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Synthesis of Cyclobutenes and Bicyclo (2.1.0) pentanes Through Platinum and Ruthenium- catalyzed Reactions

Zhenjie Ni

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ECOLE CENTRALE MARSEILLE*Institut des Sciences Moléculaires de Marseille (UMR 7313)***THESE DE DOCTORAT**

Pour obtenir le grade de:

DOCTEUR DE L'ECOLE CENTRALE MARSEILLE*Discipline: Sciences Chimiques**Ecole Doctotale des Sciences Chimiques ED 250***SYNTHESIS OF CYCLOBUTENES AND
BICYCLO[2.1.0]PENTANES THROUGH PLATINUM
AND RUTHENIUM-CATALYZED REACTIONS**

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List of Abbreviations

AcOH	acetic acid
acac	acetylacetonate
Anal.	elemental analysis
aq.	aqueous
BHT	Butylated hydroxytoluene
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Boc	<i>N-tert</i> -butoxycarbonyl
Bn	benzyl
Bz	benzoyl
br	broad (spectroscopy)
cat.	catalytic
calcd	calculated
cod	cyclooctadiene
COSY	COrrrelation spectroScopY
Cp	cyclopentadienyl
Cp*	pentamethylcyclopentadienyl
δ	NMR scale
d	doublet
DCE	1,2-dichloroethane
DCM	dichloromethane
DEPT	Distortionless Enhancement by Polarization Transfer
DIAD	diisopropylazodicarboxylate
DMA	dimethylacetamide
DMAD	dimethyl acetylenedicarboxylate
DMAP	4-dimethylamino pyridine
DMF	dimethylformamide
DMP	Dess-Martin periodinane
DMPU	<i>N,N'</i> -dimethyl- <i>N,N'</i> -propylene urea
DMSO	dimethylsulfoxide
dppe	1,2-diphenylphosphinoethane

EDC·HCl	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
<i>ee</i>	enantiomeric excess
equiv	equivalent
h	hour
HMBC	Heteronuclear Multiple Bond Correlation
HMQC	Heteronuclear Multiple-Quantum Correlation
HOBt	1-hydroxybenzotriazole hydrate
HPLC	High Performance Liquid Chromatography
HRMS	High Resolution Mass Spectroscopy
Hz	hertz
IR	infrared spectroscopy
λ	wavelength
M	molarity
m	multiplet
MCPs	methylenecyclopropanes
MeCN	acetonitrile
m.p.	melting point
Ms	methanesulfonyl
NBS	<i>N</i> -bromosuccinimide
NMP	<i>N</i> -methylpyrrolidone
NOESY	Nuclear Overhauser Enhancement Spectroscopy
PE	petroleum ether
<i>R_f</i>	retention factor value
rt	room temperature
s	singlet
t	triplet
TBAF	<i>tetra</i> -butylammonium fluoride
TBAI	<i>tetra</i> -butylammonium iodide
TBS	<i>tert</i> -butyldimethylsilyl
TC	thiophene-2-carboxylate
TCPC	tetracarbomethoxypalladacyclopentadiene
Tf	trifluoromethanesulfonyl

TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TMS	trimethylsilyl
Ts	<i>para</i> -toluenesulfonyl

Table of Contents

General Introduction	1
Chapter I Bibliographic Overview of Transition-Metal Catalyzed Synthesis of Cyclobutenes	3
<i>Introduction</i>	4
1.1 Transition-metal Catalyzed Intermolecular [2+2] Cycloadditions of Alkenes and Alkynes.....	5
1.1.1 Nickel.....	5
1.1.2 Palladium.....	7
1.1.3 Ruthenium.....	8
1.1.4 Cobalt.....	11
1.1.5 Rhodium.....	14
1.1.6 Gold.....	15
1.1.7 Silver.....	16
1.1.8 Rhenium.....	17
1.1.9 Iridium.....	17
1.1.10 Iron.....	17
1.1.11 Copper.....	18
1.2 Transition-metal Catalyzed Intramolecular [2+2] Cycloadditions of Enynes.....	20
1.2.1 Palladium.....	20
1.2.2 Platinum.....	21
1.2.3 Gold.....	25
1.2.4 Ruthenium.....	29
1.2.5 Nickel.....	32
1.2.6 Gallium.....	33
1.2.7 Cobalt.....	33
1.3 Transition-metal Catalyzed Intramolecular [2+2] Cycloadditions of Allenynes.....	34
1.3.1 Platinum.....	34
1.3.2 Rhodium.....	35
1.3.3 Molybdenum.....	36
1.4 Cyclobutenes Formation Through Metal-Catalyzed Ring Expansion Reactions.....	37
1.4.1 Platinum.....	37
1.4.2 Palladium.....	38
1.4.3 Silver.....	39
1.4.4 Rhodium.....	40
1.4.5 Gold.....	41
1.4.6 Copper.....	42
<i>Conclusion</i>	44

Chapter II Cyclobutene Formation in PtCl₂-Catalyzed Cycloisomerizations of Heteroatom-Tethered 1,6-Enynes	45
<i>Introduction</i>	46
2.1 Purpose of the initial project.....	50
2.2 Preliminary investigations.....	51
2.3 Cyclobutene formation in PtCl ₂ -catalyzed cycloisomerization of heteroatom-tethered 1,6-enynes.....	53
2.3.1 The solvent screening.....	53
2.3.2 The role of amide solvent.....	55
2.3.3 Determination the structure of cyclobutene 3	56
2.3.3.1 ¹ H NMR and ¹³ C NMR of cyclobutene 3	56
2.3.3.2 NOESY of cyclobutene 3	56
2.3.3.3 X-ray diffraction of the cyclobutene 3	57
2.4 Scope of the Pt-Catalyzed Cycloisomerization of Hetero- atom-Tethered 1,6-Enynes..	58
2.4.1 Cycloisomerization of <i>N</i> -tethered enynes with disubstitution α to nitrogen atom ...	58
2.4.2 Cycloisomerization of <i>N</i> -tethered enynes with monosubstitution at the propargylic or allylic position.....	62
2.4.3 Cycloisomerization of <i>N</i> -tethered enynes without substitution at the propargylic carbon atom.....	65
2.4.4 Cycloisomerization of <i>O</i> -tethered enynes with disubstitution α to nitrogen atom...	68
2.4.5 Attempted Cycloisomerization of carbon-tethered enynes.....	71
2.5 Studies on the reaction mechanism.....	72
2.5.1 Insights on the role of DMA as a ligand.....	72
2.5.2 Proposal of mechanism for the formation of cyclobutene.....	75
2.5.3 Deuterium labeling experiments.....	75
<i>Conclusion</i>	78

Chapter III A New Approach to the Bicyclo[2.1.0]pentane Framework through the Ruthenium-Catalyzed Cyclopropanation of Cyclobutenes with Tertiary Propargylic Carboxylates	79
3.1 The bicyclo[2.1.0]pentane framework: synthetic methods and synthetic utility.....	80
3.1.1. Syntheses from 2,3-diazabicyclo[2.2.1]hept-2-enes.....	80
3.1.2. Syntheses from cyclobutenes and carbene precursors.....	81
3.1.3. Synthetic utility of bicyclic [2.1.0] structures.....	82
3.2 Presentation and purpose of the project.....	84
3.2 Preliminary studies.....	86
3.2.1 Cyclopropanation of model substrate 32	86

3.2.2 Determination of the structure of tricyclic compound 86	86
3.2.2.1 ¹ H NMR and ¹³ C NMR of 86	86
3.2.2.2 NOESY of 86	87
3.3 Scope of the Ruthenium-Catalyzed Cyclopropanation of Cyclobutenes with Tertiary Propargylic Carboxylates	88
3.3.1 Ruthenium-Catalyzed Cyclopropanation of Cyclobutenes	88
3.3.2 Ruthenium-Catalyzed cyclopropanation of cyclobutene 14 with various propargylic carboxylates	91
3.3.3 Substituents effects on the ruthenium-catalyzed cyclopropanation of cyclobutenes	93
3.3.3.1 Cyclobutene monosubstituted at sp ² carbon atom 107	93
3.3.3.2 Cyclobutene monosubstituted at sp ³ carbon atom 113	93
3.3.3.3 Disubstituted cyclobutenes 114 and 117	95
3.3.3.4 Sterically congested cyclobutene 122	96
<i>Conclusion</i>	98
General Conclusion	99
Experimental Section	102
I. Preparation of 1,6-enynes.	104
II. PtCl ₂ -catalyzed enyne cycloisomerizations	134
III. Deuterium labeling experiments	147
IV. Preparation of tertiary propargyl carboxylates	151
V. Preparation of cyclobutenes 107 , 113 , 117 and 122	154
VI. CpRuCl(PPh ₃) ₂ -catalyzed cyclopropanation of cyclobutenes	159

General Introduction

In our laboratory, we are interested in novel transition metal catalyzed reactions based on the *atom economy* principle,¹ such as addition, cycloaddition and cycloisomerization reactions. In this manuscript we present a two-steps atom-economic synthesis of bicyclo[2.1.0]pentanes through the sequential Pt-catalyzed cycloisomerization of heteroatom-tethered 1,6-enynes and Ru-catalyzed cyclopropanation of cyclobutenes with tertiary propargyl acetates. The manuscript contains three chapters and an experimental part.

Chapter I. This chapter is a bibliographical survey summarizing the main results of metal catalyzed [2+2] cycloadditions for the synthesis of cyclobutenes. The reactions are presented according to the metal catalyst.

Chapter II. This chapter provides the deep and thorough study of cyclobutene formation in Pt-catalyzed cycloisomerizations of heteroatom-tethered 1,6-enynes. It is shown that the presence of alkyl substituent(s) at propargyl position and the use of weakly coordinating solvents such as DMA are the key elements favoring the formation of cyclobutenes.

Chapter III. Presented herein is the development of a new approach to bicyclo[2.1.0]pentanes through the ruthenium-catalyzed cyclopropanation of cyclobutenes with tertiary propargylic carboxylates. It provides a safe method which avoid the use of hazardous carbene precursors to generate functionalized bicyclo[2.1.0]pentane frameworks in high yields under mild conditions.

¹ a) Trost, B. M. *Science* **1991**, 254, 1471-1477. b) Trost, B. M. *Angew. Chem. Int. Ed.* **1995**, 34, 259-281.

Chapter I

Bibliographic Overview of Transition-Metal

Catalyzed Synthesis of Cyclobutenes

Introduction

The [2+2] cycloaddition of an alkene and/or alkyne represents the synthetic method of choice for the direct access to cyclobutane derivatives. This process is thermally forbidden according to the Woodward-Hoffmann rules.¹ However, it can be achieved through thermal reactions via biradical intermediates,² by photoreactions,³ and by the use of Lewis acid-catalyzed reactions.⁴ While the first two pathways of [2+2] cycloadditions can be tedious procedures and often narrow in scope, the development of efficient, alternative metal-catalyzed procedures would present an advantageous solution.

On the basis of the electronic demand of reactants of the well-established Diels-Alder reaction, earlier reports dealing with transition-metal catalyzed [2+2] cycloadditions of alkenes and alkynes focused on intermolecular reactions with compounds containing highly strained carbon-carbon double bonds such as norbornadiene (NBD) or related congeners and electron-deficient alkynes. These reactions were first described in the early sixties to afford bicyclo[2.2.1]heptane-fused cyclobutenes featuring *exo* stereochemistry and then thoroughly investigated in the nineties by the group of Mitsudo which expanded the scope of these reactions to nonactivated or neutral alkynes using well-defined ruthenium catalysts.

In recent years, efforts were devoted to expand the scope to cyclic or acyclic nonactivated alkenes and in the development of new catalysts. In this context, cycloisomerization reactions of 1,n-enynes, enallenes, yne-allenes allow for the more facile intramolecular [2+2] cycloaddition and provide ring-fused cyclobutenes or cyclobutanes. To date, enantioselective versions of these reactions using chiral catalysts have attracted very little interest and future work should focus on the design of catalysts to achieve new syntheses of chiral cyclobutanes or cyclobutenes. This chapter focused mainly on transition-metal catalyzed inter- and intramolecular [2+2] cycloadditions of alkenes and alkynes with emphasis on the metal catalyst and mechanistic principles. Recent methodologies involving ring expansion reactions of methylenecyclopropanes to cyclobutenes, although out of the frame of this

¹ *The Conservation of Orbital Symmetry*; Woodward, R. B., Hoffmann, R., Eds.; Academic Press: New York, 1970.

² Baldwin, J. E. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Paquette, L. A., Eds.; Pergamon: Oxford, 1991; Vol. 5, p 63.

³ Crimmins, M. T. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Paquette, L. A., Eds.; Pergamon: Oxford, 1991; Vol. 5, p 123.

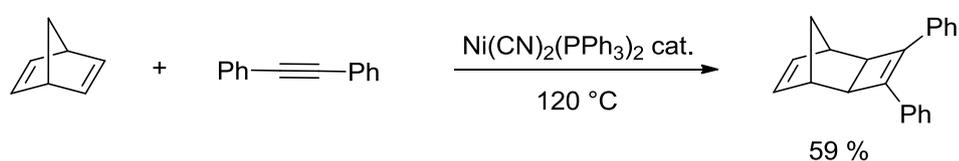
⁴ a) Snider B. B.; Spindell, D. K. *J. Org. Chem.*, **1980**, *45*, 5017–5020. b) Narasaka, K.; Hayashi, Y.; Iwasawa, N.; Sakurai, H. *Chem. Lett.* **1989**, 1581-1584. c) Engler, T. A.; Letavic, M. A.; Reddy, J. P. *J. Am. Chem. Soc.* **1991**, *113*, 5068-5070. d) Mitani, M.; Sudoh, T.; Koyama, K. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 1683-1687. e) Knolker, H. J.; Baum, E.; Schmitt, O. *Tetrahedron Lett.* **1998**, *39*, 7705-7708. f) Padwa, A.; Lipka, H.; Watterson, S. H.; Murphree, S. S. *J. Org. Chem.* **2003**, *68*, 6238-6250.

chapter, will be considered.

1.1 Transition-metal Catalyzed Intermolecular [2+2] Cycloadditions of Alkenes and Alkynes

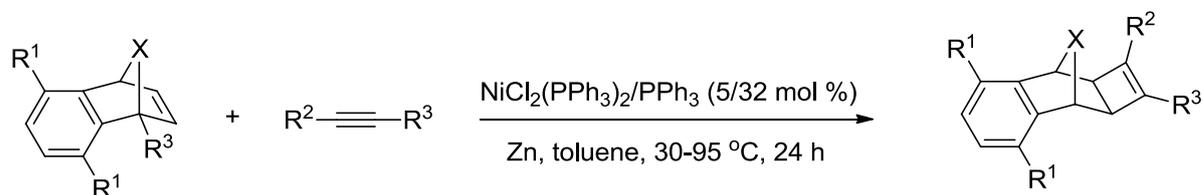
1.1.1 Nickel

The coupling of 2,5-norbornadiene (NBD) and 1,2-diphenylethyne in the presence of nickel catalyst reported by Schrauzer in 1964 represents the first transition-metal catalyzed alkene-alkyne [2+2] cycloaddition to form a cyclobutene (Scheme 1).⁵



Scheme 1. Nickel-catalyzed [2+2] cycloaddition of norbornadiene and alkyne

Since then, the metal-catalyzed [2+2] cycloadditions of norbornene and norbornadiene has been thoroughly studied. A variety of transition-metal catalysts have been developed for the [2+2] cycloaddition of alkynes with alkenes to date and the topic was recently reviewed.⁶ Cheng and co-workers reported that reduction of nickel phosphine complexes $[\text{Ni}(\text{PPh}_3)_2\text{Cl}_2]$ with zinc catalyzed stereoselectively the [2+2] cycloaddition of oxa- or azabenzonorbornadienes with various alkynes to give *exo*-cyclobutene derivatives (Scheme 2).⁷



⁵ Schrauzer, G. N.; Glockner, P. *Chem. Ber.* **1964**, 97, 2451–2462.

⁶ Tam, W.; Goodreid, J.; Cockburn, N. *Curr. Org. Synth.* **2009**, 6, 219-238.

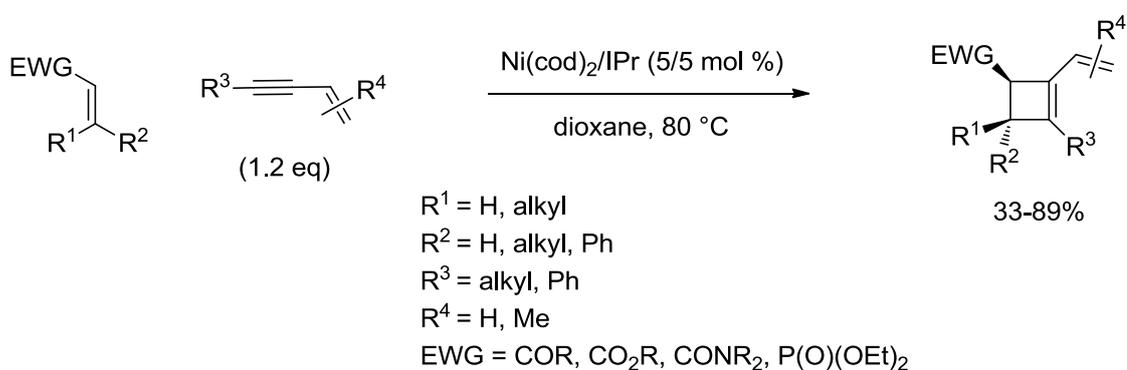
⁷ Huang, D.-J.; Rayabarapu, D. K.; Li, L.-P.; Sambaiah, T.; Cheng, C.-H. *Chem. Eur. J.* **2000**, 6, 3706-3713.

X	R ¹	R ²	R ³	yield (%)
O	H	Ph	Ph	85
O	H	Ph	Me	82
O	H	H	<i>n</i> -C ₅ H ₁₁	55
O	H	Ph	CO ₂ Et	64
O	H	Ph	CH(OEt) ₂	90*
O	H	CO ₂ Et	CO ₂ Et	83**
O	OMe	H	<i>n</i> -C ₅ H ₁₁	42
O	OMe	Ph	Me	86
O	OMe	Ph	Ph	76
O	OMe	Ph	CO ₂ Et	95
O	H	Ph	CH(OEt) ₂	96*
NCO ₂ Me	H	Ph	Ph	98

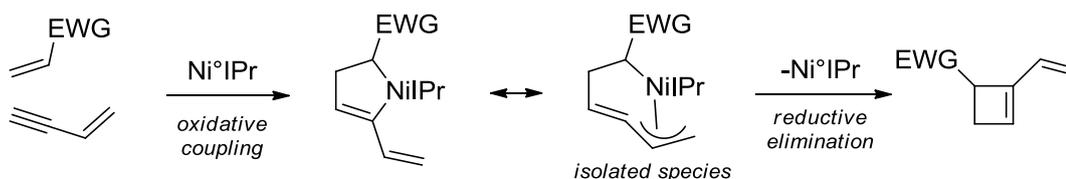
* isolated as the aldehyde, ** MeCN as the solvent

Scheme 2. Nickel-catalyzed [2+2] cycloaddition of oxa(aza)benzonorbornenes and alkynes

An *in situ* generated NHC-nickel(0) complex that catalyzes the intermolecular [2+2] cycloaddition of conjugated enynes with electron-deficient alkenes as well as electronically neutral norbornene or 1-decene to form cyclobutenes was reported by Ogoshi and co-workers (Scheme 3).⁸ The use of conjugated enynes instead of alkynes circumvented side reactions such as oligomerizations and cyclotrimerizations. The isolation and characterization of stable η^3 -butadienyl nickelacycle as a reaction intermediate was further demonstrated through its conversion to the vinylcyclobutene in the presence of an excess of electron-poor alkene.



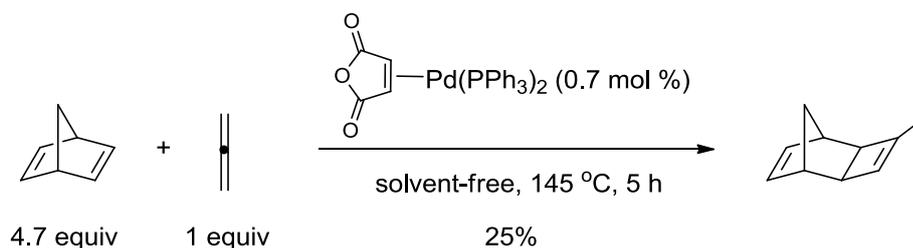
⁸ Nishimura, A.; Ohashi, M.; Ogoshi, S. *J. Am. Chem. Soc.* **2012**, *134*, 15692-15695.



Scheme 3. Nickel-catalyzed [2+2] cycloaddition of enynes with electron-deficient alkenes

1.1.2 Palladium

In the early 70's, Coulson described a single and presumably the first example of palladium catalyzed [2+2] cycloaddition between norbornadiene and propa-1,2-diene giving rise to *exo*-3-methyltricyclo[4.2.1.0^{2,5}]nona-3,7-diene (Scheme 4).⁹ Although the catalyst charge is rather low (0.7 mol %), the adduct was isolated from distillation of the crude reaction mixture in 25% yield. It was shown that upon substitution of propyne for propa-1,2-diene in the reaction, no cycloadduct was formed. Thus, *in situ* isomerization of propyne to propa-1,2-diene was ruled out, and that raises the issue of the intracyclic location of the double bond.

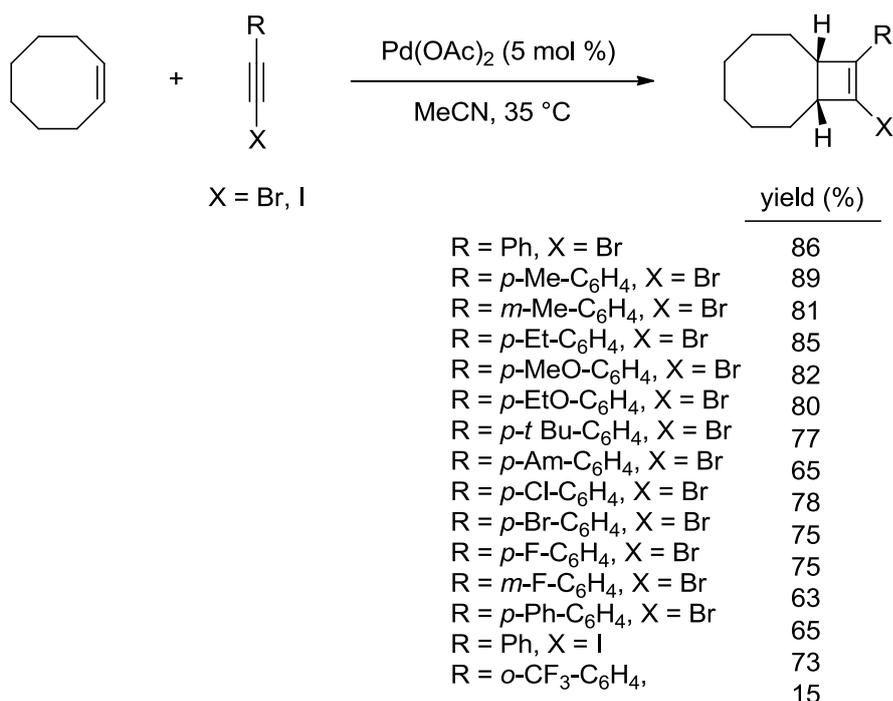


Scheme 4. Palladium-catalyzed [2+2] cycloaddition of propadiene with norbornadiene

During studies on palladium-catalyzed addition of bromo-1-alkynes to norbornene derivatives to form 2-bromo-7-alkynylnorbornanes, Jiang and co-workers found that reactions carried out with cyclooctene in place of norbornene resulted selectively with the formation of cyclobutenes in moderate to good yields (Scheme 5).¹⁰ The behavior of cyclooctene to undergo these cycloadditions is unique. Open-chain alkenes, such as 4-octene afforded only mixture of products while reactions with terminal alkenes were unsuccessful. Cycloalkenes, such as cyclopentene gave Heck-type compounds, although reaction conditions were quite different (PdBr₂/dppp, Zn/ZnI₂ in MeCN at rt).

⁹ Coulson, D. R. *J. Org. Chem.* **1972**, *37*, 1253–1254.

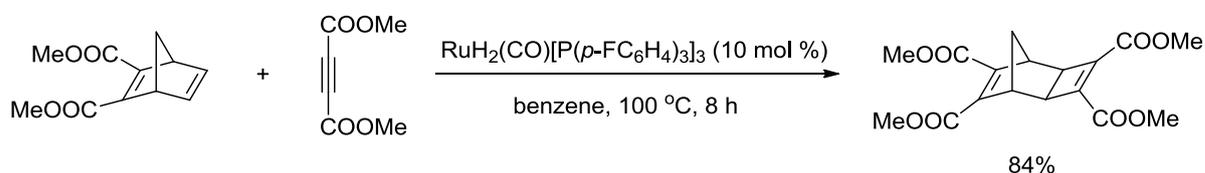
¹⁰ Li, Y.; Liu, X.; Jiang, H.; Liu, B.; Chen, Z.; Zhou, P. *Angew. Chem. Int. Ed.*, **2011**, *50*, 6341–6345.



Scheme 5. Palladium-catalyzed [2+2] cycloaddition of haloalkynes and cyclooctene

1.1.3 Ruthenium

In early studies on ruthenium catalyzed [2+2] intermolecular cycloadditions, Mitsudo and co-workers reported that treatment of norbornene and dimethyl acetylenedicarboxylate (DMAD) in benzene with a dihydride ruthenium complex such as RuH₂(PPh₃)₄ afforded the *exo*-tricyclo[4.2.1.0^{2,5}]non-3-ene system in high yields (Scheme 6).¹¹ Further studies from the same group revealed that RuH₂(CO)[P(*p*-FC₆H₄)₃]₃, RuH₂(CO)(PPh₃)₃ and Ru(cod)(cot) were effective catalysts, and optimum reaction temperature was 80-100°C. Although the [2+2] cycloaddition was applied to various bicyclic[2.2.1] alkenes including 7-oxa norbornadienes only reactions with DMAD as the alkyne were successful.¹²



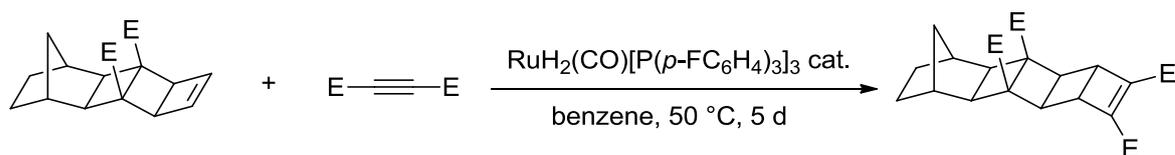
Scheme 6. Ruthenium-catalyzed [2+2] cycloaddition of norbornenes and DMAD

This method was applied to the synthesis of a new range of rigid linear rods based on the *n*

¹¹ Mitsudo, T.; Kokuryo, K.; Takegami, Y. *J. Chem. Soc., Chem. Commun.* **1976**, 722-723.

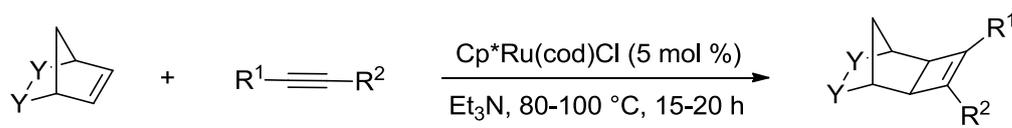
¹² a) Mitsudo, T.; Kokuryo, K.; Shinsugi, T.; Nakagawa, Y.; Watanabe, Y.; Takegami, Y. *J. Org. Chem.* **1979**, *44*, 4492-4496. b) Mitsudo, T.; Hori, Y.; Watanabe, Y. *J. Organomet. Chem.* **1987**, *334*, 157-167.

adderanes (Scheme 7).¹³



Scheme 7. Ruthenium-catalyzed [2+2] cycloaddition of cyclobutenes and DMAD

Later, Mitsudo's group reported that Cp**Ru*(cod)Cl greatly improved the efficiency of the [2+2] cycloaddition of various norbornenes and expanded the scope to non-activated alkynes (Scheme 8).¹⁴ The labile cod ligand to generate reactive unsaturated ruthenium species is essential to achieve the cycloaddition, since Cp*Ru*Cl(PPh₃)₂ exhibits no catalytic activity. Quite curiously the reactions worked better when carried out in triethylamine as the solvent. Thus, ruthenacyclopentene intermediate formed by oxidative coupling cannot undergo β-hydride elimination and leads to cyclobutene via reductive elimination.



1 Y = CH₂

2 Y-Y = CH=CH

1(2)/alkyne/*Ru* = 40(100)/20/1

	Y = CH ₂	Y-Y = CH=CH
R ¹ = R ² = Ph	88%	23%
R ¹ = Ph, R ² = CO ₂ Et	60%	74%
R ¹ = Me, R ² = CO ₂ Me	79%	87%
R ¹ = R ² = CO ₂ Me		37%
R ¹ = R ² = <i>n</i> -C ₅ H ₁₁	40%	

Scheme 8. Ruthenium-catalyzed [2+2] cycloaddition of bicyclic alkenes and alkynes

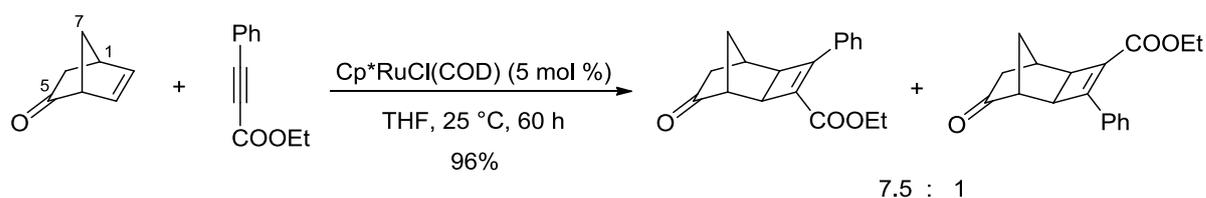
In contrast with the results of Mitsudo, Tenaglia and Giordano reported that Cp*Ru*Cl(PPh₃)₂ activated with catalytic amount of methyl iodide was also able to effect cycloadditions.¹⁵ The real precatalyst was shown to be Cp*Ru*Cl(PPh₃)₂ and although PPh₃ is less prone to dissociate from the metal with respect to cod, the reaction was achieved by increasing the temperature to 90 °C. The additive effect of methyl iodide was also demonstrated for the chemoselectivity of the reaction, i.e. [2+2] versus [2+2+2] cycloaddition.

¹³ Warrener, R. N.; Abbenante, G.; Kennard, C. H. L. *J. Am. Chem. Soc.* **1994**, *116*, 3645-3646.

¹⁴ Mitsudo, T.; Naruse, H.; Kondo, T.; Ozaki, Y.; Watanabe Y. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 580-581.

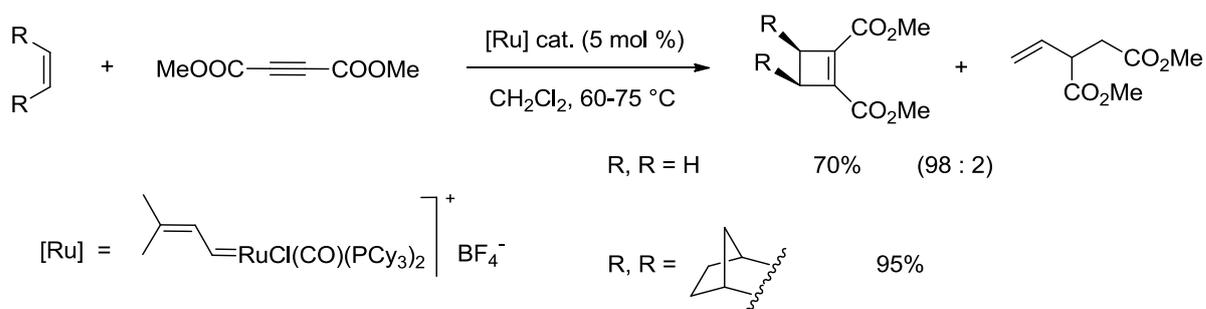
¹⁵ Tenaglia, A.; Giordano, L. *Synlett* **2003**, 2333-2336.

Tam's group reinvestigated thoroughly the [2+2] cycloaddition with substituted norbornenes or norbornadienes with electron-deficient alkynes using the Mitsudo protocol (Scheme 9). These studies aimed to the control of regio- and stereoselectivities of cycloadditions using remote substituent effects on C-5,¹⁶ C-7,¹⁷ positions in norbornene as well as C-2 and/or C-3 of norbornadienes.¹⁸ Thus, the major regioisomer adduct (7.5/1) observed in the Ru-catalyzed cycloaddition between bicyclo[2.2.1]hept-5-en-2-one and ethyl 3-phenylprop-2-ynoate exhibits the electron-poor substituent of cyclobutene close to the substituent of norbornene.



Scheme 9. Remote substituent effect on ruthenium-catalyzed [2+2] cycloaddition

A cationic ruthenacarbene showed high catalytic activity in [2+2] cycloaddition of electron-poor alkynes such as dimethyl acetylenedicarboxylate and norbornene derivatives or ethylene (Scheme 10).¹⁹ Interestingly no ring-opening metathesis products were observed with the cationic ruthenacarbene.



Scheme 10. A ruthenacarbene catalyst for [2+2] cycloaddition

Mezzetti and co-workers recently described the first enantioselective ruthenium-catalyzed Ficini cycloaddition of cyclic alkylidene β -ketoesters and ynamides to produce

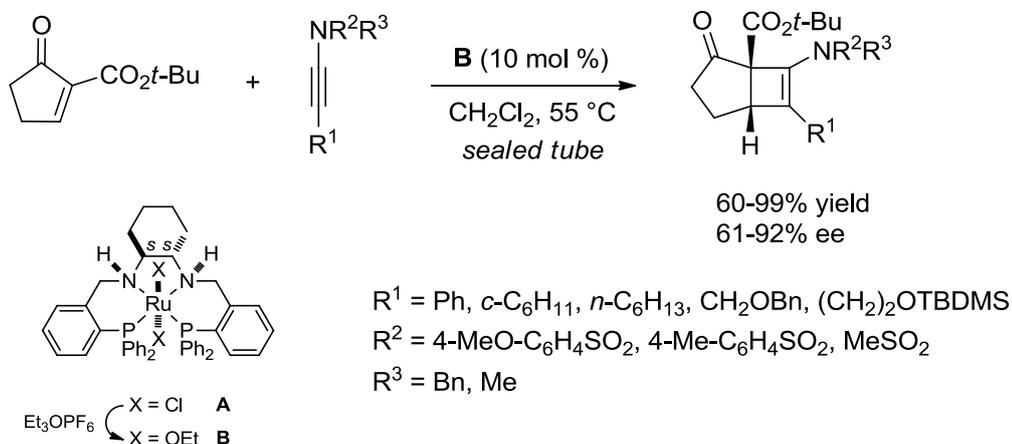
¹⁶ Jordan, R. W.; Tam, W. *Org. Lett.* **2000**, *2*, 3031-3034.

¹⁷ Jordan, R. W.; Tam, W. *Org. Lett.* **2001**, *3*, 2367-2370.

¹⁸ Jordan, R. W.; Tam, W. *Tetrahedron Lett.* **2002**, *43*, 6051-6054.

¹⁹ Yi, C. S.; Lee, D. W.; Chen, Y. *Organometallics* **1999**, *18*, 2043-2045.

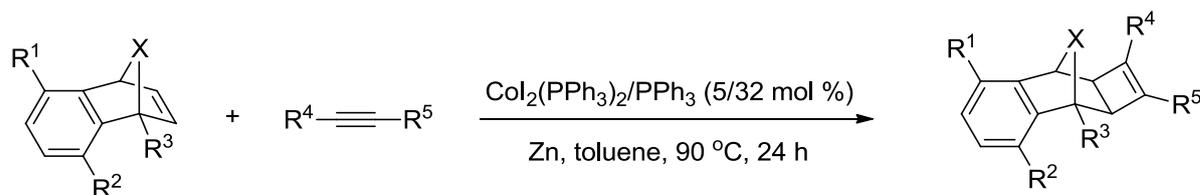
bicyclo[3.2.0]heptane-based enamides (Scheme 11).²⁰ The active catalytic species is generated *in situ* by treatment of Noyori's complex **A** with triethyloxonium hexafluorophosphate to form the elusive dicationic complex [Ru(OEt)₂(PNNP)](PF₆)₂.



Scheme 11. Ruthenium-catalyzed enantioselective Ficini cycloaddition

1.1.4 Cobalt

Cheng and co-workers reported that cobalt(II) complexes were effective catalysts for the [2+2] cycloaddition. Bicyclic alkenes and alkynes in toluene reacted smoothly in the presence of Co(PPh₃)₂I₂, PPh₃, and Zn as reducing agent to afford the corresponding *exo*-cyclobutene derivatives in fair to excellent yields (Scheme 12).²¹



alkene/alkyne/CoI₂(PPh₃)₂/PPh₃/Zn = 1/10/0.1/0.8/10 mmol

²⁰ Schotes, C.; Bigler, R.; Mezzetti, A. *Synthesis* **2012**, *44*, 513-526.

²¹ Chao, K. C.; Rayabarapu, D. K.; Wang, C.-C.; Cheng, C.-H. *J. Org. Chem.* **2001**, *66*, 8804-8810.

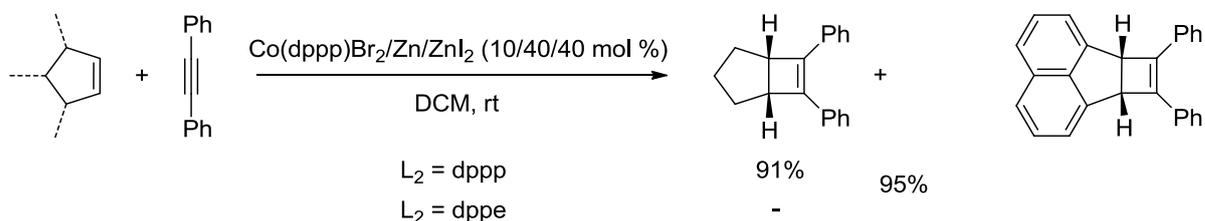
X	R ¹	R ²	R ³	R ⁴	R ⁵	yield (%)
O	H	H	H	Ph	Ph	88
O	H	H	H	TMS	H	85
O	H	H	H	C(Me) ₂ OH	H	83
O	H	H	H	TMS	CO ₂ Et	90
O	H	H	H	Ph	Me	60
O	OMe	H	H	Ph	Ph	71
O	OMe	H	H	TMS	H	38/46*
O	OMe	H	H	C(Me) ₂ OH	H	43/33*
O	OMe	OMe	H	TMS	H	46
O	OMe	OMe	Me	Ph	Ph	60
NCO ₂ Me	H	N	H	Ph	Ph	86
NCO ₂ Me	H	N	H	TMS	H	42/29*
NCO ₂ Me	H	N	H	C(Me) ₂ OH	H	95

* 2 regioisomers

Scheme 12. Cobalt-catalyzed [2+2] cycloaddition of oxa(aza)benzonorbornenes and alkynes

The alkynes that are active in this cobalt-catalyzed reaction are different from those of the previous nickel-promoted reaction reported by the same group.⁸ Both monosubstituted and dialkyl acetylenes undergo the cycloaddition. In addition, highly substituted oxabenzonorbornadienes are also effective for the reaction.

Under modified catalytic conditions, namely replacing the triphenylphosphine ligand with the bidentate 1,2-diphenylphosphinoethane (dppe) and zinc iodide²² as additive, Treutwein and Hilt reported cobalt-catalyzed [2+2] cycloadditions giving better yields of adducts using an equimolar alkene/alkyne ratio (Scheme 13).²³ Alongside diverse norbornenes, cyclopentene and acenaphthylene were competent alkenes using a twofold catalyst loading.



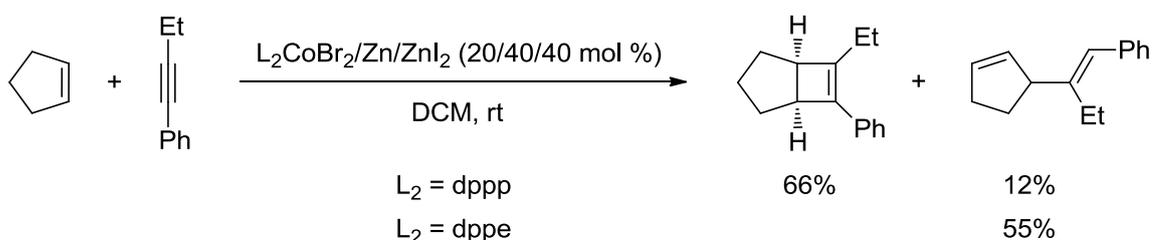
Scheme 13. Cobalt-catalyzed [2+2] cycloaddition of cyclopentenes and alkynes

In 2010, Hilt reported the cobalt-catalyzed [2+2] cycloaddition vs Alder-ene reaction of cyclic alkenes with internal alkynes, which depends on the electronic nature of the alkyne as

²² This catalyst combination was originally reported by Snyder for the [4+2+2] cycloaddition of norbornenes and butadiene. See : Ma, B.; Snyder, J. K. *Organometallics* **2002**, *21*, 4688-4695.

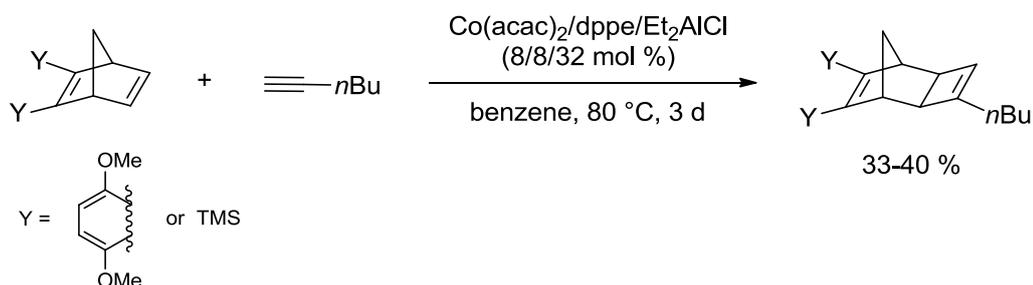
²³ Treutwein, J.; Hilt, G. *Angew. Chem. Int. Ed.* **2008**, *47*, 6811-6813.

well as the bite angle of the bidentate phosphine ligand used (Scheme 14).²⁴ For instance, cyclopentene and but-1-ynylbenzene afforded the [2+2] adduct as the major compound in the presence of $\text{CoBr}_2(\text{dppp})$ whereas the Alder-ene adduct was the only product formed in the presence of $\text{CoBr}_2(\text{dppe})$. Curiously, cyclohexene was found unaffected in these reactions. On the contrary, cycloheptene gave rise to the [2+2] adducts in low yields.



Scheme 14. Ligand dependence of cobalt-catalyzed cycloaddition versus Alder-ene reaction

Cobalt Ziegler-type catalysts were investigated by Lautens and Tam to promote [2+2] cycloadditions involving terminal alkynes and electron-rich ynophiles (Scheme 15).²⁵



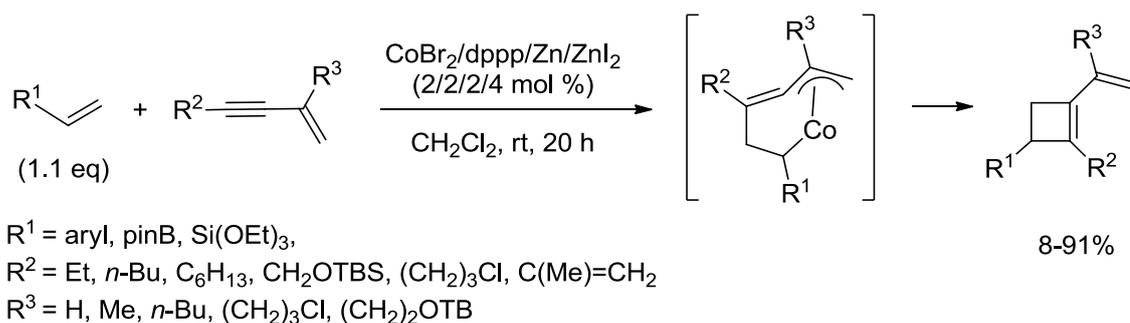
Scheme 15. Cobalt-catalyzed [2+2] cycloaddition of norbornenes and terminal alkynes.

Very recently, based on their previous work with nickel catalysts, Ogoshi and co-workers disclosed the cross-dimerization of simple alkenes with 1,3-enynes leading to conjugated vinylicyclobutenes (Scheme 16).²⁶ The mechanism proposed based on a η^3 -butadienyl cobaltacycle is similar to the one reported with the nickel catalyst (§ 1.1.1).

²⁴ Hilt, G.; Paul, A.; Treutwein, J. *Org. Lett.* **2010**, *12*, 1536-1539.

²⁵ Tam, W. Unpublished results. Cited in Lautens, M.; Klute, W.; Tam W. *Chem. Rev.*, **1996**, *96*, 49-92.

