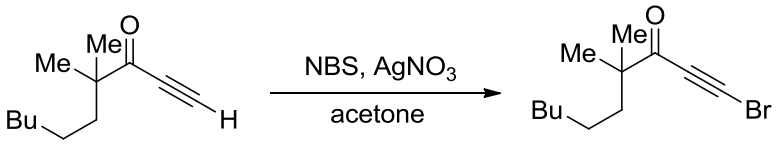
This compound was prepared following the procedure **A** by replacing the (trimethylsiyl)ethynyl lithium (1.5 equiv) with ethynyl magnisum bromide (2 equiv). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 3.20 (s, 1H), 1.65 – 1.56 (m, 2H), 1.31 – 1.21 (m, 6H), 1.16 (m, 8H), 0.87 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 193.53, 79.86, 79.37, 48.14, 39.44, 31.57, 29.79, 24.43, 23.50, 22.54, 14.01; IR (neat): 2961, 2932, 2089, 1676, 1466, 1387; ESI$^+$ calculated for $[C_{12}H_{20}NaO]^+$: 203.14, found 203.09.

4,4-dimethyl-1-(triethylsilyl)dec-1-yn-3-one (T1-1-TES)



This compound was prepared following the procedure **A** by replacing the (trimethylsiyl)ethynyl lithium (1.5 equiv) with (triethylsiyl)ethynyl lithium (1.5 equiv). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 1.64 – 1.58 (m, 2H), 1.32 – 1.17 (m, 8H), 1.15 (s, 6H), 1.02 (t, *J* = 7.9 Hz, 9H), 0.90 – 0.84 (m, 3H), 0.68 (q, *J* = 7.9 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 193.97, 101.76, 96.88, 48.03, 39.93, 31.61, 29.86, 24.55, 23.81, 22.57, 14.01, 7.33, 3.92; IR (neat): 2959, 2933, 2876, 2146, 1673, 1469, 1096, 1067, 729; ESI$^+$ calculated for $[C_{18}H_{34}NaOSi]^+$: 317.23, found 317.16.

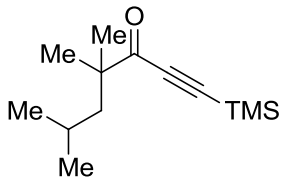
1-bromo-4,4-dimethyldec-1-yn-3-one (T1-4)



T1-1-H **T1-4**

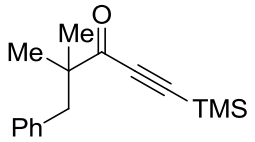
NBS (213 mg) was added in one portion to a mixture of **T1-1-H** (1 mmol, 180 mg), $AgNO_3$ (8.5 mg), and acetone (10 mL). The above solution was stirred for 2 hours at room temperature and then concentrated under reduced pressure. The residue was purified by chromatography on silica gel to afford the desired product **T1-4** (233 mg, 90%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 1.62 – 1.53 (m, 2H), 1.34 – 1.15 (m, 8H), 1.15 (s, 6H), 0.92 – 0.83 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR (101 MHz, $cdcl_3$) δ 192.58, 78.46, 57.16, 48.31, 39.45, 31.58, 29.75, 24.44, 23.59, 22.56, 14.06; IR (neat): 2960, 2931, 2858, 2174, 1674, 1387, 1103, 1070; ESI$^+$ calculated for $[C_{12}H_{19}NaOBr]^+$: 281.05, 283.05, found 280.99, 282.99.

4,4,6-trimethyl-1-(trimethylsilyl)hept-1-yn-3-one (T2-1-SM)



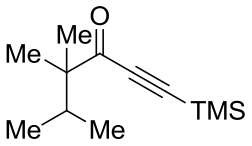
This compound was prepared following the procedure **A** by replacing hexyl iodide with 1-bromo-2-methylpropane. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 1.62 (m, 3H), 1.16 (s, 6H), 0.87 (d, *J* = 6.6 Hz, 6H), 0.24 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 194.41, 100.69, 99.28, 48.71, 48.17, 25.11, 24.60, 24.11, -0.75; IR (neat): 2961, 2931, 2148, 1672, 1471, 1456, 1252, 1060; ESI$^+$ calculated for $[C_{13}H_{24}NaOSi]^+$: 247.15, found 247.09.

4,4-dimethyl-5-phenyl-1-(trimethylsilyl)pent-1-yn-3-one (T2-2-SM)



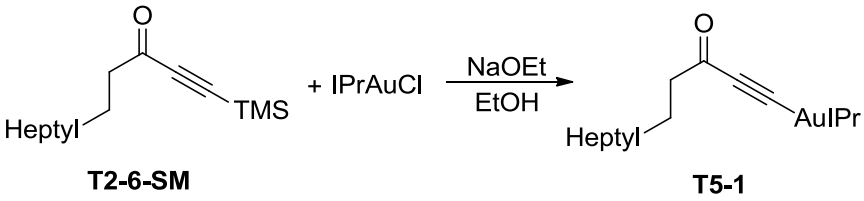
This compound was prepared following the procedure **A** by replacing hexyl iodide with benzyl chloride. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.27 – 7.24 (m, 2H), 7.23 – 7.19 (m, 1H), 7.14 (dd, *J* = 6.9, 1.8 Hz, 2H), 2.92 (s, 2H), 1.16 (s, 6H), 0.26 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 193.25, 137.26, 130.27, 128.01, 126.47, 100.50, 100.19, 49.09, 45.05, 23.72, -0.73; IR (neat): 3091, 3063, 2967, 2153, 2087, 1671, 1252, 1080, 846; ESI$^+$ calculated for $[C_{16}H_{22}NaOSi]^+$: 281.13, found 281.05.

4,4,5-trimethyl-1-(trimethylsilyl)hex-1-yn-3-one (T2-5-SM)



This compound was prepared following the procedure **A** by replacing hexyl iodide with 2-iodo propane. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 2.20 – 2.08 (m, 1H), 1.07 (s, 6H), 0.85 (d, *J* = 6.9 Hz, 6H), 0.24 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 194.49, 100.70, 98.79, 51.08, 33.73, 20.05, 17.46, -0.71, -0.72; IR (neat): 2966, 2151, 1672, 1466, 1395, 1252, 1083, 1049, 846; ESI$^+$ calculated for $[C_{12}H_{22}NaOSi]^+$: 233.13, found 233.08.

(1,3-bis(2,6-diisopropylphenyl)-1H-imidazol-2(3H)-ylidene)(3-oxododec-1-yn-1-yl)gold (T5-1)

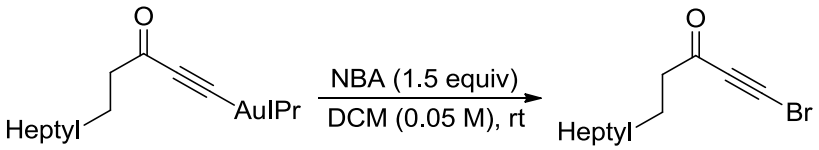


T2-6-SM **T5-1**

NaOEt (0.1 mL, 0.5 M) was added dropwise to a mixture of **T2-6-SM** (13.3 mg, 0.053 mmol), IPrAuCl (31 mg, 0.05 mmol), and EtOH (1 mL) at room temperature under argon. The mixture was allowed to stir overnight at the same temperature. Then the mixture was quenched with saturated ammonium chloride solution and extracted with ether. The combined organic extract was washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by chromatography on silica gel to afford the desired product **T5-1** (26.8 mg, 70%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.50 (t, *J* = 7.8 Hz, 2H), 7.29 (d, *J* = 7.8 Hz, 4H), 7.14 (s, 2H), 2.55 (hept, *J* = 7.0 Hz, 4H), 2.37 (t, *J* = 7.5 Hz, 2H), 1.50 (m, 2H), 1.33 (d, *J* = 6.9 Hz, 12H), 1.21 (m, 24H), 0.86 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 189.95, 188.39, 145.56, 138.20, 133.96, 130.61,

124.18, 123.30, 103.35, 45.74, 31.85, 29.39, 29.36, 29.25, 29.05, 28.80, 24.56, 24.30, 23.98, 22.65, 14.09; IR (neat): 3162, 3121, 3076, 2962, 2926, 2868, 2098, 1646, 1491, 803, 758; ESI^+ calculated for $[C_{39}H_{55}NaOAuN_2]^+$: 787.39, found 787.24.

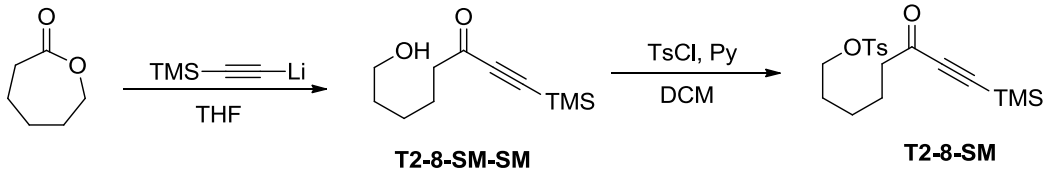
1-bromododec-1-yn-3-one (T5-3)



T5-1 **T5-3**

NBA (20.6 mg, 1.5 equiv) was added in one portion to a mixture of **T5-1** (0.1 mmol, 76.6 mg) and DCM (2 mL). The above solution was stirred for 36 hours at room temperature and then concentrated under reduced pressure. The residue was purified by chromatography on silica gel to afford the desired product **T5-3** (18.2 mg, 70%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 2.55 (t, *J* = 7.4 Hz, 2H), 1.66 (p, *J* = 7.2 Hz, 2H), 1.34 – 1.19 (m, 12H), 0.88 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 186.57, 80.01, 56.77, 45.37, 31.83, 29.34, 29.25, 29.21, 28.88, 23.84, 22.64, 14.08; IR (neat): 2955, 2927, 2855, 2178, 1680, 1466, 1136, 1098; ESI^+ calculated for $[C_{12}H_{19}KOBr+MeOH]^+$: 329.05, 331.05, found 328.99, 330.99.

6-oxo-8-(trimethylsilyl)oct-7-yn-1-yl 4-methylbenzenesulfonate (T2-8-SM)

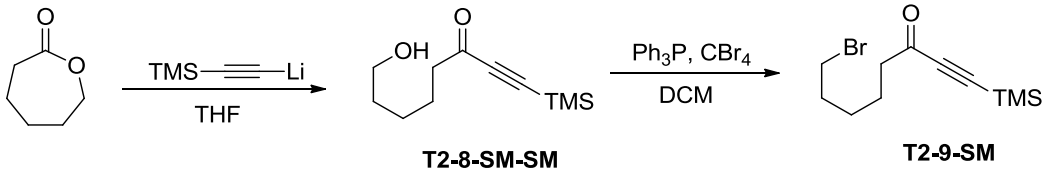


T2-8-SM-SM **T2-8-SM**

BuLi (22 mmol) was added dropwise to a mixture of trimethylsilyl acetylene (2.9 mL, 22 mmol) and THF (100 mL) at -78 ℃. The mixture was allowed to stir for 30 minutes at -78 ℃. Then ε-caprolactone (2.2 mL, 20 mmol) was added in one portion. The mixture was allowed

to stir for 90 minutes at -78 ℃ before it was quenched with 10% HCl solution and extracted with ether. The combined organic extract was washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to give **T2-8-SM-SM** (3.2 g, crude)**,** which was used without purification. 424 mg (2 mmol) of the above crude product **T2-8-SM -SM** was disolved in 10 mL DCM. Pyridine (0.65 mL, 8 mmol) and TsCl (571 mg, 3 mmol) were added in this order to the above DCM solution. The resulting mixture was allowed to stir at room temperature overnight. After the reaction finished, the reaction mixture was quenched with 1M HCl solution (12 mL) and extracted with Et_2O. The combined organic extract was washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by chromatography on silica gel to afford the desired product **T2-8-SM** (659 mg, 90%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.78 (d, *J* = 8.3 Hz, 2H), 7.45 – 7.31 (m, 2H), 4.02 (t, *J* = 6.4 Hz, 2H), 2.52 (t, *J* = 7.3 Hz, 2H), 2.45 (s, 3H), 1.70 – 1.62 (m, 2H), 1.62 – 1.58 (m, 2H), 1.38 – 1.30 (m, 2H), 0.24 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 187.21, 144.72, 133.13, 129.82, 127.86, 101.89, 97.94, 70.15, 44.88, 28.61, 24.73, 23.07, 21.62, -0.78; IR (neat): 2959, 2148, 1676, 1598, 1360, 1252, 1189, 1177, 847; ESI$^+$ calculated for $[C_{18}H_{26}NaSO_4Si]^+$: 389.12, found 389.03.

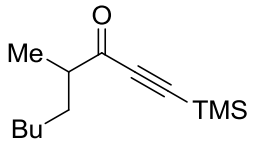
8-bromo-1-(trimethylsilyl)oct-1-yn-3-one (T2-9-SM)



Ph_3P (1.04 g) and CBr_4 (1.09 g) were stirred in DCM (50 mL) at 0 ℃ for 17 minutes. Then, 551 mg (2.6 mmol) of the crude **T2-8-SM-SM** was added to the above reaction mixture. The resulting solution was allowed to stir at 0 ℃ for 1 hour. After the reaction finished, the

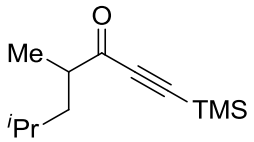
reaction mixture was quenched with water and extracted with DCM. The combined organic extract was washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by chromatography on silica gel to afford the desired product **T2-9-SM**. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 3.40 (t, *J* = 6.7 Hz, 2H), 2.58 (t, *J* = 7.3 Hz, 2H), 1.88 (dt, *J* = 14.9, 6.9 Hz, 2H), 1.69 (p, *J* = 7.4 Hz, 2H), 1.51 – 1.43 (m, 2H), 0.24 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 187.38, 101.92, 97.93, 44.96, 33.35, 32.42, 27.44, 22.97, -0.77; IR (neat): 2980, 2865, 2863, 2151, 1678, 1458, 1356, 1252, 1104, 847; ESI$^+$ calculated for $[C_{11}H_{19}NaOBrSi+MeOH]^+$: 329.05, 331.05, found 328.97, 330.97.

4-methyl-1-(trimethylsilyl)non-1-yn-3-one (S40a-SM)



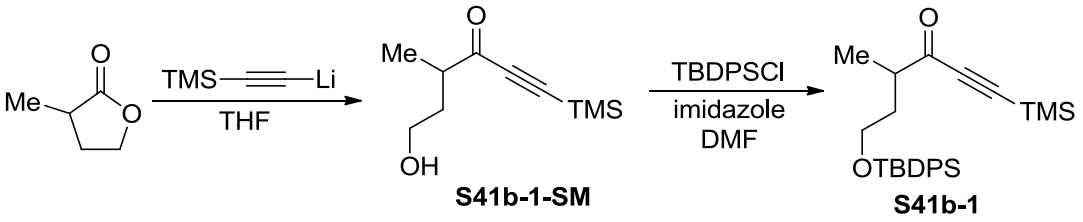
This compound was prepared following the procedure **B**. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 2.54 (h, *J* = 6.9 Hz, 1H), 1.81 – 1.70 (m, 1H), 1.46 – 1.36 (m, 1H), 1.35 – 1.23 (m, 6H), 1.15 (d, *J* = 6.9 Hz, 3H), 0.88 (t, *J* = 6.9 Hz, 3H), 0.24 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 192.04, 101.19, 98.47, 48.28, 32.65, 31.71, 26.59, 22.40, 15.84, 13.97, -0.75; IR (neat): 2961, 2932, 2860, 2150, 1676, 1459, 1252, 847; ESI$^+$ calculated for $[C_{13}H_{24}NaOSi]^+$: 247.15, found 247.09.

4,6-dimethyl-1-(trimethylsilyl)hept-1-yn-3-one (S40b-SM)



This compound was prepared following the procedure **B**.^{1}H NMR (500 MHz, Chloroform-*d*) δ 2.63 (h, *J* = 7.0 Hz, 1H), 1.66 (ddt, *J* = 32.0, 13.4, 7.0 Hz, 2H), 1.23 (dt, *J* = 13.4, 7.0 Hz, 1H), 1.15 (d, *J* = 6.9 Hz, 3H), 0.91 (dd, *J* = 12.7, 6.5 Hz, 6H), 0.25 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 192.19, 101.17, 98.62, 46.43, 41.98, 25.77, 22.69, 22.40, 16.36, -0.74; IR (neat): 2960, 2148, 1677, 1468, 1252, 1082, 847; ESI^+ calculated for $[C_{12}H_{22}NaOSi+MeOH]^+$: 265.16, found 265.09.

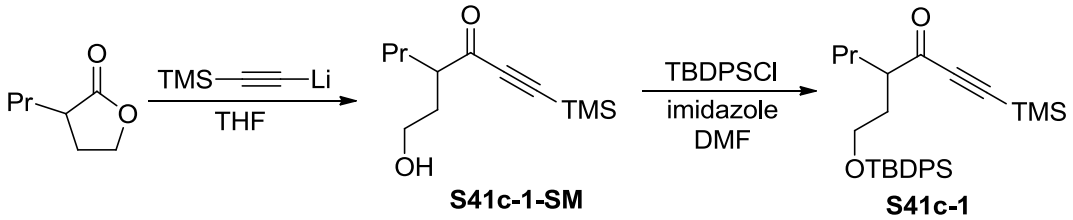
6-((tert-butyldiphenylsilyl)oxy)-4-methyl-1-(trimethylsilyl)hex-1-yn-3-one (S41b-1)



S41b-1-SM was synthesized according to reported procedure (*J. Org. Chem.*, **2012**, *77*, 3846). TBDPSCl (0.11 mL) was added to a solution of **S41b-1-SM** (0.35 mmol, 70 mg), imidazole (71 mg), and DMF (2mL). The resulting mixture was allowed to stir at room temperature overnight. After the reaction finished, the reaction mixture was quenched with 1M HCl solution (5 mL) and extracted with Et_2O. The combined organic extract was washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by chromatography on silica gel to afford the desired product **S41b-1**. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.67 (dt, *J* = 8.0, 1.8 Hz, 4H), 7.50 – 7.34 (m, 6H), 3.77 – 3.60 (m, 2H), 2.85 (h, *J* = 6.9 Hz, 1H), 2.15 (ddd, *J* = 13.8, 12.6, 6.6 Hz, 1H), 1.64 (dt, *J* = 14.0, 6.0 Hz, 1H), 1.17 (d, *J* = 7.0 Hz, 3H), 1.06 (s, 9H), 0.25 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 191.40, 135.55, 133.71, 133.62, 129.61, 127.65, 101.41, 98.44, 61.27, 45.19,

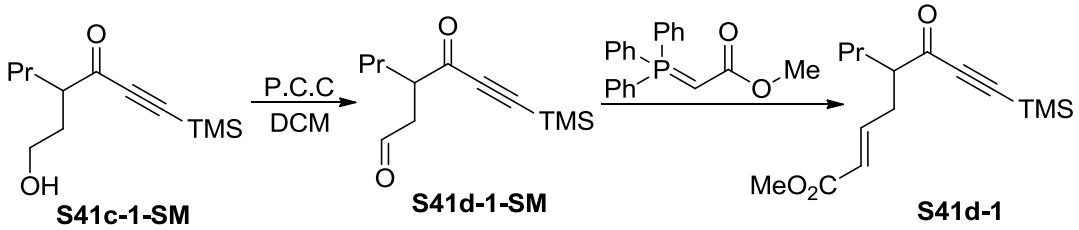
35.18, 26.81, 19.18, 15.70, -0.71; IR (neat): 3073, 3050, 2961, 2932, 2153, 2092, 1676, 1473, 1112, 846; ESI$^+$ calculated for $[C_{26}H_{36}NaO_2Si_2]^+$: 459.20, found 459.10.

4-(2-((tert-butyldiphenylsilyl)oxy)ethyl)-1-(trimethylsilyl)hept-1-yn-3-one (S41c-1)



S41c-1 was synthesized using the same method as **S41b-1**. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.66 (dt, *J* = 8.1, 2.0 Hz, 4H), 7.46 – 7.34 (m, 6H), 3.65 (t, *J* = 6.2 Hz, 2H), 2.77 (tt, *J* = 8.2, 5.4 Hz, 1H), 2.07 (ddt, *J* = 14.3, 8.7, 6.2 Hz, 1H), 1.78 – 1.64 (m, 2H), 1.51 – 1.42 (m, 1H), 1.38 – 1.27 (m, 2H), 1.05 (s, 9H), 0.91 (t, *J* = 7.3 Hz, 3H), 0.24 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 191.38, 135.56, 135.54, 133.70, 133.63, 129.58, 127.63, 101.64, 98.19, 61.62, 50.81, 33.81, 33.43, 26.80, 20.25, 19.16, 14.06, -0.71; IR (neat): 3073, 3050, 2959, 2932, 2858, 2153, 1674, 1473, 1428, 1252, 1112, 1092, 846; ESI$^+$ calculated for $[C_{28}H_{40}NaO_2Si_2]^+$: 487.25, found 487.13.

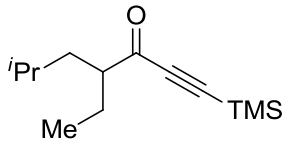
(E)-methyl 6-oxo-5-propyl-8-(trimethylsilyl)oct-2-en-7-ynoate (S41d-1)



P.C.C (1.5 equiv, 259 mg) was added to a solution of **S41c-1-SM** (0.8 mmol, 200 mg) and DCM (6mL). The resulting mixture was allowed to stir at room temperature overnight. After the reaction finished, the reaction mixture was first filtered through a short silica gel and then

washed with 1M HCl solution (5 mL) and extracted with DCM. The combined organic extract was washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to afford the crude **S41d-1-SM** (about 0.4 mmol), which was then dissolved in DCM (4 mL). To the above DCM solution was added methyl 2-(triphenylphosphoranylidene)acetate (0.44 mmol, 147 mg). The resulting mixture was allowed to stir at room temperature overnight. After the reaction finished, the reaction mixture was quenched with water and extracted with DCM. The combined organic extract was washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by chromatography on silica gel to afford the desired product **S41d-1** (100 mg, 90%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 6.86 (dt, *J* = 15.6, 7.2 Hz, 1H), 5.86 (d, *J* = 15.6 Hz, 1H), 3.72 (s, 3H), 2.78 – 2.51 (m, 2H), 2.37 (dddd, *J* = 14.9, 7.5, 5.8, 1.5 Hz, 1H), 1.73 (dddd, *J* = 13.5, 9.9, 7.6, 5.6 Hz, 1H), 1.56 – 1.45 (m, 1H), 1.40 – 1.25 (m, 2H), 0.92 (t, *J* = 7.3 Hz, 3H), 0.25 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 189.74, 166.55, 145.45, 123.10, 101.13, 99.61, 52.59, 51.47, 33.26, 32.99, 20.04, 13.99, -0.80; IR (neat): 2960, 2934, 2875, 2150, 1728, 1675, 1253, 1143, 1044; ESI$^+$ calculated for $[C_{15}H_{24}NaO_3Si]^+$: 303.14, found 303.05.

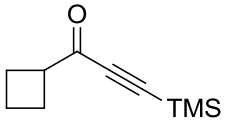
4-ethyl-6-methyl-1-(trimethylsilyl)hept-1-yn-3-one (S41e-1)



This compound was prepared following the procedure **B**. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 2.49 (tt, *J* = 8.8, 5.3 Hz, 1H), 1.75 – 1.63 (m, 2H), 1.56 (dddd, *J* = 21.5, 13.4, 10.1, 5.9 Hz, 2H), 1.25 (ddd, *J* = 13.5, 8.2, 5.4 Hz, 1H), 0.92 – 0.87 (m, 9H), 0.24 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 192.23, 101.30, 98.36, 53.93, 40.38, 26.01, 25.06, 23.10, 22.17, 11.56, -0.74;

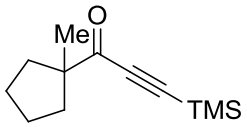
IR (neat): 2961, 2934, 2873, 2151, 2090, 1673, 1467, 1253, 1058, 847; ESI^+ calculated for $[C_{13}H_{24}KOSi]^+$: 263.12, found 263.07.

1-cyclobutyl-3-(trimethylsilyl)prop-2-yn-1-one (T3-1-SM)



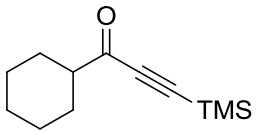
This compound was prepared following the procedure **B**. ^1H NMR (500 MHz, Chloroform-*d*) δ 3.40 – 3.25 (m, 1H), 2.41 – 2.28 (m, 2H), 2.20 (dtdd, *J* = 12.6, 8.4, 4.2, 2.1 Hz, 2H), 1.99 (dp, *J* = 11.1, 8.6 Hz, 1H), 1.92 – 1.80 (m, 1H), 0.24 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 189.50, 100.92, 99.06, 47.35, 24.54, 17.83, -0.73; IR (neat): 2955, 2148, 1757, 1250, 1134, 845; ESI^+ calculated for $[C_{10}H_{16}NaOSi+MeOH]^+$: 235.11, found 235.05.

1-(1-methylcyclopentyl)-3-(trimethylsilyl)prop-2-yn-1-one (T3-3-SM)



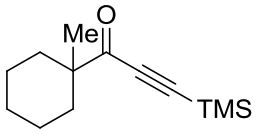
This compound was prepared following the procedure **B**. ^1H NMR (500 MHz, Chloroform-*d*) δ 2.24 – 2.13 (m, 2H), 1.68 (hd, *J* = 5.1, 3.6 Hz, 4H), 1.47 – 1.39 (m, 2H), 1.24 (s, 3H), 0.24 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 193.42, 100.61, 98.79, 55.85, 36.90, 25.47, 23.87, -0.72; IR (neat): 2961, 2151, 1670, 1252, 1100, 845; ESI^+ calculated for $[C_{12}H_{20}NaOSi+MeOH]^+$: 263.14, found 263.07.

1-cyclohexyl-3-(trimethylsilyl)prop-2-yn-1-one (T3-4-SM)



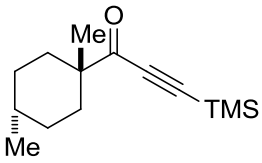
This compound was prepared following the procedure **B**. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 2.38 (tt, *J* = 11.1, 3.6 Hz, 1H), 1.97 (dq, *J* = 11.1, 3.3, 2.5 Hz, 2H), 1.78 (dt, *J* = 12.7, 3.7 Hz, 2H), 1.70 – 1.62 (m, 1H), 1.46 – 1.35 (m, 2H), 1.35 – 1.13 (m, 3H), 0.24 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 191.23, 101.41, 98.39, 51.99, 28.13, 25.76, 25.35, -0.72; IR (neat): 2933, 2856, 2151, 1673, 1451, 1252, 871; ESI$^+$ calculated for $[C_{12}H_{20}NaOSi]^+$: 263.14, found 263.07.

1-(1-methylcyclohexyl)-3-(trimethylsilyl)prop-2-yn-1-one (T3-5-SM)



This compound was prepared following the procedure **B**. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 2.11 – 1.98 (m, 2H), 1.56 – 1.50 (m, 2H), 1.49 – 1.25 (m, 6H), 1.14 (s, 3H), 0.24 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 194.14, 100.46, 98.49, 48.43, 34.38, 25.70, 24.77, 22.71, -0.71; IR (neat): 2962, 2934, 2855, 2149, 1669, 1450, 1252, 1080, 846; ESI$^+$ calculated for $[C_{13}H_{22}NaOSi]^+$: 245.13, found 245.07.

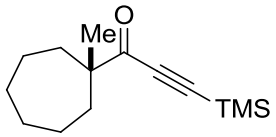
1-(1,4-dimethylcyclohexyl)-3-(trimethylsilyl)prop-2-yn-1-one (T3-6-SM)



This compound was prepared following the procedure **B**. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 1.74 – 1.66 (m, 2H), 1.64 – 1.55 (m, 4H), 1.35 (ddq, *J* = 14.5, 7.2, 3.6 Hz, 1H), 1.18 (s,

3H), 1.16 – 1.08 (m, 2H), 0.92 (d, J = 6.6 Hz, 3H), 0.24 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 194.66, 100.38, 99.20, 47.36, 32.55, 31.83, 29.88, 21.97, 19.54, -0.69; IR (neat): 2929, 2857, 2148, 2092, 1669, 1466, 866; ESI$^+$ calculated for $[C_{14}H_{24}KOSi]^+$: 275.12, found 275.04.

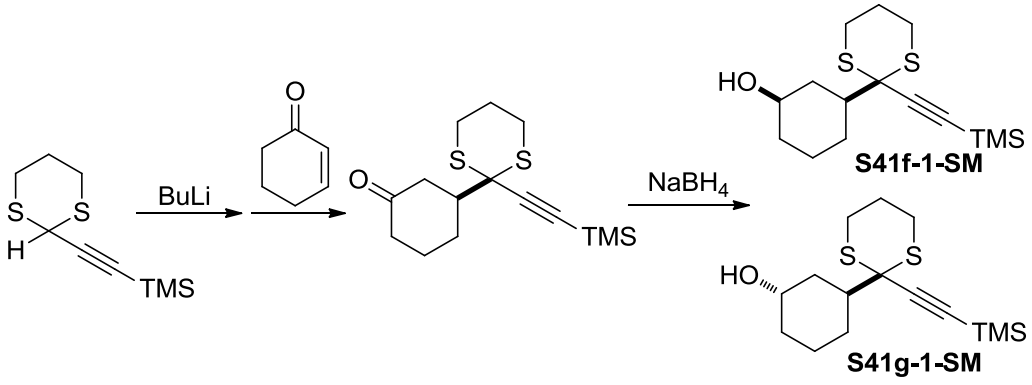
1-(1-methylcycloheptyl)-3-(trimethylsilyl)prop-2-yn-1-one (T3-7-SM)



This compound was prepared following the procedure **B**. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 2.12 (ddd, J = 13.3, 6.3, 2.7 Hz, 2H), 1.58 – 1.38 (m, 10H), 1.16 (s, 3H), 0.24 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 194.19, 100.78, 98.80, 51.29, 36.50, 30.24, 26.13, 23.43, -0.72; IR (neat): 2962, 2927, 2148, 2089, 1669, 1466, 1251, 1041, 845; ESI$^+$ calculated for $[C_{14}H_{24}NaOSi]^+$: 259.15, found 259.09.

***cis*-3-(2-((trimethylsilyl)ethynyl)-1,3-dithian-2-yl)cyclohexanol (S41f-1-SM)**

***trans*-3-(2-((trimethylsilyl)ethynyl)-1,3-dithian-2-yl)cyclohexanol (S41g-1-SM)**

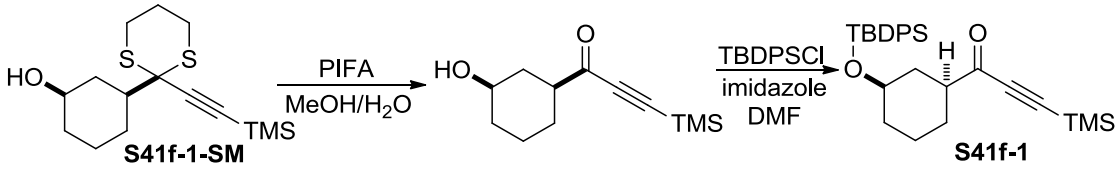


BuLi (3 mL, 2.5 M) was added dropwise to a mixture of ((1,3-dithian-2-yl)ethynyl)-trimethylsilane (1.4 g, 6.5 mmol) and THF (50 mL) at -78 ℃. The mixture was allowed to stir

for 60 minutes at -78 ℃. Then HMPA (2.3 mL, 2 equiv) was added in one portion. The mixture was allowed to stir for 30 minutes at -78 ℃, then cyclohexenone (0.6 mL, 6.5 mmol) was added in one portion to the above reaction mixture. The reaction was allowed to warm up to room temperature within four hours. After the reaction finished, the reaction mixture was quenched with saturated ammonium chloride solution (20 mL) and extracted with Et_2O. The combined organic extract was washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was directly dissolved in ethanol (100 mL). $NaBH_4$ (228 mg, 6mmol) was then added to the above ethanol solution at 0 ℃. The resulting mixture was allowed to stir at the same temperature for 10 minutes. After the reaction finished, the reaction mixture was quenched with saturated ammonium chloride solution (20 mL) and extracted with Et_2O. The combined organic extract was washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by chromatography on silica gel to afford the desired product **S41f-1-SM** (5 mmol, 1.57 g) and **S41g-1-SM** (1 mmol, 315 mg). **S41f-1-SM**: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 3.62 (tt, *J* = 10.9, 4.2 Hz, 1H), 3.33 (ddd, *J* = 14.2, 12.8, 2.5 Hz, 2H), 2.87 – 2.76 (m, 2H), 2.52 – 2.39 (m, 1H), 2.14 (dddd, *J* = 12.9, 6.8, 5.0, 3.3 Hz, 2H), 2.02 – 1.96 (m, 1H), 1.92 – 1.83 (m, 2H), 1.83 – 1.75 (m, 1H), 1.37 (td, *J* = 12.2, 10.9 Hz, 1H), 1.33 – 1.14 (m, 3H), 0.22 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 102.62, 93.04, 70.68, 51.62, 45.84, 37.41, 35.30, 28.68, 26.99, 25.97, 23.50, 0.20; IR (neat): 2936, 2904, 2861, 2156, 1451, 1249, 1054, 843; ESI$^+$ calculated for $[C_{15}H_{26}NaOS_2Si]^+$: 337.11, found 337.02. **S41g-1-SM**: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 4.24 (p, *J* = 2.9 Hz, 1H), 3.33 (dddd, *J* = 14.3, 12.8, 2.6, 1.4 Hz, 2H), 2.81 (dtd, *J* = 14.3, 3.2, 1.7 Hz, 2H), 2.34 – 2.17 (m, 2H), 2.13 (dtd, *J* = 13.6, 4.2, 2.1 Hz, 1H), 1.87 – 1.67 (m, 3H), 1.62 (ddt, *J* = 13.8, 9.0, 2.5 Hz, 2H), 1.50 – 1.30 (m, 3H), 0.22 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 102.88, 92.89, 66.52, 52.17, 41.03,

34.73, 32.24, 28.61, 28.59, 27.77, 26.00, 19.81, 0.23; IR (neat): 2932, 2904, 2153, 1428, 1248, 843; ESI$^+$ calculated for $[C_{15}H_{26}NaOS_2Si]^+$: 337.11, found 337.02.

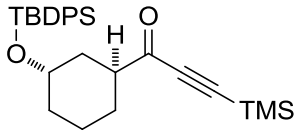
1-(3-((tert-butyldiphenylsilyl)oxy)cyclohexyl)-3-(trimethylsilyl)prop-2-yn-1-one (S41f-1)



[Bis(trifluoroacetoxy)iodo]benzene (255 mg, 1.1 equiv) was added portionwise to a mixture of **S41f-1-SM** (170 mg, 0.54 mmol), water (1mL), and MeOH (10 mL) at 0 ℃. The mixture was allowed to stir for 10 minutes at 0 ℃. Then the reaction mixture was quenched with saturated ammonium chloride solution (20 mL) and extracted with Et_2O. The combined organic extract was washed with saturated $NaHCO_3$, brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The concentrated residue was directly dissolved in DMF (4 mL). Imidazole (73 mg, 1.08 mmol) and TBDPSCl (0.14 mL, 0.54 mmol) was then added to the above DMF solution at room temperature. The resulting mixture was allowed to stir at the same temperature overnight. After the reaction finished, the reaction mixture was quenched with saturated ammonium chloride solution (20 mL) and extracted with Et_2O. The combined organic extract was washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by chromatography on silica gel to afford the desired product **S41f-1** (148 mg, 60%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.70 – 7.65 (m, 4H), 7.45 – 7.40 (m, 2H), 7.37 (ddd, *J* = 8.3, 6.4, 1.5 Hz, 4H), 3.63 (tt, *J* = 10.4, 4.0 Hz, 1H), 2.27 (tt, *J* = 11.7, 3.6 Hz, 1H), 2.18 (dtd, *J* = 11.8, 3.8, 1.9 Hz, 1H), 1.89 – 1.81 (m, 1H), 1.76 (ddt, *J* = 13.8, 7.3, 3.7 Hz, 2H), 1.60 – 1.49 (m, 1H), 1.33 – 1.20 (m, 2H), 1.15 – 1.07 (m, 1H), 1.06 (s, 9H), 0.24 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 189.62,

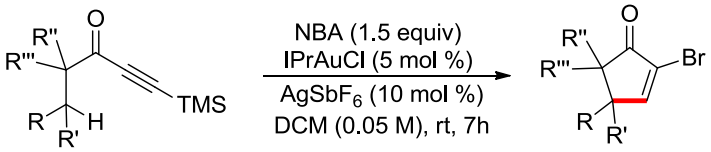
135.75, 135.73, 134.54, 134.31, 129.57, 129.54, 127.53, 127.50, 101.20, 98.81, 71.36, 50.62, 37.06, 35.12, 27.08, 26.95, 23.04, 19.13, -0.72; IR (neat): 3072, 3053, 2934, 2858, 1673, 1428, 1252, 1111, 846, 702; ESI^+ calculated for $[C_{28}H_{38}NaO_2Si_2]^+$: 485.23, found 485.12.

1-(3-((tert-butyldiphenylsilyl)oxy)cyclohexyl)-3-(trimethylsilyl)prop-2-yn-1-one (S41g-1)



This compound was synthesized using the same method as **S41f-1**. ^1H NMR (500 MHz, Chloroform-*d*) δ 7.67 (dt, *J* = 8.0, 1.2 Hz, 4H), 7.45 – 7.40 (m, 2H), 7.40 – 7.35 (m, 4H), 4.14 (s, 1H), 3.03 (tt, *J* = 11.4, 3.5 Hz, 1H), 2.09 – 1.97 (m, 2H), 1.88 (dddd, *J* = 16.3, 12.8, 8.1, 3.4 Hz, 1H), 1.61 – 1.52 (m, 2H), 1.46 – 1.33 (m, 2H), 1.27 – 1.19 (m, 1H), 1.10 (s, 9H), 0.24 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 191.35, 135.74, 135.69, 134.44, 134.06, 129.63, 129.56, 127.59, 127.52, 101.38, 98.31, 67.25, 46.97, 35.23, 32.56, 27.47, 27.04, 19.61, 19.34, -0.70; IR (neat): 2966, 2930, 2858, 2091, 1643, 1428, 1251, 1105; ESI^+ calculated for $[C_{28}H_{38}NaO_2Si_2]^+$:485.23, found 485.12.

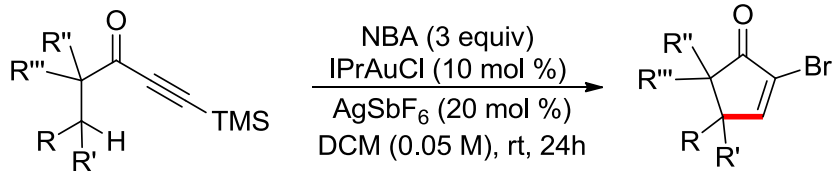
General procedure C: Gold-catalyzed cyclopentenones synthesis via intramolecular insertions into unactivated C(sp^3)-H bonds



NBA (1.5 equiv, 62 mg), IPrAuCl (5 mol%, 9.3 mg), and $AgSbF_6$ (10 mol%, 10.3 mg) were added in this order to a mixture of ynone **SM** (0.3 mmol) and DCM (6 mL) in a vial at room temperature. The reaction mixture was stirred at room temperature for 7 hours. Upon

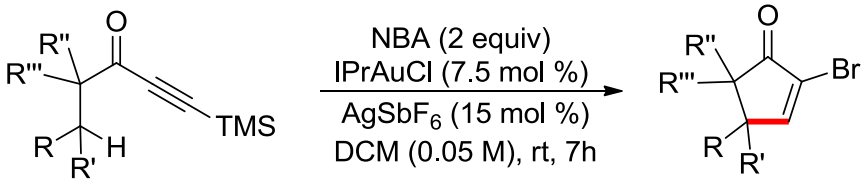
completion, the mixture was concentrated and the residue was purified by chromatography on silica gel (eluent: hexanes/ethyl acetate) to afford the desired product.

General procedure D: Gold-catalyzed cyclopentenones synthesis via intramolecular insertions into unactivated C(sp^3)-H bonds



NBA (3 equiv, 124 mg), IPrAuCl (10 mol%, 18.6 mg), and $AgSbF_6$ (20 mol%, 20.6 mg) were added in this order to a mixture of ynone (0.3 mmol) and DCM (6 mL) in a vial at room temperature. The reaction mixture was stirred at room temperature for 24 hours. Upon completion, the mixture was concentrated and the residue was purified by chromatography on silica gel (eluent: hexanes/ethyl acetate) to afford the desired product.

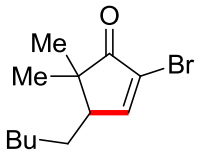
General procedure E: Gold-catalyzed cyclopentenones synthesis via intramolecular insertions into unactivated C(sp^3)-H bonds



NBA (2 equiv, 82.2 mg), IPrAuCl (7.5 mol%, 14.4 mg), and $AgSbF_6$ (15 mol%, 16.2 mg) were added in this order to a mixture of ynone (0.3 mmol) and DCM (6 mL) in a vial at room temperature. The reaction mixture was stirred at room temperature for 7 hours. Upon

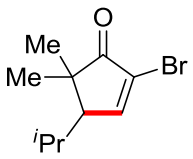
completion, the mixture was concentrated and the residue was purified by chromatography on silica gel (eluent: hexanes/ethyl acetate) to afford the desired product.

2-bromo-5,5-dimethyl-4-pentylcyclopent-2-enone (T1-2)



This compound was prepared in 95% yield (74.1 mg) using **T1-1-TMS** (0.3 mmol) as the substrate according to the general procedure **C**. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.68 (d, *J* = 2.7 Hz, 1H), 2.49 (ddd, *J* = 9.6, 5.7, 2.7 Hz, 1H), 1.60 – 1.55 (m, 1H), 1.49 (ddtd, *J* = 12.4, 8.0, 4.2, 3.6, 2.4 Hz, 1H), 1.42 – 1.24 (m, 6H), 1.16 (s, 3H), 1.04 (s, 3H), 0.93 – 0.87 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 206.59, 162.84, 123.32, 52.62, 46.18, 31.88, 29.67, 27.63, 25.47, 22.50, 20.94, 13.99; IR (neat): 3060, 2959, 2931, 2859, 1726, 1589, 1466, 842; ESI^{+} calculated for $[C_{12}H_{29}NaOBr]^{+}$: 281.05, 283.05, found 280.98, 282.98.

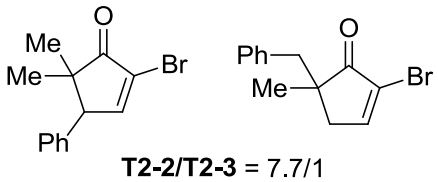
2-bromo-4-isopropyl-5,5-dimethylcyclopent-2-enone (T2-1)



This compound was prepared in 91% yield (63.1 mg) using **T2-1-SM** (0.3 mmol) as the substrate according to the general procedure **C**. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.71 (d, *J* = 2.7 Hz, 1H), 2.31 (dd, *J* = 7.0, 2.8 Hz, 1H), 1.89 (dq, *J* = 13.4, 6.7 Hz, 1H), 1.19 (s, 3H), 1.13 (s, 3H), 1.10 (d, *J* = 6.6 Hz, 3H), 0.92 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 206.40, 161.37, 123.50, 59.49, 46.55, 27.99, 26.79, 23.11, 20.70, 20.56; IR (neat): 3068,

2965, 2933, 2873, 1726, 1590, 1463, 928, 840; ESI$^+$ calculated for $[C_{10}H_{15}NaOBr]^+$: 253.02, 255.02, found 252.96, 254.96.

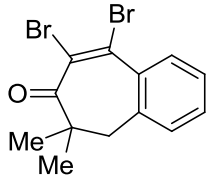
2-bromo-5,5-dimethyl-4-phenylcyclopent-2-enone (T2-2) & 5-benzyl-2-bromo-5-methylcyclopent-2-enone (T2-3)



T2-2/T2-3 = 7.7/1

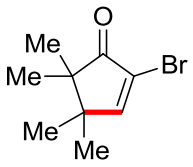
Compound **T2-2/T2-3** was prepared in 72% yield (57.2 mg) using **T2-2-SM** (0.3 mmol) as the substrate according to the general procedure **C**. The ratio of **T2-2/T2-3** is 7.7/1 according to ^{1}H NMR. ^{1}H NMR (500 MHz, Chloroform-*d*) (major) δ 7.76 (d, *J* = 2.7 Hz, 1H), 7.38 – 7.28 (m, 3H), 7.08 – 7.04 (m, 2H), 3.85 (d, *J* = 2.8 Hz, 1H), 1.33 (s, 3H), 0.63 (s, 3H); ^{1}H NMR (500 MHz, Chloroform-*d*) (selected peaks for minor) δ 7.52 (t, *J* = 3.0 Hz, 1H), 3.01 (d, *J* = 13.4 Hz, 1H), 2.74 (dd, *J* = 19.1, 3.0 Hz, 1H), 2.67 (d, *J* = 13.4 Hz, 1H), 2.30 (dd, *J* = 19.1, 3.0 Hz, 1H), 1.22 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 206.19, 206.12, 160.51, 159.78, 137.82, 136.83, 129.89, 128.65, 128.39, 128.24, 127.60, 126.76, 124.57, 124.23, 58.30, 47.48, 47.02, 43.69, 40.60, 25.80, 24.62, 22.74; IR (neat): 3063, 3027, 2970, 2928, 1726, 1591, 1496, 1453, 1382, 840, 703; ESI$^+$ calculated for $[C_{13}H_{13}NaOBr]^+$: 287.00, 289.00, found 286.94, 288.94.

8,9-dibromo-6,6-dimethyl-5H-benzo[7]annulen-7(6H)-one (T2-4)



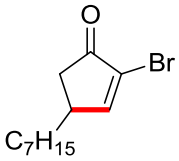
This compound was prepared in 7% yield (7.0 mg) using **T2-2-SM** (0.3 mmol) as the substrate according to the general procedure **C**. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.62 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.32 (td, *J* = 7.6, 1.6 Hz, 1H), 7.29 – 7.26 (m, 1H), 7.14 (dd, *J* = 7.3, 1.5 Hz, 1H), 2.95 (s, 2H), 1.19 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 202.88, 136.14, 136.00, 130.75, 129.88, 129.55, 128.09, 127.53, 122.60, 55.89, 43.98, 25.00; IR (neat): 3068, 3027, 2963, 2929, 1701, 1383, 1101, 755; ESI$^+$ calculated for $[C_{13}H_{12}Br_2NaO+MeOH]^+$: 396.94, 398.94, 400.94, found 396.85, 398.86, 400.85.

2-bromo-4,4,5,5-tetramethylcyclopent-2-enone (T2-5)



This compound was prepared in 79% yield (51.2 mg) using **T2-5-SM** (0.3 mmol) as the substrate according to the general procedure **C**. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.47 (s, 1H), 1.10 (s, 6H), 1.07 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 206.68, 168.31, 121.31, 50.08, 47.09, 24.79, 22.19, 22.18; IR (neat): 3053, 2973, 1725, 1591, 837, 743; ESI$^+$ calculated for $[C_9H_{13}NaOBr+MeOH]^+$: 271.03, 273.03, found 270.97, 272.97.

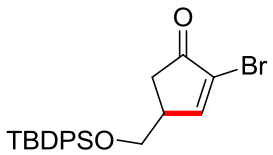
2-bromo-4-heptylcyclopent-2-enone (T2-6)



This compound was prepared in 74% yield (57.6 mg) using **T2-6-SM** (0.3 mmol) as the substrate according to the general procedure **C**. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.71 (d, *J* = 2.8 Hz, 1H), 2.94 – 2.86 (m, 1H), 2.68 (dd, *J* = 18.9, 6.3 Hz, 1H), 2.19 – 2.10 (m, 1H),

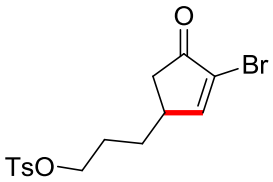
1.57 (ddd, *J* = 15.0, 7.9, 4.2 Hz, 1H), 1.48 – 1.20 (m, 11H), 0.88 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 201.26, 165.65, 125.41, 40.53, 39.44, 34.63, 31.73, 29.44, 29.09, 27.29, 22.59, 14.04; IR (neat): 3063, 2958, 2926, 2855, 1725, 1588, 1465, 923; ESI$^+$ calculated for $[C_{12}H_{19}BrNaO+MeOH]^+$: 313.08, 315.08, found 313.01, 315.01.

2-bromo-4-(((tert-butyldiphenylsilyl)oxy)methyl)cyclopent-2-enone (T2-7)



This compound was prepared in 51% yield (65.6 mg) using **T2-7-SM** (0.3 mmol) as the substrate according to the general procedure **D**. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.63 – 7.59 (m, 5H), 7.47 – 7.43 (m, 2H), 7.42 – 7.36 (m, 4H), 3.77 (dd, *J* = 10.1, 5.1 Hz, 1H), 3.70 (dd, *J* = 10.1, 6.1 Hz, 1H), 3.09 (dddd, *J* = 8.7, 6.6, 4.9, 2.3 Hz, 1H), 2.58 (dd, *J* = 18.8, 6.5 Hz, 1H), 2.33 (dd, *J* = 18.8, 2.0 Hz, 1H), 1.04 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 200.86, 162.81, 135.58, 135.49, 132.98, 132.90, 129.97, 129.93, 127.84, 127.83, 126.73, 64.80, 42.97, 35.87, 26.77, 19.18; IR (neat): 3070, 3050, 2930, 2858, 1724, 1589, 1427, 1112, 741; ESI$^+$ calculated for $[C_{22}H_{25}NaBrO_2Si]^+$: 453.07, 451.07, found 450.97, 452.97.

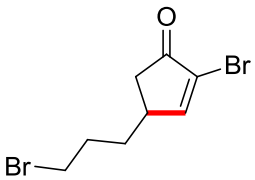
3-(3-bromo-4-oxocyclopent-2-en-1-yl)propyl 4-methylbenzenesulfonate (T2-8)



This compound was prepared in 72% yield (80.5 mg) using **T2-8-Sm** (0.3 mmol) as the substrate according to the general procedure **E**. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.81 – 7.75 (m, 2H), 7.63 (d, *J* = 2.8 Hz, 1H), 7.36 (d, *J* = 8.0 Hz, 2H), 4.06 (t, *J* = 6.0 Hz, 2H),

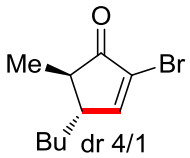
2.94 – 2.85 (m, 1H), 2.67 (dd, *J* = 18.9, 6.4 Hz, 1H), 2.46 (s, 3H), 2.07 (dd, *J* = 18.9, 2.0 Hz, 1H), 1.80 – 1.61 (m, 3H), 1.50 (dtd, *J* = 13.2, 8.4, 6.1 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 200.44, 164.21, 145.00, 132.97, 129.92, 127.85, 126.16, 69.62, 39.73, 39.03, 30.47, 26.63, 21.65; IR (neat): 3037, 2922, 2853, 1732, 1581, 1461, 1175.

2-bromo-4-(3-bromopropyl)cyclopent-2-enone (T2-9)



This compound was prepared in 70% yield (59.2 mg) using **T2-9-SM** (0.3 mmol) as the substrate according to the general procedure **E**. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.70 (d, *J* = 2.7 Hz, 1H), 3.43 (t, *J* = 6.5 Hz, 2H), 2.98 – 2.92 (m, 1H), 2.72 (dd, *J* = 18.9, 6.4 Hz, 1H), 2.17 (dd, *J* = 18.9, 2.0 Hz, 1H), 1.95 (dqd, *J* = 9.6, 6.3, 3.5 Hz, 2H), 1.78 (ddt, *J* = 12.5, 9.7, 6.3 Hz, 1H), 1.68 – 1.60 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 200.57, 164.42, 126.13, 39.73, 39.17, 33.02, 32.74, 30.24; IR (neat): 3065, 2961, 2924, 2858, 1717, 1642, 1587, 1285, 926; ESI^{+} calculated for $[C_8H_{10}NaBr_2O+MeOH]^{+}$: 334.93, 336.92, 338.92, found 334.85, 336.84, 338.85.

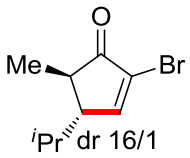
2-bromo-4-butyl-5-methylcyclopent-2-enone (S40a-P)



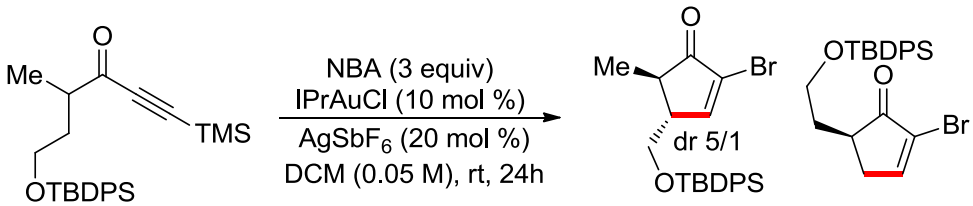
This compound was prepared in 84% yield (58.2 mg) using **S40a-SM** (0.3 mmol) as the substrate according to the general procedure **C**. ^{1}H NMR for the major diastereomer (500

MHz, Chloroform-*d*) δ 7.66 (d, *J* = 2.7 Hz, 1H), 2.47 – 2.40 (m, 1H), 2.09 (qd, *J* = 7.5, 2.2 Hz, 1H), 1.67 – 1.30 (m, 5H), 1.23 (d, *J* = 7.5 Hz, 3H), 0.92 (t, *J* = 7.0 Hz, 3H); selected ^{1}H NMR for the minor diastereomer (500 MHz, Chloroform-*d*) δ 7.77 (d, *J* = 3.0 Hz, 1H), 2.93 (dtd, *J* = 9.1, 6.0, 2.9 Hz, 1H), 2.63 (dt, *J* = 14.4, 7.5 Hz, 1H), 1.15 (d, *J* = 7.6 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 204.16, 203.93, 164.51, 163.92, 124.65, 124.34, 49.34, 45.59, 44.20, 42.64, 33.62, 30.03, 29.85, 29.50, 22.75, 22.67, 15.66, 13.92, 13.89, 11.45; IR (neat): 3063, 2960, 2931, 2872, 1719, 1587, 1456, 1276, 876; ESI^{+} calculated for $[C_{10}H_{15}NaOBr]^{+}$: 253.02, 255.02, found 252.96, 254.96.

2-bromo-4-isopropyl-5-methylcyclopent-2-enone (S40b-P)



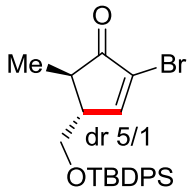
This compound was prepared in 66% yield (43.0 mg) using **S40b-SM** (0.3 mmol) as the substrate according to the general procedure **C**. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.70 (d, *J* = 2.6 Hz, 1H), 2.31 (dt, *J* = 6.5, 2.4 Hz, 1H), 2.20 (qd, *J* = 7.4, 2.2 Hz, 1H), 1.87 – 1.78 (m, 1H), 1.24 (d, *J* = 7.4 Hz, 3H), 0.99 (d, *J* = 6.7 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 204.08, 163.02, 124.62, 56.02, 42.68, 31.41, 20.12, 19.96, 16.50; IR (neat): 3068, 2963, 2930, 1718, 1587, 1465, 1374, 875; ESI^{+} calculated for $[C9H_{13}NaOBr]^{+}$: 239.00, 241.00, found 238.95, 240.95.



78% **S41b-2/S41b-3 = 6/1**

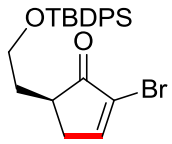
Compound **S41b-2/S41b-3** was prepared in 78% total yield (103.8 mg) using **S41b-1** (0.3 mmol) as the substrate according to the general procedure **D**.

2-bromo-4-(((tert-butyldiphenylsilyl)oxy)methyl)-5-methylcyclopent-2-enone (S41b-2)



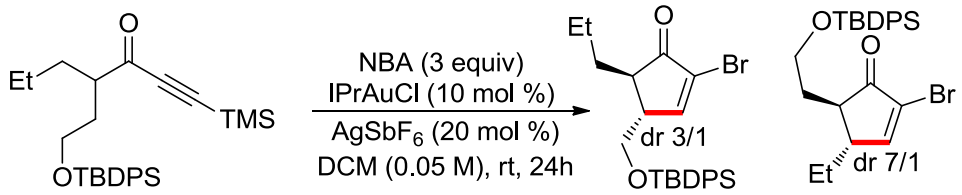
^{1}H NMR (600 MHz, Chloroform-*d*) for the major diastereomer δ 7.65 – 7.60 (m, 4H), 7.55 (d, *J* = 2.7 Hz, 1H), 7.45 (t, *J* = 7.4 Hz, 2H), 7.40 (t, *J* = 7.4 Hz, 4H), 3.76 (qd, *J* = 10.2, 5.7 Hz, 2H), 2.62 (tt, *J* = 5.5, 2.6 Hz, 1H), 2.31 (qd, *J* = 7.5, 2.4 Hz, 1H), 1.21 (d, *J* = 7.4 Hz, 3H), 1.05 (s, 9H);); selected ^{1}H NMR for the minor diastereomer (500 MHz, Chloroform-*d*) δ 7.49 (d, *J* = 3.1 Hz, 1H), 3.77 (t, *J* = 4.6 Hz, 2H), 3.06 (p, *J* = 4.7 Hz, 1H), 2.60 (p, *J* = 7.3 Hz, 1H), 1.26 (d, *J* = 7.2 Hz, 3H), 1.01 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 203.60, 161.16, 135.59, 135.50, 132.99, 132.93, 129.98, 129.93, 127.85, 127.83, 125.59, 64.30, 51.85, 41.93, 26.80, 19.19, 15.22; IR (neat): 3070, 3045, 2996, 2963, 2927, 1770, 1757, 1246, 1113, 1060, 1379; ESI$^+$ calculated for $[C_{23}H_{27}NaBrO_2Si]^+$: 467.08, 465.09, found 464.99, 466.98.

2-bromo-5-(2-((tert-butyldiphenylsilyl)oxy)ethyl)cyclopent-2-enone (S41b-3)



^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.71 (t, *J* = 3.0 Hz, 1H), 7.65 (dd, *J* = 7.3, 2.6 Hz, 4H), 7.41 (dq, *J* = 14.5, 7.4 Hz, 6H), 3.82 (dt, *J* = 11.3, 5.8 Hz, 1H), 3.78 – 3.70 (m, 1H), 2.79 (ddd, *J* = 19.0, 6.6, 3.2 Hz, 1H), 2.72 – 2.65 (m, 1H), 2.41 (dt, *J* = 19.0, 2.6 Hz, 1H), 2.19

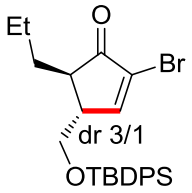
(ddt, *J* = 13.1, 9.4, 4.9 Hz, 1H), 1.59 (m, 1H), 1.04 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 203.75, 160.46, 135.52, 133.49, 133.45, 129.70, 127.71, 125.44, 61.78, 41.17, 35.01, 33.92, 26.83, 19.15; IR (neat): 3073, 2931, 2858, 1722, 1428, 1111, 823, 742; ESI$^+$ calculated for $[C_{23}H_{27}NaBrO_2Si]^+$: 467.08, 465.09, found 464.99, 466.98.



71% **S41c-2/S41c-3** = **1/4**

Compound **S41c-2/S41c-3** was prepared in 71% total yield (100.4 mg) using **S41c-1** (0.3 mmol) as the substrate according to the general procedure **D**.

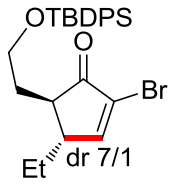
2-bromo-4-(((tert-butyldiphenylsilyl)oxy)methyl)-5-propylcyclopent-2-enone (S41c-2)



^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.62 (ddd, *J* = 7.9, 3.6, 1.6 Hz, 5H), 7.48 – 7.43 (m, 2H), 7.43 – 7.37 (m, 4H), 3.78 (dd, *J* = 10.1, 4.9 Hz, 1H), 3.66 (dd, *J* = 10.2, 6.6 Hz, 1H), 2.70 (ddt, *J* = 7.0, 4.9, 2.4 Hz, 1H), 2.22 (ddd, *J* = 8.9, 4.8, 2.1 Hz, 1H), 1.74 – 1.66 (m, 1H), 1.45 – 1.35 (m, 1H), 1.31 – 1.22 (m, 2H), 1.05 (s, 9H), 0.87 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 203.31, 161.91, 135.61, 135.51, 132.98, 132.95, 129.98, 129.93, 127.84, 125.77, 64.88, 49.92, 46.48, 33.13, 26.81, 20.17, 19.18, 14.01; IR (neat): 3070, 3053,

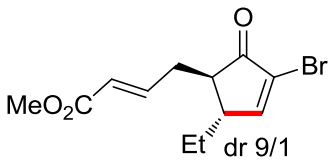
2958, 2931, 2858, 1724, 1428, 1112, 741; ESI^+ calculated for $[C_{25}H_{31}NaO_2SiBr]^+$: 493.12, 495.12, found 493.02, 495.02.

2-bromo-5-(2-((tert-butyldiphenylsilyl)oxy)ethyl)-4-ethylcyclopent-2-enone (S41c-3)



^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.68 (d, *J* = 2.7 Hz, 1H), 7.67 – 7.64 (m, 4H), 7.46 – 7.37 (m, 6H), 3.88 – 3.80 (m, 1H), 3.75 (ddd, *J* = 10.5, 7.2, 5.3 Hz, 1H), 2.60 (tt, *J* = 6.7, 2.4 Hz, 1H), 2.36 (ddd, *J* = 7.9, 5.4, 2.1 Hz, 1H), 2.10 – 2.01 (m, 1H), 1.77 – 1.60 (m, 1H), 1.55 (dq, *J* = 14.2, 7.4 Hz, 1H), 1.04 (s, 9H), 0.98 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 203.52, 163.84, 135.54, 135.53, 133.52, 133.45, 129.67, 127.68, 124.67, 61.39, 48.47, 46.97, 33.73, 26.90, 26.82, 19.13, 11.31; IR (neat): 3071, 3050, 2960, 2931, 2858, 1722, 1589, 1472, 1428, 1111, 702; ESI^+ calculated for $[C_{25}H_{31}NaO_2SiBr]^+$: 493.12, 495.12, found 493.02, 495.02.

(E)-methyl 4-((1R,5R)-3-bromo-5-ethyl-2-oxocyclopent-3-en-1-yl)but-2-enoate (S41d-2)

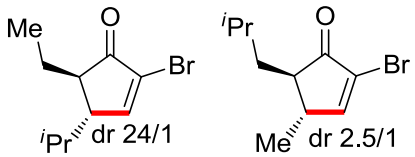


S41d-2

This compound was prepared in 79% yield (56.0 mg) using **S41d-1** (0.3 mmol) as the substrate according to the general procedure **C**. ^{1}H NMR (500 MHz, Chloroform-*d*) for the major diastereomer δ 7.70 (d, *J* = 2.7 Hz, 1H), 6.85 (dt, *J* = 15.3, 7.5 Hz, 1H), 5.90 (dt, *J* =

15.5, 1.5 Hz, 1H), 2.74 – 2.66 (m, 1H), 2.53 (tt, *J* = 6.9, 2.5 Hz, 1H), 2.43 (dtd, *J* = 14.4, 8.1, 1.4 Hz, 1H), 2.26 (ddd, *J* = 8.3, 4.8, 2.2 Hz, 1H), 1.65 – 1.52 (m, 2H), 0.99 (t, *J* = 7.4 Hz, 3H); selected ^{1}H NMR for the minor diastereomer (500 MHz, Chloroform-*d*) δ 7.86 (d, *J* = 3.2 Hz, 1H), 7.05 – 6.99 (m, 1H), 3.01 – 2.96 (m, 1H), 2.81 (dddd, *J* = 16.4, 6.0, 4.3, 2.0 Hz, 1H), 1.84 – 1.75 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 201.87, 166.32, 164.07, 144.64, 124.58, 123.78, 51.58, 48.77, 47.61, 33.38, 26.84, 11.46; IR (neat): 3063, 2963, 1722, 1659, 1587, 1436, 1276, 1170; ESI^{+} calculated for $[C_{12}H_{15}NaO_3Br]^{+}$: 309.01, 311.01, found 308.94, 310.93.

2-bromo-5-ethyl-4-isopropylcyclopent-2-enone (S41e-2) 2-bromo-5-isobutyl-4-methylcyclopent-2-enone (S41e-3)

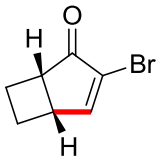


S41e-2/S41e-3 = 1.6/1

Compound **S41e-2/S41e-3** was prepared in 82% total yield (56.9 mg) using **S41e-1** (0.3 mmol) as the substrate according to the general procedure **C**. Selected ^{1}H NMR for the major diastereomer of **S41e-3** (500 MHz, Chloroform-*d*) ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.59 (s, 1H), 2.61 (m, 1H), 2.08 (m, 1H), 1.24 (d, *J* = 7.2 Hz, 3H), 0.98 (d, *J* = 6.8 Hz, 6H); Selected ^{1}H NMR for the minor diastereomer of **S41e-3** (500 MHz, Chloroform-*d*) δ 3.08 (m, 1H), 2.54 (dt, *J* = 10.5, 5.8 Hz, 1H), 1.08 (d, *J* = 7.2 Hz, 3H); Selected ^{1}H NMR for the major diastereomer of **S41e-2** (500 MHz, Chloroform-*d*) δ 7.70 (s, 1H), 2.44 (d, *J* = 5.8 Hz, 1H), 2.16 (t, *J* = 6.4 Hz, 1H), 1.87 – 1.80 (m, 1H), 1.66 (ddt, *J* = 21.0, 14.2, 6.8 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 203.99, 203.83, 203.40, 165.39, 165.17, 163.38, 160.56, 125.01, 124.35, 124.27, 52.92, 50.42, 48.72, 46.24, 42.69, 40.56, 38.77, 34.61, 31.59, 25.96, 25.93,

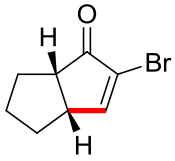
24.77, 23.39, 22.91, 21.98, 21.62, 20.35, 19.59, 16.15, 13.00, 10.81; IR (neat): 3063, 2961, 2931, 2873, 1720, 1588, 1463, 1270, 939; ESI^+ calculated for $[C_{10}H_{15}NaOBr+MeOH]^+$: 285.05, 287.05, found 284.94, 286.98.

3-bromobicyclo[3.2.0]hept-3-en-2-one (T3-1)



This compound was prepared in 73% yield (41.0 mg) using **T3-1-SM** (0.3 mmol) as the substrate according to the general procedure **C**. ^1H NMR (500 MHz, Chloroform-*d*) δ 7.82 (d, *J* = 3.3 Hz, 1H), 3.47 – 3.38 (m, 1H), 3.18 – 3.11 (m, 1H), 2.60 – 2.44 (m, 2H), 1.90 – 1.77 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 204.02, 163.50, 128.62, 41.58, 39.63, 23.28, 20.04; IR (neat): 3058, 2989, 2948, 1714, 1572, 1385, 1294, 1025, 857; ESI^+ calculated for $[C_7H_7NaOBr]^+$: 208.96, 210.96, found 208.91, 210.90.

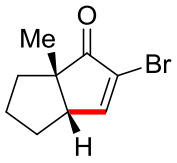
2-bromo-4,5,6,6a-tetrahydropentalen-1(3aH)-one (T3-2)



This compound was prepared in 84% yield (50.7 mg) using **T3-2-SM** (0.3 mmol) as the substrate according to the general procedure **C**. ^1H NMR (500 MHz, Chloroform-*d*) δ 7.61 (d, *J* = 3.1 Hz, 1H), 3.33 (ddt, *J* = 8.8, 5.3, 2.7 Hz, 1H), 2.86 (dd, *J* = 10.4, 5.7 Hz, 1H), 1.96 (dd, *J* = 13.2, 6.2 Hz, 1H), 1.83 – 1.62 (m, 4H), 1.30 (ddq, *J* = 17.5, 11.2, 5.7, 5.1 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 204.87, 164.59, 125.65, 48.32, 45.61, 30.35, 29.42, 23.85; IR

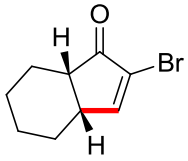
(neat): 3058, 2953, 2866, 1717, 1584, 1277, 935; ESI$^+$ calculated for [C_8H_9NaOBr+MeOH]$^+$: 255.00, 257.00, found 254.93, 256.93.

2-bromo-6a-methyl-4,5,6,6a-tetrahydropentalen-1(3aH)-one (T3-3)



This compound was prepared in 87% yield (56.2 mg) using **T3-3-SM** (0.3 mmol) as the substrate according to the general procedure **C**. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.57 (d, *J* = 3.0 Hz, 1H), 2.87 (dt, *J* = 9.5, 2.3 Hz, 1H), 1.97 (dd, *J* = 13.0, 6.1 Hz, 1H), 1.83 (tdd, *J* = 12.1, 8.9, 6.2 Hz, 1H), 1.70 – 1.59 (m, 2H), 1.42 (td, *J* = 12.5, 6.2 Hz, 1H), 1.29 (ddd, *J* = 19.9, 12.9, 7.0 Hz, 1H), 1.24 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 206.81, 163.35, 124.39, 53.44, 53.39, 38.32, 29.29, 24.58, 22.29; IR (neat): 3060, 2956, 2867, 1718, 1586, 1448, 910, 815; ESI$^+$ calculated for [$C_9H_{11}NaOBr$]$^+$: 236.99, 238.99, found 236.93, 238.93.

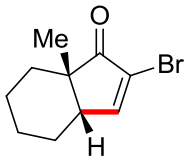
2-bromo-3a,4,5,6,7,7a-hexahydro-1H-inden-1-one (T3-4)



This compound was prepared in 74% yield (47.7 mg) using **T3-4-SM** (0.3 mmol) as the substrate according to the general procedure **C**. ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.72 (d, *J* = 3.2 Hz, 1H), 3.02 – 2.95 (m, 1H), 2.56 (q, *J* = 6.3 Hz, 1H), 2.02 – 1.91 (m, 2H), 1.75 (tt, *J* = 14.0, 6.4 Hz, 1H), 1.53 (ddt, *J* = 17.7, 11.4, 6.0 Hz, 2H), 1.39 (ddq, *J* = 15.2, 7.4, 4.5, 3.6 Hz, 1H), 1.28 (ddq, *J* = 19.9, 10.4, 5.0 Hz, 1H), 1.23 – 1.15 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 203.42, 164.81, 124.83, 44.31, 40.40, 28.05, 22.89, 21.22, 21.03; IR (neat): 3063,

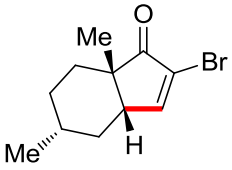
2937, 2858, 1725, 1581, 1448, 1272; ESI$^+$ calculated for [$C_9H_{11}NaOBr$+MeOH]$^+$: 269.02, 271.01, found 268.94, 270.95.

2-bromo-7a-methyl-3a,4,5,6,7,7a-hexahydro-1H-inden-1-one (T3-5)



This compound was prepared in 90% yield (61.8 mg) using **T3-5-SM** (0.3 mmol) as the substrate according to the general procedure **C**. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.60 (d, *J* = 2.7 Hz, 1H), 2.62 (td, *J* = 5.7, 2.8 Hz, 1H), 1.85 (dddd, *J* = 13.9, 10.2, 6.3, 4.2 Hz, 1H), 1.68 – 1.41 (m, 5H), 1.39 – 1.31 (m, 2H), 1.17 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 206.71, 163.61, 123.89, 48.36, 46.25, 31.05, 25.44, 22.90, 19.64, 19.15; IR (neat): 3068, 2939, 2862, 1727, 1587, 1449, 1379, 1047, 743; ESI$^+$ calculated for [$C_{10}H_{13}KOBr$+MeOH]$^+$: 299.00, 301.00, found 298.96, 300.96.

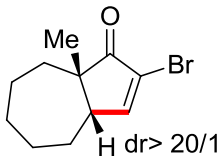
2-bromo-5,7a-dimethyl-3a,4,5,6,7,7a-hexahydro-1H-inden-1-one (T3-6)



This compound was prepared in 93% yield (67.8 mg) using **T3-6-SM** (0.3 mmol) as the substrate according to the general procedure **C**. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.55 (d, *J* = 2.5 Hz, 1H), 2.72 (dt, *J* = 6.4, 2.5 Hz, 1H), 1.80 (ddd, *J* = 13.5, 4.6, 2.5 Hz, 1H), 1.56 – 1.34 (m, 5H), 1.19 (s, 3H), 1.09 – 1.00 (m, 1H), 0.91 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 206.61, 163.33, 123.49, 48.32, 46.23, 33.88, 32.17, 28.99, 26.81, 22.44,

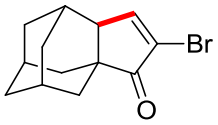
20.79; IR (neat): 3068, 2927, 2869, 1723, 1589, 1456, 1378, 1282, 763; ESI^+ calculated for $[C_{11}H_{15}KOBr+MeOH]^+$: 313.02, 315.02, found 312.90, 314.90.

2-bromo-8a-methyl-4,5,6,7,8,8a-hexahydroazulen-1(3aH)-one (T3-7)



This compound was prepared in 90% yield (65.6 mg) using **T3-7-SM** (0.3 mmol) as the substrate according to the general procedure **C**. ^1H NMR (500 MHz, Chloroform-*d*) δ 7.60 (d, *J* = 2.9 Hz, 1H), 2.70 (dt, *J* = 8.9, 3.2 Hz, 1H), 1.91 (ddd, *J* = 14.0, 9.6, 3.5 Hz, 1H), 1.72 – 1.67 (m, 2H), 1.63 – 1.34 (m, 7H), 1.14 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 207.49, 164.96, 123.09, 54.68, 50.17, 35.02, 31.20, 30.91, 27.35, 26.17, 24.67; IR (neat): 3058, 2925, 2854, 1720, 1592, 1448, 1277, 816; ESI^+ calculated for $[C_{11}H_{15}NaOBr+MeOH]^+$: 297.05, 299.04, found 296.98, 298.98.

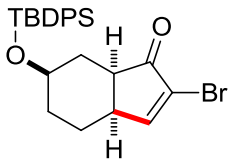
2-bromo-5,6,7,8,9,9a-hexahydro-3a,7:5,9-dimethanocyclopenta[8]annulen-3(4H)-one (T3-8)



This compound was prepared in 79% yield (63.3 mg) using **T3-8-SM** (0.3 mmol) as the substrate according to the general procedure **C**. ^1H NMR (500 MHz, Chloroform-*d*) δ 7.61 (d, *J* = 1.6 Hz , 1H), 2.88 (s, 1H), 2.30 (m, 1H), 2.12 (m, 2H), 1.98 (m, 1H), 1.86 (m, 2H), 1.78 (m, 5H), 1.71 – 1.60 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 203.95, 159.02, 124.71, 52.96, 49.22, 39.18, 38.79, 36.76, 35.19, 32.30, 30.25, 28.27, 27.60; IR (neat): 3053, 2919, 2855,

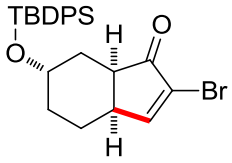
1716, 1447, 1242, 923; ESI$^+$ calculated for [$C_{13}H_{15}NaOBr$+MeOH]$^+$: 321.05, 323.04, found 320.97, 322.97.

2-bromo-6-((tert-butyldiphenylsilyl)oxy)-3a,4,5,6,7,7a-hexahydro-1H-inden-1-one (S41f-2)



This compound was prepared in 74% yield (34.8 mg) using **S41f-1** (0.1 mmol) as the substrate according to the general procedure **C**. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.70 (d, *J* = 3.2 Hz, 1H), 7.69 – 7.66 (m, 2H), 7.64 – 7.59 (m, 2H), 7.44 – 7.31 (m, 6H), 3.98 (ddd, *J* = 8.9, 5.2, 3.8 Hz, 1H), 2.91 (dtd, *J* = 9.7, 6.7, 3.2 Hz, 1H), 2.50 – 2.44 (m, 1H), 2.20 (dt, *J* = 14.2, 5.3 Hz, 1H), 1.77 (dddd, *J* = 26.2, 11.9, 7.5, 4.3 Hz, 2H), 1.70 – 1.64 (m, 1H), 1.41 (dq, *J* = 10.3, 4.3 Hz, 2H), 1.01 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 202.30, 163.76, 135.94, 135.78, 134.27, 133.77, 129.61, 129.54, 127.54, 127.51, 124.42, 66.53, 41.72, 39.07, 31.53, 30.53, 26.90, 23.37, 19.07; IR (neat): 3070, 3050, 2996, 2930, 2856, 1727, 1428, 1108, 1067, 1009; ESI$^+$ calculated for [$C_{25}H_{29}NaO_2SiBr$]$^+$: 493.10, 491.10, found 491.01, 493.01.

2-bromo-6-((tert-butyldiphenylsilyl)oxy)-3a,4,5,6,7,7a-hexahydro-1H-inden-1-one (S41g-2)



This compound was prepared in 78% yield (36.7 mg) using **S41g-1** (0.1 mmol) as the substrate according to the general procedure **C**. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.64

(m, 5H), 7.48 – 7.33 (m, 6H), 3.87 (p, *J* = 5.5 Hz, 1H), 3.06 – 2.97 (m, 1H), 2.83 (q, *J* = 6.9 Hz, 1H), 2.08 – 1.97 (m, 1H), 1.89 (t, *J* = 6.4 Hz, 2H), 1.60 (dd, *J* = 14.0, 5.5 Hz, 1H), 1.45 (ddt, *J* = 14.2, 10.4, 5.0 Hz, 1H), 1.06 (m, 10H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 203.27, 164.05, 135.69, 135.66, 134.31, 133.92, 129.71, 129.61, 127.66, 127.58, 124.79, 67.22, 42.52, 39.73, 31.50, 31.34, 26.97, 25.56, 19.16; IR (neat): 3073, 3045, 2931, 2857, 1720, 1427, 1110, 822; ESI$^+$ calculated for $[C_{25}H_{29}NaO_2SiBr]^+$: 493.10, 491.10, found 491.01, 493.01.

2.7 References

(1) Christian Bruneau, P. D. *Metal Vinylidenes and Allenylidenes in Catalysis: From Reactivity to Applications in Synthesis, Wiley-VCH, Weinheim,* **2008**.

(2) Mamane, V.; Hannen, P.; Fürstner, A. *Chemistry – A European Journal* **2004**, *10*, 4556.

(3) Soriano, E.; Marco-Contelles, J. *Organometallics* **2006**, *25*, 4542.

(4) Morán-Poladura, P.; Rubio, E.; González, J. M. *Angewandte Chemie International Edition* **2015**, *54*, 3052.

(5) Ye, L.; Wang, Y.; Aue, D. H.; Zhang, L. *Journal of the American Chemical Society* **2012**, *134*, 31.

(6) Hashmi, A. S. K.; Braun, I.; Nösel, P.; Schädlich, J.; Wieteck, M.; Rudolph, M.; Rominger, F. *Angewandte Chemie International Edition* **2012**, *51*, 4456.

(7) Bucher, J.; Wurm, T.; Nalivela, K. S.; Rudolph, M.; Rominger, F.; Hashmi, A. S. K. *Angewandte Chemie International Edition* **2014**, *53*, 3854.

(8) Harris, R. J.; Widenhoefer, R. A. *Angewandte Chemie International Edition* **2015**, *54*, 6867.

(9) Schnermann, M. J.; Overman, L. E. *Journal of the American Chemical Society* **2011**, *133*, 16425.

(10) Geng, F.; Liu, J.; Paquette, L. A. *Organic Letters* **2002**, *4*, 71.

(11) Kuhn, C.; Roulland, E.; Madelmont, J.-C.; Monneret, C.; Florent, J.-C. *Organic & Biomolecular Chemistry* **2004**, *2*, 2028.

(12) Karpf, M.; Dreiding, A. S. *Helvetica Chimica Acta* **1979**, *62*, 852.

(13) Karpf, M.; Huguet, J.; Dreiding, A. S. *Helvetica Chimica Acta* **1982**, *65*, 13.

(14) Williamson, B. L.; Tykwinski, R. R.; Stang, P. J. *Journal of the American Chemical Society* **1994**, *116*, 93.

(15) Carlos Lima, J.; Rodriguez, L. *Chemical Society Reviews* **2011**, *40*, 5442.

(16) Hansmann, M. M.; Rominger, F.; Hashmi, A. S. K. *Chemical Science* **2013**, *4*, 1552.

(17) Jin, L.; Melaimi, M.; Kostenko, A.; Karni, M.; Apeloig, Y.; Moore, C. E.; Rheingold, A. L.; Bertrand, G. *Chemical Science* **2016**, *7*, 150.

(18) Xiao, X.-S.; Kwong, W.-L.; Guan, X.; Yang, C.; Lu, W.; Che, C.-M. *Chemistry – A European Journal* **2013**, *19*, 9457.

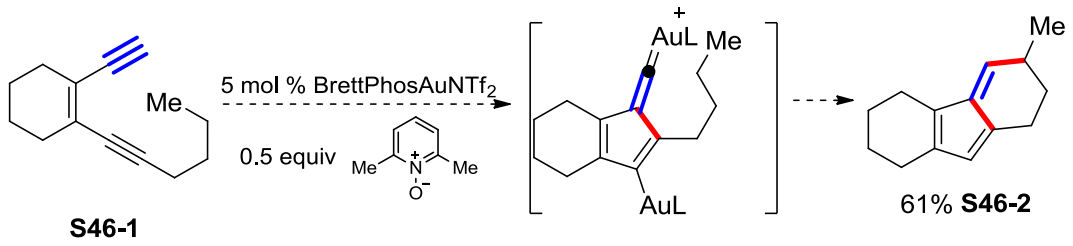
(19) Wang, Y.; Zarca, M.; Gong, L.-Z.; Zhang, L. *Journal of the American Chemical Society* **2016**, *138*, 7516.

Chapter 3. C-H Functionalization via Insertion into Unactivated C(sp^3)-H Bonds by Hypothetical Gold Benzyne Intermediates

3.1 Initial 'Gold Benzyne' Chemistry Discovery with a Reassigned Structure

In 2011, before I joined our group, Longwu discovered the previously mentioned gold-catalyzed diyne cyclosiomerization and vinylidene C-H insertion chemistry (Scheme 33).[1] After finishing the gold vinylidene chemistry, he extended it from using benzene-fused diyne to cyclohexene-fused enediyne **S46-1** as the substrate (Scheme 46). Under his previously developed conditions, the enediyne chemistry proceeded smoothly to afford a product in 61% yield. According to his previous publication, he proposed the same gold vinylidene C-H insertion mechanism and tentatively assigned the fulvene type structure **S46-2**, although there were questions why the 6-membered ring is formed in the C-H insertion step. After this enediyne experiment, he left the lab for a new job and I took over the project.

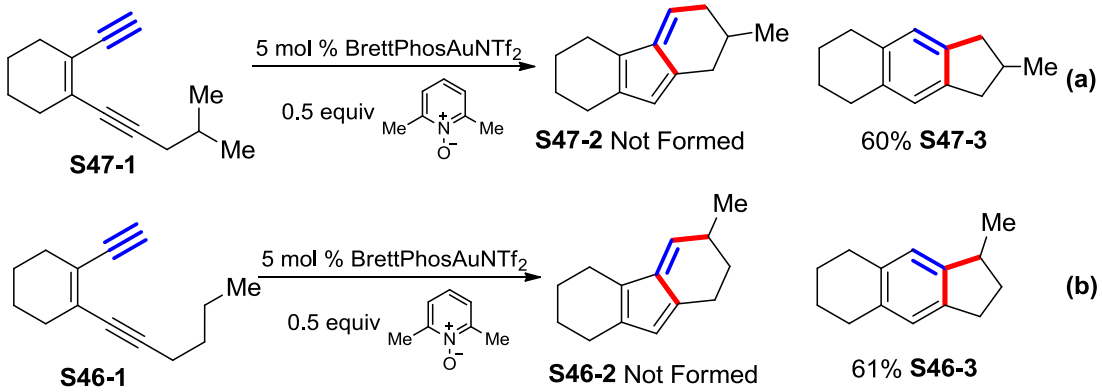
Scheme 46. Longwu's Extension with Enediyne after the Gold Vinylidene Chemistry



Since the reaction conditions were considered optimized at that time, I directly studied the reaction scope. When the enediyne substrate **S47-1** was subjected to the gold catalysis conditions, the starting material was consumed gradually and I isolated 60% yield of a product (Scheme 47a). However, the product's proton and C13 NMR didn't match the fulvene type structure **S47-2**. GC-MS of the product showed the same molecular weight as

the starting material. For the C13 NMR, there were only 8 different signals indicating that the product structure was symmetrical. Assisted by 2D-NMR techniques, I eventually figured out the correct product structure as **S47-3**. This unexpected result is surprising to me and my advisor. I then double checked Lonwu's last experiment using enediyne **S46-1**. Again, the fulvene product was not formed and the isolated product was only the indane type **S46-3** (Scheme 47b).

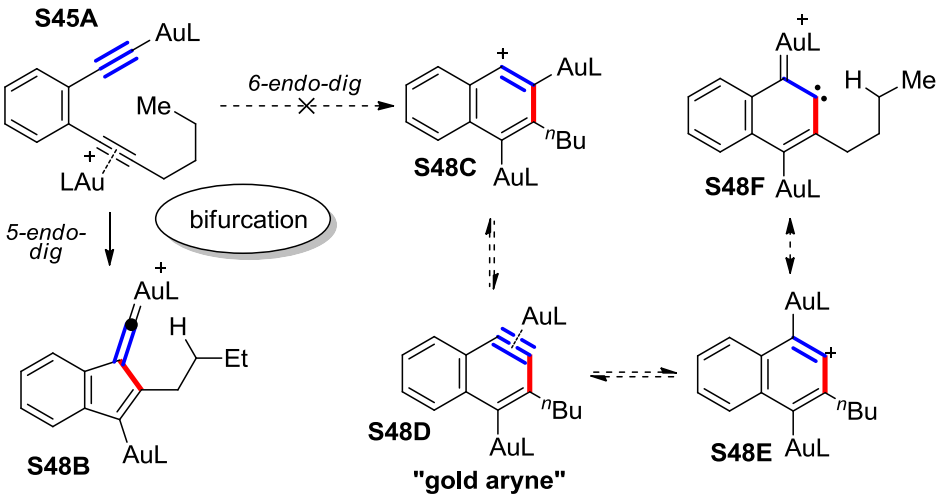
Scheme 47. My Initial Discovery with Revised Structure



Although unexpected, this type of six-member aromatic cyclization product actually has been predicted in the previous gold vinylidene paper by DFT calculations (Scheme 48).[1] It was proposed that the benzene fused 1,2-diyne was dually activated by two cationic gold complexes and then the regioselective *5-endo-dig* cyclization from the β-carbon of the gold acetylide **S48A** resulted in gold vinylidene **S48B** for C-H insertion. In the same paper, Professor Don Aue performed theoretical study on the reaction mechanism and he found a very interesting bifurcation phenomenon. According to his DFT calculation, besides the *5-endo-dig* cyclization leading to gold vinylidene **S48**B, there is another possible cyclization pathway: *6-endo-dig* cyclizaiton. He even showed that the α-auronaphthyl cation **S48C** from the *6-endo-dig* cyclization easily isomerized into another regioisomer **S48E** via a low barrier

gold aryne transition state **S48D**. The newly formed α-auronaphthyl cation was more stable. And its resonance structure "α-carbene gold carbene" **S48F** could insert into C-H bond, which was also predicted by Aue's calculation.

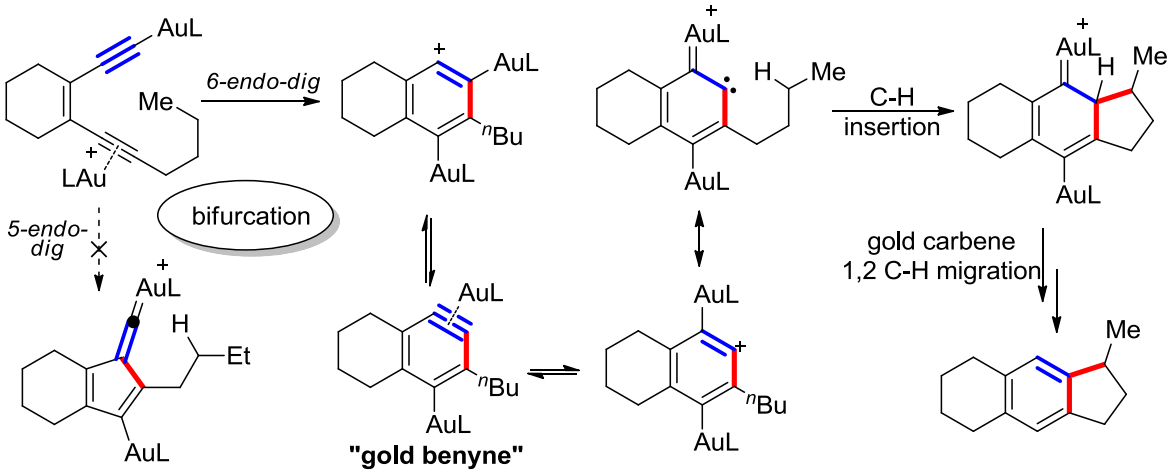
Scheme 48. Bifurcation Mechanism Proposed by Aue



However, this gold aryne reactivity predicted by Aue's calculation was never observed in the previous labmate's gold vinylidene project. I was lucky to continue with his unfinished enediyne chemistry and figured out the correct structure and realized the 'gold benzyne' chemistry (Scheme 49). Precisely speaking, our enediyne cycloisomerization only involves a gold aryne transition state. In this paper, we call such reactions involving this type of transition states as 'gold benzyne' chemistry for simplicity and for the novelty of the concept. The bifurcation switch from *5-endo-dig* to *6-endo-dig* using these two different substrates could be explained by the gained aromatic stabilization. When the substrate was benzene fused diyne, the additional aromaticity gained was 28 kcal/mol (36 kcal/mol for benzene and 64 kcal/mol for naphthalene). Thus, the 6-endo-dig cyclization for simple enediyne was favored by 8 kcal/mol due to the formation of a benzene ring compared to the benzene fused

diyne. During our paper's review period, Hashmi et al.[2] reported a gold-catalyzed thiophene-fused diyne cycloisomerization reaction and they proposed almost identical mechanism and their DFT calculations also supported such 'gold benzyne' mechanism and our rationale of the reactivity divergence.

Scheme 49. Rational for Our Enediyne Cycloisomerization

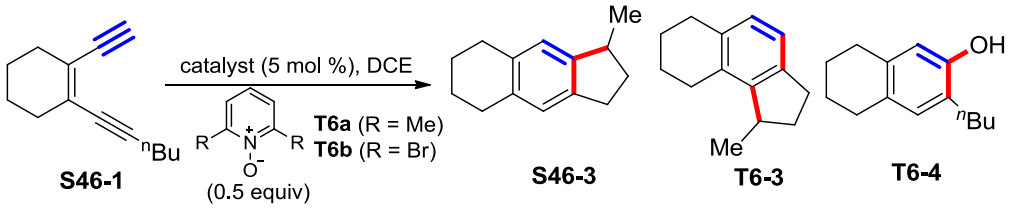


3.2 Conditions Optimization for 'Gold Benzyne' Chemistry

Since the enediyne cycloisomerization reaction worked with a different mechanism, I reoptimized the reaction conditions (Table 6). As shown above, the C-H insertion reaction already worked with BrettPhosAuNTf$_2$ (5 mol %) and 2,6-lutidine *N*-oxide (**T6a**, 0.5 equiv) in 1,2-dichloroethane (DCE) (entry 1). Besides the desired product **S46-3**, small amount of phenol product **T6-4** was also isolated, which was a result of water addition to 'gold benzyne' in the form of α-aurophenyl cation. The trace amount of regioisomeric side product **T6-3** was likely formed via a similar mechanism proposed by Liu et al.[3] The additive **T6a** was a weak base to help the formation of the gold acetylide complex. Without it, the reaction was sluggish (entry 2). Among all the other weak organic bases examined (entry 3-

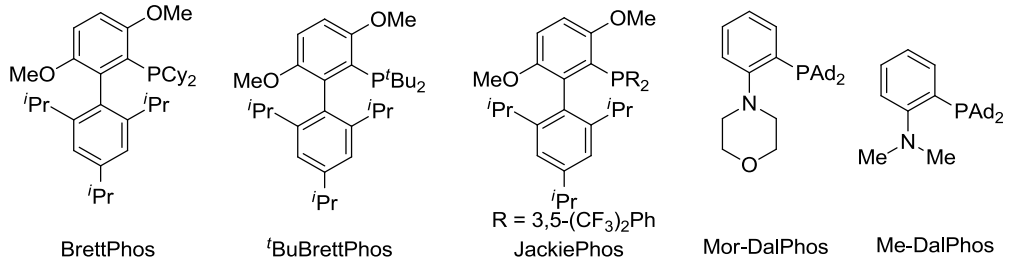
5), only 2,6-lutidine provided similar efficiency while the reaction was slowed down due to is stronger basicity.

Table 6. Initial Reaction Discovery and Optimization.[a]



entry	catalyst	base	temp/time	**S46-3/ T6-3/ T6-4**[b]
1	BrettPhosAuNTf$_2$	**T6a**	rt/17 h	61%/trace/9%
2	BrettPhosAuNTf$_2$	-	rt/24 h	24%/trace/4%
3	BrettPhosAuNTf$_2$	**T6b**	rt/24 h	28%/trace/4%
4	BrettPhosAuNTf$_2$	TsNa	rt/24 h	30%/trace/5%
5	BrettPhosAuNTf$_2$	lutidine	60 ˚C /24 h	61%/trace/4%
6	^{t}BuBrettPhosAuNTf$_2$	**T6a**	60 ˚C/24 h	45%/trace/10%
7	JackiePhosAuNTf$_2$	**T6b**[c]	rt/20 h	50%/ trace/trace
8	**Mor-DalPhosAuNTf$_2$**	**T6a**	**60 ˚C/11 h**	**83%**[d]**/trace/trace**
9	Mor-DalPhosAuCl/NaBAr$^F{}_4$	**T6a**	60 ˚C/20 h	76%/ trace/trace
10	Me-DalPhosAuNTf$_2$	**T6a**	80 ˚C/36 h	9%/35%/trace
11	Ph$_3$PAuNTf$_2$	**T6a**	60 ˚C/3.5 h	8%/54%/trace

[a] Reaction run in flame-dried vial using dry DCE as solvent. [**S46-1**] = 0.05 M. [b] Estimated by ^{1}H NMR using diethyl phthalate as the internal reference. [c] 1.1 Equiv. [d] Isolated yield.



With the best base additive, we then screened various gold catalysts. Generally, this dual gold catalysis required steric bulky phosphine ligands (entry 5-9), such as BrettPhos, ^{t}BuBrettPhos, JackiePhos, and Mor-DalPhos, with the Mor-DalPhos[4] most effective. The

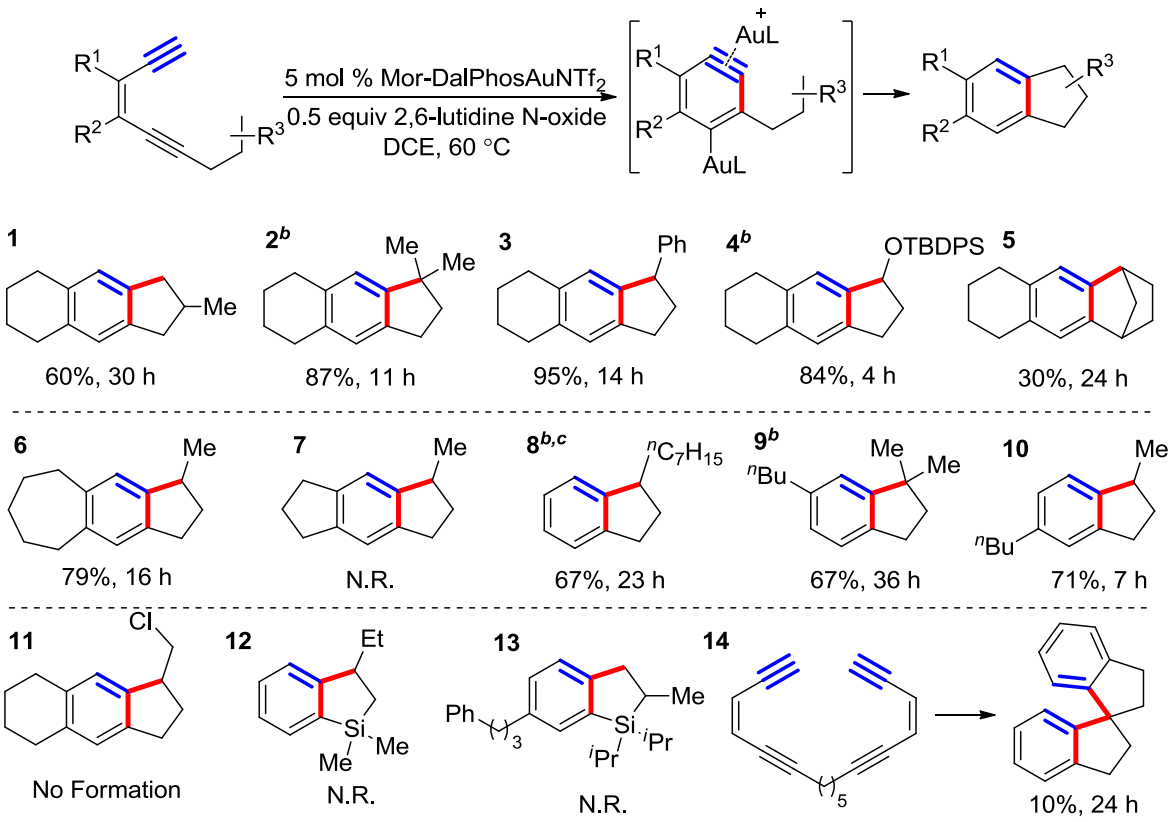
desired product was isolated in a good 83% yield and the side products **T6-3** and **T6-4** were almost undetectable. The non-coordinating counteranion $BAr^F{}_4^-$ led to no improvement (entry 9). Interestingly, a slightly smaller catalyst Me-DalPhosAuNTf$_2$ greatly changed the reaction mechanism with more **T6-3** formed. In the same vein, sterically even less hindered catalyst $Ph_3PAuNTf_2$ caused more **T6-3** formation.

3.3 Reactivity Study of 'Gold Benzyne'

With the optimized conditions in mind, we then investigated the general reactivity of our 'gold benzyne' in terms of C-H insertion reactions as well as nucleophilic additions and cycloaddition reactions.

For all C-H insertion reactions, vials were dried in oven and molecular sieves were added to prevent the 'gold benzyne' hydration reations (Table 7). The cyclohexene fused 'gold benzyne' inserted into primary C-H bonds in moderate yield (entry 1), which supported our carbene C-H insertion mechanism and largely ruled out the possible 1,5-hydride migration pathway. The more nucleophilic methine C-H bonds react readily, and the indane product with a newly formed quarternary carbon center was isolated in 87% yield (entry 2). The benzylic and ethereal C-H bonds were also easily inserted by the 'gold benzyne' with no 1,5-hydride migration problem (entry 3,4). However, the insertion into cyclopentane ring to form a bicyclo[2.2.1]heptene structure was difficult, apparently due to the ring strain, and only 30% of desired product was detected (entry 5).

Table 7. Scope of 'Gold Benzyne' C-H Insertion Reactions[a]

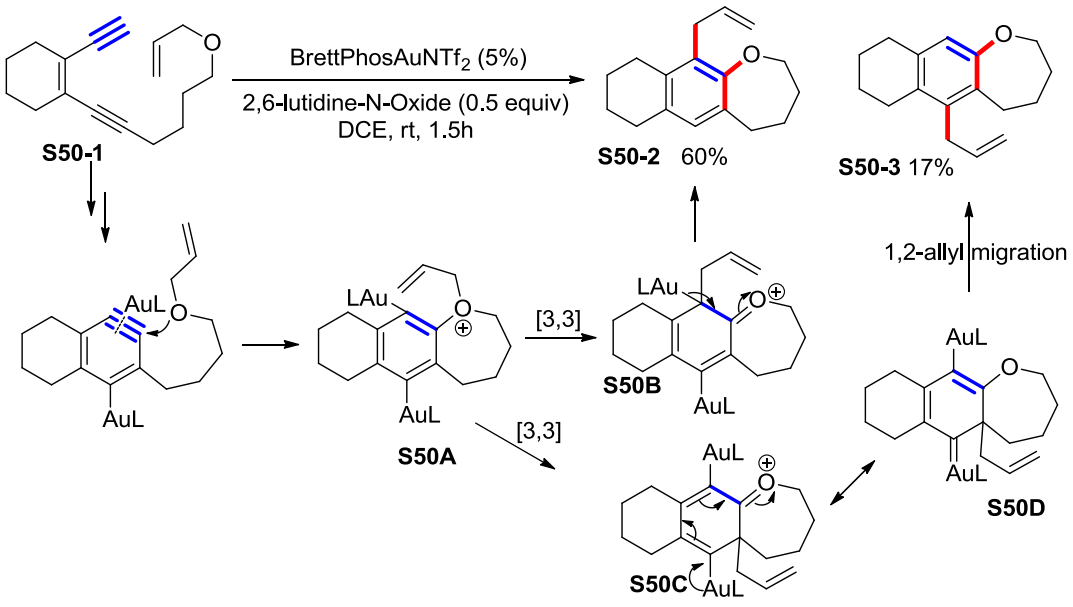


[a] [**1**] = 0.05 M. Reactions were run in flame-dried vials in the presence of 4 Å MS. Isolated yield were reported. [b] BrettPhosAuNTf$_2$ was used. [c] 2,6-Dibromopyridine-*N*-oxide was used instead.

The R^1 and R^2 groups on the backbone of enediyne were then varied. While the cycloheptene fused enediyne reacted as efficient as the cyclohexene fused one (entry 6), the cyclopentene fused one surprisingly showed totally no reactivity (entry 7). This can be attributed to the fact that the cyclopentene backbone spread the two alkyne moieties away due to its large bond angle and thus the 6-endo-dig cyclization became very difficult. To our delight, the simplest enediyne with no substituent on the alkene part also cyclized into 'gold benzyne' for C-H insertion (entry 8). Such enediyne was easily synthesized from *cis*-1,2-dichloroethlene via two Sonagashira reactions. We could also put substituent on any side of

the alkene without changing the reaction mechanism or affecting the 'gold benzyne' C-H insertion reactivity (entry 9,10). Interestingly, 'gold benzyne' could not insert into a 4-chorobutyl group probably due to the inductive deactivating effect by the chlorine atom (entry 11). Unfortunately, no reaction happened to the enediyne with silyl group bonded to one alkyne part (entry 12,13). Our benzyne C-H insertion method could be applied for the synthesis of 5,5-spiro tetracyclic compound (entry 14). The product was generated in only 10% yield after two continuous 'gold benzyne' formation and C-H insertion process.

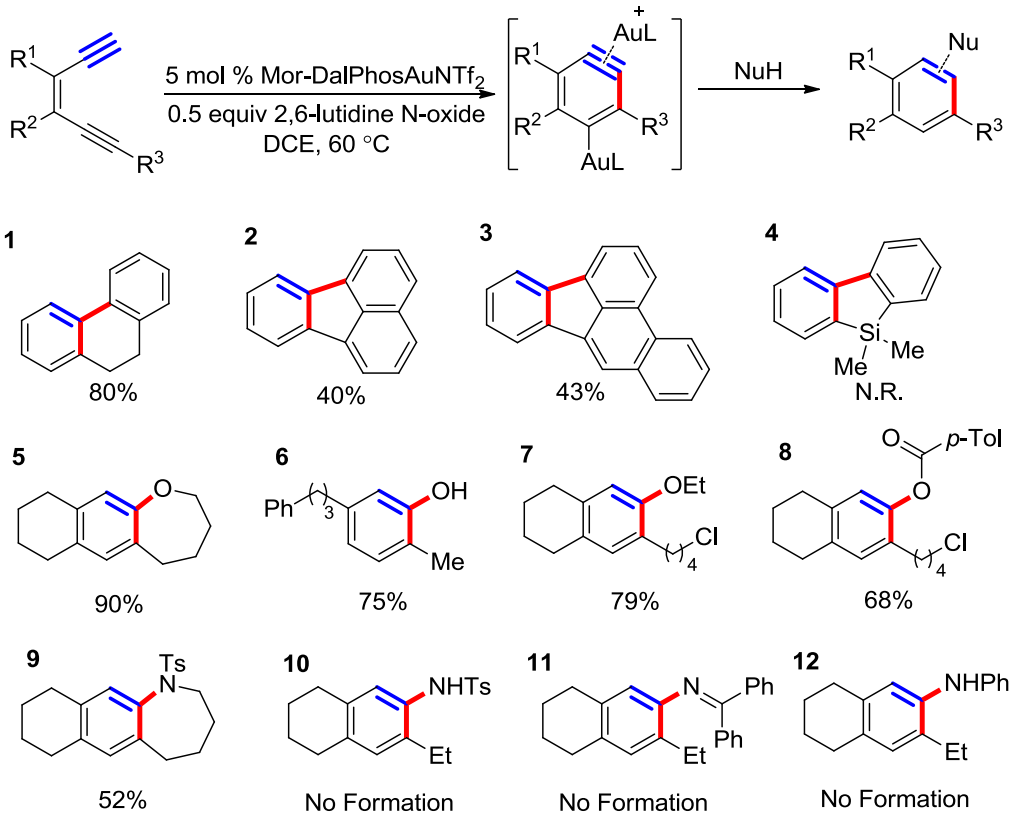
Scheme 50. 'Gold Benzyne' Reaction with Allyl Ether



The cycloisomerization of enediyne **S50-1** occurred but didn't afford any C-H insertion products (Scheme 50). Instead, a formal C-O bond insertion product **S50-2** was identified in 60% yield and together with another isomeric product **S50-3**. Due to the inductive deactivation on the C(sp^3)-H bonds from the allyoxyl group, the 'gold benzyne' C-H insertion was retarded. Instead, the oxygen atom attacked the 'gold benzyne' and subsequent

3,3-sigmatropic rearrangement of **S50A** led to two different oxocarbenium ions **S50B** and **S50C**. The aromatization and protodeauration of **S50B** afforded the main product **S50-2**. The minor product **S50-3** could be explained by the gold carbene induced 1,2-allyl migration of **S50D**, which was a resonance structure of **S50C**.

Table 8. 'Gold Benzyne' Nucleophilic Addition Reactions[a]



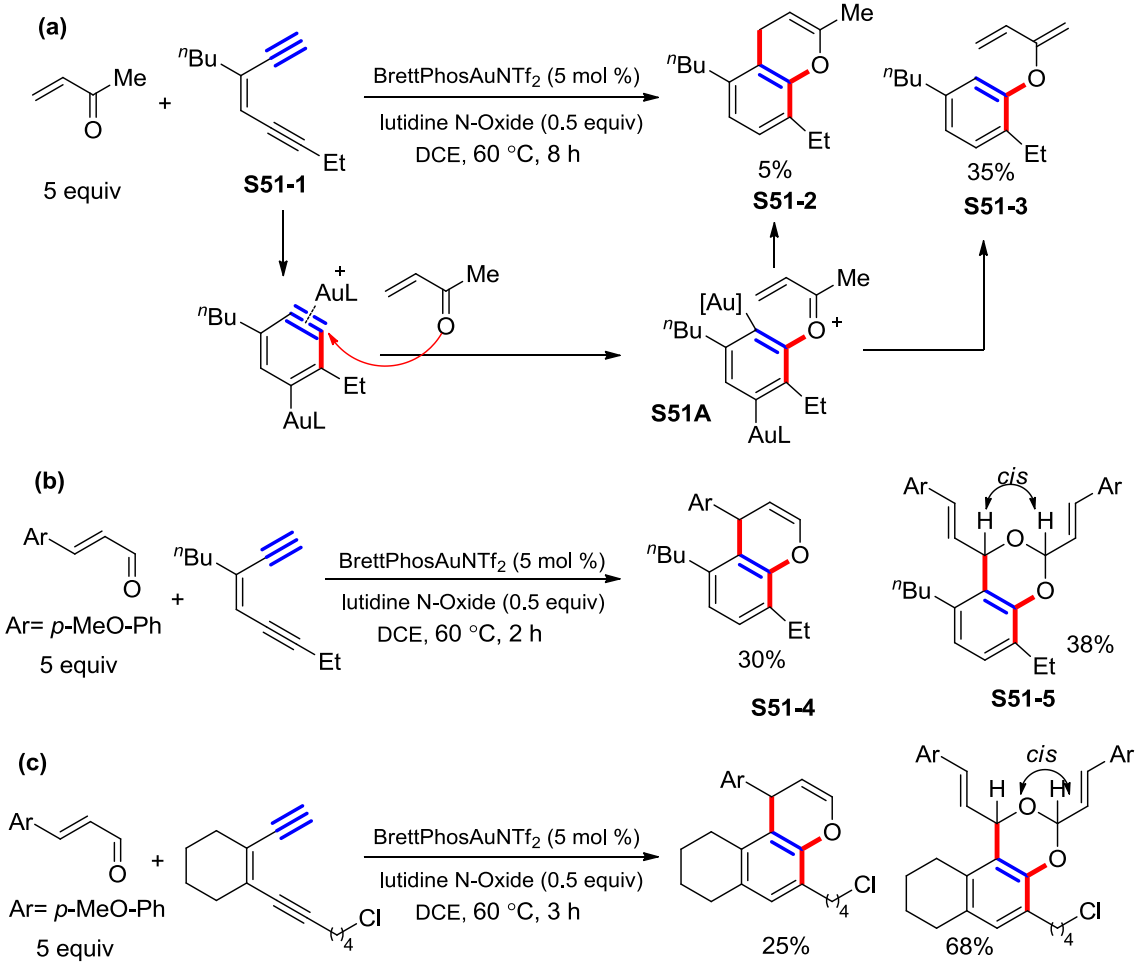
Besides the C-H insertion reactions, 'gold benzyne' could also undergo nucleophilic addition reactions (Table 8) as a result of the α-aurophenyl cation intermediate. For example, tethered phenyl group efficiently harvested 'gold benzyne' generating a biaryl product (entry 1). Such Friedel-Crafts process could be applied for polyaromatics synthesis (entry 2, 3). Again, we got in problem for the cycloisomerization of enediyne silane case (entry 4). There is no reaction for this type of enediyne and the starting material remained. Heteroatom

nucleophiles were then tested for benzyne addition. A tethered free hydroxyl group efficiently trapped 'gold benzyne' and C-H insertion reaction didn't occur (entry 5). 'Gold benzyne' could also be trapped intermolecularly by oxygen based nucleophiles like water, alcohol, and carboxylic acid (entry 6-8). Much to our surprise, for the above three nucleophilic additions, only one regioisomeric product was formed. Such regiospecific reactivity made our 'gold benzyne' suprior to the transition metal free benzynes.[5-7] Tethering strategy also applied for the tosyl amide addition. Tetrahydrobenzazepine was collected in 52% yield and again no competing C-H insertion product was detected (entry 9). Unfortunately, tosyl amide couldn't react with 'gold benzyne' intermolecularly. Other nitrogen nucleophiles like imine, carbomate, and aniline also failed to trap the 'gold benzyne' (entry 10-12).

Cycloaddition reactions like Diels-Alder reaction and dipolar [3+2] reaction are very characteristic for arynes.[8-10] However, such reactivity was never observed when our 'gold benzyne' was treated with furan, diene, nitrone, or azide. Interestingly, I isolated small amount of [4+2] cycloaddition product **S51-2** using methyl vinyl ketone as heterodiene (Scheme 51a). At the same time, simple aryl vinyl ether **S51-3** was isolated as the major product, which indicated that the reaction intermediate was the oxocarbenium ion **S51A** from the carbonyl addition to 'gold benzyne'. According to this mechanism, the aryl vinyl ether formation could be avoided by using α,β-unsaturated aldehyde. Indeed, when *para*-methoxyl cinnamyl aldehyde was mixed with enediyne **S51-1** under our gold catalysis conditions, the [4+2] product was significantly improved to 30% yield (Scheme 51b). To our surprise, we isolated a [2+2+2] product **S51-5** as a single diastereomer from cycloaddition between two aldehyde molecules and one 'gold benzyne'. This unexpected result again indicated the stepwise mechanism for the 'gold benzyne' reaction with α,β-unsaturated

carbonyl compounds. Such [4+2] and [2+2+2] reactions also applied for other 'gold benzyne' species, albeit with a different product distribution (Scheme 51c). Noteworthy, all the above cycloaddition reactions are regiospecific as well.

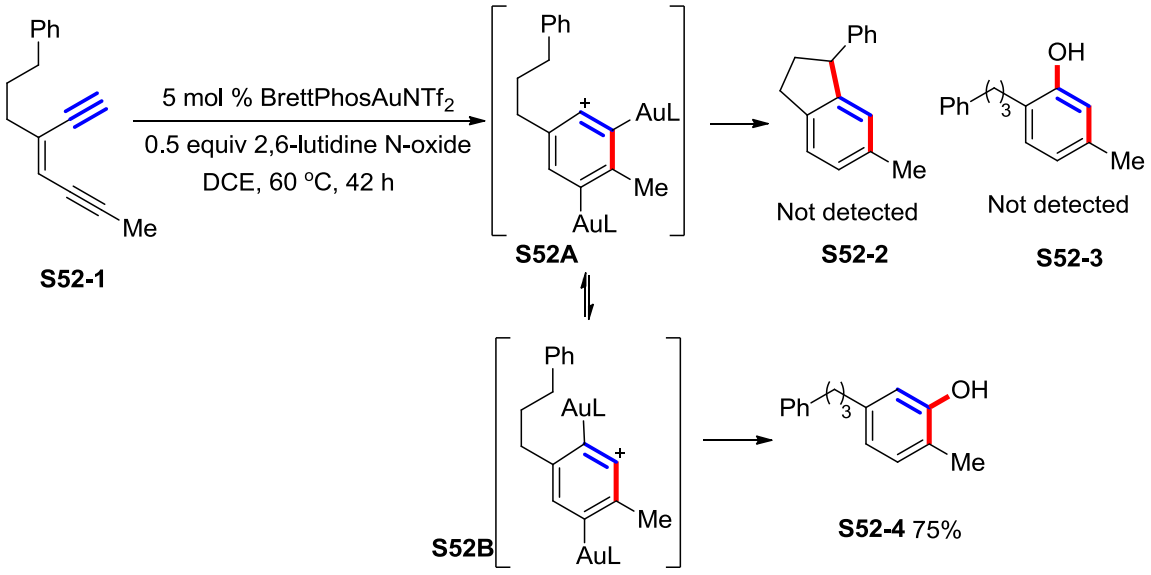
Scheme 51. 'Gold Benzyne' Cycloaddition Reactions



In order to switch the regioselectivity, we designed the enediyne substrate **S52-1** and intentionally put a methyl group on the alkyne's terminus carbon to avoid any C-H insertion on this part and installed 3-phenylpropyl group on the alkene backbone for any possible C-H insertion reaction (Scheme 52). This 3-phenylpropyl group was α to the phenyl cation **S52A**

generated from the initial *6-endo-dig* cyclization event. Although the resonance structure of **S52A** was also a α-carbene gold carbene, no C-H insertion product **S52-2** was ever detected. The only product formed was phenol **S52-4**, which originated from the water addition to phenyl cation **S52B**. The other regioisomeric water addition product **S52-3** was not observed.

Scheme 52. Regioselectivity Study with Properly Designed Substrate

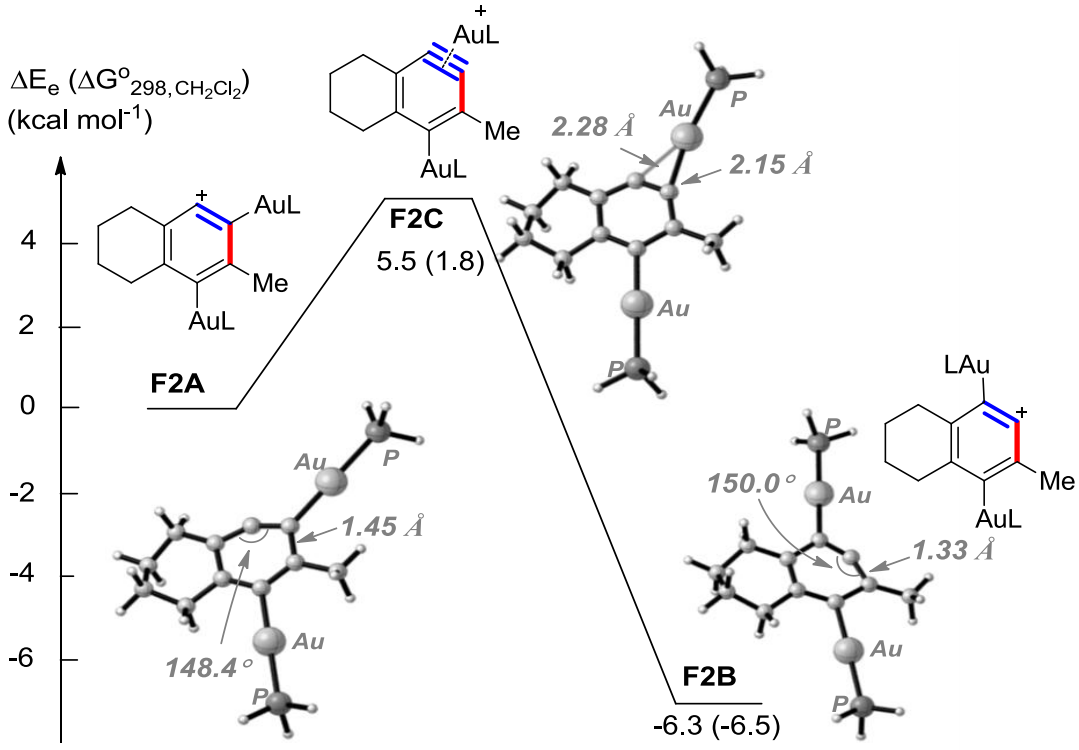


3.4 Mechanistic Studies

We are very intrigued by such regioselectivity for both the 'gold benzyne' C-H insertion reaction and nucleophilic addition reaction (Scheme 52). At the end of this project, we collaborated with Professor Don Aue again for theoretical study. Aue's DFT calculation on the energy of two different ortho-aurophenyl cation and 'gold benzyne' very nicely explained our regiospecific outcome (Figure 2). According to his calculation, our 'gold benzyne' is again a transition state for the isomerization between the two phenyl cations. And the barrier between the ortho-aurophenyl cation **F2A** and 'gold benzyne' **F2C** was low. As a result, **F2A** could easily isomerize into the other phenyl cation **F2B**, which was more

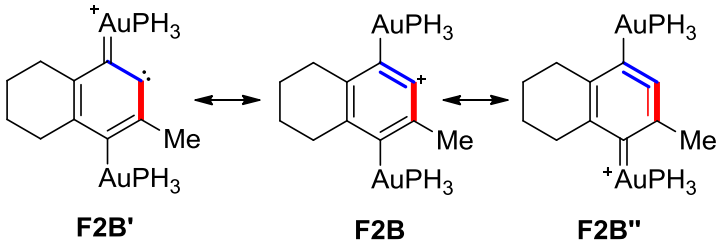
stable by 6.5 kcal/mol. The enhanced stability of **F2B** could be explained by its bent allene resonance structure **F2B''**, where the phenyl cation was partially stabilized by the neighbouring alkenyl gold part of the benzene ring (Figure 3). The bent allene resonance contribution was reflected by the shortened C2-C3 bond length and expanded C1-C2-C3 bond angle.

Figure 2. DFT Calculation on Three Gold Complexes

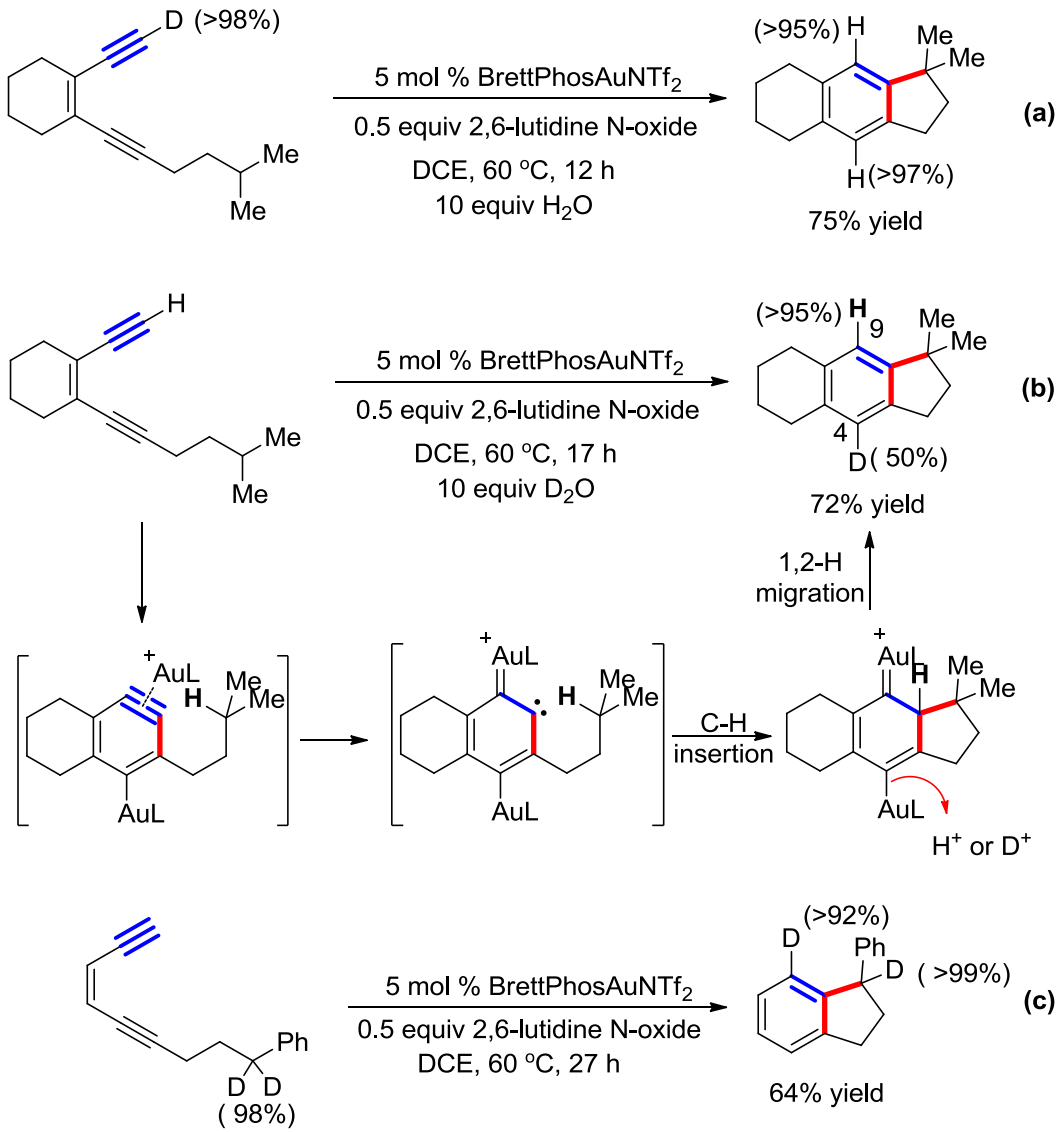


The rearrangement of **F2A** to **F2B**, energy diagram with electronic energies and free energies in methylene chloride in parentheses, and structures optimized at the M06/6-31+G(d,p)/SDD(Au) level.

Figure 3. The Resonance Structures of F2B



Scheme 53. Deuterium Labeling Experiments



Deuterium labeling experiments were then performed to shed light on the mechanism of 'gold benzyne' C-H insertion reactions (Scheme 53). As shown in Scheme 53a, when the enediyne with more than 98% deuterium at the alkyne's terminus carbon was subjected to gold catalysis with 10 equivalent of water, there was nearly no deuterium remaining in the final product, which was consistent with the first step of our proposed mechanism: cationic gold complex reacted with terminal alkyne to form gold acetylide. As a result, deuterium was carried away by weak base and exchanged with proton. On the other hand, if nondeuterated starting material was used together with extra D_2O, half of the C(4)-H was deuterated but no deuterium was incoorporated in C(9)-H (Scheme 53b). This result matched our carbene C-H insertion mechanism, where the C(4)-Au bond was protonated and C(9)-H was formed after two continuous C-H insertion process. Such continuous C-H insertion mechanism could be further proved by Scheme 49c, where deuterium atom was selectively migrated.[11]

3.5 Conclusion

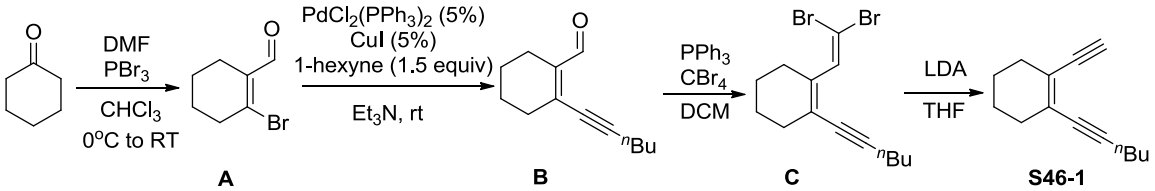
In this project, I have reassigned the product structure from my labmate's previous result and discovered a novel approach to gold arynes (although later proved as a transition state). An interesting bifurcation switch mechanism was proposed for this dual gold-catalyzed cycloisomerization process of *cis*-enediynes. The divergent reactivity could be explained by the difference in aromaticity of the formed arene ring and is supported by DFT calculation. The 'gold benzyne' was actually a transition state between two isomermeric ortho-aurophenyl cations, with one much more stable than the other. Consequentially, our 'gold benzyne' could undergo regiospecific nucleophilic addition reactions. 'Gold benzyne' also showed other unique reactivites different from tranditionally generated transition metal free benzynes. Although the pericyclic cycloaddition reactions didn't apply for our 'gold

benzyne', we realized the first 'gold benzyne' C(sp^3)-H insertion reaction via an α-carbene gold carbene resonance structure.

3.6 Experimental details

General. Ethyl acetate (ACS grade), hexanes (ACS grade), diethyl ether (ACS grade), were purchased from Fisher Scientific and used without further purification. Anhydrous toluene and 1,2-dichloroethane were bought from Acros and used directly. Commercially available reagents were used without further purification. Reactions were monitored by thin layer chromatography (TLC) using Silicycle precoated silica gel plates. Flash column chromatography was performed over Silicycle silica gel (230-400 mesh). ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian 400 MHz spectrometer, a Varian 500 MHz Unity plus spectrometer, and a Varian 600 MHz Unity plus spectrometer, using residue solvent peaks as internal standards ($CDCl_3$, ^{1}H: 7.26 ppm; ^{13}C: 77.00 ppm). Infrared spectra were recorded with a Perkin Elmer FT-IR spectrum 2000 spectrometer and are reported in reciprocal centimeter (cm^{-1}). Mass spectra were recorded with Waters micromass ZQ detector using electrospray method.

General Procedure A: preparation of *cis*-enediyne S46-1



PBr_3 (41.7 mL, 412.5 mmol) was added dropwise to a mixture of DMF (35.4 mL, 458.4 mmol) and chloroform (240 mL) at 0 ℃, and the mixture was stirred for 1h before the addition of cyclohexanone (15.0 g, 180 mmol) at 0 ℃. The resulting solution was allowed to

warm up to room temperature and stirred overnight. After the reaction finished, the reaction mixture was poured into 1 L ice/water, neutralized with solid $NaHCO_3$, and extracted with DCM. The combined organic extract was washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by chromatography on silica gel to afford the product **A**.

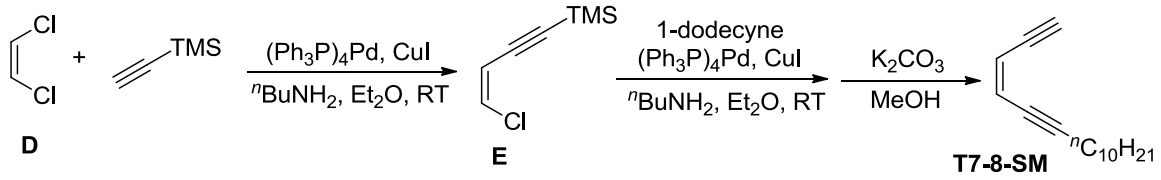
CuI (81 mL, 5%), $PdCl_2(PPh_3)_2$ (298 mg, 5%) was added to a triethylamine solution (10 mL) of **A** (1.6 g, 8.5 mmol) at RT, and the mixture was stirred for 5 min before the addition of 1-hexyne (1.47 mL, 12.7 mmol) at rt. The resulting solution was stirred overnight. After the reaction finished, the reaction mixture was quenched with saturated $NaHCO_3$ solution, extracted with EtOAc. The combined organic extract was washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by chromatography on silica gel to afford the product **B**.

CBr_4 (3.45g) was added to a DCM solution (20 mL) of PPh_3 (5.5 g) at 0 ℃. After 2 min, **B** (980 mg) was added the above solution. After 2h at 0 ℃, 100 mL hexanes was added to give precipitate. The solid was filtered off and the solution was concentrated under reduced pressure. The residue was purified by chromatography on silica gel to afford the product **C**.

At -78 ℃, LDA (12.5 mmol) was added dropwise to a THF solution (5.0 mL) of **C** (5 mmol). The resulting solution was stirred at the same temperature for half an hour. The reaction mixture was quenched with saturated NH_4Cl solution, extracted with EtOAc. The combined organic extract was washed with brine, dried over anhydrous $MgSO_4$, and concentrated

under reduced pressure. The residue was purified by chromatography on silica gel to afford the product **S46-1**.

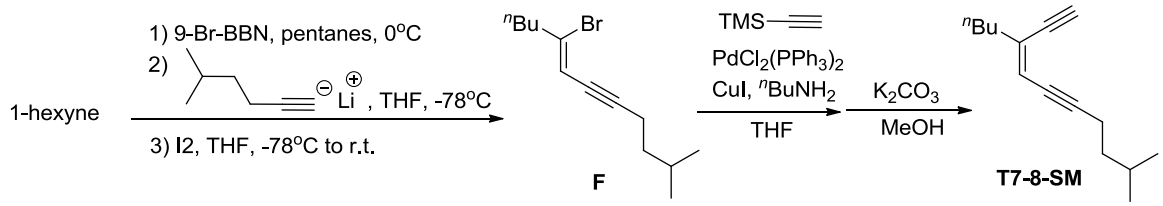
General Procedure B: preparation of *cis*-enediyne T7-8-SM



^{n}BuNH$_2$ (8.8 mL, 2 equiv), (Z)-1,2-dichloroethylene **D** (7 mL, 84 mmol), and trimethylsilylacetylene (6.26 mL, 44 mmol) were added to a Et_2O suspension (200 mL) of $Pd(PPh_3)_4$ (1.5 g, 3%) and CuI (240 mg, 3%). The reaction mixture was stirred at RT overnight before it was concentrated under reduced pressure. The residue was purified by chromatography on silica gel to afford the product **E**.

^{n}BuNH$_2$ (0.26 mL, 2 equiv), **E** (205 mg, 1.3 mmol), and 1-dodecyne (0.28 mL, 1.3 mmol) were added to a Et_2O suspension (2.6 mL) of $Pd(PPh_3)_4$ (82.4 mg, 3%) and CuI (13 mg, 3%). The reaction mixture was stirred at RT overnight before it was concentrated under reduced pressure. The residue was added to a MeOH suspension (3.0 mL) of K_2CO_3 (360 mg). After 10 min, the reaction mixture was concentrated under reduced pressure and purified by chromatography on silica gel to afford the product **T7-8-SM**.

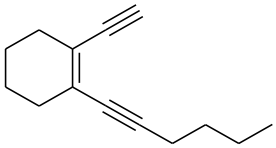
General Procedure C: preparation of *cis*-enediyne T7-9-SM



F was synthesized according to literature procedure (Martín, R.; Rivero, M. R.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2006**, *45*, 7079.).

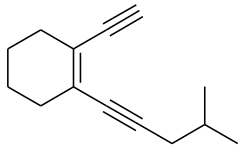
$^{n}BuNH_2$ (0.26 mL, 2 equiv), **F** (260 mg, 1.3 mmol), and trimethylsilylacetylene (0.28 mL, 1.3 mmol) were added to a THF suspension (5 mL) of $PdCl_2(PPh_3)_2$ (27.4 mg, 3%) and CuI (13 mg, 3%). The reaction mixture was stirred at 60 ℃ for 6 hours before it was concentrated under reduced pressure. The residue was added to a MeOH suspension (3.0 mL) of K_2CO_3 (360 mg). After 10 min, the reaction mixture was concentrated under reduced pressure and purified by chromatography on silica gel to afford the product **T7-9-SM**.