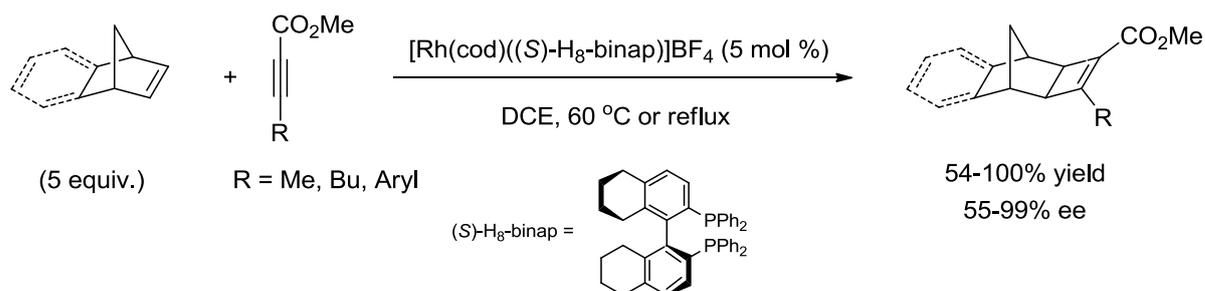
²⁶ Nishimura, A.; Tamai, E.; Ohashi, M.; Ogoshi, S. *Chem. Eur. J.* **2014**, *20*, 6613-6617.



Scheme 16. Cobalt-catalyzed [2+2] cycloaddition of 1,3-enynes and terminal alkenes.

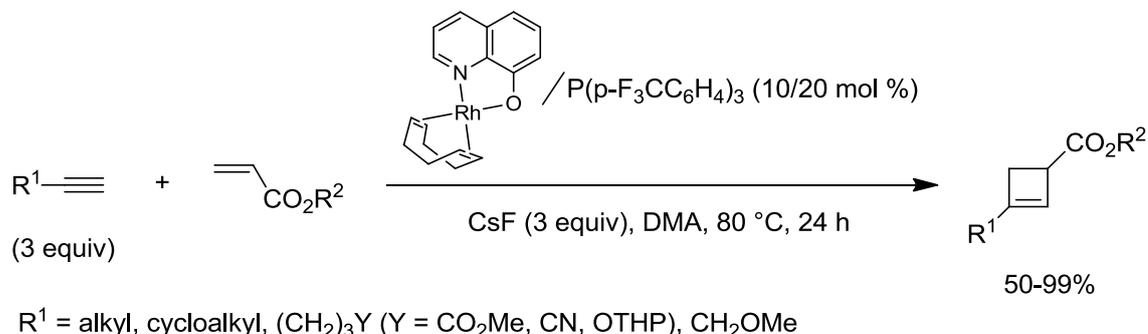
1.1.5 Rhodium

The enantioselective [2+2] cycloaddition of norbornene derivatives and electron-deficient alkynes using a chiral rhodium catalyst proceeded efficiently to give chiral tri- and tetracyclic cyclobutenes in moderate to high ee (up to 99% ee) (Scheme 17).²⁷



Scheme 17. Rhodium-catalyzed enantioselective [2+2] cycloaddition of norbornenes and alkynes

Kakiuchi reported the first catalytic intermolecular [2+2] cycloaddition of terminal alkynes with electron-deficient alkenes in the presence of an 8-quinolinolato rhodium/phosphine complex (Scheme 18).²⁸ The reaction proceeds with high yields and complete regioselectivity to give cyclobutenes having polar functional groups.

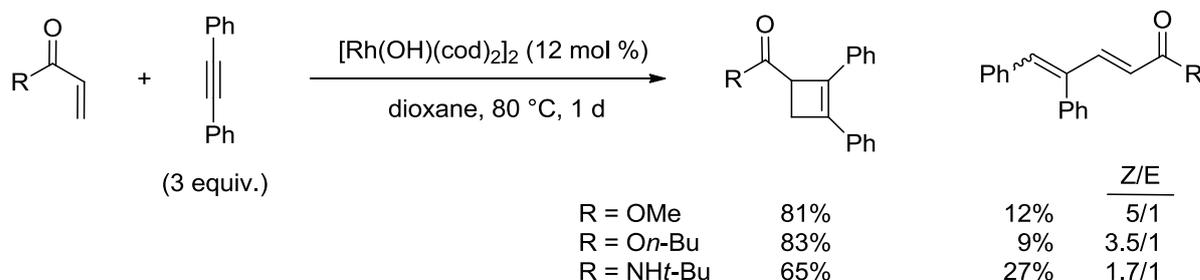


²⁷ Shibata, T.; Takami, K.; Kawachi, A. *Org. Lett.* **2006**, *8*, 1343-1345.

²⁸ Sakai, K.; Kochi, T.; Kakiuchi, F. *Org. Lett.* **2013**, *15*, 1024-1027.

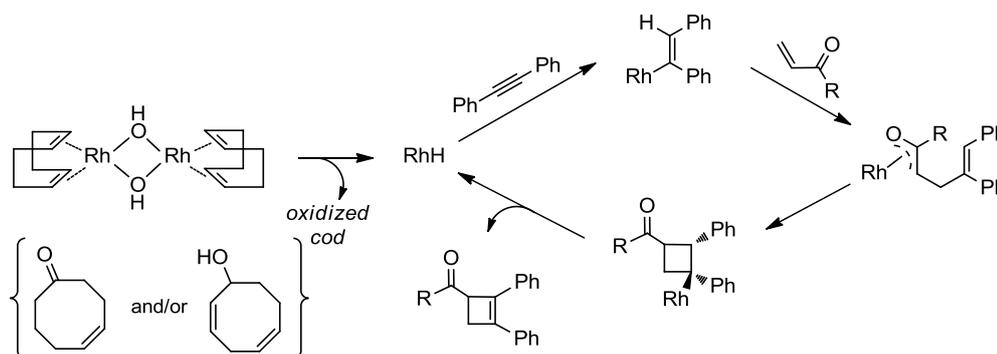
Scheme 18. Rhodium-catalyzed [2+2] cycloaddition of electron-deficient alkenes and terminal alkynes

Taking advantage of the "ligand-consuming" methodology to generate metal-hydride species, Baba and co-workers reported new applications to the [2+2] cycloaddition of diphenylethyne and electron-poor alkenes (Scheme 19).²⁹



Scheme 19. Rhodium-catalyzed [2+2] cycloaddition of electron-deficient alkenes and internal alkynes

Thus, oxidation of the cyclooctadiene (cod) ligand of complex $[\text{Rh}(\text{OH})(\text{cod})]_2$ released *in situ* the coordinatively unsaturated Rh-H species and "oxidized" cod(s) (Scheme 20). The vinylrhodium species, formed through *syn*-hydrometalation of the alkyne, can add across the electron-deficient alkene to give a rhodium-enolate species which upon intramolecular C=C bond insertion led to a cyclobutylrhodium species. The β -H elimination restores the catalytic Rh-H and releases the cyclobutene adduct.



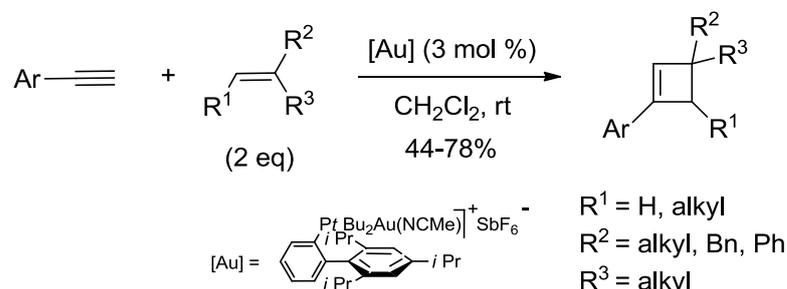
Scheme 20. Proposed mechanism of the rhodium-catalyzed [2+2] cycloaddition

1.1.6 Gold

Echavarren has recently showed that sterically hindered cationic Au(I) complexes are able to catalyze a regioselective, intermolecular coupling of terminal alkynes with alkenes to give

²⁹ Motokura, K.; Nakayama, K.; Miyaji, A.; Baba, T. *ChemCatChem* **2011**, 3, 1419-1421.

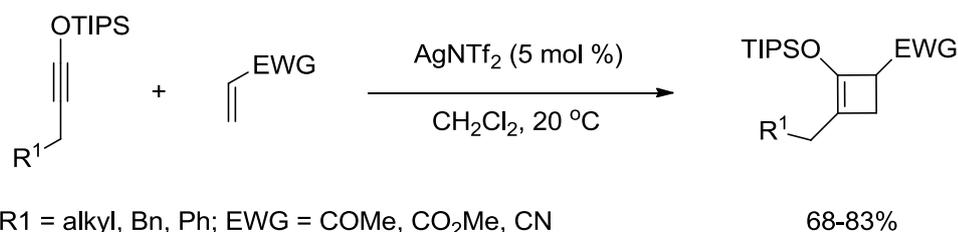
cyclobutenes in moderate to good yields (Scheme 21).³⁰ The reaction proceeds satisfactorily with alkynes substituted with both electron-rich and electron-poor groups.



Scheme 21. Cationic gold(I)-catalyzed [2+2] cycloaddition of alkynes with alkenes

1.1.7 Silver

In 2004, Kozmin group disclosed the first silver-catalyzed [2+2] cycloadditions of siloxyalkynes with electron-deficient alkenes as an efficient method to access highly functionalized siloxycyclobutenes (Scheme 22).³¹ AgNTf₂ was found the best to effect the cycloaddition of α,β -unsaturated ketones, nitriles, and esters with siloxyalkynes. Aryl-substituted siloxyalkynes were also well tolerated. (*E*)- and (*Z*)-crotonates gave the same trans-substituted siloxycyclobutene, suggesting that the reaction proceeds via a stepwise mechanism.



Scheme 22. Silver-catalyzed [2+2] cycloaddition of siloxyalkynes with electron-deficient alkenes

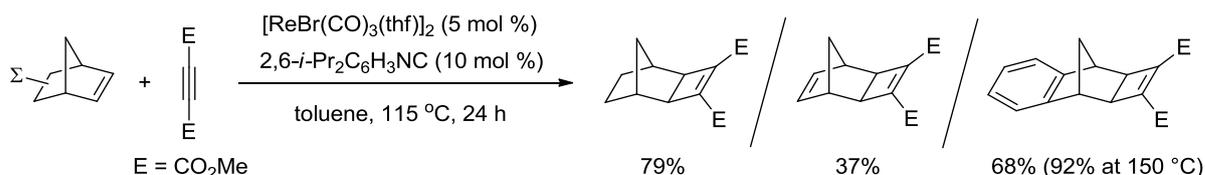
The presumed mechanism proceeds through nucleophile (siloxyalkyne) based activation with silver, followed by 1,4-addition and trapping of the ketenium ion. Interestingly, these siloxycyclobutenes were further functionalized through their ester, nitrile, and ketone functionalities, allowing the synthesis of small libraries.

³⁰ López-Carrillo, V.; Echavarren, A. M. *J. Am. Chem. Soc.* **2010**, *132*, 9292-9294.

³¹ Sweis, R. F.; Schramm, M. P.; Kozmin, S. A. *J. Am. Chem. Soc.* **2004**, *126*, 7442-7443.

1.1.8 Rhenium

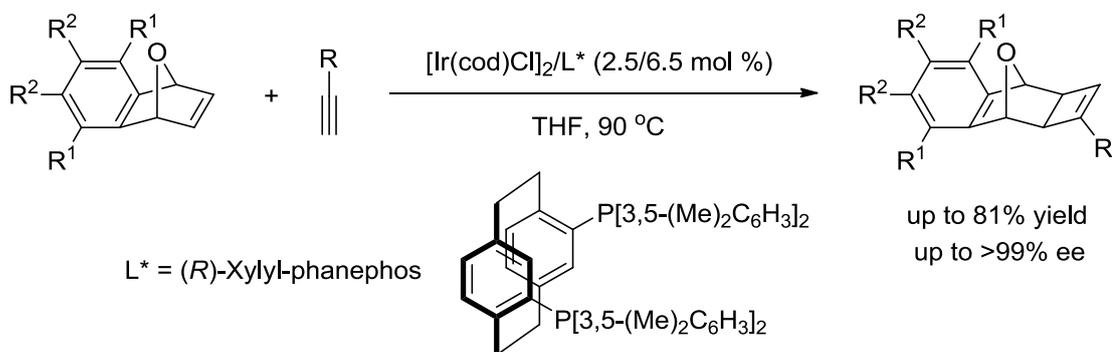
In 2007, Kuninobu and Takai reported the [2+2] cycloaddition of norbornenes with internal and terminal acetylenes using a rhenium complex $[\text{ReBr}(\text{CO})_3(\text{thf})]_2$, as a catalyst and 2,6-diisopropylphenyl isocyanide as additive (Scheme 23).³² Although the exact role of the isocyanide was not clearly established, its presence inhibited the polymerization of alkynes. In these reactions, electron-poor alkynes gave the best yields.



Scheme 23. Rhenium-catalyzed [2+2] cycloaddition of norbornenes and alkynes

1.1.9 Iridium

The first catalytic asymmetric [2+2] cycloaddition of oxabicyclic alkenes and terminal alkynes was developed by Shao and co-workers (Scheme 24).³³ Thus, the iridium-catalyzed enantioselective [2+2] cycloaddition allows the formation of chiral cyclobutenes with excellent enantioselectivity up to 99% ee.



Scheme 24. Iridium-catalyzed enantioselective [2+2] cycloaddition of norbornenes and alkynes

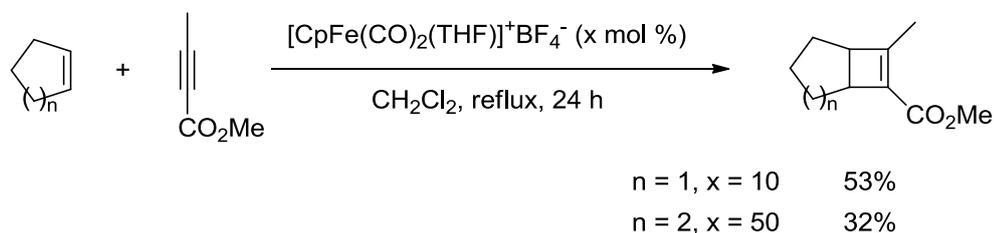
1.1.10 Iron

In 1982, Rosenblum and Scheck reported the first examples of iron-catalyzed intermolecular [2+2] cycloaddition of propiolic esters with alkenes to form cyclobutenyl esters (Scheme

³² Kuninobu, Y.; Yu, P.; Takai, K. *Chem. Lett.* **2007**, *36*, 1162-1163.

³³ Fan, B.-M.; Li, X.-J.; Peng, F.-Z.; Zhang, H.-B.; Chan, A. S. C.; Shao, Z.-H. *Org. Lett.* **2010**, *12*, 304-306.

25).³⁴ The reaction was best carried out using a cationic cyclopentadienyliron complex as the catalyst.

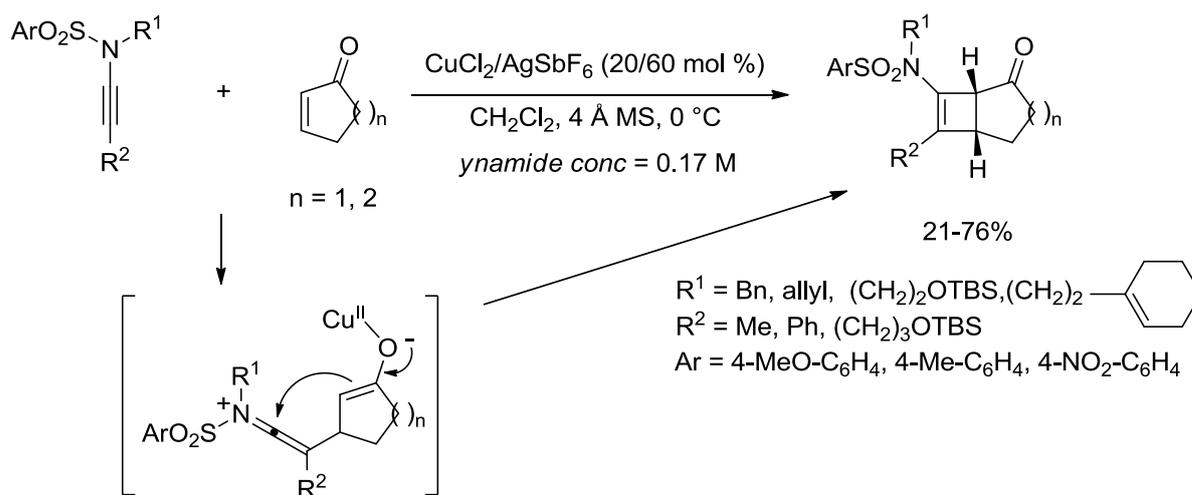


Scheme 25. Iron-catalyzed [2+2] cycloaddition of alkenes with electron-poor alkynes

The cycloaddition with 1,2-disubstituted acyclic alkenes required 20 mol % of catalyst. Thus, reactions with (*E*)- and (*Z*)- but-2-enes demonstrated the stereospecificity of the cycloaddition consistent with, but not requiring, a concerted mechanism for the cyclobutene formation. On the other hand, the reactions with 1,1-disubstituted or trisubstituted alkenes required stoichiometric amounts of iron complexes to form iron-coordinated lactones (33-53%).

1.1.11 Copper

The utility of cationic Cu(II) species to catalyze the Ficini [2+2] cycloaddition of *N*-sulfonyl-substituted ynamides and cyclic enones was reported by Hsung group (Scheme 26).³⁵



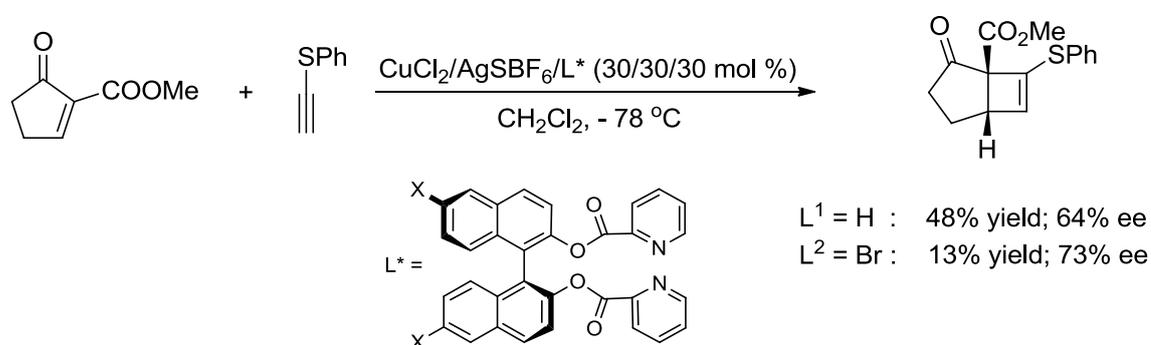
Scheme 26. Copper-catalyzed Ficini [2+2] cycloaddition of ynamides and cyclic enones

³⁴ Rosenblum, M.; Scheck, D. *Organometallics* **1982**, *1*, 397-399.

³⁵ Li, H.; Hsung, R. P.; DeKorver, K. A.; Wei, Y. *Org. Lett.* **2010**, *12*, 3780-3783.

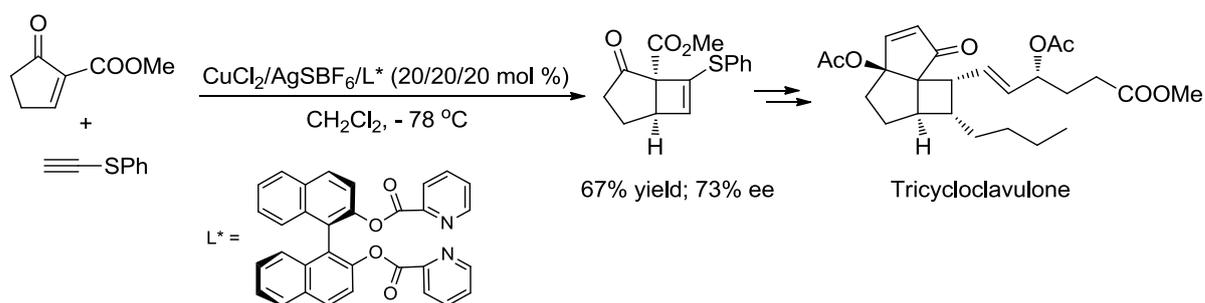
The reaction is believed to proceed through a nucleophilic 1,4-addition of the ynamide onto the Cu(II)-activated enone. On the other hand, a Cu(II)-activation of ynamide generating a cationic keteniminium-copper species followed by a conjugate addition to the enone (similarly as a cuprate) can not be ruled out.

Using a substoichiometric amount (20-30 mol %) of copper(II) salt with chiral binol-derived bis-pyridine ligand, Iguchi and Ito have achieved the enantioselective [2+2] cycloaddition reaction of 2-methoxycarbonyl-2-cyclopenten-1-one and thioalkynes with enantiomeric excesses up to 73% (Scheme 27).³⁶



Scheme 27. Copper-catalyzed [2+2] cycloaddition of thioalkyne with electron-poor alkene

The authors demonstrated the synthetic utility of the enantioenriched bicyclic ketones in total synthesis of the marine prostanoid (+)-tricycloclavulone having a unique tricyclo[5.3.0.0^{1,4}]decane skeleton and six chiral centers (Scheme 28).³⁷



Scheme 28. Copper-catalyzed enantioselective [2+2] cycloaddition in Tricycloclavulone synthesis

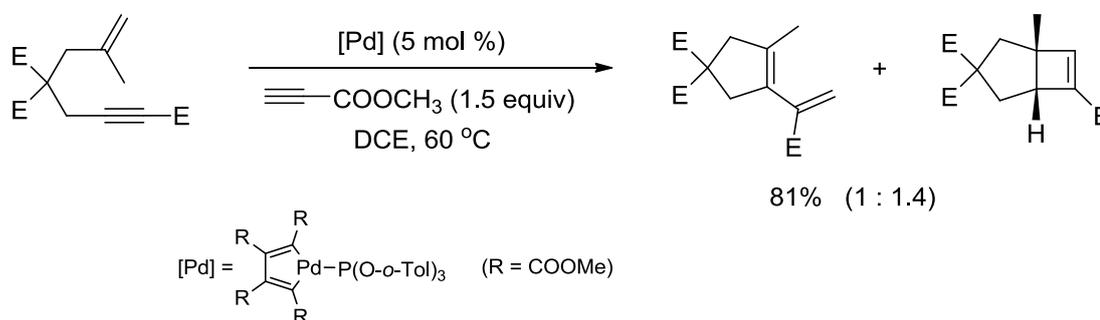
³⁶ Takenaka, Y.; Ito, H.; Hasegawa, M.; Iguchi, K. *Tetrahedron*, **2006**, *62*, 3380-3388.

³⁷ Ito, H.; Hasegawa, M.; Takenaka, Y.; Kobayashi, T.; Iguchi, K. *J. Am. Chem. Soc.* **2004**, *126*, 4520-4521.

1.2 Transition-metal Catalyzed Intramolecular [2+2] Cycloadditions of Enynes

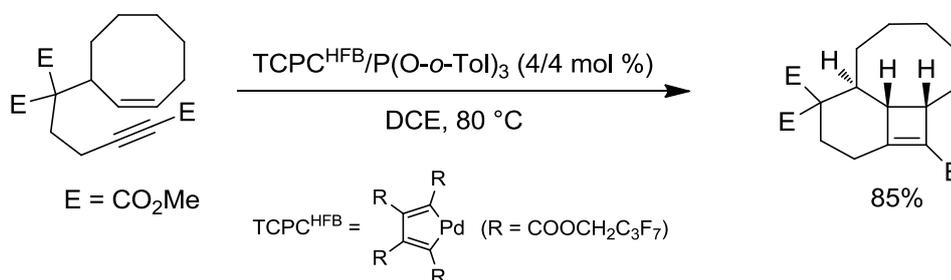
1.2.1 Palladium

During studies related to cycloisomerization of 1,6-enynes, Trost reported that electron-deficient tetracarbomethoxypalladacyclopentadiene (TCPC) in the presence of tri-*o*-tolylphosphite and 1.1equiv of dimethyl acetylenedicarboxylate leads to a 1:1.4 mixture of 1,3-diene and cyclobutene adducts respectively (Scheme 29).³⁸



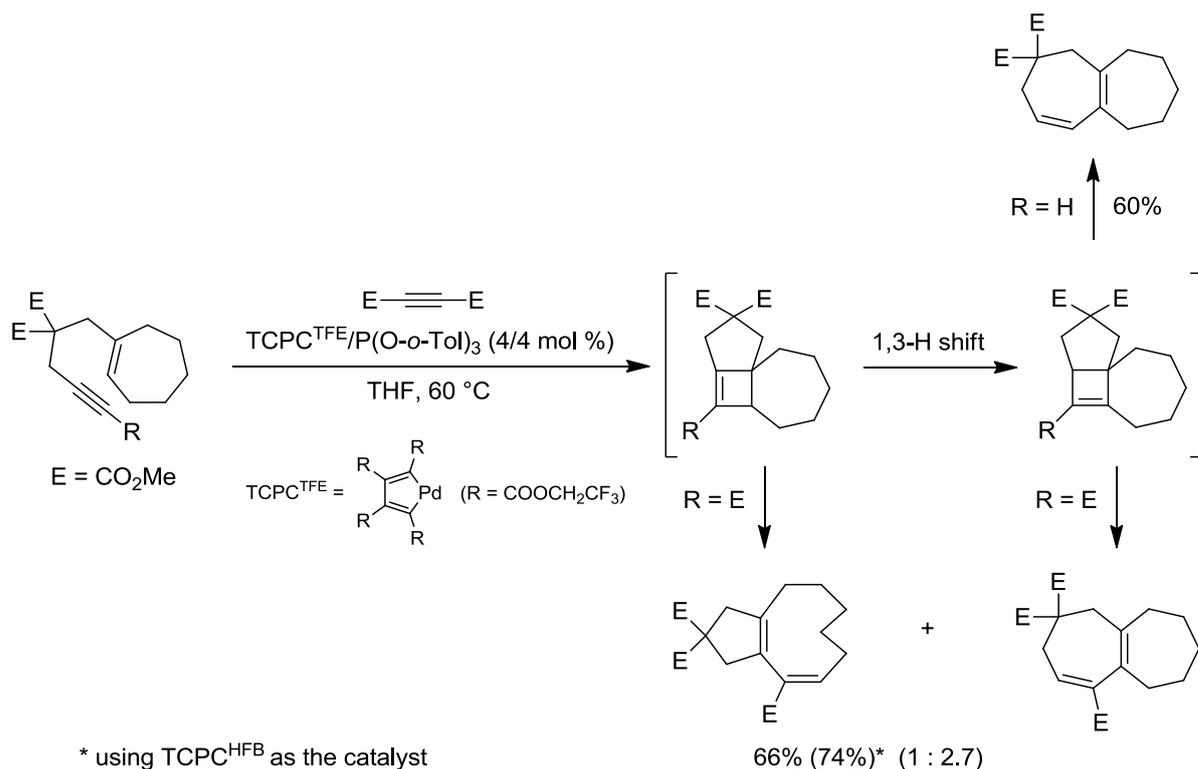
Scheme 29. Palladacycle-catalyzed cycloisomerization of 1,6-enynes

Initially, it was proposed the intermediacy of a cyclobutene, which undergo conrotatory ring opening to produce the rearranged diene, and a 1,3-H shift, presumably metal-catalyzed, to form the more stable bicyclic cyclobutene. These studies provided *the first examples of of transition-metal catalyzed skeletal reorganization (aka enyne methathesis) of 1,6-enynes during cycloisomerization.*



Scheme 30. A stable cyclobutene through palladacycle-catalyzed cycloisomerization of 1,7-enynes

³⁸ Trost, B. M.; Tanoury, G. J. *J. Am. Chem. Soc.* **1988**, *110*, 1636-1638.



Scheme 31. Palladacycle-catalyzed cycloisomerization of 1,6-enynes

Support for this mechanism proposal came from isolation of less strained cyclobutenes from 1,7-enynes³⁹ (Scheme 30) and products arising from cycloreversion of isomeric cyclobutenes from 1,6-enynes⁴⁰ (Scheme 31) within cycloisomerizations carried out with modified palladacycles TCPC^{HFB} and TCPC^{TFE} respectively.

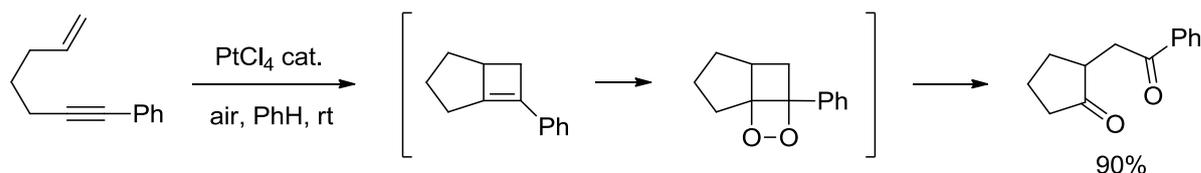
1.2.2 Platinum

Blum and co-workers reported the first indirect observation of 1,6-enyne conversion to cyclobutene using a platinum catalyst. Treatment of 1-phenyl-hept-6-en-1-yne with catalytic amount of PtCl₄ in benzene at room temperature under exclusion of air afforded "a labile hydrocarbon that readily polymerizes during the work-up". The authors hypothesized the formation of the highly sensitive anti-Bredt cyclobutene adduct. Thus, the reaction was performed under air to give a 1,4-dione whose formation was tentatively explained through the oxidative cleavage of a cyclobutene intermediate (Scheme 32).⁴¹

³⁹ Trost, B. M.; Yanai, M.; Hoogsteen, K. *J. Am. Chem. Soc.* **1993**, *115*, 5294-5295.

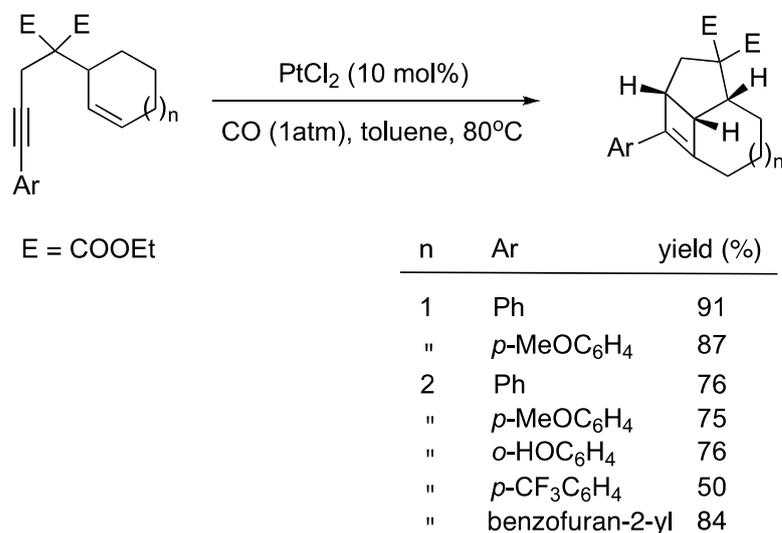
⁴⁰ Trost, B. M.; Trost, M. K. *Tetrahedron Lett.* **1991**, *32*, 3647- 3650.

⁴¹ Blum, J.; Beer-Kraft, H.; Badrieh, Y. *J. Org. Chem.* **1995**, *60*, 5567-5569.



Scheme 32. Indirect observation of cyclobutene in cycloisomerization of 1,6-enyne

Fürstner and co-workers described the cycloisomerizations of 1,6-enynes in the presence of catalytic amounts of platinum(II) chloride in toluene to produce cyclobutenes derivatives.⁴² The bicyclic adducts were obtained with substrates containing internal alkynes bearing electron-rich aryl substituents (Scheme 33). The reactions are better carried out under an atmosphere of carbon monoxide, which had a significant effect on increasing the rates of production of cyclobutenes while decreasing the rate of competing formation of rearranged alkenylcyclopentenes. The carbon monoxide is believed to act as a temporary π -acidic ligand that increases the electrophilicity of the metal template intermediates. Gimbert proposed an alternative explanation based on DFT calculations.⁴³ In the presence of CO, enyne coordination to platinum as a $[\text{PtCl}_2(\eta^4\text{-}(1,6\text{-enyne}))]$ complex is disfavored to the detriment of $[(\text{CO})\text{PtCl}_2(\eta^2\text{-yne})]$ complex thus triggering the cycloisomerization.



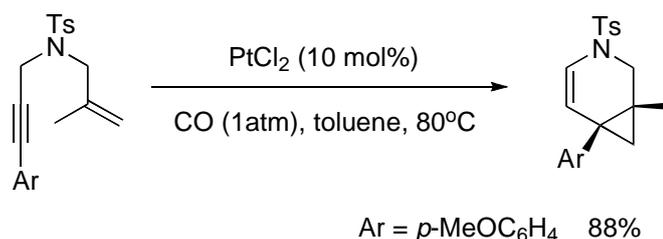
Scheme 33. Platinum-catalyzed cycloisomerization of 1,6-enynes to form cyclobutenes

The behavior of substrates bearing an heteroatom in the tether was strikingly different; these enynes failed to give cyclobutenes and were only converted to the known azabicyclic

⁴² Fürstner, A.; Davies, P. W.; Gress, T. *J. Am. Chem. Soc.* **2005**, *127*, 8244-8245.

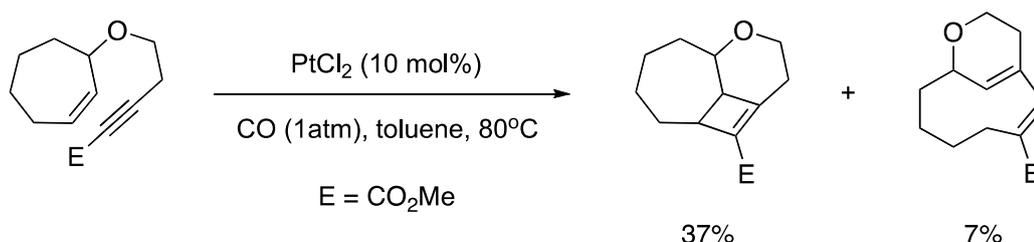
⁴³ Gimbert, Y.; Fensterbank, L.; Gandon, V.; Goddard, J.-P.; Lesage, D. *Organometallics* **2013**, *32*, 374-376.

[4.1.0]heptenes (Scheme 34).⁴⁴



Scheme 34. Platinum-catalyzed cycloisomerization of heteroatom-tethered 1,6-enynes

However, a single example of cyclobutene adduct was reported using 1,7-enyne with an oxygen atom in the tether and electron-withdrawing substituent at the alkyne. Alongside a bridged bicyclic diene was also formed (7%). Owing to the "poor stability" of the adduct, the product was isolated low yield (Scheme 35).

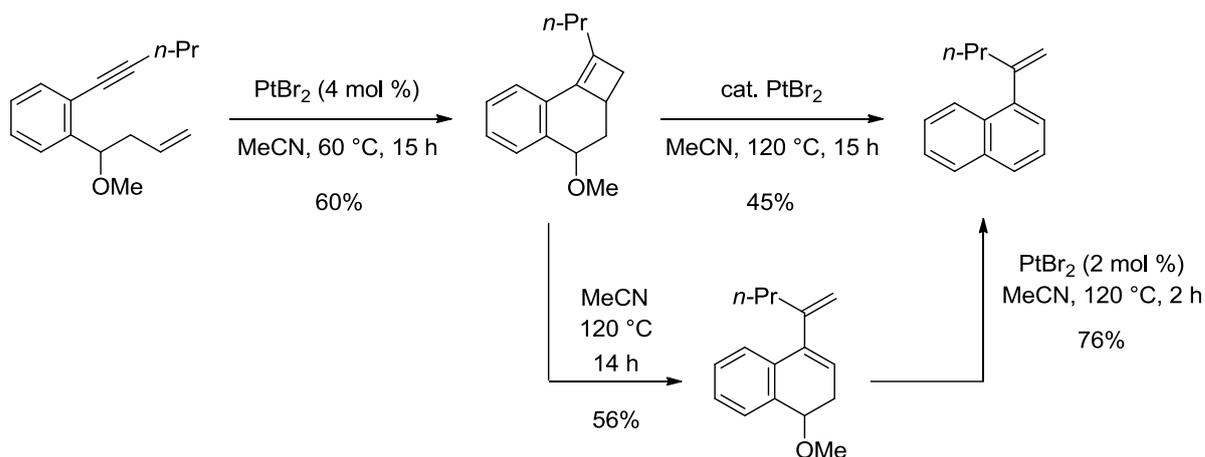


Scheme 35. Platinum-catalyzed cycloisomerization of oxygen-tethered 1,7-enynes

In 2005, Yamamoto group reported a single example of [2+2] cycloaddition of 1,7-enyne connected through an aromatic ring catalyzed by PtBr₂ in acetonitrile at 60 °C (Scheme 36).⁴⁵ At higher temperature (120 °C), the cyclobutene cycloreversion to 1,3-diene takes place and further elimination of methanol led to 1-vinylnaphtalene compounds. It was shown that the platinum intervenes as Lewis acid to promote the methanol elimination while the cycloreversion is an uncatalyzed thermal process. Surprisingly, the scope of this [2+2] cycloaddition was not investigated.

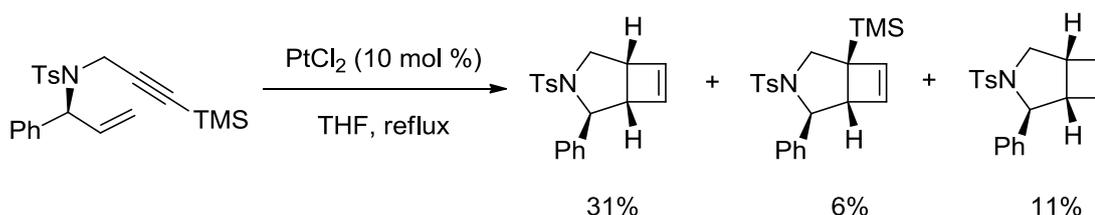
⁴⁴ Fürstner, A.; Stelzer, F.; Szillat, H. *J. Am. Chem. Soc.* **2001**, *123*, 11863-11869.

⁴⁵ Bajracharya, G. B.; Nakamura, I.; Yamamoto, Y. *J. Org. Chem.* **2005**, *70*, 892-897.



Scheme 36. Platinum-catalyzed cyclobutene formation through cycloisomerization of 1,7-enynes

You and co-workers found that chiral *N*-allyl,*N*-propargylamines with a TMS group at the terminal sp carbon undergo [2+2] cycloaddition in the presence of PtCl₂ to afford the desilylated cyclobutene alongside TMS-substituted and over-reduced compounds as minor products (Scheme 37).⁴⁶

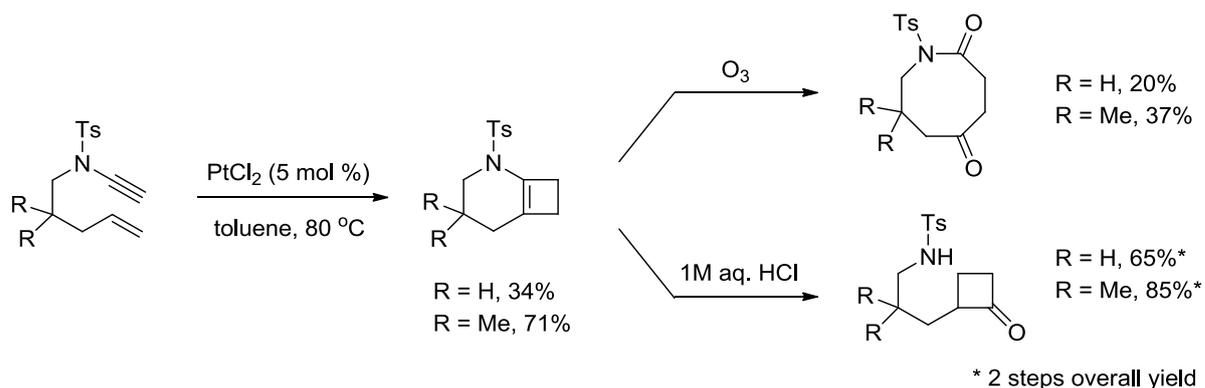


Scheme 37. Platinum-catalyzed cyclobutene formation from silylated 1,7-enynes

Cycloisomerization studies by Malacria group involving 1,7-ene-ynamides in the presence of 10 mol % platinum(II) chloride resulted in the formation of piperidine-fused cyclobutenes (Scheme 38).⁴⁷ Interestingly, the location of the double bond at rings junction allowed the synthesis of eight-membered lactams through its oxidative cleavage. Because of the sensitivity of the compounds to moisture and partial degradation on purification process, the crude reaction mixtures treated with aqueous HCl gave 1-(3-aminopropyl)cyclobutanones.

⁴⁶ Xia, J.-B.; Liu, W.-B.; Wang, T.-M.; You, S.-L. *Chem Eur. J.* **2010**, *16*, 6442–6446.

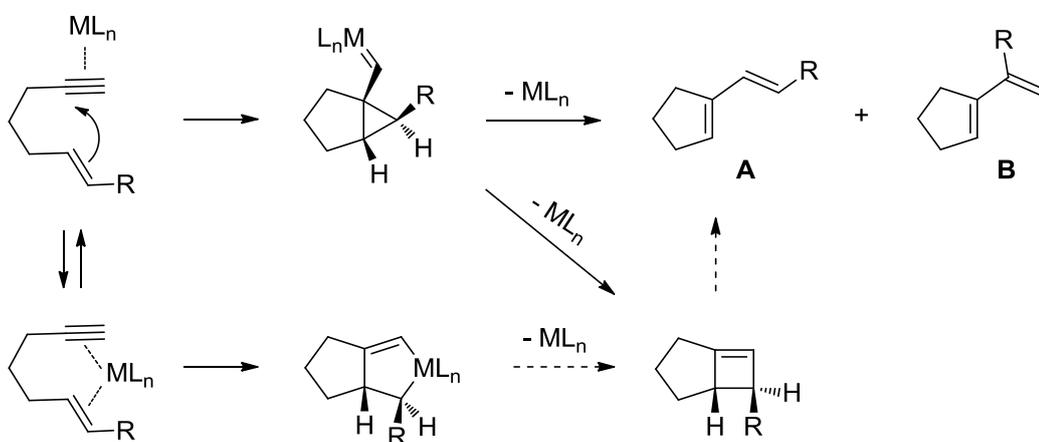
⁴⁷ a) Marion, F.; Coulomb, J.; Courillon, C.; Fensterbank, L.; Malacria, M. *Org. Lett.* **2004**, *6*, 1509–1511. b) Marion, F.; Coulomb, J.; Servais, A.; Courillon, C.; Fensterbank, L.; Malacria *Tetrahedron* **2006**, *62*, 3856–3871.



Scheme 38. Platinum-catalyzed cyclobutene formation through cycloisomerization of 1,7-ene-ynamides

1.2.3 Gold

Cyclobutenes have been invoked as putative intermediates in certain transition-metal catalyzed skeletal rearrangements of 1,6-enynes which occurred through a single C-C bond cleavage of the alkene to give diene **A**. The conrotatory ring-opening (cycloreversion) of cyclobutenes leading to diene **A** may account for its formation. However metathesis-like products **B** resulting from a double C-C bond cleavage (alkene and alkyne) require a different mechanism rationalization (Scheme 39).

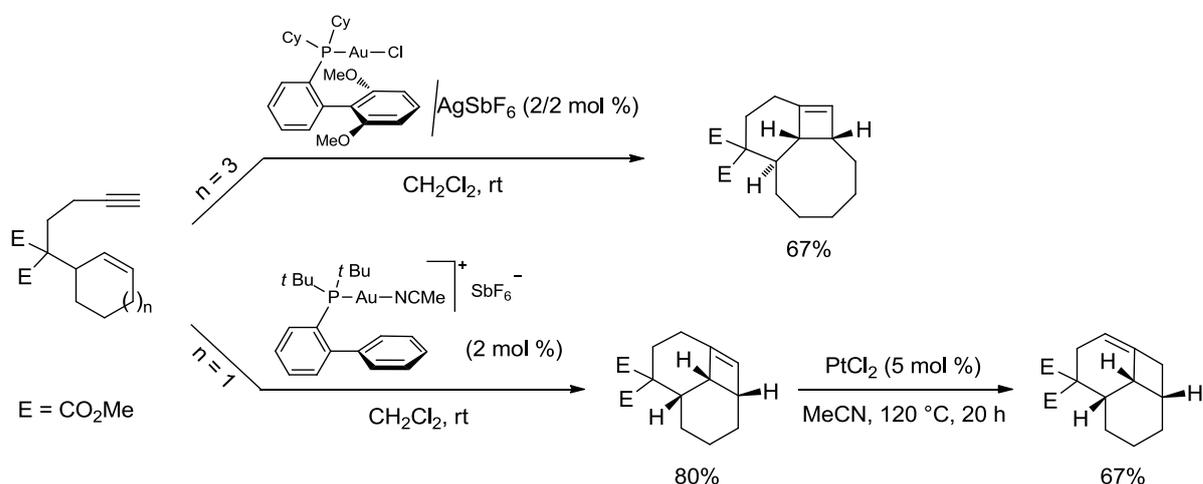


Scheme 39. Two general pathways for transition-metal catalyzed reactions of 1,6-enynes.