1-Ethynyl-2-hex-1-ynyl-cyclohexene (S46-1)



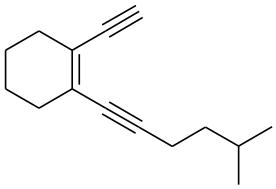
This compound was prepared following the general procedure A. ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.15 (s, 1H), 2.38 (t, J = 6.9 Hz, 2H), 2.27 – 2.14 (m, 4H), 1.60 (tt, J = 3.9, 2.3 Hz, 4H), 1.57 – 1.50 (m, 2H), 1.50 – 1.43 (m, 2H), 0.91 (t, J = 7.3 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 128.60, 123.31, 94.87, 84.59, 81.04, 79.83, 30.82, 30.47, 29.75, 21.82, 21.78, 21.76, 19.27, 13.58; IR (neat): 2956, 2872, 2212, 1651, 1451, 1233; GCMS-EI *m*/*z* 186 (M^+).

1-Ethynyl-2-(4-methyl-pent-1-ynyl)-cyclohexene (S47-1)



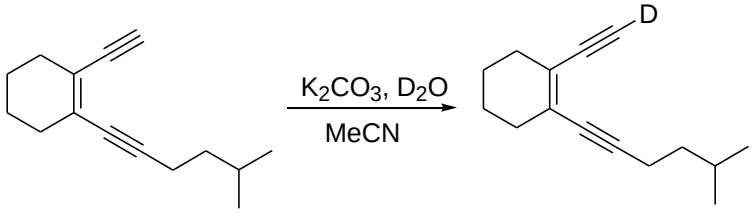
This compound was prepared following the general procedure A. ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.16 (s, 1H), 2.27 (d, *J* = 6.4 Hz, 2H), 2.25 – 2.16 (m, 4H), 1.85 (dp, *J* = 13.2, 6.6 Hz, 1H), 1.61 (ddd, *J* = 6.4, 3.8, 2.5 Hz, 4H), 1.01 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 128.68, 123.26, 93.83, 84.69, 81.92, 79.87, 30.51, 29.76, 28.77, 28.18, 21.96, 21.79, 21.76; IR (neat): 2956, 2934, 2870, 2212, 1717, 1464, 1168; GCMS-EI *m*/*z* 186 (M^+).

1-Ethynyl-2-(5-methyl-hex-1-ynyl)-cyclohexene (T7-2-SM)



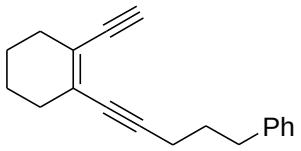
This compound was prepared following the general procedure A. ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.15 (s, 1H), 2.39 (t, *J* = 7.3 Hz, 2H), 2.26 – 2.11 (m, 4H), 1.77 (m, 1H), 1.60 (t, *J* = 3.4 Hz, 4H), 1.45 (q, *J* = 7.2 Hz, 2H), 0.90 (d, *J* = 6.7, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 128.63, 123.32, 94.94, 84.60, 80.95, 79.83, 37.66, 30.47, 29.76, 27.05, 22.17, 21.79, 21.77, 17.63; IR (neat): 2956, 2932, 2219, 2091, 1644; GCMS-EI *m*/*z* 200 (M^+).

1-Ethynyl-2-(5-methyl-hex-1-ynyl)-cyclohexene (T7-2-SM-d_1)



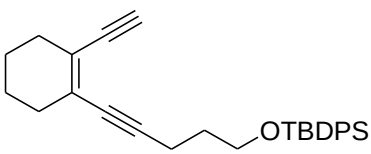
T7-2-SM (200mg, 1mmol) and K_2CO_3 (252mg, 1.5 mmol) were added to dry MeCN (4 mL). The mixture was allowed to stir under N_2 at room temperature for half an hour before D_2O (1.8 mL, 100 equiv) was added. After 1 hour, the reaction mixture was concentrated under reduced pressure and purified by chromatography on silica gel to afford the product **T7-2-SM-*d*$_1$** in 85% yield. ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.39 (t, *J* = 7.3 Hz, 2H), 2.27 – 2.18 (m, 4H), 1.77 (dp, *J* = 13.4, 6.7 Hz, 1H), 1.60 (ddd, *J* = 6.4, 3.8, 2.6 Hz, 4H), 1.45 (q, *J* = 7.2 Hz, 2H), 0.90 (d, *J* = 6.7 Hz, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 128.61, 123.32, 94.93, 80.95, 37.66, 30.47, 29.77, 27.05, 22.17, 21.80, 21.77, 17.63; IR (neat): 2953, 2931, 2578, 2216, 1450; GCMS-EI *m*/*z* 201 (M^+).

[5-(2-Ethynyl-cyclohex-1-enyl)-pent-4-ynyl]-benzene (T7-3-SM)



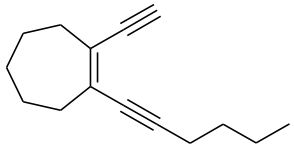
This compound was prepared following the general procedure A. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.29 (t, *J* = 7.5 Hz, 2H), 7.24 – 7.21 (m, 2H), 7.21 – 7.17 (m, 1H), 3.18 (s, 1H), 2.87 – 2.75 (m, 2H), 2.41 (t, *J* = 6.8 Hz, 2H), 2.32 – 2.13 (m, 4H), 1.96 – 1.78 (m, 2H), 1.63 (td, *J* = 3.9, 1.9 Hz, 4H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 141.77, 128.58, 128.51, 128.28, 125.79, 123.57, 94.26, 84.70, 81.71, 80.04, 34.58, 30.48, 30.37, 29.80, 21.79, 21.76, 18.99; ; IR (neat): 3026, 2933, 2860, 2214, 1722, 1496, 1453; GCMS-EI *m*/*z* 248 (M^+).

tert-Butyl-[5-(2-ethynyl-cyclohex-1-enyl)-pent-4-ynyloxy]-diphenyl-silane (T7-4-SM)



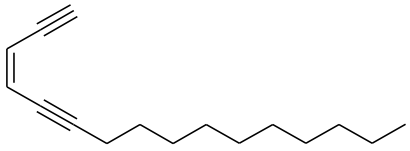
This compound was prepared following the general procedure A. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.68 (dt, *J* = 6.7, 1.5 Hz, 4H), 7.49 – 7.33 (m, 6H), 3.80 (t, *J* = 6.1 Hz, 2H), 3.02 (s, 1H), 2.55 (t, *J* = 7.0 Hz, 2H), 2.22 (dt, *J* = 7.8, 4.0 Hz, 2H), 2.17 – 2.14 (m, 2H), 1.90 – 1.70 (m, 2H), 1.61 (p, *J* = 3.1 Hz, 4H), 1.06 (s, 9H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 135.56, 133.91, 129.51, 128.46, 127.60, 127.57, 123.41, 94.29, 84.52, 81.22, 79.97, 62.48, 31.75, 30.43, 29.76, 26.83, 21.79, 21.76, 19.22, 16.19; IR (neat): 3284, 3071, 2931, 2858, 2219, 2094, 1428, 1111; GCMS-EI *m*/*z* 426 (M^+).

1-Ethynyl-2-hex-1-ynyl-cycloheptene (T7-6-SM)



This compound was prepared following the general procedure A. ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.28 (s, 1H), 2.52 – 2.17 (m, 6H), 1.79 – 1.67 (m, 2H), 1.61 – 1.50 (m, 6H), 1.50 – 1.41 (m, 2H), 0.91 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 134.57, 128.91, 96.06, 86.20, 82.78, 80.73, 35.35, 34.47, 32.15, 30.84, 26.06, 25.90, 21.88, 19.44, 13.61; IR (neat): 2924, 2087, 1643, 1217, 1095; GCMS-EI *m*/*z* 200 (M^+).

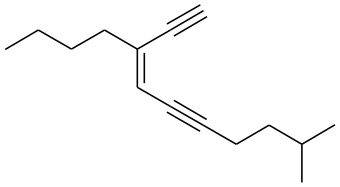
Hexadec-3-ene-1,5-diyne (T7-8-SM)



This compound was prepared following the general procedure B. ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.90 (dtd, *J* = 10.8, 2.2, 0.9 Hz, 1H), 5.72 (dd, *J* = 10.9, 2.4 Hz, 1H), 3.29 (dd, *J* = 2.4, 0.9

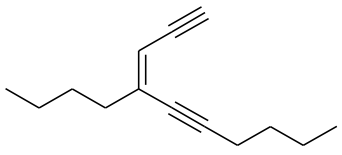
Hz, 1H), 2.40 (td, *J* = 7.1, 2.3 Hz, 2H), 1.64 – 1.51 (m, 2H), 1.43 (tt, *J* = 9.0, 6.1 Hz, 2H), 1.33 – 1.20 (m, 12H), 0.88 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 122.49, 116.91, 99.72, 83.65, 80.94, 77.82, 31.90, 29.59, 29.53, 29.32, 29.14, 28.81, 28.57, 22.68, 19.77, 14.11; IR (neat): 3289, 3036, 2926, 2855, 2216, 2101; GCMS-EI *m*/*z* 216 (M^+).

5-Ethynyl-11-methyl-dodec-5-en-7-yne (T7-9-SM)



This compound was prepared following the general procedure C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.71 (d, *J* = 1.1 Hz, 1H), 3.28 (s, 1H), 2.39 (td, *J* = 7.4, 2.2 Hz, 2H), 2.18 (td, *J* = 7.6, 1.2 Hz, 2H), 1.76 (dp, *J* = 13.4, 6.7 Hz, 1H), 1.54 – 1.48 (m, 2H), 1.45 (q, *J* = 7.3 Hz, 2H), 1.32 (h, *J* = 7.3 Hz, 2H), 0.90 (m, 9H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 132.89, 116.91, 96.32, 83.08, 82.60, 78.21, 37.61, 36.36, 30.28, 27.09, 22.16, 21.97, 17.73, 13.81; IR (neat): 3315, 2957, 2928, 2870, 2214, 1645, 1467; GCMS-EI *m*/*z* 202 (M^+).

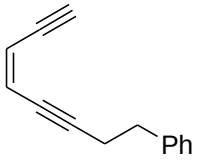
7-Prop-2-ynylidene-undec-5-yne (T7-10-SM)



This compound was prepared following the general procedure C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.55 (s, 1H), 3.14 (s, 1H), 2.42 (t, *J* = 7.0 Hz, 2H), 2.17 (t, *J* = 7.6 Hz, 2H), 1.51 (m, 6H), 1.32 (m, 2H), 0.91 (m, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.73, 111.64, 98.75, 81.88,

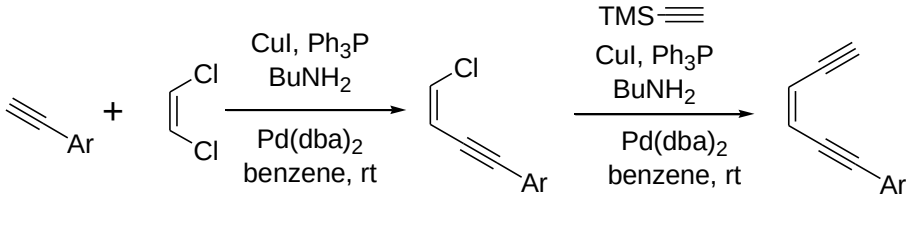
80.79, 79.28, 37.15, 30.72, 30.27, 21.98, 21.84, 19.38, 13.82, 13.57; IR (neat): 3315, 2958, 2933, 2873, 2216, 1647, 1466; GCMS-EI *m*/*z* 188 (M^+).

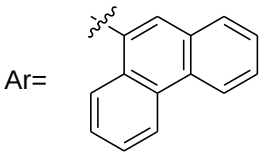
Oct-5-ene-3,7-diynyl-benzene (T8-1-SM)



This compound was prepared following the general procedure B. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.33 – 7.27 (m, 4H), 7.25 – 7.21 (m, 1H), 6.11 – 5.84 (m, 1H), 5.75 (dd, *J* = 10.9, 2.4 Hz, 1H), 3.30 (d, *J* = 2.3 Hz, 1H), 2.91 (t, *J* = 7.6 Hz, 2H), 2.72 (td, *J* = 7.5, 2.2 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 140.46, 128.47, 128.36, 126.29, 122.17, 117.23, 98.53, 83.88, 80.84, 78.39, 34.95, 21.93; IR (neat): 3060, 3026, 2925, 2857, 2211, 1453, 1428; GCMS-EI *m*/*z* 180 (M^+).

Z-1-(9'-Phenanthyl)hexa-3-ene-1,5-diyne (T8-3-SM)



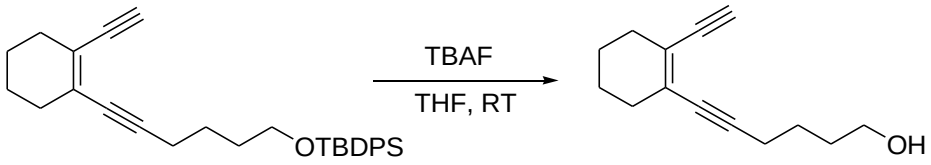


9-Ethynylphenanthrene (5.00 g, 24.72 mmol), cis-1,2-dichloroethylene (5.60 mL, 74.17 mmol), copper(I) iodide (0.48 g, 2.52 mmol), triphenylphosphine (0.77 g, 2.94 mmol), bis(dibenzylideneacetone)palladium(0) (0.44 g, 0.77 mmol), n-butylamine (6.30 mL, 63.74

mmol) and benzene (26 mL) were sequentially added to a 100 mL round bottom flask and stirred at room temperature for 24 h under nitrogen. The reaction mixture was then poured into saturated aqueous ammonium chloride and extracted twice with diethyl ether. The organic layers were combined and washed twice with saturated aqueous ammonium chloride, dried over $MgSO_4$, and concentrated in vacuo to give a very dark brown solid which was subsequently purified by flash column chromatography using silica gel (0.25% CH_2Cl_2/hexanes) to afford the Z-4-chloro-1-(9'-phenanthyl)but-3-ene-1-yne (4.22 g, 65%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.70-8.65 (m, 2H), 8.59-8.57 (m, 1H), 8.06 (s, 1H), 7.87 (d, J = 8.0 Hz, 1H), 7.72-7.66 (m, 3H), 7.61 (t, J = 7.6 Hz, 1H), 6.56 (d, J = 7.2 Hz, 1H), 6.28 (d, J = 7.2 Hz, 1H). To the above compound (3.10 g, 11.80 mmol), ethynyltrimethylsilane (2.50 mL, 17.69 mmol), copper(I) iodide (0.25 g, 1.31 mmol), triphenylphosphine (0.55 g, 2.09 mmol), bis(dibenzylideneacetone) palladium(0) (0.35 g, 0.61 mmol), n-butylamine (3.73 mL, 37.74 mmol) and benzene (12 mL) were sequentially added to a 50 mL round bottom flask and stirred at room temperature for 24 h under nitrogen. The reaction mixture was then poured into saturated aqueous ammonium chloride and extracted twice with diethyl ether. The organic layers were combined and washed twice with saturated aqueous ammonium chloride, dried over $MgSO_4$, and concentrated in vacuo to give a very dark red liquid which was subsequently purified by flash column chromatography using silica gel (0.35% CH_2Cl_2/hexanes) to afford the Z-1-trimethylsilyl-6-(9'-phenanthyl)hexa-3-ene-1,5-diyne (3.42 g, 89%) as a red liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.70 (d, J = 8.0 Hz, 1H), 8.67 (d, J = 8.4 Hz, 1H), 8.61 (d, J = 8.0 Hz, 1H), 8.08 (s, 1H), 7.86 (d, J = 7.6 Hz, 1H), 7.72-7.67 (m, 3H), 7.62 (t, J = 7.6 Hz, 1H), 6.26 (d, J = 11.2 Hz, 1H), 6.02 (d, J = 11.2 Hz, 1H), 0.33 (s, 9H). To a solution of the above compound (3.00 g, 9.25 mmol) in methanol (26 mL) and diethyl ether (4.5 mL), potassium carbonate (3.00 g,

21.7 mmol) was added and stirred at room temperature for 2 h under nitrogen. The reaction mixture was then diluted with water and extracted twice with diethyl ether. The organic layers were combined and washed twice with water, dried over $MgSO_4$, and concentrated in vacuo to give the title compound (2.10 g, 90%) as a very dark red-brown solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.69-8.62 (m, 3H), 8.05 (s, 1H), 7.86 (d, J = 8.0 Hz, 1H), 7.72-7.66 (m, 3H), 7.60 (t, J = 6.8 Hz, 1H), 6.31 (d, J = 10.8 Hz, 1H), 5.97 (dd, J = 10.8, 2.4 Hz, 1H), 3.55 (d, J = 2.4 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 132.50, 131.11, 130.88, 130.53, 130.03, 128.70, 127.71, 127.19, 127.11, 127.00, 126.95, 122.69, 122.62, 121.80, 119.30, 118.43, 95.85, 91.10, 85.29, 81.40; IR (neat): 3057, 2187, 2091, 1451, 724; EI m/z 252 (M+).

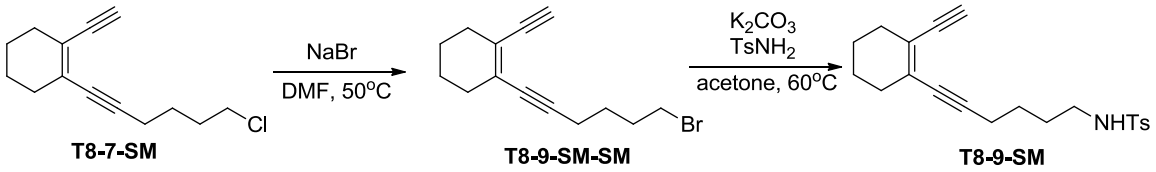
6-(2-Ethynyl-cyclohex-1-enyl)-hex-5-yn-1-ol (T8-5-SM)



Compound **T7-4-SM** was prepared following the general procedure A. The corresponding free alcohol **T8-5-SM** was prepared according to the following procedure: to a solution of **T7-4-SM** (440 mg, 1mmol) in THF (5 mL) was added *tert*-butylammonium fluoride (1.0 M in THF, 1.1mL) at RT. After the reaction finished, the reaction mixture was quenched with saturated $NaHCO_3$ solution, extracted with EtOAc. The combined organic extract was washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by chromatography on silica gel to afford the product **T8-5-SM** in 80% yield. ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.65 (t, *J* = 6.4 Hz, 2H), 3.17 (s, 1H), 2.41 (t, *J* = 6.8 Hz, 2H), 2.27 – 2.08 (m, 4H), 1.72 (tt, *J* = 8.6, 6.1 Hz, 2H), 1.67 – 1.54 (m, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 128.38, 123.53, 94.27, 84.58, 81.42, 80.00, 62.28, 31.65, 30.36,

29.71, 24.88, 21.70, 21.68, 19.28; IR (neat): 3393, 2935, 2279, 2091, 1642, 1241; ESI+ calculated for $[C_{14}H_{18}NaO]^+$: 225.13, found 225.15.

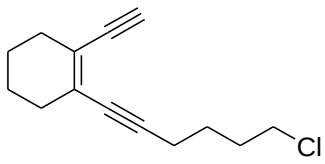
N-[6-(2-Ethynyl-cyclohex-1-enyl)-hex-5-ynyl]-4-methyl-benzenesulfonamide (T8-9-SM)



To a stirred solution of sodium bromide (0.51g) in DMF (5 mL) at RT was added **T8-7-SM** (220 mg). The mixture was heated at 60 ℃ for 3 days before the reaction mixture was quenched with water, extracted with EtOAc. The combined organic extract was washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by chromatography on silica gel to afford the product **T8-9-SM-SM**.

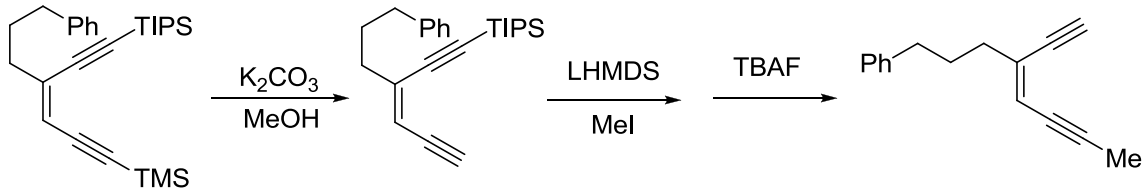
To a stirred solution of **T8-9-SM-SM** (0.21g) in acetone (1 mL) at RT was added K_2CO_3 (207 mg), and $TsNH_2$ (123 mg). The mixture was heated at 60 ℃ for 24 hours before it was concentrated under reduced pressure. The residue was purified by chromatography on silica gel to afford the product **T8-9-SM**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.1 Hz, 2H), 7.31 (d, *J* = 8.1 Hz, 2H), 4.43 (t, *J* = 6.3 Hz, 1H), 3.16 (s, 1H), 2.97 (q, *J* = 6.7 Hz, 2H), 2.43 (s, 3H), 2.36 (t, *J* = 6.7 Hz, 2H), 2.19 (m, 4H), 1.78 – 1.49 (m, 8H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.35, 136.94, 129.68, 128.27, 127.08, 123.81, 93.63, 84.64, 81.78, 80.16, 42.71, 30.36, 29.79, 28.53, 25.47, 21.74, 21.72, 21.50, 19.04; IR (neat): 2930, 2837, 2861, 2217, 2088, 1433, 1158; ESI+ calculated for $[C_{21}H_{25}NnaO_2S]^+$: 378.15, found 378.16.

1-(6-Chloro-hex-1-ynyl)-2-ethynyl-cyclohexene (T8-7-SM)



This compound was prepared following the general procedure A. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.58 (t, *J* = 6.6 Hz, 2H), 3.18 (s, 1H), 2.44 (t, *J* = 6.8 Hz, 2H), 2.25 – 2.16 (m, 4H), 2.03 – 1.91 (m, 2H), 1.79 – 1.67 (m, 2H), 1.61 (ddd, *J* = 6.4, 3.9, 2.5 Hz, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 128.35, 123.83, 93.61, 84.60, 81.82, 80.06, 44.59, 31.45, 30.40, 29.80, 25.85, 21.77, 21.75, 18.86; IR (neat): 2933, 2861, 2223, 2090, 1642, 1434; GCMS-EI *m*/*z* 220 (M^+).

(Z)-(4-ethynyloct-4-en-6-ynyl)benzene (1q)

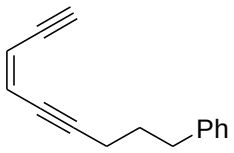


T8-6-SM-SM-SM **T8-6-SM-SM** **T8-6-SM**

Compound **T8-6-SM-SM-SM** was prepared following the general procedure C. **T8-6-SM-SM-SM** (166 mg) was added to a MeOH suspension (2.0 mL) of K_2CO_3 (120 mg). After 10 min, the reaction mixture was concentrated under reduced pressure and purified by chromatography on silica gel to afford the product **T8-6-SM-SM** (50 mg), which was then dissolved in THF (1.0 mL) and cooled to -78 ℃ followed by the addition of LHMDS (0.6 mL, 1M), warmed to 0 ℃ and stirred for another 30 min, cooled back to -78 ℃ followed by the addition of MeI (56uL, 6 equiv.) and slowly warmed to room temperature for 12h. The reaction mixture was quenched with saturated NH_4Cl solution, extracted with EtOAc. The combined organic extract was washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was dissolved in THF (2 mL), to which

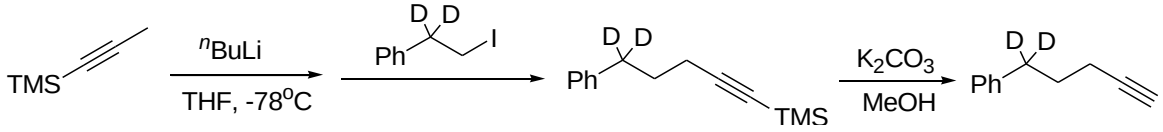
was added *tert*-butylammonium fluoride (1.0 M in THF, 0.18 mL) at RT. After the reaction finished, the reaction mixture was quenched with saturated $NaHCO_3$ solution, extracted with EtOAc. The combined organic extract was washed with brine, dried over anhydrous MgSO4, and concentrated under reduced pressure. The residue was purified by chromatography on silica gel to afford the product **T8-6-SM**. 1H NMR (600 MHz, $CDCl_3$) δ 7.29 (t, J = 7.6 Hz, 2H), 7.19 (m, 3H), 5.82 – 5.49 (m, 1H), 3.33 (s, 1H), 2.70 – 2.53 (m, 2H), 2.23 (t, J = 7.4 Hz, 2H), 2.05 (d, J = 2.3 Hz, 3H), 1.89 (p, J = 7.6 Hz, 2H); 13C NMR (151 MHz, CDCl3) δ 141.87, 132.31, 128.41, 128.29, 125.78, 117.29, 91.92, 83.39, 82.29, 77.34, 36.03, 34.87, 29.63, 4.70; IR (neat): 3085, 3026, 2926, 2217, 1715; GCMS-EI *m/z* 208 (M+).

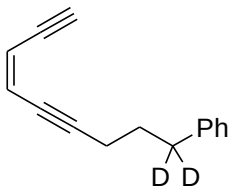
Non-6-ene-4,8-diynyl-benzene (S53c-SM)



This compound was prepared following the general procedure B. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.29 (t, *J* = 7.6 Hz, 2H), 7.24 – 7.15 (m, 3H), 5.93 (dt, *J* = 11.0, 2.3 Hz, 1H), 5.76 (dd, *J* = 10.9, 2.4 Hz, 1H), 3.31 (d, *J* = 2.3 Hz, 1H), 2.79 (t, *J* = 7.6 Hz, 2H), 2.43 (td, *J* = 6.9, 2.2 Hz, 2H), 1.89 (p, *J* = 7.1 Hz, 2H); ^{13}C NMR (151 MHz, $cdcl_3$) δ 141.57, 128.57, 128.33, 125.88, 122.36, 117.22, 98.95, 83.83, 81.00, 78.43, 34.60, 30.13, 19.13; IR (neat): 3283, 3061, 3026, 2928, 2858, 2210, 1496, 747;GCMS-EI *m*/*z* 194 (M^+).

Non-6-ene-4,8-diynyl-1,1-d_2-benzene (S53c-SM-d_2)





S53c-SM-d_2

(2-iodo-1,1-*d*2-ethyl)benzene (>98% deuterium) was prepared according to literature procedure (Ye, L.; Wang, Y.; Aue, D. H.; Zhang, L. *J. Am. Chem. Soc.* **2012**, *134*, 31.).

To a flame dried 100mL round bottomed flask, trimethyl(pro-1-ynyl)silane (0.9 mL, 6 mmol) was added followed by THF (30 mL). The flask was cooled to -78 ℃ and ^{n}BuLi (3.8 mL, 1.6 M solution in hexanes) was added dropwise. The reaction mixture was held at -78 ℃ for 1 hour before (2-iodo-1,1-*d*2-ethyl)benzene was added slowly. The resulting yellow solution was stirred at room temperature for 22h before it was quenched with saturated NH_4Cl solution, extracted with EtOAc. The combined organic extract was washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was added to a MeOH suspension (10 mL) of K_2CO_3 (1500 mg). After 10 min, the reaction mixture was concentrated under reduced pressure and purified by chromatography on silica gel to afford pent-4-ynyl-1,1-d_2-benzene in 40% yield.

Compound **S53c-SM-d_2** was prepared following the general procedure B. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (t, *J* = 7.6 Hz, 2H), 7.25 – 7.14 (m, 3H), 6.00 – 5.87 (m, 1H), 5.76 (dd, *J* = 10.9, 2.4 Hz, 1H), 3.31 (d, *J* = 2.4 Hz, 1H), 6.13 – 5.86 (m, 1H), 2.43 (td, *J* = 6.9, 2.3 Hz, 2H), 1.88 (t, *J* = 7.0 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 141.49, 128.55, 128.32, 125.88, 122.35, 117.21, 98.96, 83.83, 81.00, 78.43, 29.96, 19.08; IR (neat): 3286, 3025, 2930, 2209, 1731, 1495, 737; GCMS-EI *m*/*z* 196 (M^+).

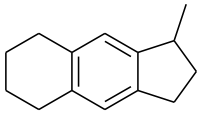
General procedure D: gold-catalyzed cycloisomerization of *cis*-enediynes: intramolecular C-H/O-H/N-H insertion

2,6-dibromopyridine *N*-oxide or lutidine *N*-oxide (0.15 mmol), BrettPhosAuNTf$_2$ (15.3 mg, 0.015 mmol) or Mor-DalPhosAuNTf$_2$ (14.4 mg, 0.015 mmol), and 4Å Molecular Sieves (75 mg) were added in this order to a solution of *cis*-enediyne (0.30 mmol) in DCE (6.0 mL) at room temperature. The reaction mixture was stirred at 60 ℃ and the progress of the reaction was monitored by TLC. Upon completion, the mixture was concentrated and the residue was purified by chromatography on silica gel (eluent: hexanes/ethyl acetate) to afford the desired product.

General procedure E: gold-catalyzed cycloisomerization of *cis*-enediynes: intermolecular nucleophilic addition and pericyclic reaction

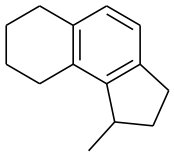
lutidine *N*-oxide (0.15 mmol), nucleophiles (5 or 10 equiv) and BrettPhosAuNTf$_2$ (15.3 mg, 0.015 mmol) were added in this order to a solution of *cis*-enediyne (0.30 mmol) in DCE (6.0 mL) at room temperature. The reaction mixture was stirred at 60 ℃ and the progress of the reaction was monitored by TLC. Upon completion, the mixture was concentrated and the residue was purified by chromatography on silica gel (eluent: hexanes/ethyl acetate) to afford the desired product.

1-Methyl-2,3,5,6,7,8-hexahydro-1H-cyclopenta[b]naphthalene (S46-3)



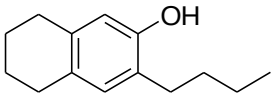
This compound was prepared in 83% isolated yield using lutidine *N*-oxide as the additive and Mor-DalPhosAuNTf$_2$ as catalyst according to the general procedure D. 1H NMR (500 MHz, CDCl3) δ 7.00 (s, 1H), 6.96 (s, 1H), 3.18 (h, J = 7.3 Hz, 1H), 2.98 – 2.75 (m, 6H), 2.42 – 2.26 (m, 1H), 1.85 (p, J = 3.2 Hz, 4H), 1.63 (dq, J = 12.2, 8.6 Hz, 1H), 1.33 (d, J = 6.9 Hz, 3H); 13C NMR (126 MHz, CDCl3) δ 146.18, 141.24, 134.85, 134.80, 124.82, 123.65, 39.03, 35.07, 30.99, 29.60, 29.52, 23.48, 23.46, 19.91; IR (neat): 3000, 2928, 2857, 2839, 1739, 1485, 860; GCMS-EI m/z 186 (M+).

1-Methyl-2,3,6,7,8,9-hexahydro-1H-cyclopenta[a]naphthalene (T6-3)



This compound was prepared using lutidine N-oxide as the additive and $Ph_3PAuNTf_2$ as catalyst according to the general procedure D. ^{1}H NMR (600 MHz, CDCl3) δ 7.02 (d, J = 7.5 Hz, 1H), 6.92 (d, J = 7.6 Hz, 1H), 3.35 – 3.24 (m, 1H), 3.10 – 3.00 (m, 1H), 2.91 – 2.71 (m, 6H), 2.25 (ddt, J = 12.4, 10.3, 8.5 Hz, 1H), 2.00 – 1.71 (m, 5H), 1.19 (d, J = 7.0 Hz, 3H); ^{13}C NMR (151 MHz, CDCl3) δ 147.23, 140.16, 134.81, 132.74, 127.54, 121.62, 37.93, 33.98, 30.47, 29.54, 26.30, 23.26, 23.22, 19.01; IR (neat): 3066, 3002, 2928, 2858, 1437, 801; GCMS-EI m/z 186 (M+).

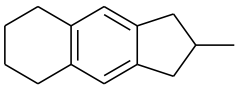
3-Butyl-5,6,7,8-tetrahydro-naphthalen-2-ol (T6-4)



This compound was prepared using lutidine N-oxide as the additive and Mor-DalPhosAuNTf$_2$ as catalyst in wet DCE according to the general procedure D. ^{1}H NMR (600

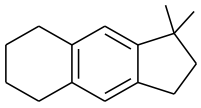
MHz, CDCl3) δ 6.80 (s, 1H), 6.48 (s, 1H), 4.47 (s, 1H), 2.67 (m, 4H), 2.58 – 2.47 (m, 2H), 1.76 (m, 4H), 1.61 – 1.53 (m, 2H), 1.39 (h, J = 7.4 Hz, 2H), 0.94 (t, J = 7.4 Hz, 3H); ^{13}C NMR (151 MHz, CDCl3) δ 151.06, 135.64, 130.55, 129.08, 125.97, 115.17, 32.25, 29.39, 29.03, 28.53, 23.49, 23.21, 22.68, 13.99; IR (neat): 2926, 2856, 1515, 1423, 1095, 859; GCMS-EI m/z 204 (M+).

2-Methyl-2,3,5,6,7,8-hexahydro-1H-cyclopenta[b]naphthalene (S47-3)



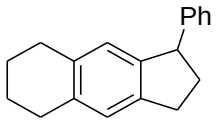
This compound was prepared in 60% isolated yield using lutidine N-oxide as the additive and Mor-DalPhosAuNTf$_2$ as catalyst according to the general procedure D.^{1}H NMR (600 MHz, $CDCl_3$) δ 6.92 (s, 2H), 3.00 (dd, *J* = 14.9, 7.1 Hz, 2H), 2.80 – 2.68 (m, 4H), 2.51 (m, 3H), 1.92 – 1.74 (m, 4H), 1.15 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 141.11, 134.73, 124.91, 40.75, 34.70, 29.50, 23.46, 20.75; IR (neat): 3001, 2949, 2857, 1616, 1437, 832; GCMS-EI m/z 186 (M+).

1,1-Dimethyl-2,3,5,6,7,8-hexahydro-1H-cyclopenta[b]naphthalene (T7-2-P)



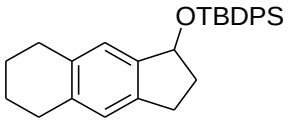
This compound was prepared in 87% isolated yield using lutidine N-oxide as the additive and BrettPhosAuNTf$_2$ as catalyst according to the general procedure D.^{1}H NMR (600 MHz, $CDCl_3$) δ 6.94 (s, 1H), 6.87 (s, 1H), 2.85 (t, *J* = 7.2 Hz, 2H), 2.82 – 2.74 (m, 4H), 1.92 (t, *J* = 7.2 Hz, 2H), 1.81 (hept, *J* = 4.8 Hz, 4H), 1.27 (s, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 150.04, 140.18, 134.99, 134.95, 124.96, 122.48, 43.56, 41.70, 29.65, 29.61, 29.52, 28.67, 23.46, 23.44; IR (neat): 3008, 2931, 2858, 1643, 1485, 733; GCMS-EI m/z 200 (M+).

1-Phenyl-2,3,5,6,7,8-hexahydro-1H-cyclopenta[b]naphthalene (T7-3-P)



This compound was prepared in 95% isolated yield using lutidine N-oxide as the additive and BrettPhosAuNTf$_2$ as catalyst according to the general procedure D. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.34 (dd, *J* = 8.3, 6.9 Hz, 2H), 7.27 – 7.22 (m, 3H), 7.04 (s, 1H), 6.70 (s, 1H), 4.29 (t, *J* = 8.3 Hz, 1H), 3.01 (ddd, *J* = 15.6, 8.5, 3.5 Hz, 1H), 2.91 (dt, *J* = 15.9, 8.4 Hz, 1H), 2.87 – 2.76 (m, 2H), 2.69 (t, *J* = 6.2 Hz, 2H), 2.57 (dtd, *J* = 12.6, 7.8, 3.6 Hz, 1H), 2.07 (dq, *J* = 12.6, 8.7 Hz, 1H), 1.84 – 1.73 (m, 4H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 145.60, 144.31, 141.62, 135.38, 135.18, 128.40, 128.12, 126.18, 125.26, 124.78, 51.37, 36.79, 31.41, 29.57, 29.49, 23.42, 23.41; IR (neat): 3024, 3000, 2838, 2928, 1437, 783; GCMS-EI m/z 248 (M+).

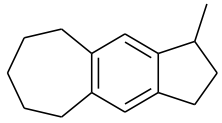
tert-Butyl-(2,3,5,6,7,8-hexahydro-1H-cyclopenta[b]naphthalen-1-yloxy)-diphenyl-silane (T7-4-P)



This compound was prepared in 84% isolated yield using lutidine N-oxide as the additive and BrettPhosAuNTf$_2$ as catalyst according to the general procedure D. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.76 (m, 4H), 7.55 – 7.36 (m, 6H), 6.91 (s, 1H), 6.88 (s, 1H), 5.27 (t, *J* = 6.6 Hz, 1H), 2.89 (ddd, *J* = 15.5, 8.6, 3.5 Hz, 1H), 2.79 – 2.68 (m, 4H), 2.59 (dt, *J* = 15.8, 8.1 Hz, 1H), 2.14 (dddd, *J* = 12.5, 7.8, 6.6, 3.5 Hz, 1H), 1.98 (dtd, *J* = 12.5, 8.4, 6.6 Hz, 1H), 1.79 (qq, *J* = 4.2, 2.2 Hz, 4H), 1.13 (s, 9H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 142.93, 140.02, 136.60, 135.97, 135.97, 135.08, 134.56, 134.35, 129.54, 129.53, 127.53, 127.51, 124.96,

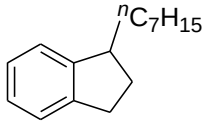
124.87, 36.73, 29.63, 29.58, 29.20, 27.05, 23.38, 23.35, 19.28; IR (neat): 3071, 3053, 2930, 2856, 1641, 1427, 1110; GCMS-EI m/z 426 (M+).

1-Methyl-1,2,3,5,6,7,8,9-octahydro-cyclohepta[f]indene (T7-6-P)



This compound was prepared in 79% isolated yield using lutidine N-oxide as the additive and Mor-DalPhosAuNTf$_2$ as catalyst according to the general procedure D. ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.99 (s, 1H), 6.95 (s, 1H), 3.16 (h, *J* = 7.2 Hz, 1H), 2.91 – 2.74 (m, 6H), 2.31 (dtd, *J* = 11.6, 7.7, 3.6 Hz, 1H), 1.85 (dddd, *J* = 16.6, 12.3, 7.6, 2.9 Hz, 1H), 1.75 – 1.57 (m, 4H), 1.30 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 146.30, 141.38, 141.35, 125.01, 123.85, 39.12, 36.76, 36.63, 34.96, 32.80, 31.05, 28.59, 28.53, 19.95; IR (neat): 3004, 2922, 2848, 1642, 1490, 828; GCMS-EI m/z 200 (M+).

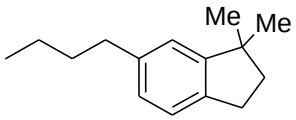
1-Heptyl-indan (T7-8-P)



This compound was prepared in 67% isolated yield using 2,6-dibromopyridine-N-oxide as the additive and BrettPhosAuNTf$_2$ as catalyst according to the general procedure D at room temperature. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.24 – 7.20 (m, 2H), 7.16 (m, 2H), 3.10 (m, 1H), 2.93 (ddd, *J* = 15.8, 8.6, 4.6 Hz, 1H), 2.84 (dt, *J* = 15.9, 8.0 Hz, 1H), 2.29 (dtd, *J* = 12.4, 7.9, 4.5 Hz, 1H), 1.85 (m, 1H), 1.68 (m, 1H), 1.46 – 1.26 (m, 11H), 0.91 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (151 MHz, $cdcl_3$) δ 147.85, 144.03, 126.10, 125.91, 124.35, 123.55, 44.88, 35.06,

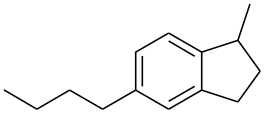
32.18, 31.91, 31.43, 29.89, 29.35, 27.72, 22.70, 14.12; IR (neat): 3067, 3020, 2955, 2925, 2854, 1644, 781; GCMS-EI m/z 216 (M+).

6-Butyl-1,1-dimethyl-indan (T7-9-P)



This compound was prepared in 67% isolated yield using lutidine N-oxide as the additive and BrettPhosAuNTf$_2$ as catalyst according to the general procedure D. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.11 (d, *J* = 7.5 Hz, 1H), 6.97 (d, *J* = 8.9 Hz, 2H), 2.86 (t, *J* = 7.2 Hz, 2H), 2.60 (t, *J* = 7.9 Hz, 2H), 1.92 (t, *J* = 7.2 Hz, 2H), 1.67 – 1.57 (m, 2H), 1.39 (h, *J* = 7.4 Hz, 2H), 1.26 (s, 6H), 0.95 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 152.58, 141.08, 139.94, 126.31, 124.10, 121.97, 43.82, 41.64, 35.76, 34.06, 29.65, 28.60, 22.54, 13.99; IR (neat): 3005, 2955, 2930, 2858, 1489, 818; GCMS-EI m/z 202 (M+).

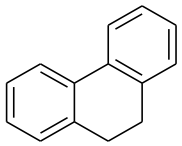
5-Butyl-1-methyl-indan (T7-10-P)



This compound was prepared in 71% isolated yield using lutidine N-oxide as the additive and Mor-DalPhosAuNTf$_2$ as catalyst according to the general procedure D. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.12 (d, *J* = 7.6 Hz, 1H), 7.07 (d, *J* = 1.6 Hz, 1H), 7.05 – 6.97 (m, 1H), 3.18 (h, *J* = 7.2 Hz, 1H), 2.96 – 2.74 (m, 2H), 2.66 – 2.56 (m, 2H), 2.33 (dtd, *J* = 12.3, 7.7, 3.8 Hz, 1H), 1.69 – 1.56 (m, 3H), 1.40 (h, *J* = 7.3 Hz, 2H), 1.31 (d, *J* = 6.9 Hz, 3H), 0.96 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 146.00, 143.95, 140.85, 126.26, 124.34, 122.81, 39.04,

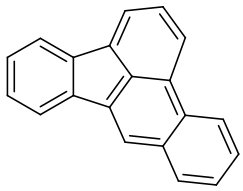
35.54, 34.94, 34.02, 31.37, 22.48, 19.94, 13.98; IR (neat): 3007, 2956, 2858, 1456, 1315, 823; GCMS-EI m/z 188 (M+).

9,10-Dihydro-phenanthrene (T8-1-P)



This compound was prepared in 80% isolated yield using 2,6-dibromopyridine-N-oxide as the additive and BrettPhosAuNTf$_2$ as catalyst according to the general procedure D. The spetra data matched the literature's data. [4] ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.78 (d, *J* = 7.7 Hz, 2H), 7.33 (td, *J* = 7.7, 6.6, 3.1 Hz, 2H), 7.26 (dd, *J* = 5.3, 2.6 Hz, 4H), 2.90 (s, 4H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 137.37, 134.47, 128.10, 127.36, 126.93, 123.68, 29.04; IR (neat): 3066, 3017, 2936, 2891, 2834, 1485, 745; GCMS-EI m/z 180 (M+).

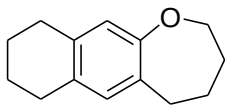
benzo[e]acephenanthrylene (T8-3-P)



This compound was prepared in 43% isolated yield using lutidine N-oxide as the additive and BrettPhosAuNTf$_2$ as catalyst according to the general procedure D at 80 ℃. The reaction was done in dry DCE at 80ºC in 24 hours. The spetra data matched the literature's data. [5] ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.67 (d, *J* = 8.0 Hz, 1H), 8.47 (d, *J* = 8.1 Hz, 1H), 8.24 (s, 1H), 8.10 – 8.05 (m, 1H), 8.04 – 7.99 (m, 2H), 7.98 – 7.91 (m, 1H), 7.78 (dd, *J* = 8.1, 7.2 Hz, 1H), 7.73 – 7.67 (m, 1H), 7.67 – 7.61 (m, 1H), 7.47 – 7.39 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 140.70, 138.54, 137.04, 135.12, 134.04, 132.14, 130.75, 130.22, 128.22, 128.12, 127.61,

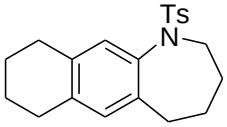
127.47, 127.05, 126.81, 123.17, 121.93, 121.67, 121.52, 121.39, 119.56; GCMS m/z-EI 252 (M+).

1,2,3,4,7,8,9,10-Octahydro-6-oxa-cyclohepta[b]naphthalene (T8-5-P)



This compound was prepared in 90% isolated yield using lutidine N-oxide as the additive and BrettPhosAuNTf$_2$ as catalyst according to the general procedure D at room temperature. ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.84 (s, 1H), 6.73 (s, 1H), 4.07 – 3.88 (m, 2H), 2.82 – 2.74 (m, 2H), 2.74 – 2.65 (m, 4H), 1.95 (m, 2H), 1.78 (p, *J* = 3.2 Hz, 4H), 1.75 – 1.69 (m, 2H); ^{13}C NMR (151 MHz, $cdcl_3$) δ 158.01, 135.89, 132.79, 131.76, 130.67, 121.18, 73.64, 34.11, 32.64, 28.94, 28.64, 26.66, 23.37, 23.15; IR (neat): 3012, 2926, 2856, 2837, 1617, 1500, 1253, 1106, 818; GCMS-EI m/z 202 (M+).

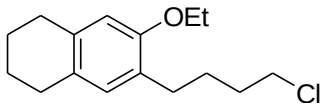
1-(Toluene-4-sulfonyl)-2,3,4,5,7,8,9,10-octahydro-1H-naphtho[2,3-b]azepine (T8-9-P)



This compound was prepared in 52% isolated yield using lutidine N-oxide as the additive and Mor-DalPhosAuNTf$_2$ as catalyst according to the general procedure D. The reaction was done in dry DCE at 60 ℃ in 24 hours. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.62 (d, *J* = 8.2 Hz, 2H), 7.25 (d, *J* = 8.1 Hz, 2H), 6.97 (s, 1H), 6.79 (s, 1H), 3.90 – 3.56 (m, 1H), 2.68 (m, 4H), 2.42 (s, 3H), 2.30 (t, *J* = 5.7 Hz, 2H), 1.80 – 1.66 (m, 6H), 1.50 (m, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 142.85, 139.24, 138.69, 137.20, 136.82, 135.60, 130.48, 129.76, 129.43, 127.16,

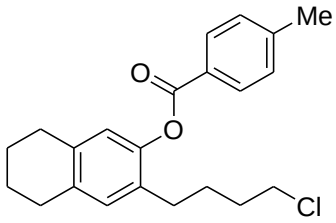
51.01, 33.77, 29.75, 28.94, 28.84, 26.17, 23.07, 22.99, 21.52; IR (neat): 3009, 2929, 2854, 1498, 1344, 1157, 1019, 814; GCMS-EI m/z 355 (M+).

6-(4-Chloro-butyl)-7-ethoxy-1,2,3,4-tetrahydro-naphthalene (T8-7-P)



This compound was prepared in 79% isolated yield using lutidine N-oxide as the additive and BrettPhosAuNTf$_2$ as catalyst according to the general procedure E at room temperature. The reaction was done in dry DCE with 10 equiv. EtOH at room temperature in 10 hours. ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.82 (s, 1H), 6.53 (s, 1H), 3.99 (q, *J* = 7.0 Hz, 2H), 3.57 (t, *J* = 6.8 Hz, 2H), 2.76 – 2.64 (m, 4H), 2.59 (t, *J* = 7.5 Hz, 2H), 1.87 – 1.68 (m, 8H), 1.41 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 154.66, 135.37, 130.37, 128.45, 127.87, 111.73, 63.48, 45.10, 32.40, 29.48, 29.04, 28.50, 27.38, 23.49, 23.30, 15.00; IR (neat): 2957, 2924, 2853, 1732, 1463, 1287, 1121; GCMS-EI m/z 266 (M+).

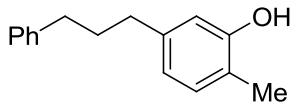
4-Methoxy-benzoic acid 3-(4-chloro-butyl)-5,6,7,8-tetrahydro-naphthalen-2-yl ester (T8-8-P)



This compound was prepared in 68% isolated yield using lutidine N-oxide as the additive and BrettPhosAuNTf$_2$ as catalyst according to the general procedure E. The reaction was done in dry DCE with 5 equiv. *p*-toluic acid at 60 ℃ in 24 hours. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, *J* = 8.2 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 6.97 (s, 1H), 6.85 (s, 1H), 3.50 (t, *J* = 6.2 Hz,

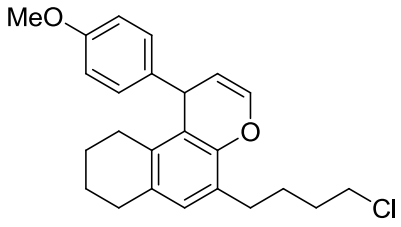
2H), 2.91 – 2.69 (m, 4H), 2.53 (t, *J* = 7.1 Hz, 2H), 2.47 (s, 3H), 1.92 – 1.68 (m, 8H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 165.41, 146.73, 144.32, 136.17, 134.83, 130.58, 130.56, 130.11, 129.31, 126.79, 122.40, 44.85, 32.18, 29.19, 29.00, 28.90, 27.42, 23.15, 22.96, 21.73; IR (neat): 2930, 2860, 1733, 1267, 1095, 748; ESI+ calculated for $[C_{22}H_{25}ClNaO_2]^+$: 379.14, found 379.14.

2-methyl-5-(3-phenylpropyl)phenol (T8-6-P)



This compound was prepared in 75% isolated yield using lutidine N-oxide as the additive and BrettPhosAuNTf2 as catalyst according to the general procedure D. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.29 (t, J = 7.6 Hz, 2H), 7.20 (t, J = 5.9 Hz, 3H), 7.03 (d, J = 7.6 Hz, 1H), 6.69 (d, J = 7.6 Hz, 1H), 6.62 (s, 1H), 4.62 (s, 1H), 2.68 – 2.63 (m, 2H), 2.58 (t, J = 7.7 Hz, 2H), 2.23 (s, 3H), 1.94 (p, J = 7.7 Hz, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 153.58, 142.27, 141.60, 130.79, 128.42, 128.27, 125.70, 120.78, 114.95, 35.36, 34.89, 32.82, 15.30; IR (neat): 3085, 3062, 2932, 2857, 1624, 1114; GCMS-EI m/z 226 (M+).

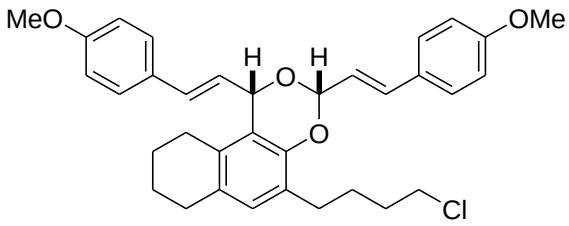
5-(4-Chloro-butyl)-1-(4-methoxy-phenyl)-7,8,9,10-tetrahydro-1H-benzo[f]chromene



This compound was prepared in 25% isolated yield using lutidine N-oxide as the additive and BrettPhosAuNTf$_2$ as catalyst according to the general procedure E. The reaction was done in

dry DCE with 5 equiv. 3-(4-Methoxy-phenyl)-propenal at 60 ℃ in 3 hours. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.12 – 6.96 (m, 2H), 6.90 – 6.75 (m, 3H), 6.56 (dd, *J* = 5.9, 0.8 Hz, 1H), 5.09 (dd, *J* = 5.9, 5.1 Hz, 1H), 4.50 (d, *J* = 5.0 Hz, 1H), 3.78 (s, 3H), 3.61 (t, *J* = 6.7 Hz, 2H), 2.67 (q, *J* = 6.4, 5.1 Hz, 4H), 2.53 (dt, *J* = 16.8, 5.7 Hz, 1H), 2.09 (ddd, *J* = 16.6, 7.6, 5.8 Hz, 1H), 1.92 – 1.85 (m, 2H), 1.83 – 1.75 (m, 2H), 1.74 – 1.52 (m, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 157.84, 147.52, 138.88, 138.32, 133.79, 131.70, 129.08, 128.57, 126.47, 121.12, 113.96, 106.64, 55.18, 45.04, 37.21, 32.40, 29.52, 29.11, 27.40, 25.82, 23.05, 22.64; IR (neat): 3059, 2996, 2929, 2858, 2835, 1508, 1246, 1036, 829; GCMS-EI m/z 382 (M+).

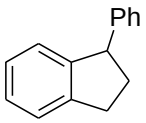
5-(4-Chloro-butyl)-1,3-bis-[2-(4-methoxy-phenyl)-vinyl]-7,8,9,10-tetrahydro-1H-naphtho[2,1-d][1,3]dioxine



This compound was prepared in 68% isolated yield using lutidine N-oxide as the additive and $BrettPhosAuNTf_2$ as catalyst according to the general procedure E. The reaction was done in dry DCE with 5 equiv. 3-(4-Methoxy-phenyl)-propenal at 60 ℃ in 3 hours. ^{1}H NMR (600 MHz, $C_2D_4Cl_2$) δ 7.40 (dd, *J* = 8.6, 2.0 Hz, 2H), 7.36 – 7.28 (m, 2H), 6.91 – 6.77 (m, 6H), 6.73 – 6.63 (m, 1H), 6.24 (ddd, *J* = 16.1, 4.8, 1.9 Hz, 1H), 6.01 – 5.88 (m, 1H), 5.73 – 5.59 (m, 1H), 5.50 – 5.35 (m, 1H), 3.78 (s, 3H), 3.77 (s, 3H), 3.57 (td, *J* = 6.8, 1.9 Hz, 2H), 2.67 (d, *J* = 6.5 Hz, 2H), 2.60 (q, *J* = 6.7 Hz, 2H), 2.49 (ddt, *J* = 21.3, 16.6, 6.8 Hz, 2H), 1.86 – 1.68 (m, 6H), 1.62 – 1.51 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.77, 159.49, 150.08, 134.48, 133.89, 132.61, 130.08, 129.34, 129.10, 128.62, 128.25, 128.01, 127.98, 127.60, 125.69, 122.34, 121.92, 113.97, 113.90, 97.50, 76.70, 55.26, 45.04, 32.33, 29.33, 28.42,

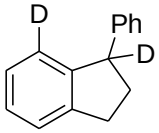
27.31, 26.95, 23.03, 22.72; IR (neat): 3028, 2997, 2930, 2857, 1512, 1129, 1034; ESI+ calculated for $[C_{34}H_{37}ClKO_4]^+$: 583.20, found 583.05.

1-Phenyl-indan (S53c-P)



This compound was prepared using lutidine N-oxide as the additive and BrettPhosAuNTf$_2$ as catalyst according to the general procedure D. The reaction was done in dry DCE at 60 ℃ in 24 hours. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (ddt, *J* = 7.9, 6.6, 1.7 Hz, 3H), 7.26 – 7.18 (m, 4H), 7.14 (t, *J* = 7.4 Hz, 1H), 6.97 (d, *J* = 7.5 Hz, 1H), 4.35 (t, *J* = 8.4 Hz, 1H), 3.07 (ddd, *J* = 15.8, 8.6, 3.7 Hz, 1H), 2.97 (dt, *J* = 16.0, 8.4 Hz, 1H), 2.68 – 2.53 (m, 1H), 2.08 (dqd, *J* = 12.6, 8.7, 0.9 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 146.82, 145.40, 144.31, 128.43, 128.09, 128.08, 126.51, 126.32, 126.27, 124.90, 124.32, 51.64, 36.54, 31.82; GCMS-EI m/z 194 (M+).

1-Phenyl-1,7-*d*$_2$-indan (S53c-P-*d*$_2$)



This compound was prepared in 64% isolated yield using lutidine N-oxide as the additive and BrettPhosAuNTf$_2$ as catalyst according to the general procedure D. The reaction was done in dry DCE at 60 ℃ in 27 hours. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.34 – 7.28 (m, 3H), 7.25 – 7.21 (m, 1H), 7.22 – 7.16 (m, 3H), 7.13 (d, *J* = 7.4 Hz, 1H), 3.06 (ddd, *J* = 15.7, 8.6, 3.6 Hz, 1H), 3.01 – 2.91 (m, 1H), 2.58 (ddd, *J* = 12.0, 7.9, 3.6 Hz, 1H), 2.07 (dt, *J* = 12.6, 8.7 Hz, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 146.67, 145.36, 144.32, 128.41, 128.04, 126.50, 126.24,

126.19, 124.30, 36.40, 31.80; IR (neat): 3058, 3022, 2954, 2927, 1493, 1455, 1250, 1076, 712; GCMS-EI m/z 196 (M+).

3.7 References

(1) Ye, L.; Wang, Y.; Aue, D. H.; Zhang, L. *Journal of the American Chemical Society* **2012**, *134*, 31.

(2) Hansmann, M. M.; Rudolph, M.; Rominger, F.; Hashmi, A. S. K. *Angewandte Chemie International Edition* **2013**, *52*, 2593.

(3) Taduri, B. P.; Ran, Y.-F.; Huang, C.-W.; Liu, R.-S. *Organic Letters* **2006**, *8*, 883.

(4) Luo, Y.; Ji, K.; Li, Y.; Zhang, L. *Journal of the American Chemical Society* **2012**, *134*, 17412.

(5) Roberts, J. D.; Simmons, H. E.; Carlsmith, L. A.; Vaughan, C. W. *Journal of the American Chemical Society* **1953**, *75*, 3290.

(6) Hamura, T.; Ibusuki, Y.; Sato, K.; Matsumoto, T.; Osamura, Y.; Suzuki, K. *Organic Letters* **2003**, *5*, 3551.

(7) Ikawa, T.; Nishiyama, T.; Shigeta, T.; Mohri, S.; Morita, S.; Takayanagi, S.-i.; Terauchi, Y.; Morikawa, Y.; Takagi, A.; Ishikawa, Y.; Fujii, S.; Kita, Y.; Akai, S. *Angewandte Chemie International Edition* **2011**, *50*, 5674.

(8) Gómez, B.; Guitián, E.; Castedo, L. *Synlett* **1992**, *1992*, 903.

(9) Saá, C.; Guitián, E.; Castedo, L.; Saá, J. M. *Tetrahedron Letters* **1985**, *26*, 4559.

(10) Newman, M. S.; Kannan, R. *The Journal of Organic Chemistry* **1976**, *41*, 3356.

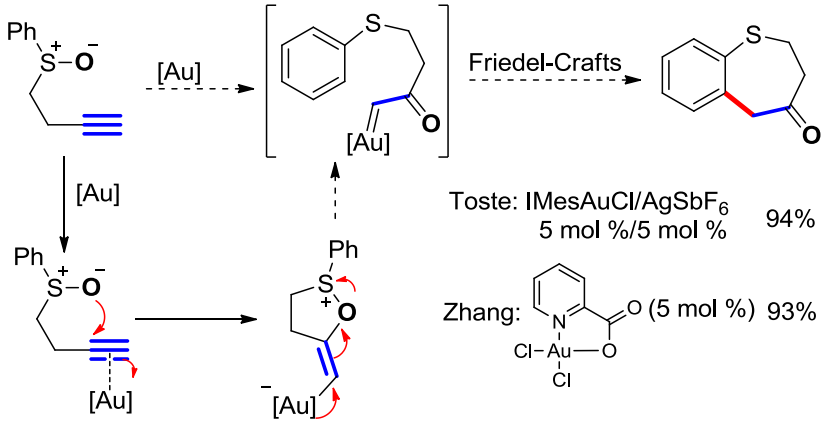
(11) Wang, Y.; Yepremyan, A.; Ghorai, S.; Todd, R.; Aue, D. H.; Zhang, L. *Angewandte Chemie International Edition* **2013**, *52*, 7795.

Chapter 4. C-H Functionalization via Insertion into Unactivated C(sp^3)-H Bonds by Oxidatively Generated Gold Carbenes

4.1 Introduction to Oxidative Gold Carbene Chemistry

In 2007, our group[1] and Toste group[2] independently reported that under mild homogeneous gold catalysis conditions, terminal or internal alkynes could be oxidized into α-oxo gold carbenes through an oxygen atom transfer oxidation process intramolecularly from a tethered sulfoxide moiety (Scheme 54).

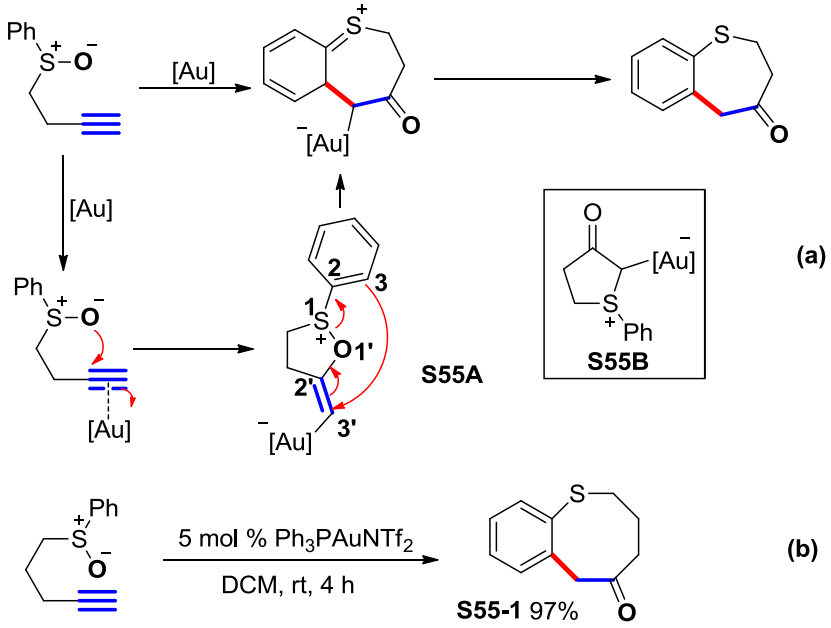
Scheme 54. Our Group and Toste Group's Initial Discoveries of Alkyne Oxidation



Although our group and the Toste group initially proposed the gold carbene mechanism for the above reaction, our continuous mechanistic studies proved that the final product actually originated from a [3,3]-sigmatropic rearrangement of alkyne/sulfoxide adduct **S55A** (Scheme 55a).[3] This revised mechanism explained the excellent reaction efficiency for the selective seven member ring formation over the competitive sulfide trapping of highly electrophilic gold carbene to form a sulfur ylide **S55B**. Benefited by such [3,3]

rearrangement mechanism, even eight membered sulfur containing cyclic ketone **S55-1** could be synthesized in quantitative yield (Scheme 55b).

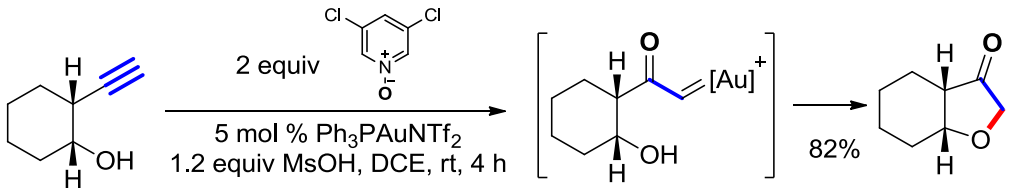
Scheme 55. Our Revised Mechanism for Alkynyl Sulfoxide Reaction



The concept of oxygen atom transfer from sulfoxide to alkyne to generate gold carbene is very attractive because it provided a non-diazo and catalytic approach to metal carbenes using safe and readily available alkynes. However, the sulfoxide tethering stragety was limited becaused it not only complicated the substrate synthesis but also introduced undesirable sulfide moiety in the final product. An intermolecular alkyne oxidation using simple alkynes and external oxygen transfer oxidants would circumvent these issues and make C-C triple bonds in the presence of oxidant as versatile replacement of hazardous diazo compounds in gold carbene chemistry. In 2010, the first intermolecular oxidation process was realized by our group using pyridine *N*-oxide derivatives as external oxidant (Scheme 56).[4] The in-situ generated α-oxo gold carbenes facilely inserted into tethered

hydroxyl groups and dihydrofuran-3-ones were expediently synthesized from homopropargyl alcohols.

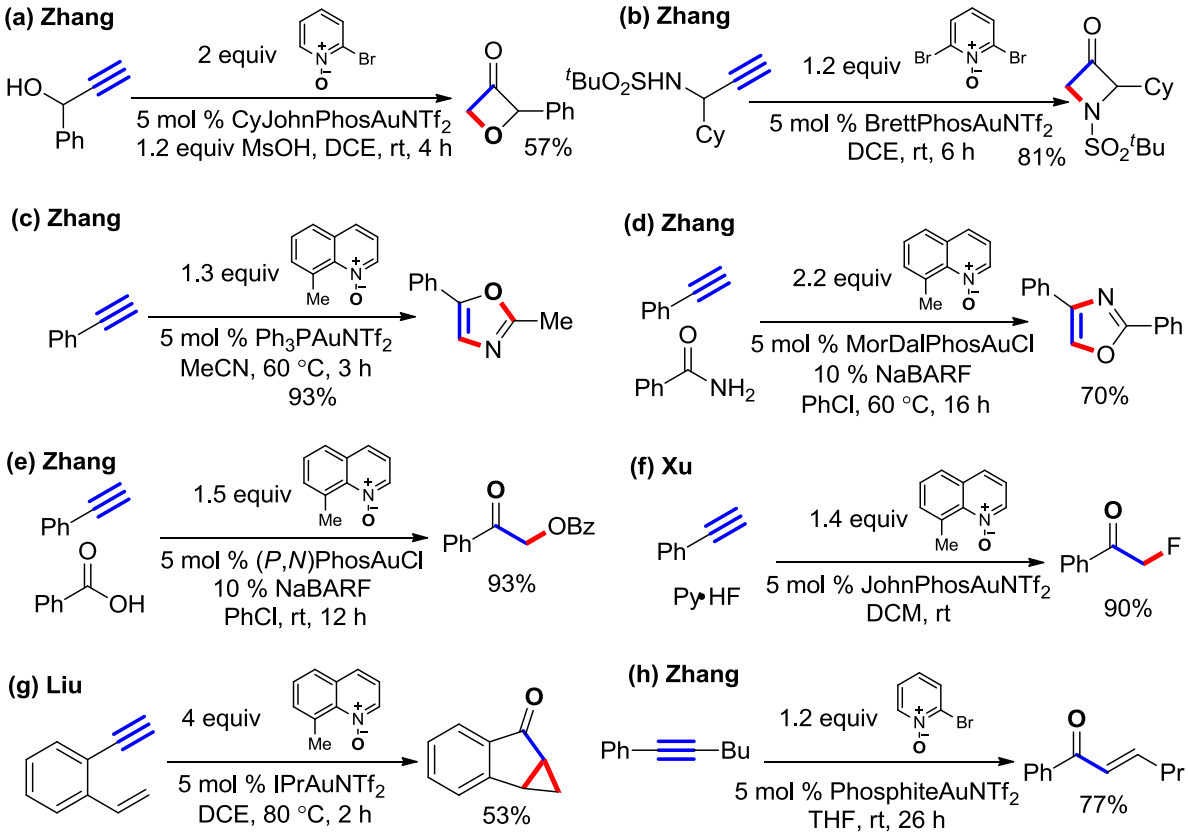
Scheme 56. First Intermolecular Generation of α-Oxo Gold Carbenes



Ever since our group developed the above intermolecular oxidation reaction, the reactivities of such oxidatively generated gold carbenes have been widely investigated by our group and many others with more than one hundred papers published on this specific topic.[5,6] Like other transition metal carbenes from diazo ketones, our oxidatively generated gold carbenes reacted with various types of functional groups (Scheme 57). For example, gold carbene could be trapped intramolecularly by free hydroxyl groups[7] and protected amines[8] to form 4-member heterocycles from readiliy accessible propargyl alcohols and propargyl amines (Scheme 57a, b). External nucleophiles, like carboxylic acids,[9] amides,[10] nitriles,[11] and pyridine hydrogen fluoride[12] also harvested the oxidatively generated gold carbenes for functionalized molecule synthesis from all hydrocarbon alkynes (Scheme 57c-f). Liu et al.[13] for the first time demonstrated that these gold carbenes could react with tethered olefins to form cyclopropanes (Scheme 57g). Later, the asymmetrical version of this oxidative cyclopropanation reaction was realized by our group[14] and J. Zhang group.[15] Our group[16] also showed that α-oxo gold carbenes reacted efficiently with tethered electron-rich aromatics and various substituted chroman-3-ones were synthesized rapidly from simple aryl propargyl ethers via this Friedel-Crafts reaction. Interestingly, the oxidation of internal

alkynes led to α,β-unsaturated ketones presumably through a 1,2 hydride migration mechanism, and the regioselectivity of enone formation could be tuned by ligand, temperature, and external oxidant (Scheme 57h).[17] Recently, this transformation has been successfully applied in the total synthesis of complex natural products citrinadins A and B.[18]

Scheme 57. General Reactivities of Oxidatively Generated Gold Carbenes

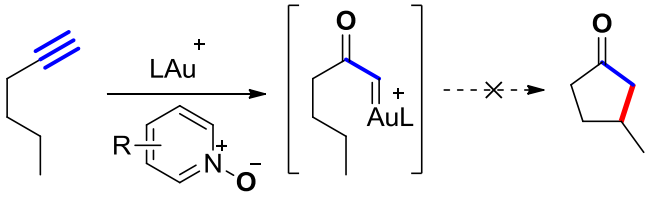


4.2 Challenge in Oxidative Gold Carbene Chemistry: C(sp^3)-H Insertion Reaction

Although the oxidative gold carbene chemistry has been extensively studied for years by several groups, the gold carbene insertion into unactivated C(sp^3)-H bonds has never been reported (Scheme 58), which however should be a very straightforward idea and a reasonably logical extension from gold carbene O-H/N-H insertion reactions. On the other

hand, Nolan et al. has demonstrated that this type of gold carbene is capable of C(sp^3)-H insertions.[19] Our oxidatively generated gold carbenes presumably would also be capable of this type of chemistry. Attracted by this valuable and streamlining C(sp^3)-H insertion synthetic stragety, several labmates of our group have attempted this but never succeeded.