Echavarren and co-workers reported experimental and theoretical studies aimed to shed light into this complex mechanism issue. Cyclobutenes were effectively formed through cycloisomerization of 1,7-enynes using bulky and electron-rich phosphine-coordinated cationic gold catalysts (Scheme 40).⁴⁸ It was shown that isolable cyclobutenes were

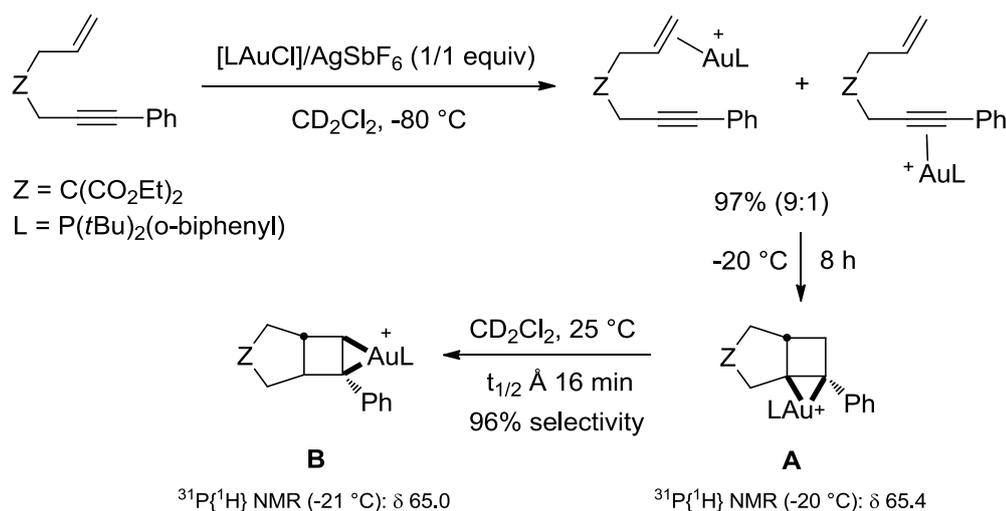
⁴⁸ Nieto-Oberhuber, C.; López, S.; Muñoz, M. P.; Cárdenas, D. J.; Buñuel, E.; Nevado, C.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2005**, *44*, 6146-6148.

reluctant to undergo the ring-opening under thermal conditions (120-150 °C). When the cycloreversion was attempted using a catalytic amount of PtCl₂ at 120 °C as described by Y. Yamamoto,⁴⁵ only the double bond isomerization to the less constrained compound was observed.



Scheme 40. Stable cyclobutenes in Au-catalyzed cycloisomerization of 1,7-enynes

Very recently, Widenhoefer and his group reported a direct observation of a cationic gold(I)-bicyclo[3.2.0]hept-1(7)-ene complex generated in the cycloisomerization of a 1,6-enyne (Scheme 41).⁴⁹



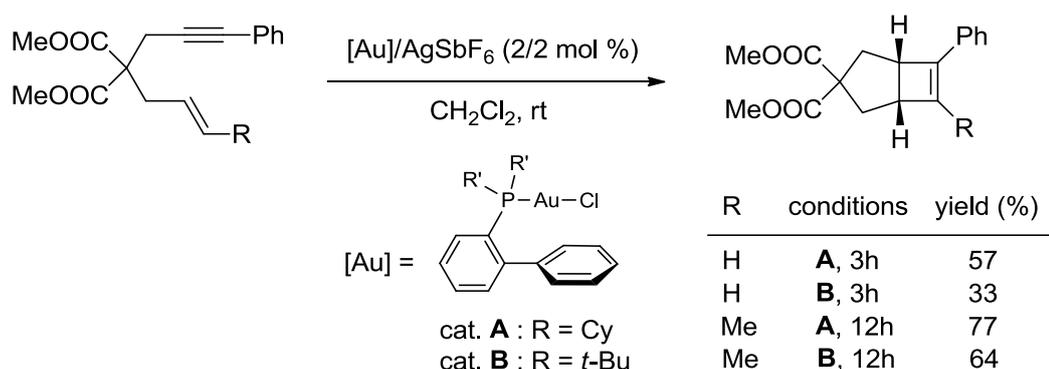
Scheme 41. Cyclobutene-gold intermediates observed through NMR spectroscopy

The stoichiometric reaction of 7-phenyl-1,6-enyne with [LAuCl]/AgSbF₆ (L =

⁴⁹ Brooner, R. E. M.; Brown, T. J.; Widenhoefer, R. A. *Angew. Chem., Int. Ed.* **2013**, *52*, 6259-6261.

2-(di-*t*-butylphosphino)biphenyl) at -20 °C led to a selective (97%) formation of the gold-bicyclo[3.2.0]hept-1(7)-ene complex **A**. At room temperature, this complex undergoes a rapid 1,3-[H] shift ($t_{1/2} \approx 16$ min) to form the gold-bicyclo[3.2.0]hept-1(7)-ene complex **B** with more than 90% selectivity. The metallacyclopropane character of these complexes was established by ^{13}C NMR studies.

In the course of studies on Au-catalyzed [4+2] cycloadditions, Echavarren and co-workers found that treatment of 1,6-enynes with cationic gold complexes afforded cyclobutenes (Scheme 42).⁵⁰ The authors assumed the change of selectivity to the lack of stabilization of the developing positive charge by the alkene substituent. Indeed, enynes with gem-substitution at terminal carbon atom of alkene produced only [4+2] cycloadducts involving participation of the aryl group.

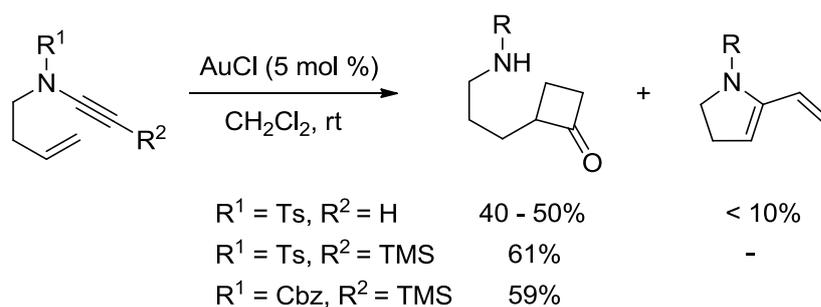


Scheme 42. Cationic gold complexes for [2+2] cycloaddition of 1,6-enynes

Cossy and co-workers reported examples of gold-catalyzed cycloisomerizations of 1,6-ene-ynamides that lead to substituted cyclobutanones (Scheme 43).⁵¹ Non-isolable pyrrolidine-fused cyclobutenes are postulated as intermediates, and upon exposure to ambient moisture on work-up process generate the cyclobutanones. Even trimethylsilyl-substituted ynamides underwent protodesilylation to afford non-silylated products. By contrast, the platinum(II)-catalyzed cycloisomerization of the homologous 1,7-ene-ynamides allowed isolation of cyclobutene adducts, although in rather low yields.⁴⁷ The reaction proceeds with high levels of diastereoselectivity when substituents are present on the butenyl chain.

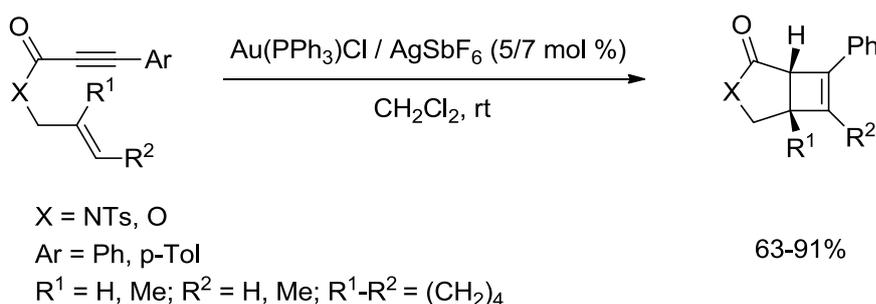
⁵⁰ a) Nieto-Oberhuber, C.; López, S.; Echavarren, A. M. *J. Am. Chem. Soc.* **2005**, *127*, 6178-6179. b) Nieto-Oberhuber, C.; Pérez-Galán, P.; Herrero-Gómez, E.; Lauterbach, T.; Rodríguez, C.; López, S.; C.; Bour, C.; Rosellón, A.; Cárdenas, D. J.; Echavarren, A. M. *J. Am. Chem. Soc.* **2008**, *130*, 269-279.

⁵¹ Couty, S.; Meyer, C.; Cossy, J. *Angew. Chem. Int. Ed.* **2006**, *45*, 6726-6730.



Scheme 43. Non-isolable cyclobutenes through Gold-catalyzed cycloisomerization of 1,6-ene-ynamides

Investigations by Kang and Chung on Au(I)-catalyzed cycloisomerizations of amide- or ester-tethered 1,6-enynes showed that cyclobutene-fused γ -lactams or γ -esters were formed in fair to excellent yields (Scheme 44).⁵² The observed selectivity ([2+2] cycloadditions versus other paths) was supported by DFT calculations.

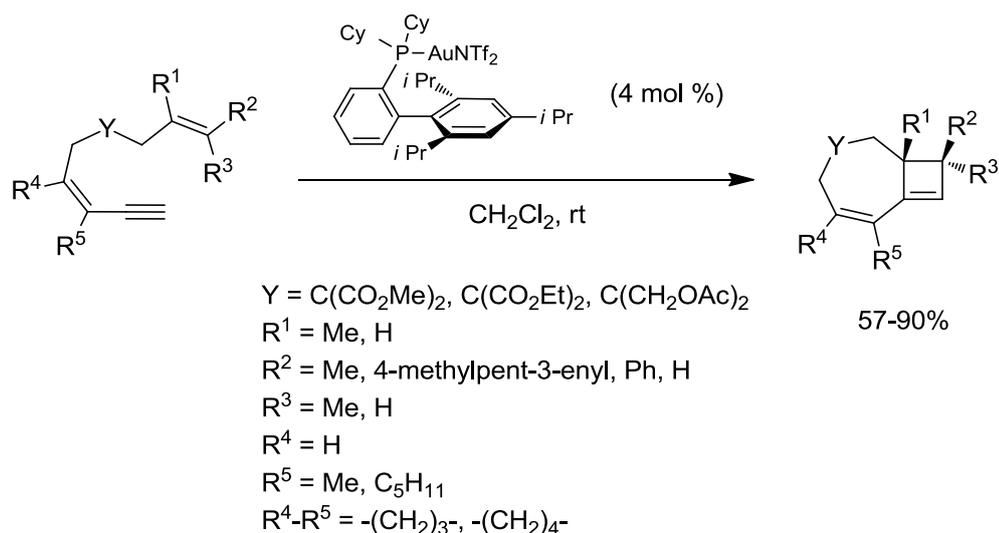


Scheme 44. Gold-catalyzed synthesis of cyclobutene-fused γ -lactams (or lactones)

During studies on cycloisomerization of 1,8-enynes with gold catalysts directed towards the synthesis of seven-membered carbocyclic rings, Gagosz and Odabachian found that stable ring-fused cyclobutenes were formed (Scheme 45).⁵³ In addition, these cyclobutenes further reacted with cationic gold(I) to release cyclohepta-1,3-dienes. The *Z* configuration of the internal double bond within the substrates is not mandatory. Single examples of enynes with a saturated tether are described to give the bicyclic cyclobutenes with significant decreased yields (41-49%).

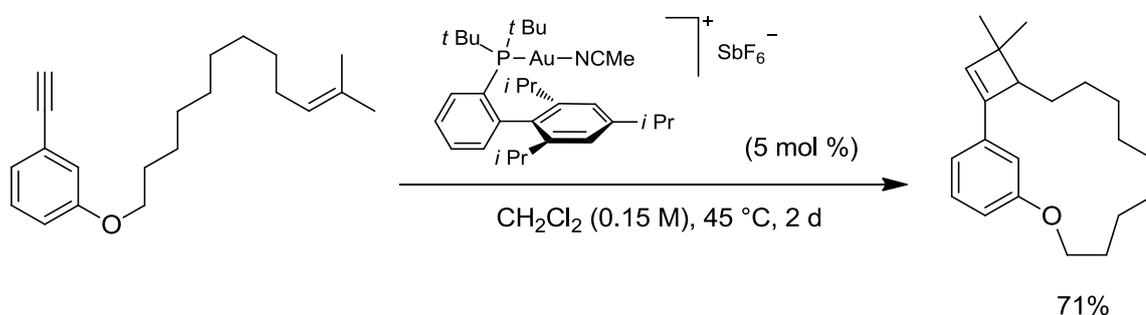
⁵² Lee, Y. T.; Kang, Y. K.; Chung, Y. K. *J. Org. Chem.* **2009**, *74*, 7922–7934.

⁵³ Odabachian, Y.; Gagosz, F. *Adv. Synth. Catal.* **2009**, *351*, 379-386.



Scheme 45. Gold(I)-catalyzed [2+2] cycloadditions of enyne-enes

Recently, Echavarren group have transposed their gold-catalyzed [2+2] cycloaddition of enynes³⁰ to an intramolecular version providing an interesting route to macrocyclization for access to 9- to 15-membered macrocycles incorporating a cyclobutene ring. A representative example leading to 15-membered oxacycle is given below (Scheme 46).⁵⁴



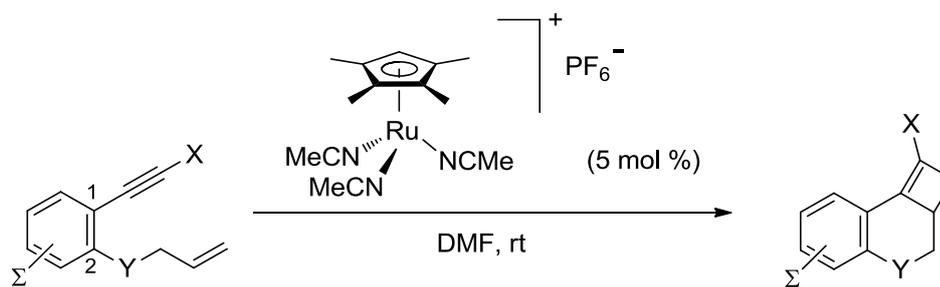
Scheme 46. Gold(I)-catalyzed macrocyclization of 1,n-enynes through [2+2] cycloaddition

1.2.4 Ruthenium

In 2007 Furstner group observed that 1,7-enyne bearing a bromine atom at alkyne terminus, undergo a [2+2] cycloaddition to form a bromocyclobutene derivative on treatment with catalytic amounts of AuCl in toluene at 80 °C. However, cyclizations of related substrates could not be achieved under the same conditions. Thus, it turns out that reactions utilizing a catalytic amount of [Cp*Ru(MeCN)₃]PF₆ in DMF were more reliable to give

⁵⁴ Obradors, C; Leboeuf, D.; Aydin, J.; M. Echavarren, A. M. *Org. Lett.* **2013**, *15*, 1576–1579.

iodo(bromo)cyclobutene derivatives with good yields under mild conditions (Scheme 47).⁵⁵



Σ	Y	X	yield (%)
5-OMe	O	I	81
5-OMe	O	Br	78*
5-OMe	O	Cl	0
4-OMe	O	I	45
3-OMe	O	I	94
3-OMe	O	Br	43
5-Br	O	I	90
5-Br	O	Br	89*
5-Ph	O	I	86
H	CH ₂	I	82*,**
H	NTs	I	88
H	NAc	I	74

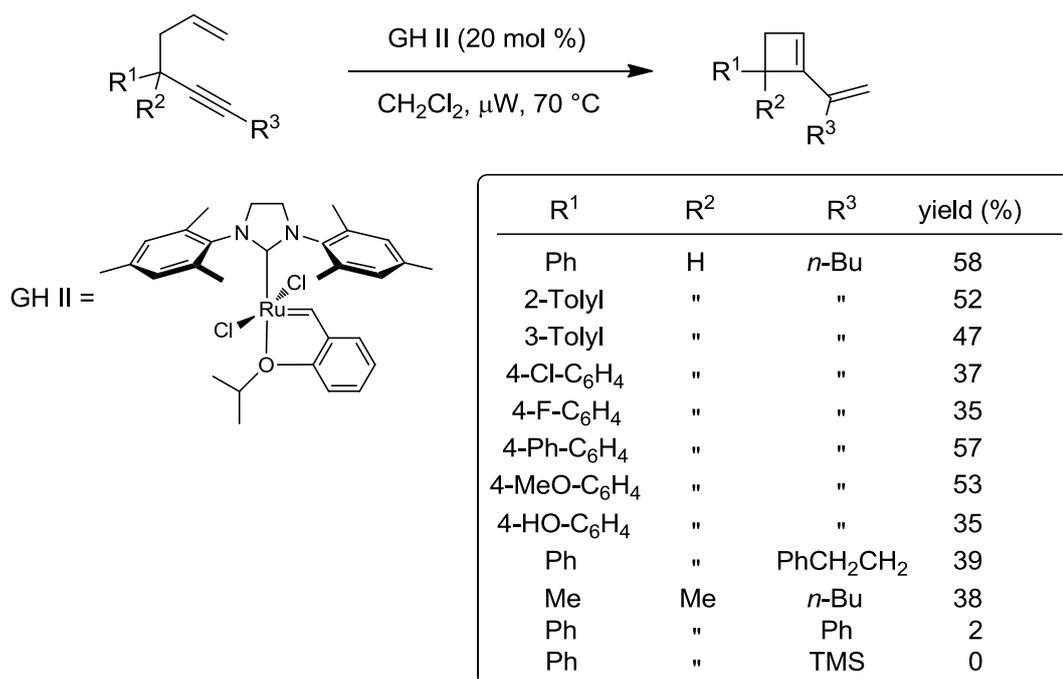
* 10 mol% of catalyst, ** In THF

Scheme 47. Ruthenium-catalyzed [2+2] cycloaddition of 1,7-enynes featuring haloalkynes

The second generation Grubbs-Hoveyda catalyst (GH II) was utilized by Debleds and Campagne for the microwave-assisted 1,5-enyne metathesis. This reaction is of particular interest to elaborate cyclobutenes as part of synthetically useful 1,3-diene units (Scheme 48).^{56a}

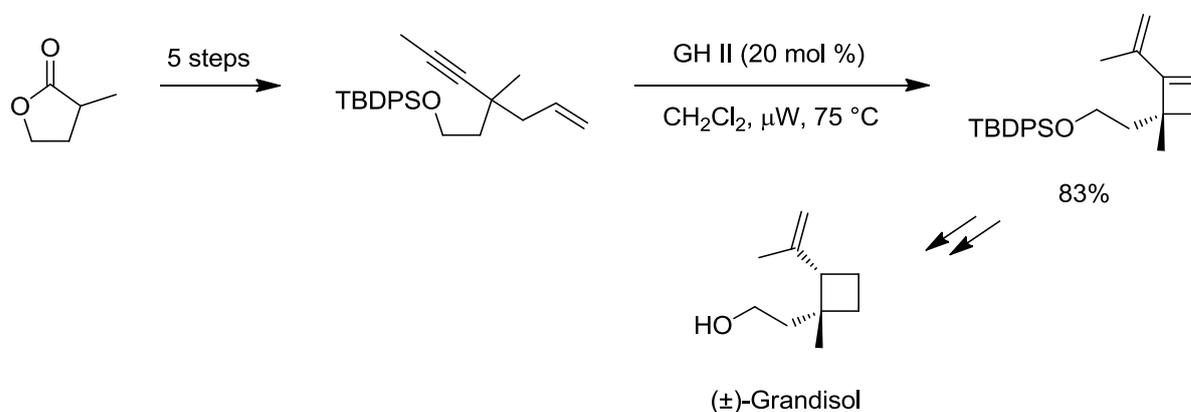
⁵⁵ Fürstner, A.; Schlecker, A.; Lehmann, C. W. *Chem. Commun.* **2007**, 4277–4279.

⁵⁶ a) Debleds, O.; Campagne, J. M. *J. Am. Chem. Soc.* **2008**, *130*, 1562-1563. b) Graham, T. J. A.; Gray, E. E.; Burgess, J. M.; Goess, B. C. *J. Org. Chem.* **2010**, *75*, 226.



Scheme 48. Ruthenium-mediated metathesis of 1,5-enynes to generate vinylcyclobutenes

Goess and co-workers utilized this microwave-assisted 1,5-enyne metathesis reaction as a key step in the synthesis of racemic Grandisol (Scheme 49), the main component of the sexually attracting pheromone of the cotton boll weevil (*Anthonomus grandis* Boheman).^{56b}

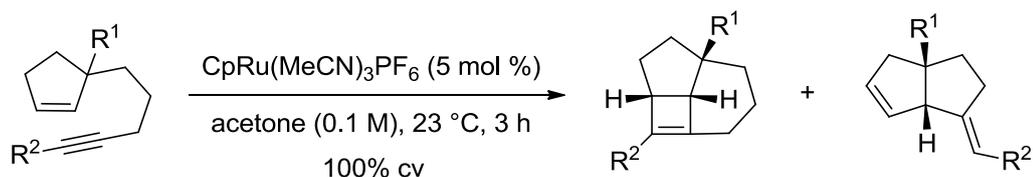


Scheme 49. Synthesis of (±)-Grandisol involving the 1,5-enyne metathesis as key step

On studying parallel reactivities in ruthenium- and palladium-catalyzed cycloisomerizations of 1,7-enynes, Trost group showed that formal [2+2] cycloadditions were observed with cationic Ru(I) catalyst, along with bicyclic cycloisomers in nearly 1:1 ratio (Scheme 50).⁵⁷ In contrast, the bicyclic isomers were exclusively formed in reactions conducted with Pd(0)

⁵⁷ Trost, B. M.; Gutierrez, A. C.; Ferreira, E. M. *J. Am. Chem. Soc.* **2010**, *132*, 9206–9218.

catalyst combined with formic acid.



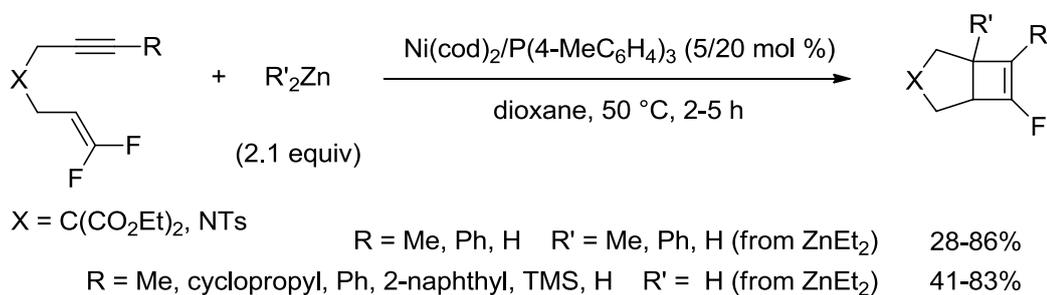
R ¹	R ²	isolated yield	
CO ₂ Me	CO ₂ Me	89*	
CH ₂ OH	CO ₂ Me	43	53
CH ₂ OTBS	CO ₂ Me	46	42
CH ₂ OAc	CO ₂ Me	30	38
CHO	CO ₂ Me	49	50
CH ₂ OTBDPS	CHO	98*	
CH ₂ OBn	CHO	90*	

* Unseparable 1:1 mixture of bi- and tricyclic adducts

Scheme 50. Ruthenium-catalyzed cycloisomerization of 1,7-enynes

1.2.5 Nickel

In 2010, Chatani group reported a nickel-catalyzed alkylative cyclization of 1,6-enynes bearing a geminal difluoro group at the alkene terminus with organozinc reagents that leads to bicyclo[3.2.0]heptene derivatives (Scheme 51). In this process, it was shown that the *trans*-fluorine atom is stereoselectively replaced with the alkyl group (R = Me, Ph) of the zinc reagent. When diethylzinc (R' = Et) was used, a reductive bicycloannulation takes place. This resulted presumably after transmetalation of ethyl group from zinc to nickel and subsequent β -H-elimination thus generating Ni-H species.



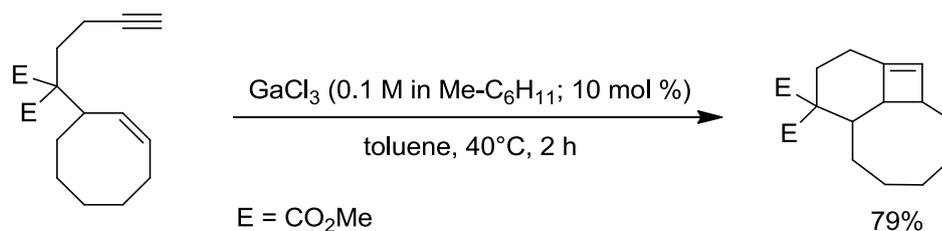
Scheme 51. Nickel-catalyzed bicycloannulation of difluoro-1,6-enynes with organozinc reagents

It is assumed that organozinc functions as a Lewis base with respect to Ni(0) and a Lewis acid with respect to the vinylic C-F bond. Although narrow in scope (only gem-difluoro or *trans*-monofluoroalkenes can be employed), this alkylative annulation represents a new type

of coupling reaction with cyclization.⁵⁸

1.2.6 Gallium

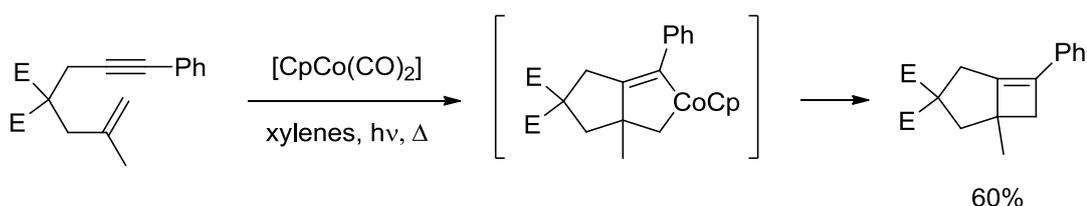
During studies on gallium(III)-catalyzed cycloisomerizations of enynes, Chatani and Murai described a single example of cyclobutene formation from a 1,7-enyne (Scheme 52).⁵⁹



Scheme 52. Gallium-catalyzed 1,7-enyne cycloisomerization

1.2.7 Cobalt

Malacria group reported a single example of a cobalt-mediated formation of a stable [2+2] cycloadduct from a 1,6-enyne under stoichiometric and harsh conditions (boiling xylenes).⁶⁰ The cyclobutene is formed through the reductive elimination of a cobaltacyclopentene intermediate having an angular methyl group which precludes the β -H elimination path. The stability of the anti-Bredt olefin is ascribed to the presence of a phenyl substituent (Scheme 53).



Scheme 53. Cobalt-mediated cyclobutene formation from 1,6-enyne

⁵⁸ Takachi, M.; Dr. Kita, Y.; Dr. Tobisu, M.; Fukumoto, Y.; Chatani, N. *Angew. Chem., Int. Ed.* **2010**, *49*, 8717-8720.

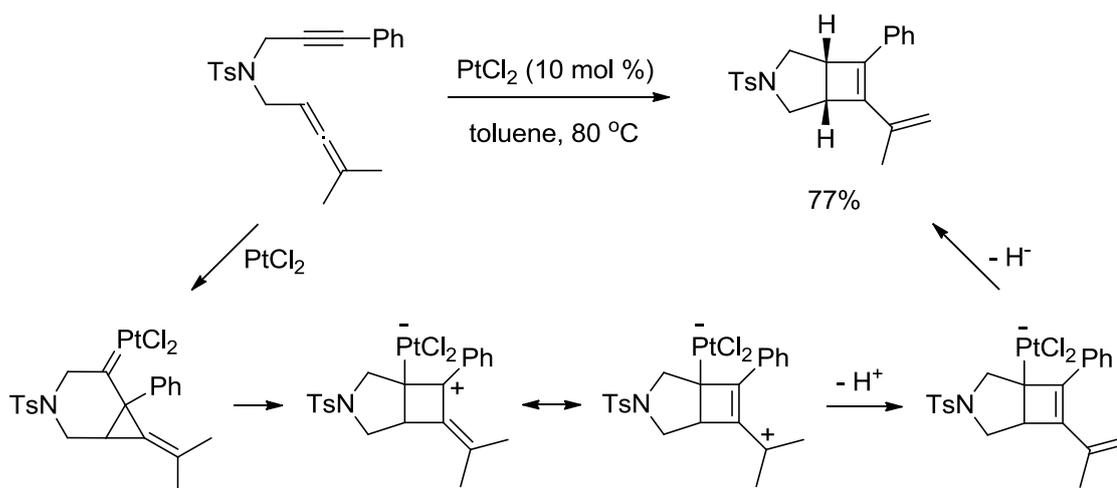
⁵⁹ Chatani, N.; Inoue, H.; Kotsuma, T.; Murai, S. *J. Am. Chem. Soc.* **2002**, *124*, 10294-10295.

⁶⁰ Buisine, O.; Aubert, C.; Malacria, M. *Chem. Eur. J.* **2001**, *7*, 3517-3525.

1.3 Transition-metal Catalyzed Intramolecular [2+2] Cycloadditions of Allenynes

1.3.1 Platinum

Murakami and co-workers reported that treatment of allenynes with 10 mol % of PtCl_2 in toluene at 80°C resulted in formation of 2-vinylcyclobutenes (Scheme 54).⁶¹ This result is quite unusual in light of Malacria's earlier report on the formation of bicyclo[4.3.0]nonadienes from structurally similar enynes. Substrates scope studies revealed that reactions were carried out efficiently with allenynes featuring gem-dialkyl substitution at terminal carbon atom of the allene, internal alkynes and heteroatom (NTs, O) in the tether. In addition to the use of a sulfonamide tether, the allenynes utilized in Murakami's study contained exclusively bis-substituted alkynes while those employed by Malacria and co-workers were terminal alkynes. Indeed, the Murakami group noted that the use of an allenyne containing a terminal alkyne or an all-carbon tether produced complex mixtures of products. The proposed mechanism starts, as in many other related reactions, with intramolecular cyclopropanation to give a platinumcarbene. Subsequent [1,2]-carbon shift generates a zwitterion intermediate depicted in two resonance forms. Elimination of a proton, followed by protodemetalation of the alkylplatinum complex releases the vinylcyclobutene adduct.

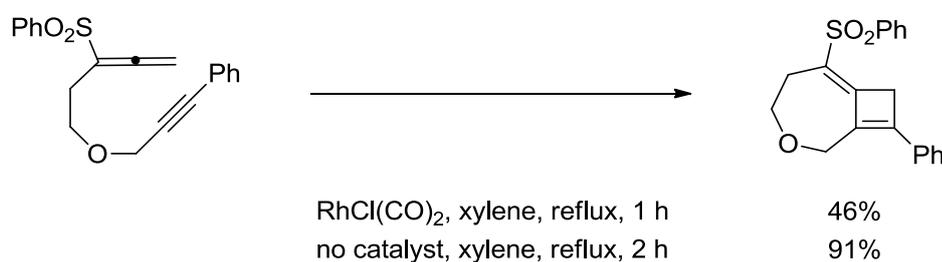


Scheme 54. Platinum(II)-catalyzed cycloisomerization of 1,6-allenynes

⁶¹ Matsuda, T.; Kadowaki, S.; Goya, T.; Murakami, M. *Synlett* **2006**, 575–578.

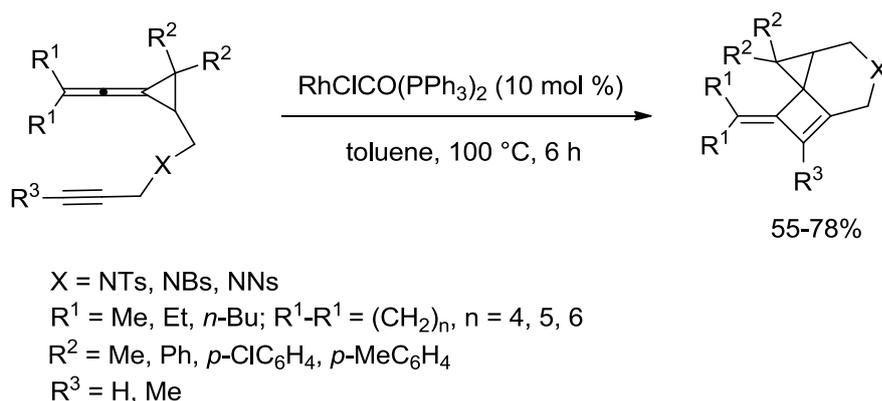
1.3.2 Rhodium

During studies on the scope and limitations of the PKR, Mukai reported that *O*-tethered 1,8-allenynes, bearing a phenylsulfonyl group at C-3, exposed to a catalytic amount of dicarbonylrhodium(I) chloride dimer underwent [2+2] cycloaddition to form bicyclic cyclobutenes in moderate yields (Scheme 55).⁶² Surprisingly, the thermal non-catalyzed reactions of these enynes afforded the same products in significantly improved yields (twofold yield). These results raised the question of catalytic role of rhodium complex in such reactions.



Scheme 55. Rhodium-catalyzed [2+2] cycloaddition of β -allenyl-propargylethers

More recently, Shi and Lu reported the rhodium(I)-catalyzed intramolecular cycloadditions of alkynes and vinylidenecyclopropanes to provide functionalized polycyclic compounds containing cyclobutene moiety in a highly regioselective manner (Scheme 56).⁶³



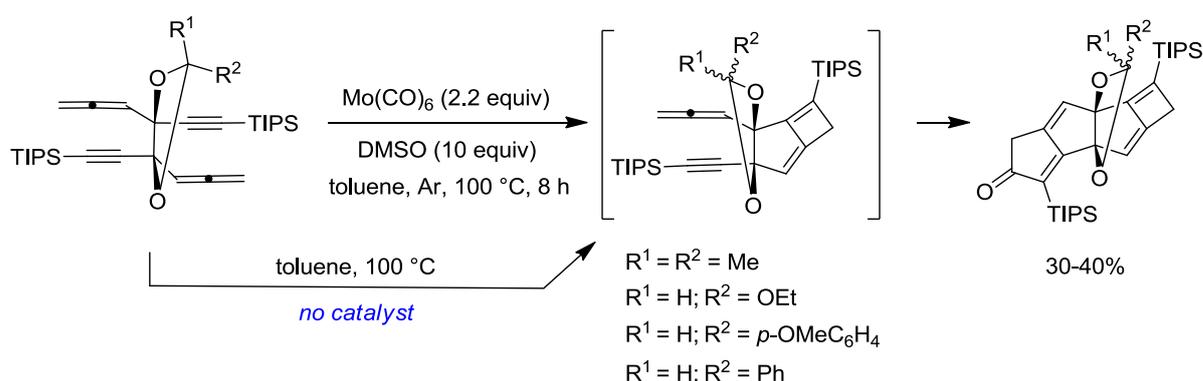
Scheme 56. Rhodium-catalyzed intramolecular [2+2] cycloaddition of alkynes and vinylidenecyclopropanes

⁶² Mukai, C.; Hara, Y.; Miyashita, Y.; Inagaki, F. *J. Org. Chem.* **2007**, 72, 4454–4461.

⁶³ Lu, B.-L.; Shi, M. *Angew. Chem., Int. Ed.* **2011**, 50, 12027-12031.

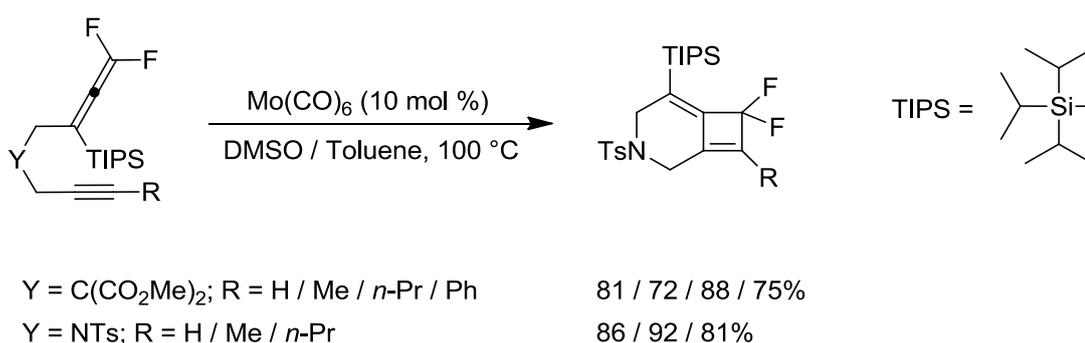
1.3.3 Molybdenum

Similar observations were reported by Cook and co-workers during studies on molybdenum hexacarbonyl mediated Pauson-Khand reactions (PKR) of bis-1,6-allenynes.⁶⁴ Under stoichiometrical conditions, the expected products from a double PKR were not observed. Instead, the isolated pentacyclic products resulted from two distinct reactions: a PKR and a [2+2] cycloaddition (Scheme 57). The authors showed that the cycloaddition resulted under thermal, non-catalyzed conditions.



Scheme 57. Molybdenum-catalyzed [2+2] cycloaddition of 1,5-ynallenes

Hammond's group reported the synthesis of fused gem-difluorocyclobutenes through the regioselective molybdenum(0)-catalyzed intramolecular [2+2] cycloaddition of allene-ynes (Scheme 58).⁶⁵



Scheme 58. Molybdenum-catalyzed intramolecular [2+2] cycloaddition of alkynes and difluoroallenes

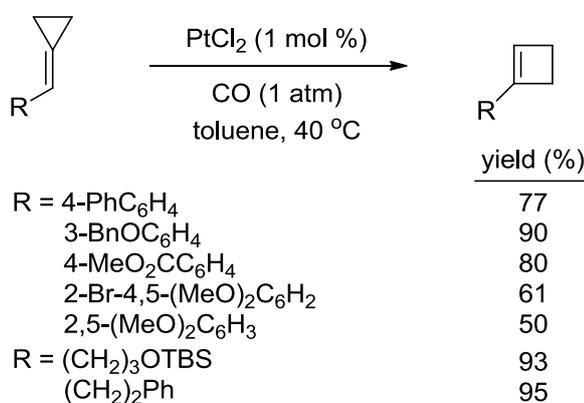
⁶⁴ Cao, H.; Flippen-Anderson, J.; Cook, J. M. *J. Am. Chem. Soc.* **2003**, *125*, 3230-3231.

⁶⁵ Shen, Q.; Hammond, G. B. *J. Am. Chem. Soc.* **2002**, *124*, 6534-6535.

1.4 Cyclobutenes Formation Through Metal-Catalyzed Ring Expansion Reactions

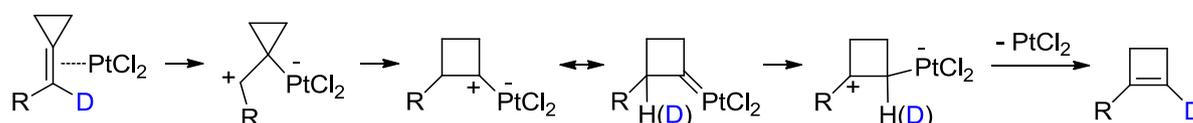
1.4.1 Platinum

Aryl- and alkyl-substituted methylenecyclopropanes (MCPs) were converted to cyclobutenes using catalytic amounts of PtCl₂ in toluene under mild conditions.⁶⁶ The reaction was significantly accelerated when performed under an atmosphere of CO. Under these conditions, the catalyst loading can be reduced to 1 mol % (Scheme 59).



Scheme 59. Pt-Catalyzed isomerization of MCPs to cyclobutenes

The mechanism proposed involves coordination of Pt(2+) to the double bond of MCP to generate a stabilized cyclopropylmethyl cation prone to rearrange to the cyclobutenyl cation complex which likely has carbene character. [1,2]-H shift followed by elimination of PtCl₂ releases the cyclobutene product (Scheme 60). This mechanism is consistent with the deuterium-labeling experiment.



Scheme 60. Mechanism of the Pt-Catalyzed isomerization of MCPs to cyclobutenes

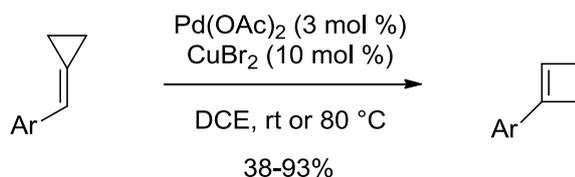
Enantiomerically pure alkylidenecyclopropanes undergo this rearrangement to produce

⁶⁶ Fürstner, A.; Aïssa, C. *J. Am. Chem. Soc.* **2006**, *128*, 6306-6307.

cyclobutene with a complete preservation of the stereogenic center.⁶⁷

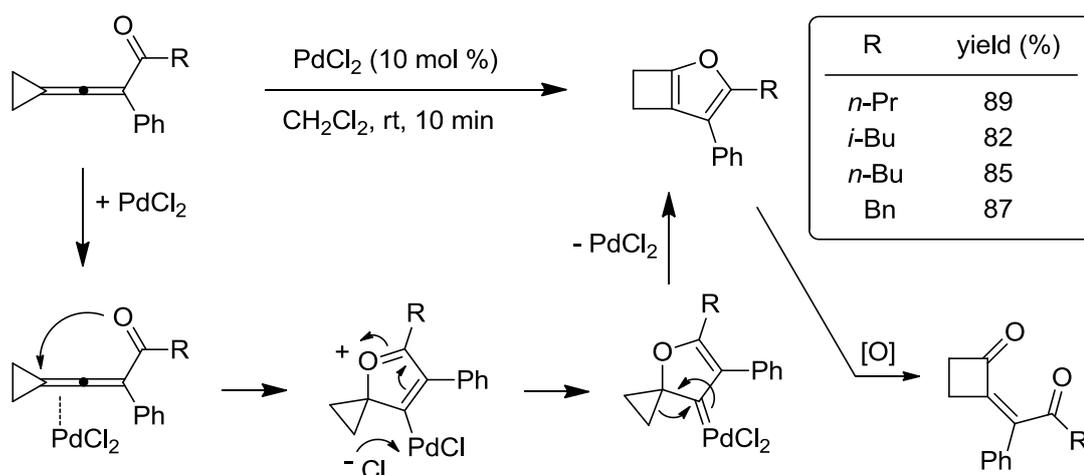
1.4.2 Palladium

Shi's group reported a similar ring enlargement reactions using Pd(OAc)₂ and CuBr₂ in 1,2-dichloroethane under mild conditions (Scheme 61). The reaction was only effective for aryl-substituted MCPs, no reaction occurred with the alkyl-substituted ones. Electron-donating groups on the aryl ring promoted significantly the reaction in few hours at room temperature. Either an electron-withdrawing group or no substituent on the aromatic ring retarded the reactions, which required higher temperature (80 °C) and longer reaction time to achieve good conversions. Among various bromide salts to promote the generation *in situ* of PdBr₂, cupric(II) bromide was found the more efficient.



Scheme 61. Pd-catalyzed Isomerization of MCPs to cyclobutenes.

In 2012, Wu's group reported the palladium(II)-catalyzed cycloisomerization of 1,2-allenylketones leading to furan-fused cyclobutenes, which are versatile intermediates for further elaboration (Scheme 62).⁶⁸



Scheme 62. Conversion of 3-cyclopropylidene prop-2-en-1-ones to furan-fused cyclobutenes

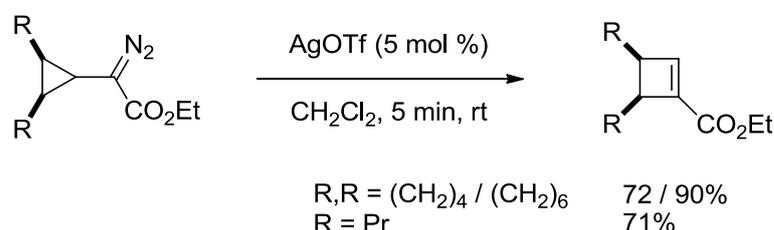
⁶⁷ Marsawa, A.; Fürstner, A.; Marek, I. *Chem. Commun.*, **2009**, 5760-5762.

⁶⁸ Miao, M.; Cao J.; Zhang, J.; Huang, X.; Wu, L. *Org. Lett.* **2012**, *14*, 2718-2721.

For instance, a highly selective formation of functionalized 2-alkylidenecyclobutanones can be achieved in the presence of PdCl₂ (10 mol %) and Dess-Martin periodinane (DMP).

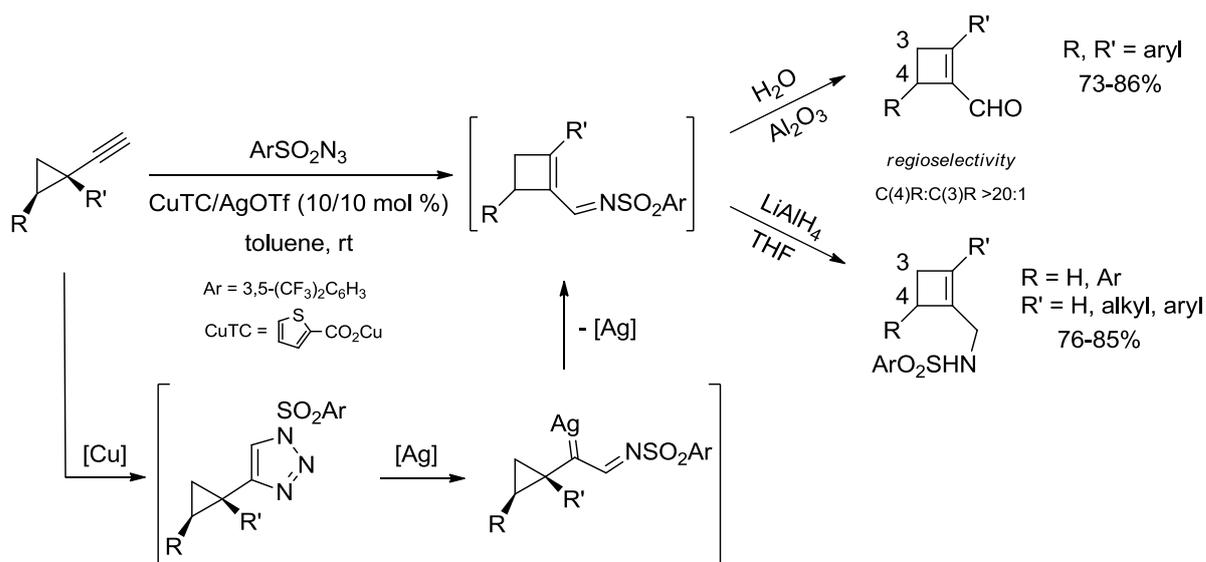
1.4.3 Silver

In 2008, Tang and co-workers reported an highly selective, silver(I) triflate-catalyzed ring expansion of cyclopropyl-substituted α -diazoesters to produce polysubstituted cyclobutenones (Scheme 63)⁶⁹ with excellent chemoselectivity and regioselectivity. In addition, it was shown that the ring expansion took place stereospecifically with the migrating carbon atom retaining its configuration during the silver-catalyzed process.