Scheme 58. Unsuccessful C(sp^3)-H Insertions by Oxidatively Generated Gold Carbenes

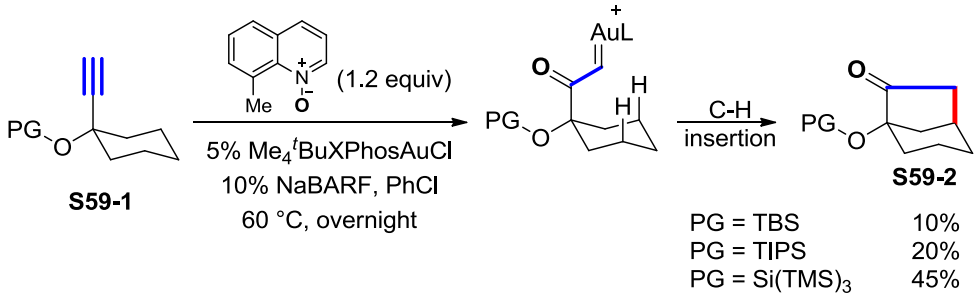


4.3 Our Initial Approach to the Above Challenge: the Thorpe-Ingold Effect

As the theme of my graduate research is C(sp^3)-H functionalization via gold catalysis, I thought the above challenge was a topic for my graduate research. After failing to get any C(sp^3)-H insertion product using 1-dodecyne, 3-phenyl-1-propyne, and 3-cyclohexyl-1-proyne, I tried the cyclohexylacetylene substrate **S59-1** (Scheme 59). I thought it should be a better substrate for the C-H insertion reaction because a large protecting group on the propargyl alcohol would position the C-C triple bond at the axial position of the cyclohexane ring and hence present the two axial C(sp^3)-H bonds in the vicinity of the subsequently generated alpha-oxo gold carbene intermediate. After extensive variation of the protecting group and screening of the reaction conditions, we are very delighted to find TBS protected propargyl alcohol (S59-1, PG = TBS) was successfully converted into bridged cyclopentanone (S59-2, PG = TBS). Although only in 10% yield, this reaction established itself the first realization of oxidatively generated gold carbene C(sp^3)-H insertion reaction. When the size of the protecting group was increased from TBS to TIPS and $Si(TMS)_3$,

stronger conformation control was achieved and the yield of the C-H insertion product was improved steadily from 10% to 20% and 45%.

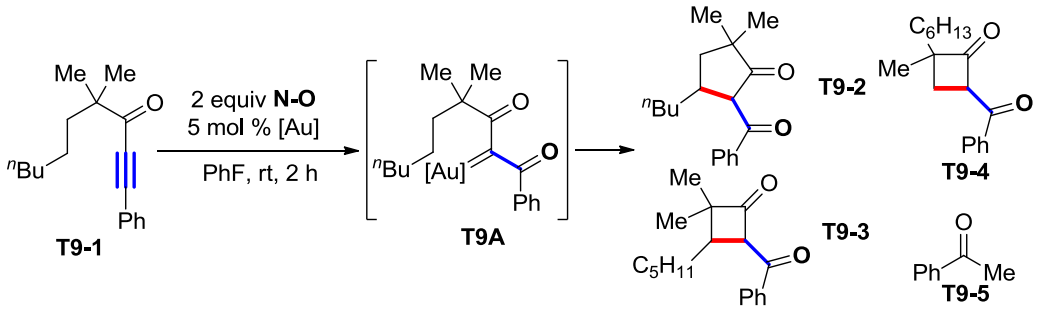
Scheme 59. First Realization of C(sp^3)-H Insertions by Oxidatively Generated Gold Carbenes



4.4 Our 2nd Generation Strategy: Reactions of Alkynones Facilitated by the Thorpe-Ingold Effect

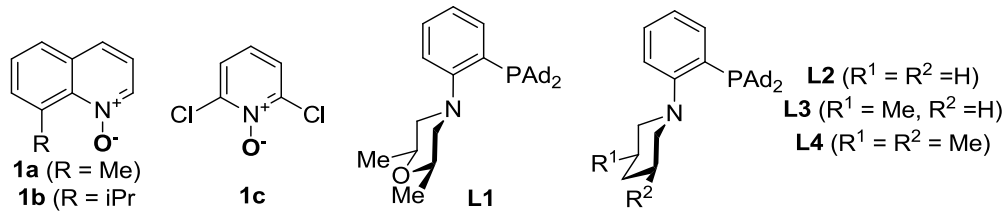
Our initial approach (Scheme 59) clearly demonstrated the importance of the Thorpe-Ingold effect. However, even when the protecting group was the super sized silyl group, we could only get 45% yield, which indicated the Thorpe-Ingold effect was not enough and we need a better design. Using developed gold carbene chemistry and rhodium carbene chemistry as inspiration, I decided to use alkynones such as **T9-1** as substrate for three considerations: (1) after oxidation, the extra benzoyl group will provide more steric hinderance to the gold carbene center and thus slow down potential intermolecular reactions and (2) at the same time, the benzoyl group will make the gold carbene more reactive and accelerate the intramolecular reaction and (3) the gem-dimethyl groups will further facilitate the intramolecular reaction due to the Thorpe-Ingold effect.

Table 9. Initial Reaction Discovery and Conditions Optimization[a]



entry	catalyst (5 mol %)	*N*-oxide	yield[b]	
			T9-2/T9-3/T9-4[c]	**T9-5**
1	$Ph_3PAuNTf_2$	**1a**	30% (9.5/1/1.1)	7%
2	BrettPhosAuNTf$_2$	**1a**	61% (1.1/1/1)	20%
3	IPrAuNTf$_2$	**1a**	63% (7.9/1/0)	11%
4	IMesAuCl/AgNTf$_2$	**1a**	57% (15.7/1/0)	7%
5	Mor-DalPhosAuNTf$_2$	**1a**	70% (6.7/1/0)	12%
6	**L1**AuCl/AgNTf$_2$	**1a**	59% (7.7/1/0)	7%
7	**L2**AuCl/AgNTf$_2$	**1a**	65% (10.0/1/0)	10%
8	**L3**AuCl/AgNTf$_2$	**1a**	68% (11.0/1/0)	8%
9	**L4**AuCl/AgNTf$_2$	**1a**	72% (13.2/1/0)	7%
10	**L4**AuCl/AgOTf	**1a**	67% (12.8/1/0)	12%
11	**L4**AuCl/AgSbF$_6$	**1a**	67% (12.2/1/0)	10%
12[d]	**L4**AuCl/NaBAr$^F{}_4$ (10 mol %)	**1a**	71% (9.5/1/0)	5%
13	**L4**AuCl/AgNTf$_2$	**1b**	84%[e] (13.7/1/0)	8%
14[f]	**L4**AuCl/AgNTf$_2$	**1c**	75% (13.0/1/0)	6%
15	IMesAuCl/AgNTf$_2$	**1b**	74% (13.8/1/0)	10%

[a] [**T9-1**] = 0.05 M. [b] Estimated by ^{1}H NMR using diethyl phthalate as the internal reference. [c] As mixtures of tautomers and diastereomers. [d] 12 h. Isolated yield. [e] 77% isolated yield. [f] Overnight.



Much to our delight, this design worked even with the prototypical triphenylphosphine ligand (Table 9, entry 1).[20] Besides the desired cyclopentanone product **T9-2**, I also identified two different cyclobutanone products **T9-3** and **T9-4** as a result of gold carbene insertion into the β-C(sp^3)-H bonds. This unexpected result was surprising to us and also reflected the superior reactivity of our acceptor/acceptor gold carbene **T9A**. Small amount of acetophenone **T9-5** was generated as a side product. The C-H insertion reactions could be improved by using bulky and electron-rich BrettPhos as ligand (entry 2). However, there was no selectivity for the three different products. Electron-rich IPrAuNTf$_2$ afforded mild reaction efficiency similar to BrettPhosAuNTf$_2$ but with much better chemo- and regioselectivity (entry 3). No cyclobutanone **T9-4** resulting from insertion into methyl C-H bond was detected, indicating that the reactivity of our gold carbene was indeed attenuated, which is consistent with the fact IPr is a better sigma-donor ligand than phosphines. Moreover, a serviceable regioselectivity was observed as cyclopentanone **T9-2** and cyclobutanone **T9-3** were isolated as a 7.9/1 mixture. Interestingly, a slightly smaller N-heterocyclic carbene liand (IMes) offered better regioselectivity (entry 3). Electron-rich *P*,*N*-bidentate ligands were then applied for our gold carbene C-H insertion reactions as they have been documented to be able to attenuate the reactivity of α-oxo gold carbenes via *P*,*N* biscoordiantion to gold center.[9,10] Indeed, different from the BrettPhos one, the reactivity of Mor-DalPhos gold carbene was similar to the IPr one and no methyl insertion occurred (entry 5). Other more electron-rich and sterically hindered *P*,*N*-bidentate ligands were then examined. While installing two methyl groups on the morpholine ring of Mor-DalPhos only slightly increased the selectivity (entry 6), the replacement of the whole morpholine ring with more electron-rich piperidine one was more fruitful (entry 7). Steadily improved regioselectivity and yield was observed as the piperidine ring was sterically more shielding

and electronically more donating (entry 6-9). Best efficiency and good regioselectivity was achieved with ligand **L4** (entry 9). Interestingly, less coordinating or non-coordinating counteranions like OTf^-, SbF_6^-, and $BARF^-$ diminished the yield and selectivity (entry 10-12). Other commercially available oxidants were then tested. The more hindered 8-isopropylquinoline *N*-oxide permitted the best yield with similar regioselectivity (entry 13), while 2,6-dichloropyridine *N*-oxide was not as efficient (entry 14). The best oxidant also improved the yield of $IMesAuNTf_2$ catalyzed reaction (entry 15). Small amount of acetophenone was observed in all the cases. The generation of it will be elucidated later.

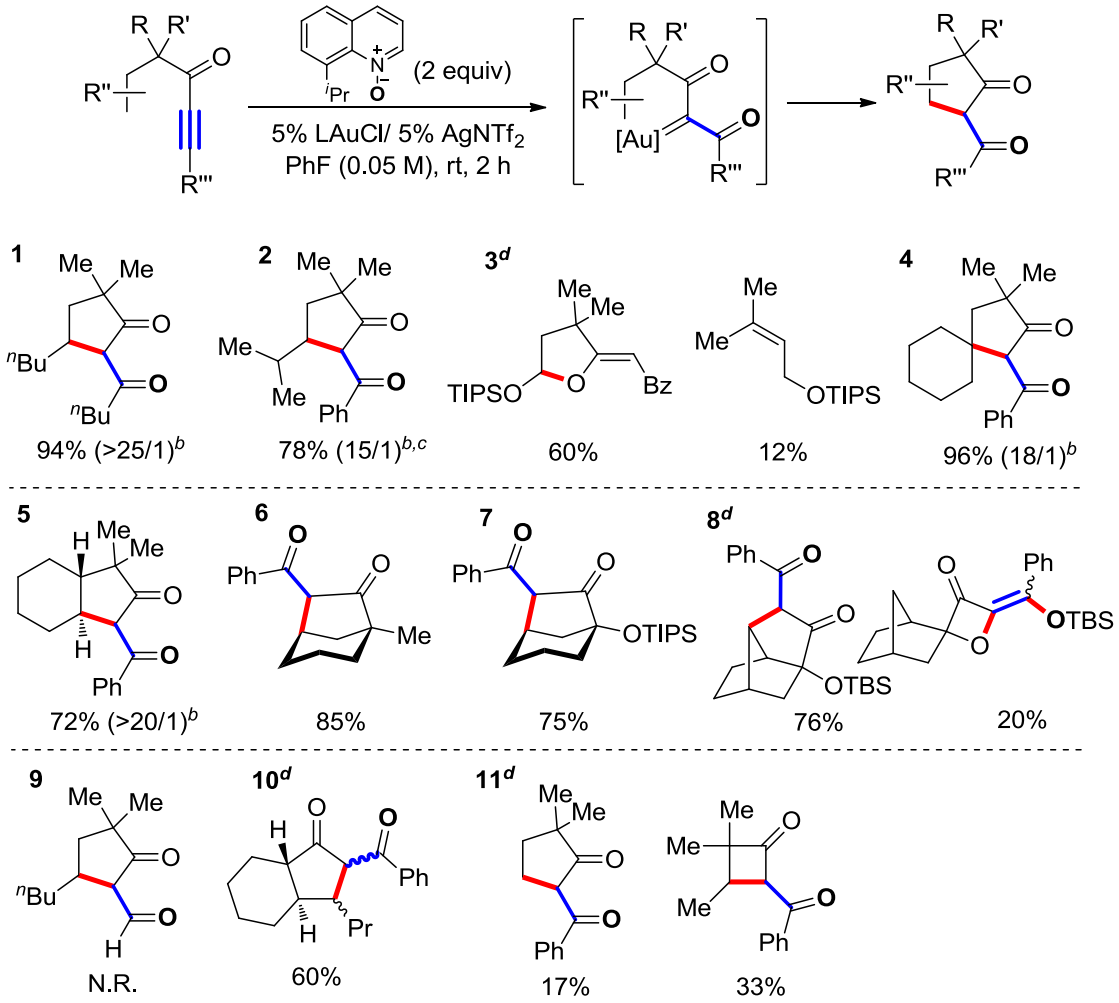
4.5 Substrate Scope Study for Cyclopentanone Synthesis

Being able to attenuate the reactivity of our oxidatively generated gold carbene **T9A** for chemo- and regioselective $C(sp^3)$-H insertions, I then further investigated the reaction scope for the synthesis of various types of cyclopentanones.

First of all, the alkynyl part of our ynone substrate is not limited to aromatic one. Aliphatic alkyne worked even better with excellent yield and regioselectivity (Table 10, entry 1). The gold carbene insertion into sterically hindered methylene group was probmatic using **L4** as ligand. Such issue could be solved using less bulky but similarly electron-rich IMes ligand (entry 2). There was no C-H insertion into the neighbouring methine group. Instead of the expected C-H insertion, our gold carbene induced a 1,5-hydride shift from the ethereal position of protected alcohol (entry 3). Cyclic acetal from the intramolecular cylization of gold enolate to oxycarbenium ion was isolated as the major product together with 12% olefin product which will be explained in the following mechanism discussion section. Tertiary C-H bond could be facilely inserted by our gold carbene leading to a 6,5-spiro cyclopentanone product (entry 4). No 1,5-hydride shift occurred during the tertiary C-

H insertion event reflecting the concerted nature of such process. Equatorial C(sp^3)-H bonds and axial C(sp^3)-H bonds of cyclohexyl ring are both reactive towards gold carbenes and the chemoselective outcome could be attributed to the conformational alignment of the carbene center and the C(sp^3)-H bonds (entry 5-7).

Table 10. C(sp^3)-H Insertion Reactions using Ynones with α-Carbon Fully Substituted[a]



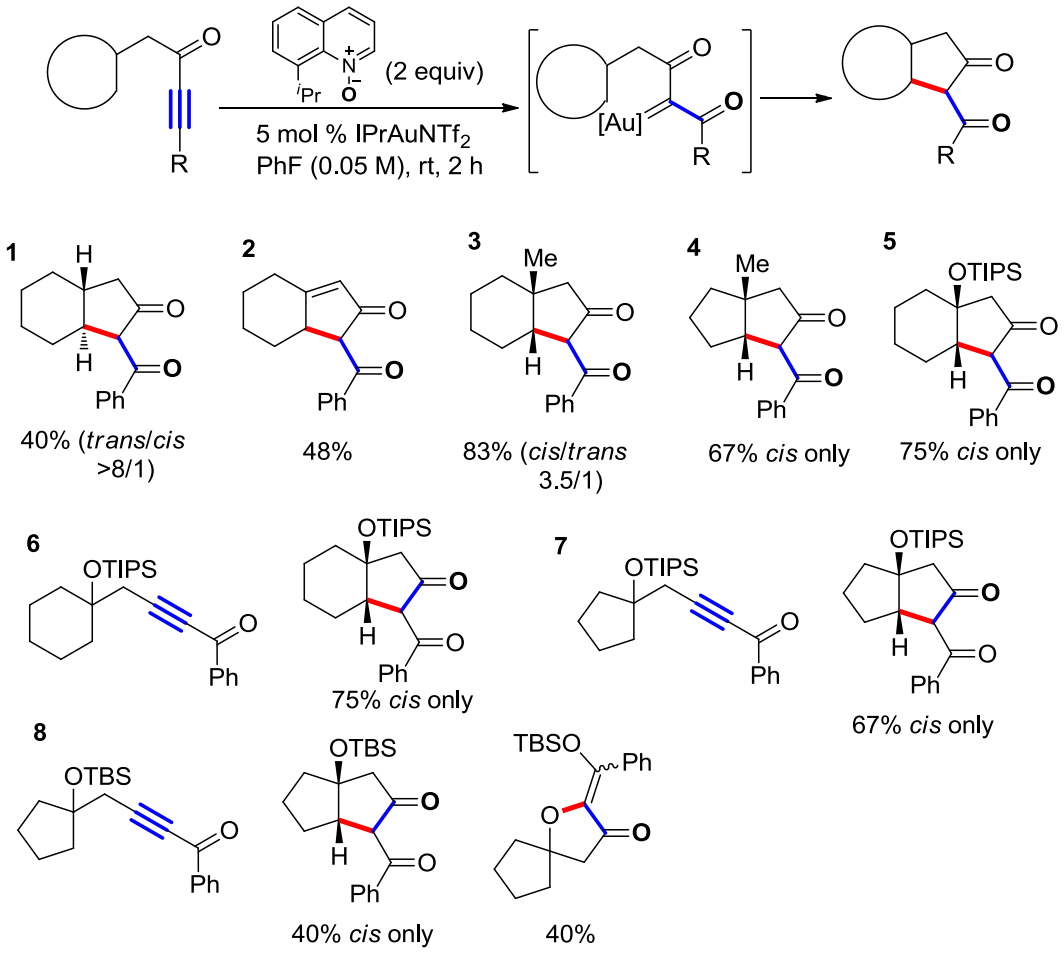
[a] Reaction conditions: Ynone (0.05 M in PhF), **L4**AuCl/$AgNTf_2$ (5 mol%), **1b** (2 equiv), rt, 2 h. [b] Cyclopentanone/cyclobutanones. [c] IMesAuCl/$AgNTf_2$ (5 mol%) as catalyst. [d] IPrAuNTf$_2$ (5 mol%) as catalyst.

For entry 7 and 8, the α-hydroxyl ketone substrates were easily synthesized from cyclohexanone and norcamphor using Alan Katritzky's benzotriazole umplung strategy. Once protected with TIPS or TBS group, such ynones with α-hydroxyl groups could undergo C-H insetion efficiently (entry 8, 9). The TBS group however did not adequately shield the nucleophilic oxygen from our gold carbene and there was 20% silyl ether addition product (entry 8). Interestingly, terminal alkynone was inert under our oxidative conditions (entry 9). If the gold carbene and the alkyl group were trans to each other on a cyclohexane ring (entry 10), C-H insertion also worked, affording a new class of 6,5 fused cyclopentanone. Finally, when there are two methyl groups and one ethyl group present, the regioselectivity was reversed favoring the cyclobutanone formation (entry 11). The cyclopentanone was disfavored due to the low reactivity of methyl C-H bonds.

Our chemistry is not limited to the substrates with α-quarternary carbons (Table 11). Removal of the two gem-dimethyl groups from the case in Table 9, entry 5 diminished the C-H insertion yield in the absence of the Thorpe-Ingold effect (Table 11, entry 1). Interestingly, the main product was still 6,5-*trans* fused cyclopentanone presumably due to the more stable *trans*-decalin type of transition state for the C-H insertion step. Improved reaction was realized when the cyclohexyl ring and gold carbene part were fixed conformationally by C-C double bond (entry 2). With a methyl group substituted at the β-carbon, the Thorpe-Ingold effect significantly enhanced the desired C-H insertion reaction (entry 3). The relatively low cis/trans selectivity with regard to the ring fusion could be attributed to the conformational flexibility of the cyclohexane ring. On the other hand, for insertion into cyclopentane ring, only *cis*-fused 5,5 cyclopentanone was detected, which is expected as the trans-fused isomer is much more strained (entry 4). Compared to entry 3, a sterically bukly TIPSO group rendered exclusively *cis*-selective C-H insertion because the gold carbene moiety was forced

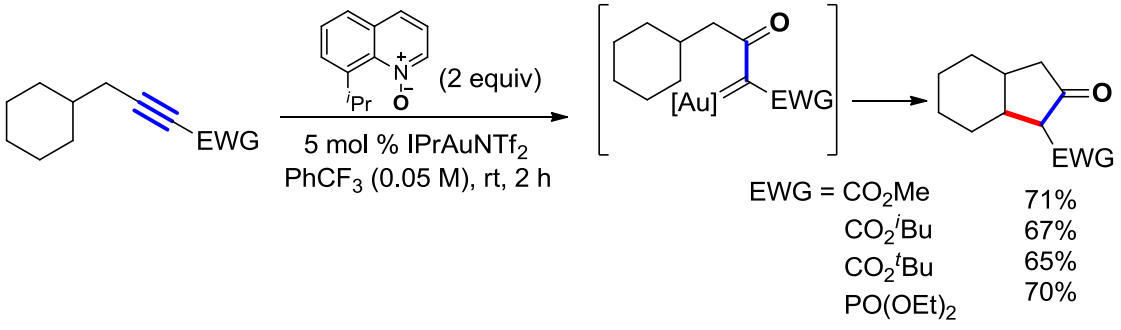
at the axial position and only had access to equatorial C-H bonds for insertion (entry 5). More interestingly, the alkynyl ketone substrate used in entry 6 is isomeric to that in entry 5 with regard to the ynone orientation. When it was subjected to our oxidative gold catalysis, the same *cis*-product was isolated in 75% yield, identical to that in entry 5, which is consistent with the symmetric nature of the β-diketone-α gold carbene intermediates. Like entry 6, the alkynone substrates for entry 7 and 8 could be facilely synthesized from cyclopentone within three steps and they were all suitable for C-H insertions. Again, the TBS protecting group was not sufficient to mask the oxygen atom in entry 8 and the oxygen from this TBS protected tertiary alcohol competitively reacted with gold carbene.

Table 11. Constructions of Fused Bicyclic Cyclopentanones[a]



As shown above, our gold carbene facilely inserted into various linear or cyclic alkyl groups, furnishing synthetically versatile cyclopentanones. However, these reactions were usually facilitated by the Thorpe-Ingold effect. Without it, for example, the insertion into the simple and non-substituted cyclohexyl ring was sluggish (Table11, entry 1). This is certainly a limitation and I decided to solve this problem. With little success in improving the 40% yield by further optimizing the reaction conditions, I then modified the substrate structure (Scheme 60) by installing other electron-withdrawing groups at the terminus carbon of 3-cyclohexyl-1-propyne. Upon oxidative gold catalysis, other types of acceptor/acyl gold carbenes could be generated. Much to our delight, the C-H insertion into cyclohexyl ring became much more efficient when methyl carboxylate or diethyl phosphate were used as the electron withdrawing groups. This stragety will definitely expand our carbene C-H insertion scope and another labmate is currently working on this project.

Scheme 60. Other Types of Substrates for Oxidative Gold Carbene C(sp^3)-H Insertion Reactions

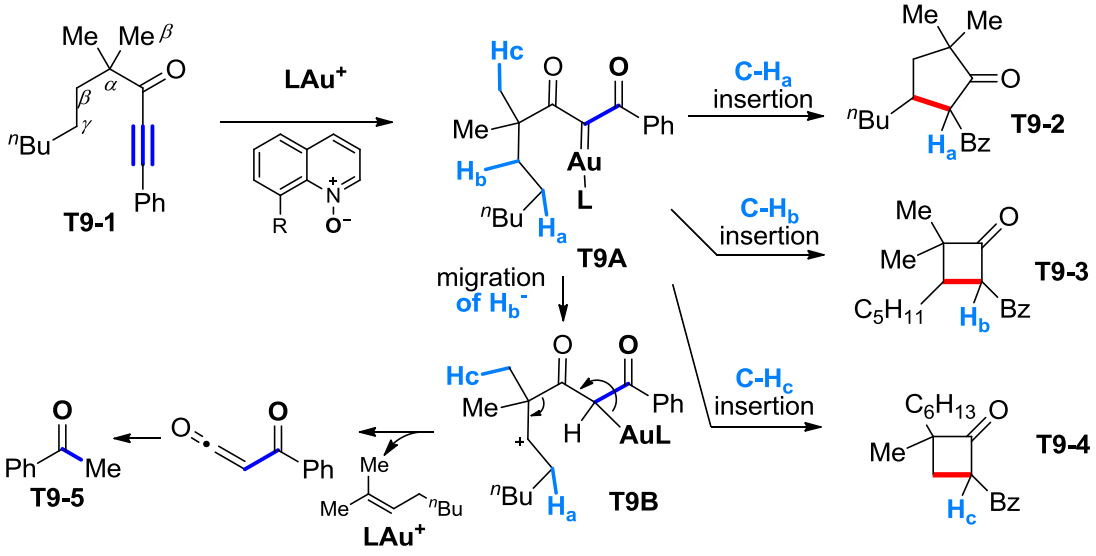


4.6 Proposed Mechanism for the Reaction of T9-1

Based on all the above observations, we proposed a mechanism, which is shown in Scheme 61. Hence, the alkynone **T9-1** is first oxidized into 1,3-dicarbonyl gold carbene

intermediate **T9A**, which could insert into either the γ C(sp^3)-H bond to form the cyclopentone product **T9-2** or the β-C(sp^3)-H bonds leading to the two cyclobutanones. On the other hand, the super electrophilic gold carbene might abstract a hydride from the β-methylene group, resulting in **T9B**. The new carbon cation together with the gold enolate then fragmented into benzoyl ketene and 2-methyl-2-octene. During the reaction or workup, the benzoyl ketene was hydrolyzed into β-ketocarboxylic acid, which then decomposed into acetophenone. The 2-methyl-2-octene was volatile but could be confirmed by GC-MS analysis of the reaction mixture. Such olefin side product was also observed in Table 10, entry 3.

Scheme 61. Proposed Mechanism for Our Gold Carbene Chemistry

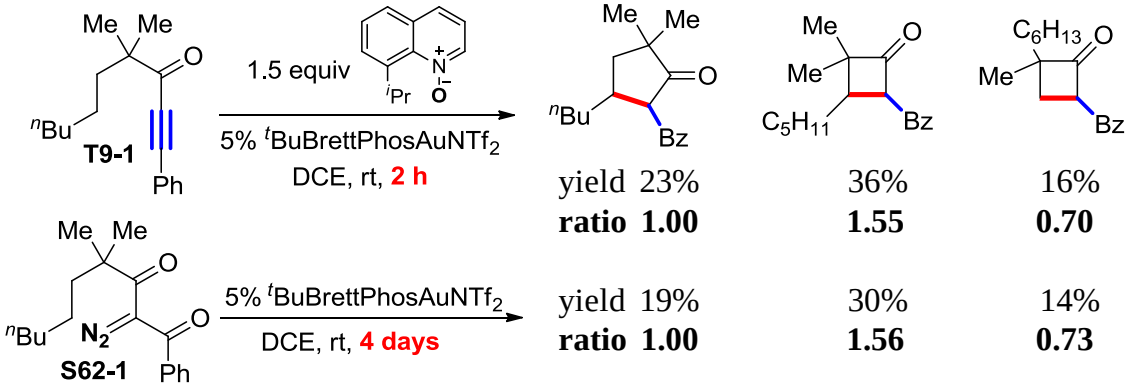


4.7 Mechanistic Studies for the Cyclopentanone Formation

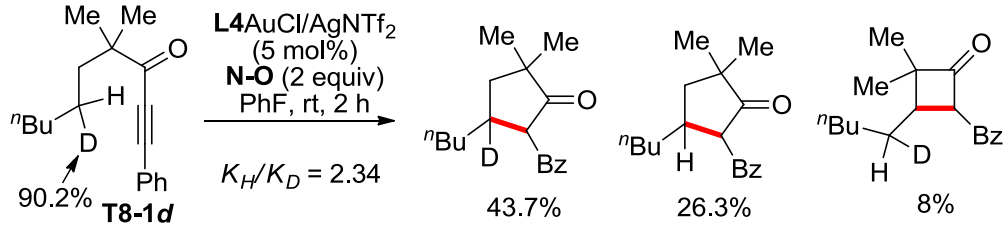
In order to offer support for the intermediacy of the 1,3-dicarbonyl gold carbene **T8A**, we synthesized its diazo counterpart **S62-1** and compared them side by side in the C-H insertion chemistry (Scheme 62). Unfortunately, the diazo compound was not reactive at all

with our best gold catalyst L4AuCl/$AgNTf_2$ or IPrAuNTf_2. ^{t}BuBrettPhosAuNTf_2 was applied to drive the reaction to completion. Compared to the four days for the diazo reaction, our alkynone chemistry only took two hours to finish at room temperature. Most importantly, similar yields were achieved with almost identical distributions between the cyclopentanone product and the two cyclobutanone ones. This control experiment strongly supported our proposed gold carbene mechanism (Scheme 61).

Scheme 62. Control Experiment Between Ynone and Diazoketone



Scheme 63. Deuterium Labeling Experiment



Deuterium labeling experiment was then performed to provide more mechanistic insights (Scheme 63). One of the two hydrogens from the γ-methylene group of alkynone **T8-1** was deuterated in order to determine the deuterium kinetic isotope effect. Interestingly, the

deuterated ynone **T8-1*d*** afforded similar yield, while the yield of the cyclobutanone was slighted increased. The internal competitive C-H/C-D insertion resulted in a significant primary KIE of 2.34, which indicated that the C-H bond is significantly elongated in the insertion transition state.

4.8 Conclusion for Cyclopentanone Synthesis

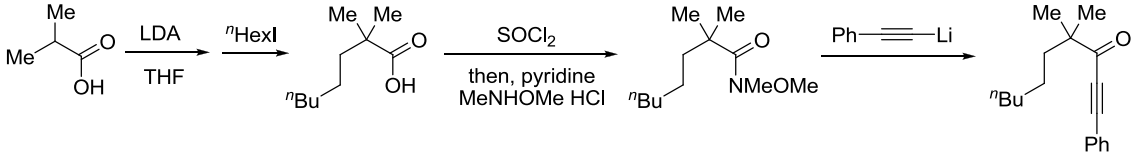
In summary, we have accomplished the first intramolecular C(sp^3)-H insertion reactions by oxidatively generated gold carbenes from alkynes. Our intitial discovery was enabled by the Thorpe-Ingold effect using terminal alkynes. Later, the C(sp^3)-H insertion reaction was significantly improved using readily available alkynone substrates. The β-diketone-α-gold carbenes generated from their gold-catalyzed oxidation were demonstrated to undergo facile insertion into various unactivated C(sp^3)-H bonds, leading to a large variety of synthetically valuable cyclopentanones including spiro-, bridged, and fused bicyclic ones. The control experiment with corresponding diazo compound supported our gold carbene C-H insertion mechanism. This straightforward approach to accepter/accepter gold carbenes and their C(sp^3)-H insertion reactivities remarkablely advanced the oxidative gold carbene chemistry and further highlighted the potential to replace hazardous diazo materials with user friendly and readily available alkynes as carbene precusors.

4.9 Experimental Details

General. Ethyl acetate (ACS grade), hexanes (ACS grade), diethyl ether (ACS grade), were purchased from Fisher Scientific and used without further purification. Anhydrous toluene and 1,2-dichloroethane were bought from Acros and used directly. Commercially

available reagents were used without further purification. Reactions were monitored by thin layer chromatography (TLC) using Silicycle precoated silica gel plates. Flash column chromatography was performed over Silicycle silica gel (230-400 mesh). ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian 400 MHz spectrometer, a Varian 500 MHz Unity plus spectrometer, and a Varian 600 MHz Unity plus spectrometer, using residue solvent peaks as internal standards ($CDCl_3$, ^{1}H: 7.26 ppm; ^{13}C: 77.00 ppm). Infrared spectra were recorded with a Perkin Elmer FT-IR spectrum 2000 spectrometer and are reported in reciprocal centimeter (cm^{-1}). Mass spectra were recorded with Waters micromass ZQ detector using electrospray method (MeCN as solvent).

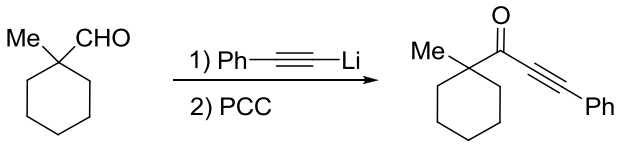
Procedure A: preparation of ynone T9-1



LDA (110 mmol) was added dropwise to a mixture of isobutyric acid (4.05 mL, 44 mmol) and THF (100 mL) at -78 ℃, and the mixture was allowed to warm up to room temperature and stirred for 1 h. Then the reaction mixture was recooled to -78 ℃ and hexyl iodide (6.5 mL, 44 mmol) was added dropwise. The resulting solution was allowed to warm up to room temperature and stirred overnight. After the reaction finished, the reaction mixture was quenched with 10% HCl solution and extracted with DCM. The combined organic extract was washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to give 2,2-dimethyloctanoic acid (6.2 g, crude)**,** which, without purification, was dissolved in thionyl chloride (30 mL). The resulting mixture was refluxed for 1 h and then concentrated under reduced pressure to give 2,2-dimethyloctanoyl chloride, which, without

purification, was dissolved in DCM (100 mL). To the above mixture was added *N,O*-dimethylhydroxylamine hydrochloride (3.3 g) and pyridine (7.3 mL) at 0 ℃. The resulting solution was allowed to warm up to room temperature and stirred overnight. After the reaction finished, the reaction mixture was quenched with 10% HCl solution and extracted with DCM. The combined organic extract was washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to give N-methoxy-N,2,2-trimethyloctanamide (6.3 g, crude)**.** 1.29 g of the above crude product was added to a THF (30 mL) solution of (phenylethynyl)lithium (9 mmol) at -78 ℃. The resulting solution was allowed to warm up to room temperature and stirred overnight. After the reaction finished, the reaction mixture was quenched with saturated NH_4Cl solution and extracted with Et_2O. The combined organic extract was washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by chromatography on silica gel to afford the desired product **T9-1** (1.33 g, 57% yield counted three steps from isobutyric acid).

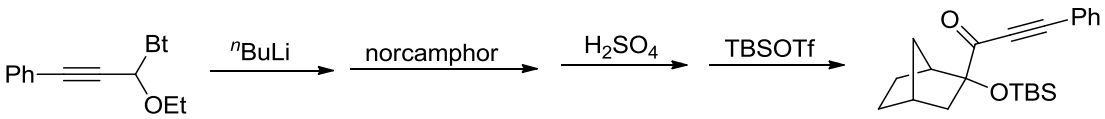
Procedure B: preparation of ynone T10-6-SM



1-methylcyclohexanecarbaldehyde (3 mmol, 378 mg) was added to a THF (10 mL) solution of (phenylethynyl)lithium (4 mmol) at -78 ℃. The resulting solution was allowed to warm up to 0 ℃ and stirred for 1h. After the reaction finished, the reaction mixture was quenched with saturated NH_4Cl solution and extracted with Et_2O. The combined organic extract was washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to give crude intermediate**,** which, without purification, was dissolved in DCM (10 mL). To

the above solution was added PCC (5 mmol, 1.08 g) at room temperature. After the reaction finished monitored by TLC, the reaction solution was passed through a short pad of silica, which was further washed with ethyl acetate. The combined organic extract was concentrated under reduced pressure. The residue was purified by chromatography on silica gel to afford the desired product **T10-6-SM** (0.411 g, 60% yield counted two steps from 1-methylcyclohexanecarbaldehyde).

Procedure C: preparation of ynone T10-8-SM

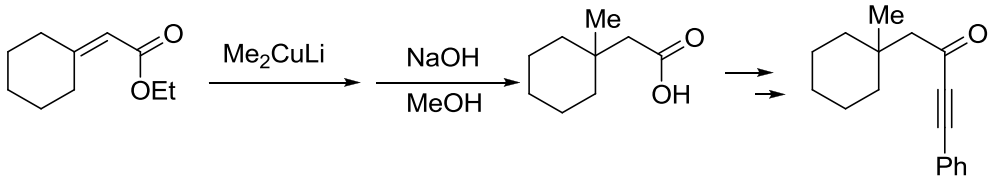


T10-8-SM-SM

^{n}BuLi (1.5 mmol) was added dropwise to a mixture of **T10-8-SM-SM** (416 mg, 1.5 mmol) and THF (20 mL) at -78 ℃, and the mixture was kept at -78 ℃ for 5 minutes before norcamphor (165 mg, 1.5 mmol) was added. The reaction mixture was stirred for another 10 minuates at -78 ℃ and quenched with water and extracted with Et_2O. The combined organic extract was washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The crude product was dissolved in acetone (20 mL). 11% H_2SO_4 (2 mL) was added to the above solution. The reaction mixture was stirred for 30 minuates at room temperature and quenched with water and extracted with Et_2O. The combined organic extract was washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The crude product was dissolved in DCM (3 mL). To the above solution was added lutidine (0.4 mL) and TBSOTf (0.35 mL) at 0 ℃. After the reaction finished monitored by TLC, the reaction mixture was quenched with water and extracted with Et_2O. The combined organic extract was washed with brine, dried over anhydrous $MgSO_4$, and

concentrated under reduced pressure. The residue was purified by chromatography on silica gel to afford the desired product **T10-8-SM** (218 mg, 46% yield counted three steps from **T10-8-SM-SM**).

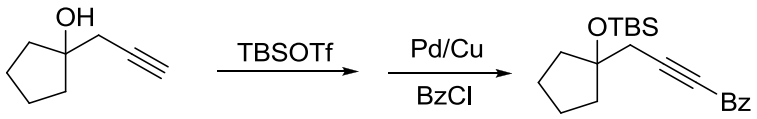
Procedure D: preparation of ynone T11-3-SM



Ethyl 2-cyclohexylideneacetate (168 mg, 1 mmol) was added to a mixture of Me_2CuLi (2 mmol) and Ether (2 mL) at -78 ℃, and the mixture was allowed to warm up to 0 ℃. The reaction mixture was stirred for another 30 minuates at 0 ℃ and quenched with NH_4Cl (saq.) and extracted with Et_2O. The combined organic extract was washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The crude product was dissolved in MeOH (3 mL). NaOH (120 mg, 3 mmol) was added to the above solution. The reaction mixture was refluxed for 5 hours and quenched with HCl (conc.) and extracted with DCM. The combined organic extract was washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The crude product was dissolved in DCM (25 mL). To the above solution was added *N*-methylmorpholine (0.12 mL), *N*,*O*-dimethylhydroxylamine hydrochloride (107 mg) and EDCI (210 mg) at 0 ℃. After the reaction finished monitored by TLC, the reaction mixture was quenched with water and extracted with DCM. The combined organic extract was washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The above crude product was added to a THF (5 mL) solution of (phenylethynyl)lithium (1.5 mmol) at -78 ℃. The resulting solution was allowed to warm up to room temperature and stirred overnight. After the

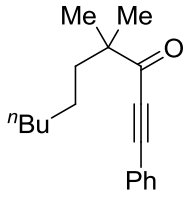
reaction finished, the reaction mixture was quenched with saturated NH_4Cl solution and extracted with Et_2O. The combined organic extract was washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by chromatography on silica gel to afford the desired product **T11-3-SM** (120 mg, 50% yield counted four steps from ethyl 2-cyclohexylideneacetate).

Procedure E: preparation of ynone T11-8-SM



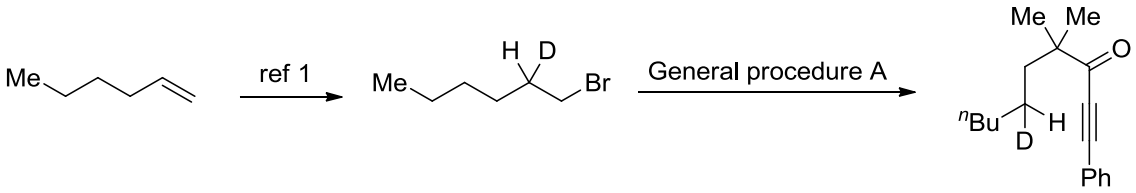
1-(Prop-2-ynyl)cyclopentanol (372mg, 3 mmol) was dissolved in DCM (3 mL). To the above solution was added lutidine (1.1 mL) and TBSOTf (0.69 mL) at 0 ℃. After the reaction finished monitored by TLC, the reaction mixture was quenched with water and extracted with DCM. The combined organic extract was washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The above crude product was added to a Et_3N (5 mL) solution of CuI (19 mg) and $PdCl_2(PPh_3)_2$ (36 mg) at room temperature. The BzCl (0.48 mL, 4 mmol) was added. The resulting solution was stirred for 4 hours. After the reaction finished, the reaction mixture was quenched with saturated NH_4Cl solution and extracted with Et_2O. The combined organic extract was washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by chromatography on silica gel to afford the desired product **T11-8-SM** (740 mg, 72% yield counted two steps from 1-(prop-2-ynyl)cyclopentanol).

4,4-dimethyl-1-phenyldec-1-yn-3-one (T9-1)



This compound was prepared following the procedure **A**. ^{1}H NMR (500 MHz, "$CDCl_3$") δ 7.60 – 7.55 (m, 2H), 7.45 (t, *J* = 7.4 Hz, 1H), 7.39 (t, *J* = 7.6 Hz, 2H), 1.72 – 1.62 (m, 2H), 1.28 (m, 8H), 1.23 (s, 6H), 0.94 – 0.79 (m, 3H); ^{13}C NMR (126 MHz, "$CDCl_3$") δ 194.33, 132.94, 130.47, 128.59, 128.58, 120.35, 91.63, 86.29, 48.34, 39.91, 31.63, 29.89, 24.58, 23.95, 22.57, 14.04; IR (neat): 3083, 3063, 2959, 2931, 2858, 2200, 1664, 1059, 757; ESI^{+} calculated for $[C_{18}H_{24}NaO+MeCN]^{+}$: 320.20, found 320.23.

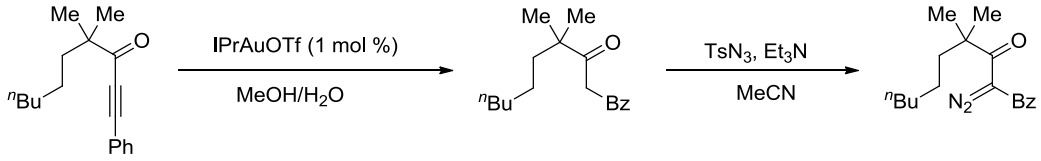
4,4-dimethyl-1-phenyldec-1-yn-3-one-*d*$_1$ (T9-1-*d*$_1$)



1-Bromohexane-*d*$_1$ was synthesized according to this reference (J. Terao, S. A. Begum, Y. Shinohara, M. Tomita, Y. Naitoh and N. Kambe. ***Chem. Commun.***, 2007, 855-857.). ^{1}H NMR (500 MHz,) δ 3.40 (d, *J* = 6.8 Hz, 2H), 1.87 – 1.79 (m, 1H), 1.42 (q, *J* = 7.2 Hz, 2H), 1.36 – 1.23 (m, 4H), 0.90 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, "$CDCl_3$") δ 77.25, 77.00, 76.75, 33.92, 32.44 (t, *J* = 19.6 Hz), 30.93, 27.77, 22.47, 13.97; Compound **T9-1-*d*$_1$** was prepared following the general procedure **A**. ^{1}H NMR (500 MHz,) δ 7.61 – 7.55 (m, 2H), 7.47 – 7.42 (m, 1H), 7.41 – 7.35 (m, 2H), 1.66 (d, *J* = 8.3 Hz, 2H), 1.25 (m, 15H), 0.91 – 0.81 (m, 3H); ^{13}C NMR (126 MHz, "$CDCl_3$") δ 194.31, 132.93, 130.46, 128.57, 120.34,

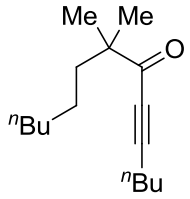
91.62, 86.29, 48.32, 39.81, 31.60, 29.78, 24.19 (t, *J* = 19.0 Hz), 23.95 (d, *J* = 2.2 Hz), 22.57, 14.03.

2-diazo-4,4-dimethyl-1-phenyldecane-1,3-dione (S62-1)



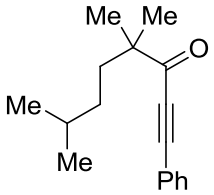
T9-1 (768 mg, 3 mmol) and IPrAuOTf (1 mol%) was added to a mixture of MeOH (1 mL) and H_2O (0.14 mL) and the mixture was stirred for 12 hours at 70 ℃ and quenched with NH_4Cl (saq.) and extracted with Et_2O. The combined organic extract was washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to afford the crude product. 220 mg of the above crude diketone was dissolved in MeCN (5 mL). TsN_3 (131 mg) and Et_3N (0.33 mL) were added to the above solution at 0 ℃. The reaction mixture was allowed to warm up to room temperature and stirred for 4 hours before it was concentrated under reduced pressure. The residue was purified by chromatography on silica gel to afford the desired product **S62-1** (160 mg, 80% yield). ^{1}H NMR (600 MHz, Chloroform-d) δ 7.60 – 7.55 (m, 2H), 7.55 – 7.51 (m, 1H), 7.44 (t, *J* = 7.7 Hz, 2H), 1.77 – 1.66 (m, 2H), 1.29 (m, 14H), 0.87 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR (151 MHz, cdcl$_3$) δ 196.29, 186.74, 137.97, 132.28, 128.42, 127.73, 48.71, 38.96, 31.65, 29.81, 24.86, 24.52, 22.57, 14.03; IR (neat):3061, 2956, 2929, 2858, 2110, 1648, 1289, 1148, 706; ESI$^+$ calculated for $[C_{18}H_{24}N_2NaO_2+MeCN]^+$: 364.20, found 364.23.

8,8-dimethyltetradec-5-yn-7-one (T10-1-SM)



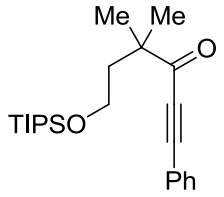
This compound was prepared following procedure **A**. ^{1}H NMR (500 MHz, Chloroform-d) δ 2.38 (t, *J* = 7.1 Hz, 2H), 1.61 – 1.53 (m, 4H), 1.50 – 1.38 (m, 2H), 1.26 (qd, *J* = 8.5, 7.7, 4.9 Hz, 6H), 1.18 (ddt, *J* = 10.8, 6.7, 2.1 Hz, 2H), 1.13 (s, 6H), 0.93 (t, *J* = 7.3 Hz, 3H), 0.87 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 194.48, 95.05, 79.11, 48.04, 39.87, 31.62, 29.86, 29.82, 24.51, 23.88, 22.57, 21.95, 18.66, 14.03, 13.45; IR (neat): 2960, 2932, 2860, 2209, 1670, 1468, 1148, 744; ESI^{+} calculated for $[C_{16}H_{28}NaO+MeCN]^{+}$: 300.23, found 300.26.

4,4,7-trimethyl-1-phenyloct-1-yn-3-one (T10-2-SM)



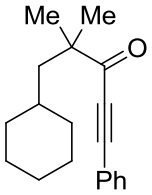
This compound was prepared following procedure **A**. ^{1}H NMR (500 MHz, Chloroform-d) δ 7.60 – 7.54 (m, 2H), 7.47 – 7.43 (m, 1H), 7.40 – 7.35 (m, 2H), 1.70 – 1.64 (m, 2H), 1.51 (dp, *J* = 13.2, 6.6 Hz, 1H), 1.23 (s, 6H), 1.17 – 1.10 (m, 2H), 0.89 (d, *J* = 6.6 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 194.32, 132.91, 130.46, 128.58, 120.34, 91.58, 86.28, 48.25, 37.69, 33.61, 28.54, 23.94, 22.49; IR (neat): 3061, 2958, 2933, 2870, 2200, 1664, 1060, 758; ESI^{+} calculated for $[C_{17}H_{22}NaO+MeCN]^{+}$: 306.18, found 306.22.

4,4-dimethyl-1-phenyl-6-(triisopropylsilyloxy)hex-1-yn-3-one (T10-3-SM)



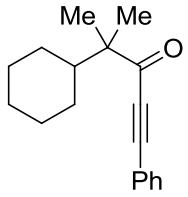
This compound was prepared following procedure **A**. ^{1}H NMR (500 MHz, Chloroform-d) δ 7.56 (d, *J* = 7.3 Hz, 2H), 7.44 (t, *J* = 7.4 Hz, 1H), 7.38 (t, *J* = 7.5 Hz, 2H), 3.74 (t, *J* = 6.9 Hz, 2H), 2.02 (t, *J* = 6.9 Hz, 2H), 1.28 (s, 6H), 1.12 – 0.97 (m, 21H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 193.36, 132.88, 130.36, 128.53, 120.47, 91.81, 86.38, 59.87, 46.88, 42.40, 24.27, 18.01, 11.97; IR (neat): 3055, 2939, 2866, 2200, 1664, 1265, 740; ESI$^+$ calculated for $[C_{23}H_{36}NaO_2Si+MeCN]^+$: 436.26, found 436.32.

5-cyclohexyl-4,4-dimethyl-1-phenylpent-1-yn-3-one (T10-4-SM)



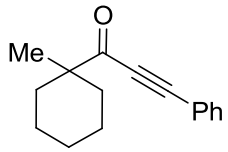
This compound was prepared following procedure **A**. ^{1}H NMR (500 MHz, Chloroform-d) δ 7.61 – 7.54 (m, 2H), 7.48 – 7.43 (m, 1H), 7.41 – 7.36 (m, 2H), 1.71 – 1.55 (m, 7H), 1.33 (m, 1H), 1.24 (s, 6H), 1.19 (m, 2H), 1.14 – 1.03 (m, 1H), 1.01 – 0.88 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 194.65, 132.90, 130.45, 128.58, 120.39, 92.01, 86.49, 48.33, 47.58, 34.71, 34.60, 26.40, 26.20, 24.81; IR (neat): 3055, 2927, 2852, 2199, 1659, 1600, 1265, 739; ESI$^+$ calculated for $[C_{19}H_{24}NaO+MeCN]^+$: 332.20, found 332.20.

4-cyclohexyl-4-methyl-1-phenylpent-1-yn-3-one (T10-5-SM)



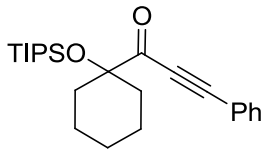
This compound was prepared following procedure **B**. ^{1}H NMR (500 MHz, Chloroform-d) δ 7.60 – 7.56 (m, 2H), 7.47 – 7.42 (m, 1H), 7.41 – 7.36 (m, 2H), 1.86 (tt, *J* = 12.0, 3.0 Hz, 1H), 1.82 – 1.75 (m, 2H), 1.71 – 1.63 (m, 3H), 1.28 (dddd, *J* = 16.5, 13.0, 9.9, 3.5 Hz, 2H), 1.20 – 1.10 (m, 7H), 1.04 (qd, *J* = 12.6, 3.2 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 194.92, 132.92, 130.43, 128.57, 120.42, 91.53, 86.54, 51.43, 44.75, 27.71, 26.94, 26.54, 20.73; IR (neat): 3055, 2987, 2932, 2199, 1659, 1600, 1422, 1265, 740; ESI^{+} calculated for $[C_{18}H_{22}NaO+MeCN]^{+}$: 318.18, found 318.22.

1-(1-methylcyclohexyl)-3-phenylprop-2-yn-1-one (T10-6-SM)



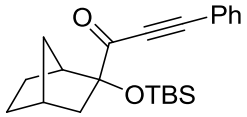
This compound was prepared following procedure **B**. ^{1}H NMR (500 MHz,) δ 7.61 – 7.55 (m, 2H), 7.47 – 7.42 (m, 1H), 7.41 – 7.35 (m, 2H), 2.15 (ddd, *J* = 12.8, 6.6, 2.9 Hz, 2H), 1.58 (ddt, *J* = 15.7, 5.5, 3.2 Hz, 2H), 1.54 – 1.28 (m, 6H), 1.22 (s, 3H); ^{13}C NMR (126 MHz, "$CDCl_3$") δ 194.36, 132.97, 130.45, 128.57, 120.36, 91.24, 86.32, 48.81, 34.55, 25.75, 22.82; IR (neat): 3061, 2931, 2199, 1661, 1445, 1066, 757; ESI^{+} calculated for $[C_{16}H_{18}NaO+MeCN]^{+}$: 290.15, found 290.18.

3-phenyl-1-(1-(triisopropylsilyloxy)cyclohexyl)prop-2-yn-1-one (T10-7-SM)



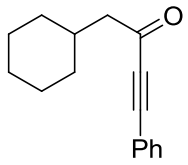
This compound was prepared following procedure **C**. ^{1}H NMR (500 MHz, Chloroform-d) δ 7.61 – 7.55 (m, 2H), 7.48 – 7.42 (m, 1H), 7.39 (t, *J* = 7.5 Hz, 2H), 2.21 (ddd, *J* = 12.4, 8.1, 3.5 Hz, 2H), 1.76 (dq, *J* = 15.2, 6.1, 4.9 Hz, 2H), 1.68 (ddd, *J* = 12.5, 7.9, 3.9 Hz, 2H), 1.55 – 1.42 (m, 3H), 1.19 – 1.02 (m, 23H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 190.10, 132.96, 130.56, 128.58, 120.28, 92.80, 86.69, 80.53, 35.41, 25.28, 22.29, 18.53, 13.94; IR (neat): 3055, 2942, 2865, 2200, 1673, 1265, 909, 739; ESI^{+} calculated for $[C_{24}H_{36}NaO_2Si+MeCN]^{+}$: 448.26, found 448.31.

1-(2-(tert-butyldimethylsilyloxy)bicyclo[2.2.1]heptan-2-yl)-3-phenylprop-2-yn-1-one (T10-8-SM)



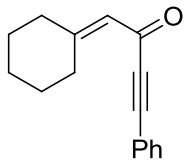
This compound was prepared following procedure **C**. ^{1}H NMR (500 MHz, Chloroform-d) δ 7.61 – 7.57 (m, 2H), 7.47 – 7.42 (m, 1H), 7.40 – 7.36 (m, 2H), 2.62 – 2.52 (m, 2H), 2.31 – 2.26 (m, 1H), 2.12 (dddd, *J* = 11.8, 9.2, 4.4, 2.2 Hz, 1H), 1.56 (dtd, *J* = 11.7, 7.2, 3.6 Hz, 1H), 1.49 – 1.40 (m, 1H), 1.36 (dddd, *J* = 11.3, 9.0, 4.4, 2.1 Hz, 1H), 1.29 (dp, *J* = 10.4, 1.9 Hz, 1H), 1.16 (ddt, *J* = 10.4, 3.3, 1.7 Hz, 1H), 1.07 (dd, *J* = 13.1, 3.3 Hz, 1H), 0.94 (s, 9H), 0.10 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 189.48, 132.99, 130.44, 128.53, 120.46, 92.79, 87.86, 87.44, 46.52, 37.41, 37.08, 35.54, 29.06, 26.00, 21.15, 18.45, -2.57, -3.16; IR (neat): 3083, 2955, 2857, 2201, 1669, 1490, 1252, 1097, 835, 757; ESI^{+} calculated for $[C_{22}H_{30}NaO_2Si+MeCN]^{+}$: 418.22, found 418.27.

1-cyclohexyl-4-phenylbut-3-yn-2-one (T11-1-SM)



This compound was prepared following procedure **B**. ^{1}H NMR (500 MHz, Chloroform-d) δ 7.61 – 7.55 (m, 2H), 7.49 – 7.42 (m, 1H), 7.38 (t, *J* = 7.5 Hz, 2H), 2.54 (d, *J* = 7.0 Hz, 2H), 2.02 (tdp, *J* = 10.8, 7.0, 3.6 Hz, 1H), 1.79 (dd, *J* = 12.7, 3.6 Hz, 2H), 1.69 (ddt, *J* = 26.1, 15.1, 3.2 Hz, 3H), 1.31 (qt, *J* = 12.6, 3.3 Hz, 2H), 1.17 (qt, *J* = 12.7, 3.3 Hz, 1H), 1.02 (qd, *J* = 12.3, 3.4 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 187.89, 133.02, 130.59, 128.59, 120.12, 90.35, 88.21, 53.18, 34.51, 33.07, 26.13, 26.08; IR (neat): 3061, 2924, 2851, 2202, 1667, 1489, 1444, 1290, 1065, 757; ESI^{+} calculated for $[C_{16}H_{18}NaO+MeCN]^{+}$: 290.15, found 290.19.

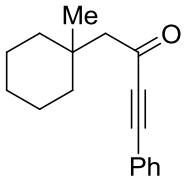
1-cyclohexylidene-4-phenylbut-3-yn-2-one (T11-2-SM)



This compound was prepared following procedure **B**. ^{1}H NMR (500 MHz, Chloroform-d) δ 7.57 (d, *J* = 7.9 Hz, 2H), 7.44 (t, *J* = 7.4 Hz, 1H), 7.37 (t, *J* = 7.6 Hz, 2H), 6.18 (s, 1H), 2.94 (t, *J* = 6.2 Hz, 2H), 2.28 – 2.14 (m, 2H), 1.70 (ddd, *J* = 19.3, 10.7, 5.9 Hz, 4H), 1.63 (q, *J* = 6.8, 6.4 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.01, 165.06, 132.87, 130.34, 128.55, 123.39, 120.56, 90.40, 89.14, 38.33, 30.61, 28.82, 28.03, 26.15; IR (neat): 3118, 3061, 2932,

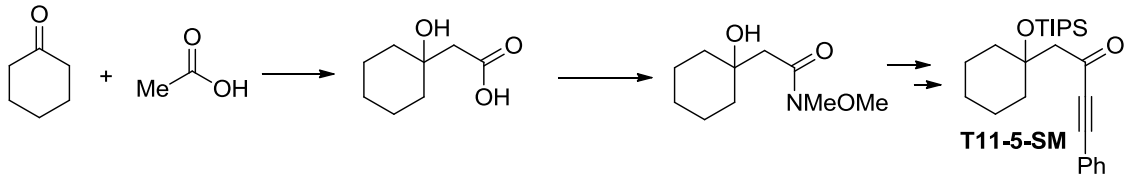
2916, 2203, 1645, 1114, 756; ESI$^+$ calculated for $[C_{16}H_{16}NaO+MeCN]^+$: 288.14, found 288.16.

1-(1-methylcyclohexyl)-4-phenylbut-3-yn-2-one (T11-3-SM)



This compound was prepared following procedure **D**. ^{1}H NMR (500 MHz, Chloroform-d) δ 7.56 (dd, *J* = 7.0, 1.6 Hz, 2H), 7.47 – 7.42 (m, 1H), 7.40 – 7.34 (m, 2H), 2.64 (s, 2H), 1.61 – 1.48 (m, 6H), 1.41 (ddt, *J* = 12.6, 10.4, 5.3 Hz, 4H), 1.12 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 187.91, 132.92, 130.57, 128.58, 120.20, 90.11, 89.80, 56.03, 38.13, 34.83, 26.08, 25.75, 21.98, 21.95; IR (neat): 3058, 2927, 2853, 2204, 1658, 1444, 1264, 1070, 757; ESI$^+$ calculated for $[C_{17}H_{20}NaO+MeCN]^+$: 304.17, found 304.21.

4-phenyl-1-(1-(triisopropylsilyloxy)cyclohexyl)but-3-yn-2-one (T11-5-SM)

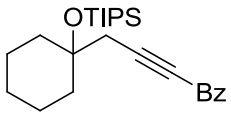


^{n}BuLi (7.5 mmol) was added to a mixture of Et_2NH (7.5 mmol) and THF (12 mL) at -78 ℃, and the mixture was allowed to warm up to 0 ℃ and stirred for 0.5 h. Then the reaction mixture was recooled to -78 ℃ and acetic acid (0.3 mL, 5 mmol) and ^{n}BuLi (5mmol) was added dropwise. The resulting solution was allowed to warm up to 0 ℃ and stirred for 0.5 h. Then the reaction mixture was recooled to -78 ℃ and cyclohexanone (1.5 mL, 15 mmol) was added dropwise. The resulting solution was allowed to warm up to room temperature and

stirred for 1 h. After acid/base extraction, the combined organic extract was washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The crude product was dissolved in DCM (28 mL). To the above solution was added *N*-methylmorpholine (1.5 mL), *N*,*O*-dimethylhydroxylamine hydrochloride (780 mg) and EDCI (920 mg) at 0 ℃. The resulting solution was allowed to warm up to room temperature and stirred overnight. After the reaction finished, the reaction mixture was quenched with water and extracted with DCM. The combined organic extract was washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The crude product was dissolved in DCM (5 mL). To the above solution was added lutidine (1.2 mL) and TIPSOTf (0.9 mL) at 0 ℃. After the reaction finished monitored by TLC, the reaction mixture was quenched with water and extracted with Et_2O. The combined organic extract was washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The above crude product was added to a THF (10 mL) solution of (phenylethynyl)lithium (6 mmol) at -78 ℃. The resulting solution was allowed to warm up to room temperature and stirred overnight. After the reaction finished, the reaction mixture was quenched with saturated NH_4Cl solution and extracted with Et_2O. The combined organic extract was washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by chromatography on silica gel to afford the desired product **T11-5-SM** (730 mg, 37% yield counted four steps from acetic acid). ^{1}H NMR (500 MHz, Chloroform-d) δ 7.59 – 7.48 (m, 2H), 7.47 – 7.41 (m, 1H), 7.38 (t, *J* = 7.5 Hz, 2H), 2.96 (s, 2H), 1.96 (ddd, *J* = 11.7, 7.6, 3.4 Hz, 2H), 1.75 (ddq, *J* = 13.8, 7.1, 3.7 Hz, 2H), 1.64 (ddd, *J* = 12.6, 8.6, 3.7 Hz, 2H), 1.43 (dddd, *J* = 34.4, 17.6, 8.6, 4.5 Hz, 4H), 1.08 (m, 21H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 186.07, 132.94, 130.55, 128.58, 120.33, 90.37, 90.08, 75.40,

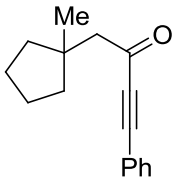
55.62, 39.04, 25.39, 23.17, 18.47, 13.71; IR (neat): 3065, 2942, 2865, 2203, 1665, 1490, 1063, 757; ESI$^+$ calculated for $[C_{25}H_{38}NaO_2Si]^+$: 421.25, found 421.31.

1-phenyl-4-(1-(triisopropylsilyloxy)cyclohexyl)but-2-yn-1-one (T11-6-SM)



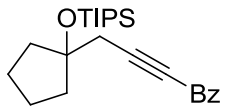
This compound was prepared following procedure **E**. ^{1}H NMR (500 MHz, Chloroform-d) δ 8.20 – 8.06 (m, 2H), 7.60 (t, *J* = 7.4 Hz, 1H), 7.47 (t, *J* = 7.7 Hz, 2H), 2.78 (s, 2H), 1.91 (ddd, *J* = 11.5, 8.4, 3.0 Hz, 2H), 1.74 (tdd, *J* = 9.9, 7.1, 4.2 Hz, 2H), 1.64 (ddd, *J* = 12.1, 7.8, 4.0 Hz, 2H), 1.47 – 1.36 (m, 4H), 1.08 (m, 21H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.00, 136.97, 133.83, 129.56, 128.44, 94.11, 81.77, 74.58, 38.30, 25.39, 22.96, 18.41, 13.65; IR (neat): 3065, 2941, 2865, 2200, 1790, 1645, 1450, 1264, 1015, 883; ESI$^+$ calculated for $[C_{25}H_{38}NaO_2Si]^+$: 421.25, found 421.31.

1-(1-methylcyclopentyl)-4-phenylbut-3-yn-2-one (T11-4-SM)



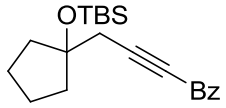
This compound was prepared following procedure **D**. ^{1}H NMR (500 MHz, Chloroform-d) δ 7.60 – 7.55 (m, 2H), 7.48 – 7.42 (m, 1H), 7.41 – 7.36 (m, 2H), 2.70 (s, 2H), 1.75 – 1.59 (m, 6H), 1.56 – 1.49 (m, 2H), 1.14 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 187.78, 132.90, 130.58, 128.59, 120.19, 90.17, 89.44, 56.71, 42.16, 39.65, 26.03, 24.02; IR (neat): 3065, 2954, 2871, 2203, 1659, 1489, 1444, 1076, 757; ESI$^+$ calculated for $[C_{16}H_{18}NaO+MeCN]^+$: 290.15, found 290.18.