Scheme 63. Conversion of cyclopropyl-substituted α -diazoesters to cyclobutenones

The same group developed the regioselective ring expansion of alkynylcyclopropanes to highly substituted cyclobutenes in a one-pot two-steps sequence combining Cu and Ag catalysis (Scheme 64).⁷⁰



Scheme 64. Dual catalysis for the conversion of alkynylcyclopropanes to cyclobutene derivatives

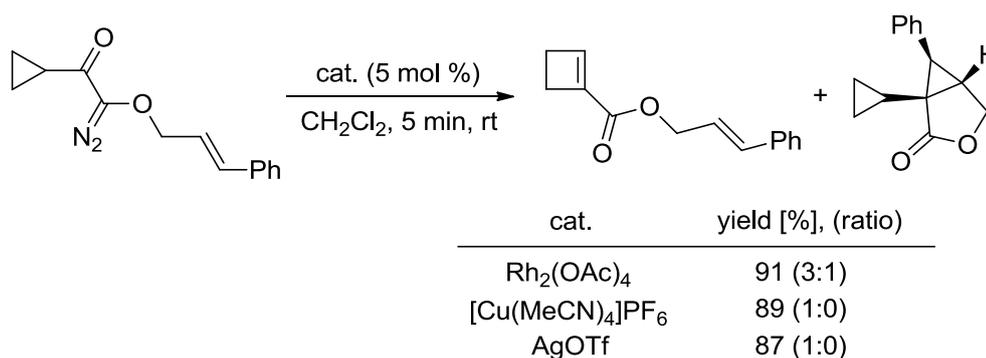
⁶⁹ Xu, H.; Zhang, W.; Shu, D.; Werness, J. B.; Tang, W. *Angew. Chem. Int. Ed.* **2008**, *47*, 8933–8936.

⁷⁰ Liu, R.; Zhang, M.; Winston-McPherson, G.; Tang, W. *Chem. Commun.* **2013**, *49*, 4376–4378.

Thus, alkynylcyclopropanes underwent a “click” [3+2] cycloaddition with arylsulfonyl azides in the presence of copper(I) thiophene-2-carboxylate (CuTC) catalyst giving rise to *N*-sulfonyl 1,2,3-triazoles, which are safe diazo compounds equivalents.⁷¹ Upon treatment of triazoles with catalytic amounts of silver triflate, the α -cyclopropyl silver carbene, thus generated, undergo a ring expansion to deliver conjugated cyclobutenyl arylsulfonyl imines. These can be hydrolyzed (Al_2O_3) or reduced (LiAlH_4) to give cyclobutene carboxaldehydes or arylsulfonylaminomethyl-substituted cyclobutenes respectively.

1.4.4 Rhodium

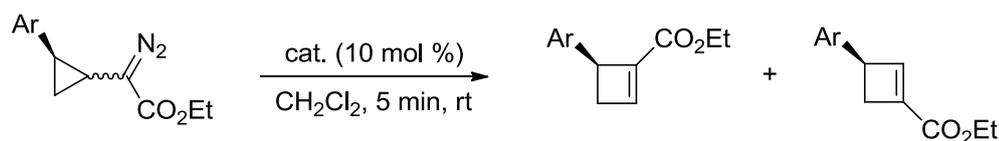
In their studies directed towards the selectivity issues of transition-metal catalyzed ring expansions of MCPs, the group of Tang reported several examples using rhodium catalysts (Scheme 65).⁷⁰ Although dirhodium tetraacetate exhibited similar efficiency compared to copper and silver salts, the reaction chemoselectivity, namely ring expansion vs intramolecular cyclopropanation, was found less satisfactory with the rhodium catalyst.



Scheme 65. Catalyst-dependence on the chemoselectivity of the ring expansion reaction

In ring expansion reactions of stereodefined aryl-substituted cyclopropanes, the rhodium catalyst displayed usually different regioselectivity compared to copper and silver catalysts (Scheme 66). The formation of the less-congested 1,3-disubstituted cyclobutene is favored sterically, while the 1,2-disubstituted cyclobutene is favored electronically, as the aryl group can stabilize the partial positive charge on the migrating benzylic carbon atom. The results observed may reflect the delicate balance between the electronic and steric effects in cyclopropyl metalcarbenes intermediates. For example, electronic effects dominate in the case of copper(I) carbene and steric effects dominate in the case of dirhodium(II) carbene.

⁷¹ a) Horneff, T.; Chuprakov, S.; Chernyak, N.; Gevorgyan, V.; Fokin, V. V. *J. Am. Chem. Soc.* **2008**, *130*, 14972-14974. b) For a review on transition-metal catalyzed reactions of 1,2,3-triazoles, see : Chattopadhyay, B.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2012**, *51*, 862-872.



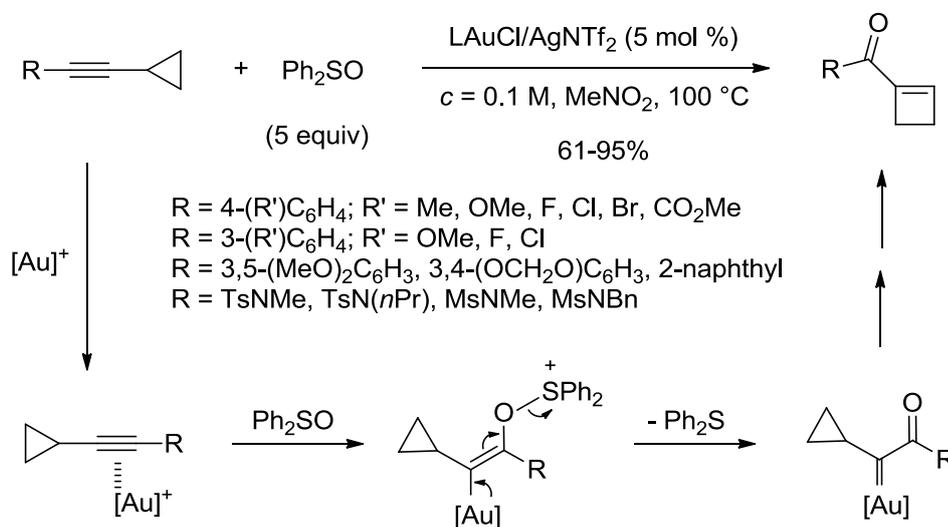
R (stereochemistry)	catalyst	ratio
Ph (trans)	[Cu(MeCN) ₄]PF ₆	5:1
"	AgOTf	1:2
"	Rh ₂ (OAc) ₄	1:7
Ph (cis)	[Cu(MeCN) ₄]PF ₆	17:1 ^a
"	AgOTf	3:1
"	Rh ₂ (OAc) ₄	1:4
4-MeOC ₆ H ₄ (trans)	[Cu(MeCN) ₄]PF ₆	1:0 ^b
"	AgOTf	1:0 ^b
"	Rh ₂ (OAc) ₄	1:2

a: 93% yield; b: 90% yield

Scheme 66. Catalyst-dependence on the regioselectivity of the migrating C-C bond

1.4.5 Gold

The access to 1-acylcyclobutenes through gold-catalyzed oxidative ring expansion reactions of alkynylcyclopropanes was developed by the Liu's group (Scheme 67).⁷²



Scheme 67. Gold-catalyzed oxidative conversion of alkynylcyclopropanes to cyclobutenyl ketones

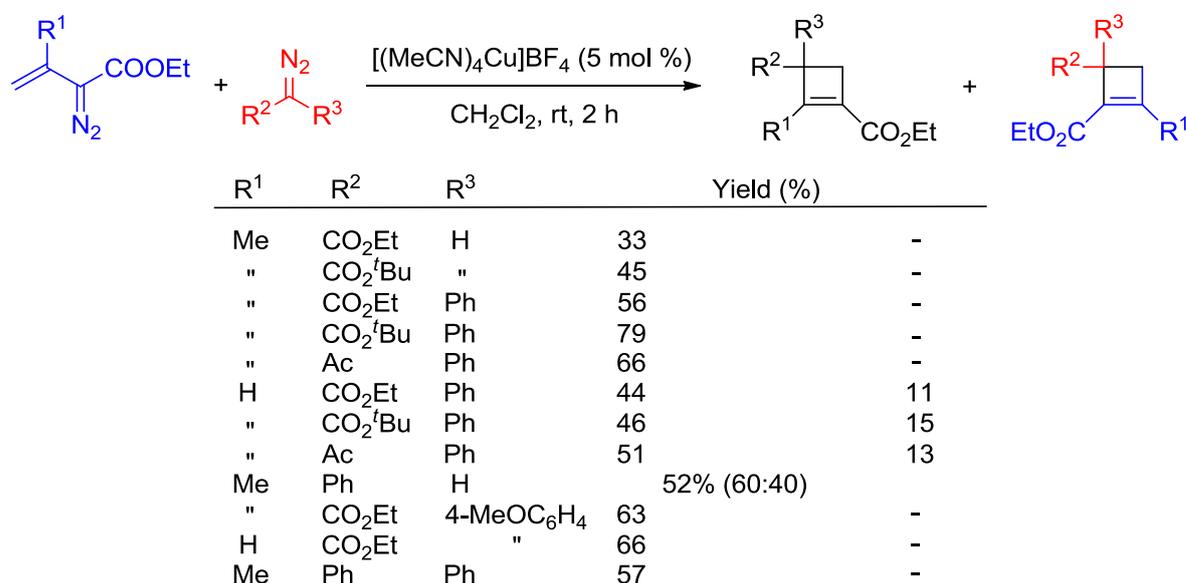
The main advantage of this approach lies on the more easier access to alkynylcyclopropanes compared to the cyclopropyl diazocarbonyl species used by Tang (§ 1.4.3). Thus, treatment of alkynylcyclopropanes with diphenylsulfoxide as the oxygen donor in the presence of *in situ* generated cationic 2-(di-*t*-butylphosphino)biphenylgold(I) triflimide catalyst occurred

⁷² Li C.-W.; Pati K.; Lin G.-Y.; Abu Sohel, S. M.; Hung H.-H.; Liu R.-S. *Angew. Chem., Int. Ed.* **2010**, *49*, 9891-9894.

smoothly, without formation of α -diketones, to give cyclobutenyl ketones (or amides) in fair to excellent yields. Satisfactory results are observed with both electron-rich and electron-withdrawing groups on the aryl substituent of alkynes. Substitution at the cyclopropane ring is tolerated and the cyclobutene formation resulted from a selective migration of the more substituted C-C cyclopropyl bond. The key gold α -carbonylcarbenoid species is formed through the regioselective nucleophilic attack of oxygen donor on activated π -alkyne complex.

1.4.6 Copper

Barluenga and co-workers reported the synthesis of functionalized cyclobutenes based on cyclization of vinyldiazoacetates with stabilized diazo compounds catalyzed with a cationic copper(I) complexes (Scheme 68).⁷³ The reaction exhibits high regioselectivity affording the cyclobutenes in moderate to acceptable yields and the 1, 3-dienes usually expected through the homo- and cross-coupling reactions were also observed as by-products. The reaction proceeds through the ring expansion of α -cyclopropyl cupra(I)carbene intermediates (*vide supra*).

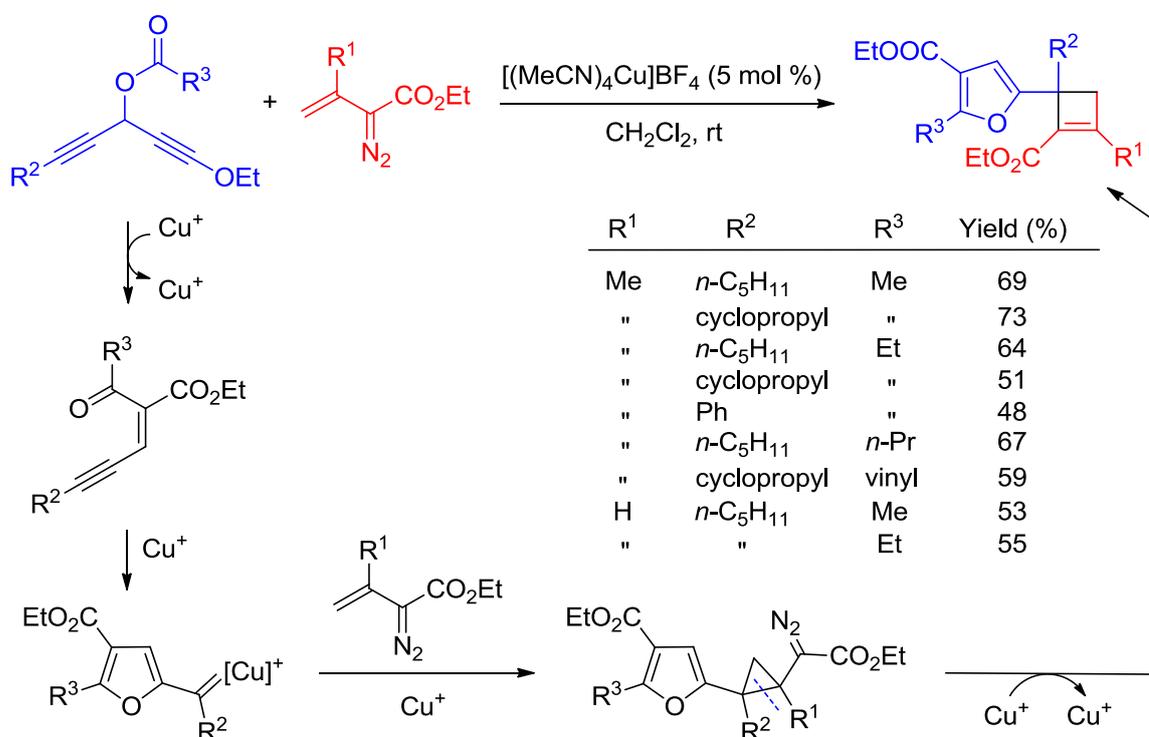


Scheme 68. Copper(I)-catalyzed cross-coupling of diazo compounds and vinyldiazoesters

More interestingly, these authors exploited the cross-coupling reaction for application to bis(propargylic) esters, which were assumed to generate *in situ* a copper(I) furylcarbene, and

⁷³ Barluenga J.; Riesgo L.; Lopez L. A.; Rubio E.; Tomás M. *Angew. Chem., Int. Ed.* **2009**, 48, 7569-7572.

vinyl diazoacetate esters (Scheme 69). The reaction worked satisfactorily to produce furyl-substituted cyclobutenes as single regioisomers.



Scheme 69. Copper(I)-catalyzed cross-coupling of bis(propargyl) esters and vinyl diazoesters to form furyl-substituted cyclobutenes

The mechanism proposed involved first a copper-mediated isomerization of the propargylic substrate to the (*E*)-Knoevenagel intermediate which upon a 5-*exo*-dig cyclization form the putative 2-furyl copper(I) carbene species. Second, this species cyclopropanates the double bond of the diazo compound to provide a cyclopropyldiazo intermediate, which in turns undergoes copper-catalyzed ring expansion to deliver the furyl-substituted cyclobutene product.

Conclusion

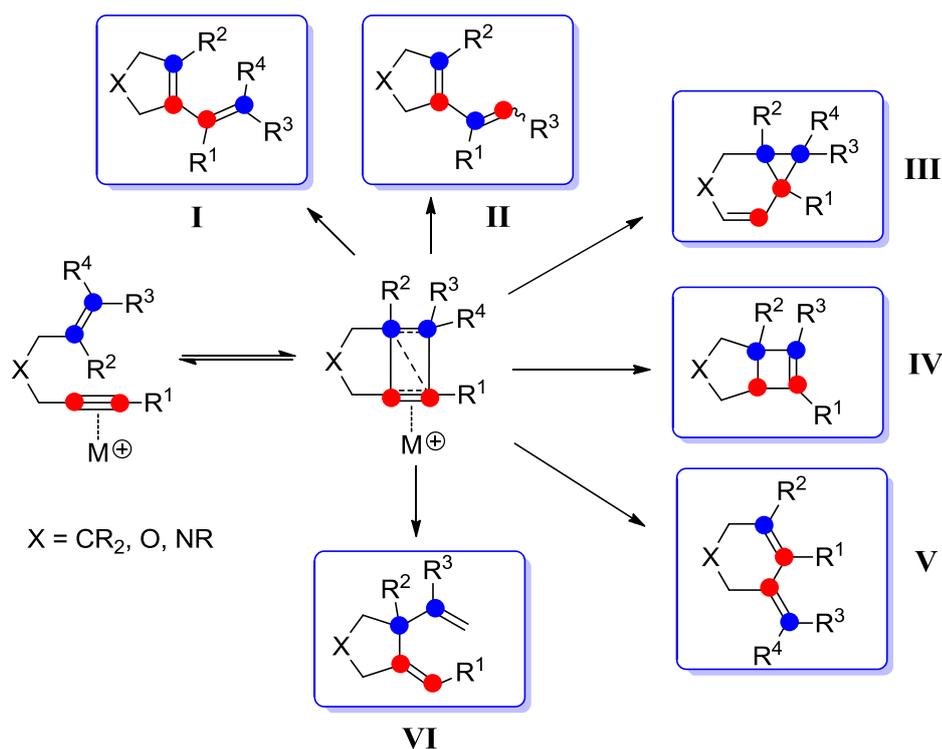
The number of metal-catalyzed methodologies to synthesize cyclobutenes has considerably increased over the past decade. Those combining alkynes and alkenes are particularly well-documented and synthetically useful, reliable methods of preparation of cyclobutenes synthons are now available. The catalytic methods present notably advantages over the thermal or photochemical conditions such as wide tolerance to functional groups, mild reaction conditions, and in a not insignificant way to increase molecular complexity of products. The potential of cyclobutenes in target-oriented synthesis is far from being achieved and future prospects will focused in the development of enantioselective versions and applications in asymmetric synthesis.

Chapter II

Cyclobutene Formation in PtCl₂-Catalyzed Cycloisomerizations of Heteroatom-Tethered 1,6-Enynes

Introduction

Transition-metal catalyzed enyne cycloisomerizations have become useful synthetic strategies for the construction of cyclic or bicyclic structures with high molecular complexity. In general, these reactions are easy to implement and require no rigorous controlled experimental conditions. In these processes, the amount of enynes equal the amount of cyclic or bicyclic products generated and no atom is wasted. These reactions fulfill the concept of *atoms economy*.¹ Among the diversity of transition metal complexes catalyzing enynes cycloisomerizations, platinum and gold complexes, which have been defined as “ π -acidic” metals, are the most utilized because of their catalytic efficiency.² An overview of the main products of platinum/gold catalyzed 1,6-enynes cycloisomerizations is now introduced.



Scheme 1. Products of platinum/gold catalyzed 1,6-enynes cycloisomerizations.

Scheme 1 summarizes the diverse arrays of products obtained in platinum/gold-catalyzed 1,6-enynes cycloisomerizations and highlights the connectivities between carbon atoms of

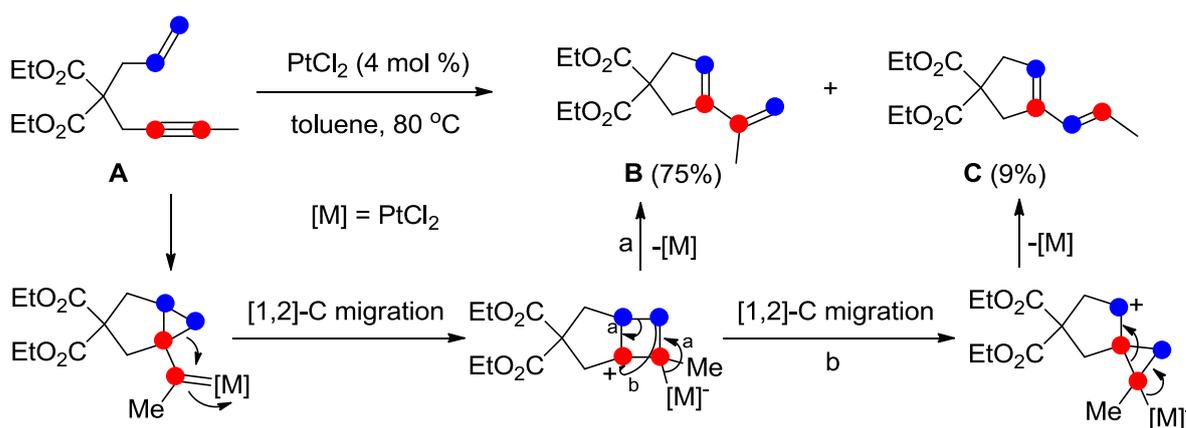
¹ a) Trost, B. M. *Science* **1991**, 254, 1471-1477. b) Trost, B. M. *Angew. Chem. Int. Ed.* **1995**, 34, 259-281.

² Fürstner, A.; Davies, P. W. *Angew. Chem. Int. Ed.* **2007**, 46, 3410-3449.

the newly created carbon-carbon bonds.³ It can be seen that cyclized products are formed with or without carbon-carbon bond(s) cleavage. According to the structural patterns of enynes, and in a less extent the reaction conditions, five-membered carbocycles **I**, **II** and **VI** that feature a 1,3- or 1,4-diene unit can be formed. Alternatively, cycloisomerizations also provide an access to six-membered dienes compounds **V** or bicyclic products **III**. The formation of cyclobutenes **IV** is quite unusual and only observed in some instances. The compounds **I-VI** are observed in various transition-metal catalyzed enynes cycloisomerizations and no metal catalyst is specific for a given type of products. In the following lines, we will mainly focus in platinum-catalyzed cycloisomerizations in continuation with studies undertaken in our laboratories. A brief discussion on the formation of each type compounds **I-VI** based on the mechanisms proposed is presented below.

* 1,3-Dienes **I** and **II**

Murai reported that treatment of enyne **A** with a catalytic amount of PtCl₂ in toluene at 80 °C resulted in the formation of dienes **B** and **C**.⁴ The reaction proceeds by activation of the alkyne with platinum thus forming a highly electrophilic (η^2 -alkyne)platinum complex. Nucleophilic attack of the alkene through 5-*exo-dig* cyclization led to the α -cyclopropyl platinacarbene. Type **I** diene **B** is obtained through a single [1,2]-C migration, rearrangement and metal elimination, while type **II** diene **C** is formed as a minor product via a double [1,2]-C migration.

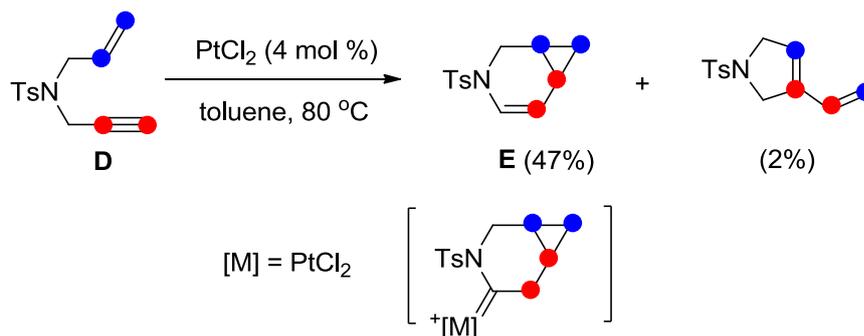


* Vinylcyclopropanes **III**

³ Jimenez-Nunez, E.; Echavarren, A. M. *Chem. Rev.* **2008**, *108*, 3326-3350.

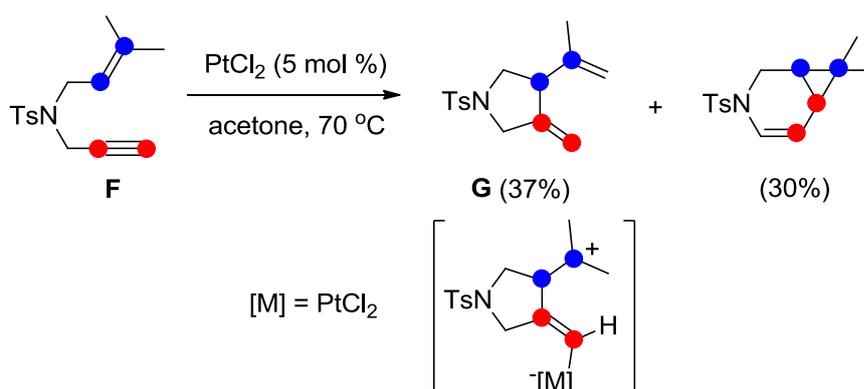
⁴ Chatani, N.; Furukawa, N.; Sakurai, H.; Murai, S. *Organometallics*, **1996**, *15*, 901-903.

In 2001, Fürstner's group described the cycloisomerization of simple nitrogen-tethered 1,6-enyne **D** in the presence of catalytic amounts of PtCl₂ in toluene to produce the cyclopropane derivative **E** (type **III**) alongside 2% of metathesis-like adduct (type **I**).⁵ It is believed that the a *6-endo-dig* cyclization generates a metalated bicyclic piperidine featuring a platinacarbene character. This species undergo a rapid 1,2-hydrogen shift and demetalation to give **E**.



* 1,4-Dienes VI

Cycloisomerization of 1,6-enyne **F** bearing gem disubstitution at terminus carbon of alkenes in the presence of catalytic amounts of PtCl₂ in acetone resulted in the formation of 1,4-diene **G** (type **VI**) alongside the cyclopropane derivative (type **III**).⁶ The *5-exo-dig* attack of the alkene onto electrophilic activated alkyne would give the stabilized homoallylic cationic intermediate, which would lead to 1,4-diene after protodemetalation.

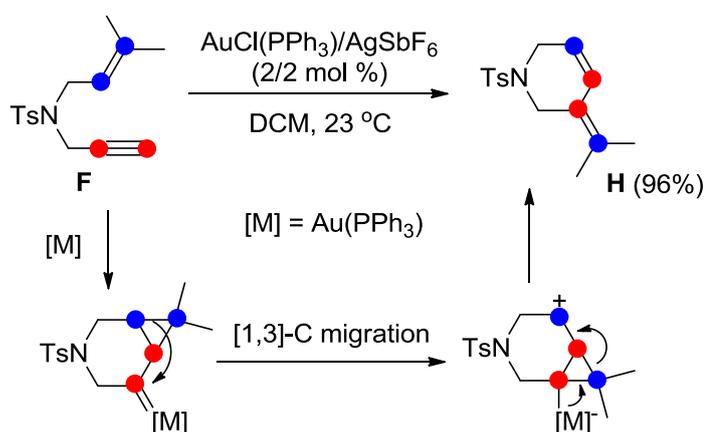


* 1,3-Dienes V

⁵ Fürstner, A.; Stelzer, F.; Szillat, H. *J. Am. Soc. Chem.* **2001**, *123*, 11863-11869.

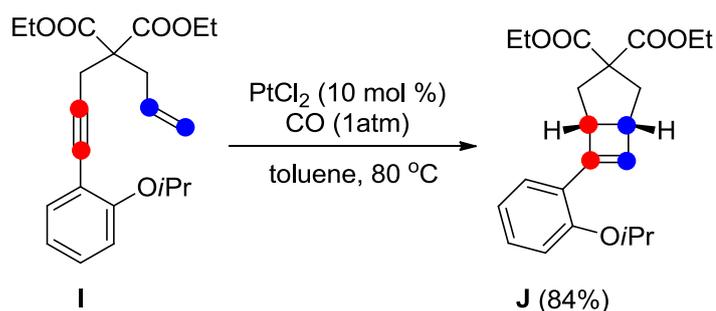
⁶ Méndez, M.; Muñoz, M. P.; Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. *J. Am. Chem. Soc.* **2001**, *123*, 10511-10520.

In 2004, Echavarren's group observed that treatment of 1,6-enyne **F** with an *in situ* generated cationic gold catalyst led to the formation of six-membered heterocyclic diene **H** (type **V**).⁷ In this process, a *6-endo-dig* cyclization led to an α -cyclopropyl auracarbene which undergoes a [1,3]-C shift to form a metalated cyclopropylmethyl cation intermediate. Upon fragmentation of this species and metal elimination, the diene adduct **H** was obtained.



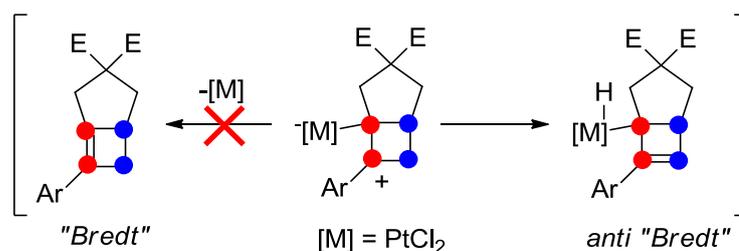
* Bicyclic Cyclobutenes IV

We have already discussed in details the formation of cyclobutenes with platinum catalysts in the precedent chapter (§ 1.2.2). Fürstner and co-workers developed these reactions under an atmosphere of carbon monoxide, which is believed to act as π -acidic ligand and thus could increase the electrophilicity of the metal center.⁸



⁷ Nieto-Oberhuber, C.; Muñoz, M. P.; Buñuel, E.; Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2004**, *43*, 2402–2406.

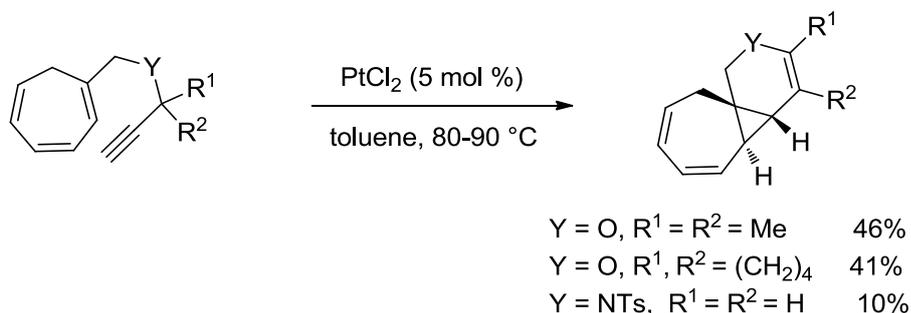
⁸ Fürstner, A.; Davies, P. W.; Gress, T. *J. Am. Chem. Soc.* **2005**, *127*, 8244–8245.



The cyclobutene adducts (type **IV**) were obtained via the cationic cyclobutyl intermediate. According to the proposed mechanism, demetallation of the cyclobutyl cation could form the cycloisomer with an unfavorable “Bredt” double bond. Instead, a proton shift to the metal followed by protodemetalation produced the cyclobutene derivatives.

2.1 Purpose of the initial project

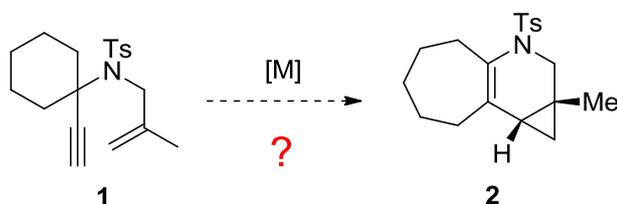
In previous studies of our group devoted to PtCl_2 -catalyzed cycloisomerizations of enynes derived from cycloheptatriene, it has been showed that certain cyclizations occurred with a [1,2]-carbon or hydrogen shift. In cases of substrates bearing a carbocycle at the propargylic carbon, the cycloisomerization took place with concomitant ring expansion to form stereodefined tricyclic compounds.⁹



Alongside the work in our group, reports dealing with transition-metal catalyzed ring

⁹ Tenaglia, A.; Gaillard, S. *Angew. Chem. Int. Ed.* **2008**, *47*, 2454-2457.

enlargement cycloisomerizations appeared in recent years.¹⁰ However, the scope of these reactions is rather narrow, only enynes with carbon or oxygen tethered are tolerated. Our initial studies focused on C-C bond migration in cycloisomerization of NTs-tethered 1,6-enynes in order to extend the scope of this interesting reaction.



2.2 Preliminary investigations

Various metal chlorides (Pt, Ir, Au, *etc.*) capable to exhibit satisfactory catalytic activity in ring expansion reactions^{9,10} were examined for the reactions of enyne **1** in toluene. The results are summarized in Table 1.

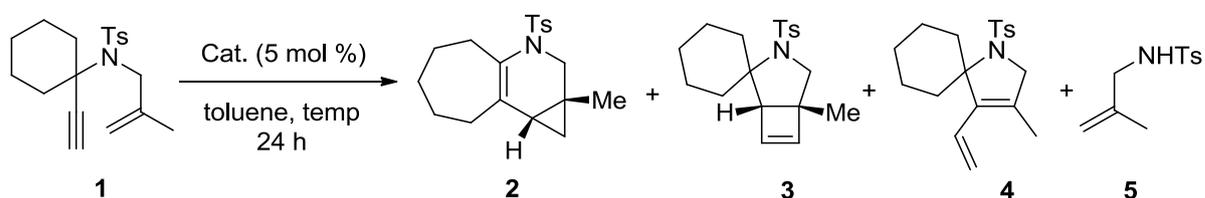


Table 1. Catalyst screening for cycloisomerization of enyne 1 in toluene^a

Entry	Catalyst	T (°C)	Product(s) ^b
1	PtCl ₂ (5 mol %)	105 °C	Complex mixture + 3 (trace)
2	PtCl ₄ (5 mol %)	rt	1 (63 %) + 4 (trace) + Complex mixture
3	PtCl ₂ /AgSbF ₆ (5/10 mol %)	rt	1 (86 %) + 4 (trace)
4	PtCl ₂ (5 mol %), CO (1 atm)	105 °C	4 (65 %)

¹⁰ a) Luzung, M. R.; Markham, J. P.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 10858-10859. b) Stevenson, S. M.; Newcomb, E. T.; Ferreira, E. M. *Chem. Commun.* **2014**, *50*, 5239-5241. c) Simonneau, A.; Harrak, Y.; Jeanne-Julien, L.; Lemièrre, G.; Mouriès-Mansuy, V.; Goddard, J.-P.; Malacria, M.; Fensterbank, L. *ChemCatChem* **2013**, *5*, 1096-1099. d) Crone, B.; Kirsch, S. F. *Chem. Eur. J.* **2008**, *14*, 3514-3522.

5	AuCl ₃ (5 mol %)	105 °C	1 (73 %) + Complex mixture
6 ^c	Au(PPh ₃)Cl/AgSbF ₆ (5/5 mol %)	rt	1 (68 %) + 4 (15 %)
7	[Ir(cod)Cl] ₂ (2.5 mol %)	105 °C	1 (83 %)
8 ^d	FeCl ₃ (10 mol %)	105 °C	1 (87 %) + 5 (trace)

^a **Reaction conditions:** **1** (0.2 mmol), catalyst (2.5-10 mol %), toluene (1 mL), C = 0.2 M, under argon. ^b Isolated yield. ^c Reaction carried out in DCE. ^d Reaction carried out in MeNO₂.

Under typical reaction conditions, treatment of enyne **1** with a catalytic amount of PtCl₂ in toluene at 105 °C (Table 1, entry 1) led to a complex mixture and no desired ring enlargement cycloisomer **2** was observed. Careful examination of the ¹H NMR revealed the presence of trace amounts of cyclobutene compound **3** with characteristic signals of ethylenic protons around δ 6.0 ppm. No significant improvement was observed using PtCl₄ in toluene at room temperature; a complex mixture of products containing traces of metathesis-like compound **4** along with recovered enyne **1** (63 %) was observed. A similar observation was made with cationic platinum species (Table 1, entry 3). Considering that CO has a beneficial effect in metal-catalyzed isomerization reactions,¹¹ the reaction with PtCl₂ was carried out under CO atmosphere (Table 1, entry 4). Under these conditions only diene **4** (65 %) was observed. AuCl₃ and [Ir(cod)Cl]₂ exhibited low conversion of **1** (Table 1, entries 5 and 7). A cationic gold complex generated *in situ* with Au(PPh₃)Cl/AgSbF₆ in DCE led to metathesis-like compound **4** (15 %) with low conversion (Table 1, entry 6). PtCl₂/AgSbF₆ in toluene behaves similarly (Table 1, entry 3). Even FeCl₃ in MeNO₂ proved to be inefficient, only trace amounts of C-N bond cleavage product **5** were observed (Table 1, entry 8).

During the period of these studies, the desired ring enlargement isomer **2** have never been observed and a report dealing with the ring expansion cycloisomerization of enynes with cationic gold catalysts appeared in mid-2013.^{10c} Meanwhile, the formation of cyclobutene **3** was unusual and rare compared to those producing metathesis-like compounds and other isomers. We thus shifted interest from ring enlargement reactions to cyclobutene formation.

¹¹ a) ref. 8. b) Fürstner, A.; Davies, P. W. *J. Am. Chem. Soc.* **2005**, *127*, 15024–15025. c) Fürstner, A.; Aïssa, C. *J. Am. Chem. Soc.* **2006**, *128*, 6306–6307.

2.3 Cyclobutene formation in PtCl₂-catalyzed cycloisomerization of heteroatom-tethered 1,6-enynes

The observation of cyclobutenes in cycloisomerization of 1,6-enynes with PtCl₂ was already reported by Fürstner's group.⁸ However, these reactions suffer from two drawbacks. First, an aryl substituent, preferably electron-rich, at the terminus alkyne carbon is mandatory to stabilize a putative benzylic cation, and second the reactions fail when a heteroatom is present in the tether.

Keeping in mind these drawbacks, **our next challenges** were defined as follows: (a) to develop the PtCl₂-catalyzed cyclization reactions of heteroatom(N, O)-tethered 1,6-enynes giving rise to heterobicyclic derivatives featuring cyclobutenes; (b) to achieve these reactions with enynes unsubstituted at alkyne terminus carbon, and (c) to investigate the reaction mechanism. *Cycloisomerizations of such enynes, featuring terminal alkynes, has never been described so far.*

2.3.1 The solvent screening

Considering that the solvent can play an important role in the selectivity of enynes cycloisomerizations,⁶ a series of solvents of diverse polarity were examined for the reaction of enyne **1**. PtCl₂, which had the potential of active catalyst for the expected reaction, was retained. The results are reported in Table 2.

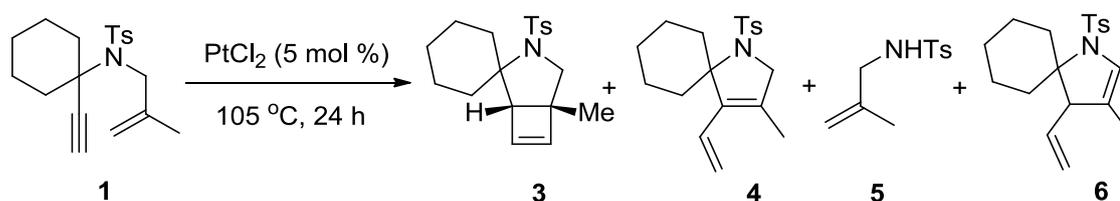


Table 2. Solvent screening in reaction of enyne **1** with PtCl₂^a

Entry	Solvent	T (°C)	Product(s) ^b
1	Toluene	105	Complex mixture + 3 (trace)
2 ^c	DCE	85	1 (40 %) + 3 (13 %) + 4 (21 %) + 6 (16 %)
3	Chloroform	60	1 (69 %) + 3 (8 %)

4	Acetone	60	1 (91 %)
5	CH ₃ COOC ₃ H ₇	85	1 (84 %) + complex mixture
6	DMSO	105	1 (33 %) + complex mixture
7	THF	60	1 (30 %) + 4 (37 %) + 3 (trace)
8	MeOH	70	5 (74 %)
9	DMF	105	3 (63 %)
10	DMPU	105	3 (88 %)
11	NMP	105	3 (87 %)
12	DMA	105	3 (98 %)
13	DMA	85	3 (95 %)

^a **Reaction conditions:** **1** (0.2 mmol), PtCl₂ (0.01 mmol, 5 mol %), DMF (1 mL), C = 0.2 M, under argon.

^b Isolated yield. ^c Yield determined by ¹H NMR of the crude reaction.

Toluene, as the typical solvent in enynes cycloisomerizations, produced a complex mixture containing trace amounts of cyclobutene **3** (Table 2, entry 1). Carrying out the reaction in DCE enabled formation of dienes **4** (21 %) and **6** (16 %), cyclobutene **3** (13 %) alongside unreacted enyne **1** (40 %) (Table 2, entry 2). Chloroform, acetone or propyl acetate are unsuited and allow to recover enyne **1** in 69%, 91% and 84% yield respectively (Table 2, entries 3-5). Reaction in DMSO led to a complex mixture along with enyne **1**, while THF as the solvent produced trace amount of cyclobutene **3**, diene **4** (37 %) and recovered enyne **1** (Table 2, entries 6-7). Surprisingly, a protic and nucleophilic solvent such as methanol which usually participated in enyne cyclizations,⁶ led only to the C-N bond cleavage product **5** (Table 2, entry 8). A remarkable breakthrough was achieved when the reaction was carried out in DMF. We were pleased to find that cyclobutene **3** was formed in a satisfactory 63% yield (Table 2, entry 9). Other amide and even imide solvents such as NMP, DMA and DMPU exhibited excellent selectivity allowing formation of **3** with significant increased yields (Table 2, entries 10-12). DMA proved to be the best one.¹² Furthermore, the reaction in DMA could be conducted at a lower temperature (85 °C) without deleterious effect on the yield (95 %) (Table 2, entry 13).

¹² For similar observations in ruthenium-catalyzed cycloisomerizations of 1,7-enynes, see: Trost, B. M.; Gutierrez, A. C.; Ferreira, E. M. *J. Am. Chem. Soc.* **2010**, *132*, 9202–9218.

2.3.2 The role of amide solvent

In order to shed light on the role of the amide in the reaction of **1** with PtCl₂, a series of experiments under various conditions were conducted and summarized in Table 3.

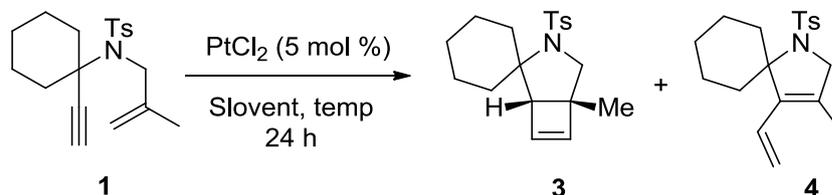


Table 3. Reaction of enyne 1 with PtCl₂ under various condition^a

Entry	Reaction conditions	T (°C)	Product(s) ^b
1	DMF	105	3 (63 %)
2	DCE, Bu ₄ N ⁺ NBH ₄ ⁻ (5 mol%)	85	Complex mixture + 3 (trace) + 4 (trace)
3	DMA	85	3 (95 %)
4	DMA/toluene (1/1)	105	3 (78 %)
5	DMA/toluene (1/9)	105	3 (75 %) + 4 (trace)
6	DMA (20 mol %)/toluene	105	3 (63 %) + 4 (trace)

^a **General:** **1** (0.2 mmol), PtCl₂ (0.01 mmol, 5 mol%), solvent (1 mL), C = 0.2 M, under argon. ^b Isolated yield.

Several reports showed that DMF is able to reduce some noble metal salts (Ag, Au) to their zerovalent species.¹³ We hypothesized that this event could occur with PtCl₂. To this end, the reaction of **1** was carried out in DCE with PtCl₂ and an organo-soluble reducing agent, namely tetrabutylammonium borohydride,¹⁴ in order to generate Pt(0) species *in situ*. Under

¹³ a) James, Y. Yu.; Serge Schreiner.; Vaska, L. *Inorg. Chim. Acta* **1990**, *70*, 145-147. b) Pastoriza-Santos, I.; Liz-Marzán, L. M. *Langmuir* **1999**, *15*, 948-951. c) Han, M. Y.; Quek, C. H.; Huang, W.; Chew, C. H.; Gan, L. M. *Chem. Mater.* **1999**, *11*, 1144-1147. d) Pastoriza-Santos, I.; Koktysh, D. S.; Mamedov, A. A.; Giersig, M.; Kotov, N. A.; Liz-Marzan, L. M. *Langmuir* **2000**, *16*, 2731-2735. e) Pastoriza-Santos, I.; Liz-Marzan, L. *Pure Appl. Chem.* **2000**, *72*, 83-90. f) Pastoriza-Santos, I.; Liz-Marzan, L. M. *Langmuir* **2002**, *18*, 2888-2894. g) Tom, R. T.; Nair, A. S.; Singh, N.; Aslam, M.; Nagendra, C. L.; Philip, R.; Vijayamohanan, K.; Pradeep, T. *Langmuir* **2003**, *19*, 3439-3445. h) Neshet, G.; Marom, G.; Avnir, D. *Chem. Mater.* **2008**, *20*, 4425-4432. i) Pastoriza-Santos, I.; Liz-Marzan, L. *Adv. Funct. Mater.* **2009**, *19*, 679-688. j) Seth, K.; Purohit, P.; Chakraborti, A. K. *Org. Lett.* **2014**, *16*, 2334-2337.