1-phenyl-4-(1-(triisopropylsilyloxy)cyclopentyl)but-2-yn-1-one (T11-7-SM)



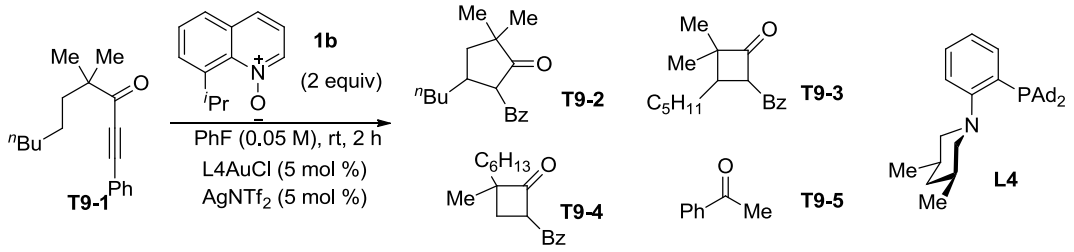
This compound was prepared following procedure **E**. ^{1}H NMR (500 MHz, Chloroform-d) δ 8.21 – 8.07 (m, 2H), 7.65 – 7.56 (m, 1H), 7.47 (t, *J* = 7.7 Hz, 2H), 2.83 (s, 2H), 2.02 – 1.92 (m, 2H), 1.89 – 1.78 (m, 4H), 1.71 – 1.61 (m, 2H), 1.06 (m, 21H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.99, 136.93, 133.84, 129.55, 128.44, 94.36, 83.36, 80.79, 39.99, 32.65, 24.00, 18.31, 13.39; IR (neat): 3055, 2986, 2944, 2866, 2306, 2201, 1647, 1265, 909, 739; ESI^+ calculated for $[C_{24}H_{36}NaO_2Si+MeCN]^+$: 448.26, found 448.31.

4-(1-(tert-butyldimethylsilyloxy)cyclopentyl)-1-phenylbut-2-yn-1-one (T11-8-SM)



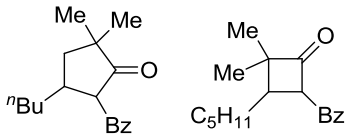
This compound was prepared following procedure **E**. ^{1}H NMR (500 MHz, Chloroform-d) δ 8.16 (dd, *J* = 8.3, 1.4 Hz, 2H), 7.64 – 7.54 (m, 1H), 7.47 (t, *J* = 7.8 Hz, 2H), 2.78 (s, 2H), 1.90 – 1.77 (m, 6H), 1.66 (pd, *J* = 8.0, 3.4 Hz, 2H), 0.87 (s, 9H), 0.13 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.02, 136.93, 133.85, 129.58, 128.46, 94.43, 83.54, 80.74, 39.71, 32.30, 25.70, 23.78, 18.08, -2.52; IR (neat): 3061, 2956, 2856, 2238, 2202, 1646, 1264, 1069, 835, 773; ESI^+ calculated for $[C_{21}H_{30}NaO_2Si+MeCN]^+$: 406.22, found 406.27.

Procedure F: Gold-catalyzed cyclopentanones synthesis via intramolecular insertions into unactivated C(sp^3)-H bonds



L4AuCl (7.2 mg), and $AgNTf_2$ (3.9 mg) were added in this order to a mixture of ynone **T9-1** (51.2 mg, 0.2 mmol), *N*-oxide **1b** (74.8 mg, 0.4 mmol), and PhF (4 mL) in a vial at room temperature. The reaction mixture was stirred at room temperature and the progress of the reaction was monitored by TLC. Upon completion, the mixture was concentrated and the residue was purified by chromatography on silica gel (eluent: hexanes/ethyl acetate) to afford the desired product **T9-2**.

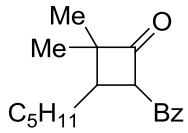
5-benzoyl-4-butyl-2,2-dimethylcyclopentanone (T9-2)



13.7:1

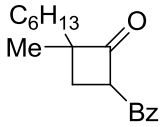
This compound was prepared in 77% yield according to procedure **F**, as a 11.6:1 mixture of cyclopentanone: cyclobutanone isomers, only major peaks are reported. ^{1}H NMR (500 MHz,) δ 8.02 – 7.98 (m, 2H), 7.58 (t, *J* = 7.3 Hz, 1H), 7.49 (t, *J* = 7.7 Hz, 2H), 3.98 (d, *J* = 10.5 Hz, 1H), 3.11 – 2.97 (m, 1H), 2.12 (dd, *J* = 12.7, 6.5 Hz, 1H), 1.51 – 1.35 (m, 3H), 1.34 – 1.16 (m, 4H), 1.14 (s, 3H), 1.09 (s, 3H), 0.83 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, "$CDCl_3$") δ 215.95, 195.88, 137.27, 133.25, 129.43, 128.50, 64.04, 47.81, 43.38, 36.22, 35.43, 29.92, 24.19, 23.82, 22.70, 13.91; IR (neat): 3058, 2959, 2857, 1738, 1647, 1596, 1508, 1277, 821, 736; ESI^{+} calculated for $[C_{18}H_{24}NaO_2+MeCN]^{+}$: 336.19, found 336.22.

4-benzoyl-2,2-dimethyl-3-pentylcyclobutanone (T9-3)



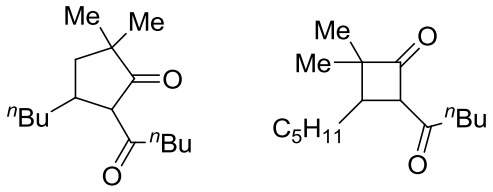
This compound exists as a mixture of cyclopentanone: cyclobutanone isomers, only selected peaks for **T9-3** are reported. ^{1}H NMR (500 MHz,) δ 8.07 – 8.01 (m, 2H), 7.64 – 7.54 (m, 1H), 7.49 (td, *J* = 7.7, 2.1 Hz, 2H), 4.72 (d, *J* = 8.1 Hz, 1H), 2.91 (td, *J* = 8.6, 6.5 Hz, 1H), 1.76 – 1.65 (m, 1H), 1.53 – 1.24 (m, 7H), 1.22 (s, 6H), 0.88 (m, 3H); ^{13}C NMR (126 MHz, "$CDCl_3$") δ 199.78, 183.93, 129.34, 126.38, 122.34, 121.57, 64.66, 52.40, 30.23, 24.90, 23.14, 21.04, 16.04, 15.52, 10.85, 7.01; GCMS *m*/*z* 272 (M^+).

4-benzoyl-2-hexyl-2-methylcyclobutanone (T9-4)



This compound is not separatable from **T9-2** and **T9-3**. Compound **T9-4** exists as a 1:1 mixture of diastereomers. Combined peaks of the two diasteromers are selected and reported from the mixture NMR of **T9-2**, **T9-3**, and **T9-4**. ^{1}H NMR (500 MHz, Chloroform-d) δ 5.13 (dd, *J* = 9.6, 7.1 Hz, 1H), 5.08 (dd, *J* = 9.8, 7.0 Hz, 1H), 2.85 (dd, *J* = 11.7, 7.1 Hz, 1H), 2.67 (dd, *J* = 11.7, 7.0 Hz, 1H), 1.89 (dd, *J* = 11.6, 9.7 Hz, 1H), 1.20 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 207.05, 207.00, 190.56, 190.25, 65.98, 65.59, 63.64, 63.43, 36.78, 35.25, 31.75, 31.69, 29.75, 29.69, 26.34, 26.25, 25.43, 25.25, 24.60, 24.28, 22.67, 22.63, 21.28, 20.11, 14.14; GCMS *m*/*z* 272 (M^+).

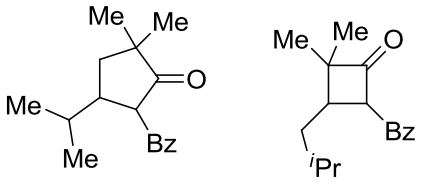
4-butyl-2,2-dimethyl-5-pentanoylcyclopentanone (T10-1-P)



>25:1

This compound was prepared in 94% yield according to procedure **F**, as a >25:1 mixture of cyclopentanone: cyclobutanone isomers, only major peaks are reported.[1]H NMR (500 MHz, Chloroform-d) δ 3.06 (d, *J* = 10.5 Hz, 1H), 2.87 – 2.70 (m, 2H), 2.48 (dt, *J* = 17.7, 7.2 Hz, 1H), 2.00 (dd, *J* = 12.6, 6.6 Hz, 1H), 1.70 – 1.49 (m, 3H), 1.46 – 1.11 (m, 8H), 1.08 (s, 3H), 0.98 (s, 3H), 0.89 (m, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 215.92, 205.17, 68.45, 47.39, 43.69, 42.92, 35.34, 34.40, 29.83, 25.28, 23.99, 23.76, 22.74, 22.19, 13.96, 13.83; IR (neat): 2958, 2930, 2873, 2859, 1740, 1708, 1466; ESI$^+$ calculated for $[C_{16}H_{28}NaO_2+MeCN]^+$: 316.23, found 316.26.

5-benzoyl-4-isopropyl-2,2-dimethylcyclopentanone (T10-2-P)

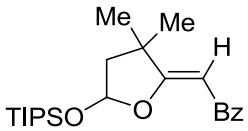


15:1

This compound was prepared in 78% yield according to procedure **F**. Catalyst, IMesAuCl (5 mol %)/$AgNTf_2$ (5 mol %). Compound **T10-2-P** exists as a 15:1 mixture of cyclopentanone: cyclobutanone isomers, only major peaks are reported.[1]H NMR (500 MHz, Chloroform-d) δ

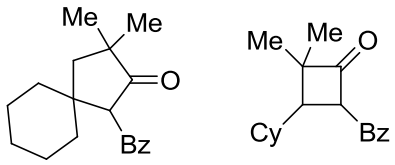
8.02 (dd, *J* = 7.2, 1.6 Hz, 2H), 7.60 – 7.55 (m, 1H), 7.51 – 7.46 (m, 2H), 4.07 (d, *J* = 10.2 Hz, 1H), 2.88 (dddd, *J* = 12.1, 10.2, 8.5, 6.7 Hz, 1H), 2.10 (dd, *J* = 12.6, 6.7 Hz, 1H), 1.56 – 1.43 (m, 2H), 1.13 (s, 3H), 1.10 (s, 3H), 0.95 (d, *J* = 6.7 Hz, 3H), 0.77 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 215.82, 196.05, 137.10, 133.17, 129.44, 128.51, 62.24, 48.27, 43.11, 41.69, 33.86, 23.84, 23.65, 21.86, 20.11; IR (neat): 3054, 2929, 2852, 1736, 1655, 1599, 1264, 1170, 740; ESI$^+$ calculated for $[C_{17}H_{22}NaO_2+MeCN]^+$: 322.18, found 322.21.

2-(3,3-dimethyl-5-(triisopropylsilyloxy)dihydrofuran-2(3H)-ylidene)-1-phenylethanone (T10-3-P)



This compound was prepared in 60% yield according to procedure **F**. Catalyst, $IPrAuNTf_2$ (5 mol %). ^{1}H NMR (400 MHz, Chloroform-d) δ 7.85 (d, *J* = 7.3 Hz, 2H), 7.46 (t, *J* = 7.3 Hz, 1H), 7.40 (t, *J* = 7.4 Hz, 2H), 6.01 (d, *J* = 5.2 Hz, 1H), 5.82 (s, 1H), 2.06 (dd, *J* = 12.8, 5.3 Hz, 1H), 1.91 (d, *J* = 12.7 Hz, 1H), 1.49 (s, 3H), 1.30 (s, 3H), 1.20 – 0.99 (m, 23H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 189.57, 179.61, 140.45, 131.28, 128.09, 127.80, 102.05, 92.96, 46.29, 43.56, 29.69, 28.69, 17.78, 17.67, 11.85; IR (neat): 3061, 2944, 2867, 1665, 1606, 1463, 1222, 1166, 963, 769; ESI$^+$ calculated for $[C_{23}H_{36}NaO_3Si+MeCN]^+$: 452.26, found 452.31.

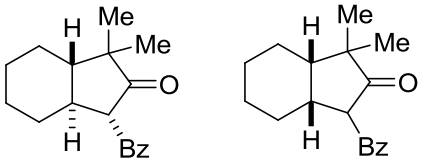
1-benzoyl-3,3-dimethylspiro[4.5]decan-2-one (T10-4-P)



18.2:1

This compound was prepared in 96% yield according to procedure **F**, as a 18.2:1 mixture of cyclopentanone: cyclobutanone isomers, only major peaks are reported. ^{1}H NMR (500 MHz, Chloroform-d) δ 7.97 (d, *J* = 7.5 Hz, 2H), 7.58 (t, *J* = 7.3 Hz, 1H), 7.48 (t, *J* = 7.7 Hz, 2H), 4.36 (s, 1H), 2.27 (d, *J* = 13.4 Hz, 1H), 1.95 (d, *J* = 13.4 Hz, 1H), 1.71 – 1.15 (m, 10H), 1.23 (s, 3H), 1.21 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 219.79, 196.93, 138.24, 133.21, 128.68, 128.68, 67.35, 47.88, 45.91, 43.10, 39.43, 34.01, 28.25, 27.50, 25.74, 22.79, 22.38; IR (neat): 3065, 2928, 2855, 1738, 1666, 1448; ESI^+ calculated for $[C_{19}H_{24}NaO_2+MeCN]^+$: 348.19, found 348.23.

3-benzoyl-1,1-dimethylhexahydro-1H-inden-2(3H)-one (T10-5-P)

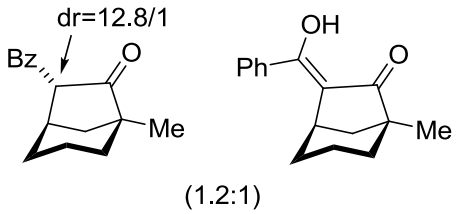


(>20/1)

This compound was prepared in 72% yield according to procedure **F**, as a >20:1 mixture of *trans*: *cis* isomers, only major peaks (*trans isomer*) are reported. ^{1}H NMR (500 MHz, Chloroform-d) δ 7.97 (dd, *J* = 7.3, 1.6 Hz, 2H), 7.61 – 7.55 (m, 1H), 7.48 (t, *J* = 7.7 Hz, 2H), 3.95 (d, *J* = 11.4 Hz, 1H), 2.51 (qd, *J* = 11.5, 3.5 Hz, 1H), 1.93 (tt, *J* = 11.7, 2.7 Hz, 2H), 1.80 (tq, *J* = 8.2, 3.2 Hz, 2H), 1.48 – 1.28 (m, 4H), 1.22 – 1.13 (m, 1H), 1.09 (s, 3H), 0.94 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 216.23, 196.20, 137.43, 133.28, 129.35, 128.48, 63.27,

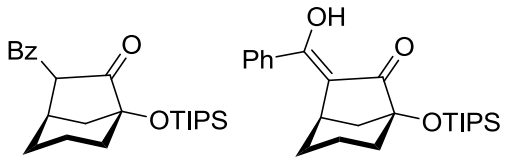
51.81, 49.22, 41.61, 31.38, 26.28, 26.20, 25.66, 22.98, 18.27; IR (neat): 3061, 2928, 2855, 1740, 1671, 1448, 1330, 1281, 1035, 750; ESI$^+$ calculated for $[C_{18}H_{22}NaO_2+MeCN]^+$: 334.18, found 334.21.

7-benzoyl-5-methylbicyclo[3.2.1]octan-6-one (T10-6-P)



This compound was prepared in 85% yield according to procedure **F**, as a 1.2:1 mixture of keto: enol tautomers. Combined peaks of the keto and enol tautomers are reported. ^{1}H NMR (500 MHz, Chloroform-d) δ 13.71 (s, 1H, enol), 8.03 (dd, *J* = 7.5, 1.6 Hz, 2H, keto), 7.77 – 7.70 (m, 2H, enol), 7.63 – 7.52 (m, 1H, keto), 7.49 (t, *J* = 7.7 Hz, 2H, keto), 7.45 (dd, *J* = 5.3, 2.0 Hz, 3H, enol), 4.11 (d, *J* = 2.7 Hz, 1H, keto), 3.22 (td, *J* = 4.6, 3.9, 1.8 Hz, 1H, enol), 2.89 (dt, *J* = 5.7, 3.1 Hz, 1H, keto), 2.27 (ddt, *J* = 11.9, 4.9, 2.3 Hz, 1H, keto), 1.93 – 1.38 (m, 15H), 1.10 (s, 3H, enol), 1.05 (s, 1H, keto); ^{13}C NMR (126 MHz, $CDCl_3$) δ 215.92, 214.71, 194.96, 164.25, 136.16, 134.30, 133.32, 130.54, 129.40, 128.49, 128.38, 127.90, 113.42, 62.35, 49.24, 47.53, 46.20, 42.37, 38.65, 36.49, 35.37, 35.32, 30.27, 30.04, 20.59, 20.09, 19.84; IR (neat): 3061, 2929, 2867, 1747, 1672, 1611, 1596, 1448, 1331, 1229, 1036, 774; ESI$^+$ calculated for $[C_{16}H_{18}NaO_2+MeCN]^+$: 306.15, found 306.19.

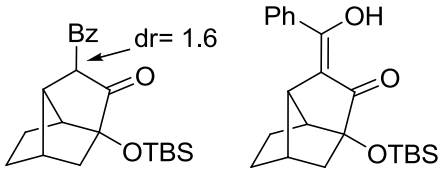
7-benzoyl-5-(triisopropylsilyloxy)bicyclo[3.2.1]octan-6-one (T10-7-P)



(1:1)

This compound was prepared in 75% yield according to procedure **F**, as a 1:1 mixture of keto: enol tautomers. Combined peaks of the keto and enol tautomers are reported. ^{1}H NMR (500 MHz, Chloroform-d) δ 13.66 (s, 1H), 8.05 (d, *J* = 7.7 Hz, 2H), 7.73 (d, *J* = 7.7 Hz, 2H), 7.58 (t, *J* = 7.3 Hz, 1H), 7.52 – 7.42 (m, 5H), 4.05 (s, 1H), 3.25 (t, *J* = 4.7 Hz, 1H), 2.99 (d, *J* = 4.9 Hz, 1H), 2.59 (dt, *J* = 9.9, 4.1 Hz, 1H), 2.22 – 2.16 (m, 1H), 1.97 (tt, *J* = 9.3, 3.6 Hz, 2H), 1.92 – 1.53 (m, 13H), 1.15 – 1.03 (m, 24H), 0.98 (t, *J* = 4.6 Hz, 20H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 210.40, 210.30, 193.44, 165.31, 136.26, 133.88, 133.34, 130.78, 129.68, 128.47, 128.44, 128.06, 110.86, 82.13, 80.82, 60.02, 47.46, 43.00, 39.20, 37.15, 34.41, 33.07, 29.66, 29.57, 20.40, 20.14, 18.26, 18.25, 18.13, 18.11, 13.34, 13.18; IR (neat): 3061, 2942, 2865, 1754, 1676, 1597, 1573, 1462, 1331, 1251, 1182, 1083, 883; ESI^{+} calculated for $[C_{24}H_{36}NaO_3Si+MeCN]^{+}$: 464.26, found 464.31.

T10-8-P

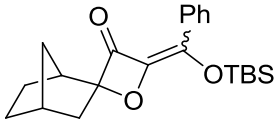


(2.6:1)

This compound was prepared in 76% yield according to procedure **F**. Catalyst, $IPrAuNTf_2$ (5 mol %). Compound **T10-8-P** exists as a 2.6:1 mixture of keto: enol tautomers. Combined peaks are reported and the integration of methyl from TBS group is set to 6. ^{1}H NMR (500

MHz, Chloroform-d) δ 12.28 (s, 0.25H), 8.02 (d, *J* = 7.6 Hz, 0.8H), 7.98 (d, *J* = 7.7 Hz, 0.5H), 7.65 (dd, *J* = 7.1, 2.6 Hz, 0.6H), 7.59 (t, *J* = 7.3 Hz, 0.7H), 7.50 (t, *J* = 7.7 Hz, 1.3H), 7.44 (d, *J* = 5.9 Hz, 0.9H), 4.39 (s, 0.4H), 4.27 (d, *J* = 4.9 Hz, 0.26H), 2.88 (d, *J* = 2.3 Hz, 0.3H), 2.59 (s, 0.8H), 2.54 – 2.44 (m, 0.5H), 2.38 (d, *J* = 5.7 Hz, 0.3H), 2.33 – 2.18 (m, 1H), 2.03 (dd, *J* = 13.0, 5.5 Hz, 0.3H), 1.94 – 1.59 (m, 4.6H), 1.35 – 1.21 (m, 1H), 1.19 – 1.13 (m, 0.28H), 0.95 – 0.84 (m, 9H), 0.22 – -0.05 (m, 22H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 209.27, 207.17, 206.87, 195.42, 194.27, 163.85, 136.70, 136.40, 133.57, 133.46, 133.38, 130.61, 129.48, 128.90, 128.73, 128.68, 128.54, 128.40, 128.02, 127.45, 119.30, 108.01, 89.49, 88.45, 88.42, 55.63, 55.40, 53.81, 49.53, 47.79, 45.82, 44.92, 44.31, 41.40, 39.85, 38.53, 37.30, 36.16, 34.56, 33.75, 33.70, 33.52, 26.04, 25.91, 25.89, 25.84, 20.51, 19.61, 19.20, 18.31, 18.29, 18.23, -2.89, -2.91, -3.02, -3.05, -3.13; IR (neat): 2956, 2927, 2855, 1757, 1643, 1322, 1249, 1123, 837; ESI$^+$ calculated for $[C_{22}H_{30}NaO_3Si+MeCN]^+$: 434.21, found 434.26.

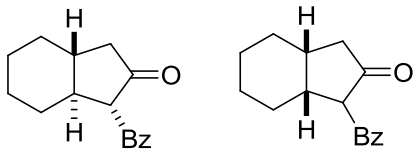
4'-((tert-butyldimethylsilyloxy)(phenyl)methylene)spiro[bicyclo[2.2.1]heptane-2,2'-oxetan]-3'-one (T10-8-SP)



This compound was prepared in 20% yield according to procedure **F**. Catalyst, $IPrAuNTf_2$ (5 mol %). ^{1}H NMR (500 MHz, Chloroform-d) δ 7.87 (d, *J* = 7.5 Hz, 2H), 7.37 (t, *J* = 7.5 Hz, 2H), 7.32 (t, *J* = 7.3 Hz, 1H), 2.62 (d, *J* = 4.2 Hz, 1H), 2.34 (d, *J* = 4.5 Hz, 1H), 2.14 (dt, *J* = 14.0, 3.7 Hz, 1H), 1.96 (dddd, *J* = 14.0, 9.7, 3.8, 2.0 Hz, 1H), 1.70 (d, *J* = 10.5 Hz, 1H), 1.68 – 1.50 (m, 3H), 1.47 – 1.35 (m, 2H), 1.01 (s, 9H), 0.27 (s, 3H), 0.27 (s, 3H); ^{13}C NMR (126

MHz, $CDCl_3$) δ 190.29, 147.45, 136.17, 133.72, 129.17, 128.18, 125.66, 108.07, 43.14, 38.82, 37.49, 36.12, 28.40, 25.83, 21.59, 18.76, -3.88, -4.00; IR (neat): 3055, 2930, 2856, 1771, 1609, 1265, 895, 739; ESI^+ calculated for $[C_{22}H_{30}NaO_3Si+MeCN]^+$: 434.21, found 434.26.

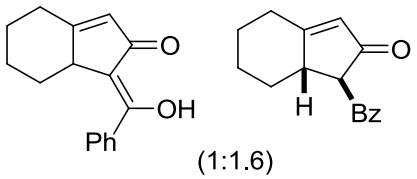
1-benzoylhexahydro-1H-inden-2(3H)-one (T11-1-P)



(>8:1)

This compound was prepared in 40% yield according to procedure **F**. Catalyst, $IPrAuNTf_2$ (5 mol %). Solvent, DCE. Compound **T11-1-P** exists as a >8:1 mixture of *trans*: *cis* isomers, only major peaks (*trans isomer*) are reported. ^1H NMR (500 MHz, Chloroform-d) δ 7.98 – 7.93 (m, 2H), 7.58 (t, *J* = 7.4 Hz, 1H), 7.49 (t, *J* = 7.7 Hz, 2H), 3.94 (d, *J* = 12.1 Hz, 1H), 2.49 (dd, *J* = 17.8, 6.6 Hz, 1H), 2.35 (qd, *J* = 11.6, 3.3 Hz, 1H), 2.13 – 1.98 (m, 2H), 1.93 – 1.79 (m, 3H), 1.77 – 1.67 (m, 1H), 1.50 – 1.34 (m, 2H), 1.26 (dqd, *J* = 39.4, 12.0, 3.4 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 211.44, 196.17, 137.45, 133.35, 129.22, 128.54, 64.18, 46.80, 45.94, 41.11, 31.25, 30.53, 26.18, 25.98; IR (neat): 3054, 2927, 2852, 1743, 1668, 1598, 1508, 1448, 1256, 1170, 739; ESI^+ calculated for $[C_{16}H_{18}NaO_2+MeCN]^+$: 306.15, found 306.18.

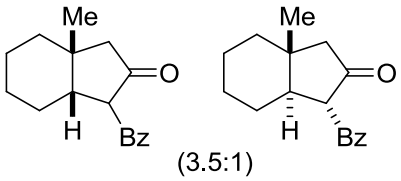
1-benzoyl-5,6,7,7a-tetrahydro-1H-inden-2(4H)-one (T11-2-P)



(1:1.6)

This compound was prepared in 48% yield according to procedure **F**. Catalyst, $IPrAuNTf_2$ (5 mol %). Compound **T11-2-P** exists as a 1.6:1 mixture of keto: enol tautomers. ^{1}H NMR (500 MHz, Chloroform-d) δ 14.33 (s, 1H, enol), 8.08 – 8.04 (m, 2H, keto), 7.73 (dd, *J* = 6.8, 3.1 Hz, 2H, enol), 7.63 – 7.57 (m, 1H, keto), 7.51 (t, *J* = 7.7 Hz, 2H, keto), 7.46 (m, 3H, enol), 6.12 – 6.04 (m, 1H, enol), 5.83 – 5.77 (m, 1H, keto), 4.14 (d, *J* = 2.4 Hz, 1H, keto), 3.45 (dd, *J* = 12.0, 5.3 Hz, 1H, enol), 3.36 – 3.28 (m, 1H, keto), 2.96 – 2.70 (m, 2H, keto+enol), 2.48 – 2.30 (m, 2H, keto+enol), 2.21 (dh, *J* = 10.9, 2.8 Hz, 1H, keto), 2.12 – 1.95 (m, 3H, keto+enol), 1.89 (ddd, *J* = 13.8, 5.0, 2.8 Hz, 1H, keto), 1.69 (dq, *J* = 10.9, 3.2, 2.6 Hz, 1H, enol), 1.57– 1.22 (m, 6H, keto+enol), 0.82 (qd, *J* = 12.8, 3.4 Hz, 1H, enol); ^{13}C NMR (126 MHz, $CDCl_3$, enol+keto) δ 201.87, 200.53, 195.10, 185.16, 176.92, 165.52, 136.86, 134.70, 133.34, 130.47, 129.65, 128.51, 128.43, 127.90, 125.61, 124.42, 113.54, 62.58, 45.66, 45.50, 34.20, 32.46, 31.06, 30.77, 27.97, 26.88, 25.18, 24.70; IR (neat): 3065, 2934, 2855, 1705, 1671, 1624, 1445; ESI$^+$ calculated for $[C_{16}H_{16}NaO_2+MeCN]^+$: 304.13, found 304.17.

1-benzoyl-3a-methylhexahydro-1H-inden-2(3H)-one (T11-3-P)

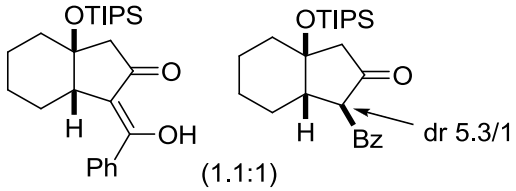


(3.5:1)

This compound was prepared in 83% yield according to procedure **F**. Catalyst, $IPrAuNTf_2$ (5 mol %). Compound **T11-3-P** exists as a 3.5:1 mixture of *cis*: *trans* isomers. Compound *cis*

exists as a 3:1 mixture of keto: enol tautomers. ^{1}H NMR (500 MHz, Chloroform-d, *cis*-**enol+keto**) δ 14.13 (s, 1H, enol), 8.01 (d, *J* = 7.7 Hz, 2H, keto), 7.73 (d, *J* = 7.4 Hz, 2H, enol), 7.60 (t, *J* = 7.3 Hz, 1H, keto), 7.51 (t, *J* = 7.6 Hz, 2H, keto), 7.45 (d, *J* = 6.7 Hz, 3H, enol), 4.46 (d, *J* = 11.4 Hz, 1H, keto), 2.95 – 2.84 (m, 1H, keto), 2.74 – 2.64 (m, 2H, enol), 2.34 (d, *J* = 17.7 Hz, 1H, keto), 2.26 (d, *J* = 17.8 Hz, 1H, keto), 1.94 (d, *J* = 17.4 Hz, 1H, enol), 1.77 (m, 2H, enol+keto), 1.64 – 1.31 (m, 12H, enol+keto), 1.28 (s, 3H, keto), 1.17 – 1.11 (m, 2H, enol), 1.08 (s, 3H, enol); ^{13}C NMR (126 MHz, $CDCl_3$, *cis*-**enol+keto**) δ 211.97, 210.88, 195.90, 168.24, 137.40, 133.37, 133.33, 130.58, 129.36, 129.26, 128.56, 128.54, 128.52, 128.42, 127.73, 58.97, 56.11, 46.31, 46.05, 44.44, 37.73, 35.73, 35.03, 34.18, 30.06, 29.82, 24.23, 23.92, 22.74, 22.06, 21.63, 20.16; ^{1}H NMR (500 MHz, Chloroform-d, *trans*) δ 7.99 (dd, *J* = 14.2, 7.6 Hz, 2H), 7.59 (t, *J* = 5.8 Hz, 1H), 7.50 (m, 2H), 4.05 (d, *J* = 12.8 Hz, 1H), 2.58 (td, *J* = 12.3, 3.3 Hz, 1H), 2.31 – 2.26 (m, 1H), 2.22 (d, *J* = 17.1 Hz, 1H), 1.83 (dd, *J* = 12.6, 3.7 Hz, 2H), 1.70 –1.32 (m, 6H), 1.05 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 211.71, 196.32, 137.51, 133.34, 129.27, 128.53, 59.78, 55.70, 48.83, 38.38, 37.13, 26.16, 24.13, 21.58, 18.46; IR (neat): 3061, 2926, 2858, 1742, 1674, 1594, 1447; ESI^{+} calculated for $[C_{17}H_{20}NaO_2+MeCN]^{+}$: 320.16, found 320.19.

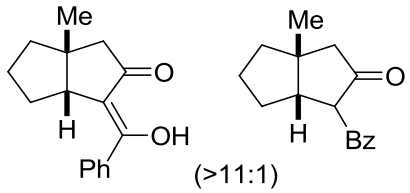
1-benzoyl-3a-(triisopropylsilyloxy)hexahydro-1H-inden-2(3H)-one (T11-5-P)



This compound was prepared in 75% yield according to procedure **F**. Catalyst, $IPrAuNTf_2$ (5 mol %). Compound **T11-5-P** exists as a 1.2:1 mixture of enol: keto tautomers. ^{1}H NMR (500

MHz, Chloroform-d) δ 13.86 (s, 1H, enol), 7.99 (d, *J* = 7.4 Hz, 2H, keto), 7.73 – 7.67 (m, 2H, enol), 7.59 (q, *J* = 7.2 Hz, 1H, enol), 7.52 – 7.46 (m, 2H, keto), 7.45 – 7.40 (m, 3H, keto+enol), 4.35 (d, *J* = 11.6 Hz, 1H, keto), 3.22 – 3.16 (m, 1H, keto), 2.94 (dd, *J* = 11.6, 5.8 Hz, 1H, enol), 2.83 (d, *J* = 17.2 Hz, 1H, enol), 2.71 (d, *J* = 16.9 Hz, 1H, keto), 2.51 (d, *J* = 16.9 Hz, 1H, keto), 2.31 (d, *J* = 17.2 Hz, 1H, enol), 2.07 (dt, *J* = 13.6, 3.9 Hz, 1H, enol), 1.96 (m, 2H, keto+enol), 1.87 (d, *J* = 14.2 Hz, 1H, keto), 1.83 –0.85 (m, 54H, keto+enol); ^{13}C NMR (126 MHz, $CDCl_3$, keto+enol) δ 209.72, 208.80, 194.77, 167.65, 137.20, 134.48, 133.48, 133.46, 130.49, 129.39, 128.80, 128.60, 128.40, 127.90, 127.53, 116.21, 79.41, 74.25, 59.57, 54.91, 49.71, 47.64, 46.41, 36.25, 35.94, 31.93, 24.10, 23.91, 22.68, 21.08, 20.02, 18.47, 18.44, 18.32, 18.30, 18.25, 18.20, 13.45, 13.30, 13.23; IR (neat): 3055, 2941, 2865, 1748, 1678, 1597, 1265, 738; ESI$^+$ calculated for $[C_{25}H_{38}NaO_3Si]^+$: 437.25, found 437.28.

1-benzoyl-3a-methylhexahydropentalen-2(1H)-one (T11-4-P)

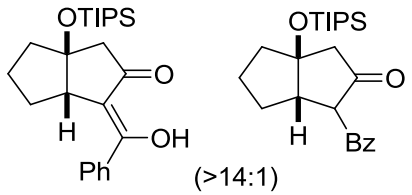


(>11:1)

This compound was prepared in 67% yield according to procedure **F**. Catalyst, $IPrAuNTf_2$ (5 mol %). Compound **T11-4-P** exists as a >11:1 mixture of enol: keto tautomers, only major enol peaks are reported. ^{1}H NMR (500 MHz, Chloroform-d) δ 14.98 (s, 1H), 7.86 – 7.76 (m, 2H), 7.50 – 7.40 (m, 3H), 3.14 (dd, *J* = 9.0, 4.5 Hz, 1H), 2.53 (d, *J* = 18.8 Hz, 1H), 2.40 (d, *J* = 18.9 Hz, 1H), 2.11 – 2.01 (m, 1H), 1.73 – 1.54 (m, 4H), 1.45 (ddd, *J* = 12.3, 7.8, 5.0 Hz, 1H), 1.23 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 208.13, 171.75, 134.61, 130.96, 128.30,

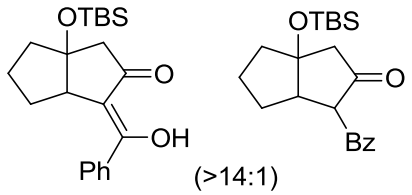
128.20, 115.09, 52.01, 50.36, 45.76, 40.96, 34.69, 28.26, 25.54; IR (neat): 3054, 2949, 2862, 1739, 1598, 1572, 1447, 1368, 1266, 739; ESI^+ calculated for $[C_{16}H_{18}NaO_2+MeCN]^+$: 306.15, found 306.18.

1-benzoyl-3a-(triisopropylsilyloxy)hexahydropentalen-2(1H)-one (T11-7-P)



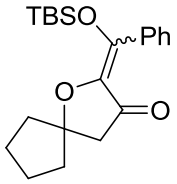
This compound was prepared in 67% yield according to procedure **F**. Catalyst, $IPrAuNTf_2$ (5 mol %). Compound **T11-7-P** exists as a >14:1 mixture of enol: keto tautomers, only major enol peaks are reported. ^1H NMR (500 MHz, Chloroform-d) δ 14.82 (s, 1H), 7.78 (d, *J* = 2.0 Hz, 2H), 7.50 – 7.43 (m, 3H), 3.46 (dd, *J* = 9.2, 4.8 Hz, 1H), 2.85 (d, *J* = 18.6 Hz, 1H), 2.76 (d, *J* = 18.5 Hz, 1H), 2.21 – 2.11 (m, 1H), 1.97 – 1.91 (m, 1H), 1.87 – 1.76 (m, 2H), 1.56 (p, *J* = 6.9 Hz, 1H), 1.34 – 1.24 (m, 1H), 1.05 (m, 21H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 206.08, 171.88, 134.38, 131.10, 128.35, 128.14, 114.52, 86.80, 54.27, 51.33, 41.49, 32.98, 24.85, 18.26, 13.16; IR (neat): 3065, 2944, 2866, 1743, 1638, 1609, 1569, 1102; ESI^+ calculated for $[C_{24}H_{36}NaO_3Si+MeCN]^+$: 464.26, found 464.31.

1-benzoyl-3a-(tert-butyldimethylsilyloxy)hexahydropentalen-2(1H)-one (T11-8-P)



This compound was prepared in 40% yield according to procedure **F**. Catalyst, $IPrAuNTf_2$ (5 mol %). Compound **T11-8-P** exists as a >14:1 mixture of enol: keto tautomers, only major enol peaks are reported. ^{1}H NMR (500 MHz, Chloroform-d) δ 14.82 (s, 1H), 7.79 (d, *J* = 7.1 Hz, 2H), 7.46 (m, 3H), 3.45 (dd, *J* = 9.2, 5.0 Hz, 1H), 2.79 (d, *J* = 18.5 Hz, 1H), 2.72 (d, *J* = 18.6 Hz, 1H), 2.14 (dq, *J* = 14.6, 7.9 Hz, 1H), 1.91 (dt, *J* = 12.8, 6.5 Hz, 1H), 1.79 (tt, *J* = 13.9, 7.0 Hz, 1H), 1.70 (dt, *J* = 13.1, 6.7 Hz, 1H), 1.54 (dt, *J* = 13.0, 6.5 Hz, 1H), 1.23 (dq, *J* = 13.0, 6.9, 6.5 Hz, 1H), 0.87 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 205.94, 171.88, 134.35, 131.11, 128.33, 128.19, 114.56, 86.94, 53.87, 50.93, 40.98, 33.02, 25.68, 24.84, 17.85, -2.65, -2.75; IR (neat): 3050, 2958, 2859, 1597, 1574, 1497, 1469, 1361, 1258, 1096, 830, 795; ESI$^+$ calculated for $[C_{21}H_{30}NaO_3Si+MeCN]^+$: 422.21, found 422.22.

2-((tert-butyldimethylsilyloxy)(phenyl)methylene)-1-oxaspiro[4.4]nonan-3-one (T11-8-SP)



This compound was prepared in 40% yield according to procedure **F**. Catalyst, $IPrAuNTf_2$ (5 mol %). ^{1}H NMR (500 MHz, Chloroform-d) δ 7.47 (dd, *J* = 6.6, 3.1 Hz, 2H), 7.33 (q, *J* = 3.2, 2.7 Hz, 3H), 2.70 (s, 2H), 2.08 (ddd, *J* = 11.3, 6.8, 2.4 Hz, 2H), 1.99 – 1.85 (m, 2H), 1.81 – 1.64 (m, 4H), 0.89 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 196.47, 140.87, 136.03, 134.72, 129.20, 129.02, 127.43, 89.34, 48.00, 38.78, 25.51, 23.75, 18.49, -4.31; IR (neat): 3058, 2956, 2858, 1724, 1595, 1304, 1256, 1154, 1056, 979, 832, 782; ESI$^+$ calculated for $[C_{21}H_{30}NaO_3Si+MeCN]^+$: 422.21, found 422.22.

4.10 References

(1) Li, G.; Zhang, L. *Angewandte Chemie International Edition* **2007**, *46*, 5156.

(2) Shapiro, N. D.; Toste, F. D. *Journal of the American Chemical Society* **2007**, *129*, 4160.

(3) Lu, B.; Li, Y.; Wang, Y.; Aue, D. H.; Luo, Y.; Zhang, L. *Journal of the American Chemical Society* **2013**, *135*, 8512.

(4) Ye, L.; Cui, L.; Zhang, G.; Zhang, L. *Journal of the American Chemical Society* **2010**, *132*, 3258.

(5) Zheng, Z.; Wang, Z.; Wang, Y.; Zhang, L. *Chemical Society Reviews* **2016**.

(6) Zhang, L. *Accounts of Chemical Research* **2014**, *47*, 877.

(7) Ye, L.; He, W.; Zhang, L. *Journal of the American Chemical Society* **2010**, *132*, 8550.

(8) Ye, L.; He, W.; Zhang, L. *Angewandte Chemie International Edition* **2011**, *50*, 3236.

(9) Ji, K.; Zhao, Y.; Zhang, L. *Angewandte Chemie International Edition* **2013**, *52*, 6508.

(10) Luo, Y.; Ji, K.; Li, Y.; Zhang, L. *Journal of the American Chemical Society* **2012**, *134*, 17412.

(11) He, W.; Li, C.; Zhang, L. *Journal of the American Chemical Society* **2011**, *133*, 8482.

(12) Zeng, X.; Liu, S.; Shi, Z.; Liu, G.; Xu, B. *Angewandte Chemie International Edition* **2016**, n/a.

(13) Vasu, D.; Hung, H.-H.; Bhunia, S.; Gawade, S. A.; Das, A.; Liu, R.-S. *Angewandte Chemie International Edition* **2011**, *50*, 6911.

(14) Ji, K.; Zheng, Z.; Wang, Z.; Zhang, L. *Angewandte Chemie International Edition* **2015**, *54*, 1245.

(15) Qian, D.; Hu, H.; Liu, F.; Tang, B.; Ye, W.; Wang, Y.; Zhang, J. *Angewandte Chemie International Edition* **2014**, *53*, 13751.

(16) Wang, Y.; Ji, K.; Lan, S.; Zhang, L. *Angewandte Chemie International Edition* **2012**, *51*, 1915.

(17) Lu, B.; Li, C.; Zhang, L. *Journal of the American Chemical Society* **2010**, *132*, 14070.

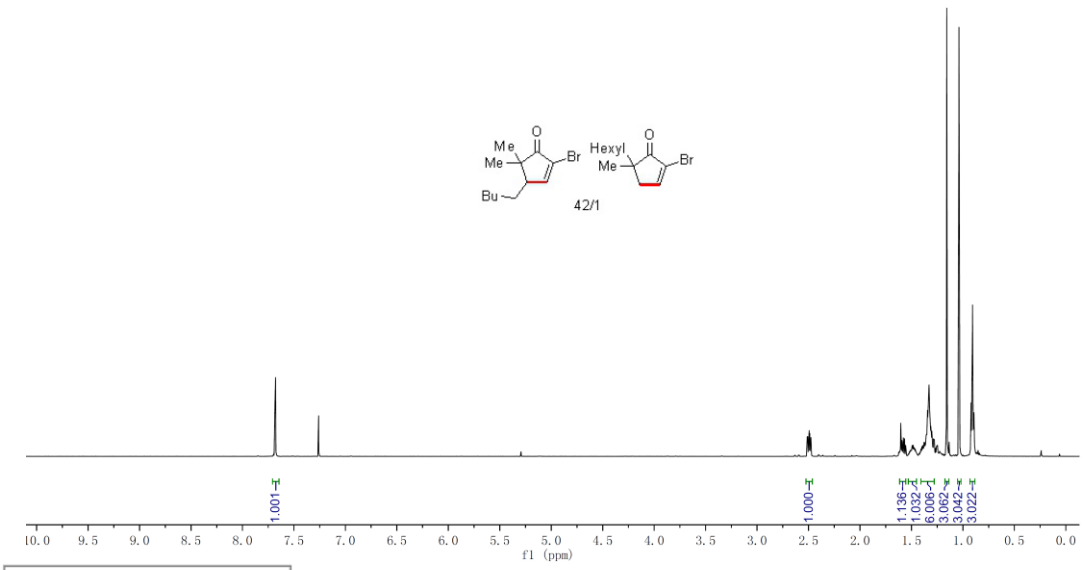
(18) Bian, Z.; Marvin, C. C.; Pettersson, M.; Martin, S. F. *Journal of the American Chemical Society* **2014**, *136*, 14184.

(19) Fructos, M. R.; de Frémont, P.; Nolan, S. P.; Díaz-Requejo, M. M.; Pérez, P. J. *Organometallics* **2006**, *25*, 2237.

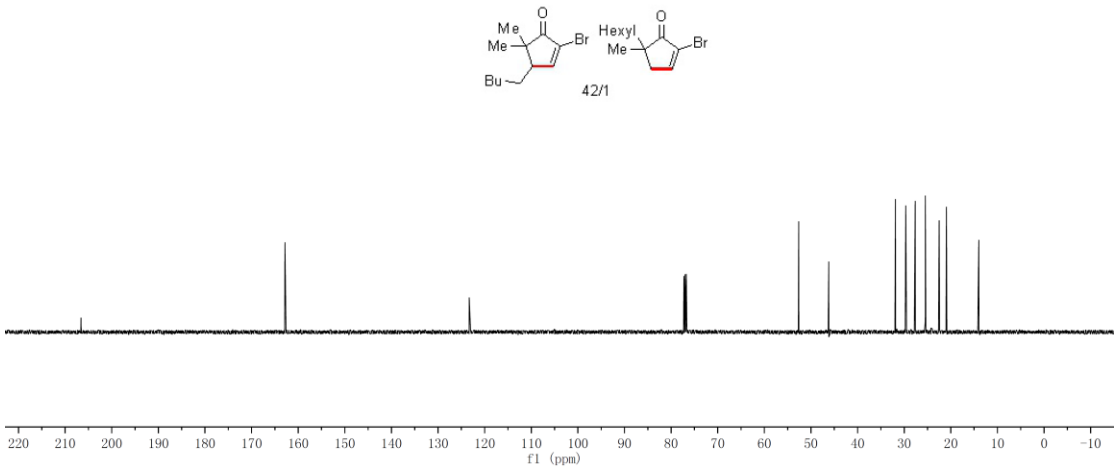
(20) Wang, Y.; Zheng, Z.; Zhang, L. *Journal of the American Chemical Society* **2015**, *137*, 5316.

Chapter 5. Appendix: NMR NMR Spectra

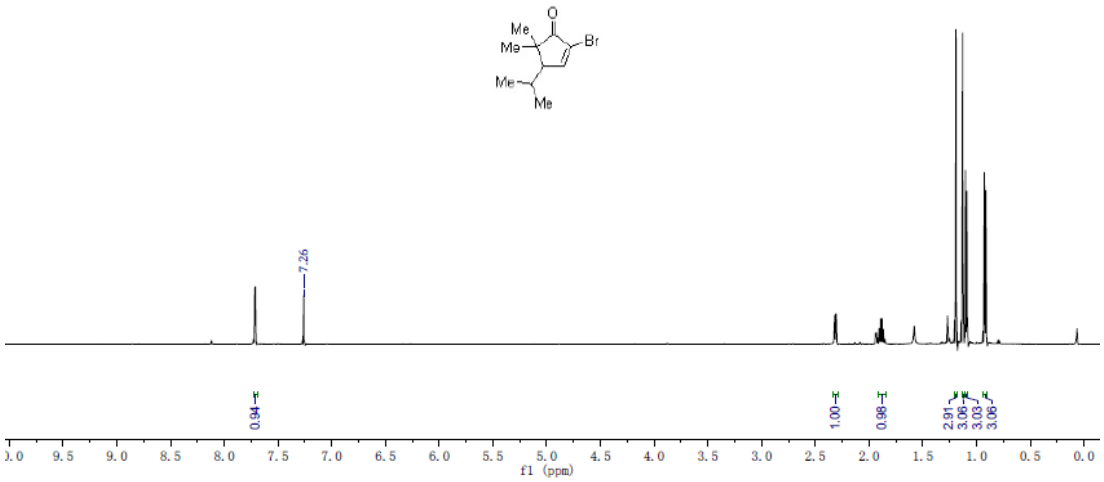
Parameter	Value
1 Title	youliang-5-298A-P
2 Solvent	CDCl3
3 Spectrometer Frequency	499.86
4 Nucleus	1H



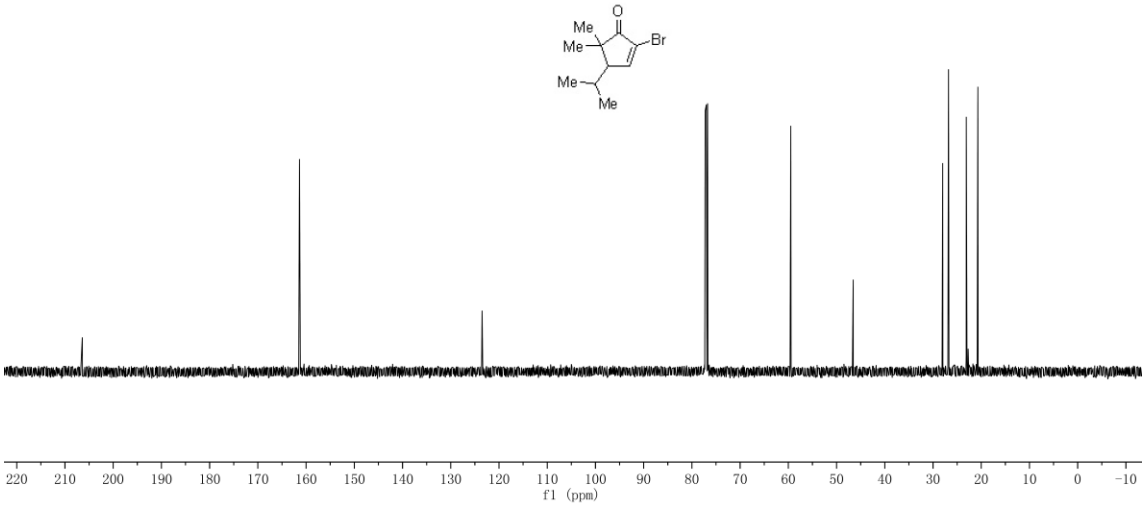
Parameter	Value
1 Title	youliang-5-298A-P-C13e
2 Solvent	CDCl3
3 Spectrometer Frequency	125.70
4 Nucleus	13C



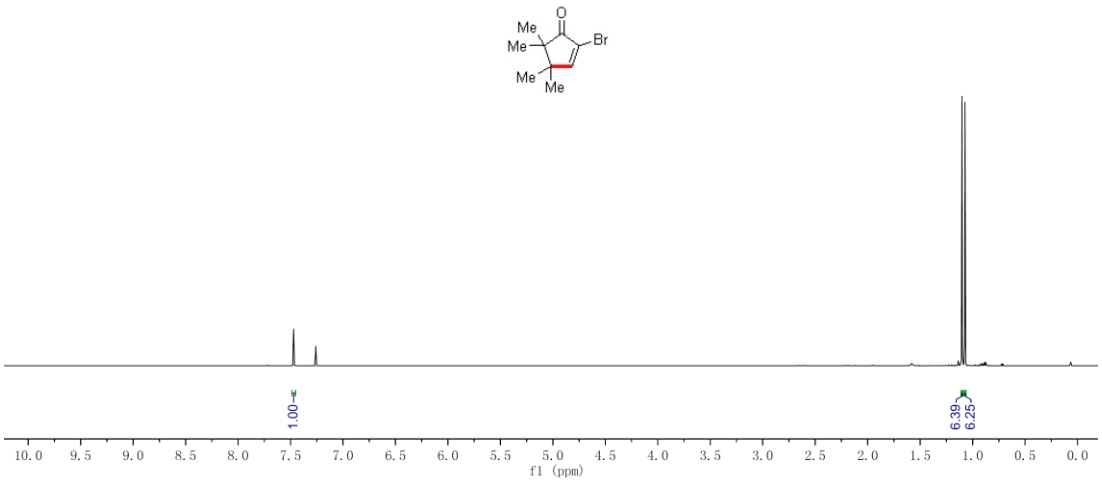
Parameter	Value
1 Title	youliang-5-300-B-P
2 Solvent	CDCl3
3 Temperature	25.0
4 Relaxation Delay	10.0000
5 Spectrometer Frequency	499.86



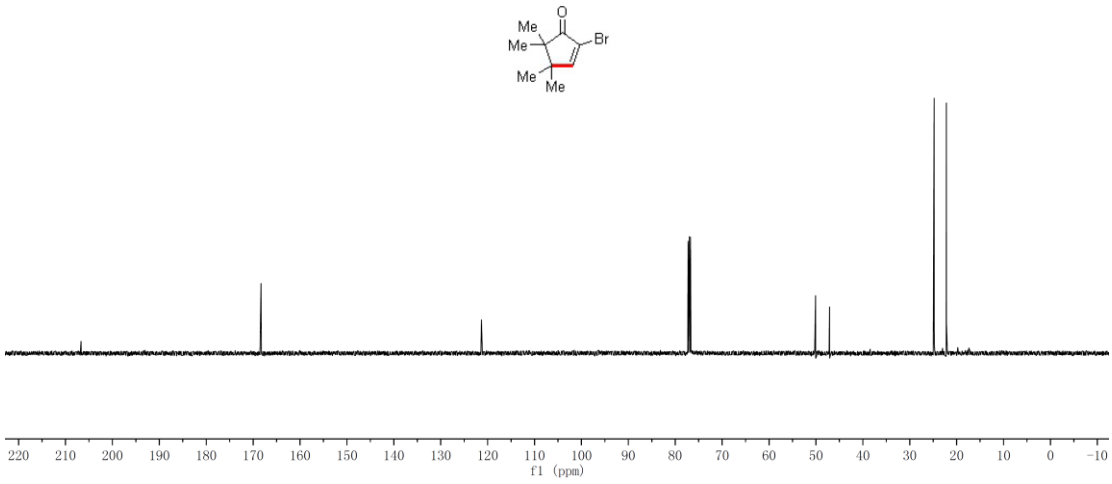
Parameter	Value
1 Title	youliang-5-300-B-P-C13f
2 Solvent	CDCl3
3 Temperature	25.0
4 Relaxation Delay	1.0000
5 Spectrometer Frequency	125.70



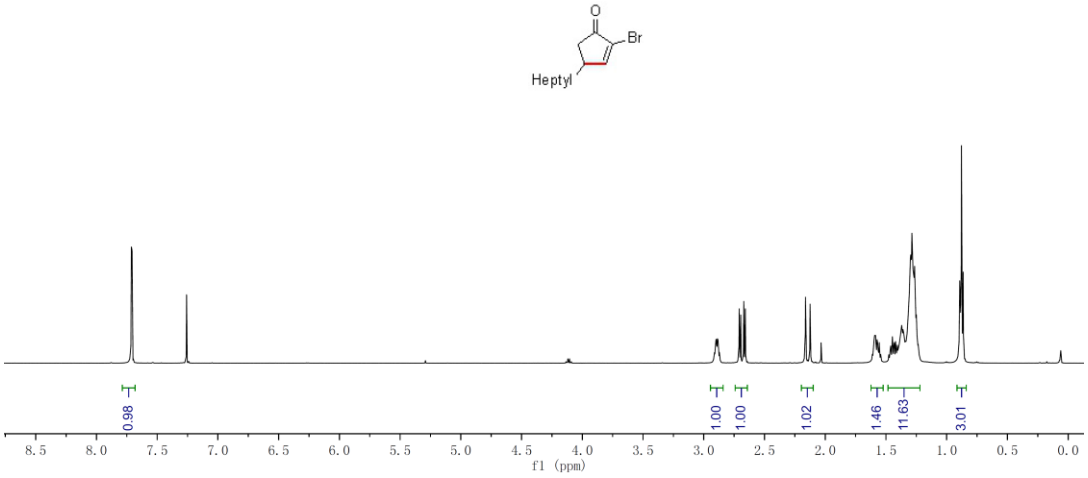
Parameter	Value
1 Title	youliang-5-229C-P
2 Solvent	CDCl3
3 Spectrometer Frequency	499.86
4 Nucleus	1H



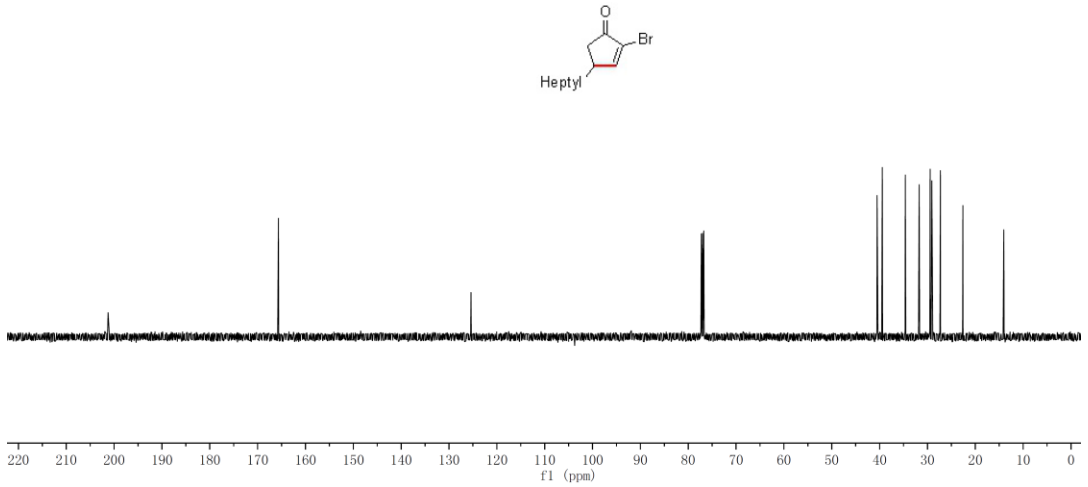
Parameter	Value
1 Title	youliang-5-229C-P-C13i
2 Solvent	CDCl3
3 Spectrometer Frequency	125.70
4 Nucleus	13C



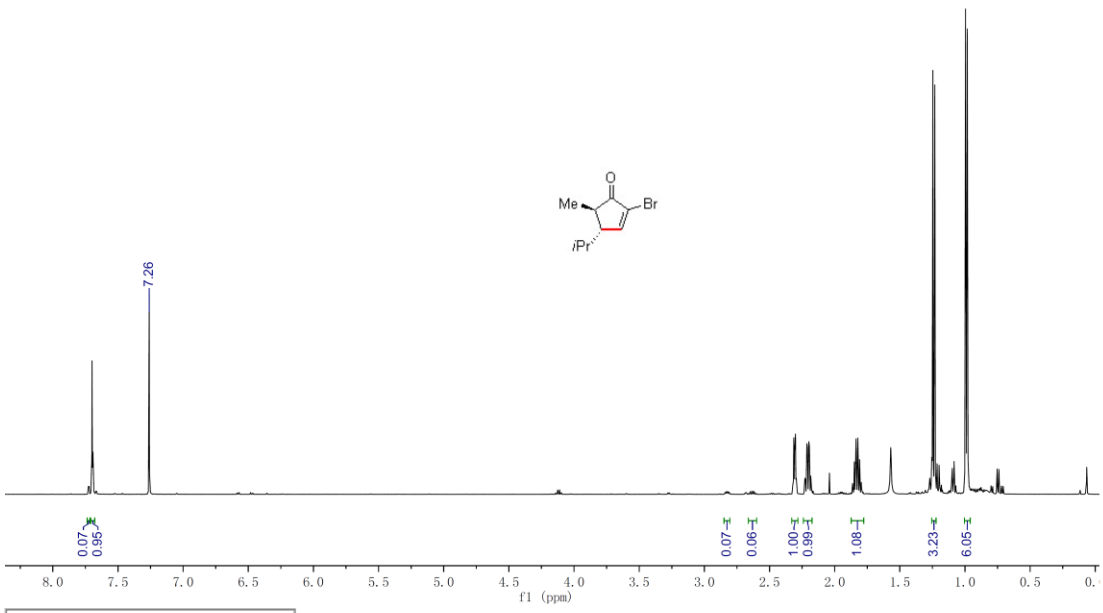
Parameter	Value
1 Title	youliang-5-298B-P-again
2 Solvent	CDCl3
3 Spectrometer Frequency	499.86
4 Nucleus	1H



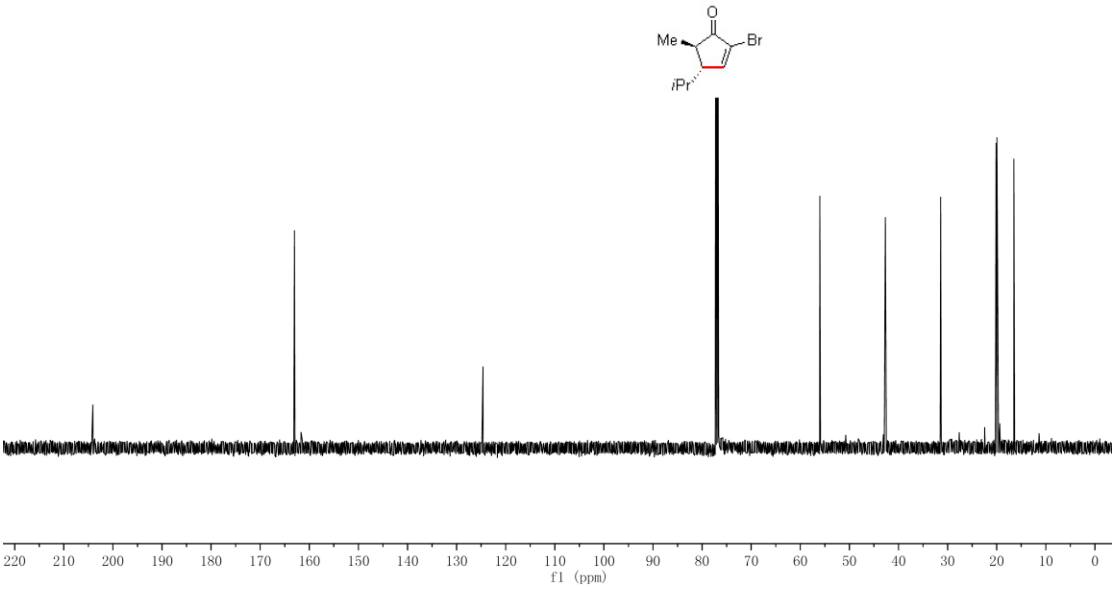
Parameter	Value
1 Title	youliang-5-298B-P-again-C13d
2 Solvent	CDCl3
3 Spectrometer Frequency	125.70
4 Nucleus	13C

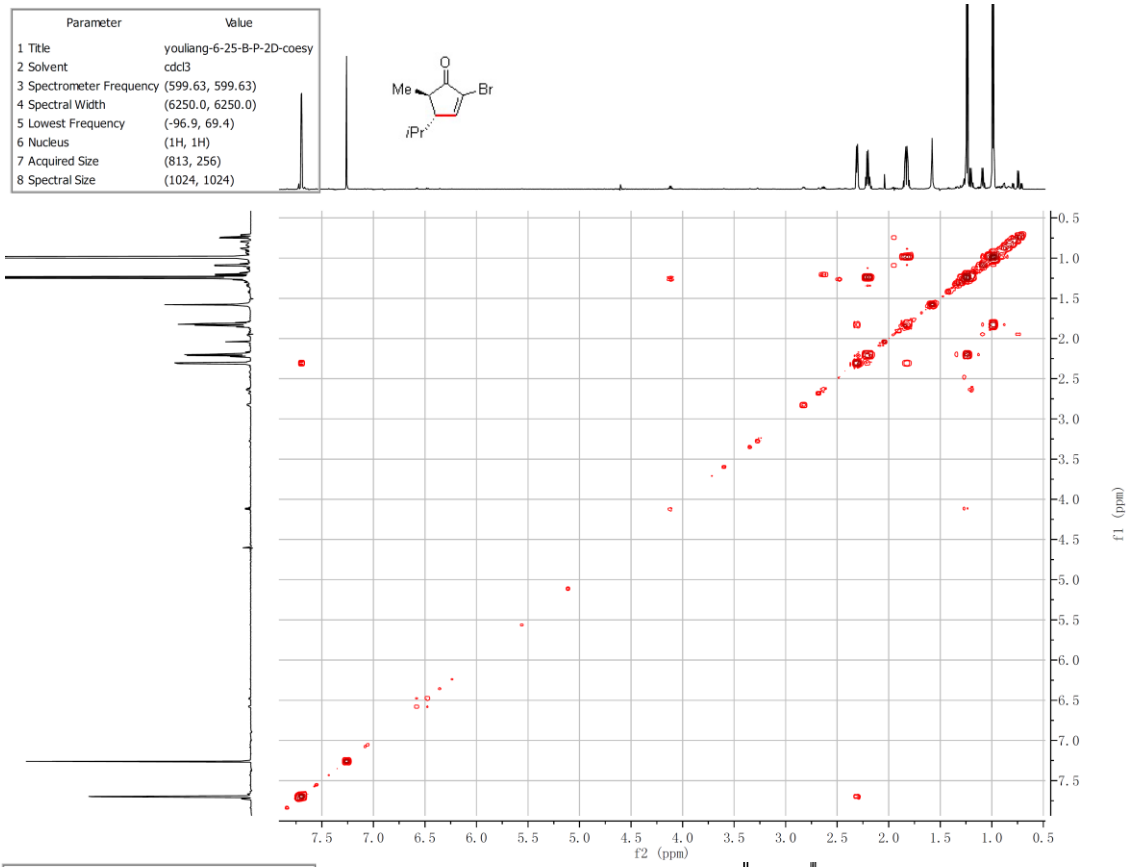


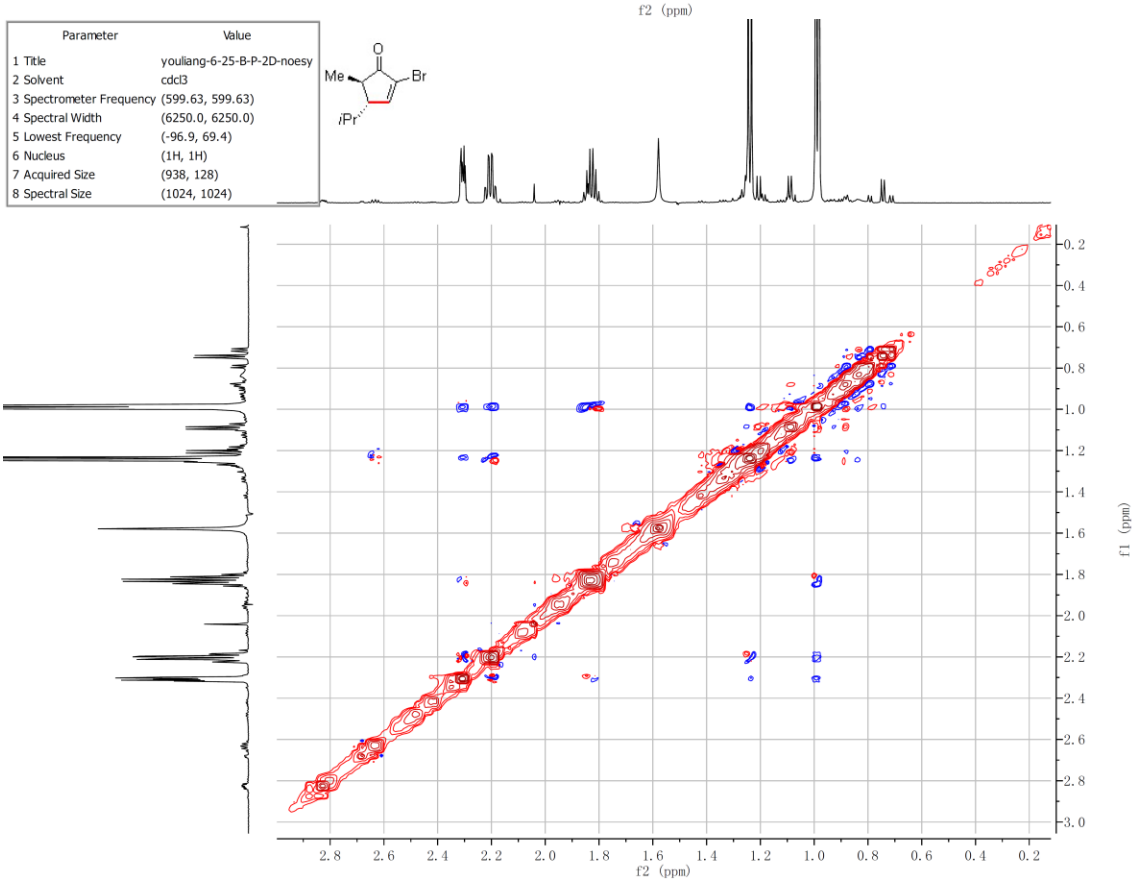
Parameter	Value
1 Title	youliang-6-25B-P
2 Solvent	CDCl3
3 Spectrometer Frequency	499.86
4 Nucleus	1H



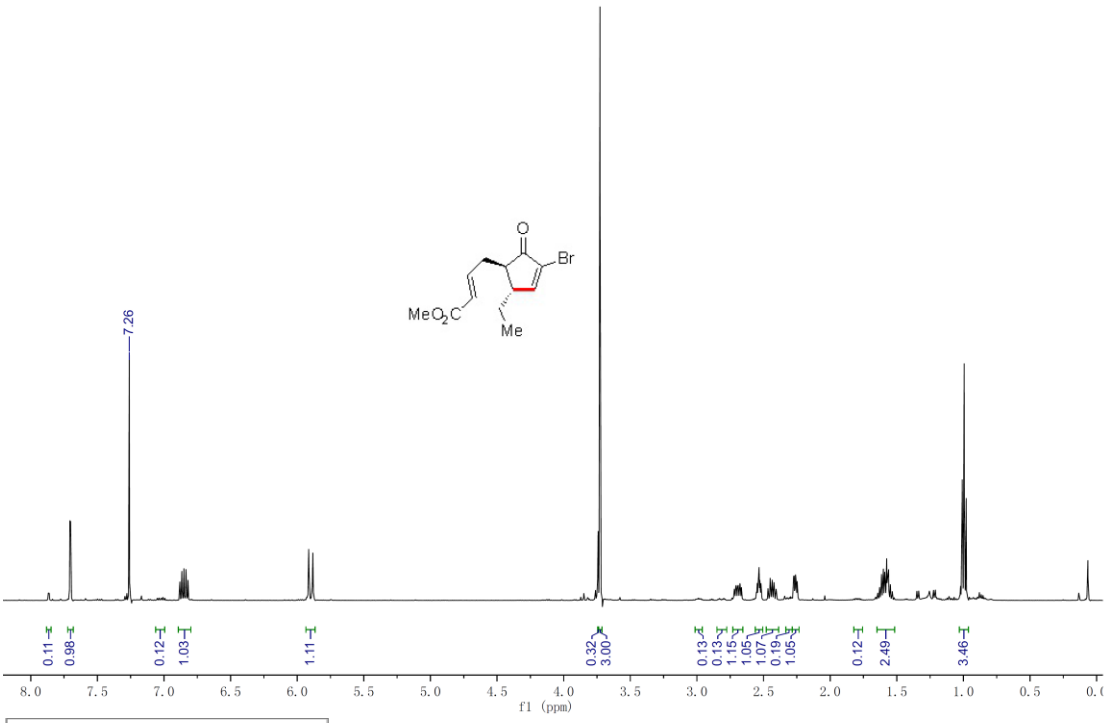
Parameter	Value
1 Title	youliang-6-25B-P-C13i
2 Solvent	CDCl3
3 Spectrometer Frequency	125.70
4 Nucleus	13C



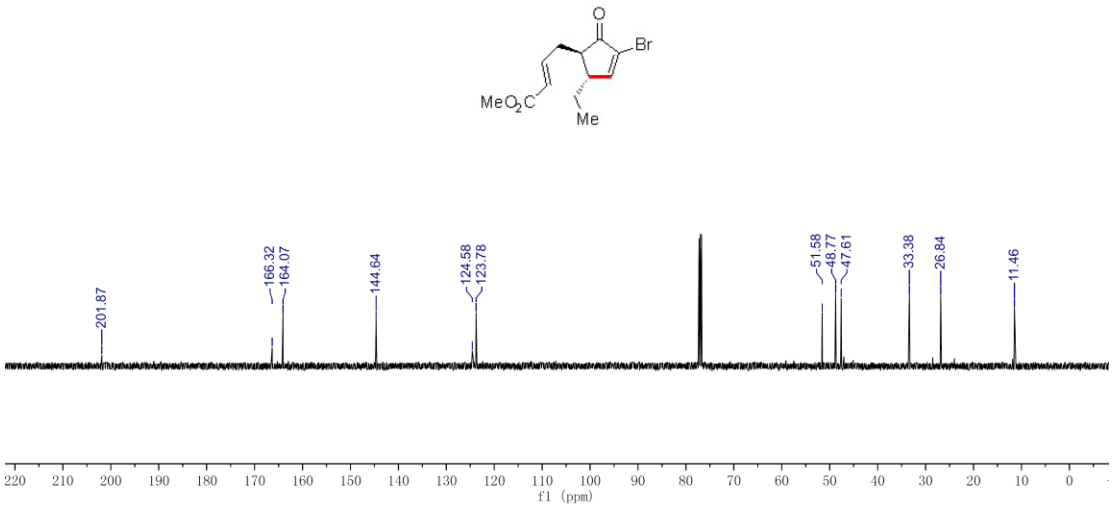

Parameter Value
1 Title youliang-6-25-B-P-2D-coesy
2 Solvent cdcl3
3 Spectrometer Frequency (599.63, 599.63)
4 Spectral Width (6250.0, 6250.0)
5 Lowest Frequency (-96.9, 69.4)
6 Nucleus (1H, 1H)
7 Acquired Size (813, 256)
8 Spectral Size (1024, 1024)
Me
Br
iPr
f2 (ppm)
f1 (ppm)

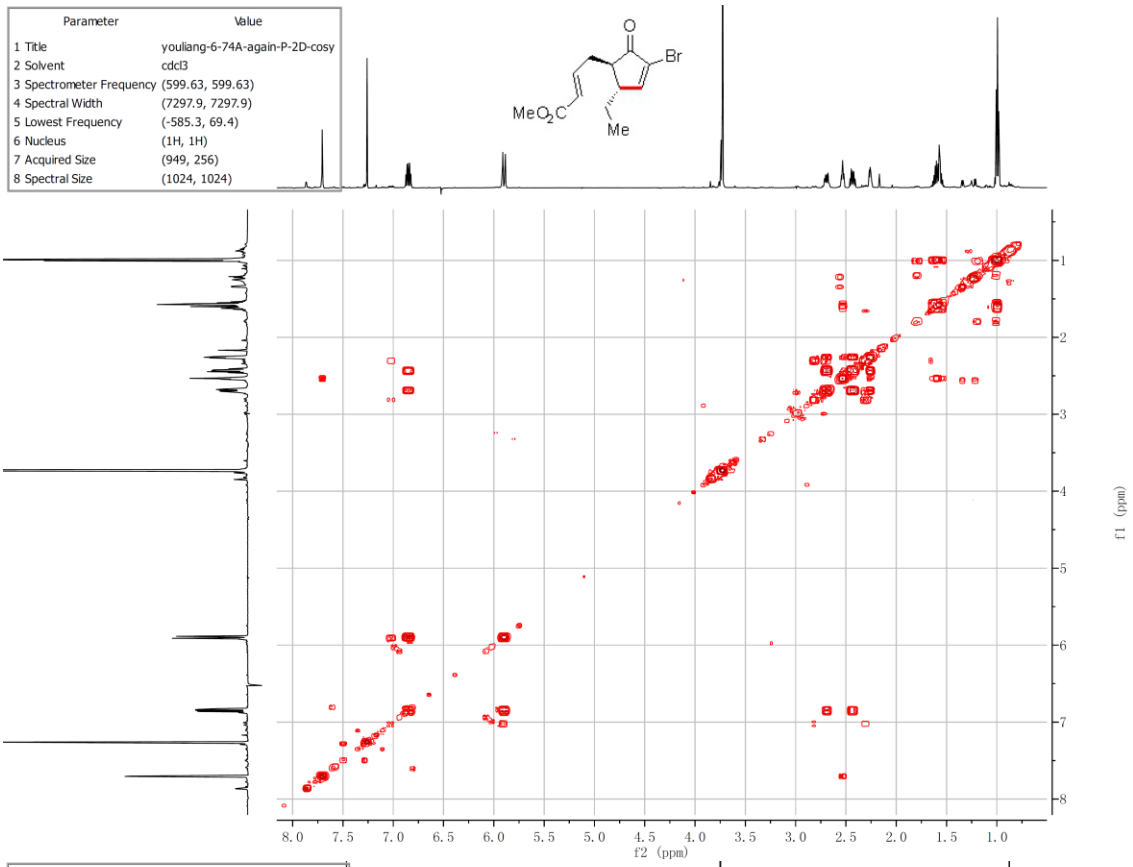

Parameter Value
1 Title youliang-6-25-B-P-2D-noesy
2 Solvent cdcl3
3 Spectrometer Frequency (599.63, 599.63)
4 Spectral Width (6250.0, 6250.0)
5 Lowest Frequency (-96.9, 69.4)
6 Nucleus (1H, 1H)
7 Acquired Size (938, 128)
8 Spectral Size (1024, 1024)
Me
Br
iPr
f2 (ppm)
f1 (ppm)

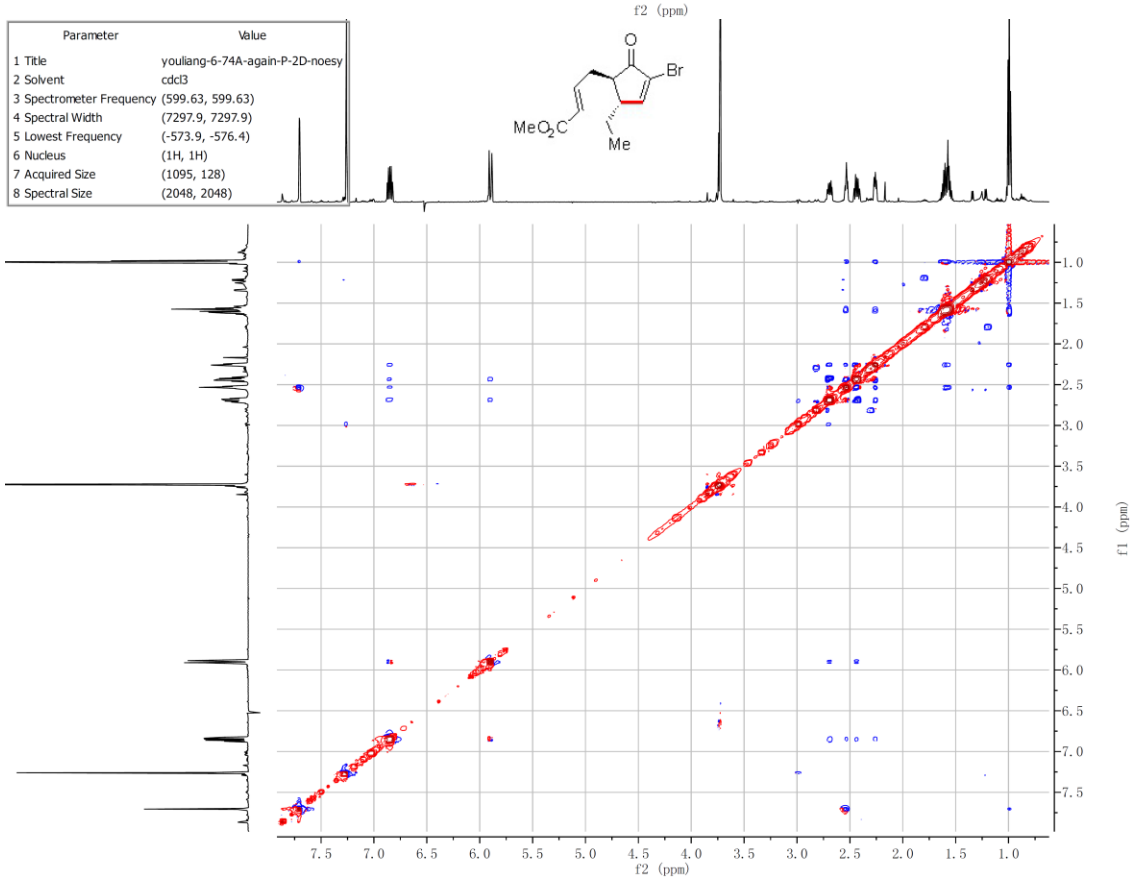
Parameter	Value
1 Title	youliang-6-74A-again-P
2 Solvent	CDCl3
3 Spectrometer Frequency	499.86
4 Nucleus	1H



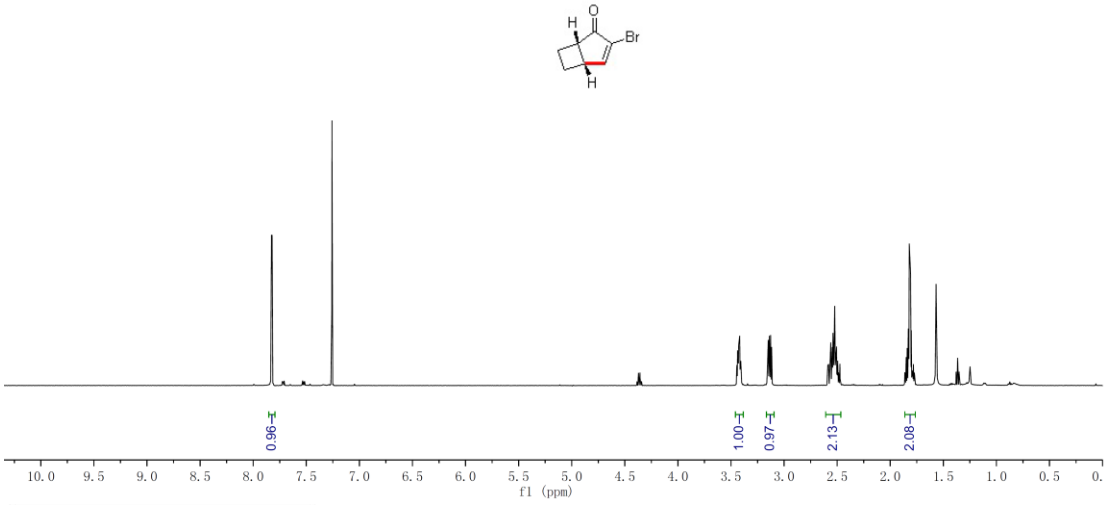
Parameter	Value
1 Title	youliang-6-74A-again-P-C13e
2 Solvent	CDCl3
3 Spectrometer Frequency	125.70
4 Nucleus	13C



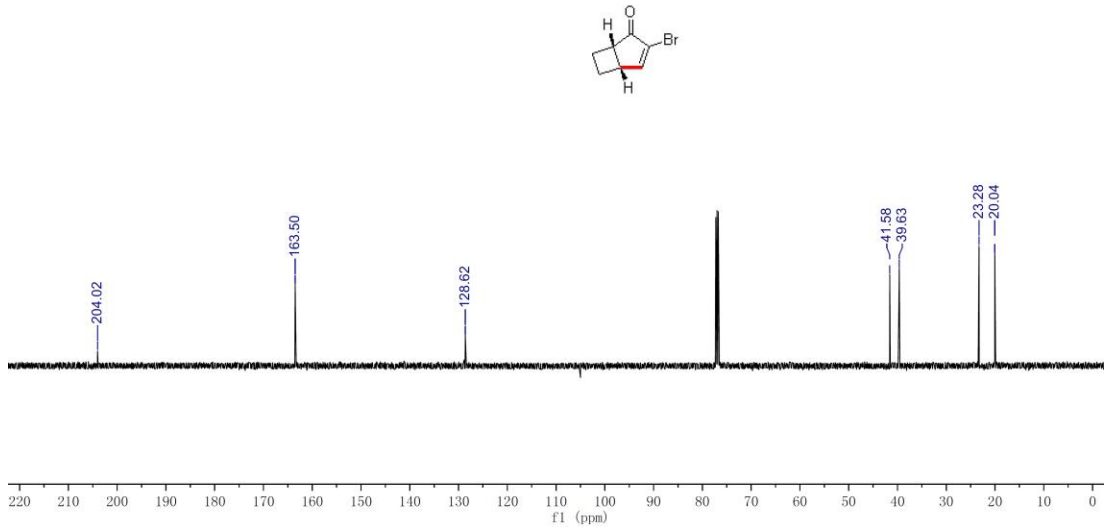

Parameter Value
1 Title youliang-6-74A-again-P-2D-cosy
2 Solvent cdcl3
3 Spectrometer Frequency (599.63, 599.63)
4 Spectral Width (7297.9, 7297.9)
5 Lowest Frequency (-585.3, 69.4)
6 Nucleus (1H, 1H)
7 Acquired Size (949, 256)
8 Spectral Size (1024, 1024)
O
Br
MeO2C
Me
f2 (ppm)
f1 (ppm)


Parameter Value
1 Title youliang-6-74A-again-P-2D-noesy
2 Solvent cdcl3
3 Spectrometer Frequency (599.63, 599.63)
4 Spectral Width (7297.9, 7297.9)
5 Lowest Frequency (-573.9, -576.4)
6 Nucleus (1H, 1H)
7 Acquired Size (1095, 128)
8 Spectral Size (2048, 2048)
O
Br
MeO2C
Me
f2 (ppm)
f1 (ppm)

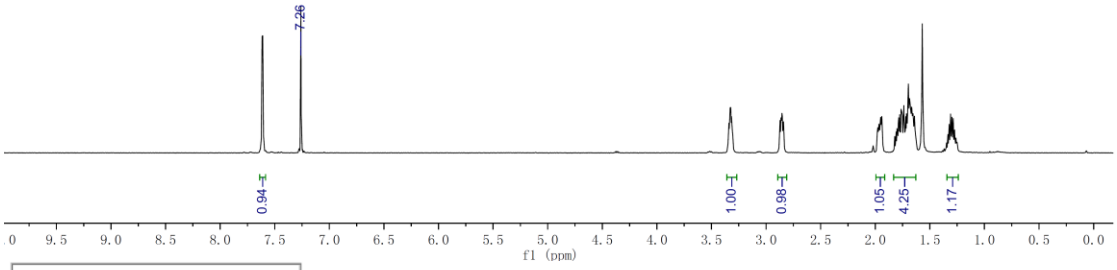
Parameter	Value
1 Title	youliang-6-41C1-P
2 Solvent	CDCl3
3 Spectrometer Frequency	499.86
4 Nucleus	1H



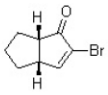
Parameter	Value
1 Title	youliang-6-41C1-P-C13z
2 Solvent	CDCl3
3 Spectrometer Frequency	125.70
4 Nucleus	13C

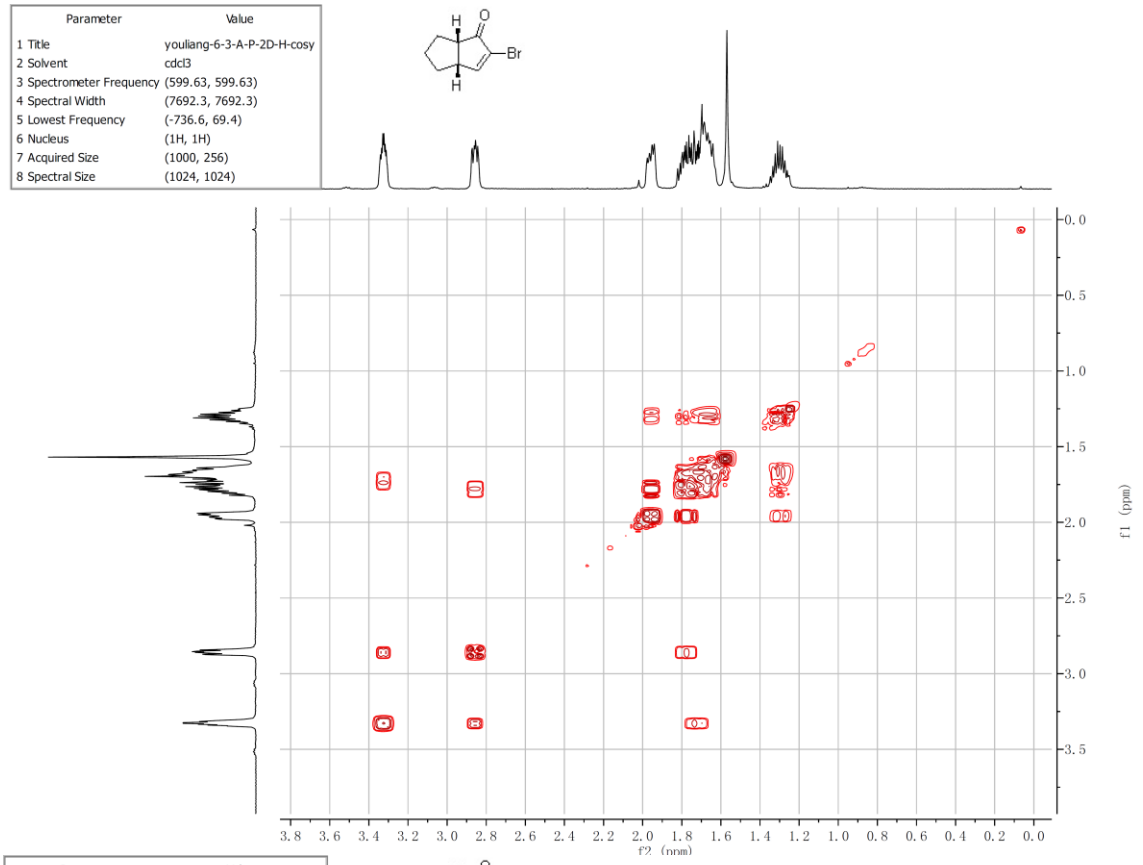


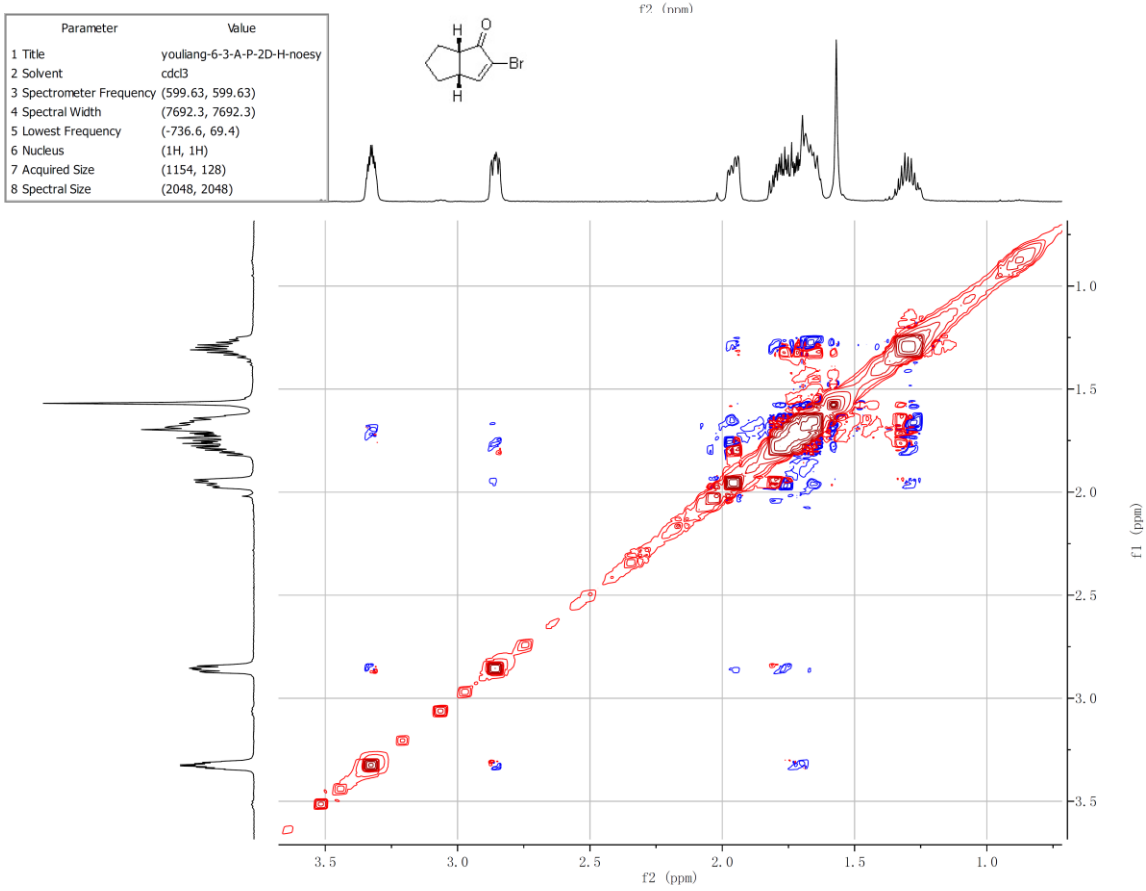
Parameter	Value
1 Title	youliang-6-3-A-P
2 Solvent	CDCl3
3 Spectrometer Frequency	499.86
4 Nucleus	1H



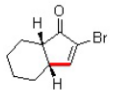
Parameter	Value
1 Title	youliang-6-3-A-P-C13k
2 Solvent	CDCl3
3 Spectrometer Frequency	125.70
4 Nucleus	13C

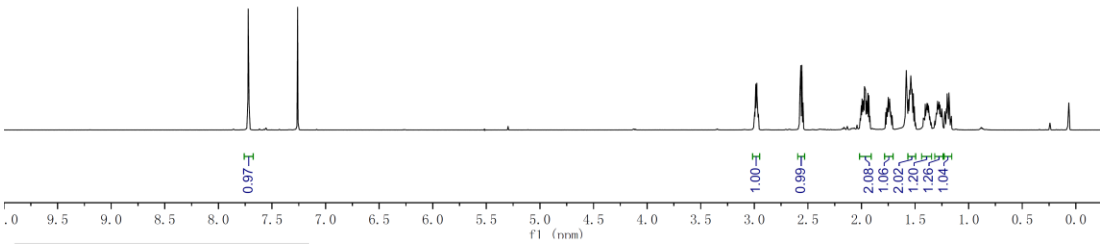



Parameter Value
1 Title youliang-6-3-A-P-2D-H-cosy
2 Solvent cdcl3
3 Spectrometer Frequency (599.63, 599.63)
4 Spectral Width (7692.3, 7692.3)
5 Lowest Frequency (-736.6, 69.4)
6 Nucleus (1H, 1H)
7 Acquired Size (1000, 256)
8 Spectral Size (1024, 1024)
H
O
Br
H
f1 (ppm)
f2 (ppm)

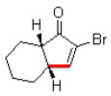

Parameter Value
1 Title youliang-6-3-A-P-2D-H-noesy
2 Solvent cdcl3
3 Spectrometer Frequency (599.63, 599.63)
4 Spectral Width (7692.3, 7692.3)
5 Lowest Frequency (-736.6, 69.4)
6 Nucleus (1H, 1H)
7 Acquired Size (1154, 128)
8 Spectral Size (2048, 2048)
H
O
Br
H
f1 (ppm)
f2 (ppm)

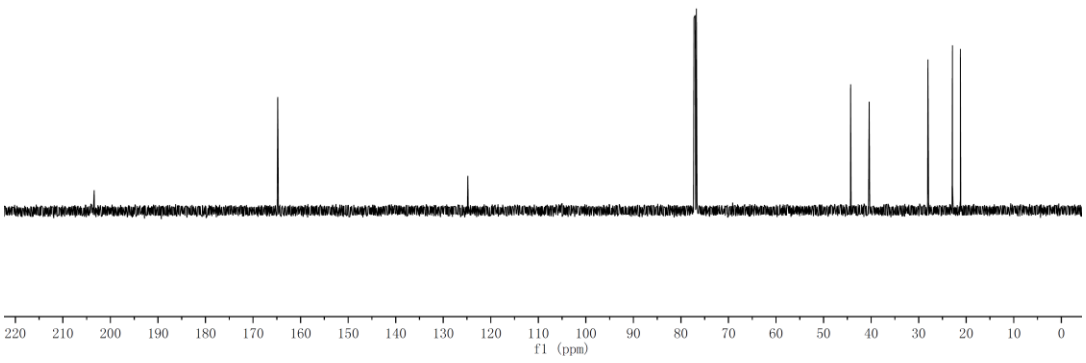
Parameter	Value
1 Title	youliang-5-299-C-P
2 Solvent	cdcl3
3 Spectrometer Frequency	599.64
4 Nucleus	1H



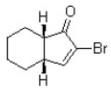


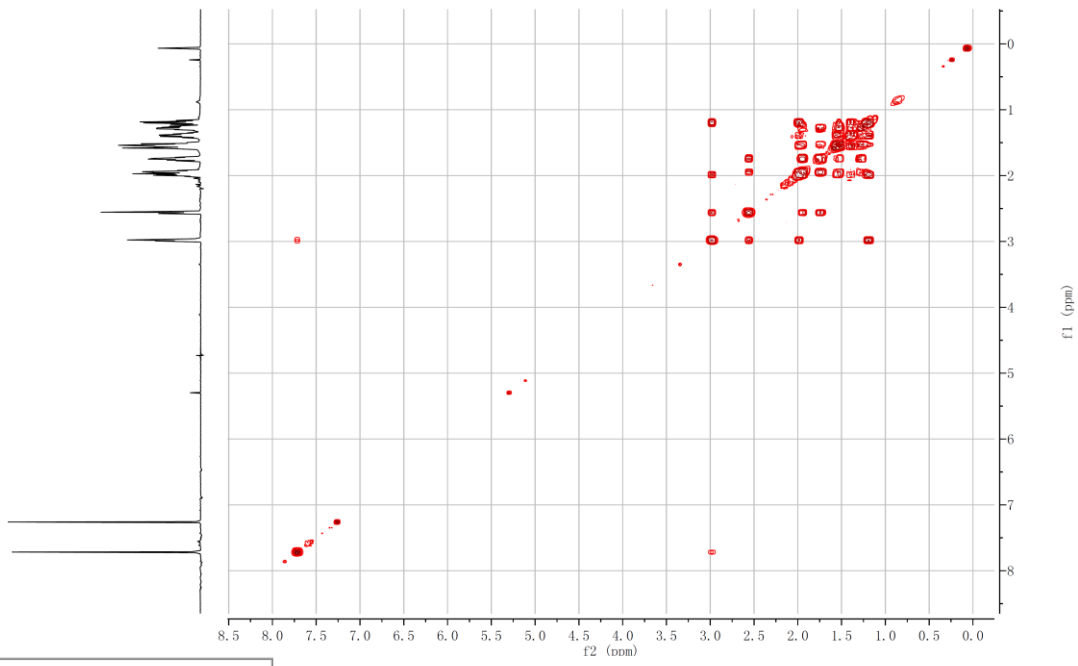
Parameter	Value
1 Title	youliang-5-299-C-P-C13I
2 Solvent	CDCl3
3 Spectrometer Frequency	125.70
4 Nucleus	13C



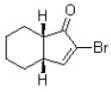


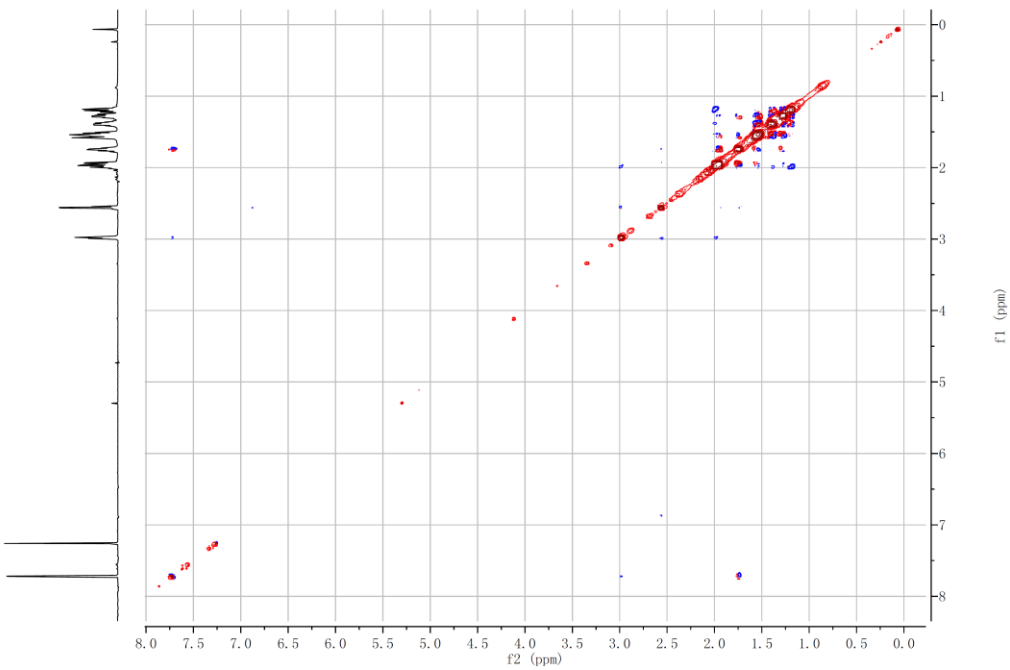
Parameter	Value
1 Title	youliang-5-299-C-P-2D-cosy
2 Solvent	cdcl3
3 Temperature	25.0
4 Relaxation Delay	1.0000
5 Spectrometer Frequency	(599.63, 599.63)
6 Spectral Width	(7692.3, 7692.3)



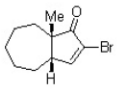


Parameter	Value
1 Title	youliang-5-299-C-P-2D-noesy
2 Solvent	cdcl3
3 Temperature	25.0
4 Relaxation Delay	1.0000
5 Spectrometer Frequency	(599.63, 599.63)
6 Spectral Width	(7692.3, 7692.3)

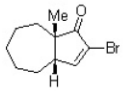


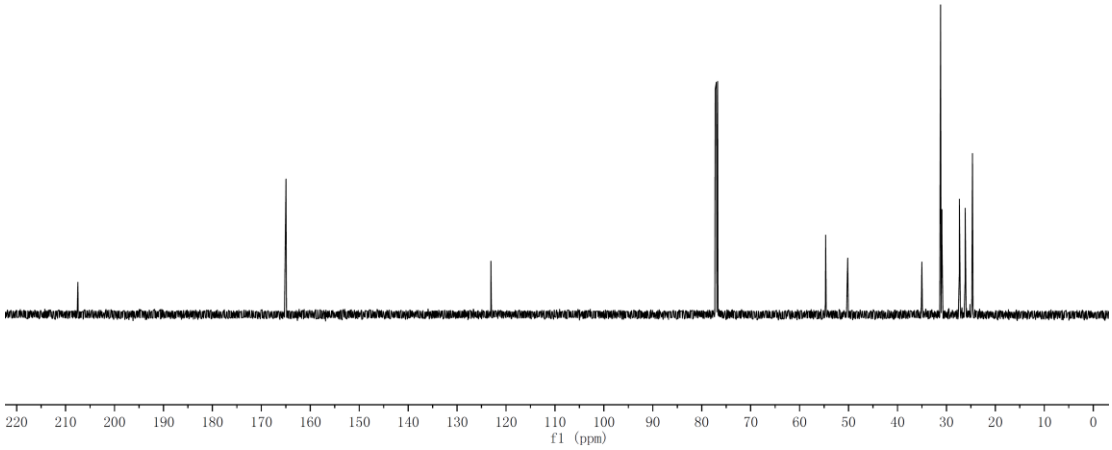


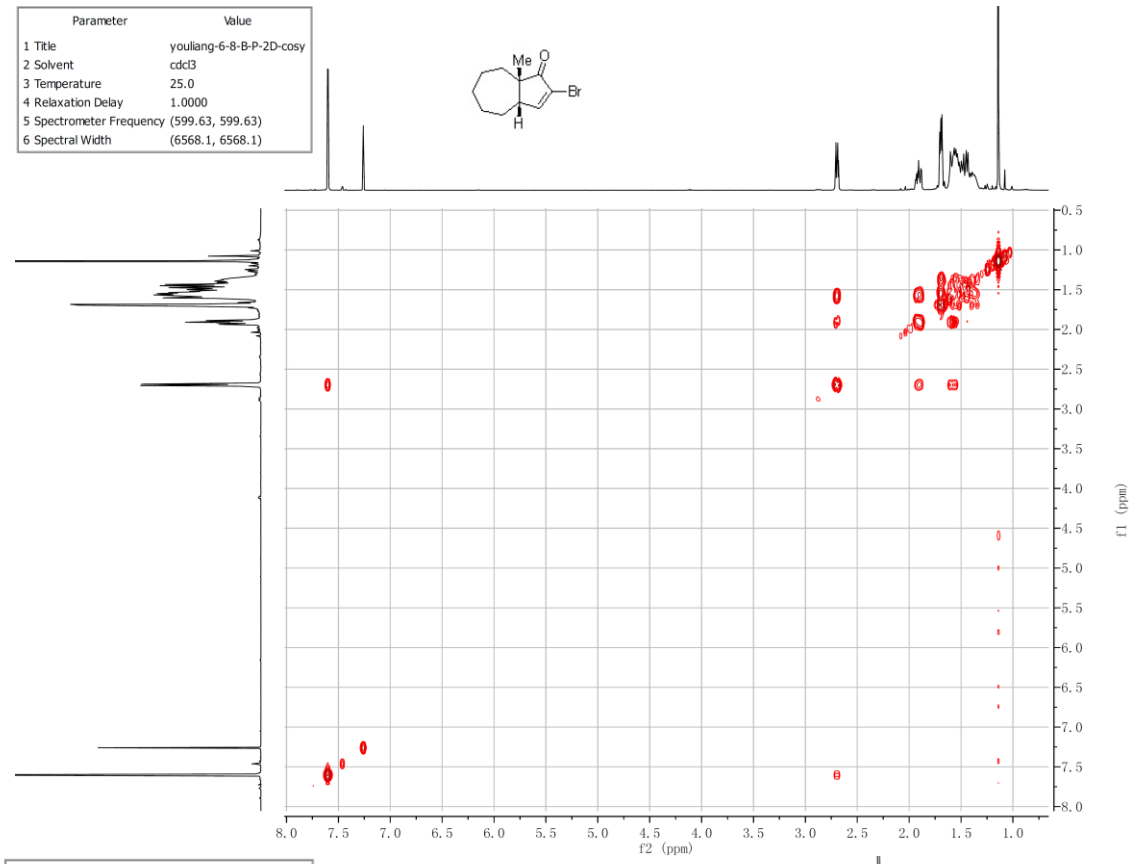
Parameter	Value
1 Title	youliang-6-8-B-P
2 Solvent	CDCl3
3 Temperature	25.0
4 Relaxation Delay	10.0000
5 Spectrometer Frequency	499.86

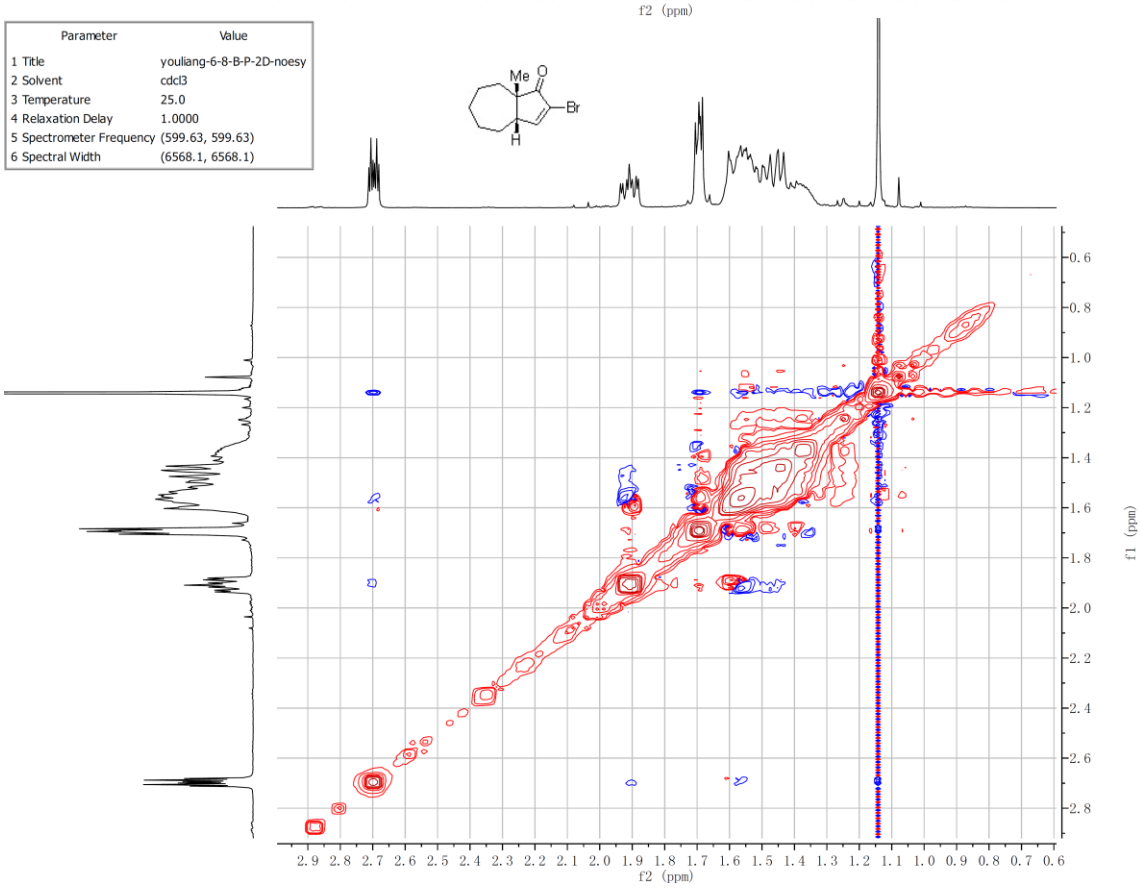


Parameter	Value
1 Title	youliang-6-8-B-P-C13f
2 Solvent	CDCl3
3 Temperature	25.0
4 Relaxation Delay	1.0000
5 Spectrometer Frequency	125.70

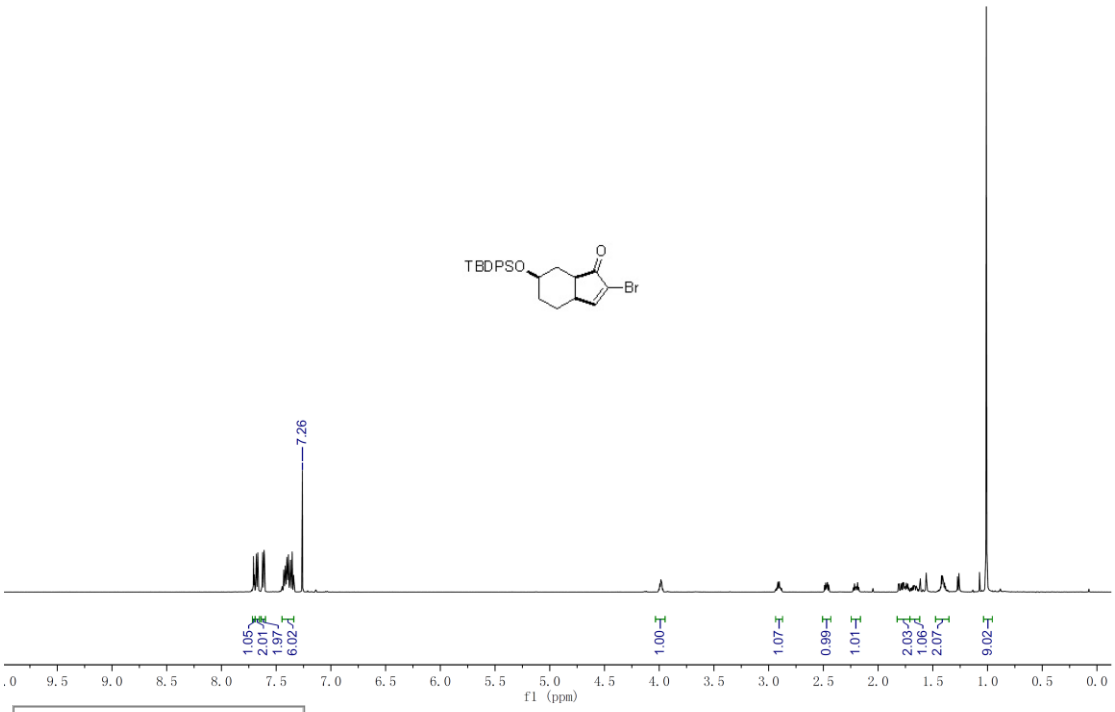




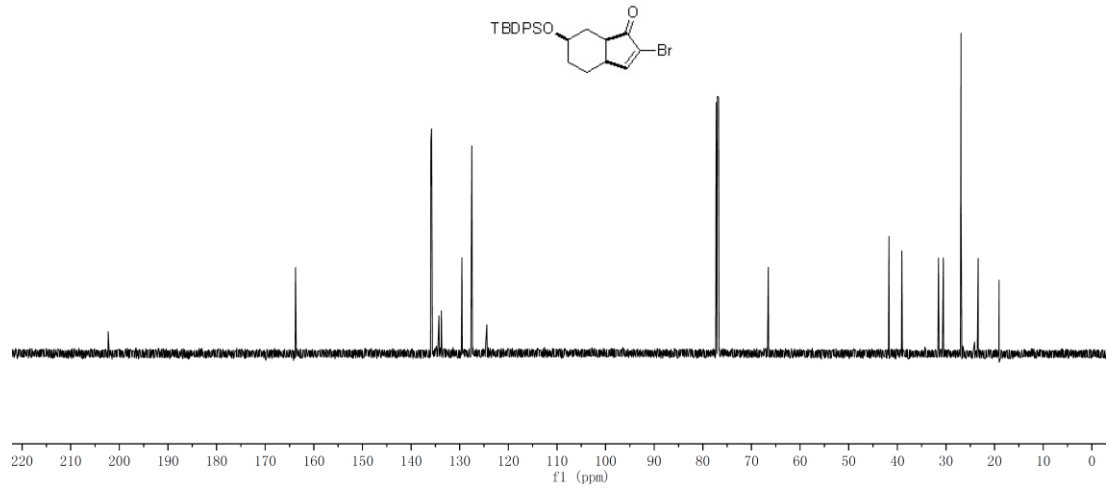

Parameter Value
1 Title youliang-6-8-B-P-2D-cosy
2 Solvent cdcl3
3 Temperature 25.0
4 Relaxation Delay 1.0000
5 Spectrometer Frequency (599.63, 599.63)
6 Spectral Width (6568.1, 6568.1)
Me
O
Br
H
f2 (ppm)
f1 (ppm)

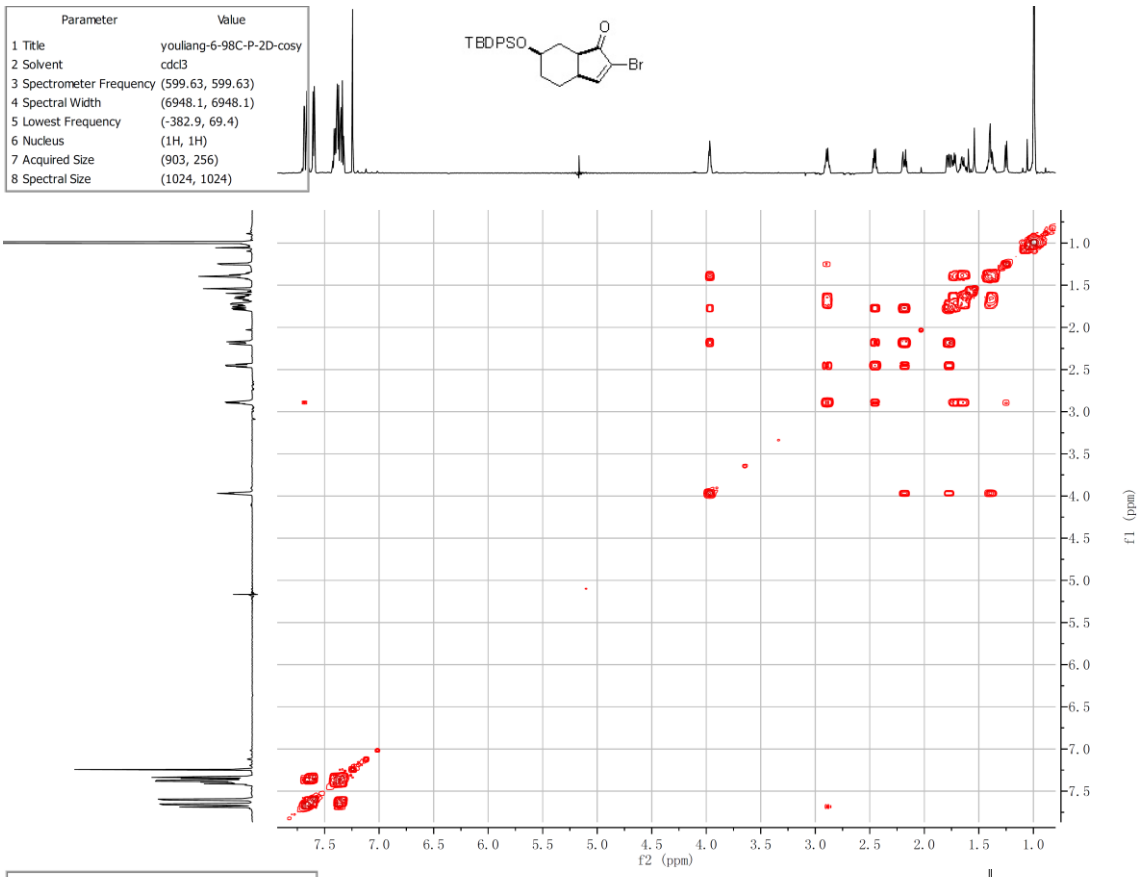

Parameter Value
1 Title youliang-6-8-B-P-2D-noesy
2 Solvent cdcl3
3 Temperature 25.0
4 Relaxation Delay 1.0000
5 Spectrometer Frequency (599.63, 599.63)
6 Spectral Width (6568.1, 6568.1)
Me
O
Br
H
f2 (ppm)
f1 (ppm)

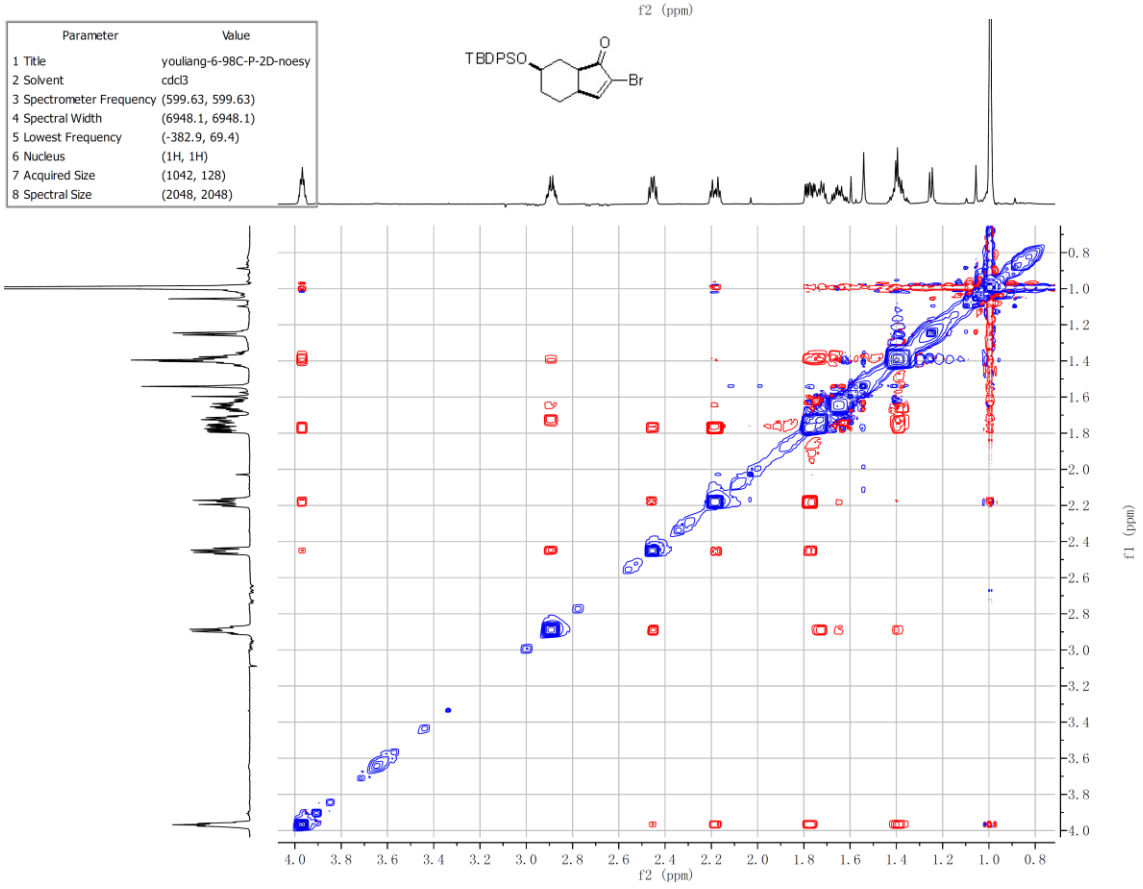
Parameter	Value
1 Title	youliang-6-98C-P
2 Solvent	CDCl3
3 Spectrometer Frequency	499.86
4 Nucleus	1H



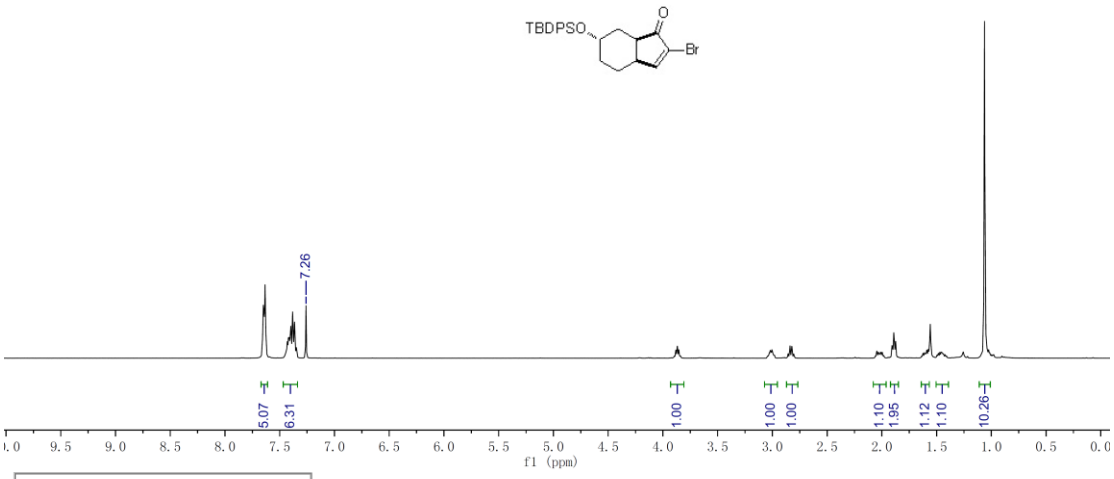
Parameter	Value
1 Title	youliang-6-98C-P-C13k
2 Solvent	CDCl3
3 Spectrometer Frequency	125.70
4 Nucleus	13C



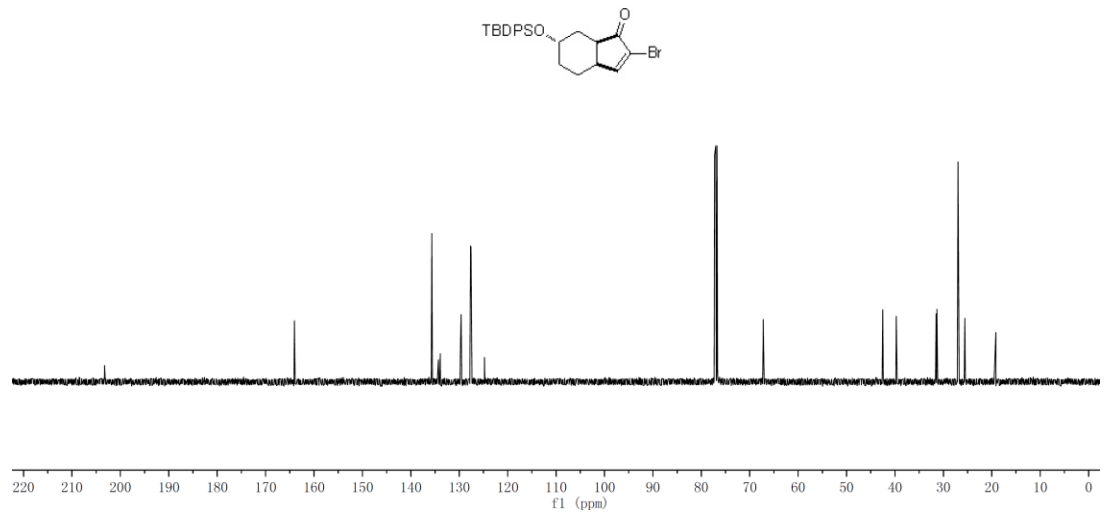

Parameter Value
1 Title youliang-6-98C-P-2D-cosy
2 Solvent cdcl3
3 Spectrometer Frequency (599.63, 599.63)
4 Spectral Width (6948.1, 6948.1)
5 Lowest Frequency (-382.9, 69.4)
6 Nucleus (1H, 1H)
7 Acquired Size (903, 256)
8 Spectral Size (1024, 1024)
TBDPSO
O
Br
f2 (ppm)
f1 (ppm)

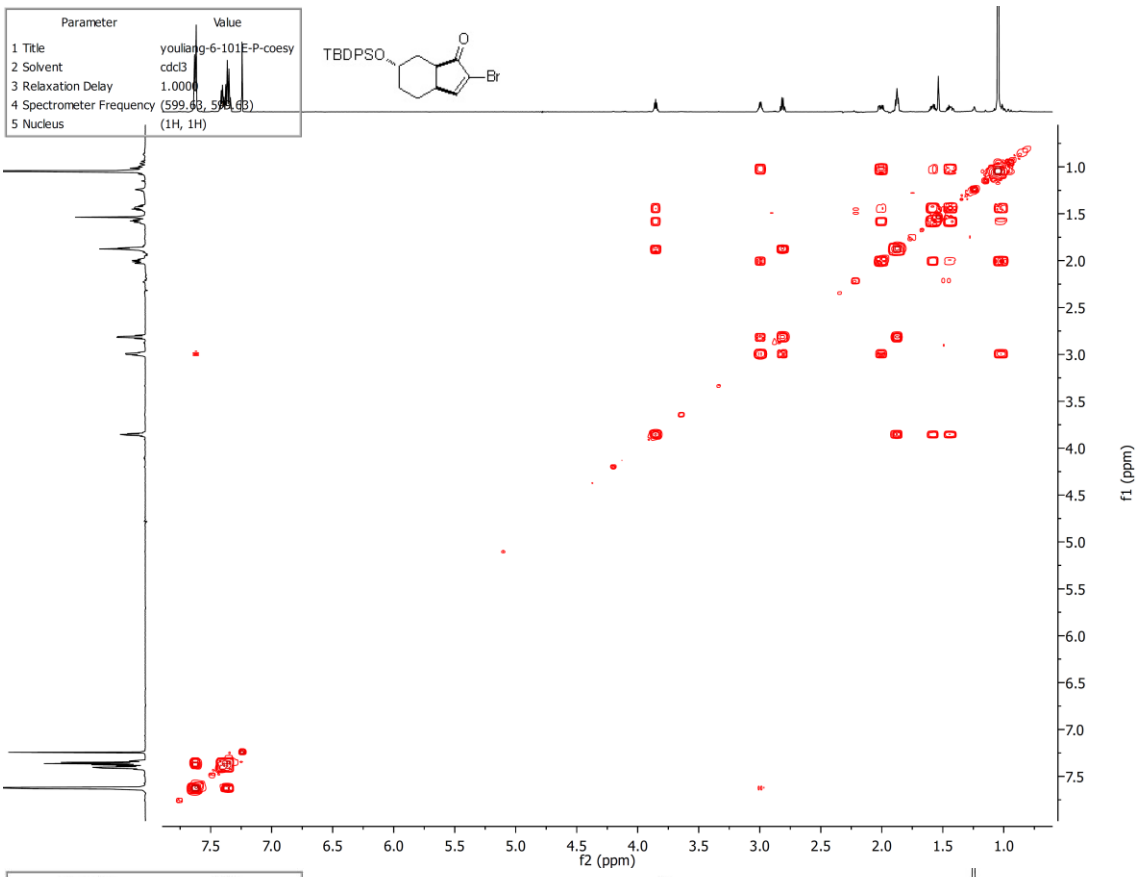

Parameter Value
1 Title youliang-6-98C-P-2D-noesy
2 Solvent cdcl3
3 Spectrometer Frequency (599.63, 599.63)
4 Spectral Width (6948.1, 6948.1)
5 Lowest Frequency (-382.9, 69.4)
6 Nucleus (1H, 1H)
7 Acquired Size (1042, 128)
8 Spectral Size (2048, 2048)
TBDPSO
O
Br
f2 (ppm)
f1 (ppm)

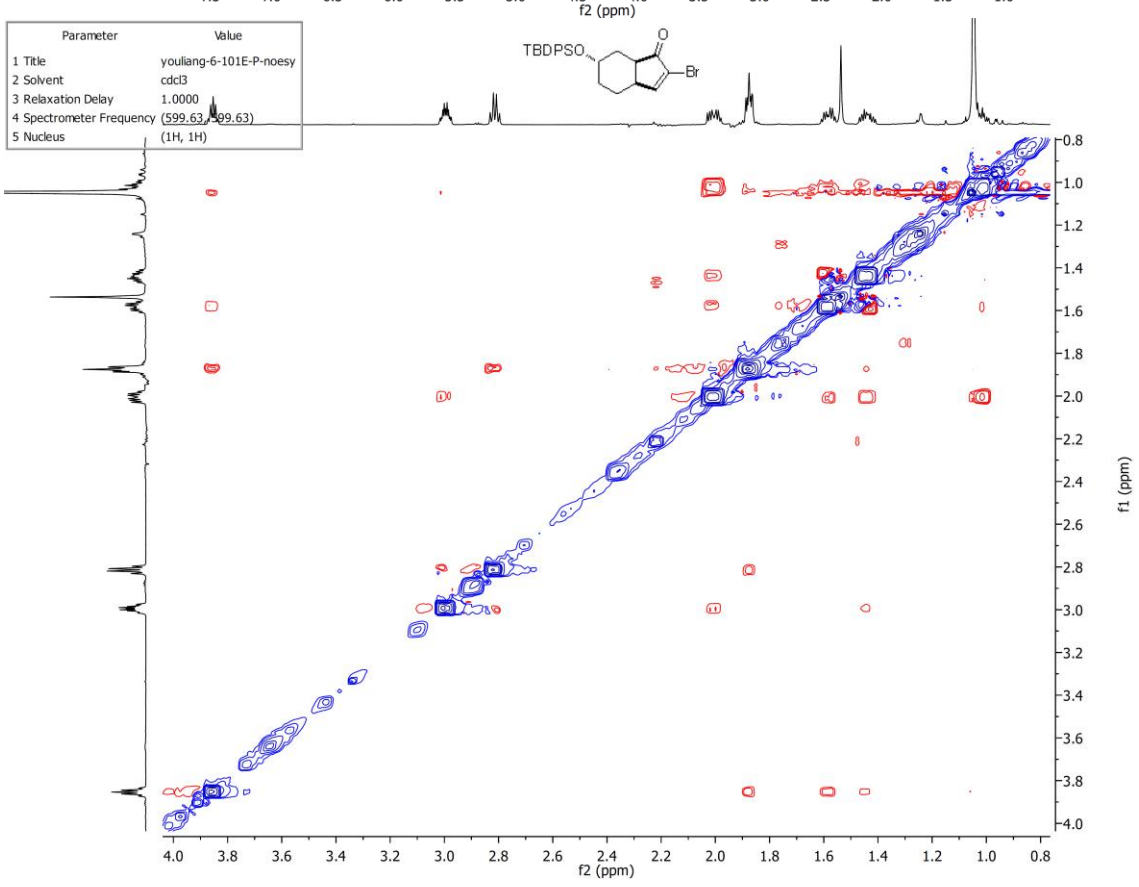
Parameter	Value
1 Title	youliang-6-101E-P
2 Solvent	cdcl3
3 Spectrometer Frequency	399.78
4 Nucleus	1H



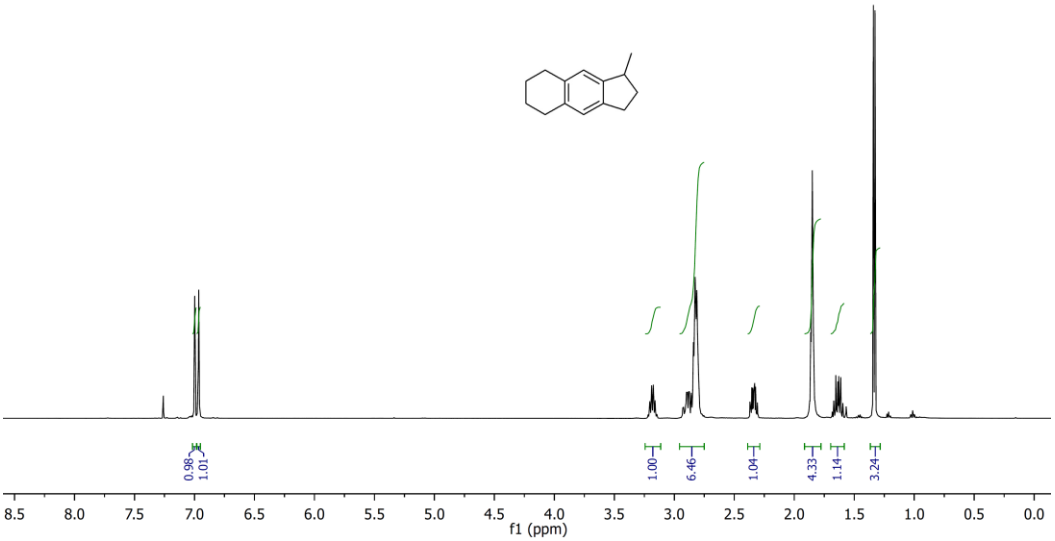
Parameter	Value
1 Title	youliang-6-101E-P-C13x
2 Solvent	CDCl3
3 Spectrometer Frequency	125.70
4 Nucleus	13C