¹⁴ Raber, D. J.; Guida, W. C. *J. Org. Chem.* **1976**, *41*, 690-696.

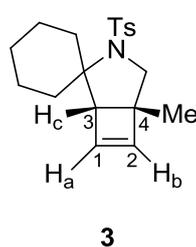
these conditions, only a complex mixture of products was observed revealing trace amounts of cyclobutene **3** and diene **4** by proton NMR of the crude (Table 3, entry 2). So, this hypothesis was definitively pushed aside.

Our next hypothesis was that amide behaves as a weakly coordinating ligand. To test this assumption, the reactions were conducted in toluene with a decrease of the concentration of DMA. The reactions conducted in mixtures DMA/toluene 1/1 or 1/9 v/v gave cyclobutene **3** with significant decreased yields (78 and 75 % respectively) (Table 3, compare entry 3 and entries 4-5). Interestingly the yield of **3** remained similar with these DMA concentrations. Finally, when using DMA in catalytic amounts (20 mol % with respect to enyne **1**) in toluene, the cyclobutene **3** was still observed in an acceptable 63% yield (Table 3, entry 6). *These results supported our second hypothesis and highlighted the role of the DMA as a weakly coordinating ligand in cycloisomerization reactions.*

2.3.3 Determination the structure of cyclobutene **3**

2.3.3.1 ^1H NMR and ^{13}C NMR of cyclobutene **3**

The assignments of ^1H NMR and ^{13}C NMR signals of cyclobutane **3** have been established through the DEPT, COSY, NOESY, HMQC and HMBC experiments. The ^1H NMR of **3** revealed distinct signals for all the protons of the bicycle. The ethylenic protons H_a and H_b were observed as doublets ($J_{\text{H}_a\text{-H}_b} = 2.8$ Hz) at δ 6.00 and 6.04 respectively; H_c and the angular methyl group were observed as singlets at δ 2.99 and 1.30 respectively. The carbon signals of the cyclobutene were observed at δ 142.3 (CH), 134.4 (CH), 58.4 (CH), 49.8 (C).

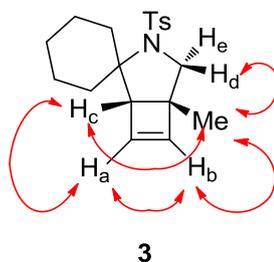


	^1H NMR	^{13}C NMR
H_a	6.00 d ($J = 2.8$ Hz)	C_1 134.4
H_b	6.04 d ($J = 2.8$ Hz)	C_2 142.3
H_c	2.99 s	C_3 58.4
H_{Me}	1.30 s	C_4 49.8

2.3.3.2 NOESY of cyclobutene **3**

The NOESY experiments revealed correlations between the cyclobutenic protons H_a and H_b , the methyl protons and the olefinic proton H_b , the olefinic proton H_a and proton H_c that allowed the assignments of protons H_a and H_b . The correlations between the methyl group at

C-4 and only one protons H_d of the methylene α to NTs as well as between the same methyl protons and proton H_c established the assignment of H_d and confirmed the *syn* relationship between the methyl group and H_c respectively. Therefore, the relative configuration of C-3 and for the quaternary carbon C-4 are (S^*) and (R^*) respectively.



Observed NOESY correlations of **3**

2.3.3.3 X-ray diffraction of the cyclobutene **3**

The analysis by X-ray diffraction of cyclobutene **3** confirmed the structure of the compound and established the relative configuration R^* (C-4) and S^* (C-3) of the carbon atoms of the rings junction (Figure 1).

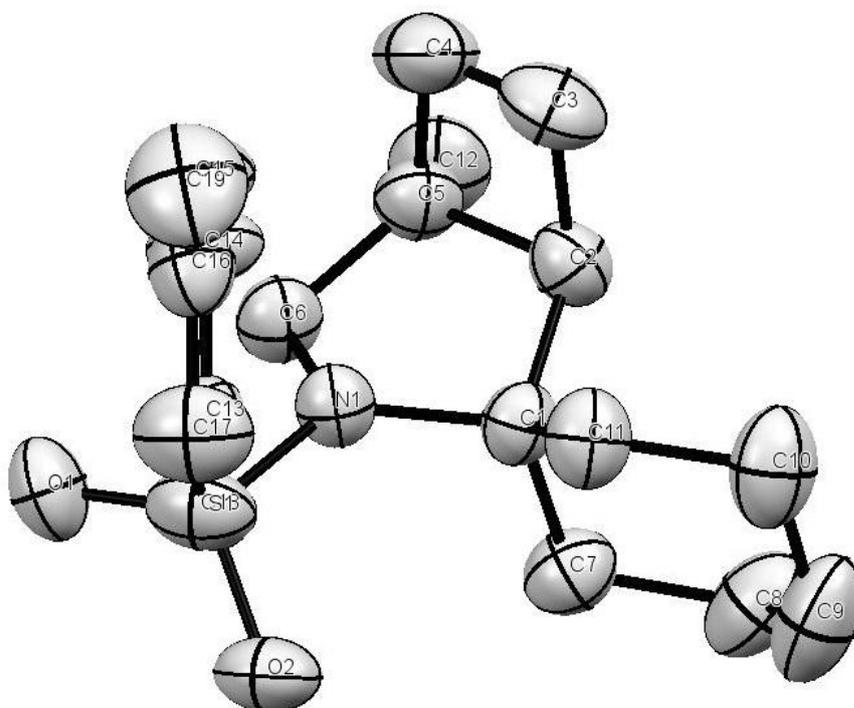


Figure 1. ORTEP of bicycle **3** (H atoms are omitted for clarity)

Selected data: a) Bond length (Å): C2-C3 = 1.511; C3-C4 = 1.302; C4-C5 = 1.507; C2-C5 = 1.571. b) Angle (°): C4-C5-C6 = 114.7; C1-C2-C3 = 117.8; H2-C2-C3 = 114.2; C4-C5-C12 = 116.8; C2-C3-C4 = 95.2; C3-C4-C5 = 95.1; C2-C5-C4 = 85.1; C3-C2-C5 = 84.7.

2.4 Scope of the Pt-Catalyzed Cycloisomerization of Hetero-atom-Tethered 1,6-Enynes

2.4.1 Cycloisomerization of *N*-tethered enynes with disubstitution α to nitrogen atom

Our initial study on the model enyne **1** has showed that the platinum-catalyzed reaction can afford cyclobutene **2** in 95 % yield (Table 4, entry 1) as a single diastereomer owing to the convex shaped bicyclo[3.2.0]heptane structure. With this promising result in hand, various enynes bearing the spirocyclohexyl group at the propargylic carbon atom were first examined. Enynes **7**, **9** and **11** with a nucleophilic or electrophilic function at the C-6 position, including phenyl, chloromethyl, (trimethylsilyl)methyl¹⁵ gave the corresponding cyclobutenes **8**, **10** and **12** in good to excellent yields (80-99 %) (Table 4, entries 2-4). Even enyne **13** with an unsubstituted allyl motif was converted to cyclobutene **14** in 80 % yield (Table 4, entry 5). Unexpectedly, enyne **15** with a bromine atom at the C-6 position was found unreactive to give the expected cyclobutene **16** (Table 4, entry 6). Enyne **17** substituted with a phenyl group at terminal carbon of alkene did not provide the corresponding cyclobutene **18** (Table 4, entry 7).

The variation of substituent at the nitrogen atom of several enynes bearing cyclohexyl group at propargylic position was briefly examined. The reactivity of methanesulfonamide **19** was similar to the corresponding *p*-tolylsulfonamide **1** to give adduct **20** in 96% yield (Table 4, entries 8 and 1), while amide **21** reacted less satisfactory to afford cyclobutene **22** in only 32% yield (Table 4, entry 9). Interestingly, carbamate **23** reacted differently to give

¹⁵ Contradictory results were reported in PtCl₂-catalyzed cycloisomerizations of related enynes featuring the allyltrimethylsilane group. Cycloisomers retaining (a, b) or not (c, d) the silane group are observed, see: (a) ref. 5. (b) Fürstner, A.; Szillat, H.; Stelzer, F. *J. Am. Chem. Soc.* **2000**, *122*, 6785-6786. (c) Fernandez-Rivas, C.; Méndez, M.; Echavarren, A. M. *J. Am. Chem. Soc.* **2000**, *122*, 1221-1222. (d) Fernandez-Rivas, C.; Méndez, M.; Nieto-Oberhuber, C.; Echavarren, A. M. *J. Org. Chem.* **2002**, *67*, 5197-5201.

oxazolidinone **24** in 58% yield through oxygen nucleophilic attack on metal-coordinated alkyne.¹⁶

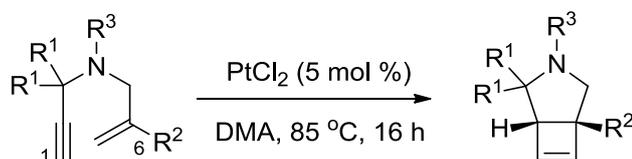
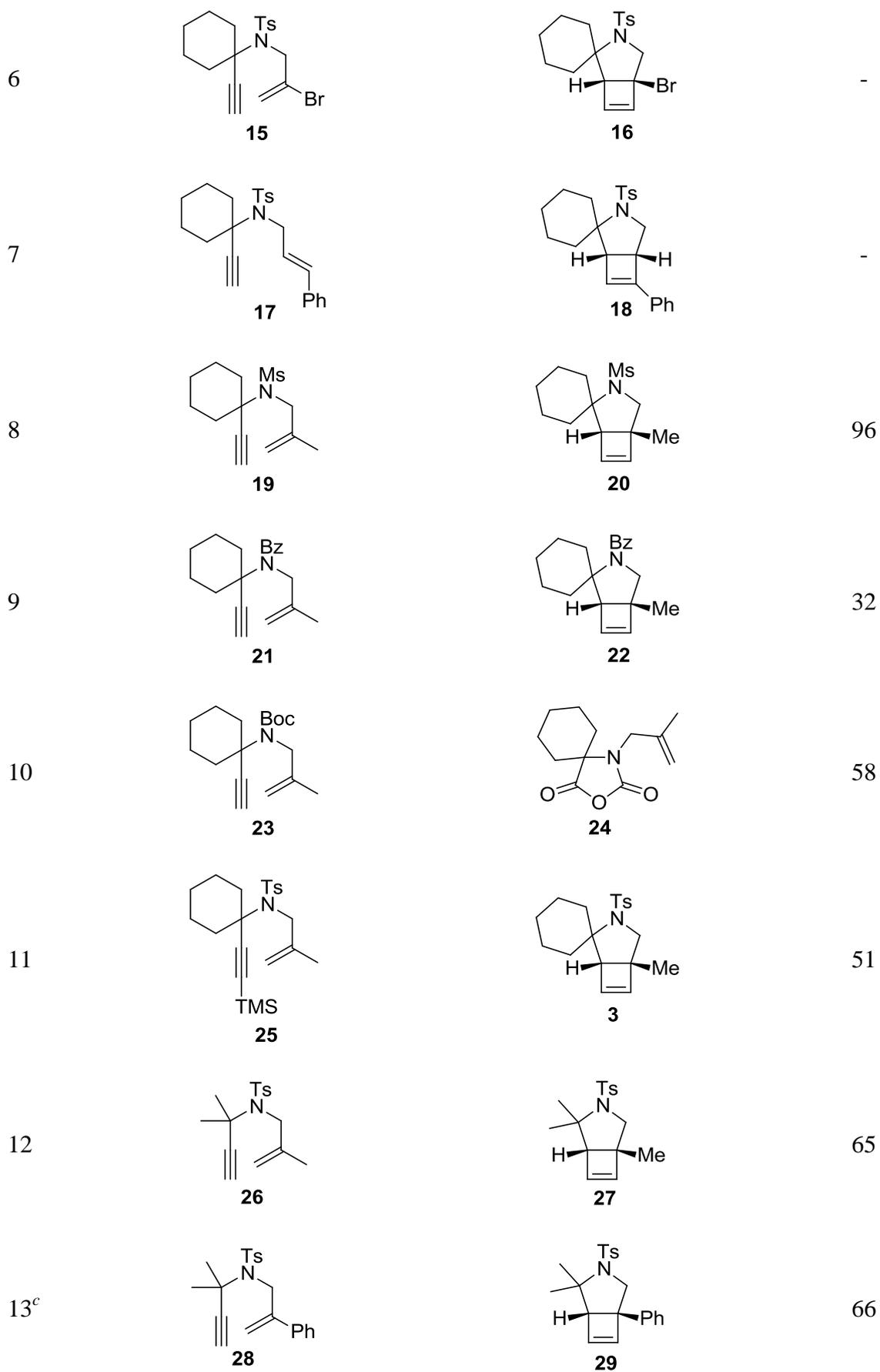
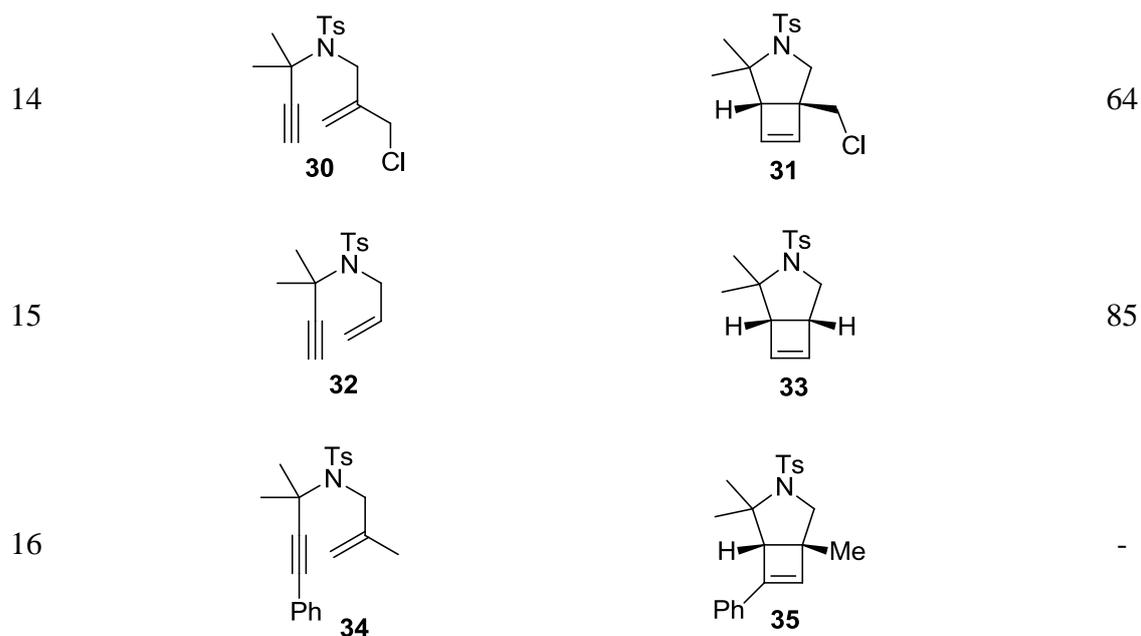


Table 4. Cycloisomerization of nitrogen-tethered enynes with disubstitution α to nitrogen atom^a

Entry	Substrate	Product	Yield (%) ^b
1			95
2			80
3			96
4			99
5			80

¹⁶ a) Robles-Machín, R.; Adrio, J.; Carretero, J. C. *J. Org. Chem.* **2006**, *71*, 5023–5026. b) Buzas, A.; Gagosz, F. *Synlett.* **2006**, 2727–2730.





^a **Reaction conditions:** Enyne (0.2 mmol), PtCl₂ (0.01 mmol, 5 mol %), DMA (1 mL), C = 0.2 M, under argon at 85°C for 16 h. ^b Isolated yield. ^c Reaction carried out with additional allyltrimethylsilane (3 equiv).

According to the work of You's group,¹⁷ the nitrogen-tethered enynes with a TMS group at the terminus alkyne carbon could produce cyclobutene adducts. In these cases, the reactions suffer from a lack of selectivity giving TMS-containing adducts along with protodesilylated and over-reduced adducts (see § 1.2.2). In order to compare our conditions with those described by You, enyne **25** was prepared and subjected to our conditions to give a clean conversion to cyclobutene **3** (51 %) alongside unreacted enyne **25** (Table 4, entry 11). Interestingly, silylated or over-reduced adducts were not observed. This result suggested that protodesilylation of the alkyne containing TMS group with residual protic sources (traces of H₂O?) underwent under our conditions prior to the reaction forming cyclobutene **3**. The presence of unreacted silylated enyne **25** may support this assumption.

A series of enynes **26**, **28**, and **30**, featuring a gem dimethyl substitution at propargylic position were also examined (Table 4, entries 12-14). These enynes were equally suited to undergo cycloisomerization to give the corresponding cyclobutenes **27**, **29**, and **31** in moderate yield (64-66 %). Enynes featuring the spirocyclohexane ring (Table 4, entries 1-3) gave the corresponding azabicycloheptenes in higher yields compared to those exhibiting a gem dimethyl substitution (Table 4, entries 12-14). Interestingly, enyne **32** with the

¹⁷ Xia, J.-B.; Liu, W.-B.; Wang, T.-M.; You, S.-L. *Chem. Eur. J.* **2010**, *16*, 6442-6446.

unsubstituted allyl group reacted similarly as enyne **13** (Table 4, entries 5 and 15). The nitrogen-tethered enyne **34** with a phenyl group on the alkyne unit was found reluctant to undergo cycloisomerization and was recovered unchanged¹⁸ (Table 4, entry 16). The same trend was observed with enyne **17** (Table 4, entry 7).

2.4.2 Cycloisomerization of *N*-tethered enynes with monosubstitution at the propargylic or allylic position

First, enynes monosubstituted at the propargylic position prone to undergo a [1,2]-H shift to give cyclopropane derivatives were examined in order to evaluate the feasibility of [2+2] cycloaddition pathway. Enyne **36** featuring a phenyl group at the propargylic position proved to be an excellent substrate to form cyclobutene **37** in a very good yield (81 %) (Table 5, entry 1), while similar enyne **38** having an extra methyl group at the C-6 position yielded the cyclobutene **39** in a lower yield (57%) (Table 5, entry 2).

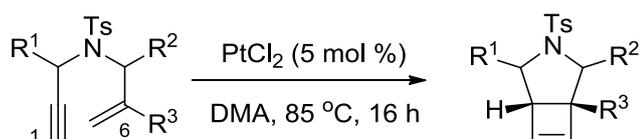
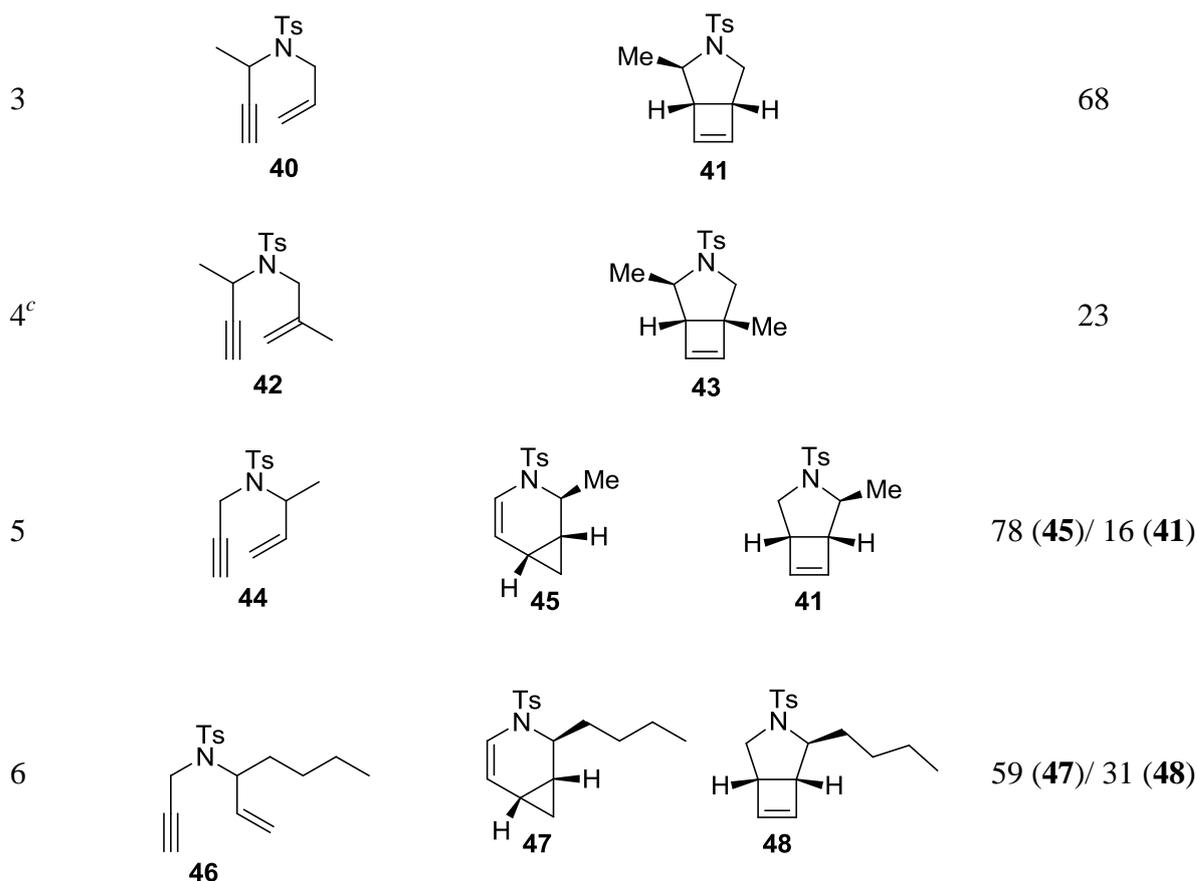


Table 5. Cycloisomerization of *N*-tethered enynes with monosubstitution at the propargylic carbon atom^a

Entry	Substrate	Product(s)	Yield(s) (%) ^b
1	<p>36</p>	<p>37</p>	81
2	<p>38</p>	<p>39</p>	57

¹⁸ This result is contradictory to the observations of Fürstner (ref. 8) and raises the question of the role of ligands, which will be discussed further.



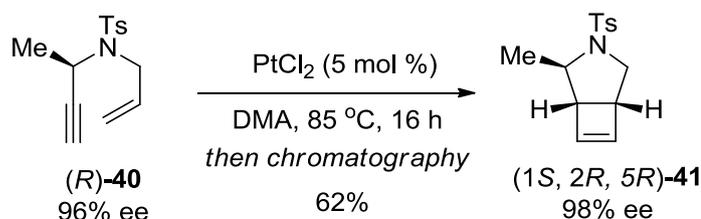
^a **Reaction conditions:** Enyne (0.2 mmol), PtCl₂ (0.01 mmol, 5 mol %), DMA (1 mL), C = 0.2 M, under argon at 85°C for 16 h. ^b Isolated yield. ^c The remaining mass balance (65% yield) accounted for an inseparable mixture of products.

The same trends were observed for enynes **40** and **42** (Table 5, entries 3-4). Enyne **40** bearing a methyl group at the propargylic position afforded cyclobutene **41** in a fair yield (68 %) (Table 5, entry 3), whereas enyne **42** was poorly converted to cyclobutene **43** (Table 5, entry 4). A possible 1,3 repulsive non-bonded interaction between the substituents at C-3 and C-6 when forming the 5-membered azacycle may explain the decreased yields observed in these cases. As expected the bicyclic adducts are obtained as single diastereomers due to the geometric constraints inherent in the [3.2.0] bicyclic structure.

The effect of the substitution at the allylic position was briefly examined with enynes **44** and **46** (Table 5, entries 5-6). The formation of cyclobutenes **41** (16%) and **48** (31%) as minor compounds is still observed along with the cyclopropanated compounds **45** (78%) and **47** (59%) respectively. Notably, a competitive [1,2]-H shift event favored the cyclopropane derivatives formation.⁵ These results showed that the substitution patterns of the enynes plays a role in the cycloisomerization selectivity and that substitution at the allylic position,

compared to the propargylic position, remains less influential for the formation of the cyclobutenes.

Owing to the remarkable diastereoselectivity of these reactions, subsection of the chiral enyne (*R*)-**40** (96 % ee) to the cyclosimerization conditions (5 mol % of PtCl₂, DMA) afforded (1*S*,2*R*,5*R*)-3-azabicyclo[3.2.0]hept-6-ene **41** in 62 % yield and 98 % ee after purification by chromatography.



The structure of bicycle **43** and its relative stereochemistry was secured by single-crystal X-ray diffraction analysis (Figure 2).

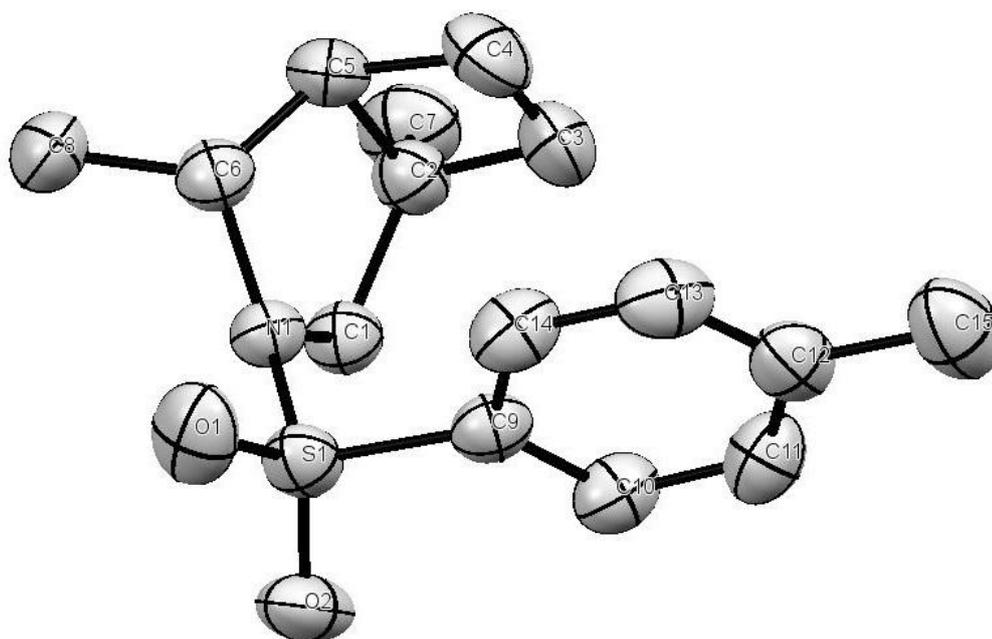
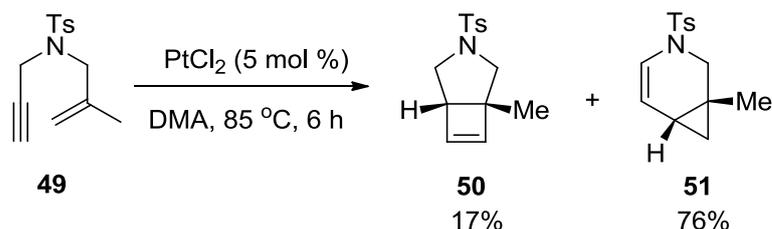


Figure 2. ORTEP of bicycle **43** (H atoms are omitted for clarity)

Selection of structural data: a) Bond length (Å): C2-C3 = 1.521; C3-C4 = 1.313; C4-C5 = 1.508; C2-C5 = 1.575. b) Angle (°): C1-C2-C3 = 114.7; C4-C5-C6 = 115.6; C4-C5-H5 = 114.9; C3-C2-C7 = 117.8; C2-C3-C4 = 95.0; C3-C4-C5 = 94.9; C2-C5-C4 = 85.6; C3-C2-C5 = 84.5.

2.4.3 Cycloisomerization of *N*-tethered enynes without substitution at the propargylic carbon atom

Since the substitution patterns of the enyne play an important role on the outcome of the cycloisomerization, the reactivity of enyne **49** with a methallyl substituent was evaluated. Under the usual conditions, cyclobutene **50** was still formed in 17% yield alongside the known cyclopropane **51** as the major cycloisomer (76%). It is noteworthy that cyclobutene **50** was not observed for the reaction performed in toluene.⁵ Thus, the [1,2]-H migration remains the preponderant path when no substituent is present at the propargylic carbon atom. *These results suggested that upon coordination of the alkyne to platinum, the propargylic substituent(s) induce a significant relative stabilization of the developing positive charge at internal *sp* carbon through hyperconjugation. This condition is necessary but not sufficient. The DMA as the coordinating solvent play a decisive role in the evolvement of ionic species intermediates to the cyclobutene formation.*



In order to get an insight into the progress of the reaction, it was decided to stop the reactions after a short period of time and to determine the ratio of the products formed. Table 6 summarizes the conversion of enyne **49** and the ratio of cyclobutene **50** to cyclopropane **51** over time. As expected, the conversion of **49** increased with the reaction time and, interestingly, the ratio **50/51** increased with the conversion of enyne **49**. These variations appear to be linear (Figures 3 and 4). We have shown that interconversion of **51** to **50** can not be achieved under the reaction conditions. Consequently, the observed ratio **50/51** have to depend most probably on the kinetics of formation of **50** and **51**.

Table 6. Cycloisomerization of *N*-tethered enyne **49^a**

Time	Conversion	Ratio of 50/51
15 min	47%	1/ 7.2

30 min	65%	1/ 6.1
45 min	79%	1/ 5.2
1 h	93%	1/ 4.7

^a **Reaction conditions:** Enyne **49** (0.2 mmol), PtCl₂ (0.01 mmol, 5 mol %), DMA (1 mL), c 0.2 M, under argon at 85°C.

Figure 3. Progress of enyne cycloisomerization

Conversion of 49 in a function of time

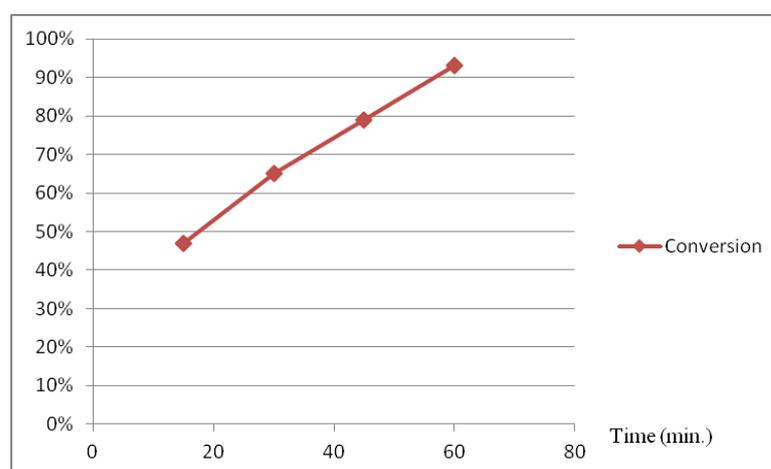
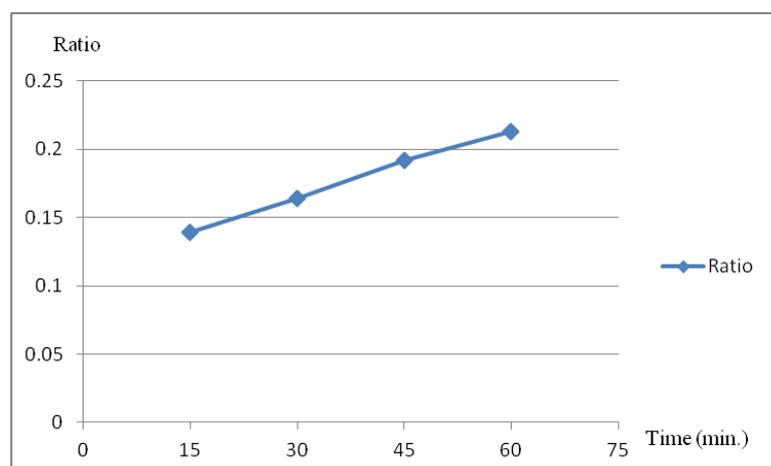


Figure 4. Progress of enyne cycloisomerization

Ratio of 50/51 in a function of time



The total conversion of enyne **49** has been observed carrying out the reaction for 6 hours. As

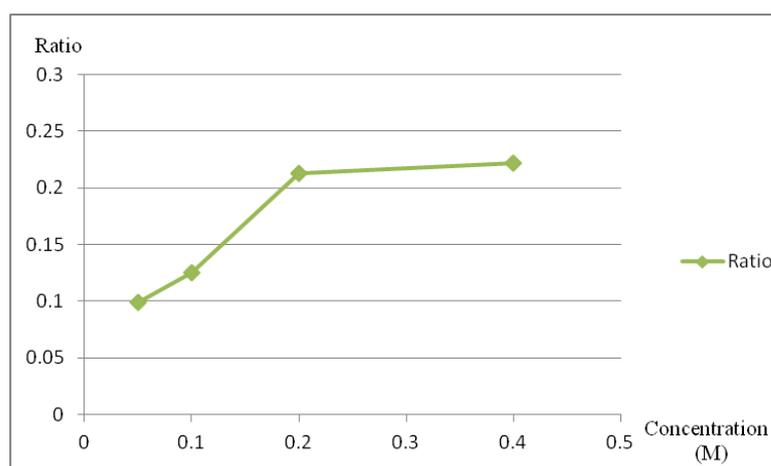
far as the kinetics of reaction are often dependent on the concentration of reactants, we investigated the influence of concentration of the **49** on the progress of the reaction (Table 7). Although the formation of **51** as the major product is observed whatever is the concentration, the best **50/51** ratio in favor of the cyclobutene is observed at 0.2 M concentration of enyne **49** and do not change significantly at higher concentration (Figure 5).

Table 7. Cycloisomerization of *N*-tethered enyne **49:
Influence of the concentration^a**

Concentration (M)	Ratio of 50/51
0.05	1/ 10.1
0.1	1/ 8.0
0.2	1/ 4.7
0.4	1/ 4.5

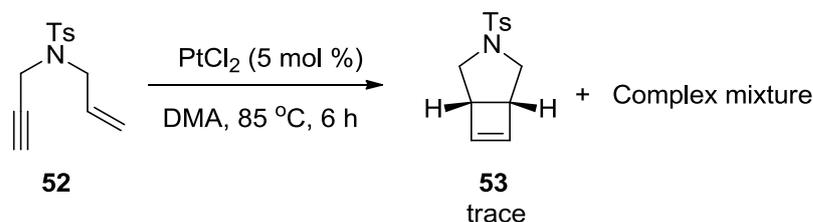
^a **Reaction conditions:** Enyne **49** (0.2 mmol), PtCl₂ (0.01 mmol, 5 mol %), DMA (0.5- 4 mL) , under argon at 85°C for 6 h, total conversion.

Figure 5. Cycloisomerization of *N*-tethered enyne **49:
Ratio of products **50/51** according to the concentration**



We have previously shown that cycloisomerization of enynes with an unsubstituted allyl motif proceeded smoothly to the corresponding cyclobutenes (see Table 4, entry 5 and Table 5, entries 1, 3 and 5). Thus, the unsubstituted enyne **52** subjected to the usual conditions afforded a complex mixture of products containing a trace amount of the desired cyclobutene

53 detected in the ^1H NMR of the crude reaction.



This result strengthens the idea that propargylic substituents would play an important role on the cyclobutene formation.

2.4.4 Cycloisomerization of *O*-tethered enynes with disubstitution α to nitrogen atom

Oxygen-tethered enynes participate equally to the cycloisomerization to give the expected bicyclic ethers although these products were more sensitive compared to the parent nitrogen compounds, and prone to undergo decomposition.⁴ To this end, the reactions of allyl-propargyl ethers were carried out with trimethylallylsilane as additive to trap the adventitious acidic species responsible for the decomposition of products.

For our initial investigation on oxygen-tethered enynes cycloisomerizations, the readily available enyne **54** having the same substitution patterns as enyne **1** was selected. Unfortunately, due to its lability, the desired cyclobutene **55** was observed in tiny amount (Table 6, entry 1). We anticipated that enyne with a phenyl group at C-6 would be a better substrate to undergo the cycloisomerization and hopefully to give the non-labile cyclobutene adduct. To our delight, this assumption was correct and the well-designed enyne **56** led to corresponding cyclobutene **57** in good yield (75 %) (Table 6, entry 2). To our knowledge, these 3-oxabicyclo[3.2.0]hept-6-ene structures formed through enyne cycloisomerization have never been reported so far. Enynes **58** and **60** containing an acid sensitive protecting group gave the corresponding cyclobutenes **59** and **61** respectively in fair yield compared to **57** (Table 6, entries 2-4). In these cases, the presence of allyltrimethylsilane as an acid scavenger is crucial for the survival of the dioxolane. For instance, reaction of enyne **58** carried out without trimethylallylsilane for 24 h afforded a mixture of cyclobutene **59** and deprotected cyclobutene **63**. Enyne **62**, prepared from the ketone deprotection of enyne **58**, gave cyclobutene **63** in 73 % yield even without additional trimethylallylsilane (Table 6,

entry 5). Enyne **64** bearing a gem diphenyl group at the propargylic carbon atom was found unsuited to undergo cycloisomerization. No cyclobutene was detected in the crude reaction mixture, instead only C-O bond cleavage compound 2-methylprop-2-en-1-ol **65** was formed in 74 % yield (Table 6, entry 6). We believed that the bisbenzylic C-O bond is weakened under the reaction conditions and easily undergoes cleavage to alleviate steric strain. The same trend was observed with enyne **66** (Table 6, entry 7).

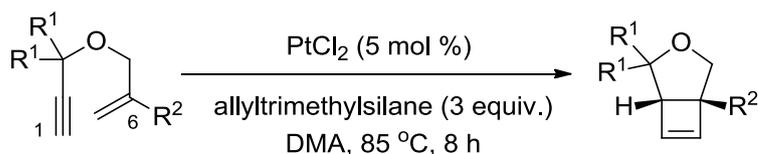
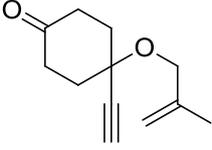
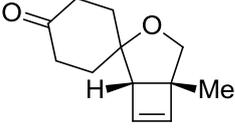
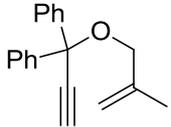
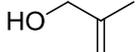
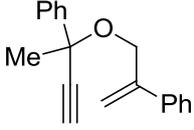
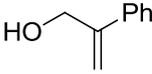
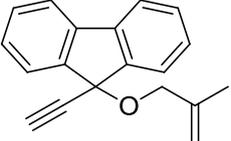
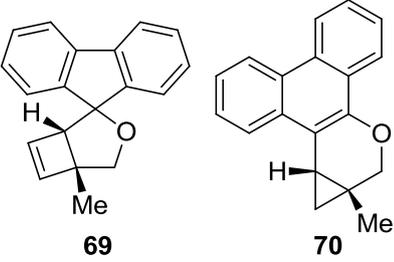
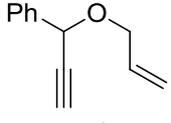
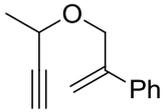
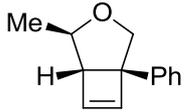


Table 6. Cycloisomerization of Oxygen-Tethered Enynes^a

Entry	Substrate	Product(s)	Yield (%) ^b
1			trace
2			75
3			55
4			55

5			73
6			74
7			61
8 ^c			21 (69)/ 63 (70)
9		Complex mixture	
10			32

^a **Reaction conditions:** Enyne (0.2 mmol), PtCl₂ (0.01 mmol, 5 mol %), allyltrimethylsilane (0.6 mmol, 3 equiv), DMA (1 mL), C = 0.2 M, under argon at 85°C for 8 h. ^b Isolated yield. ^c Yield determined by ¹H NMR of the crude reaction.

In contrast with similar enynes **64** and **66**, enyne **68** featuring a spirofluorene structure on propargylic position led to an unseparable mixture of the desired cyclobutene **69** (21 %) and the ring-expanded cycloisomer¹⁹ compound **70** (63 %), which was targeted in our initial project. (Table 6, entry 8).

¹⁹ The ring strain of cyclic structures within the enynes favoring the ring expansion cycloisomerization has precedents, see ref. 10.

Enynes **71** and **72** with monosubstitution at propargylic carbon atom have been examined (Table 6, entries 9-10). Enyne **71** with an unsubstituted allyl motif gave a complex mixture without formation of the expected cyclobutene as judged by ^1H NMR (Table 6, entry 9), while enyne **72** bearing a phenyl group at C-6 was converted to cyclobutene **73** in only 32 % yield (Table 6, entry 10).

2.4.5 Attempted Cycloisomerization of carbon-tethered enynes

Cycloisomerization of all-carbon 1,6-enynes leading to cyclobutene formation is well documented (§ 1.2). We wished to examine the behavior of such enynes under our conditions (Table 7). It was reported that enyne **74** containing a malonate carbon in the tether and aryl group at terminus alkyne carbon could produce cyclobutene **75** using platinum chloride (10 mol%) in toluene under CO atmosphere.⁸ When the reaction was performed in our conditions, enyne **74** was recovered unchanged (Table 7, entry 1).²⁰ This result showed a sharp contrast in the outcome of the reaction between reactions conducted under CO and ours performed in DMA.

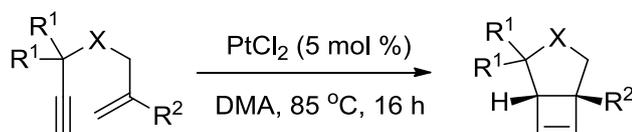
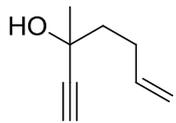
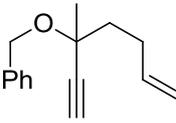


Table 7. Cycloisomerization of Carbon-Tethered Enynes^a

Entry	Substrate	Product(s)	Yield (%)
1	<p style="text-align: center;">74</p>	<p style="text-align: center;">75</p>	-
2	<p style="text-align: center;">76</p>	<p style="text-align: center;">77</p>	-

²⁰ A similar observation was already reported in entry 16 of Table 4.

3	 78	Complex mixture
4	 79	Complex mixture

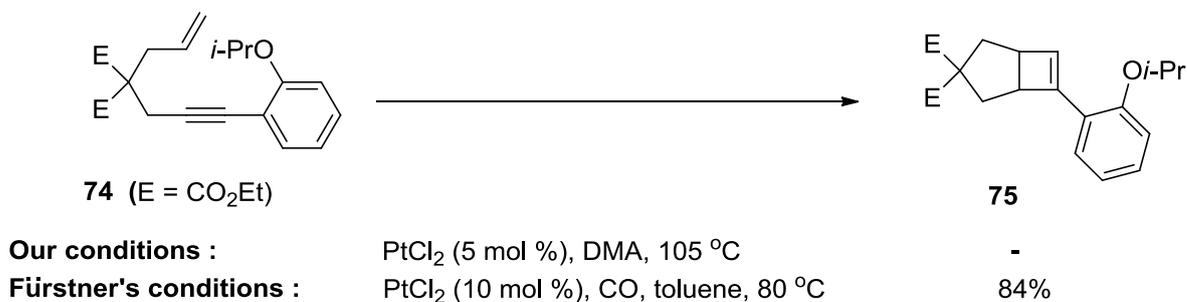
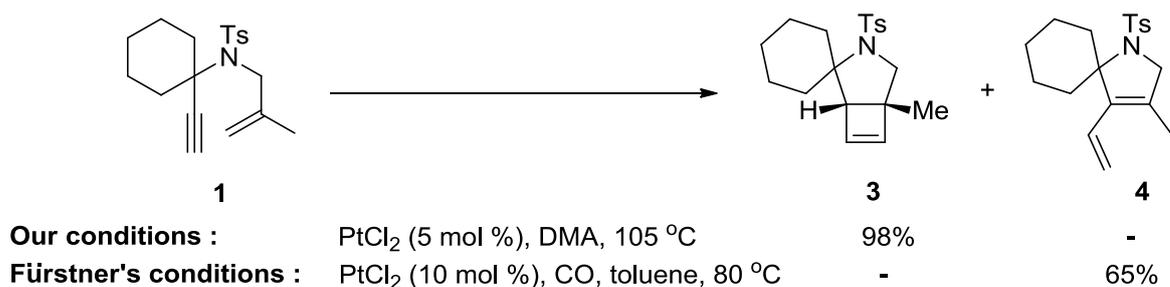
^a **Reaction conditions:** Enyne (0.2 mmol), PtCl₂ (0.01 mmol, 5 mol %), allyltrimethylsilane (3 equiv), DMA (1 mL), C = 0.2 M, under argon at 85°C for 16 h.

We were disappointed that enynes **76**, **78** and **79**, containing the structural patterns characteristic for the reaction such as the terminal alkyne and bisubstitution at the propargyl position did not form the expected cyclobutenes. Enyne **76** was recovered unchanged (Table 7, entry 2) while enynes **78** and **79** containing a tertiary alcohol and ether group respectively led to complex mixtures of products (Table 7, entries 3-4).

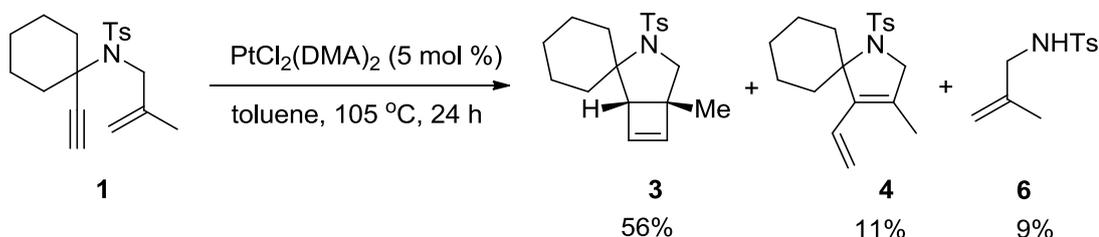
2.5 Studies on the reaction mechanism

2.5.1 Insights on the role of DMA as a ligand

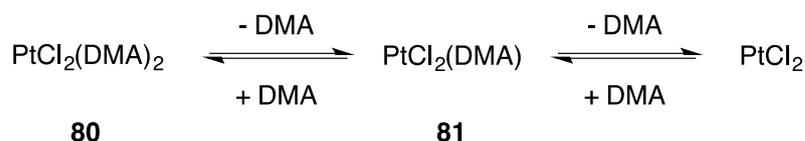
Besides the coordination site of amide (oxygen coordination) compared to CO (carbon coordination) towards platinum, the distinct role of amide was established with reactions of enynes **1** and **74**. The reaction of **1** carried out with PtCl₂ under a carbon monoxide atmosphere only led to diene **4** (65 %) (Table 1, entry 4), while cyclobutene **3** was obtained in 98 % yield in DMA as the solvent. These divergent behaviors were also observed with reactions of all-carbon enyne **74**. Treatment of **74** with PtCl₂ in toluene under CO atmosphere gave cyclobutene **75** in 84 % yield.⁸ When the reaction was performed in DMA, the enyne **74** was recovered unchanged. To date, the exact role of amide ligands favoring the formation of cyclobutenes remains to be established.



As DMA is regarded as ligand (Table 3, entry 6), the well defined complex PtCl₂(DMA)₂²¹ **80** was prepared and used as catalyst (5 mol%) in toluene at 105 °C. Under these conditions, enyne **1** was converted to cyclobutene **3** in 56 % yield along with diene **4** (11 %) and *N*-prenyl-*p*-tolylsulfonamide **6** (9 %). This result confirmed the role of DMA as a weakly coordinating solvent.

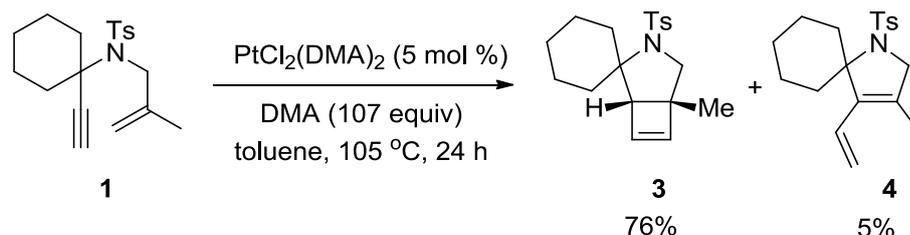


It had been shown that PtCl₂(DMA)₂ is soluble in CH₂Cl₂ at room temperature and readily releases DMA.¹⁴ Considering the weak coordinating properties of DMA, we assumed a similar behavior of this complex in toluene. Thus, PtCl₂(DMA) **81**, in equilibrium with PtCl₂(DMA)₂, has a free coordination site, which renders it able to coordinate the alkyne and

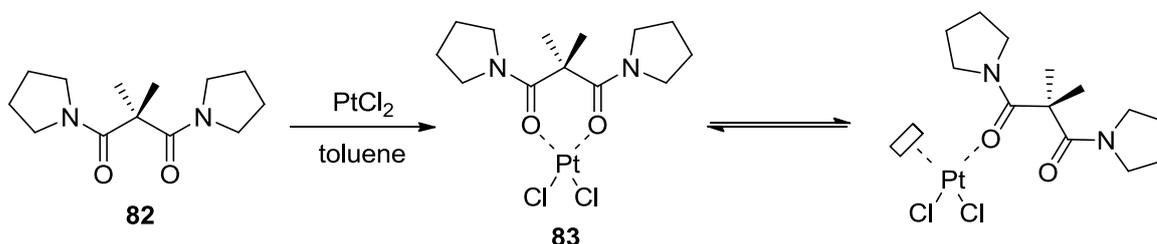


²¹ Gloria, J. M.; Susz, B. P. *Helv. Chim. Acta.* **1971**, *54*, 2251-2256.

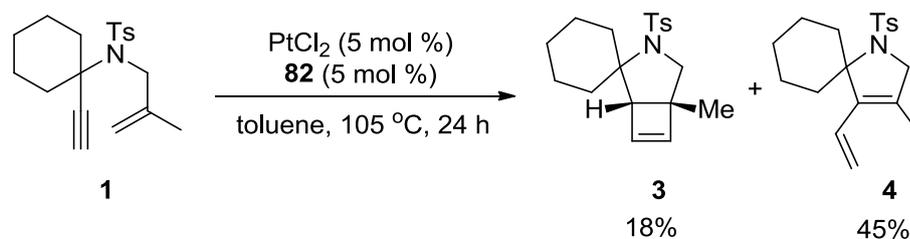
to trigger the [2 + 2] cycloaddition. Furthermore, $\text{PtCl}_2(\text{DMA})$ **81** dissociates from DMA to form PtCl_2 which is believed responsible for the formation of side products **4** and **6**. To maintain a "useful" concentration of the putative $\text{PtCl}_2(\text{DMA})$ **81**, the reaction was carried out with both **80** and additional DMA (107 equiv with respect to Pt). These conditions suppressed the C-N bond cleavage path and afforded cyclobutene **3** in increased yield (76 %) along with diene **4** in only 5 % yield.



In order to improve the selectivity, we looked briefly for other amide ligands. On the basis of the weak coordination properties of the amides, we selected the symmetrical bisamide **82** as a potential bidentate ligand.



This amide was readily prepared in two steps from 2,2-dimethylmalonic acid. We reasoned that the bidentate **82** could be relatively more bounded to Pt compared to DMA and might undergo partial dissociation from the platinum and so release one coordination site.



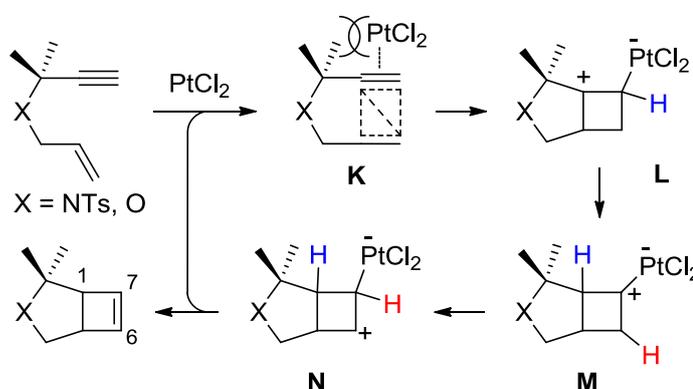
To our disappointment, subjection of **1** to PtCl_2 /**82** as a catalyst system in toluene at 105 °C

for 24 h afforded the cyclobutene **3** in only 18 % yield along with diene **4** (45 %).

We believe that a more deep thorough research is necessary for the design of new amide ligands (monodentate or hybriide) useful in platinum chemistry with future prospects in enantioselective catalysis.

2.5.2 Proposal of mechanism for the formation of cyclobutene

Considering the peculiar structural patterns that favor the formal [2+2] cycloaddition, a mechanism based on cationic intermediates can be proposed (Scheme 2). Activation of the alkyne by platinum(II) initiates cyclization of the enyne through **K** to generate a cyclobutyl cation **L**. Because of non-bonded interactions with substituent(s) at propargylic carbon atom, the platinum cannot be located at the rings junction.^{8, 22} Moreover, the resulting neopentyl-like cation is highly stabilized. Two consecutive [1,2]-H shifts through intermediates **M** and **N** followed by protodemetalation complete the formation of cyclobutene. This mechanism could explain the inertness of aryl-substituted enynes **34** and **74** and is reminiscent of the one proposed for the isomerization of methylenecyclopropanes to cyclobutenes.^{11c}

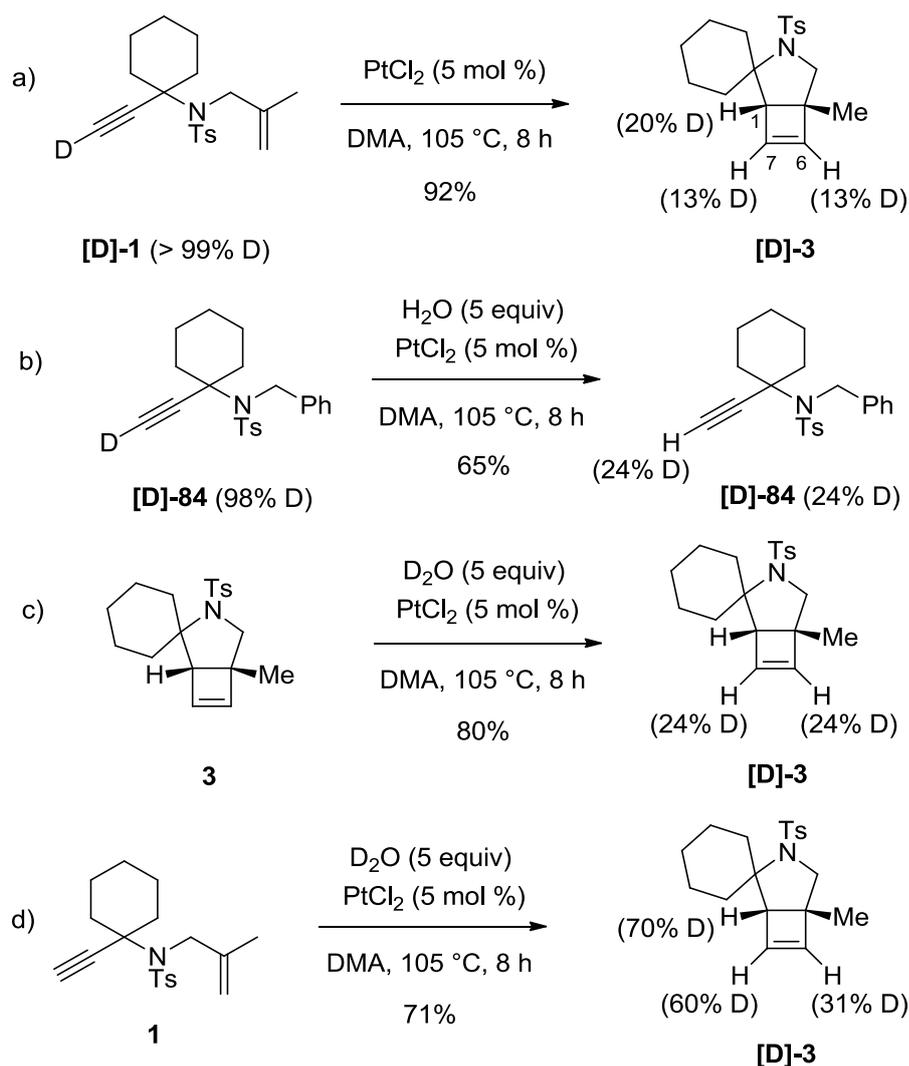


Scheme 2. Proposed reaction mechanism.

2.5.3 Deuterium labeling experiments

This mechanism proposal was probed with deuterium labeling experiments. Cyclization of [**D**]-**1** (> 99 % D) gave cyclobutene [**D**]-**3** with deuterium incorporation at C-1, C-6 and C-7 (Scheme 3, eq. a).

²² For a similar proposal in cycloisomerizations of a special class of enynes, namely eneynamides, see: Marion, F.; Coulomb, J.; Courillon, C.; Fensterbank, L.; Malacria, M. *Org. Lett.* **2004**, *6*, 1509-1511.

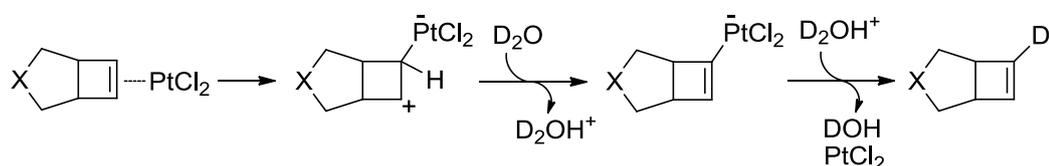


Scheme 3. Deuterium labeling experiments

The depletion of deuterium in a significant extent was attributed to the presence of residual water. To this end, deuterium to proton exchange on terminal alkyne **[D]-84** (98 % D) in the presence of H₂O was established (Scheme 3, eq. b). This should occur presumably prior to the cyclization. The incorporation of deuterium at sp² carbon atoms of **[D]-3** is not so obvious.²³ Heating cyclobutene **3** with D₂O in the presence of PtCl₂ resulted in proton to deuterium exchange only at C-6 and C-7 atoms (Scheme 3, eq. c). Finally, consistent with the above experiments, cyclization of **1a** in the presence of D₂O formed **[D]-3** that exhibits highest level of deuterium (70 %) at C-1 (Scheme 3, eq. d). These experiments are in agreement with the occurrence of the "nonclassical" cation intermediate **A** and showed that

²³ Pt-catalyzed H to D exchange at sp² (aromatics) and/or sp³ carbon atoms was reported. Homogeneous conditions: a) Kramer, P.A.; Masters, C. *J. Chem. Soc., Dalton Trans.* **1975**, 849-852. Hydrothermal conditions: b) Yamamoto, M.; Yokota, Y.; Oshima, K.; Matsubara, S. *Chem. Commun.* **2004**, 1714-1715.

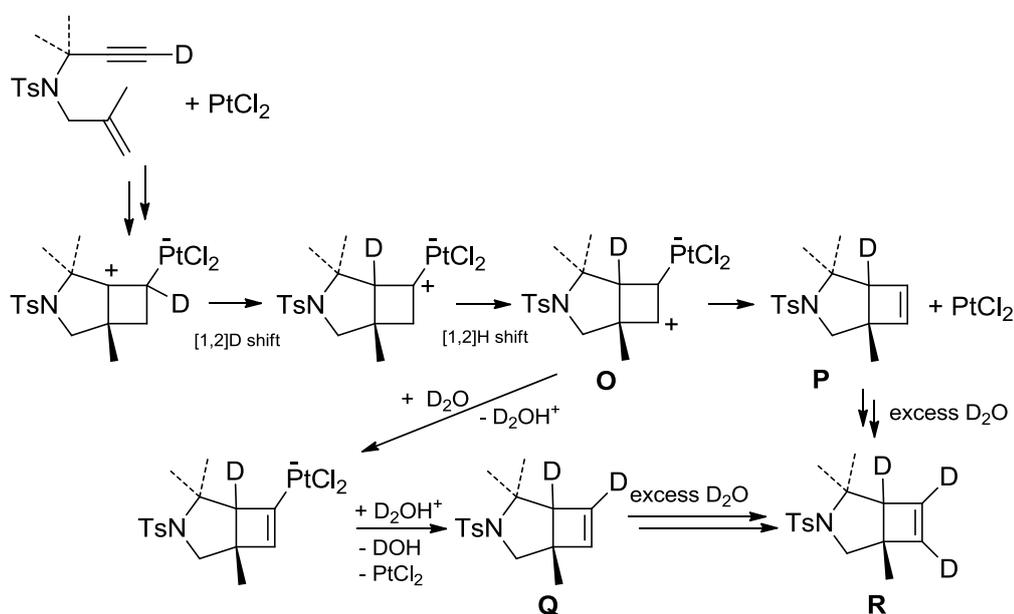
deuterium incorporation at sp^2 carbon atoms is in some extent independent of the cyclization reaction. A rationale for hydrogen to deuterium exchange on sp^2 carbon atoms based on intermediate **N** (Scheme 2) is depicted in Scheme 4.



Scheme 4. Proposed mechanism for H to D exchange at sp^2 carbon atoms.

Addition of $PtCl_2$ across the cyclobutene double bond generates a cyclobutyl cation similar to **N** (Scheme 2), which eliminates a proton to form a cyclobutenylplatinum species. Protodemetalation releases the cyclobutene incorporating the deuterium atom at the sp^2 carbon atom.

We found that deuterium incorporation at each sp^2 carbon atoms is equally distributed in reactions of equations (a) and (c) within Scheme 3, this is not the case of reaction depicted in equation (d). A reasonable explanation, consistent with the proposed mechanisms, is as follows (Scheme 5).



Scheme 5. Deuterium distribution on the cyclobutene.

Considering the H to D exchange at the alkyne and according to the mechanisms depicted in Schemes 2 and 3, intermediate **O** would be formed to give the bicyclic cyclobutene **P** with

D-incorporation at the ring junction. Intermediate **O** can also lead to the final product **Q** incorporating deuterium both at the ring junction and adjacent sp^2 carbon atom (see Scheme 3). In the presence of excess D_2O , the primary labeled compounds **P** and **Q** can further evolve into the trideuterated compound **R**. It was shown that H to deuterium exchange on sp^2 carbon atoms is observed nearly with the same extent. Since **Q** is formed before **R**, maximal deuterium concentration in **R** is observed at rings junction and sp^2 carbon adjacent to the tertiary carbon of the ring junction.

Conclusion

In summary, we have developed a ready access to 3-azabicyclo[3.2.0]hept-6-enes and their oxygen counterparts through the cycloisomerization of heteroatom-tethered 1,6-enynes catalyzed with platinum(II) dichloride. This study show that hyperconjugation through alkyl substituent(s) at the propargyl position in conjunction with the use of DMA as a weakly coordinating solvent are the key elements favoring the formation of cyclobutenes. Importantly, terminal alkynes, usually unfavorable structural features to cyclobutene formation, are well tolerated. The beneficial effect of amide solvent through its coordination properties was still observed when using it in catalytic amounts and the well-defined $PtCl_2(DMA)_2$ was identified as a precatalyst in these cycloisomerizations. In view of the limited number of hemilabile ligands employed to activate alkynes with platinum catalysts,^{11,24} amides are added to the list to improve and/or change selectivity of reactions.

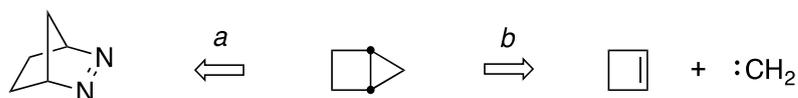
²⁴ β -pinene: a) Nakamura, I.; Bajracharya, G. B.; H. Wu, K. Oishi, Y. Mizushima, I. D. Gridnev, Y. Yamamoto, *J. Am. Chem. Soc.* **2004**, *126*, 15423-15430. cod: b) Nakamura, I.; Sato, T.; Yamamoto, Y. *Angew. Chem. Int. Ed.* **2006**, *45*, 4473-4475.

Chapter III

A New Approach to the Bicyclo[2.1.0]pentane Framework through the Ruthenium-Catalyzed Cyclopropanation of Cyclobutenes with Tertiary Propargylic Carboxylates

3.1 The bicyclo[2.1.0]pentane framework: synthetic methods and synthetic utility

The bicyclo[2.1.0]pentane, as its homologue bicyclo[1.1.0]butane, is among the most strained bicyclic alkanes. Due to their stressed structure, the sigma C-C bond shared by the fused cyclobutane and cyclopropane has a relatively weak bond energy and is prone to undergo cleavage easily to alleviate the ring strain. The calculated strain enthalpy of 56.3 kcal.mol⁻¹ arises from the sum of heat of formation (experimentally found) of 37.7 kcal.mol⁻¹ and the strain contribution (estimated with group additivity) of 18.6 kcal.mol⁻¹. The π -like character of the shared C-C bond confers typical reactivity such as electrophilic activation, cycloaddition, oxidation and even transition-metal transformations.¹ The term "housane" was coined by Paul Schleyer for the bicyclo[2.1.0]pentane framework.² There are two main basic strategies toward the synthesis of housanes (Scheme 1). The first one concerns (a) the photochemical or thermal extrusion of dinitrogen from 2,3-diazabicyclo[2.2.1]hept-2-ene and the second one (b) refers to carbene addition to cyclobutene.



Scheme 1. Main retrosynthetic strategies to the "housane" framework

3.1.1. Syntheses from 2,3-diazabicyclo[2.2.1]hept-2-enes

The synthesis of bicyclo[2.1.0]pentane was first reported by Criegge and Rimmelin³ and a detailed reliable procedure to this framework and its alkyl derivatives was described by Gassman and Mansfield in *Organic Syntheses* (Scheme 2).⁴ It started with the Diels-Alder adduct between cyclopentadiene and diethyl azodicarboxylate which upon reduction of double bond and saponification afforded 2,3-diazabicyclo[2.2.1]heptane (non isolated). On treatment of the dialkylhydrazine with copper(II) chloride, a redox reaction takes place to give the azobicyclic compound complexed with copper(I) chloride. Subsequent treatment with sodium hydroxide released 2,3-diazabicyclo [2.2.1]hept-2-ene which decomposed

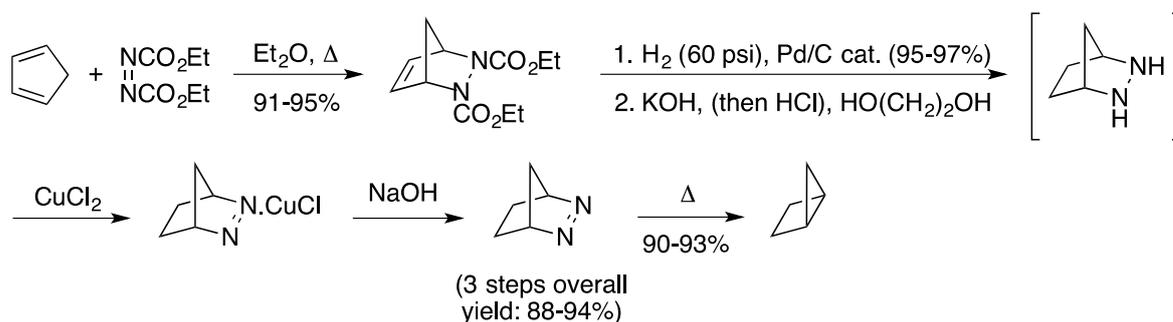
¹ a) Carpenter, B. K. In *The Chemistry of Cyclobutanes*, Rappoport, Z.; Liebman, J. F. Eds. Wiley: Chichester, 2005, Vol.1, pp. 923-954. b) Carpenter, B. K. *Org. Biomol. Chem.* **2004**, 2, 103-109.

² Engler, E. M. ; Andose, J. D. ; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1973**, 95, 8005-8025.

³ Criegge, R.; Rimmelin, A. *Chem. Ber.* **1957**, 90, 414-417.

⁴ Gassman, P. G. ; Mansfield, K. T. *Organic Syntheses, Coll. Vol. 5, p.96 (1973); Vol. 49, p.1 (1969).*

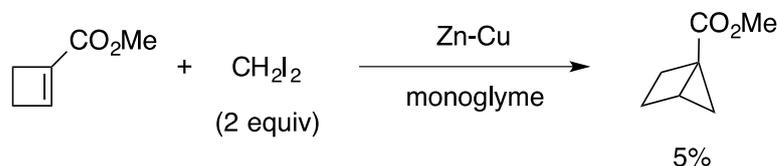
thermally with extrusion of dinitrogen to form bicyclo[2.1.0]pentane.



Scheme 2. Synthesis of bicyclo[2.1.0]pentane by Gassman and Mansfield

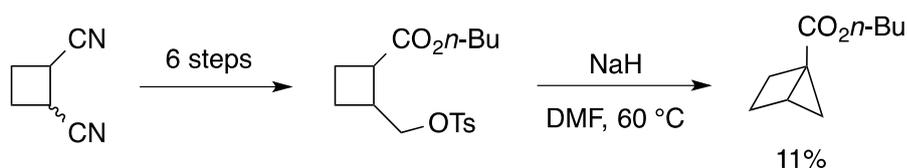
3.1.2. Syntheses from cyclobutenes and carbene precursors

The cyclopropanation of cyclobutenes through the Simmons-Smith reaction or using diazoalkanes precursors have also been proposed as alternative routes to bicyclo[2.1.0]pentanes. These methods are however less common since cyclobutenes are not easily prepared. The first examples reported for the Simmons-Smith cyclopropanation of cyclobutenes were achieved in yields not exceeding 17% (Scheme 3).⁵



Scheme 3. Simmons-Smith cyclopropanation of cyclobutene

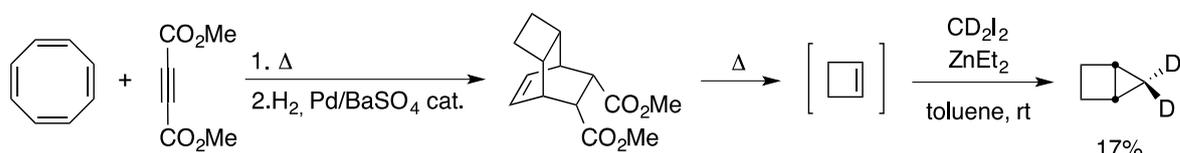
Due to the low yield observed, an alternate approach involving a tedious, multistep sequence and an intramolecular alkylation for the construction of the cyclopropane ring was explored with also low success (Scheme 4).



Scheme 4. Intramolecular alkylation route to bicyclo[2.1.0]pentanes

⁵ Gassman, P. G.; Mansfield, K. T. *J. Org. Chem.* **1967**, *32*, 915-920.

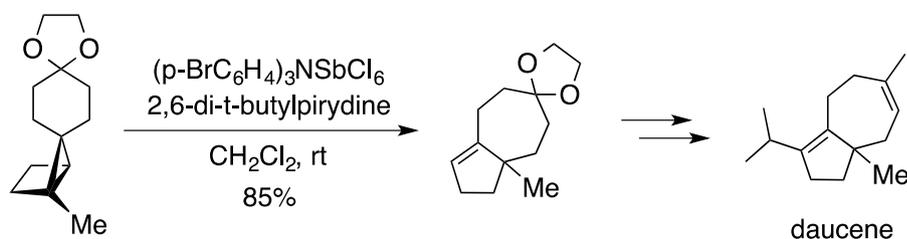
Noyori and co-workers⁶ prepared 5,5-dideuteriobicyclo[2.1.0]pentane for mechanism studies from the Diels-Alder adduct of cyclooctatetraene and dimethyl maleate through the Simmons-Smith cyclopropanation of cyclobutene generated through a retro Diels-Alder reaction (Scheme 5).



Scheme 5. Simmons-Smith reaction of cyclobutene

3.1.3. Synthetic utility of bicyclic [2.1.0] structures

Based on the method reported by Gassman and Mansfield, Little's group prepared a number of diversely functionalized housanes as synthetically useful intermediates in synthesis of natural products featuring the bicyclic [5.3.0] structure such as Daucene (Scheme 6).⁷ The key step is based on the rearrangement of housane cation radical generated with tris(4-bromophenyl)aminium hexachloroantimonate to cyclopentene and concomitant one carbon atom ring expansion of the spirocycle.



Scheme 6. Housane precursor in synthesis of (±)-Daucene

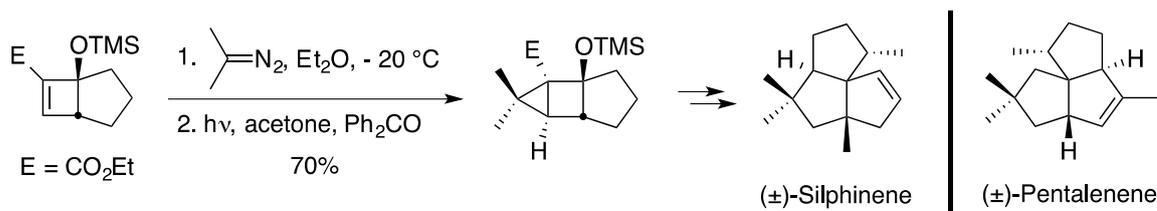
In the early nineties, the Franck-Neumann's group reported the [3+2] cycloaddition of diazoalkanes to functionalized cyclobutenes to form bicyclic Δ^1 -pyrazolines which upon photolysis released dinitrogen to give the bicyclic [2.1.0] structure which was used for the synthesis of triquinanes such as Silphinene⁸ and Pentalenene⁹ (Scheme 7).

⁶ Takaya, H.; Suzuki, T.; Kumagai, Y.; Yamakawa, M.; Noyori, R. *J. Org. Chem.* **1981**, *46*, 2846-2854.

⁷ Park, Y. S.; Little, R. D. *J. Org. Chem.* **2008**, *73*, 6807-6815.

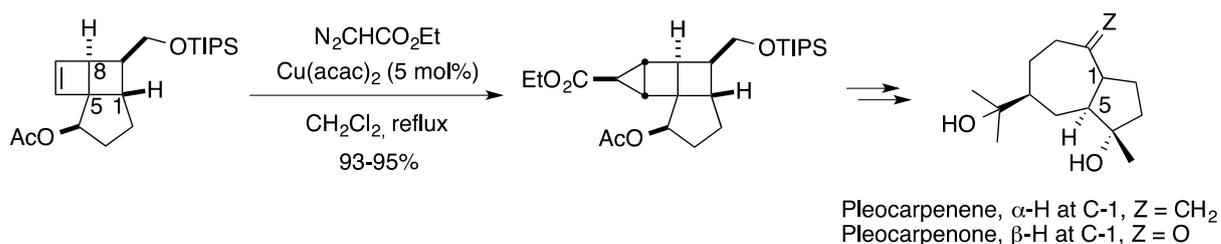
⁸ Franck-Neumann, M.; Miesch, M.; Gross, L. *Tetrahedron Lett.* **1991**, *32*, 2135-2136.

⁹ Franck-Neumann, M.; Miesch, M.; Gross, L. *Tetrahedron Lett.* **1992**, *33*, 3879-3882.



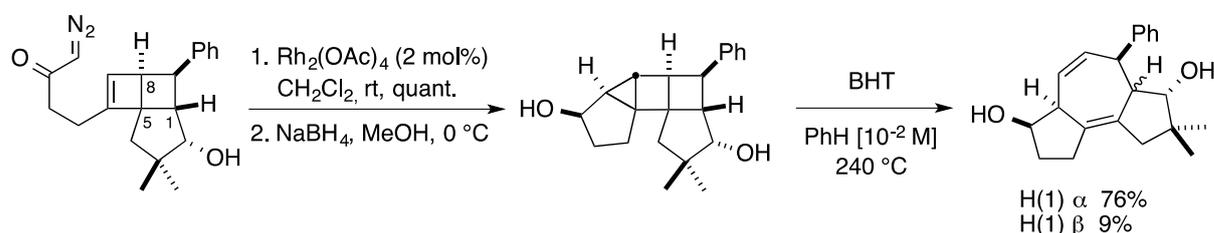
Scheme 7. Bicyclic [2.1.0] structures for the synthesis of triquinanes

In 2001, Snapper and Deak developed a modified Simmons-Smith protocol for the cyclopropanation of functionalized cyclobutene embodied in a tricyclic structure (Scheme 8).¹⁰ The cyclopropane adduct was shown to be a synthon for 5-7 ring systems via thermolysis of the strained ring systems. This provided access to the carbon framework of the guiane natural product family in two steps. Based on this strategy, the synthesis of a number of natural products such as Pleocarpenene and Pleocarpenone¹¹ was reported by the Snapper's group.



Scheme 8. Cyclopropanation of cyclobutene towards natural product syntheses

An intramolecular variant was also reported to access readily 5-7-5 and 5-7-6 fused tricyclic ring systems found in numerous natural products (Scheme 9).¹²



Scheme 9. Intramolecular cyclopropanation of cyclobutene for the synthesis of tricycles

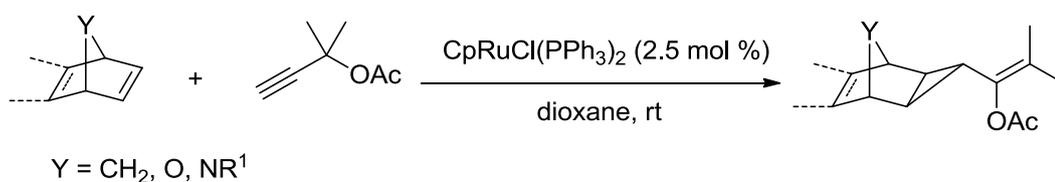
¹⁰ Deak, H. L.; Stokes, S. S.; Snapper, M. L. *J. Am. Chem. Soc.* **2001**, *123*, 5152-5153.

¹¹ Williams, M. J.; Deak, H. L.; Snapper, M. L. *J. Am. Chem. Soc.* **2007**, *129*, 486-487.

¹² He, J.; Snapper, M. L. *Tetrahedron* **2013**, *69*, 7831-7839.

3.2 Presentation and purpose of the project

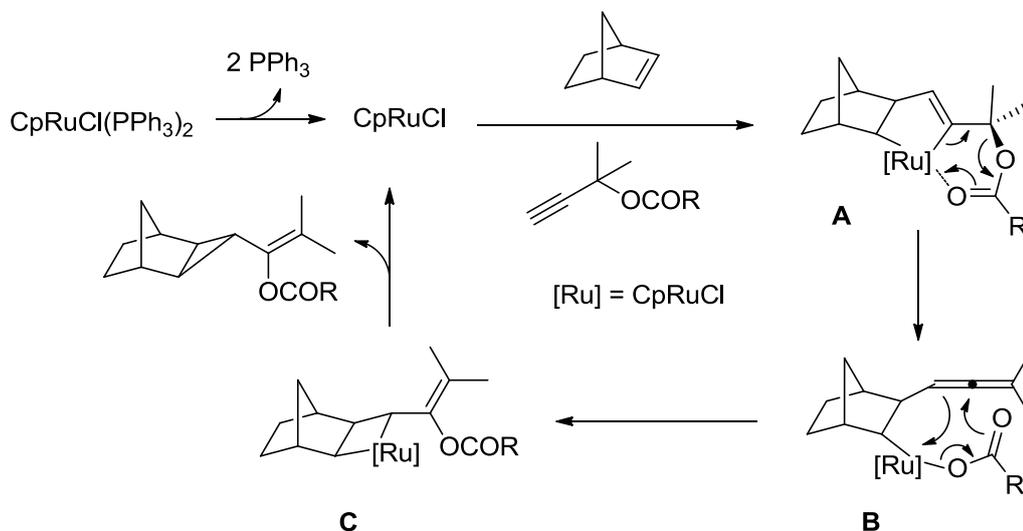
The opportunity to develop a synthetic approach to bicyclic [2.1.0] structures through the “2C+1C” methodology was given with the availability of cyclobutenes from the cycloisomerization of 1,6-enynes disclosed in § 2. This approach usually depends on the use of carbenes or carbene precursors as the “1C” synthon. Methods that avoid the use of unsafe diazo compounds are highly desirable especially for scale-up preparations. To this end, our group has developed the CpRuCl(PPh₃)₂ catalyzed cyclopropanation of bridgehead bicyclic alkenes with propargylic carboxylates affording functionalized cyclopropane-fused bicyclo[2.2.1]heptanes as single stereoisomers in good to excellent yields. Additionally, the reaction was broadened in scope and various functional groups such as ethers, esters, sulfones, anhydrides, nitriles, alcohols, ketones, imides and carbamates were well tolerated.¹³



Studies of the reaction mechanism showed that the cyclopropanation do not involve ruthenacarbene species in contrast to Uemura's ruthenium vinylcarbenoid pathway.¹⁴ The proposed mechanism involve a double carboxylate migration (Scheme 10). The coordinatively unsaturated CpRuCl species was generated *in situ* from CpRuCl(PPh₃)₂. Upon coordination with the bicyclic alkene and propargylic carboxylate and subsequent oxidative coupling the ruthenacyclopentene **A** can be formed. A carbon to ruthenium 1,2-migration of the carboxylate group generates the η^2 -allene-ruthenium intermediate **B**. An intramolecular addition of Ru-OCOR across the internal double bond give the α -vinylruthenacyclobutane **C** which upon reductive elimination releases the bicyclo[2.1.0]pentane and regenerates the CpRuCl species.¹³

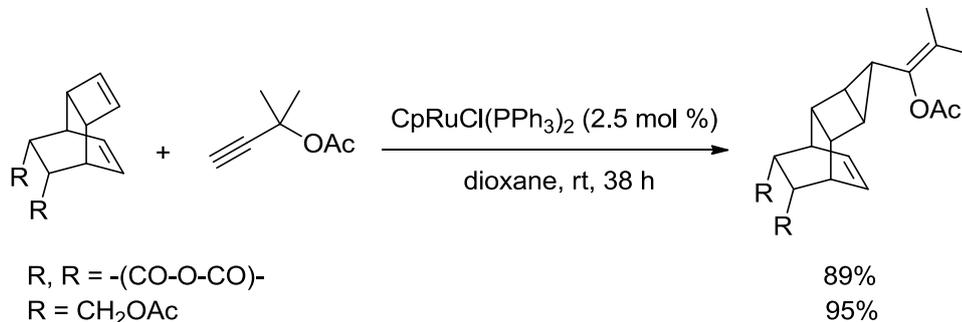
¹³ Tenaglia, A.; Marc, S. *J. Org. Chem.* **2006**, *71*, 3569-3575.

¹⁴ a) Miki, K.; Ohe, K.; Uemura, S. *Tetrahedron Lett.* **2003**, *44*, 2019-2022. b) Miki, K.; Ohe, K.; Uemura, S. *J. Org. Chem.* **2003**, *68*, 8505-8513.



Scheme 10. Mechanism of the Ru-catalyzed cyclopropanation of bicyclic alkenes

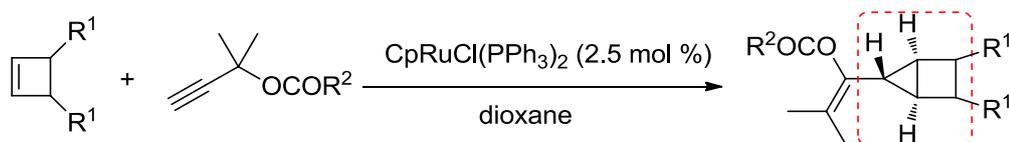
It was also briefly shown that the reaction could be applied to cyclobutenes. Thus, subjecting of bicyclo[4.2.2.0^{2,5}]deca-3,7-dienes, readily available from cycloaddition of cyclooctatetraene and maleic anhydride, to the cyclopropanation conditions afforded the expected adducts as single diastereomers.



The high chemo- and stereoselectivity exhibited in these reactions arises from the rigid structure of the substrates and the bathtub-shaped conformation of the diene responsible for the stereofacial discrimination. The reaction takes place on the most strained double bond and presumably the presence of substituents on the bicyclo[2.2.2]octene substructure prevent attack on the cyclohexene double bond.¹³

This approach to the bicyclo[2.1.0] framework was promising but the study was not further developed due to the lack of general methods to access the cyclobutenes and of the lability of these compounds. We intended to develop this reaction and the opportunity to reach this goal was offered to us with the bicyclic cyclobutenes prepared through the cycloisomerization of

heteroatom-tethered 1,6-enynes catalyzed with platinum dichloride (see § 2).

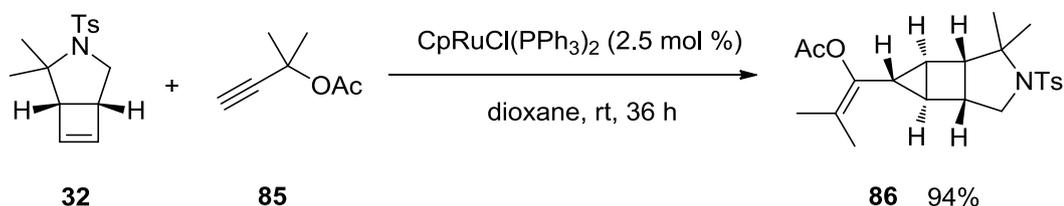


We thought that the optimized standard conditions (2.5 mol % $\text{CpRuCl}(\text{PPh}_3)_2$, dioxane, room temperature) could be suited to our present investigations. On the other hand, we wished to expand the reaction to structurally simpler alkenes and study the stereoselectivity issues with diversely substituted cyclobutenes. In this chapter, we disclose our investigations answering these issues.

3.2 Preliminary studies

3.2.1 Cyclopropanation of model substrate **32**

We initiated our studies with cyclobutene **32**. The reaction of an equimolar ratio of **32** and 2-methylbut-3-yn-2-yl acetate **85** in the presence of catalytic amount of $\text{CpRuCl}(\text{PPh}_3)_2$ proceeded smoothly at room temperature, and to our delight, the tricyclic compound **86**, featuring the bicyclo[2.1.0]pentane framework, was obtained as a single diastereomer in 94% (isolated) yield. No other byproducts were formed as judged by TLC and ^1H NMR of the crude reaction. The purification of **86** consisted in evaporation of the reaction mixture and filtration over a short pad of silicagel.

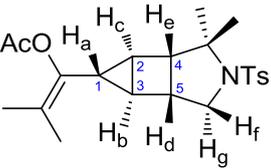


3.2.2 Determination of the structure of tricyclic compound **86**

3.2.2.1 ^1H NMR and ^{13}C NMR of **86**

The assignments of ^1H NMR and ^{13}C NMR signals of bicyclo[2.1.0]pentanes **86** have been

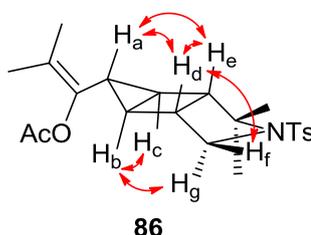
established through the DEPT, COSY, NOESY, HMQC and HMBC experiments. The ^1H NMR of **86** revealed distinct signals for all the protons of the tricycle. The cyclopropane protons H_a , H_b and H_c were observed as a broad singlet at δ 1.83 and multiplets at δ 1.52 and 1.68 respectively. The protons of ring junction H_d and H_e were observed as doublet of doublets ($J = 1.8, 4.4, 6.1$ Hz) at δ 2.33 and as doublet of doublets ($J = 1.6, 4.3$ Hz) at δ 2.04 respectively. The methylene protons H_f and H_g were observed as a doublet of doublets ($J = 6.3, 10.7$ Hz) at δ 3.44 and as a doublet ($J = 10.7$ Hz) at δ 3.65 respectively. As for the proton NMR, the ^{13}C NMR exhibits 5 lines for the carbons of the bicyclo[2.1.0]pentane substructure of **86** at δ 26.3 (C-1), 21.2 (C-2), 23.7 (C-3), 55.9 (C-4), 38.1 (C-5).

	^1H NMR	^{13}C NMR		
	H_a	1.83 br s	C_1	26.3
	H_b	1.52 m	C_2	21.2
	H_c	1.68 m	C_3	23.7
	H_d	2.33 ddd ($J = 1.8, 4.4, 6.1$ Hz)	C_4	55.9
	H_e	2.04 dd ($J = 1.6, 4.3$ Hz)	C_5	38.1
	H_f	3.44 dd ($J = 6.3, 10.7$ Hz)		
	H_g	3.65 d ($J = 10.7$ Hz)		

Scheme 11. Main assignments by NMR of **86**

3.2.2.2 NOESY of **86**

The NOESY experiments revealed correlations between the cyclopropane proton H_a , and cyclobutane protons H_d and H_e . In turn, the cyclobutane proton H_d is additionally correlated to the proton H_f of the methylene α to NTs.



Observed NOESY correlations of **86**

Moreover, the correlations between the cyclobutane protons H_b and H_c as well as between the same proton H_b and one proton H_g of the methylene α to NTs established the assignment

of H_b, H_c, H_f and H_g. The absence of correlations between the protons H_a and H_b is in agreement with the *trans* disposition of the substituents on the cyclopropane. Similarly, the missing correlations between the protons H_b and H_d determined the *trans* disposition of the substituents on the cyclobutane.

3.3 Scope of the Ruthenium-Catalyzed Cyclopropanation of Cyclobutenes with Tertiary Propargylic Carboxylates

3.3.1 Ruthenium-Catalyzed Cyclopropanation of Cyclobutenes

After the validation of our approach to the bicyclo[2.1.0] structure, we attempted to expand this CpRuCl(PPh₃)₂-catalyzed cyclopropanation reaction to other cyclobutenes, and to test new functionalities tolerance owing to the various cyclobutenes in our hands. The results are summarized in Table 1.