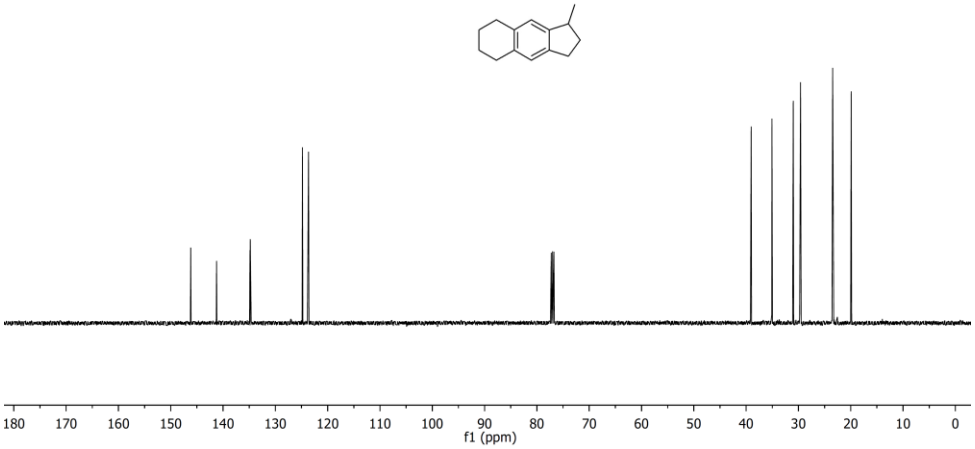

Parameter
Value
1 Title
youliang-6-101E-P-coesy
2 Solvent
cdcl3
3 Relaxation Delay
1.0000
4 Spectrometer Frequency
(599.63, 599.63)
5 Nucleus
(1H, 1H)
TBDPSO
O
Br
f2 (ppm)
f1 (ppm)

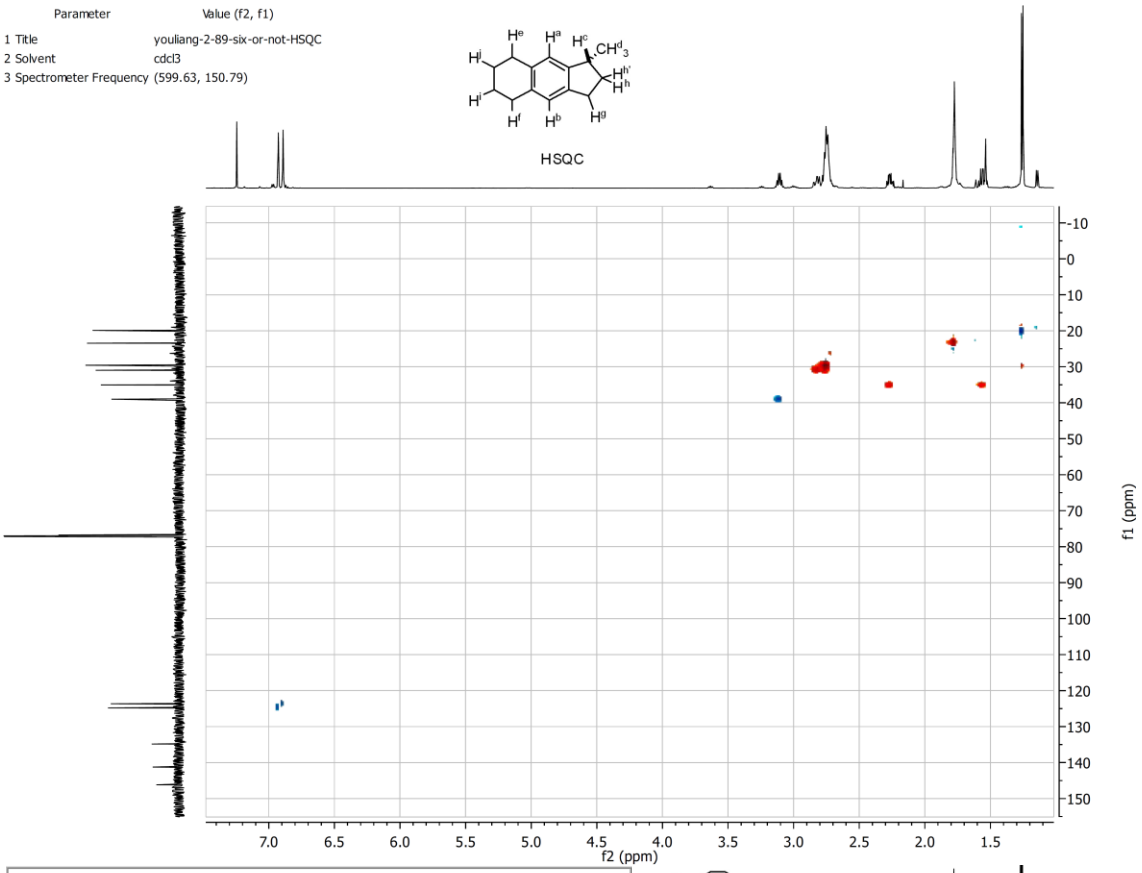

Parameter
Value
1 Title
youliang-6-101E-P-noesy
2 Solvent
cdcl3
3 Relaxation Delay
1.0000
4 Spectrometer Frequency
(599.63, 599.63)
5 Nucleus
(1H, 1H)
TBDPSO
O
Br
f2 (ppm)
f1 (ppm)

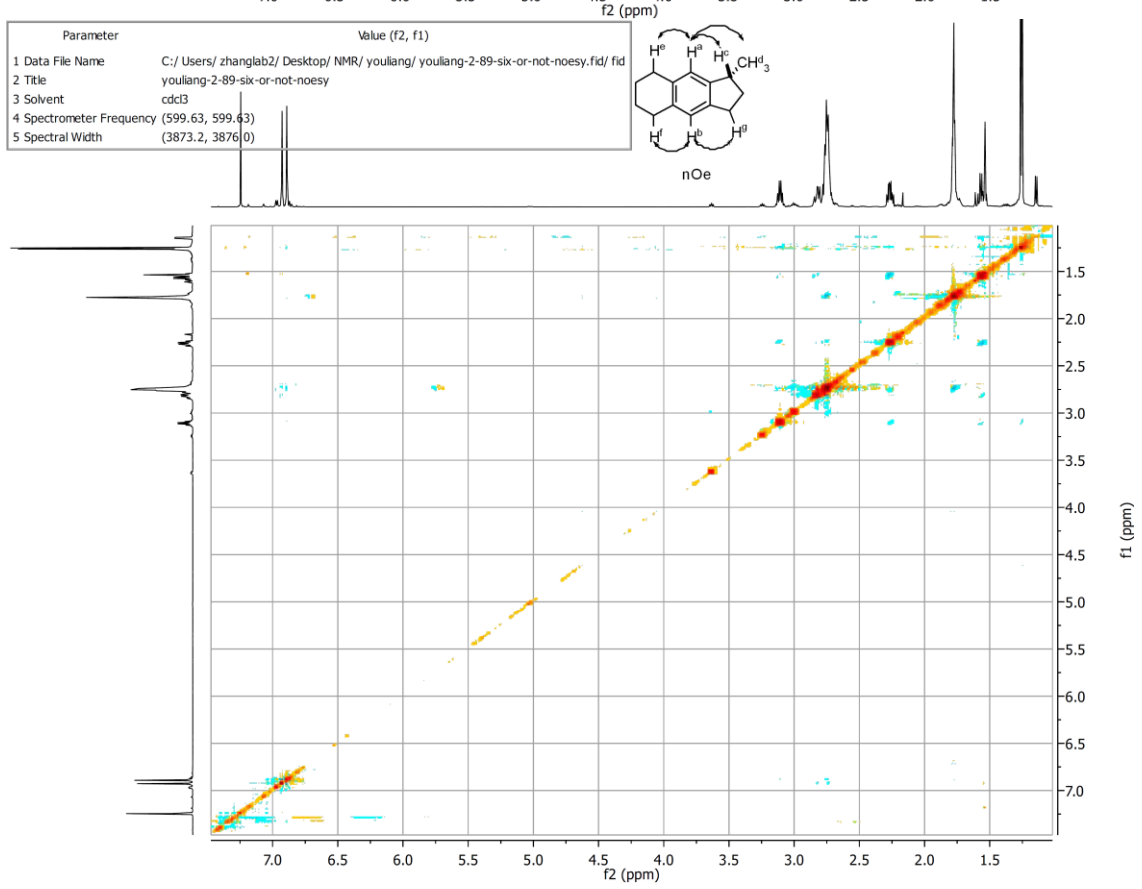
Parameter	Value
1 Data File Name	C:/ Users/ zhanglab2/ Desktop/ NMR/ youliang/ youliang-2-275-1-P1.fid/ fid
2 Title	youliang-2-275-1-P1
3 Solvent	CDCl3
4 Spectrometer Frequency	499.86



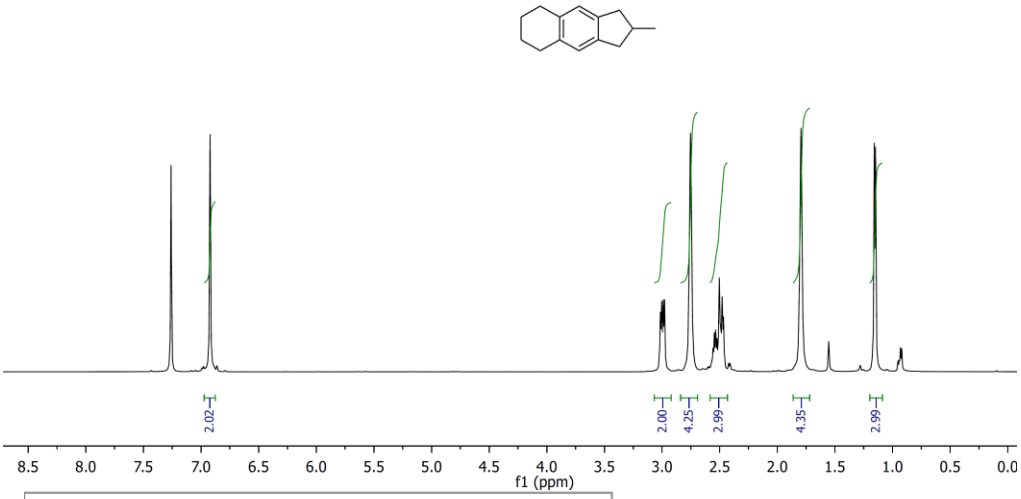
Parameter	Value
1 Data File Name	C:/ Users/ zhanglab2/ Desktop/ NMR/ youliang/ youliang-2-275-1-P1-C13c.fid/ fid
2 Title	youliang-2-275-1-P1-C13c
3 Solvent	CDCl3
4 Spectrometer Frequency	125.70



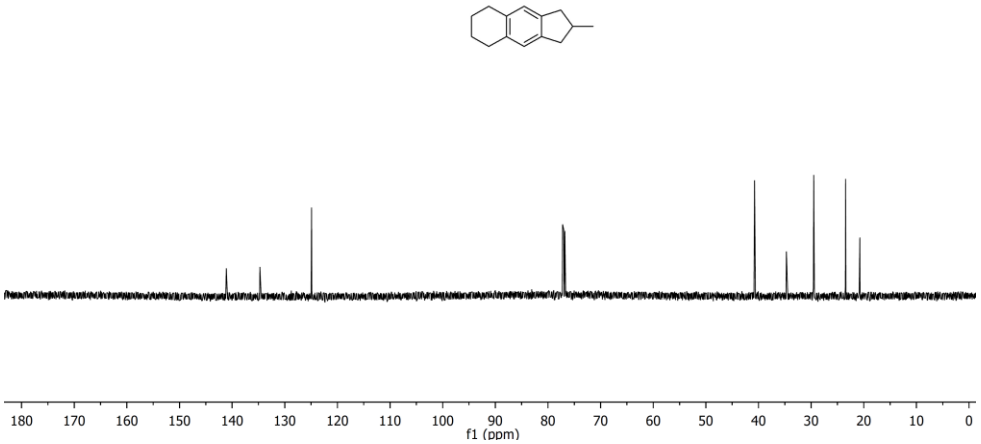

Parameter
Value (f2, f1)
1 Title
youliang-2-89-six-or-not-HSQC
2 Solvent
cdcl3
3 Spectrometer Frequency
(599.63, 150.79)
HSQC
f2 (ppm)
f1 (ppm)


Parameter
Value (f2, f1)
1 Data File Name
C:/ Users/ zhanglab2/ Desktop/ NMR/ youliang/ youliang-2-89-six-or-not-noesy.fid/ fid
2 Title
youliang-2-89-six-or-not-noesy
3 Solvent
cdcl3
4 Spectrometer Frequency
(599.63, 599.63)
5 Spectral Width
(3873.2, 3876.0)
nOe
f2 (ppm)
f1 (ppm)

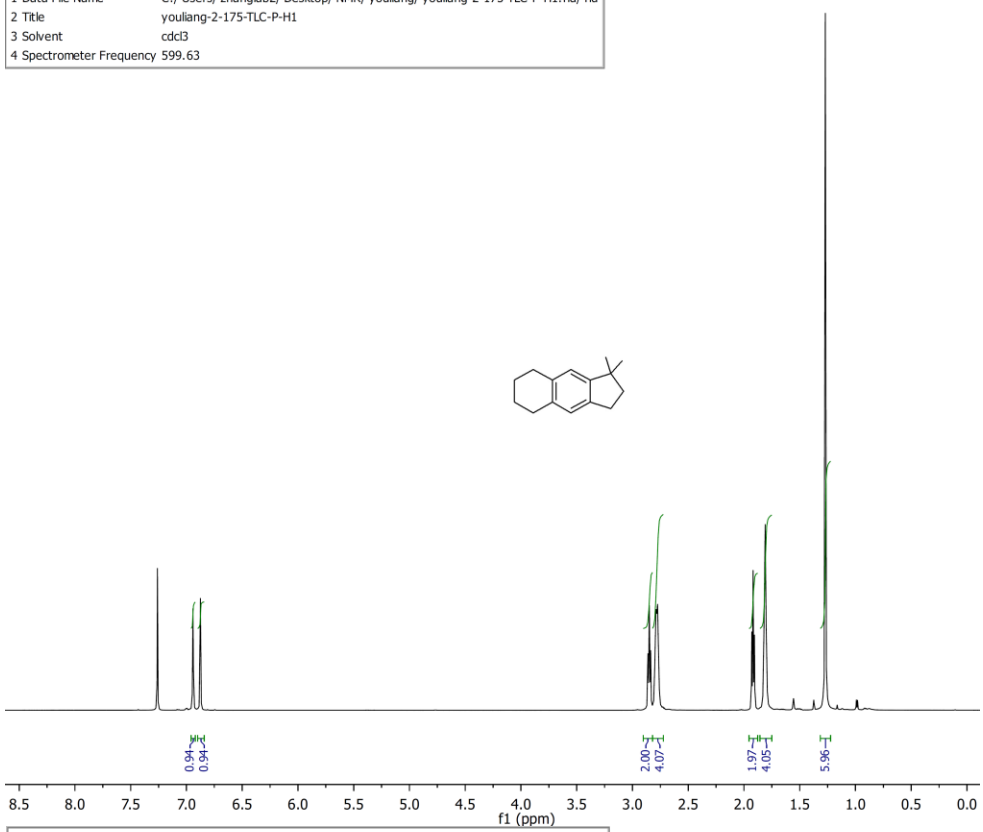
Parameter	Value
1 Data File Name	C:/ Users/ zhanglab2/ Desktop/ NMR/ youliang/ youliang-2-197-3-P-TLC2.fid/ fid
2 Title	youliang-2-197-3-P-TLC2
3 Solvent	cdcl3
4 Spectrometer Frequency	599.63



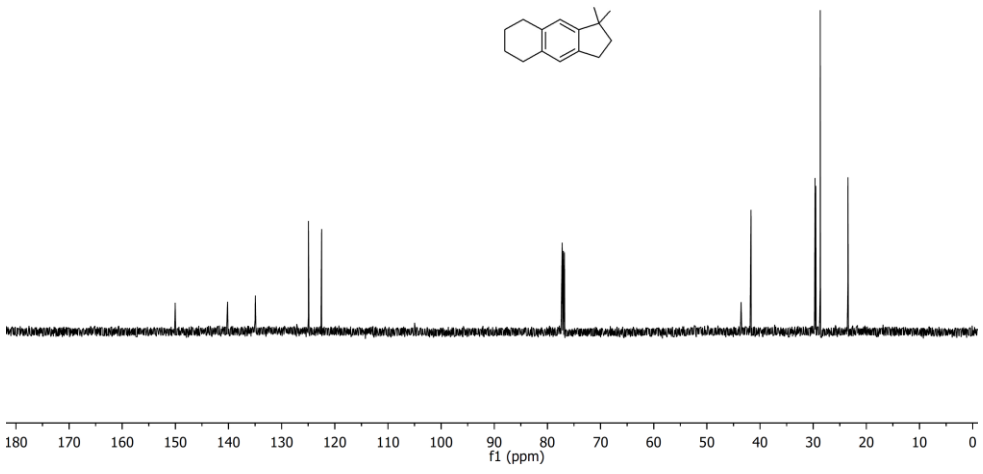
Parameter	Value
1 Data File Name	C:/ Users/ zhanglab2/ Desktop/ NMR/ youliang/ youliang-2-197-3-P-TLC2-c13c.fid/ fid
2 Title	youliang-2-197-3-P-TLC2-c13c
3 Solvent	cdcl3
4 Spectrometer Frequency	150.79



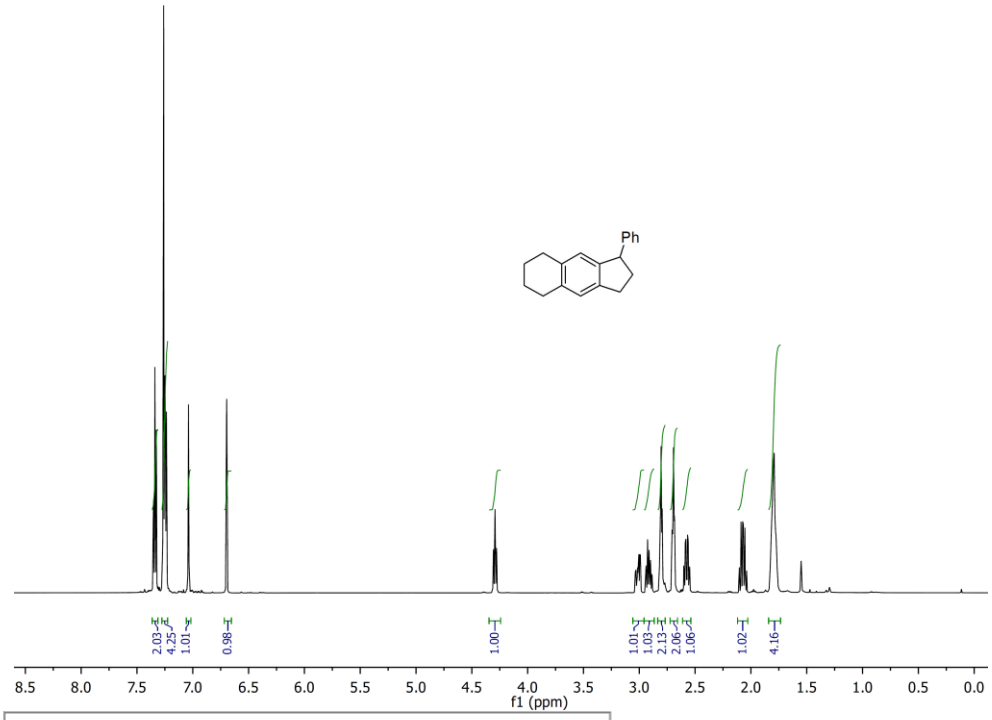
Parameter	Value
1 Data File Name	C:/ Users/ zhanglab2/ Desktop/ NMR/ youliang/ youliang-2-175-TLC-P-H1.fid/ fid
2 Title	youliang-2-175-TLC-P-H1
3 Solvent	cdcl3
4 Spectrometer Frequency	599.63



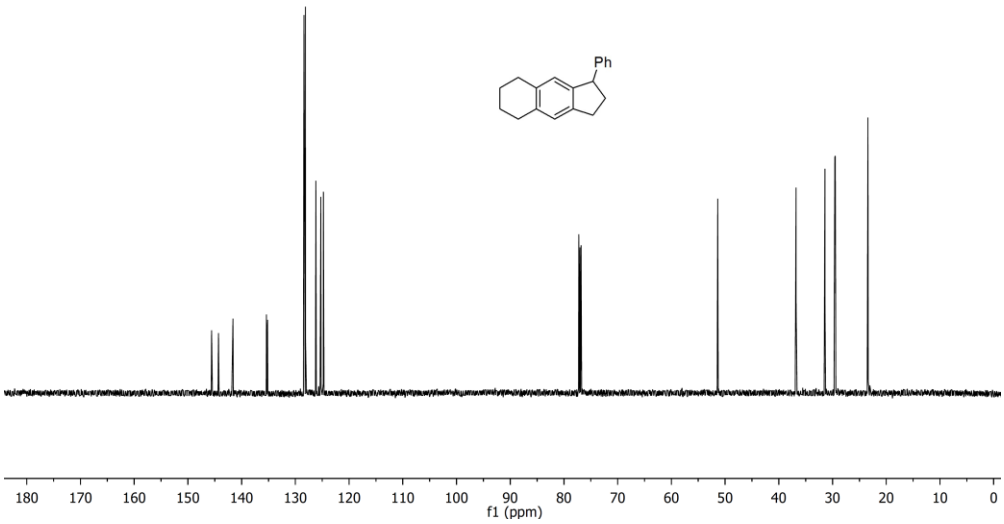
Parameter	Value
1 Data File Name	C:/ Users/ zhanglab2/ Desktop/ NMR/ youliang/ youliang-2-175-TLC-P-C13-c.fid/ fid
2 Title	youliang-2-175-TLC-P-C13-c
3 Solvent	cdcl3
4 Spectrometer Frequency	150.79



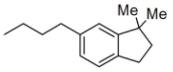
Parameter	Value
1 Data File Name	C:/ Users/ zhanglab2/ Desktop/ NMR/ youliang/ youliang-2-193-P-again.fid/ fid
2 Title	youliang-2-193-P-again
3 Solvent	cdcl3
4 Spectrometer Frequency	599.63



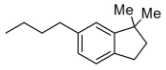
Parameter	Value
1 Data File Name	C:/ Users/ zhanglab2/ Desktop/ NMR/ youliang/ youliang-2-193-P-again-c13b.fid/ fid
2 Title	youliang-2-193-P-again-c13b
3 Solvent	cdcl3
4 Spectrometer Frequency	150.79

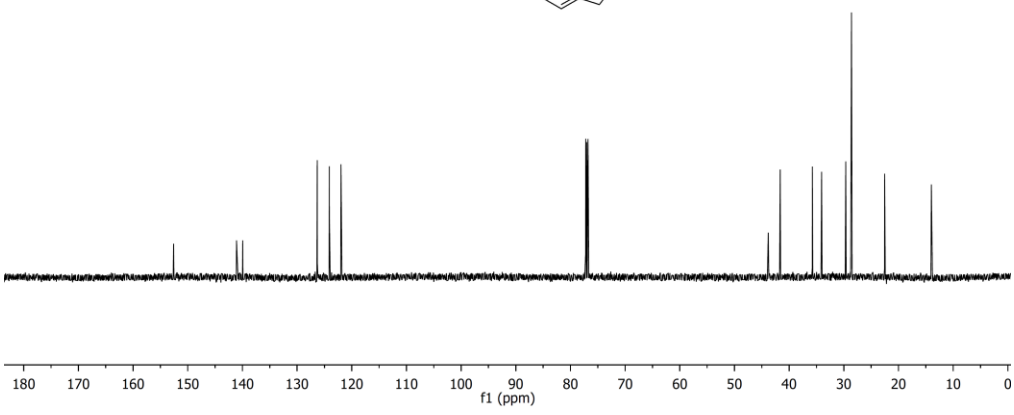


Parameter	Value
1 Data File Name	C:/ Users/ zhanglab2/ Desktop/ NMR/ youliang/ youliang-2-294-p1-2nd.fid/ fid
2 Title	youliang-2-294-p1-2nd
3 Solvent	cdcl3
4 Spectrometer Frequency	599.64

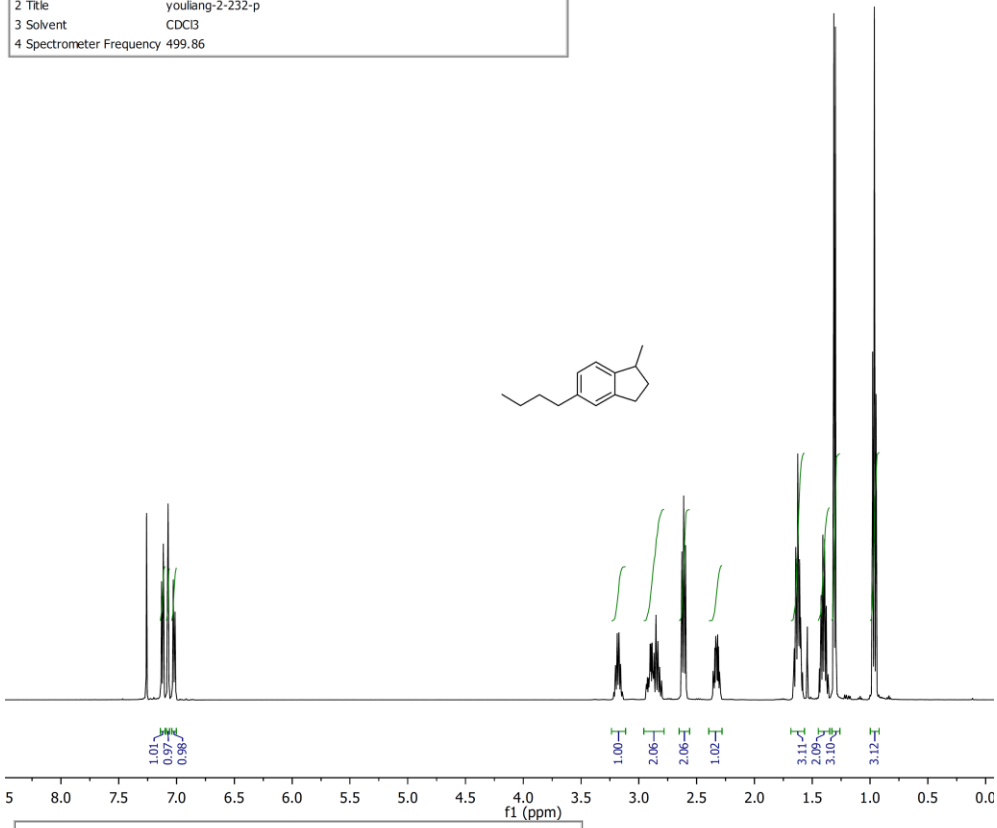


Parameter	Value
1 Data File Name	C:/ Users/ zhanglab2/ Desktop/ NMR/ youliang/ youliang-2-294-p1-C13f.fid/ fid
2 Title	youliang-2-294-p1-C13f
3 Solvent	cdcl3
4 Spectrometer Frequency	150.79

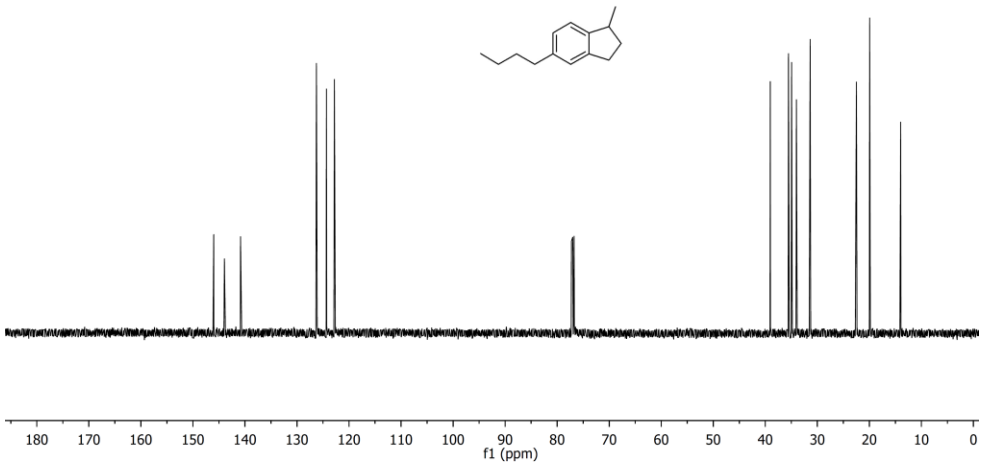




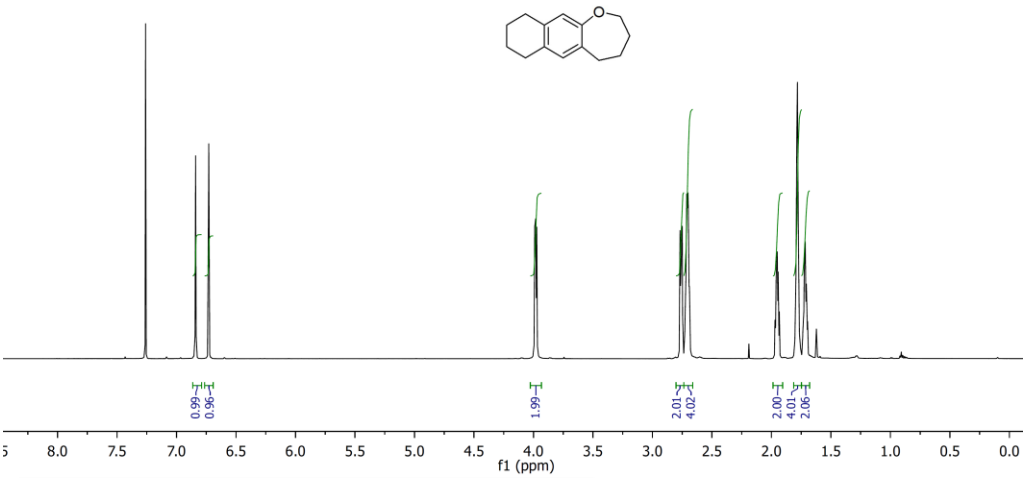
Parameter	Value
1 Data File Name	C:/ Users/ zhanglab2/ Desktop/ NMR/ youliang/ youliang-2-232-p.fid/ fid
2 Title	youliang-2-232-p
3 Solvent	CDCl3
4 Spectrometer Frequency	499.86



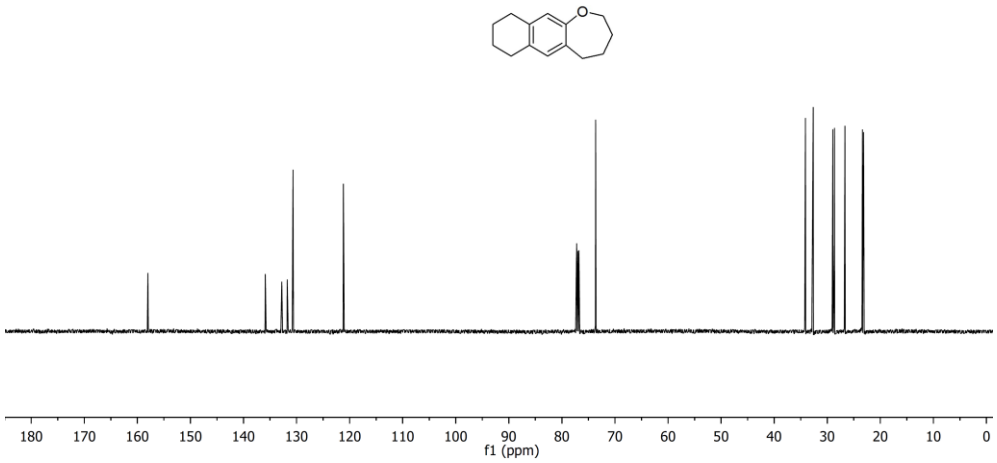
Parameter	Value
1 Data File Name	C:/ Users/ zhanglab2/ Desktop/ NMR/ youliang/ youliang-2-232-p-C13d.fid/ fid
2 Title	youliang-2-232-p-C13d
3 Solvent	CDCl3
4 Spectrometer Frequency	125.70



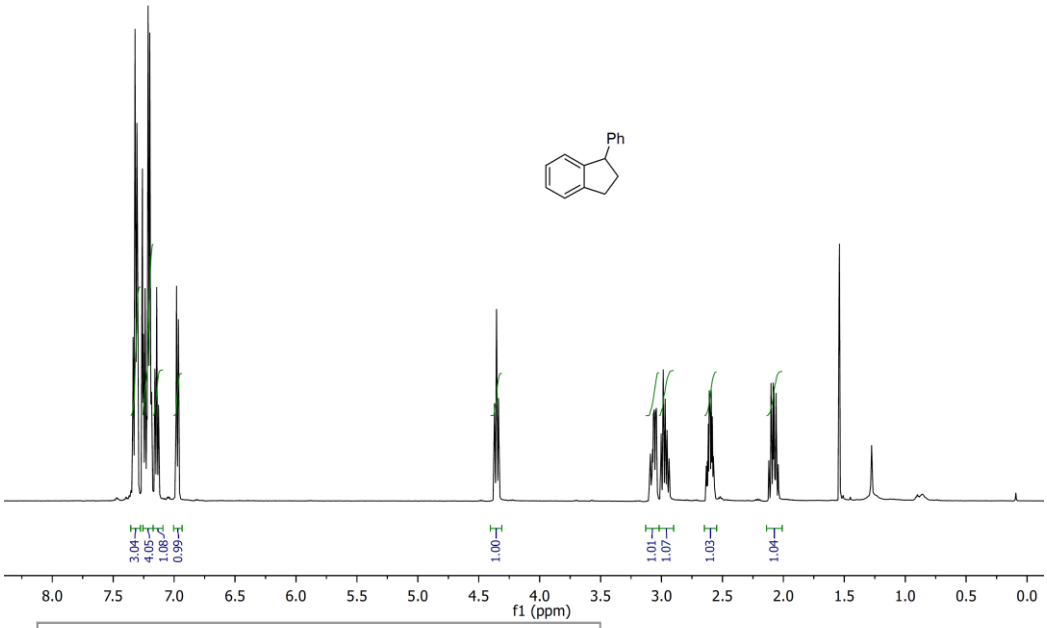
Parameter	Value
1 Data File Name	C:/ Users/ zhanglab2/ Desktop/ NMR/ youliang/ youliang-2-188-2-p.fid/ fid
2 Title	youliang-2-188-2-p
3 Solvent	cdcl3
4 Spectrometer Frequency	599.63



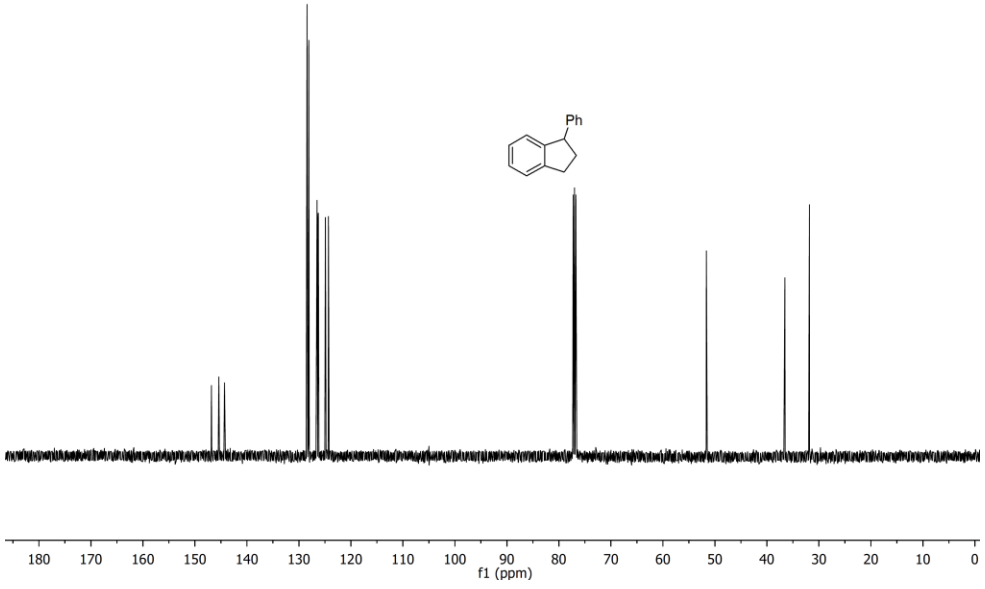
Parameter	Value
1 Data File Name	C:/ Users/ zhanglab2/ Desktop/ NMR/ youliang/ youliang-2-188-2-p-c13.fid/ fid
2 Title	youliang-2-188-2-p-c13
3 Solvent	cdcl3
4 Spectrometer Frequency	150.79



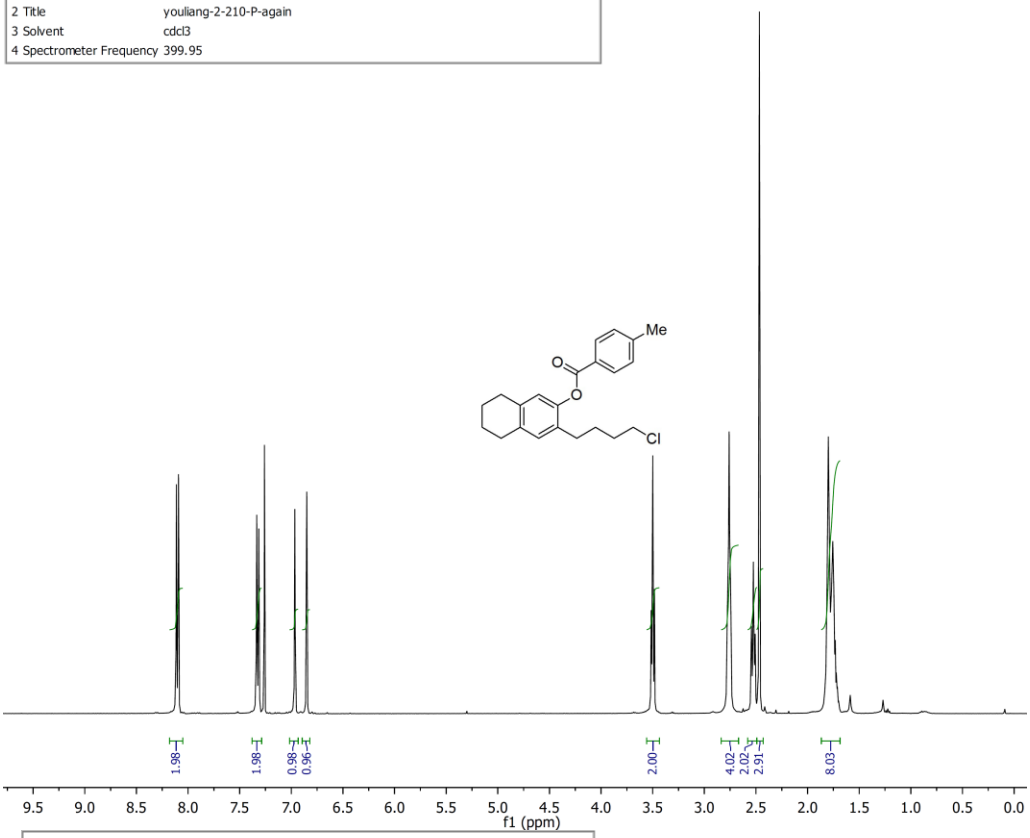
Parameter	Value
1 Data File Name	C:/ Users/ zhanglab2/ Desktop/ NMR/ youliang/ youliang-2-284-P.fid/ fid
2 Title	youliang-2-284-P
3 Solvent	CDCl3
4 Spectrometer Frequency	499.86



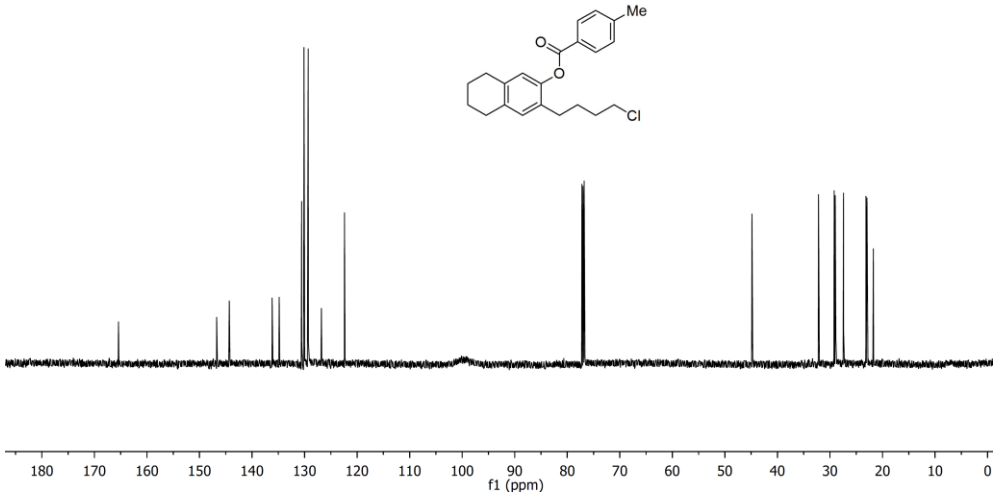
Parameter	Value
1 Data File Name	C:/ Users/ zhanglab2/ Desktop/ NMR/ youliang/ youliang-2-284-P-C13d.fid/ fid
2 Title	youliang-2-284-P-C13d
3 Solvent	CDCl3
4 Spectrometer Frequency	125.70

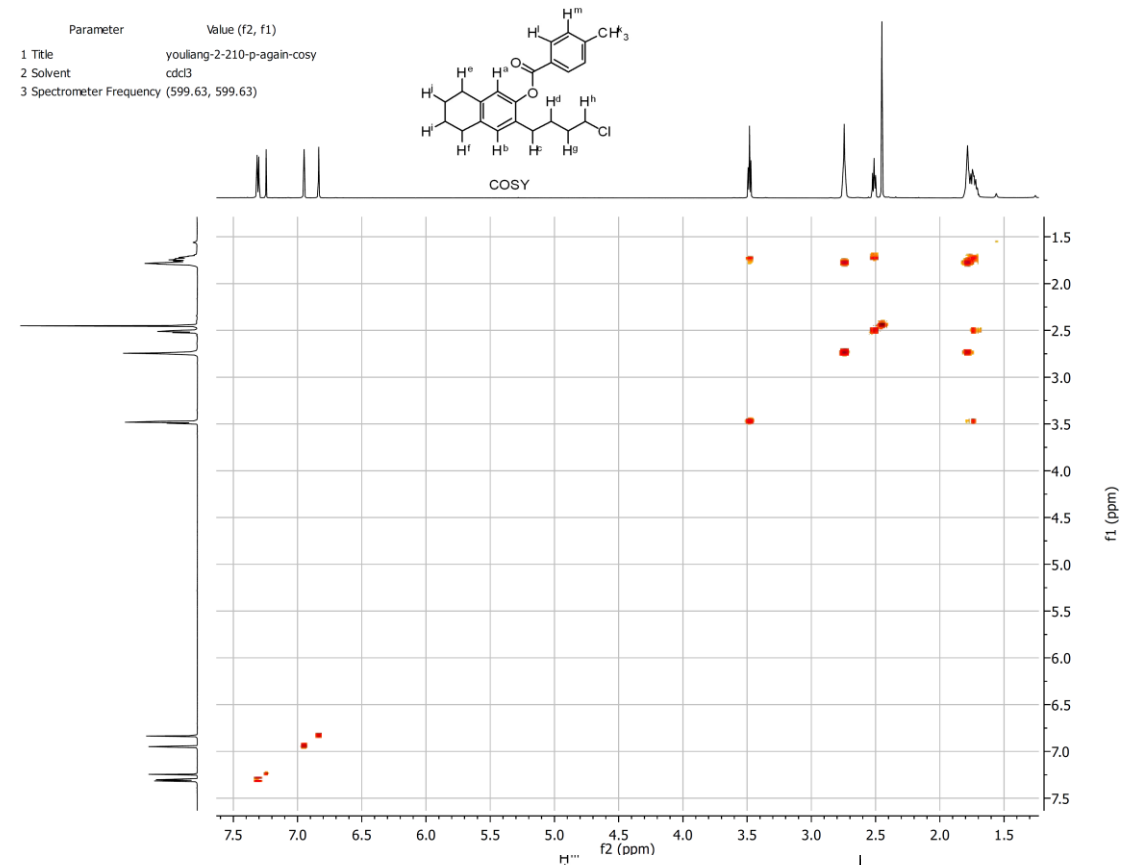


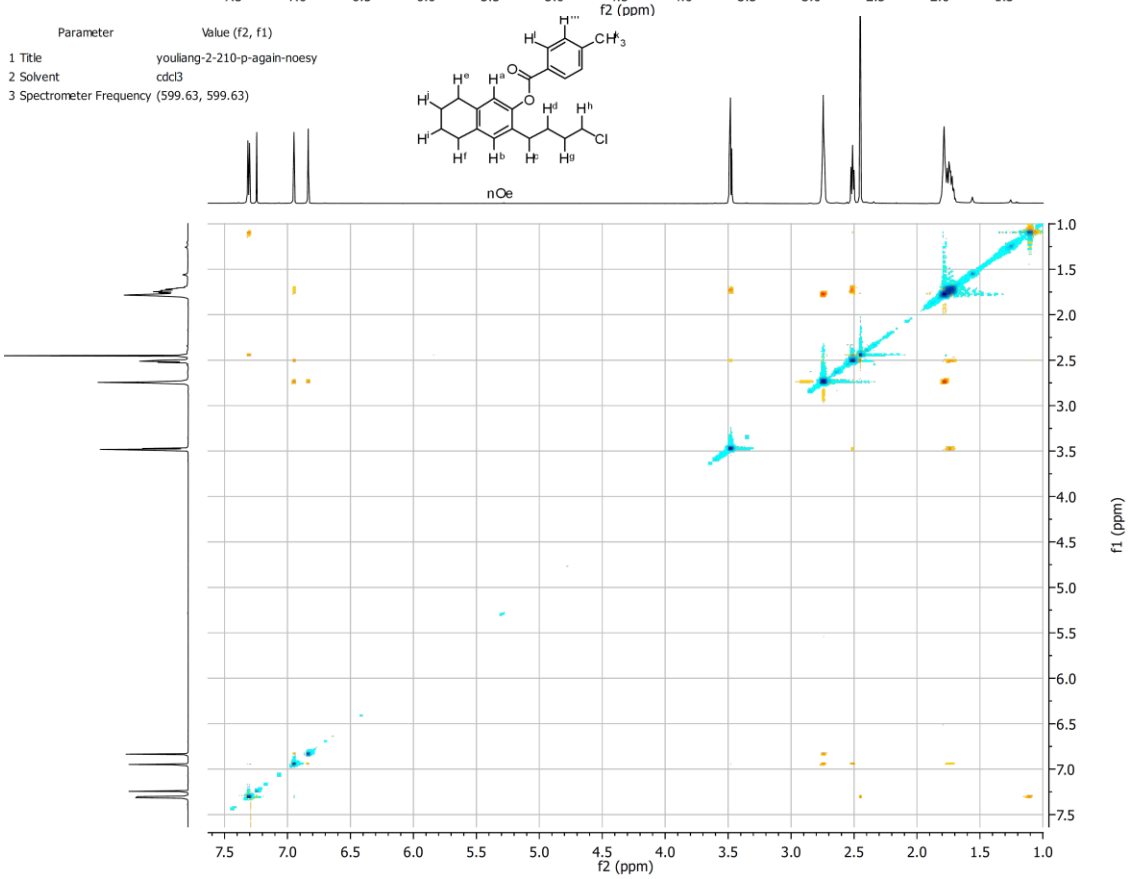
Parameter	Value
1 Data File Name	C:/ Users/ zhanglab2/ Desktop/ NMR/ youliang/ youliang-2-210-P-again.fid/ fid
2 Title	youliang-2-210-P-again
3 Solvent	cdcl3
4 Spectrometer Frequency	399.95



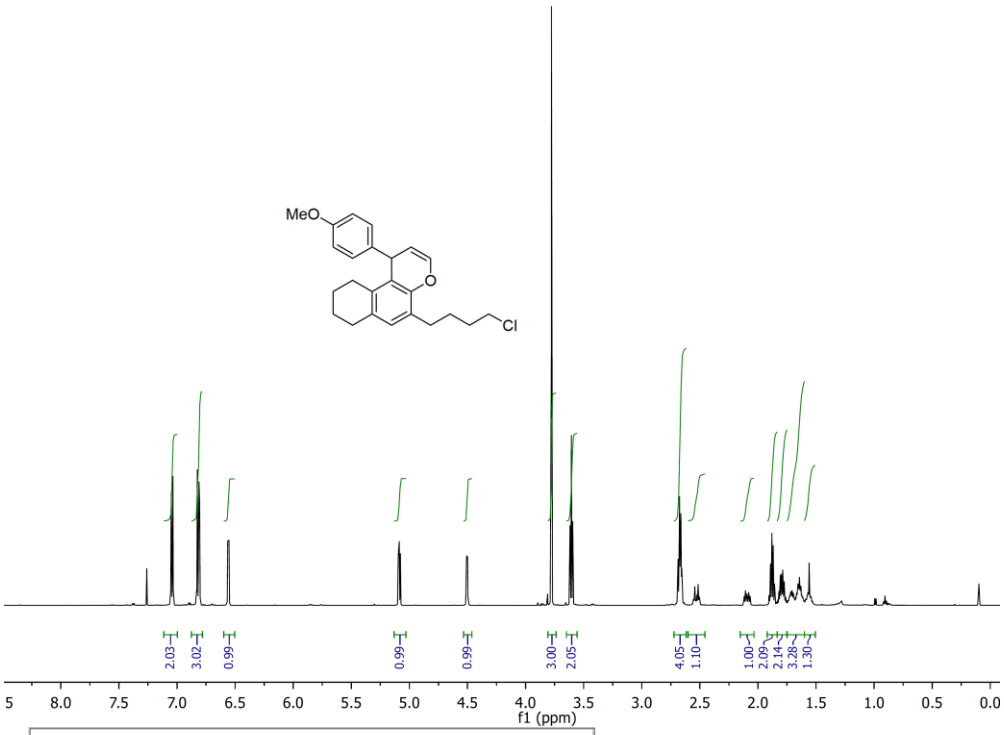
Parameter	Value
1 Data File Name	C:/ Users/ zhanglab2/ Desktop/ NMR/ youliang/ youliang-2-210-P-c13c.fid/ fid
2 Title	youliang-2-210-P-c13c
3 Solvent	cdcl3
4 Spectrometer Frequency	150.79



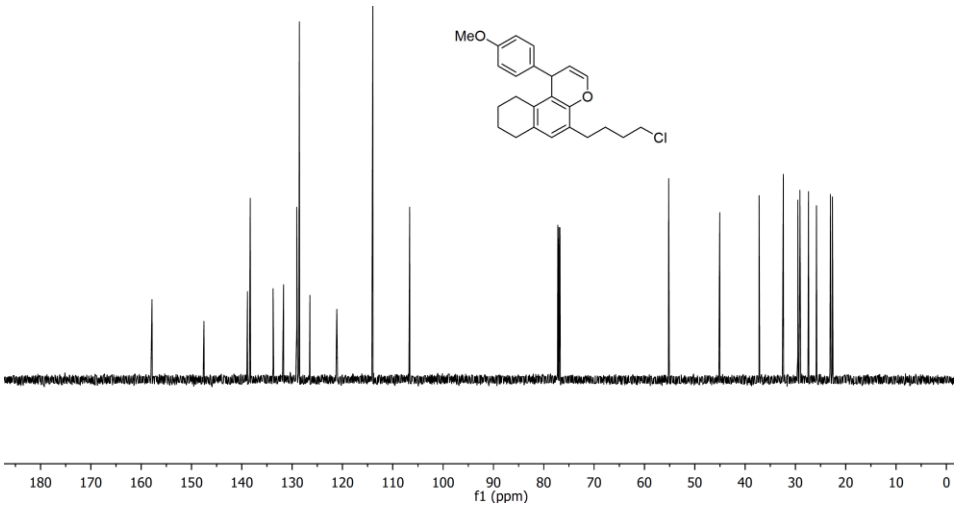

Parameter
Value (f2, f1)
1 Title
youliang-2-210-p-again-cosy
2 Solvent
cdcl3
3 Spectrometer Frequency
(599.63, 599.63)
COSY
f2 (ppm)
f1 (ppm)

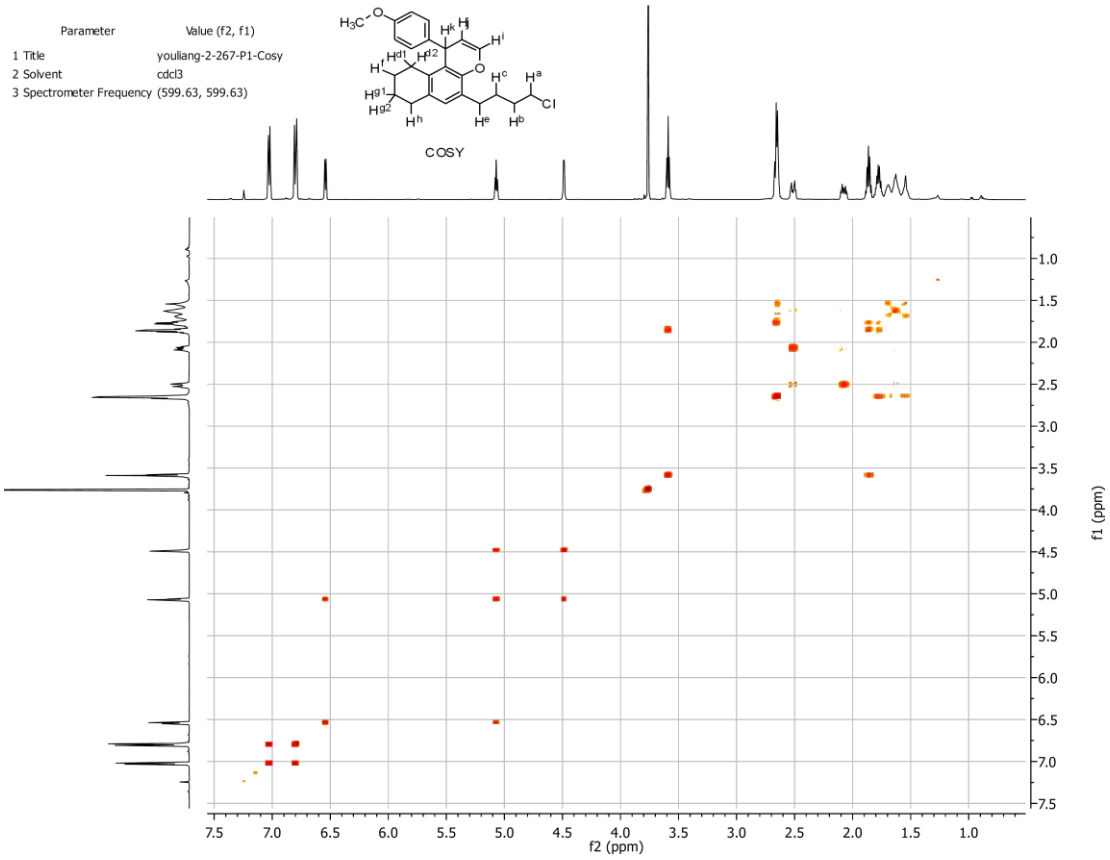

Parameter
Value (f2, f1)
1 Title
youliang-2-210-p-again-noesy
2 Solvent
cdcl3
3 Spectrometer Frequency
(599.63, 599.63)
nOe
f2 (ppm)
f1 (ppm)

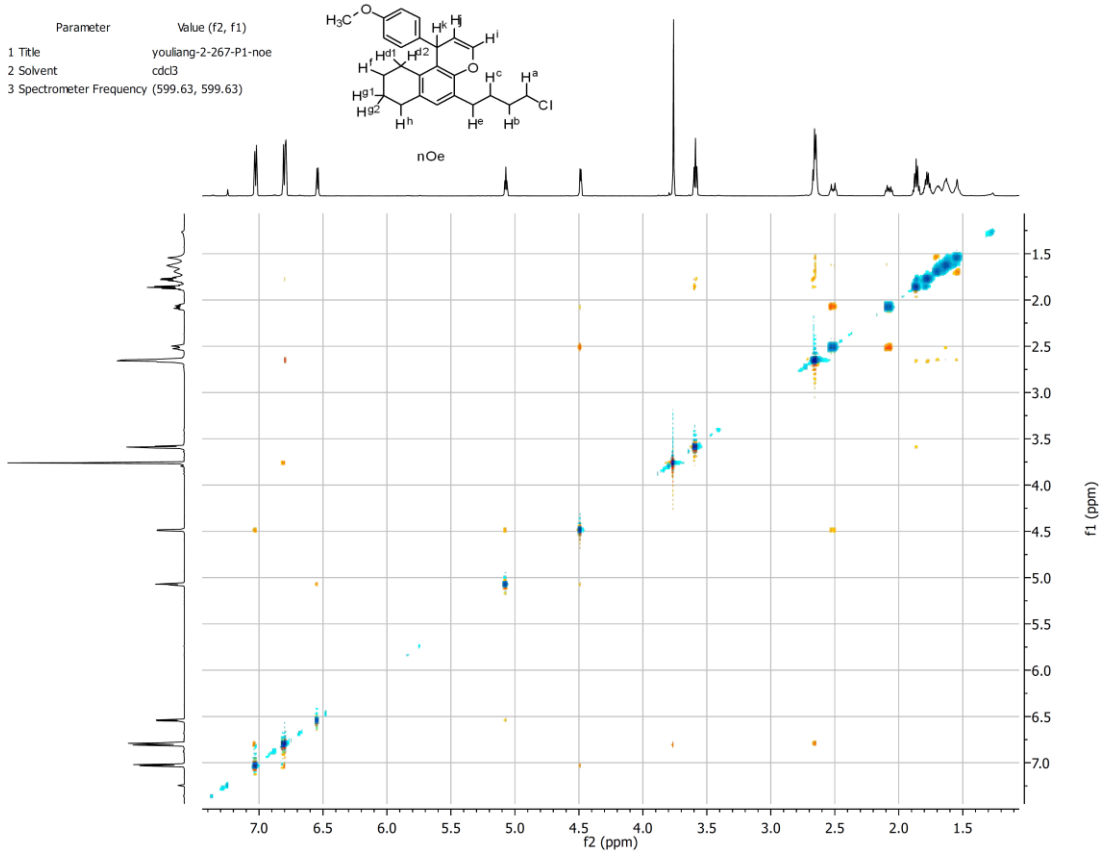
Parameter	Value
1 Data File Name	C:/ Users/ zhanglab2/ Desktop/ NMR/ youliang/ youliang-2-267-P1.fid/ fid
2 Title	youliang-2-267-P1
3 Solvent	cdcl3
4 Spectrometer Frequency	599.64



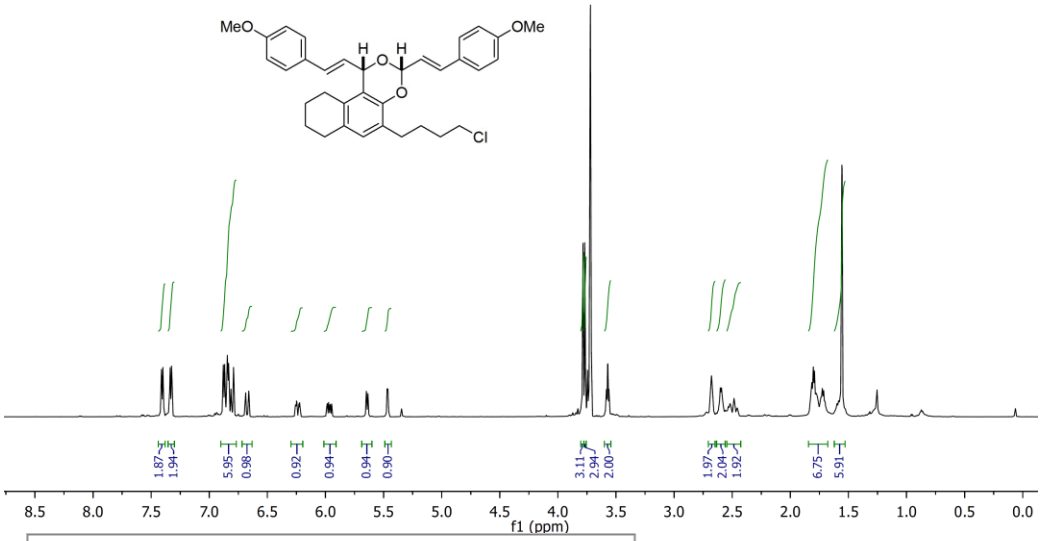
Parameter	Value
1 Data File Name	C:/ Users/ zhanglab2/ Desktop/ NMR/ youliang/ youliang-2-267-P1-C13e.fid/ fid
2 Title	youliang-2-267-P1-C13e
3 Solvent	cdcl3
4 Spectrometer Frequency	150.79



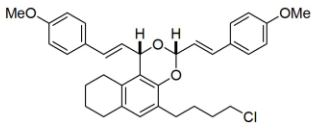

Parameter Value (f2, f1)
1 Title youliang-2-267-P1-Cosy
2 Solvent cdcl3
3 Spectrometer Frequency (599.63, 599.63)
COSY
f2 (ppm)
f1 (ppm)

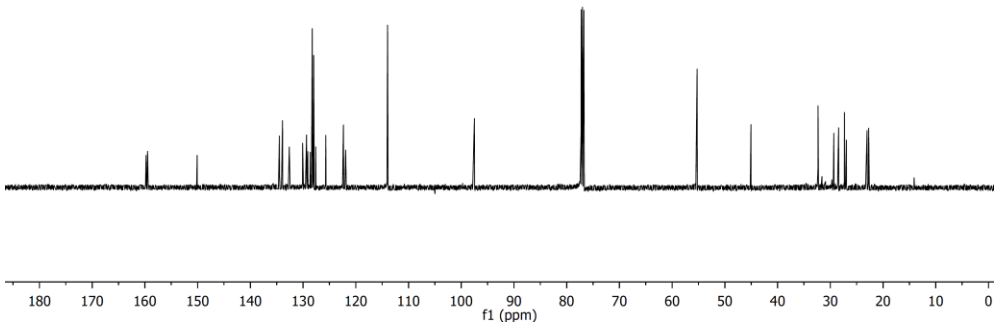

Parameter Value (f2, f1)
1 Title youliang-2-267-P1-noe
2 Solvent cdcl3
3 Spectrometer Frequency (599.63, 599.63)
nOe
f2 (ppm)
f1 (ppm)

Parameter	Value
1 Data File Name	C:/ Users/ zhanglab2/ Desktop/ NMR/ youliang/ youliang-2-267-P2-3rd.fid/ fid
2 Title	youliang-2-267-P2-3rd
3 Solvent	DCE-d4
4 Spectrometer Frequency	599.64

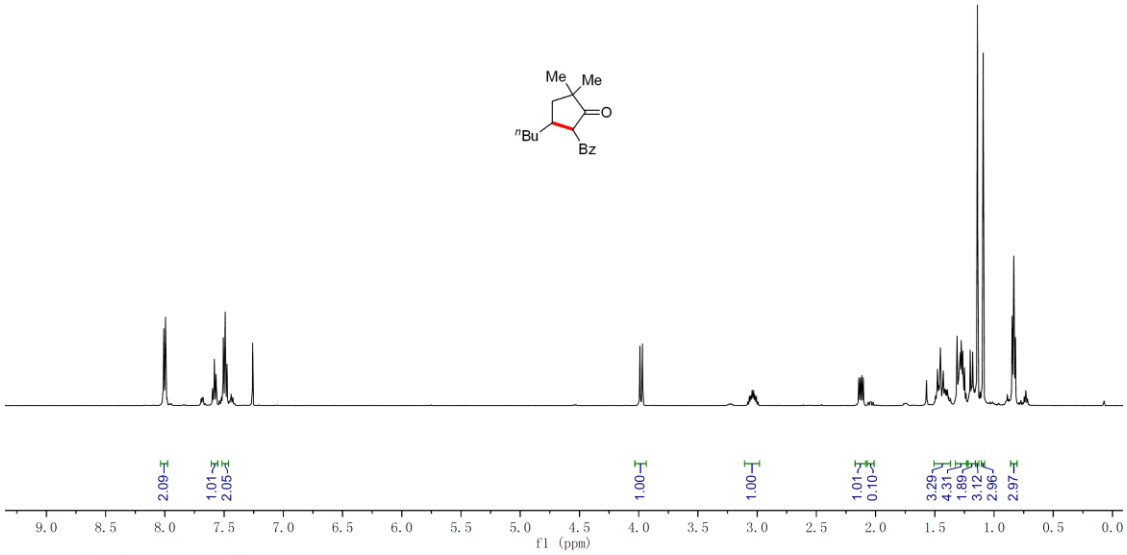


Parameter	Value
1 Data File Name	C:/ Users/ zhanglab2/ Desktop/ NMR/ youliang/ youliang-2-267-P2-again-C13g.fid/ fid
2 Title	youliang-2-267-P2-again-C13g
3 Solvent	CDCl3
4 Spectrometer Frequency	125.70