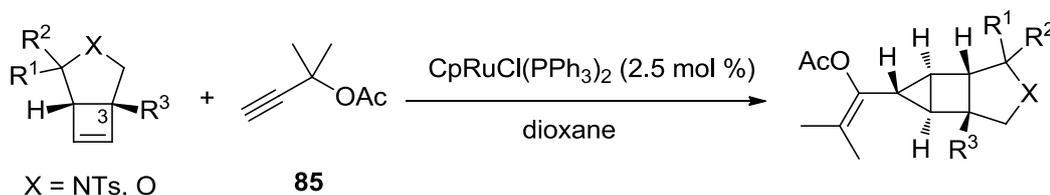
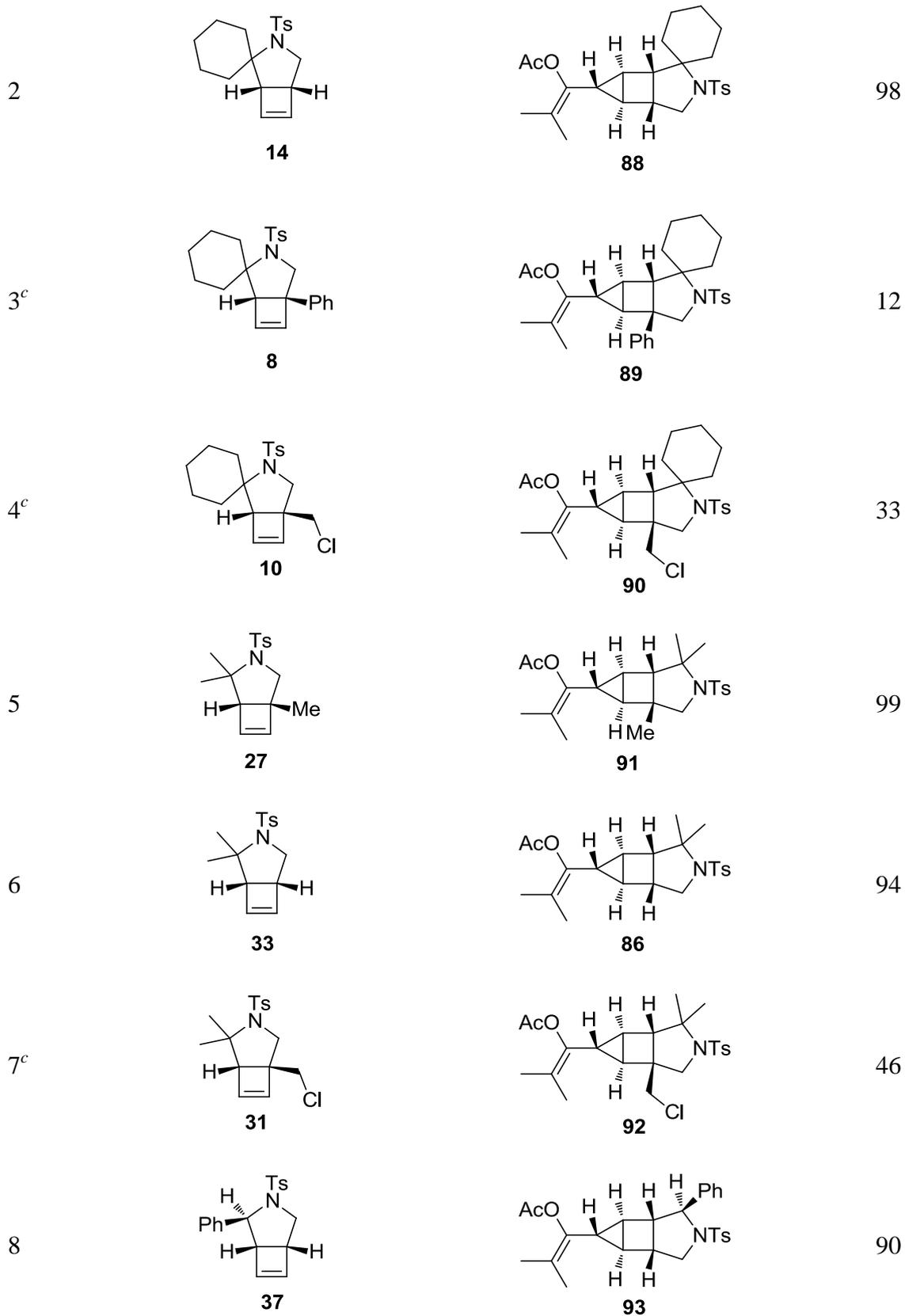
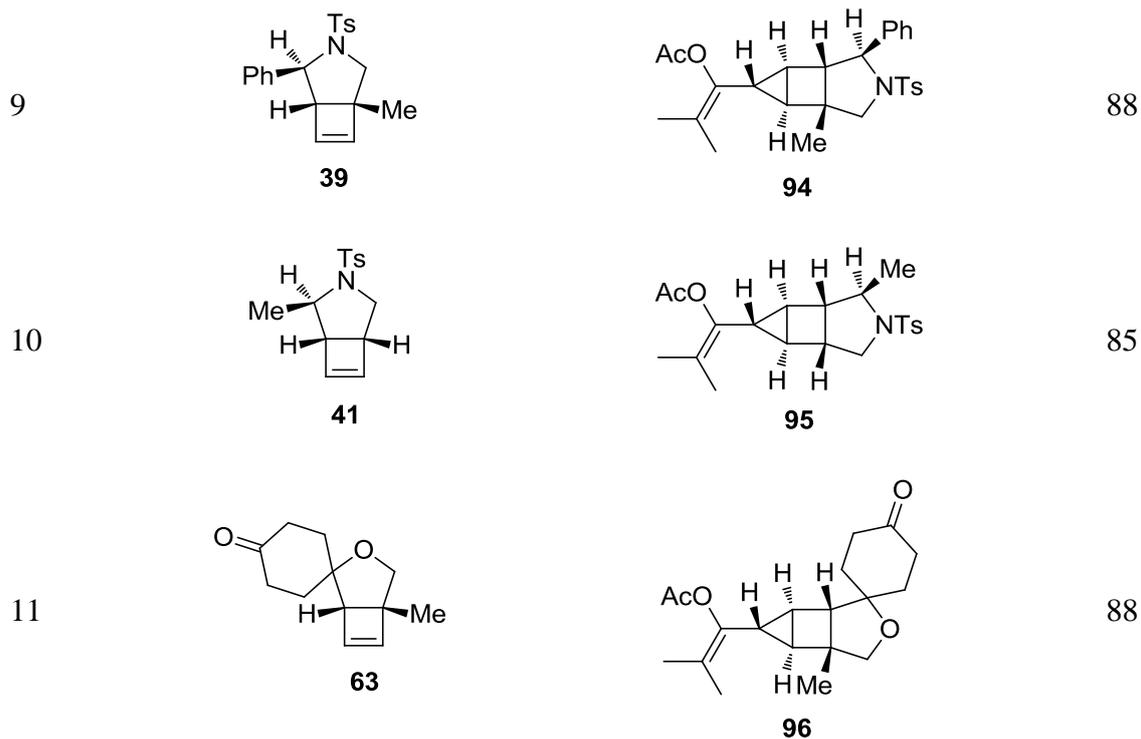


Table 1. CpRuCl(PPh₃)₂-catalyzed cyclopropanation of cyclobutenes with propargylic acetate **85**^a

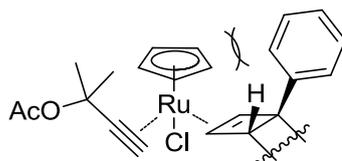
Entry	Substrate	Product	Yield (%) ^b
1	<p style="text-align: center;">3</p>	<p style="text-align: center;">87</p>	98





^a **Reaction conditions:** Cyclobutene (0.20 mmol), **85** (0.20 mmol), CpRuCl(PPh₃)₂ (0.005 mmol, 2.5 mol %), dioxane (2 mL), under argon, room temperature, 36 h. ^b Isolated yield. ^c Reaction carried out at 60 °C for 24 h.

Most of the cyclopropanation of cyclobutenes occurred smoothly at room temperature to afford the expected bicyclo[2.1.0]pentanes as single stereoisomers with high yields. The only byproduct formed is the 3-methylbuta-1,2-dien-1-yl acetate resulting from the [1,3]-acetoxy migration within acetate **85**. The influence of the substituent (at C-3) of the ring junctions on the cyclopropanation reaction was examined with various cyclobutenes bearing cyclohexyl group (Table 1, entries 1-4). It turns out that the cyclobutenes with a methyl group or a hydrogen atom at C-3, **3** and **14** respectively, were converted to the expected cyclopropanes in higher yields (Table 1, entries 1-2) compared to those having a phenyl or chloromethyl group at C-3, namely **8** and **10**, even if the reaction was carried out at 60 °C (Table 1, entries 3-4). This may be due to severe non-bonded interactions between the angular substituent (Ph, CH₂Cl) and the ligands of the metal (Cl, Cp) in the putative (alkyne)(alkene)CpRuCl intermediate prior to the oxidative cyclometalation forming the ruthenacyclopentene (Scheme 12). Thus, coordination of the double bond to the metal is accommodated with the presence of methyl substituent and prevented when the substituent become bulkier.



Scheme 12. Non-bonded interactions within intermediate complex prior to cyclometalation

This trend was also observed within the reactions of cyclobutenes **27**, **33**, and **31**, having a gem dimethyl substitution at the propargylic position (Table 1, entries 5-7). The bicyclo[2.1.0]pentanes **91** and **86** were obtained in excellent 99% and 94% yield compared to bicyclo[2.1.0]pentanes **92** formed in only 46% yield when the reaction is performed at 60 °C. Other cyclobutenes **37**, **39** and **41** with phenyl or methyl substituent were also easily subjected to the catalyzed cyclopropanation conditions to give the expected bicyclo[2.1.0]pentanes **93**, **94** and **95** in 85-90% range yields (Table 1, entries 8-10). The reactivity of oxygen-containing cyclobutene **63** was similar to its nitrogen counterparts to give bicyclo[2.1.0]pentane **96** in 88% yield (Table 1, entry 11). What is worthy of note, however, is that electrophilic functions such as halides or ketones are well tolerated under the catalytic conditions.

3.3.2 Ruthenium-Catalyzed cyclopropanation of cyclobutene **14** with various propargylic carboxylates

In order to evaluate the influence of the substituents within the propargyl carboxylates on the outcome of the reaction, the cyclopropanation of cyclobutene **14** with various tertiary propargylic carboxylates was studied under the usual conditions (Table 2). The cyclopropanation of cyclobutene **14** give the expected adducts in excellent yields (93-97%) with the tertiary propargyl carboxylates **97**, **99** and **101** (Table 2, entries 1-3). It should be noticed that electron-rich or electron-poor carboxylates, **99** and **101** respectively, have no significant influence on the yield.

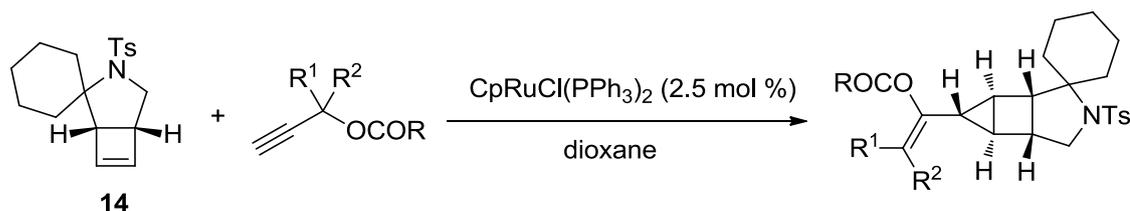
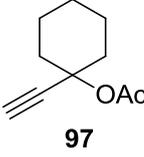
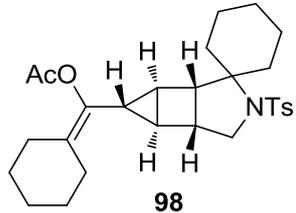
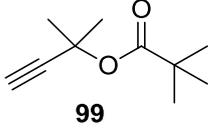
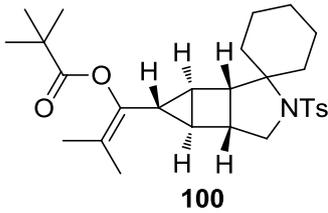
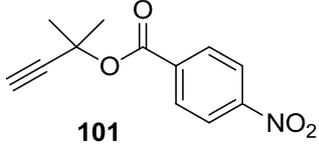
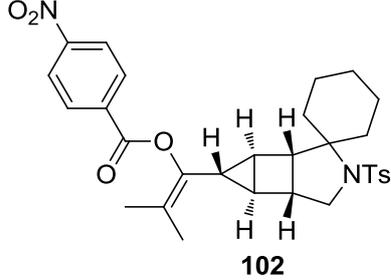
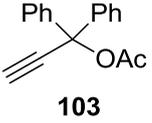
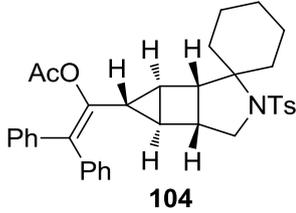


Table 2. CpRuCl(PPh₃)₂-catalyzed cyclopropanation of cyclobutene **14 with various propargylic carboxylates^a**

Entry	Substrate	Product	Yield (%) ^b
1	 97	 98	97
2	 99	 100	93
3	 101	 102	94
4 ^c	 103	 104	43

^a **Reaction conditions:** Cyclobutene (0.20 mmol), **85** (0.20 mmol), CpRuCl(PPh₃)₂ (0.005 mmol, 2.5 mol %), dioxane (2 mL), under argon, room temperature, 36 h. ^b Isolated yield. ^c Reaction carried out at 60 °C for 24 h.

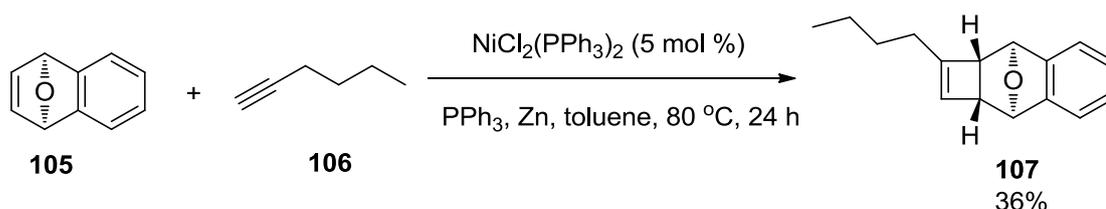
The reaction with the sterically congested carboxylate **103** give **104** in only 43% yield even if the reaction is performed at 60°C for 24 h (Table 2, entry 4). Thus, the outcome of the reaction is more sensitive to the steric effects of propargyl substituents rather than with the electronic nature of the carboxyl residue.

3.3.3 Substituents effects on the ruthenium-catalyzed cyclopropanation of cyclobutenes

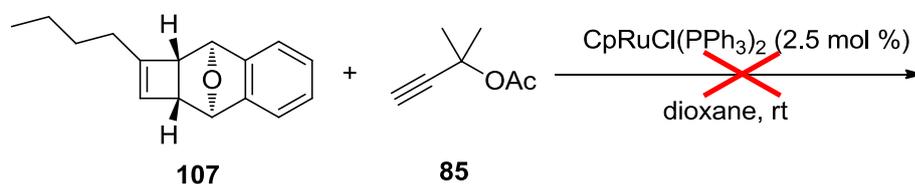
Since we have evaluated our cyclobutenes in the cyclopropanation reaction (Table 1), we wished to extend the reaction to other structurally different cyclobutenes, in particular to those monosubstituted at sp^2 and sp^3 carbon atoms.

3.3.3.1 Cyclobutene monosubstituted at sp^2 carbon atom **107**

The cyclobutene **107** was readily prepared through a nickel-catalyzed [2+2] cycloaddition as described by Cheng and co-workers.¹⁵ In our hands, the thermal reaction of 1,4-dihydro-1,4-epoxynaphthalene **105** and hex-1-yne **106** (2 equiv) in the presence of $NiCl_2(PPh_3)_2/PPh_3$ (5/80 mol %), and Zn powder (2.75 equiv) in toluene under argon atmosphere at 80 °C for 24 h afforded the cyclobutene **107** in only 36% yield.



To our disappointment, subjecting cyclobutene **107** to the ruthenium-catalyzed cyclopropanation conditions performed at room temperature did not afford the desired adduct; even if the reaction was carried out at 60 °C. We assume that the steric and electronic factors of the trisubstituted double bond prevent coordination to the ruthenium.



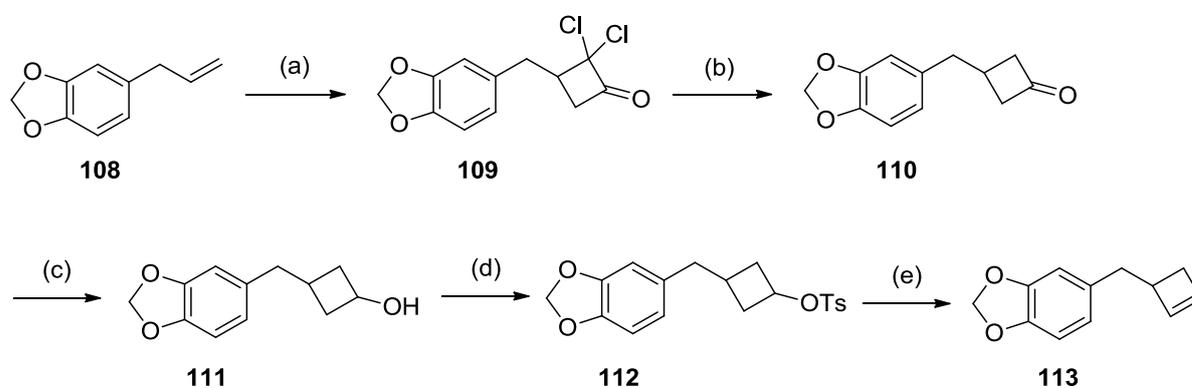
3.3.3.2 Cyclobutene monosubstituted at sp^3 carbon atom **113**

We intended to examine the reactivity of non-fused cyclobutene having one substituent at at sp^3 carbon atom and the influence of this substituent on the diastereoselectivity of the

¹⁵ Huang, D.-J.; Rayabarapu, D. K.; Li, L.-P.; Sambaiah, T.; Cheng, C-H. *Chem. Eur. J.* **2000**, *6*, 3706-3173.

cyclopropanation.

The synthesis of cyclobutene **113** was designed keeping in mind to build a non-volatile compound. Based on procedures reported by Xu, Salaün and Bassindale,¹⁶ the cyclobutene **113** was prepared using a five-steps sequence as outlined in Scheme 13. The thermal [2+2] cycloaddition of dichloroketene, generated *in situ* from trichloroacetyl chloride, with the commercially available safrole **108** in the presence of freshly prepared Zn-Cu couple and phosphorus oxychloride give the dichlorocyclobutanone **109**. Subsequent dechlorination with zinc powder in acetic acid led to cyclobutanone **110** in 22% yield over the two steps. Reduction of cyclobutanone **110** with sodium borohydride (99% yield) followed by tosylation give tosylate **112** as a 1:1 mixture of diastereomers in 85% yield.

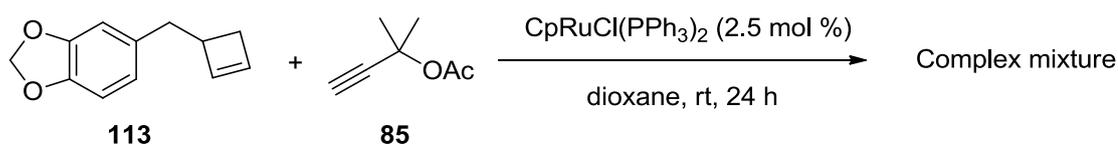


Scheme 13 Preparation of cyclobutene **113**. *Reagents and conditions:* (a) Cl_3CCOCl , Zn-Cu couple, Et_2O , rt to reflux. (b) Zn, HOAc, rt to 80°C , 22%, over the two steps. (c) NaBH_4 , MeOH, 0°C to rt, 99%. (d) TsCl, pyridine, rt, 85%. (e) $^t\text{BuOK}$, DMSO, 70°C , 61%.

Dimethyl potassium-induced elimination of *p*-toluenesulfonic acid led to the desired cyclobutene **113** in 11% overall yield over the five steps.

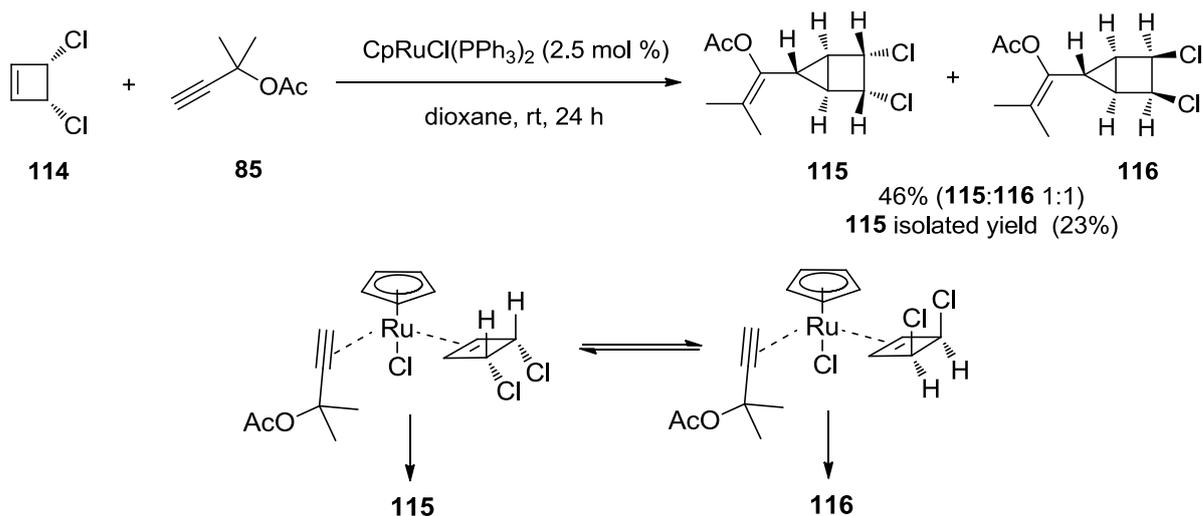
Then, we attempted the cyclopropanation reaction of monosubstituted cyclobutene **113** with propargyl acetate **85** using our standard catalytic conditions (2.5 mol % of $\text{CpRuCl}(\text{PPh}_3)_2$ in dioxane at room temperature). Disappointingly and to our surprise, the reaction produced a complex mixture of products, and the desired bicyclo[2.1.0]pentane derivative was not detected in the proton NMR of the crude. We assumed a high reactivity for the monosubstituted cyclobutene **113** in these conditions, therefore the reaction was carried out at 0°C in a 1/1 mixture dioxane/THF; the co-solvent was used to solubilize **113** at 0°C . Here again, a complex mixture was observed without the desired bicyclo[2.1.0]pentane derivative.

¹⁶ a) Xu, H.-J.; Zhu, F.-F.; Shen, Y.-Y.; Wan, X.; Feng, Y.-S. *Tetrahedron*, **2012**, 68, 4145-4151. b) Salaün, J.; Fadel, A. *Organic Syntheses, Coll. Vol. 7*, p.117 (1990); *Vol. 64*, p.50 (1986). c) Bassindale, M. J.; Hamley, P.; Harrity, J.P.A. *Tetrahedron Lett.*, **2001**, 42, 9055-9057.



3.3.3.3 Disubstituted cyclobutenes **114** and **117**

As it was observed the ruthenium-catalyzed cyclopropanation of the ring-fused cyclobutenes with propargylic carboxylates is highly efficient, the simple *cis*-3,4-disubstituted cyclobutenes also needed to be evaluated. The reaction of commercially available *cis*-3,4-dichlorocyclobutene **114** with propargyl acetate **85** was conducted, and the desired bicyclo[2.1.0]pentane **115** was isolated in only 23% yield. The bulk of the reaction was a complex mixture along with the stereoisomer **116** which could not be separated from the mixture.



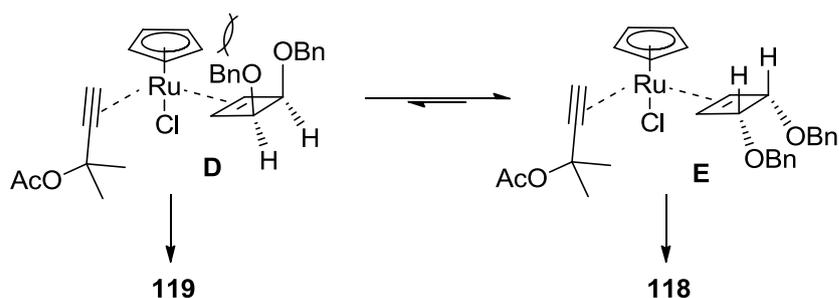
The 1/1 ratio of compounds **115/116** was determined by ^1H NMR of the crude reaction mixture. The yield and the diastereoselectivity observed for the reaction of cyclobutene **114** were dramatically decreased compared with the reaction of the bicyclic cyclobutenes reported in Table 1. The lower yield may be ascribed to the peculiarity of the chlorine substituents, which are potentially good leaving groups especially in allylic location. The loss of diastereoselectivity is less obvious; only diastereomer **115** was expected *a priori*. The stereofacial discrimination cannot be invoked in this case and a plausible explanation consists in the coordination to the metal through the chlorine atom(s), which delivers the *syn* isomer **116**. On the basis of previous investigations, we envisage that the double bond

coordinates to the CpRuCl species at both sides of the cyclobutene **114** and that the resulting complexes are in equilibrium.

Our assumption on the high reactivity of dichloride **114** was next tested with the dibenzylether **117** readily prepared by nucleophilic substitution of **114** with sodium benzyolate generated *in situ*. The cyclopropanation reaction of **117** furnished the diastereoisomers **118** and **119** (ratio 5:1) in 89% yield with the major diastereomer in agreement with our previous observations.



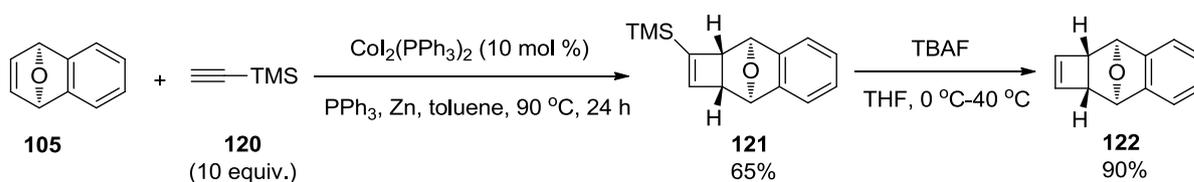
Although the efficiency of the reaction was restored, the diastereoselectivity was not fully controlled. Because ethers are not good ligands compared to chlorine, a coordination assistance of the ethers to the metal can be ruled out in this case. The Curtin-Hammett principle may account for the diastereoselectivity observed. The equilibrium between intermediate complexes **D** and **E** is in favor of **E** but the following step may be kinetically favored for **D** compared to the one for **E**.



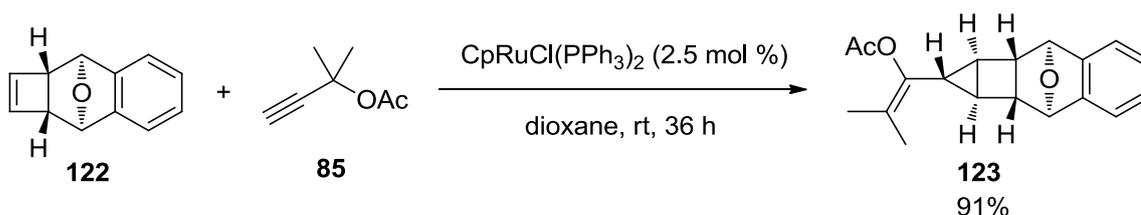
3.3.3.4 Sterically congested cyclobutene **122**

As cyclobutene embedded in rigid structures are better suited to control the diastereoselectivity of the cyclopropanation, it was decided to test the cyclobutene **122**, whose structure is closely related to the bicyclic cyclobutenes examined earlier (§ 3.3.1). The cyclobutene **122** was prepared through a cobalt-catalyzed [2+2] cycloaddition described by

Cheng group.¹⁷ The reaction of 1,4-dihydro-1,4-epoxynaphthalene **105** with ethynyltrimethylsilane **120** (10 equiv) in the presence of $\text{CoI}_2(\text{PPh}_3)_2/\text{PPh}_3$ (10/80 mol %), and Zn powder (10 equiv) in toluene under argon atmosphere at 90 °C gave the silylcyclobutene **121** in 65% yield. The desired cyclobutene **122** was then obtained after desilylation of **121** with tetrabutylammonium fluoride.¹⁸



As expected, the treatment of ring-fused cyclobutene **122** with propargyl acetate **85** and the ruthenium catalyst at room temperature afforded the desired bicyclo[2.1.0]pentane **123** as a single diastereomer in 91% yield.



The structure of bicyclo[2.1.0]pentane **123** and its relative stereochemistry was secured by single-crystal X-ray diffraction analysis (Figure 1) which confirmed the “staircase” shape of the compound.

¹⁷ Chao, K. C.; Rayabarapu, D. K.; Wang, C.-C.; Cheng, C-H. *J. Org. Chem.* **2001**, *66*, 8804-8810.

¹⁸ Day, J. J.; McFadden, R. M.; Virgil, S. C.; Kolding, H.; Alleva, J. L.; Stoltz, B. M. *Angew. Chem. Int. Ed.* **2011**, *50*, 6814-6818.

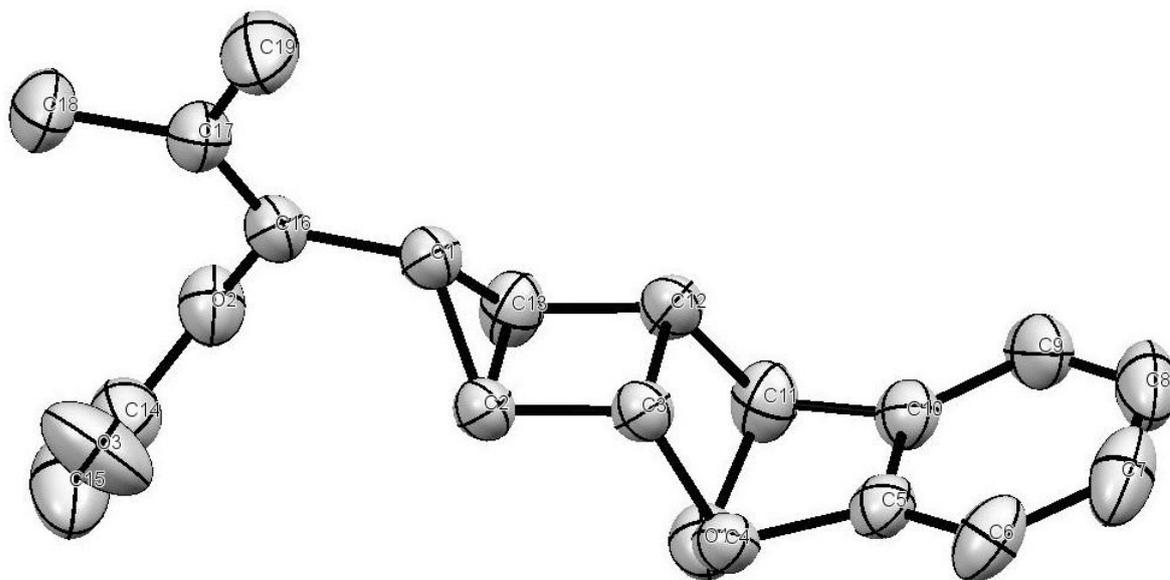


Figure 1 ORTEP for **123** (H are omitted for clarity)

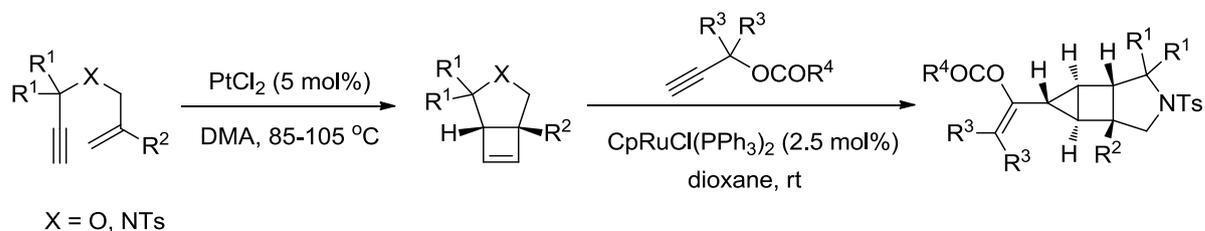
Selection of structural data: a) Bond length (Å): C1-C2 = 1.511; C1-C13 = 1.511; C2-C13 = 1.513; C2-C3 = 1.522; C3-C12 = 1.576; C12-C13 = 1.523. b) Angle (°): C2-C1-C13 = 60.1; C1-C2-C13 = 60.0; C1-C13-C2 = 59.9; C1-C2-C3 = 109.0; C1-C13-C12 = 109.3; C2-C3-C12 = 89.1; C3-C12-C13 = 88.5; C2-C13-C12 = 91.4; C3-C2-C13 = 90.2; C2-C3-C4 = 115.8; C11-C12-C13 = 115.7.

Conclusion

In this study, we have achieved an efficient protocol to access the bicyclo[2.1.0]pentane derivatives through CpRuCl(PPh₃)₂-catalyzed cyclopropanation of cyclobutenes with tertiary propargylic carboxylates in high yields under mild conditions. Tertiary propargylic carboxylates activated with certain metal complexes can be considered as “carbene” equivalents and are excellent surrogates to the hazardous diazo compounds usually utilized for the cyclopropanation reactions. The reaction exhibits excellent diastereoselectivity with structurally congested cyclobutenes. The diastereoselectivity can be adjusted with a proper choice of substituents on the cyclobutene ring. Cyclobutenes with *syn* bulky substituents at C-3 and C-4 are well suitable to induce cyclopropanation by the opposite face.

General Conclusion

In this manuscript, we have described an access to bicyclo[2.1.0]pentanes via two metal-catalyzed reactions, namely a platinum-catalyzed cycloisomerization of heteroatom-tethered 1,6-enynes and the subsequent ruthenium-catalyzed cyclopropanation of cyclobutenes with tertiary propargyl carboxylates.

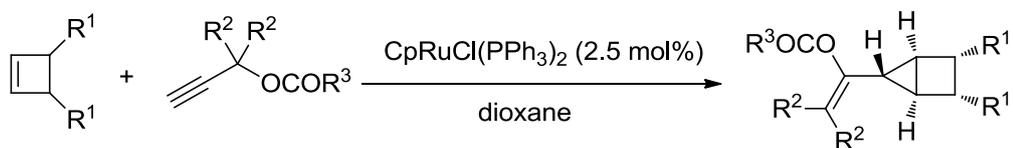


First, we have developed the Pt(II)-catalyzed formation of cyclobutenes from nitrogen and oxygen-tethered 1,6-enynes to form aza- and oxabicyclo[3.2.0]hept-6-enes respectively.

The development of these reactions represents one missing link in the arsenal of cycloisomerization reactions of such enynes. Enynes with alkyl substituents at propargyl carbon atom were best suited to undergo the cyclobutene formation. These substituents induce a significant relative stabilization of the developing positive charge at the internal sp carbon through hyperconjugation. Although necessary, this condition was not however sufficient. The ability of dimethylacetamide (DMA) among others amide solvents to coordinate platinum is the other key of the success of the reactions. The amide solvent was unique to favor the reaction path leading to cyclobutenes and can be used in catalytic amounts, thus demonstrating its coordinating properties towards the platinum. The use of well-defined $\text{PtCl}_2(\text{DMA})_2$ as the catalyst supported our assumptions. Moreover, we have shown that enynes bearing terminal alkynes are competent to undergo the formal [2+2] cycloaddition. This structural characteristic is not so common in related cycloisomerizations. On the basis of deuterium-labeling experiments, a rationale mechanism involving ionic intermediates has been proposed.

Second, the availability of cyclobutenes from the cycloisomerization of 1,6-enynes has allowed their utilization for the construction of strained bicyclo[2.1.0]pentane structures as single diastereomers in good to excellent yield through a ruthenium-catalyzed cyclopropanation. In contrast to usual methods, which make use of diazo compounds to generate a carbene, we have developed a safe method involving tertiary propargylic

carboxylates, which behave as “carbene” equivalents in presence of certain transition metal catalysts. Interestingly, ruthenacarbene intermediates were not involved in this reaction.



It was shown that the stereoselectivity of the ruthenium-catalyzed cyclopropanation of cyclobutenes depends on the nature and steric properties of substituents within the cyclobutene. 3-Substituted and 3,4-disubstituted cyclobutenes gave poor stereofacial selectivity, while compact and rigid ring-fused cyclobutenes afforded single diastereomers in good yields.

Experimental Section

General Considerations

Unless otherwise stated, all reactions were carried out in an atmosphere of dry argon using an oven-dried (120 °C) glassware. The solvents were degassed and purified by usual methods.¹ Toluene was distilled from lithium aluminum hydride. Diethyl ether and tetrahydrofuran were distilled from sodium (benzophenone ketyl). 1,2-dimethoxyethane, dichloromethane, acetonitrile and *N,N*-dimethylformamide were distilled from calcium hydride. Acetone was refluxed over potassium permanganate before being distilled. A fraction of petroleum distilled between 40-55°C was used for column chromatography. *N,N*-Dimethylacetamide (99.5%, Extra Dry over Molecular Sieve, AcroSeal®) was used as received. PtCl₂ were purchased from Strem Chemical Co. and were used as received. Analytical TLC were performed on ready-made plates coated with silica gel on aluminum (Merck 60 F₂₅₄). Products were visualized by ultraviolet light and treatment either with *p*-anisaldehyde or phosphomolybdic acid stain followed by gentle heating or with iodine stain. Flash chromatography was performed using E. Merck silica gel 60 (230-400 mesh) according to the protocol of Still, Khan and Mitra.² All melting points were recorded on Büchi apparatus and are reported uncorrected. Infrared spectra were recorded in transmission mode either neat on sodium chloride plates or in matrix of potassium bromide (KBr) on Perkin-Elmer 1700X spectrophotometer. Absorption frequencies are reported in cm⁻¹ at the highest intensity. ¹H NMR spectra were recorded on either a Bruker Avance DPX-300 or advance DPX-400 spectrometer as solutions in deuteriochloroform (CDCl₃), unless otherwise indicated. Chemical shifts are given in parts per million (δ units) downfield from tetramethylsilane using the residual solvent signal (CHCl₃ 7.26, benzene 7.15) as internal standard. Proton (¹H) NMR information is given in the following format: multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; qui, quintet; sept, septet; m, multiplet), coupling constant(s) (*J*) in Hertz (Hz), number of protons. The prefix *app* is occasionally applied when the true signal multiplicity was unresolved and br indicates the signal in question is broadened. Carbon (¹³C) NMR spectra are reported in ppm (δ) relative to residual CHCl₃ (δ 77.0) unless noted otherwise. Elemental analyses and high-resolution mass spectra (HRMS) were performed at the “Spectropôle” of the Aix Marseille Université.

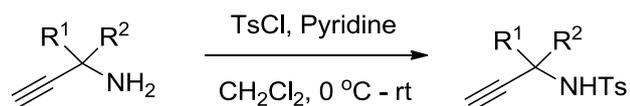
¹ Armarego, W. L. F.; Chai, C. L. L. *Purification of Laboratory Chemicals*, 5th Ed; Butterworth Heinemann: New York, 2003.

² Still, W. C.; Khan, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923-2925.

Unless otherwise specified, the physical and spectral data of the prepared complexes are in accordance with those described in the literature.

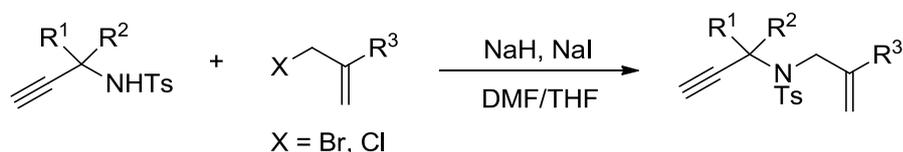
I. Preparation of 1,6-enynes.

General procedure A



Based on a modification of the procedure reported by Kitamura.³ To a cooled (0 °C) solution of propargylamine (10.0 mmol) in CH₂Cl₂ (10 mL) was added pyridine (2.43 mL, 30.0 mmol) and *p*-toluenesulfonyl chloride (2.0 g, 10.5 mmol). The mixture was stirred overnight at room temperature, concentrated in vacuo and the residue dissolved in ethyl acetate. The organic layer was washed with aqueous 10% HCl and brine, dried over Na₂SO₄, and concentrated in vacuo. The residue was purified by column chromatography over silica gel.

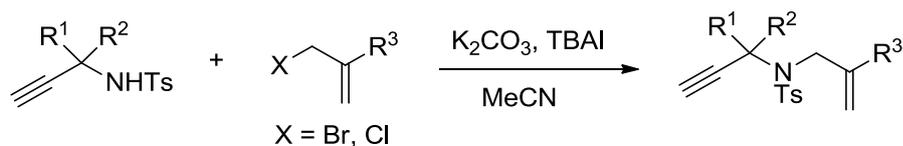
General procedure B



Based on a modification of the procedure reported by Kitamura.³ To a cooled (0 °C) suspension of NaH (60% oil dispersion washed with PE) (0.1 g, 2.5 mmol) in THF/DMF (1/2, 12 mL) was added *N*-propargyl-*p*-toluenesulfonamide (2.5 mmol). The resulting mixture was stirred for 1 h at 0 °C, then allyl halide (2.5 mmol) and NaI (0.37 g, 2.5 mmol) were added. The mixture was stirred at room temperature for 12 h, then saturated aqueous NH₄Cl was added. The aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated in vacuo. The residue was purified by column chromatography over silica gel.

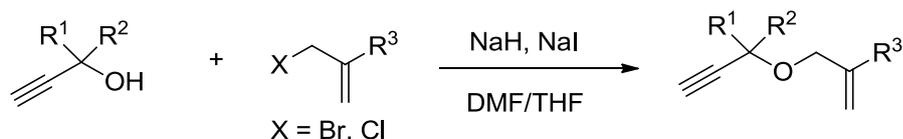
General procedure C

³ Kitamura, T.; Sato, Y.; Mori, M. *Adv. Synth. Catal.* **2002**, *344*, 678-693.



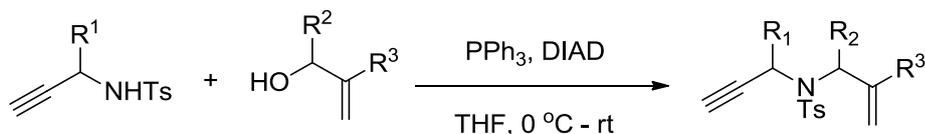
Based on a modification of the procedure reported by Arai.⁴ Propargyl-*p*-toluenesulfonamide (2.0 mmol), allyl halide (2.2 mmol), K₂CO₃ (553 mg, 4.0 mmol) and tetrabutylammonium iodide (74 mg, 0.2 mmol) were mixed in CH₃CN (10 mL). After being stirred for 14 h at 70 °C, the reaction mixture was poured into water and extracted with AcOEt (3 × 10 mL). The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated in vacuo. The residue was purified by column chromatography over silica gel.

General procedure D



Based on a modification of the procedure reported by Kitamura.³ To a cooled (0 °C) suspension of NaH (60% oil dispersion washed with PE) (2.5 mmol) in THF/DMF (1/2, 12 mL) was added propargylic alcohol (2.5 mmol). The solution was stirred at 0 °C for 1 h, then allyl halide (2.5 mmol) and NaI (375 mg, 2.5 mmol) were added. The solution was stirred at room temperature for 12 h, diluted with saturated aqueous NH₄Cl and extracted with Et₂O (3 × 10 mL). The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated in vacuo. The residue was purified by column chromatography over silica gel.

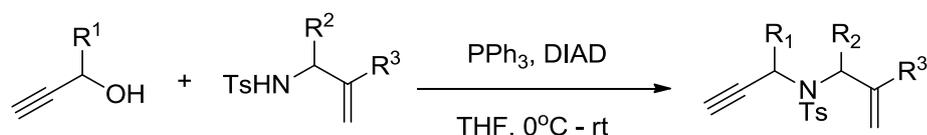
General procedure E



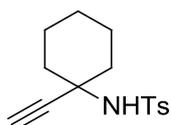
⁴ Arai, S.; Koike, Y.; Nishida, A. *Adv. Synth. Catal.* **2010**, 352, 893-900.

Based on a modification of the procedure reported by Wang.⁵ To a cooled (0 °C) solution of *N*-propargyl-*p*-toluenesulfonamide (2.0 mmol), allylic alcohol (2.0 mmol), and triphenylphosphine (0.52 g, 2.0 mmol) in THF (15 mL) was added diisopropylazodicarboxylate (0.39 mL, 2.0 mmol) at 0 °C. The reaction mixture was gradually warmed to room temperature, and then stirred overnight. The solvent was removed under vacuum and the residue was purified by flash chromatography over silica gel.

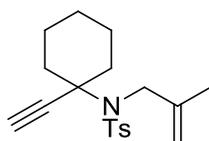
General procedure F



Based on a modification of the procedure reported by Wang.⁵ To a cooled (0 °C) solution of propargylic alcohol (2.0 mmol), *N*-allyl-*p*-toluenesulfonamide (2.0 mmol), and triphenylphosphine (0.52 g, 2.0 mmol) in THF (15 mL) was added diisopropylazodicarboxylate (0.39 mL, 2.0 mmol). The reaction mixture was gradually warmed to room temperature, and then stirred overnight. The solvent was removed under vacuum and the residue was purified by flash chromatography over silica gel.



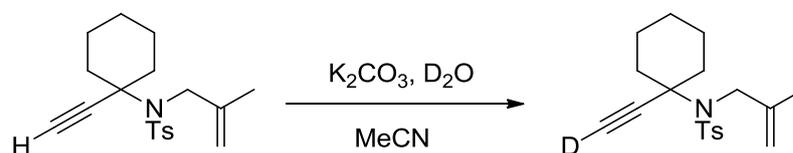
N-(1-Ethynylcyclohexyl)-4-methylbenzenesulfonamide³ was prepared according to procedure A. Yield: 69%; White solid; R_f (PE/AcOEt 5/1) 0.25; $^1\text{H NMR}$ (300 MHz, CDCl_3): δ 7.84 (d, $J = 8.3$ Hz, 2H), 7.27 (d, $J = 8.2$ Hz, 2H), 5.51 (br s, 1H), 2.41 (s, 3H), 2.12 (s, 1H), 2.03-1.99 (m, 2H), 1.78-1.48 (m, 7H), 1.24-1.12 (m, 1H); $^{13}\text{C NMR}$ (300 MHz, CDCl_3): δ 143.0 (C), 139.3 (C), 129.1 (CH \times 2), 127.6 (CH \times 2), 83.7 (C), 73.8 (CH), 54.2 (C), 38.7 (CH₂ \times 2), 24.9 (CH₂), 22.3 (CH₂ \times 2), 21.5 (CH₃).