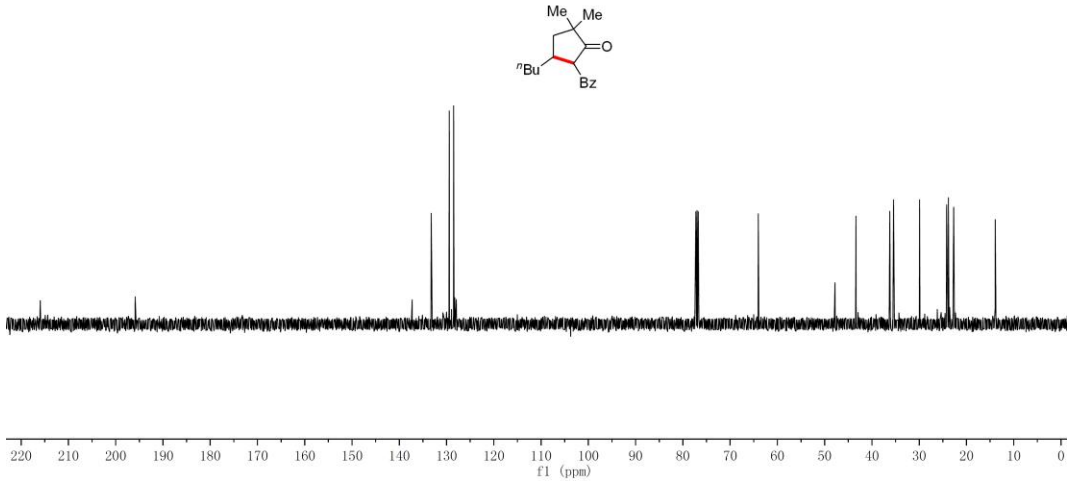




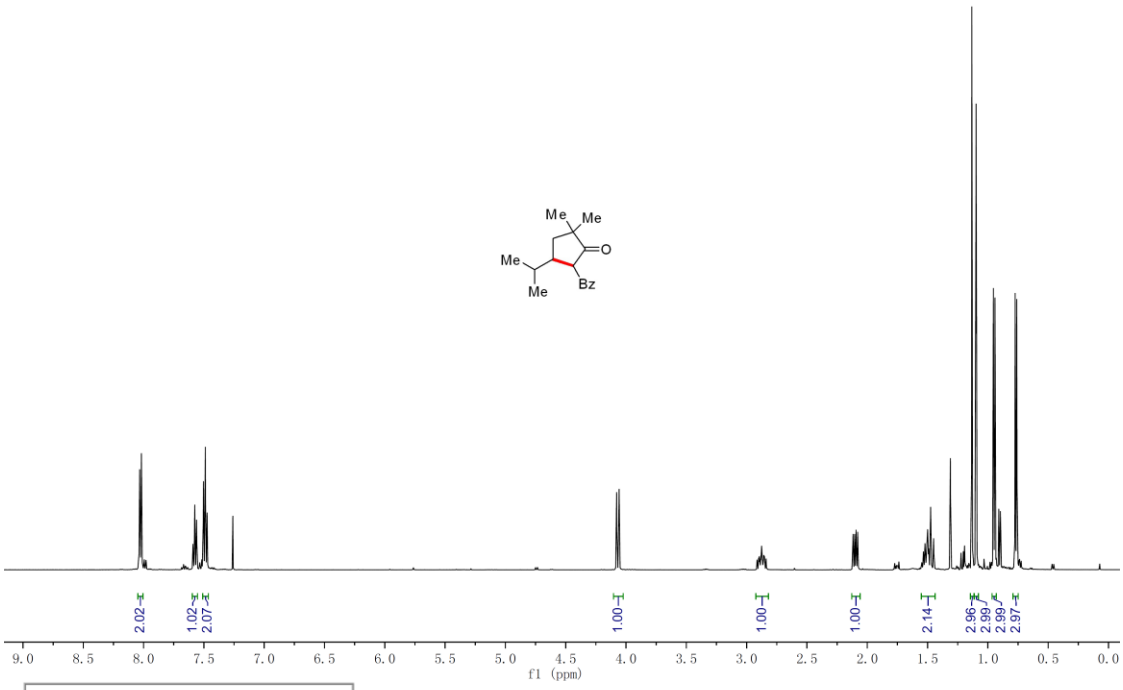
Parameter	Value
Title	youliang-5-18C-P1
Solvent	"CDCl3"
Relaxation Delay	10.0000
Spectrometer Frequency	499.86



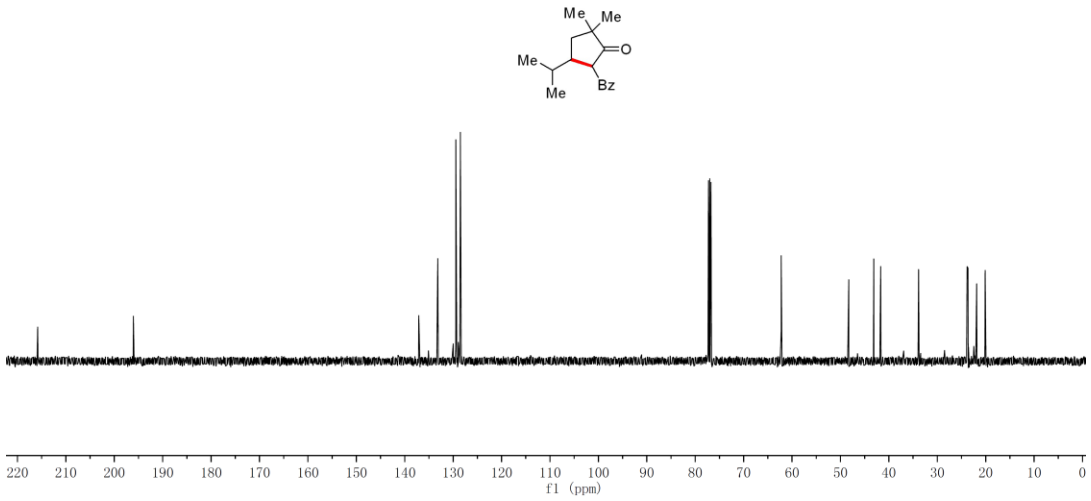
Parameter	Value
Title	youliang-5-18C-P1-C13g
Solvent	"CDCl3"
Relaxation Delay	1.0000
Spectrometer Frequency	125.70



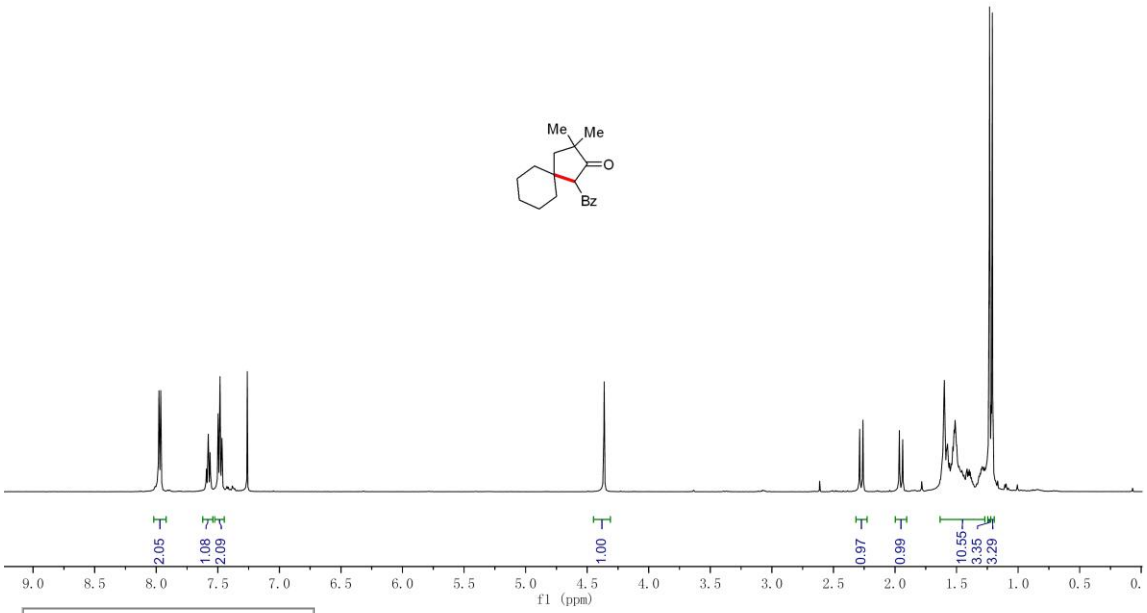
Parameter	Value
1 Title	youliang-5-100C-P-major
2 Solvent	CDCl3
3 Temperature	25.0
4 Relaxation Delay	10.0000
5 Spectrometer Frequency	499.86



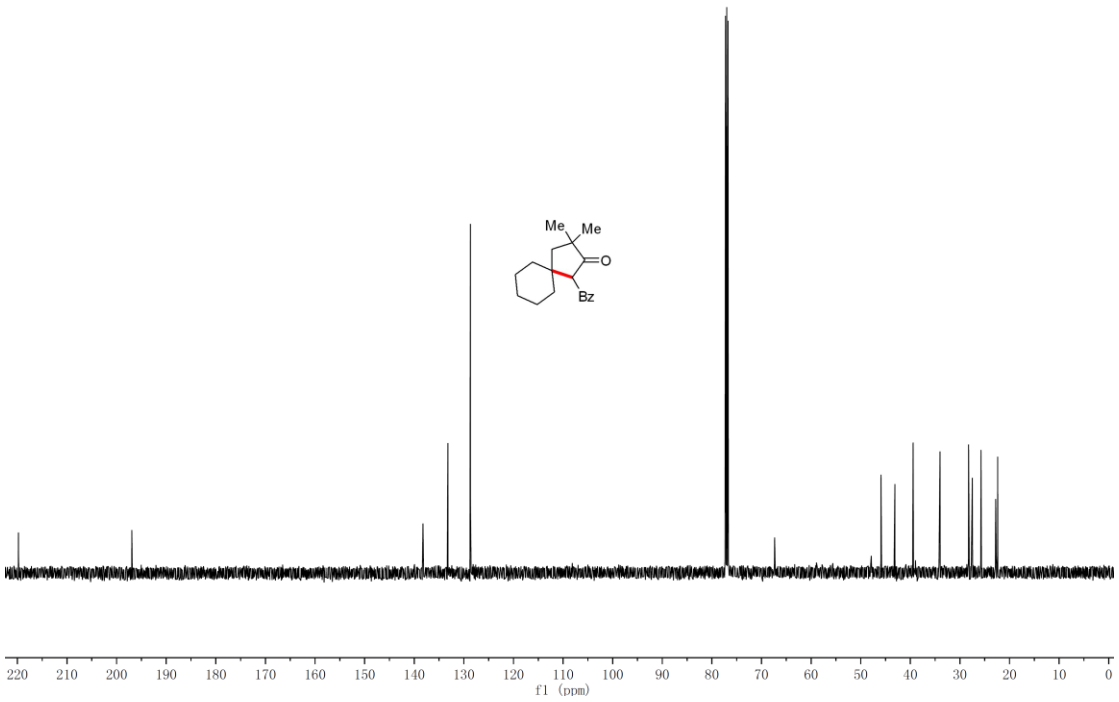
Parameter	Value
1 Title	youliang-5-100C-P-major-C13i
2 Solvent	CDCl3
3 Temperature	25.0
4 Relaxation Delay	1.0000
5 Spectrometer Frequency	125.70



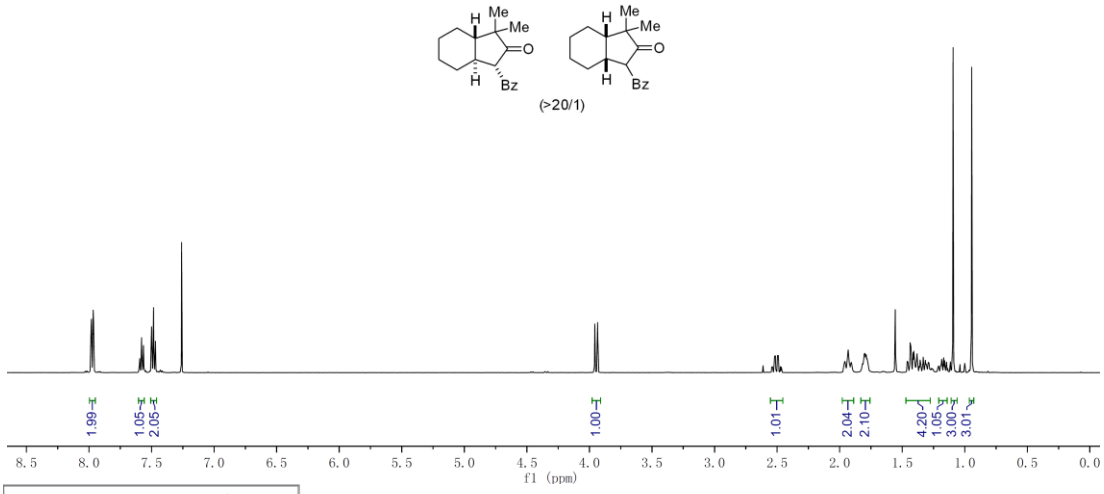
Parameter	Value
1 Title	youliang-5-104B-P
2 Solvent	CDCl3
3 Temperature	25.0
4 Relaxation Delay	10.0000
5 Spectrometer Frequency	499.86



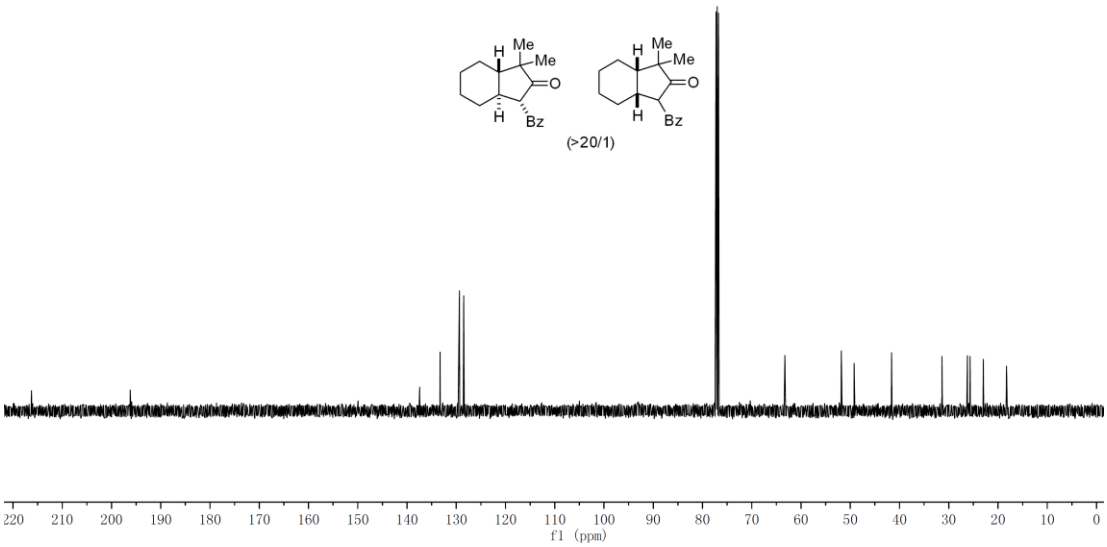
Parameter	Value
1 Title	youliang-5-104B-P-C13n
2 Solvent	CDCl3
3 Temperature	25.0
4 Relaxation Delay	1.0000
5 Spectrometer Frequency	125.70

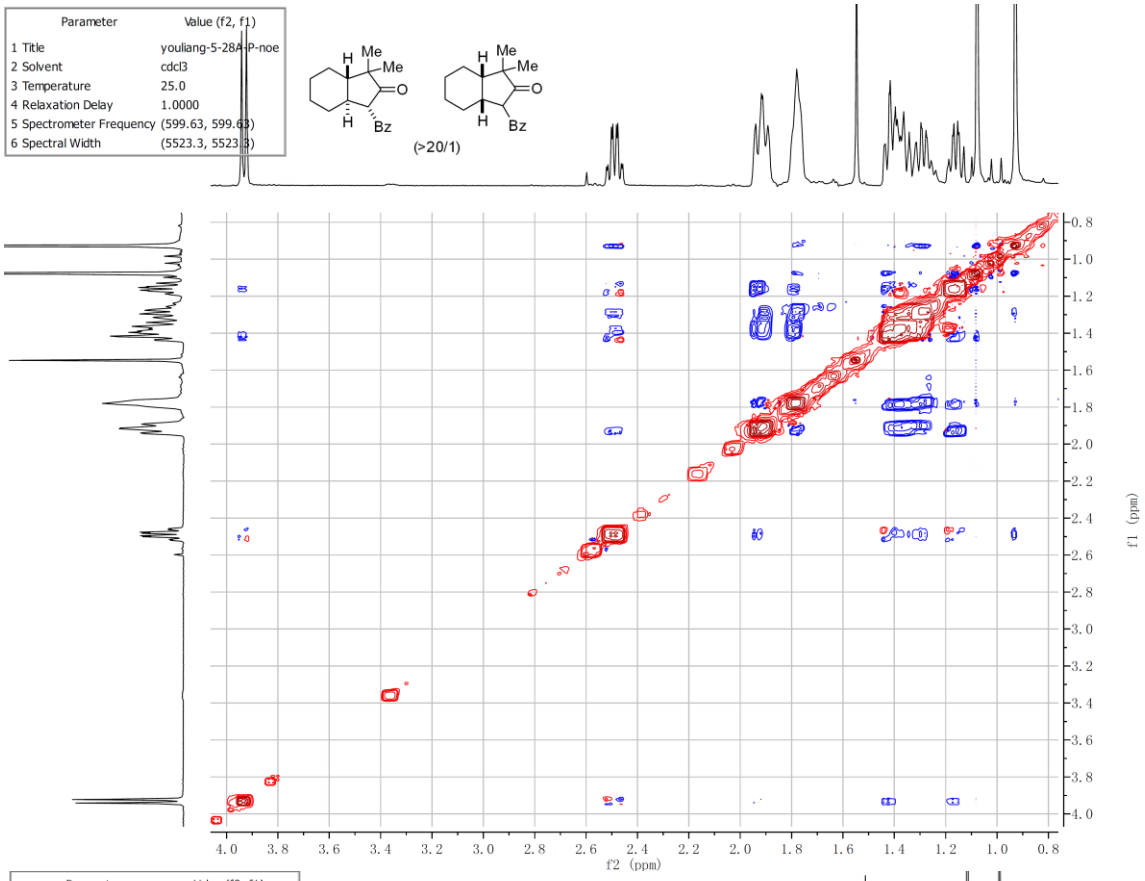


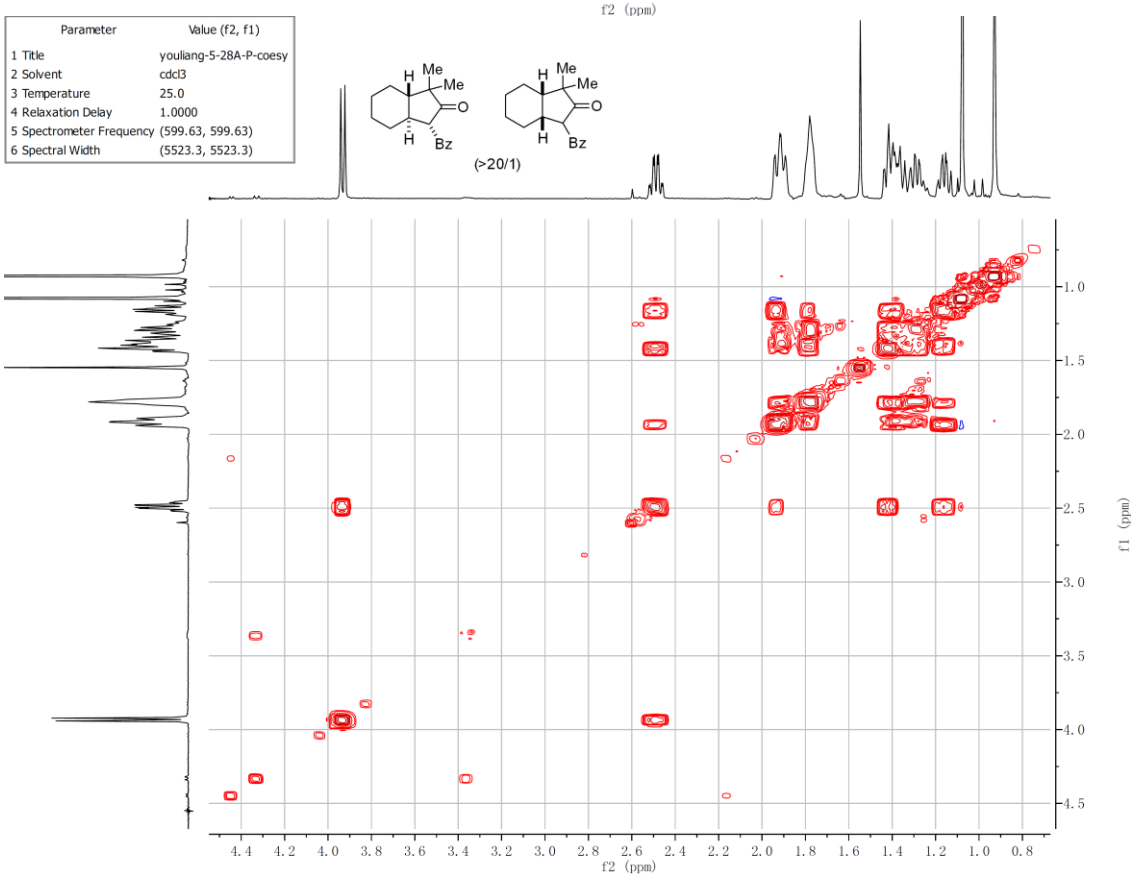
Parameter	Value
1 Title	youliang-5-28A-P
2 Solvent	CDCl3
3 Temperature	25.0
4 Relaxation Delay	10.0000
5 Spectrometer Frequency	499.86

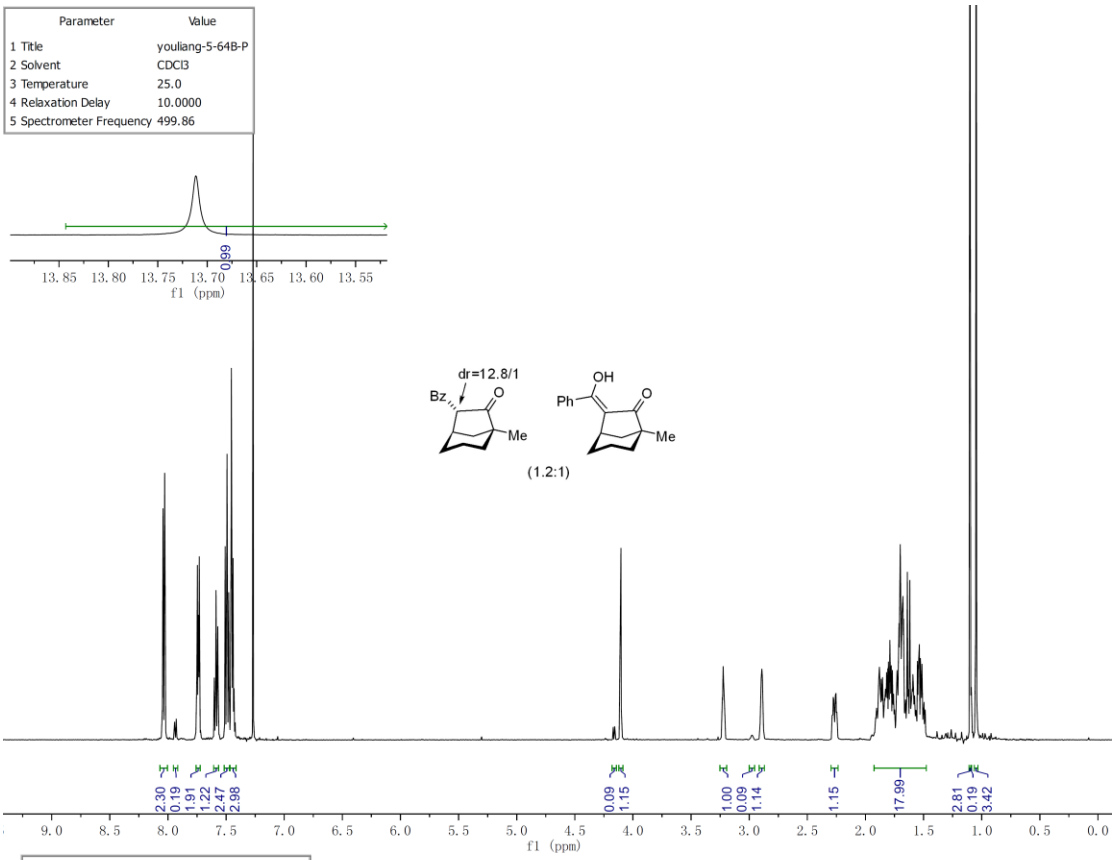


Parameter	Value
1 Title	youliang-5-28A-P-C13e
2 Solvent	CDCl3
3 Temperature	25.0
4 Relaxation Delay	1.0000
5 Spectrometer Frequency	125.70

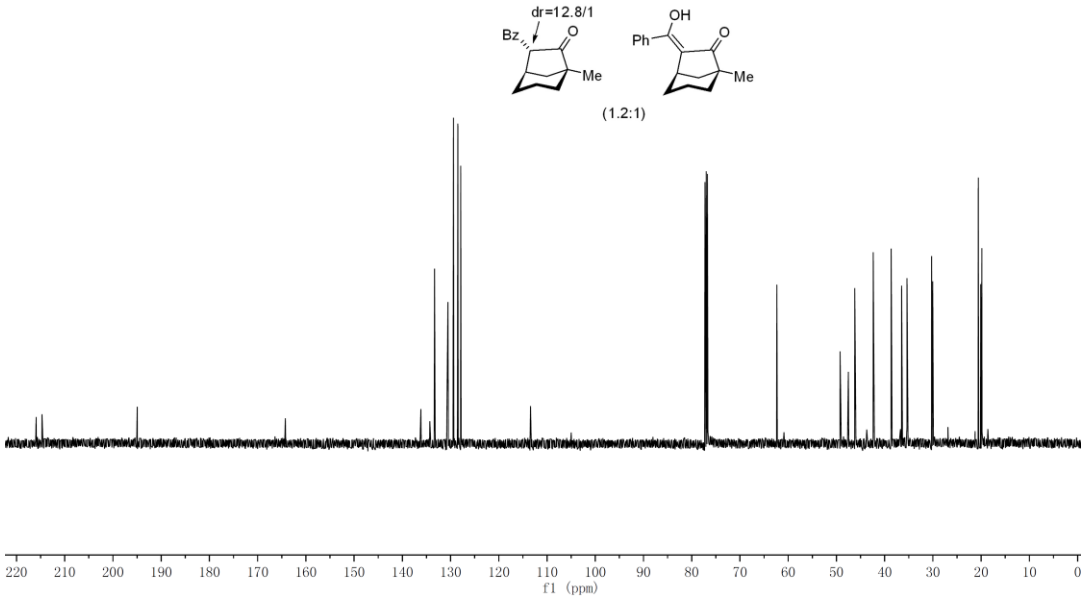


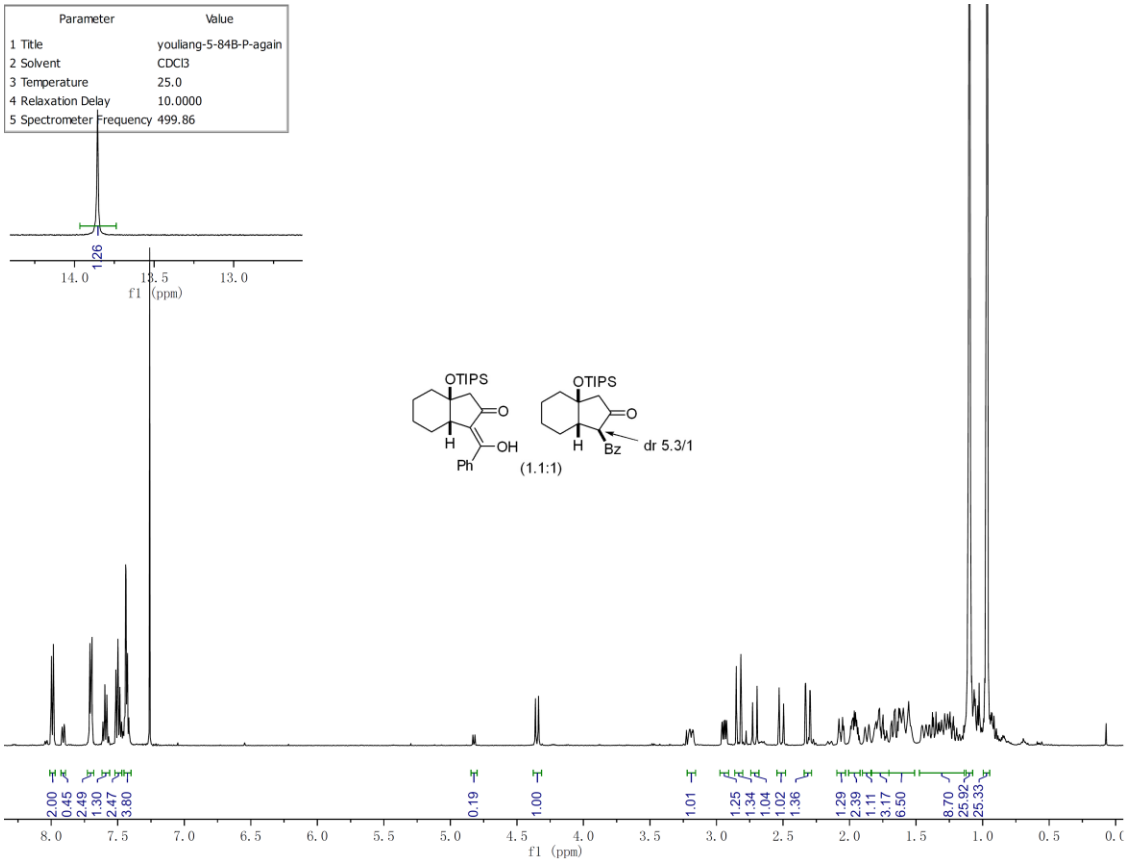

Parameter Value (f2, f1)
1 Title youliang-5-28A-P-noe
2 Solvent cdcl3
3 Temperature 25.0
4 Relaxation Delay 1.0000
5 Spectrometer Frequency (599.63, 599.63)
6 Spectral Width (5523.3, 5523.3)
(>20/1)
f2 (ppm)
f1 (ppm)

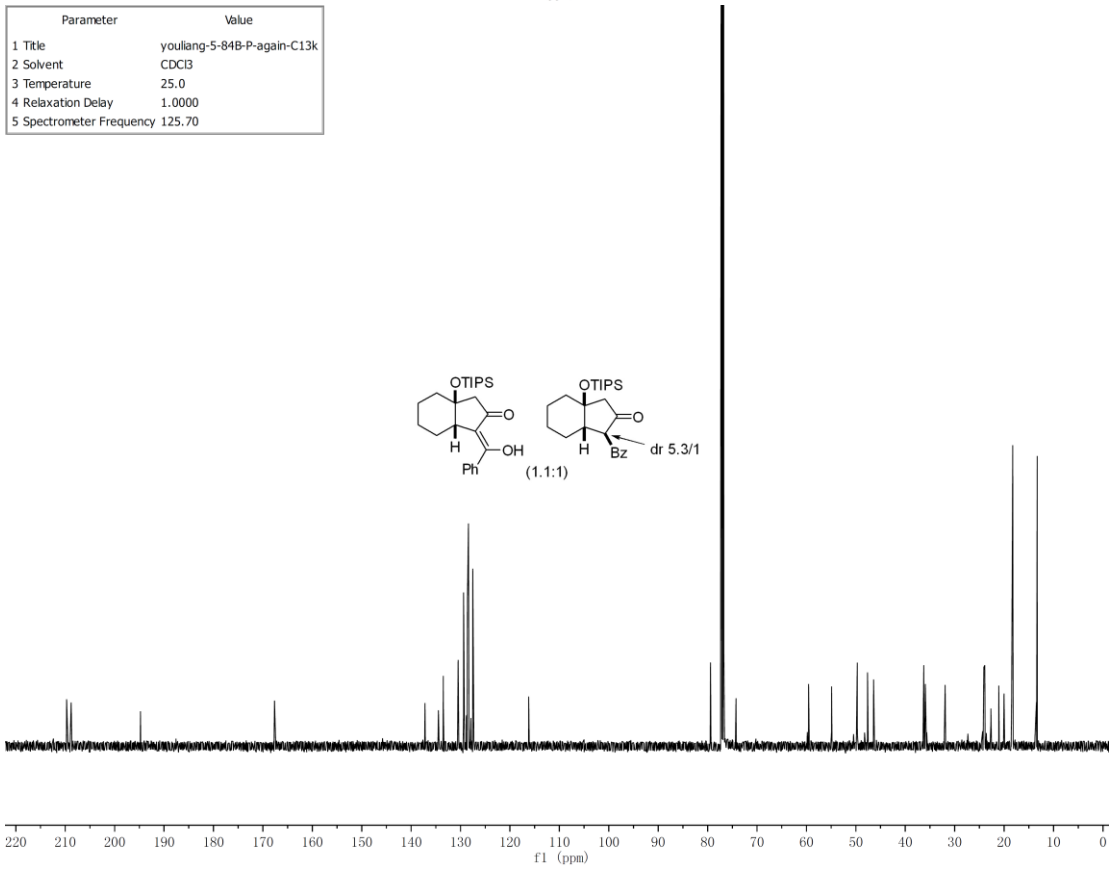

Parameter Value (f2, f1)
1 Title youliang-5-28A-P-coesy
2 Solvent cdcl3
3 Temperature 25.0
4 Relaxation Delay 1.0000
5 Spectrometer Frequency (599.63, 599.63)
6 Spectral Width (5523.3, 5523.3)
(>20/1)
f2 (ppm)
f1 (ppm)

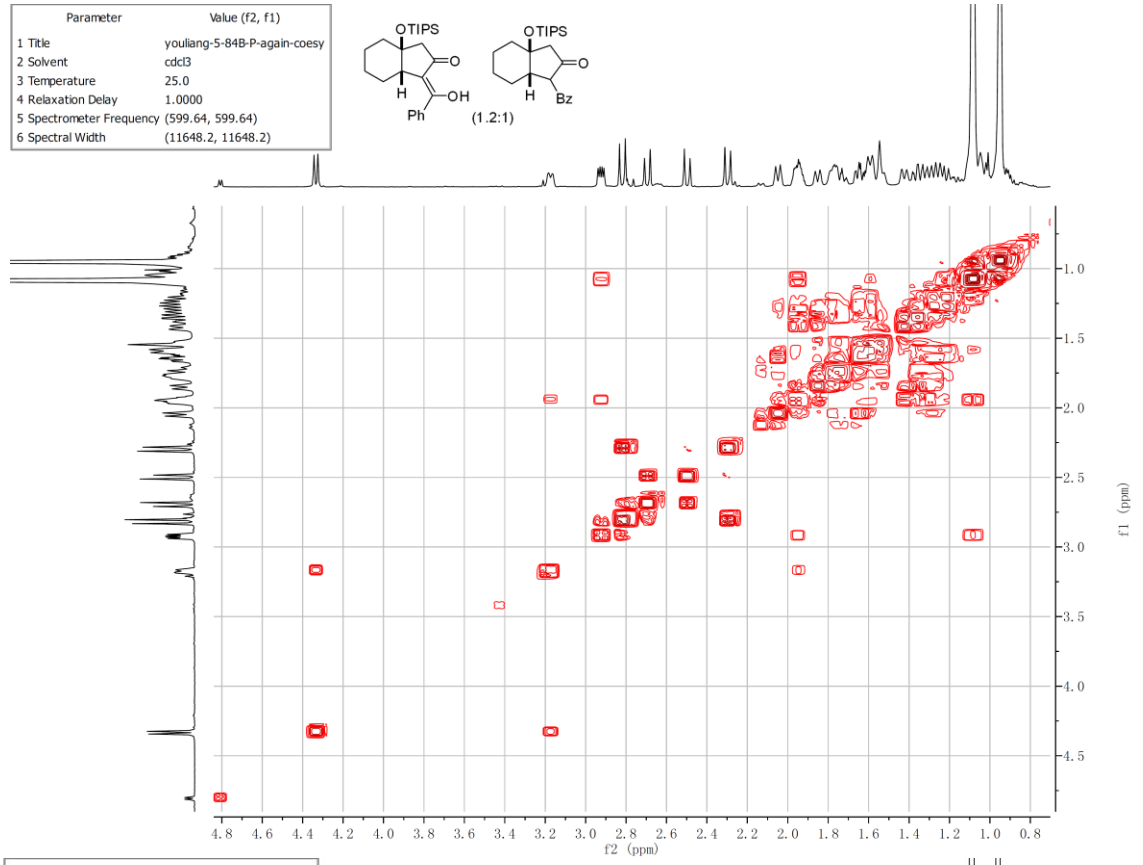


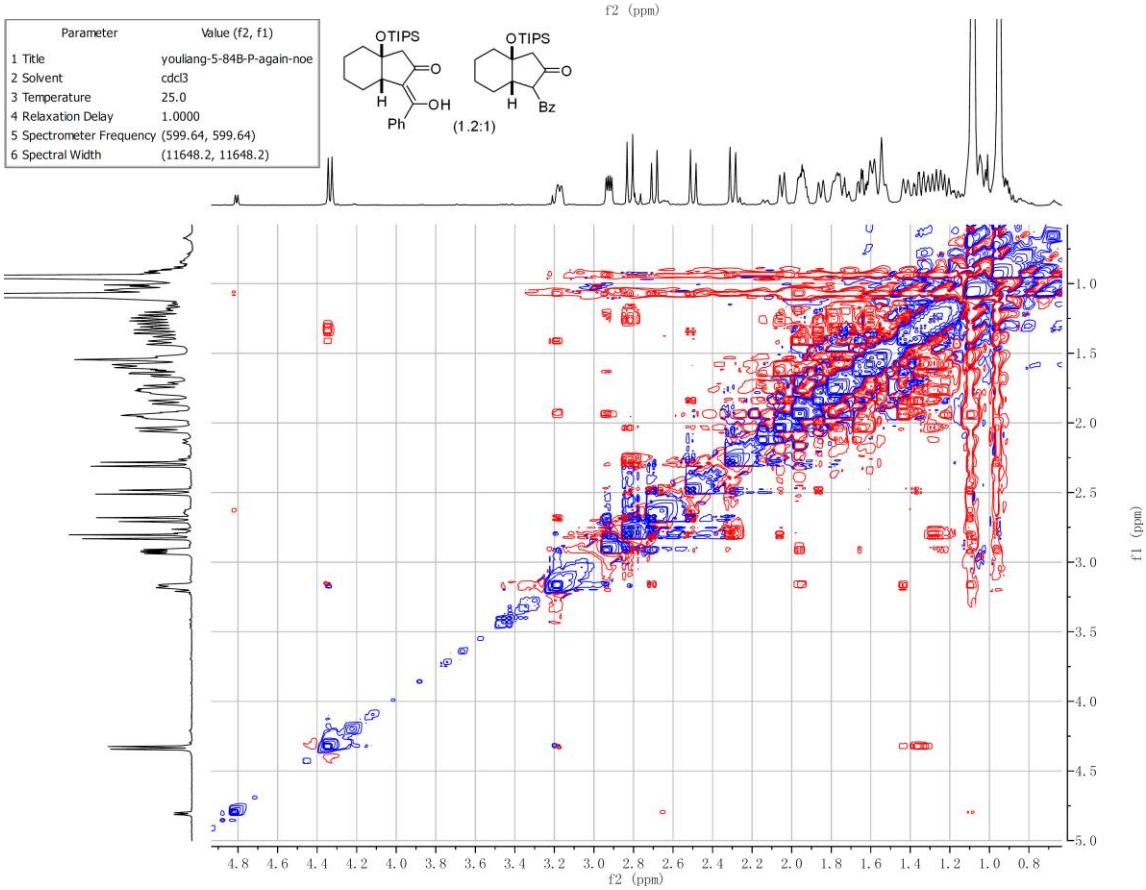
Parameter	Value
1 Title	youliang-5-64B-P-C13q
2 Solvent	CDCl3
3 Temperature	25.0
4 Relaxation Delay	1.0000
5 Spectrometer Frequency	125.70



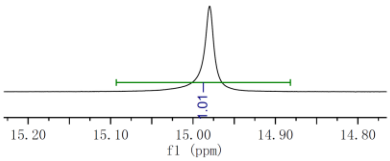

Parameter Value
1 Title youliang-5-84B-P-again
2 Solvent CDCl3
3 Temperature 25.0
4 Relaxation Delay 10.0000
5 Spectrometer Frequency 499.86
1.26
14.0 13.5 13.0
f1 (ppm)
OTIPS
OH
Ph
OTIPS
H
Bz
dr 5.3/1
(1.1:1)
2.00 0.45 2.49 1.30 2.47 3.80 0.19 1.00 1.01 1.25 1.34 1.04 1.02 1.36 1.29 2.39 1.11 3.17 6.50 8.70 25.92 25.33
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

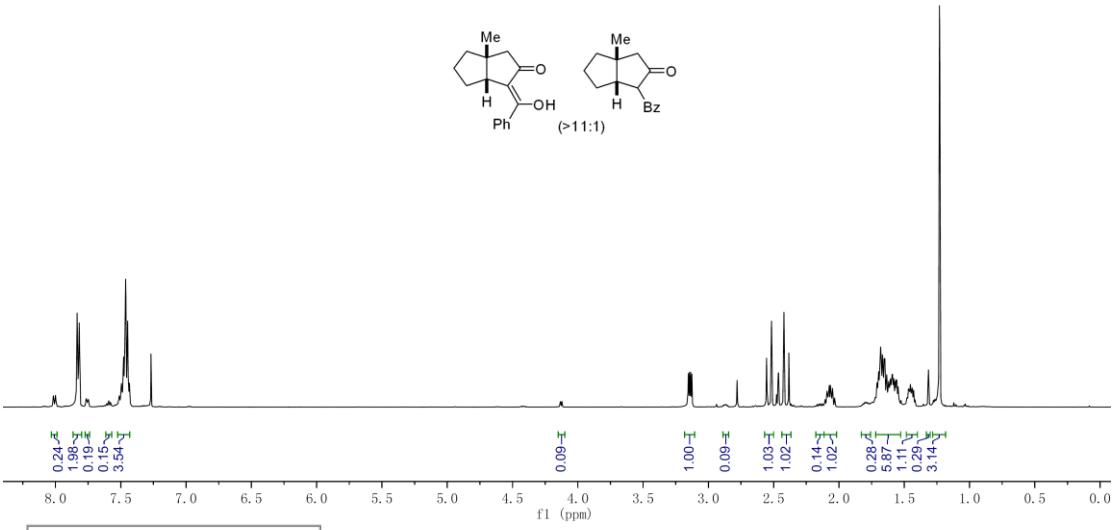

Parameter Value
1 Title youliang-5-84B-P-again-C13k
2 Solvent CDCl3
3 Temperature 25.0
4 Relaxation Delay 1.0000
5 Spectrometer Frequency 125.70
OTIPS
OH
Ph
OTIPS
H
Bz
dr 5.3/1
(1.1:1)
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


Parameter Value (f2, f1)
1 Title youliang-5-84B-P-again-coesy
2 Solvent cdcl3
3 Temperature 25.0
4 Relaxation Delay 1.0000
5 Spectrometer Frequency (599.64, 599.64)
6 Spectral Width (11648.2, 11648.2)
OTIPS
OH
Ph
H
OTIPS
O
H
Bz
(1.2:1)
f2 (ppm)
f1 (ppm)

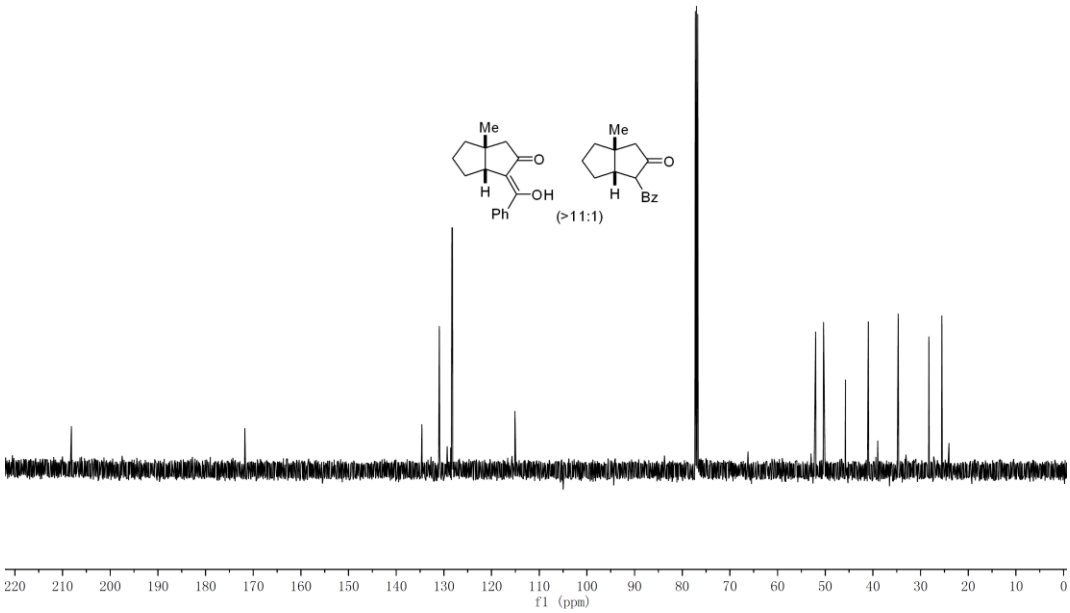

Parameter Value (f2, f1)
1 Title youliang-5-84B-P-again-noe
2 Solvent cdcl3
3 Temperature 25.0
4 Relaxation Delay 1.0000
5 Spectrometer Frequency (599.64, 599.64)
6 Spectral Width (11648.2, 11648.2)
OTIPS
OH
Ph
H
OTIPS
O
H
Bz
(1.2:1)
f2 (ppm)
f1 (ppm)

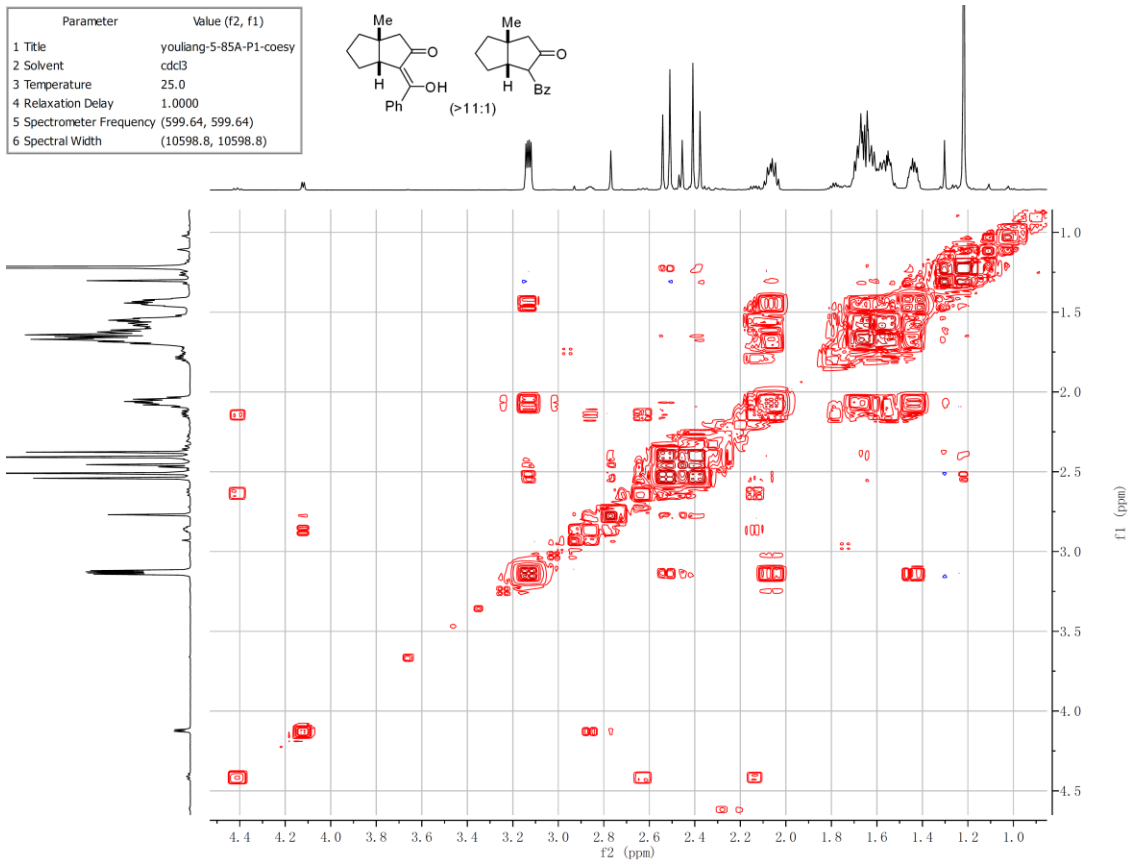
Parameter	Value
1 Title	youliang-5-85A-P1
2 Solvent	CDCl3
3 Temperature	25.0
4 Relaxation Delay	10.0000
5 Spectrometer Frequency	499.86

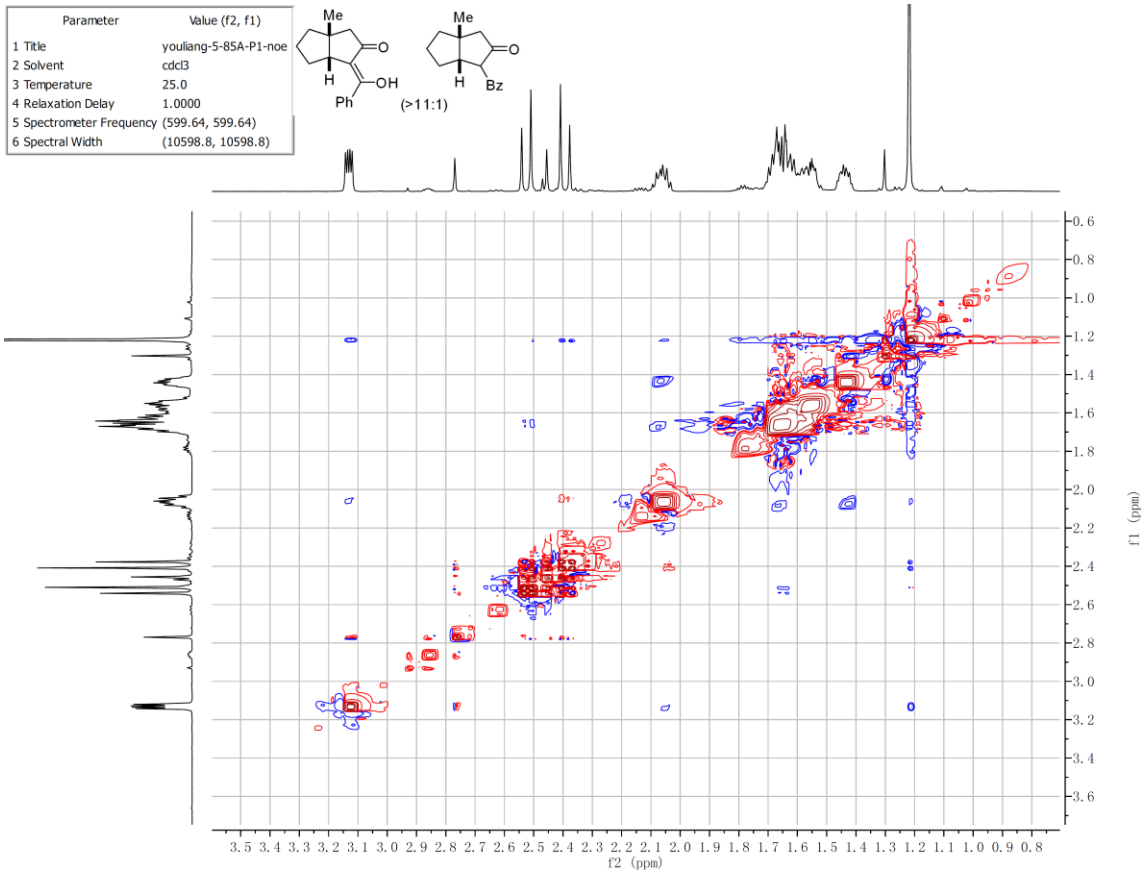


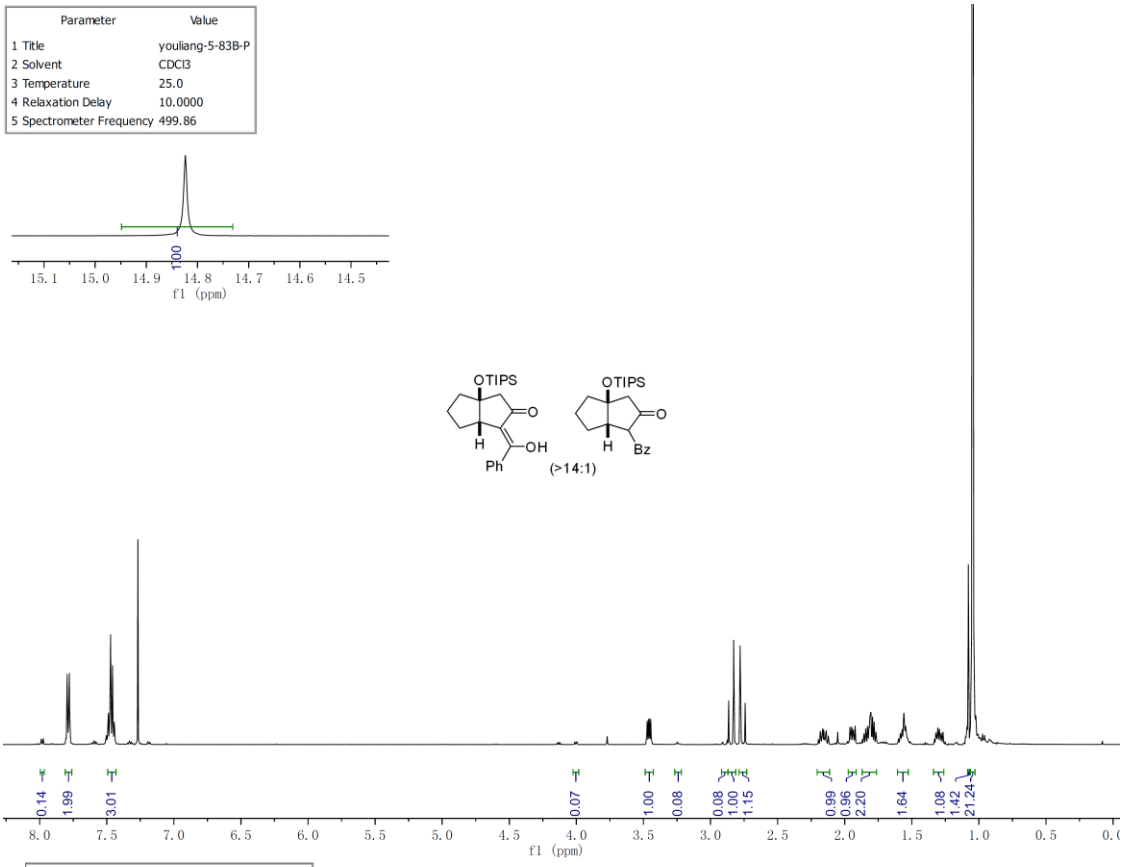


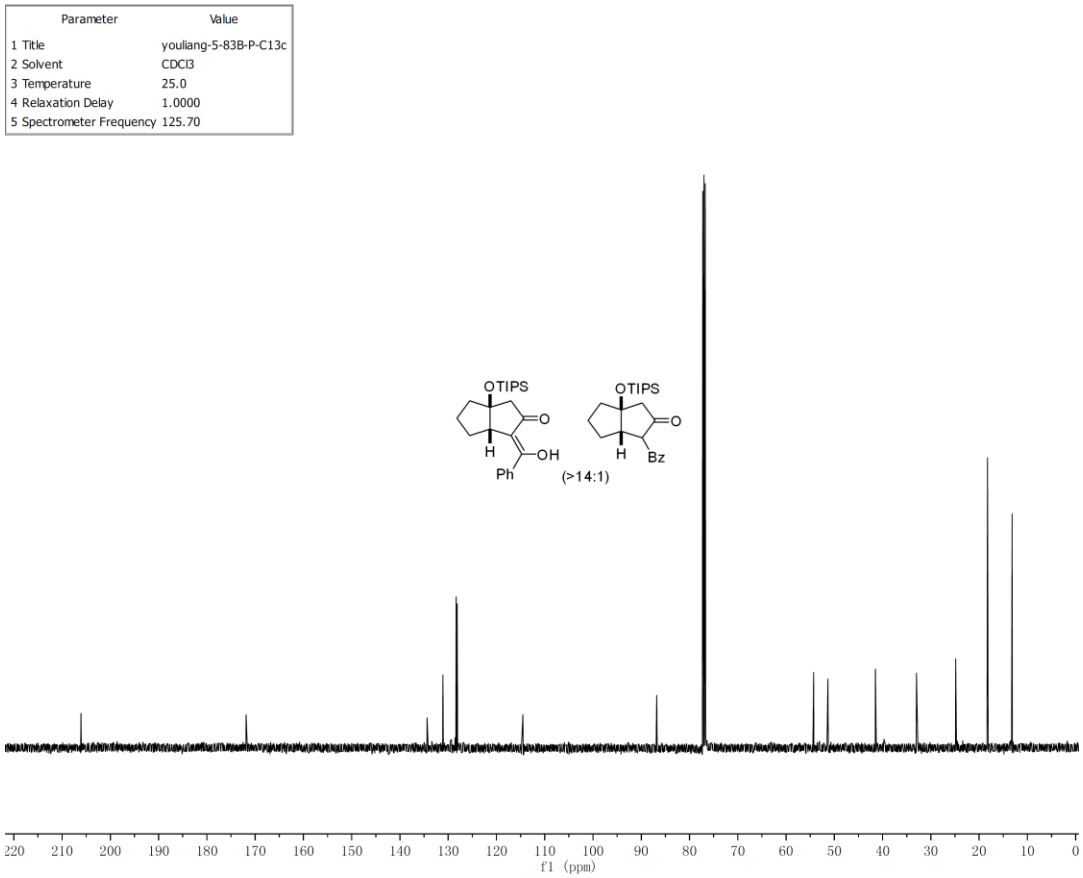
Parameter	Value
1 Title	youliang-5-85A-P1-C13h
2 Solvent	CDCl3
3 Temperature	25.0
4 Relaxation Delay	1.0000
5 Spectrometer Frequency	125.70

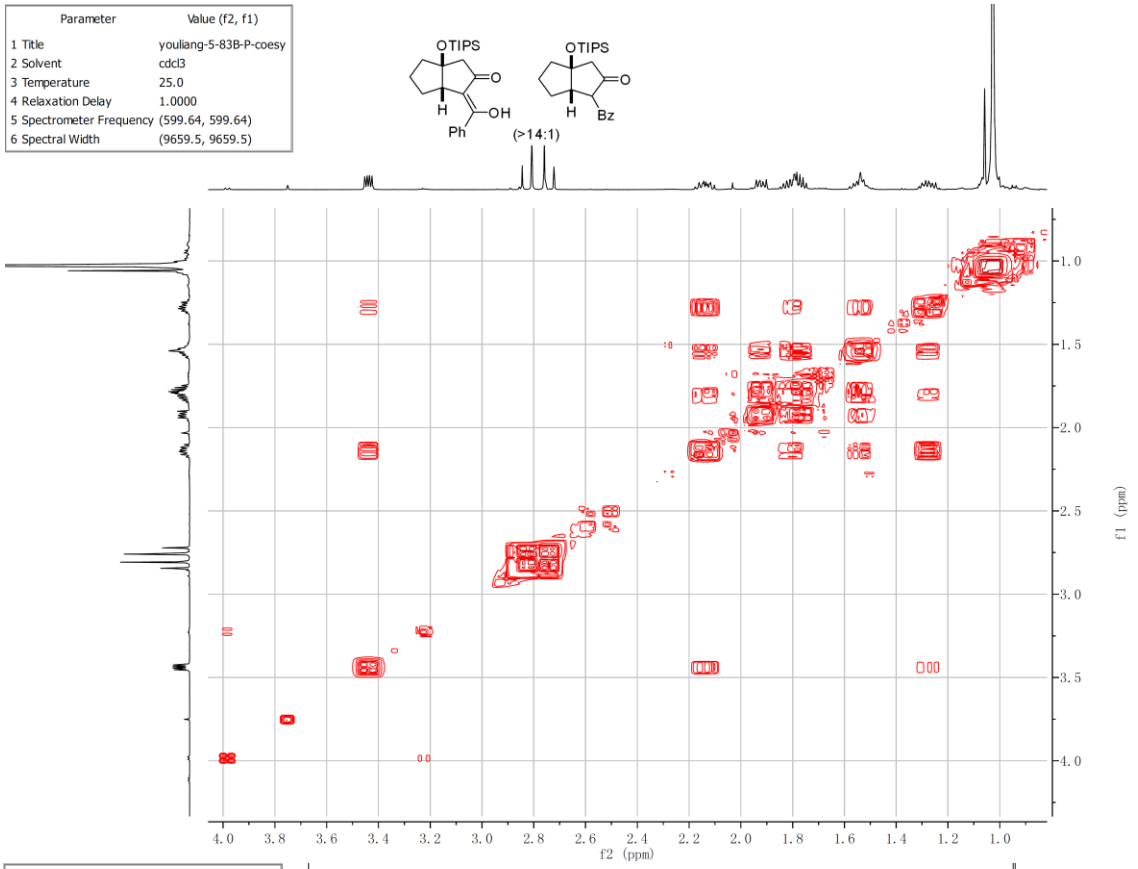


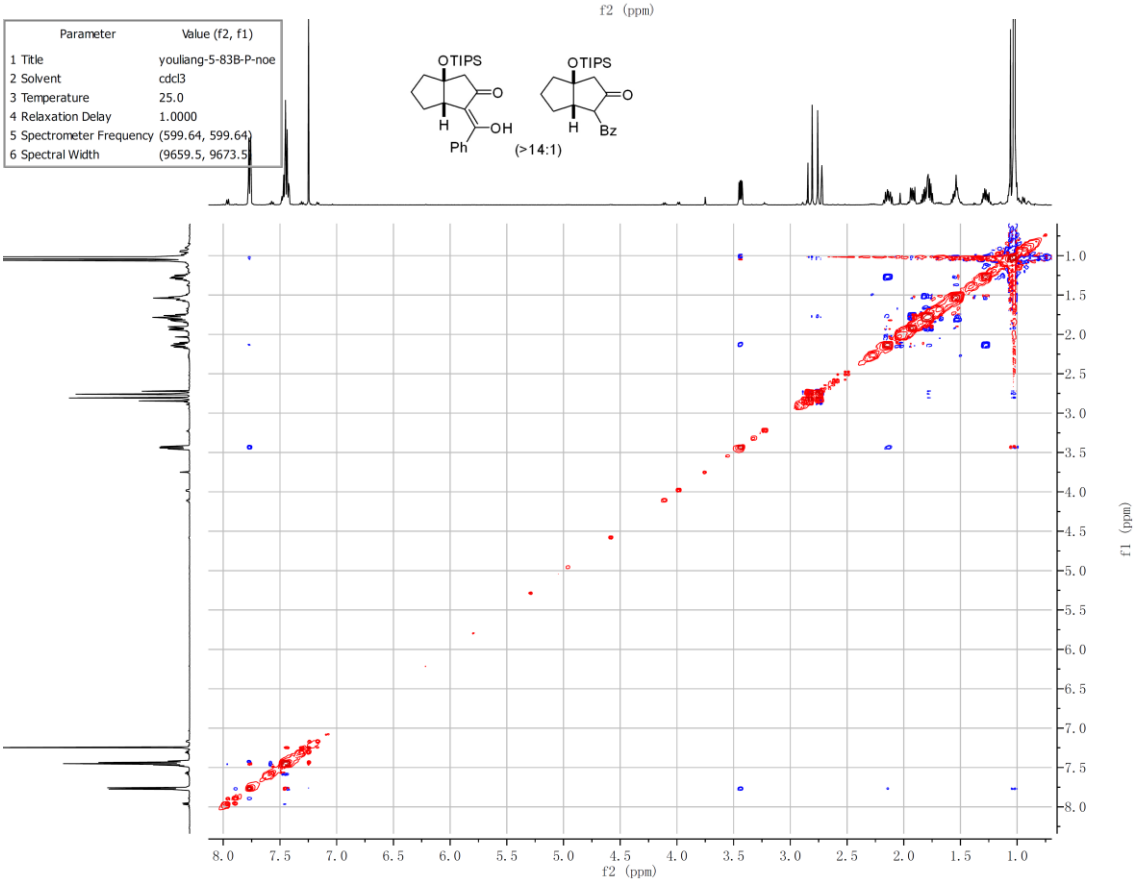

Parameter Value (f2, f1)
1 Title youliang-5-85A-P1-coesy
2 Solvent cdcl3
3 Temperature 25.0
4 Relaxation Delay 1.0000
5 Spectrometer Frequency (599.64, 599.64)
6 Spectral Width (10598.8, 10598.8)
Me
O
H
OH
Ph
(>11:1)
Me
O
H
Bz
f2 (ppm)
f1 (ppm)


Parameter Value (f2, f1)
1 Title youliang-5-85A-P1-noe
2 Solvent cdcl3
3 Temperature 25.0
4 Relaxation Delay 1.0000
5 Spectrometer Frequency (599.64, 599.64)
6 Spectral Width (10598.8, 10598.8)
Me
O
H
OH
Ph
(>11:1)
Me
O
H
Bz
f2 (ppm)
f1 (ppm)


Parameter Value
1 Title youliang-5-83B-P
2 Solvent CDCl3
3 Temperature 25.0
4 Relaxation Delay 10.0000
5 Spectrometer Frequency 499.86
1.00
f1 (ppm)
OTIPS
OH
Ph
OTIPS
H
Bz
(>14:1)
0.14
1.99
3.01
0.07
1.00
0.08
0.08
1.00
1.15
0.99
0.96
2.20
1.64
1.08
1.42
21.24
f1 (ppm)


Parameter Value
1 Title youliang-5-83B-P-C13c
2 Solvent CDCl3
3 Temperature 25.0
4 Relaxation Delay 1.0000
5 Spectrometer Frequency 125.70
OTIPS
OH
Ph
OTIPS
H
Bz
(>14:1)
f1 (ppm)


Parameter Value (f2, f1)
1 Title youliang-5-83B-P-coesy
2 Solvent cdcl3
3 Temperature 25.0
4 Relaxation Delay 1.0000
5 Spectrometer Frequency (599.64, 599.64)
6 Spectral Width (9659.5, 9659.5)
OTIPS
OH
Ph
OTIPS
Bz
(>14:1)
f2 (ppm)
f1 (ppm)


Parameter Value (f2, f1)
1 Title youliang-5-83B-P-noe
2 Solvent cdcl3
3 Temperature 25.0
4 Relaxation Delay 1.0000
5 Spectrometer Frequency (599.64, 599.64)
6 Spectral Width (9659.5, 9673.5)
OTIPS
OH
Ph
OTIPS
Bz
(>14:1)
f2 (ppm)
f1 (ppm)