⁵ Wang, K.-B.; Ran, R.-Q.; Xiu, S.-D.; Li, C.-Y. *Org. Lett.* **2013**, *15*, 2374-2377.

N-(1-Ethynylcyclohexyl)-4-methyl-*N*-(2-methylallyl)benzenesulfonamide³ (**1**) was prepared according to procedure B (yield 69%) or C (yield 89%). White solid; m.p. 96-98 °C; **R_f** (PE/Et₂O 10/1) 0.35; **¹H NMR** (400 MHz, CDCl₃): δ 7.72 (d, *J* = 8.3 Hz, 2H), 7.25 (d, *J* = 8.3 Hz, 2H), 5.12 (s, 1H), 4.94-4.93 (m, 1H), 4.11 (s, 2H), 2.41 (s, 3H), 2.24 (s, 1H), 2.07 (d, *J* = 11.2 Hz, 2H), 1.88 (td, *J* = 3.6, 12.6, 2H), 1.79 (s, 3H), 1.66-1.49 (m, 5H), 1.16-1.04 (m, 1H); **¹³C NMR** (300 MHz, CDCl₃): δ 143.3 (C), 142.9 (C), 139.4 (C), 129.2 (CH × 2), 127.5 (CH × 2), 111.8 (CH₂), 83.2 (C), 74.9 (CH), 62.3 (C), 53.5 (CH₂), 37.6 (CH₂ × 2), 24.7 (CH₂), 23.5 (CH₂ × 2), 21.5 (CH₃), 20.3 (CH₃).

N-(1-Deutero-ethynylcyclohexyl)-4-methyl-*N*-(2-methylallyl)benzenesulfonamide (**[D]-1**)

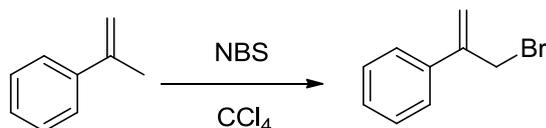


Based on a modification of the procedure reported by Bew.⁶ A flame dried 10 mL round bottomed flask was charged with *N*-(1-ethynylcyclohexyl)-4-methyl-*N*-(2-methylallyl)-benzenesulfonamide (33 mg, 1.0 mmol), potassium carbonate (207 mg, 1.5 mmol) and MeCN (4 mL). This was allowed to stir under an atmosphere of argon for 2 h, then D₂O (1 mL, 50.0 mmol) was added and left to stir for 10 h. The resulting crude reaction mixture was diluted with CH₂Cl₂ (10 mL) and transferred to a separating funnel. The organic layer was separated and dried with Na₂SO₄, filtered and concentrated under reduced pressure.

Yield: 97%, deuteration ≥ 99%; White solid; m.p. 96-97 °C; **R_f** (PE/Et₂O 10/1) 0.40; **IR** (neat) ν 2938, 2562, 1334, 1154, 913, 701, 573, 545, 523 cm⁻¹; **¹H NMR** (300 MHz, C₆D₆): δ 7.78 (d, *J* = 8.2 Hz, 2H), 6.79 (d, *J* = 8.2 Hz, 2H), 5.25 (s, 1H), 4.93-4.92 (m, 1H), 4.24 (s, 2H), 2.18-2.15 (m, 2H), 2.04 (td, *J* = 3.7, 12.6, 2H), 1.90 (s, 3H), 1.78 (s, 3H), 1.60-1.33 (m, 5H), 0.96-0.85 (m, 1H); **¹³C NMR** (300 MHz, C₆D₆): δ 143.9 (C), 142.4 (C), 140.8 (C), 129.2 (CH × 2), 127.8 (CH × 2), 112.2 (CH₂), 83.1-82.9 (C, t, *J* = 7.0 Hz), 75.4-74.8 (C-D, t, *J* = 38.1 Hz), 62.5 (C), 53.9 (CH₂), 37.9 (CH₂ × 2), 24.9 (CH₂), 23.7 (CH₂ × 2), 21.0 (CH₃), 20.4 (CH₃); **HRMS** (ESI-MS) calcd. for C₁₉H₂₅DNO₂S⁺ ([M+H]⁺): 333.1742, found 333.1742.

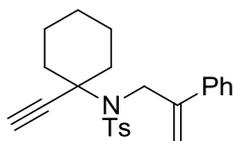
⁶ Bew, S. P.; Hiatt-Gipson, G. D.; Lovell, J. A.; Poullain, C. *Org. Lett.* **2012**, *14*, 456-459.

(1-Bromomethyl-vinyl)-benzene⁷

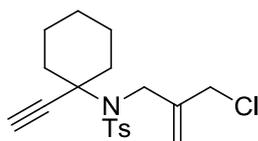


A mixture of methylstyrene (3.0 g, 25.4 mmol) and NBS (5.4 g, 30.5 mmol) suspended in CCl₄ (60 mL) was heated under reflux for 10 h and then cooled to room temperature. The precipitated succinimide was separated by filtration. After evaporation of the solvent under reduced pressure, the product was purified by bulb-to-bulb distillation (95 °C, 1 mbar).

Yield: 68%; Yellow oil; ¹H NMR (300 MHz, CDCl₃): δ 7.52-7.28 (m, 5H), 5.57 (s, 1H), 5.50 (s, 1H), 4.39 (s, 2H); ¹³C NMR (300 MHz, CDCl₃): δ 144.3 (C), 137.6 (C), 128.5 (CH × 2), 128.3 (CH), 126.1 (CH × 2), 117.3 (CH₂), 34.2 (CH₂).



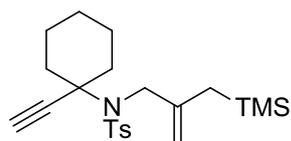
N-(1-Ethynylcyclohexyl)-4-methyl-*N*-(2-phenylallyl)benzenesulfonamide (**7**) was prepared according to procedure C. Yield: 69%; White solid; m.p. 120-122 °C; *R_f* (PE/Et₂O 10/1) 0.35; IR (neat) ν 3257, 2947, 1322, 1148, 781, 689, 586, 543 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.76 (d, *J* = 8.3 Hz, 2H), 7.42-7.26 (m, 7H), 5.59 (d, *J* = 0.8 Hz, 1H), 5.50 (d, *J* = 0.8 Hz, 1H), 4.52 (t, *J* = 1.6 Hz, 2H), 2.42 (s, 3H), 2.22 (s, 1H), 2.14 (d, *J* = 11.3 Hz, 2H), 1.93 (td, *J* = 3.5, 12.7 Hz, 2H), 1.72-1.48 (m, 5H), 1.17-1.07 (m, 1H); ¹³C NMR (300 MHz, CDCl₃): δ 145.5 (C), 143.1 (C), 139.8 (C), 138.9 (C), 129.2 (CH × 2), 128.4 (CH × 2), 127.7 (CH × 3), 126.1 (CH × 2), 114.0 (CH₂), 83.1 (C), 74.8 (CH), 62.6 (C), 51.5 (CH₂), 37.8 (CH₂ × 2), 24.7 (CH₂), 23.5 (CH₂ × 2), 21.5 (CH₃); HRMS (ESI-MS) calcd. for C₂₄H₂₈NO₂S⁺ ([M+H]⁺): 394.1835, found 394.1835.



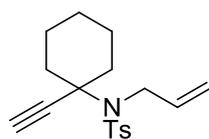
N-(2-(Chloromethyl)allyl)-*N*-(1-ethynylcyclohexyl)-4-methylbenzenesulfonamide (**9**) was prepared according to procedure C. Yield: 71%; White solid; m.p. 107-108 °C; *R_f* (PE/Et₂O

⁷ Fort, D. A.; Woltering, T. J.; Nettekoven, M.; Knust, H.; Bach, T. *Chem. Commun.* **2013**, 49, 2989-2991.

10/1) 0.25; **IR** (neat) ν 3288, 2942, 1323, 1153, 927, 697, 664, 573, 541 cm^{-1} ; **$^1\text{H NMR}$** (400 MHz, CDCl_3): δ 7.72 (d, $J = 8.3$ Hz, 2H), 7.27 (d, $J = 8.2$ Hz, 2H), 5.49 (s, 1H), 5.38 (s, 1H), 4.28 (s, 2H), 4.51 (s, 2H), 2.41 (s, 3H), 2.25 (s, 1H), 2.09 (d, $J = 11.2$ Hz, 2H), 1.87 (td, $J = 3.5, 12.6$ Hz, 2H), 1.71-1.47 (m, 5H), 1.16-1.04 (m, 1H); **$^{13}\text{C NMR}$** (300 MHz, CDCl_3): δ 143.2 (C), 142.6 (C), 138.9 (C), 129.3 ($\text{CH} \times 2$), 127.6 ($\text{CH} \times 2$), 116.8 (CH_2), 83.0 (C), 75.1 (CH), 62.7 (C), 50.4 (CH_2), 46.5 (CH_2), 37.6 ($\text{CH}_2 \times 2$), 24.7 (CH_2), 23.5 ($\text{CH}_2 \times 2$), 21.5 (CH_3); **HRMS** (ESI-MS) calcd. for $\text{C}_{19}\text{H}_{25}\text{NO}_2\text{SiCl}^+$ ($[\text{M}+\text{H}]^+$): 366.1289, found 366.1286.



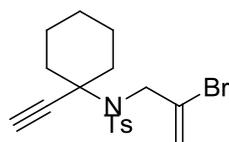
N-(1-Ethynylcyclohexyl)-4-methyl-N-(2-((trimethylsilyl)methyl)allyl)benzenesulfonamide (**11**) was prepared according to procedure C. Yield: 77%; White solid; m.p. 70-72 $^{\circ}\text{C}$; R_f (PE/Et₂O 5/1) 0.35; **IR** (neat) ν 3292, 2941, 1313, 1150, 863, 807, 683, 541 cm^{-1} ; **$^1\text{H NMR}$** (400 MHz, C_6D_6): δ 7.84 (d, $J = 8.3$ Hz, 2H), 6.79 (d, $J = 8.0$ Hz, 2H), 5.35 (d, $J = 1.7$ Hz, 1H), 4.87 (d, $J = 1.7$ Hz, 1H), 4.24 (s, 2H), 2.23 (d, $J = 11.4$ Hz, 2H), 2.10 (td, $J = 4.0, 12.7$ Hz, 2H), 1.90 (s, 3H), 1.88 (s, 1H), 1.65-1.31 (m, 7H), 0.98-0.85 (m, 1H), 0.13 (s, 9H); **$^{13}\text{C NMR}$** (300 MHz, C_6D_6): δ 145.1 (C), 142.5 (C), 140.9 (C), 129.3 ($\text{CH} \times 2$), 127.9 ($\text{CH} \times 2$), 109.7 (CH_2), 83.8 (C), 75.2 (CH), 62.5 (C), 54.6 (CH_2), 38.1 ($\text{CH}_2 \times 2$), 25.0 (CH_2), 24.3 ($\text{CH}_2 \times 2$), 23.9 (CH_2), 21.1 (CH_3), -1.2 ($\text{CH}_3 \times 3$); **HRMS** (ESI-MS) calcd. for $\text{C}_{22}\text{H}_{34}\text{NO}_2\text{SSi}^+$ ($[\text{M}+\text{H}]^+$): 404.2074, found 404.2071.



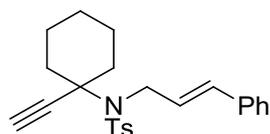
N-Allyl-*N*-(1-ethynylcyclohexyl)-4-methylbenzenesulfonamide⁸ (**13**) was prepared according to procedure C. Yield: 72%; White solid; R_f (PE/Et₂O 10/1) 0.35; **$^1\text{H NMR}$** (400 MHz, CDCl_3): δ 7.73 (d, $J = 8.3$ Hz, 2H), 7.24 (d, $J = 8.3$ Hz, 2H), 6.04 (m, 1H), 5.27 (dd, $J = 1.5, 17.3$ Hz, 1H), 5.16 (dd, $J = 1.5, 10.3$ Hz, 1H), 4.18 (dt, $J = 1.4, 5.8$ Hz, 2H), 2.41 (s, 3H), 2.36 (s, 1H), 2.08 (d, $J = 11.4$ Hz, 2H), 1.91 (td, $J = 3.9, 12.5$ Hz, 2H), 1.67-1.52 (m, 5H), 1.19-1.02 (m, 1H); **$^{13}\text{C NMR}$** (300 MHz, CDCl_3): δ 142.8 (C), 139.8 (C), 137.1 (CH), 129.3 ($\text{CH} \times 2$), 127.3 ($\text{CH} \times 2$), 116.7 (CH_2), 83.6 (C), 75.0 (CH), 62.2 (C), 50.1 (CH_2), 37.5

⁸ Monnier, F.; Vovard-Le Bray, C.; Castillo, D.; Aubert, V.; Dérien, S.; Dixneuf, P.H.; Toupet, L.; Ienco, A.; Mealli, C. *J. Am. Chem. Soc.* **2007**, *129*, 6037-6049.

(CH₂ × 2), 24.7 (CH₂), 23.5 (CH₂ × 2), 21.5 (CH₃).



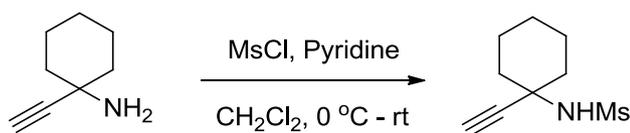
N-(2-bromoallyl)-*N*-(1-ethynylcyclohexyl)-4-methylbenzenesulfonamide (**15**) was prepared according to procedure C. Yield: 69%; Yellow solid; m.p. 120-122 °C; **R_f** (PE/Et₂O 10/1) 0.35; **IR** (neat) ν 3257, 2931, 1331, 1161, 1090, 1040, 704, 658, 545, 531 cm⁻¹; **¹H NMR** (400 MHz, CDCl₃): δ 7.73 (d, *J* = 8.3 Hz, 2H), 7.28 (d, *J* = 8.2 Hz, 2H), 6.16 (dd, *J* = 1.9, 4.0 Hz, 1H), 5.66 (dd, *J* = 1.7, 3.9 Hz, 1H), 4.32 (br s, 2H), 2.42 (s, 3H), 2.25 (s, 1H), 2.12-2.04 (m, 2H), 1.87 (td, *J* = 3.4, 12.7 Hz, 2H), 1.74-1.48 (m, 5H), 1.18-1.04 (m, 1H); **¹³C NMR** (300 MHz, CDCl₃): δ 143.5 (C), 138.5 (C), 130.4 (C), 129.4 (CH × 2), 127.7 (CH × 2), 117.5 (CH₂), 82.5 (C), 75.2 (CH), 62.7 (C), 55.3 (CH₂), 37.7 (CH₂ × 2), 24.6 (CH₂), 23.5 (CH₂ × 2), 21.6 (CH₃); **HRMS** (ESI-MS) calcd. for C₁₈H₂₃NO₂BrS⁺ ([M+H]⁺): 398.0608, found 398.0607.



N-cinnamyl-*N*-(1-ethynylcyclohexyl)-4-methylbenzenesulfonamide (**17**) was prepared according to procedure C. Yield: 83%; White solid; m.p. 124-126 °C; **R_f** (PE/Et₂O 10/1) 0.30; **IR** (neat) ν 3257, 2927, 1327, 1157, 920, 726, 658, 566, 538 cm⁻¹; **¹H NMR** (300 MHz, CDCl₃): δ 7.75 (d, *J* = 8.3 Hz, 2H), 7.39-7.35 (m, 2H), 7.34-7.30 (m, 2H), 7.26-7.22 (m, 3H), 6.56 (d, *J* = 16.0 Hz, 1H), 6.39 (dt, *J* = 6.2, 16.0 Hz, 1H), 4.35 (dd, *J* = 1.1, 6.1 Hz, 2H), 2.41 (s, 1H), 2.40 (s, 3H), 2.16-2.07 (m, 2H), 1.97 (td, *J* = 4.1, 12.4 Hz, 2H), 1.71-1.50 (m, 5H), 1.20-1.05 (m, 1H); **¹³C NMR** (300 MHz, CDCl₃): δ 142.9 (C), 140.0 (C), 136.9 (C), 131.9 (CH), 129.3 (CH × 2), 128.5 (CH × 3), 127.6 (CH), 127.3 (CH × 2), 126.5 (CH × 2), 83.8 (C), 75.3 (CH), 62.3 (C), 49.7 (CH₂), 37.6 (CH₂ × 2), 24.7 (CH₂), 23.6 (CH₂ × 2), 21.5 (CH₃); **HRMS** (ESI-MS) calcd. for C₂₄H₂₈NO₂S⁺ ([M+H]⁺): 394.1835, found 394.1839.

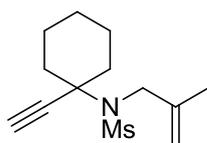
N-(1-Ethynylcyclohexyl)methanesulfonamide⁹

⁹ Takeuchi, R.; Ebata, I. *Organometallics*, **1997**, *16*, 3707-3710.



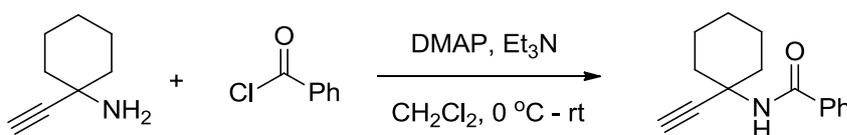
Based on a modification of the procedure reported by Kitamura.³ To a solution of propargylamine (1.35 mL, 10.0 mmol) in CH₂Cl₂ (10 mL) was added pyridine (2.43 g, 30 mmol) and methanesulfonyl chloride (0.81 mL, 10.5 mmol) at 0 °C, The solution was stirred at room temperature for 24 h and then concentrated under vacuo. The residue was dissolved in ethyl acetate, washed with aqueous 10% HCl and brine, dried over Na₂SO₄, and concentrated in vacuo. The crude solid was purified by recrystallization from AcOEt and petroleum ether to give desired compound.

Yield: 76%; White solid; ¹H NMR (300 MHz, CDCl₃): δ 4.92 (br, 1H), 3.17 (s, 3H), 2.57 (s, 1H), 2.14-2.05 (m, 2H), 1.69-1.54 (m, 7H), 1.30-1.17 (m, 1H); ¹³C NMR (300 MHz, CDCl₃): δ 84.5 (C), 74.3 (CH), 54.2 (C), 42.9 (CH₃), 39.0 (CH₂ × 2), 24.9 (CH₂), 22.3 (CH₂ × 2).



N-(1-Ethynylcyclohexyl)-*N*-(2-methylallyl)methanesulfonamide (**19**) was prepared according to procedure C. Yield: 92%; White solid; m.p. 47-49 °C; *R*_f (PE/Et₂O 3/1) 0.30; *IR* (neat) ν 3292, 2934, 1330, 1153, 909, 800, 662, 530 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 5.08 (s, 1H), 4.93 (m, 1H), 3.89 (s, 2H), 3.03 (s, 3H), 2.58 (s, 1H), 2.16 (d, *J* = 12.8 Hz, 2H), 1.85 (td, *J* = 3.8, 12.8, 2H), 1.76 (s, 3H), 1.73-1.58 (m, 5H), 1.22-1.08 (m, 1H); ¹³C NMR (300 MHz, CDCl₃): δ 143.0 (C), 111.5 (CH₂), 83.9 (C), 75.3 (CH), 61.7 (C), 52.4 (CH₂), 40.6 (CH₃), 37.8 (CH₂ × 2), 24.7 (CH₂), 23.5 (CH₂ × 2), 20.3 (CH₃); *HRMS* (ESI-MS) calcd. for C₁₃H₂₁NO₂SK⁺ ([M+K]⁺): 294.0925, found 294.0926.

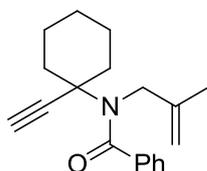
N-(1-ethynylcyclohexyl)benzamide¹⁰



¹⁰ Arcadi, A.; Cacchi, S.; Cascia, L.; Fabrizi, G.; Marinelli, F. *Org. Lett.* **2001**, 3, 2501-2504.

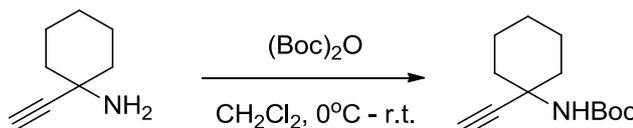
To a cooled (0 °C) solution of propargylamine (1.35 mL, 10.0 mmol) in CH₂Cl₂ (20 mL) was added triethylamine (1.67 mL, 12.0 mmol), DMAP (49 mg, 0.4 mmol) and benzoyl chloride (1.16 mL, 10.0 mmol). The solution was stirred overnight at room temperature, concentrated in vacuo and the residue was dissolved in ethyl acetate. The organic layer was washed with aqueous 10% HCl and brine, dried over Na₂SO₄, and concentrated in vacuo. The residue was purified by column chromatography over silica gel.

Yield: 71%; White solid; **R_f** (PE/Et₂O 3/1) 0.20; **¹H NMR** (300 MHz, CDCl₃): δ 7.76 (d, *J* = 7.0 Hz, 2H), 7.50-7.35 (m, 3H), 6.15 (br, 1H), 2.44 (s, 1H), 2.25-2.21 (m, 2H), 1.99-1.90 (m, 2H), 1.77-1.57 (m, 5H), 1.39-1.25 (s, 1H); **¹³C NMR** (300 MHz, CDCl₃): δ 166.4 (C=O), 135.0 (C), 131.5 (CH), 128.5 (CH × 2), 126.9 (CH × 2), 85.5 (C), 71.5 (CH), 52.1 (C), 36.9 (CH₂ × 2), 25.3 (CH₂), 22.5 (CH₂ × 2).



N-(1-Ethynylcyclohexyl)-*N*-(2-methylallyl)benzamide (**21**) was prepared according to procedure B. Yield: 59%; White solid; m.p. 88-90 °C; **R_f** (PE/Et₂O 5/1) 0.50; **IR** (neat) ν 3200, 2936, 1631, 1407, 739, 693 cm⁻¹; **¹H NMR** (300 MHz, CDCl₃): δ 7.43-7.29 (m, 5H), 5.12 (s, 1H), 4.97 (s, 1H), 3.96 (s, 2H), 2.56 (s, 1H), 2.37 (td, *J* = 4.4, 12.2 Hz, 2H), 2.22 (d, *J* = 11.6 Hz, 2H), 1.85-1.63 (m, 5H), 1.54 (s, 3H), 1.32-1.17 (m, 1H); **¹³C NMR** (300 MHz, CDCl₃): δ 172.9 (C=O), 143.5 (C), 138.8 (C), 129.2 (CH), 128.1 (CH × 2), 126.2 (CH × 2), 112.2 (CH₂), 84.7 (C), 74.7 (CH), 60.3 (C), 53.8 (CH₂), 34.3 (CH₂ × 2), 25.1 (CH₂), 23.6 (CH₂ × 2), 20.1 (CH₃); **HRMS** (ESI-MS) calcd. for C₁₉H₂₄NO⁺ ([M+H]⁺): 282.1852, found 282.1850.

tert-Butyl (1-ethynylcyclohexyl)carbamate¹¹

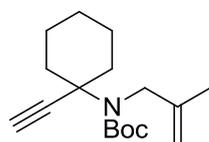


To a solution of 1-ethynylcyclohexanamine (0.68 mL, 5.0 mmol), triethylamine (0.84 mL,

¹¹ Dhand, V.; Draper, J. A.; Moore, J.; Britton, R. *Org. Lett.* **2013**, *15*, 1914-1917.

6.0 mmol), and DMAP (31 mg, 0.25 mmol) in CH₂Cl₂ (10 mL) was added a solution of di-*tert*-butyl dicarbonate (1.16 g, 5.3 mmol) in CH₂Cl₂ (8 mL). The solution was stirred at room temperature overnight, concentrated in vacuo and the residue was dissolved in ethyl acetate (30 mL). The organic layer was washed with water (20 mL) and brine (20 mL), dried over Na₂SO₄, and concentrated in vacuo. The residue was purified by recrystallization from AcOEt and petroleum ether to give desired compound.

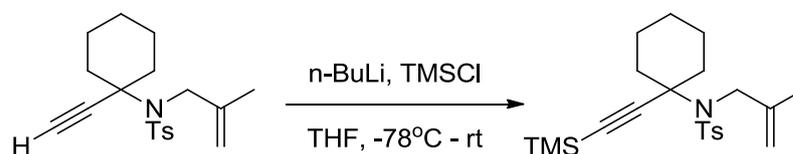
Yield: 72%; White solid; ¹H NMR (300 MHz, CDCl₃): δ 4.60 (br, 1H), 2.36 (s, 1H), 2.09-2.05 (m, 2H), 1.72-1.55 (m, 7H), 1.45 (s, 9H), 1.31-1.23 (s, 1H); ¹³C NMR (300 MHz, CDCl₃): δ 154.0 (C=O), 86.0 (C), 79.6 (C), 70.9 (CH), 51.2 (C), 37.3 (CH₂ x 2), 28.4 (CH₃ x 3), 25.3 (CH₂), 22.3 (CH₂ x 2).



tert-Butyl (1-ethynylcyclohexyl)(2-methylallyl)carbamate (**23**) was prepared according to procedure B. Yield: 85%; Colorless oil; *R_f* (PE/Et₂O 20/1) 0.45; IR (neat) ν 2931, 1692, 1366, 1235, 1157, 902, 647 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 4.88 (s, 1H), 4.82 (m, 1H), 4.01 (s, 2H), 2.49 (s, 1H), 2.15 (d, *J* = 12.1 Hz, 2H), 2.22 (td, *J* = 4.4, 12.3 Hz, 2H), 1.78-1.57 (m, 8H), 1.45 (s, 9H), 1.21-1.08 (m, 1H); ¹³C NMR (300 MHz, CDCl₃): δ 154.9 (C=O), 143.5 (C), 109.5 (CH₂), 85.4 (C), 79.9 (C), 74.0 (CH), 58.8 (C), 50.5 (CH₂), 35.6 (CH₂ x 2), 28.4 (CH₃ x 3), 25.1 (CH₂), 23.7 (CH₂ x 2), 20.1 (CH₃);

HRMS (ESI-MS) calcd. for C₁₇H₂₈NO₂⁺ ([M+H]⁺): 278.2115, found 278.2114.

4-methyl-*N*-(2-methylallyl)-*N*-(1-((trimethylsilyl)ethynyl)cyclohexyl)benzenesulfonamide (**25**)



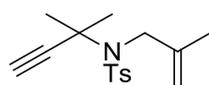
Based on a modification of the procedure reported by Kitamura.³ To a solution of *N*-(1-ethynylcyclohexyl)-4-methyl-*N*-(2-methylallyl)benzenesulfonamide (100 mg, 3.0 mmol) in THF (15 mL) was added 1.6 M ⁿBuLi (1.88 mL, 3.0 mmol) at -78°C. The solution was stirred at -78 °C for 30 minutes, and then TMSCl (0.51 mL, 4.0 mmol) was added. The

solution was warmed to room temperature within 4 h. The organic layer was washed with water, brine, dried over Na₂SO₄, and evaporated. The residue was purified by column chromatography over silica gel.

Yield: 94%; White solid; m.p. 71-72 °C; **R_f** (PE/Et₂O 30/1) 0.35; **IR** (neat) ν 2930, 1330, 1153, 867, 842, 665, 576, 548 cm⁻¹; **¹H NMR** (300 MHz, CDCl₃): δ 7.72 (d, *J* = 8.3 Hz, 2H), 7.25 (d, *J* = 8.3 Hz, 2H), 5.12 (s, 1H), 4.95-4.91 (m, 1H), 4.09 (s, 1H), 2.41 (s, 3H), 2.04-1.96 (m, 2H), 1.88 (td, *J* = 3.5, 12.4 Hz, 2H), 1.80 (s, 3H), 1.67-1.45 (m, 5H), 1.17-1.04 (m, 1H), 0.05 (s, 9H); **¹³C NMR** (300 MHz, CDCl₃): δ 143.5 (C), 142.9 (C), 139.6 (C), 129.5 (CH x 2), 127.7 (CH x 2), 112.0 (CH₂), 105.0 (C), 91.9 (C), 63.4 (C), 54.0 (CH₂), 38.0 (CH₂ x 2), 25.0 (CH₂), 23.9 (CH₂ x 2), 21.7 (CH₃), 20.6 (CH₃), 0.0 (CH₃ x 3); **HRMS** (ESI-MS) calcd. for C₂₂H₃₇N₂O₂SSi⁺ ([M+NH₄]⁺): 421.2340, found 421.2339.

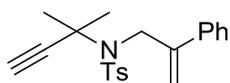


N-(1,1-Dimethyl-prop-2-ynyl)-4-methyl-benzenesulfonamide¹² was prepared according to procedure A. Yield: 64%; White solid; **R_f**(PE/AcOEt 5/1) 0.25; **¹H NMR** (300 MHz, CDCl₃): δ 7.81 (d, *J* = 8.3 Hz, 2H), 7.26 (d, *J* = 8.3 Hz, 2H), 5.39 (br s, 1H), 2.40 (s, 3H), 2.06 (s, 1H), 1.52 (s, 6H); **¹³C NMR** (300 MHz, CDCl₃): δ 143.2 (C), 138.9 (C), 129.2 (CH x 2), 127.6 (CH x 2), 85.4 (C), 71.2 (CH), 49.9 (C), 30.7 (CH₃ x 2), 21.5 (CH₃).

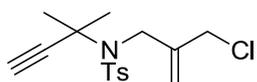


4-Methyl-*N*-(2-methylallyl)-*N*-(2-methylbut-3-yn-2-yl)benzenesulfonamide (**26**) was prepared according to procedure C. Yield: 87%; White solid; m.p. 60-62 °C; **R_f** (PE/Et₂O 10/1) 0.45; **IR** (neat) ν 3250, 1331, 1150, 899, 857, 765, 673, 576, 545 cm⁻¹; **¹H NMR** (400 MHz, CDCl₃): δ 7.72 (d, *J* = 8.3 Hz, 2H), 7.25 (d, *J* = 8.1 Hz, 2H), 5.08 (s, 1H), 4.93-4.92 (m, 1H), 4.10 (s, 2H), 2.40 (s, 3H), 2.19 (s, 1H), 1.78 (s, 3H), 1.64 (s, 6H); **¹³C NMR** (300 MHz, CDCl₃): δ 142.9 (C x 2), 139.2 (C), 129.2 (CH x 2), 127.5 (CH x 2), 112.2 (CH₂), 85.9 (C), 71.6 (CH), 56.3 (C), 53.8 (CH₂), 30.8 (CH₃ x 2), 21.4 (CH₃), 20.2 (CH₃); **HRMS** (ESI-MS) calcd. for C₁₆H₂₂NO₂S⁺ ([M+H]⁺): 292.1366, found 292.1366.

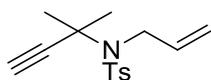
¹² Aronica, L. A.; Valentini, G.; Caporusso, A. M.; Salvadori, P. *Tetrahedron* **2007**, *63*, 6843-6854.



4-Methyl-N-(2-methylbut-3-yn-2-yl)-N-(2-phenylallyl)benzenesulfonamide (**28**) was prepared according to procedure C. Yield: 77%; White solid; m.p. 71-73 °C; R_f (PE/Et₂O 5/1) 0.40; **IR** (neat) ν 3264, 1327, 1150, 909, 701, 661, 577, 523 cm⁻¹; **¹H NMR** (400 MHz, CDCl₃): δ 7.77 (d, J = 8.3 Hz, 2H), 7.41-7.26 (m, 7H), 5.52 (d, J = 0.8 Hz, 1H), 5.47 (d, J = 0.8 Hz, 1H), 4.51 (t, J = 1.7 Hz, 2H), 2.42 (s, 3H), 2.16 (s, 1H), 1.71 (s, 6H); **¹³C NMR** (300 MHz, CDCl₃): δ 145.3 (C), 143.1 (C), 139.7 (C), 138.6 (C), 129.2 (CH \times 2), 128.3 (CH \times 2), 127.7 (CH \times 3), 126.1 (CH \times 2), 113.9 (CH₂), 85.7 (C), 71.5 (CH), 56.5 (C), 51.7 (CH₂), 30.8 (CH₃ \times 2), 21.4 (CH₃); **HRMS** (ESI-MS) calcd. for C₂₁H₂₄NO₂S⁺ ([M+H]⁺): 354.1522, found 354.1522.



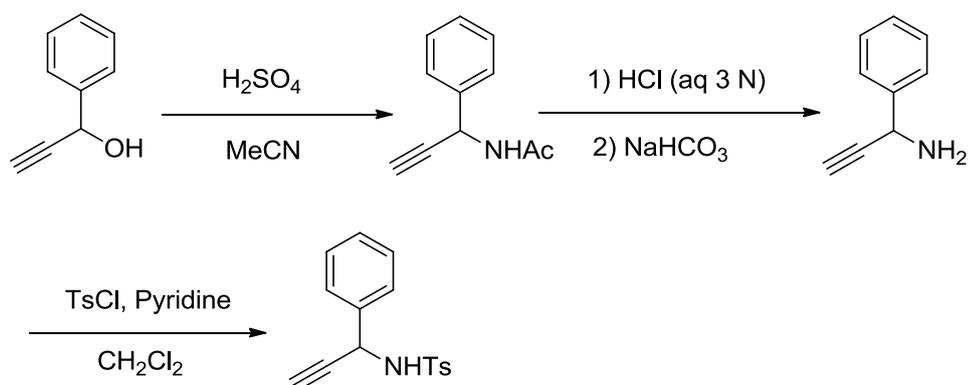
N-(2-(Chloromethyl)allyl)-4-methyl-N-(2-methylbut-3-yn-2-yl)benzenesulfonamide (**30**) was prepared according to procedure C. Yield: 66%; White solid; m.p. 102-104 °C; R_f (PE/Et₂O 4/1) 0.35; **IR** (neat) ν 3260, 1334, 1154, 1083, 927, 700, 642, 576, 538 cm⁻¹; **¹H NMR** (400 MHz, CDCl₃): δ 7.73 (d, J = 8.3 Hz, 2H), 7.28 (d, J = 8.1 Hz, 2H), 5.46 (s, 1H), 5.38 (d, J = 0.8 Hz, 1H), 4.27 (s, 2H), 4.15 (s, 2H), 2.42 (s, 3H), 2.20 (s, 1H), 1.67 (s, 6H); **¹³C NMR** (300 MHz, CDCl₃): δ 143.3 (C), 142.3 (C), 138.6 (C), 129.3 (CH \times 2), 127.6 (CH \times 2), 117.0 (CH₂), 85.6 (C), 71.8 (CH), 56.7 (C), 50.6 (CH₂), 46.3 (CH₂), 30.7 (CH₃ \times 2), 21.5 (CH₃); **HRMS** (ESI-MS) calcd. for C₁₆H₂₁NO₂SCl⁺ ([M+H]⁺): 326.0976, found 326.0976.



N-Allyl-4-methyl-N-(2-methylbut-3-yn-2-yl)benzenesulfonamide ¹³ (**32**) was prepared according to procedure C. Yield: 86%; White solid; R_f (PE/Et₂O 7/1) 0.30; **¹H NMR** (400 MHz, CDCl₃): δ 7.74(d, J = 8.3 Hz, 2H), 7.26 (d, J = 8.0 Hz, 2H), 6.02 (m, 1H), 5.27 (dd, J = 1.5, 17.2 Hz, 1H), 5.17 (dd, J = 1.5, 10.2 Hz, 1H), 4.17 (dt, J = 1.4, 5.9 Hz, 2H), 2.41 (s, 3H), 2.30 (s, 1H), 1.67 (s, 6H); **¹³C NMR** (300 MHz, CDCl₃): δ 142.9 (C), 139.7 (C), 136.7 (CH), 129.3 (CH \times 2), 127.3 (CH \times 2), 117.2 (CH₂), 86.3 (C), 71.8 (CH), 56.4 (C), 50.5 (CH₂), 30.6 (CH₃ \times 2), 21.5 (CH₃).

¹³ Shibata, T.; Toshida, N.; Yamasaki, M.; Maekawaa, S.; Takagi, K. *Tetrahedron* **2005**, *61*, 9974-9979.

4-Methyl-N-(1-phenyl-prop-2-ynyl)-benzenesulfonamide¹⁴ was prepared according to procedure A.



N-(1-phenylprop-2-yn-1-yl)acetamide¹⁵

A solution of 95% sulfuric acid (4.91 g, 50.0 mmol) in acetonitrile (20 mL) was added to a stirred mixture of 1-phenyl-2-propynyl-1-ol (1.32 g, 1.0 mmol) and anhydrous sodium sulfate (1.42 g, 10.0 mmol) in acetonitrile (30 mL) at -20 °C. The mixture was allowed to reach room temperature, left stirred for 48 h and then concentrated. The residue was poured on ice, and extracted with ether (80 mL) and then dichloromethane (80 mL). The combined organic layers were dried (Na₂SO₄), filtered, and concentrated. The residue was purified by column chromatography over silica gel to give *N*-(1-phenyl-propynyl)acetamide sufficiently pure for the next step.

Yield: 97%; White solid; **R_f** (PE/Et₂O 1/1) 0.25; **¹H NMR** (300 MHz, CDCl₃): δ 7.52-7.49 (m, 2H), 7.39-7.30 (m, 3H), 6.21-6.19 (m, 1H), 6.01 (dd, *J* = 2.3, 8.5 Hz, 1H), 2.49 (d, *J* = 2.2 Hz, 1H), 2.02 (s, 3H); **¹³C NMR** (300 MHz, CDCl₃): δ 168.9 (C=O), 138.3 (C), 128.8 (CH × 2), 128.3 (CH), 127.0 (CH × 2), 81.7 (C), 73.0 (CH), 44.5 (CH), 23.1 (CH₃).

1-Phenylprop-2-ynyl-1-amine

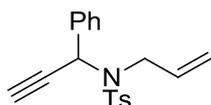
A suspension of *N*-(1-phenyl-2-propynyl) acetamide (9.0 mmol) in 3.0 N aqueous HCl (50 mL) was heated to 70 °C for 18 h. The resulting solution was extracted with Et₂O (50 mL). The aqueous layer was alkalized to pH ~ 8.5 by addition of solid NaHCO₃ and extracted with Et₂O (4 × 50 mL). The combined organic layers were dried (K₂CO₃), filtered, and concentrated in vacuo. The primary amine without further purification was converted to the corresponding tosylamide.

¹⁴ Zhan, Z.-P.; Yu, J.-I.; Liu, H.-J.; Cui, Y.-Y.; Yang, R.-F.; Yang, W.-Z.; Li, J.-P. *J. Org. Chem.* **2006**, *71*, 8298-8301.

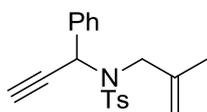
¹⁵ Messina, F.; Botta, M.; Corelli, F.; Schneider, M. P.; Fazio, F. *J. Org. Chem.* **1999**, *64*, 3767-3769.

4-Methyl-N-(1-phenyl-prop-2-ynyl)-benzenesulfonamide

Overall yield (2 steps): 63%; White solid; R_f (PE/Et₂O 2/1) 0.30; $^1\text{H NMR}$ (300 MHz, CDCl₃): δ 7.78 (d, J = 8.3 Hz, 2H), 7.47-7.44 (m, 2H), 7.35-7.28 (m, 5H), 5.33 (dd, J = 2.3, 8.7 Hz, 1H), 4.88 (d, J = 8.7 Hz, 1H), 2.44 (s, 3H), 2.32 (d, J = 2.4 Hz, 1H); $^{13}\text{C NMR}$ (300 MHz, CDCl₃): δ 143.6 (C), 137.3 (C), 137.0 (C), 129.5 (CH \times 2), 128.7 (CH \times 2), 128.5 (CH), 127.5 (CH \times 2), 127.2 (CH \times 2), 80.4 (C), 74.8 (CH), 48.9 (CH), 21.6 (CH₃).



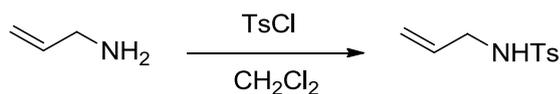
*N-Allyl-4-methyl-N-(1-phenylprop-2-yn-1-yl)benzenesulfonamide*⁴ (**36**) was prepared according to procedure E. Yield: 46%; White solid; R_f (PE/Et₂O 6/1) 0.30; $^1\text{H NMR}$ (300 MHz, CDCl₃): δ 7.81 (d, J = 8.3 Hz, 2H), 7.61-7.57 (m, 2H), 7.38-7.28 (m, 5H), 6.11 (d, J = 2.3 Hz, 1H), 5.43 (m, 1H), 4.85 (dd, J = 1.5, 17.1 Hz, 1H), 4.77 (dd, J = 1.3, 10.1 Hz, 1H), 3.79-3.62 (m, 2H), 2.45 (s, 3H), 2.40 (d, J = 2.5 Hz, 1H); $^{13}\text{C NMR}$ (300 MHz, CDCl₃): δ 143.5 (C), 136.4 (C), 135.9 (C), 134.2 (CH), 129.5 (CH \times 2), 128.3 (CH \times 3), 128.2 (CH \times 2), 127.9 (CH \times 2), 117.1 (CH₂), 78.3 (C), 76.6 (CH), 53.2 (CH), 48.0 (CH₂), 21.6 (CH₃).



4-Methyl-N-(2-methylallyl)-N-(1-phenylprop-2-yn-1-yl)benzenesulfonamide (**38**) was prepared according to procedure E. Yield: 47%; Yellow solid; m.p. 61-63 °C; R_f (PE/Et₂O 5/1) 0.50; IR (neat) ν 3277, 1354, 1162, 1094, 906, 664, 571, 547 cm⁻¹; $^1\text{H NMR}$ (400 MHz, C₆D₆): δ 7.68 (d, J = 8.3 Hz, 2H), 7.47-7.44 (m, 2H), 7.23-7.17 (m, 5H), 6.01 (d, J = 2.3 Hz, 1H), 4.53 (br s, 1H), 4.43 (br s, 1H), 3.63 (d, J = 15.4 Hz, 1H), 3.49 (d, J = 15.4 Hz, 1H), 2.34 (s, 3H), 2.27 (d, J = 2.4 Hz, 1H), 1.22 (s, 3H); $^{13}\text{C NMR}$ (400 MHz, CDCl₃): δ 143.5 (C), 140.9 (C), 135.9 (C), 135.8 (C), 129.4 (CH \times 2), 128.5 (CH \times 2), 128.3 (CH), 128.1 (CH \times 2), 127.9 (CH \times 2), 114.1 (CH₂), 77.6 (C), 76.9 (CH), 53.7 (CH), 51.5 (CH₂), 21.6 (CH₃), 19.5 (CH₃); HRMS (ESI-MS) calcd. for C₂₀H₂₂NO₂S⁺ ([M+H]⁺): 340.1366, found 340.1365.

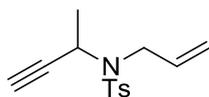
*N-Allyl-4-methyl-benzenesulfonamide*¹⁶

¹⁶ Blond, G.; Bour, C.; Salem, B.; Suffert, J. *Org. Lett.* **2008**, *10*, 1075-1078.

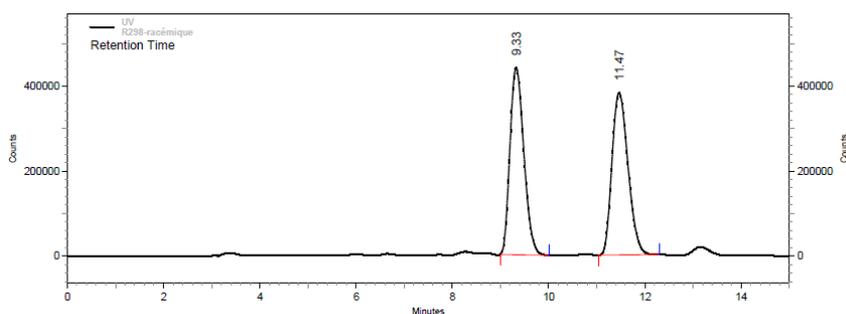


Based on a modification of the procedure reported by Kitamura.³ To a solution of allylamine (3.27 mL, 35.0 mmol) in CH₂Cl₂ (10 mL) was added *p*-toluenesulfonyl chloride (2.0 g, 10.5 mmol) at 0 °C, and the solution was stirred at room temperature overnight. The solvent was removed under reduced pressure and the residue was dissolved in ethyl acetate. The organic layer was washed with aqueous 10% HCl and brine, dried over Na₂SO₄, and evaporated. The residue was purified by column chromatography over silica gel.

Yield: 81%; Yellow solid; **R_f** (PE/ AcOEt 5/1) 0.30; **¹H NMR** (300 MHz, CDCl₃): δ 7.76 (d, *J* = 8.2 Hz, 2H), 7.29 (d, *J* = 8.1 Hz, 2H), 5.79-5.64 (m, 1H), 5.18-5.04 (m, 2H), 4.89 (br, 1H), 3.56 (d, *J* = 3.6 Hz, 2H), 2.41 (s, 3H); **¹³C NMR** (300 MHz, CDCl₃): δ 143.5 (C), 136.9 (C), 133.0 (CH), 129.7 (CH × 2), 127.2 (CH × 2), 117.5 (CH₂), 45.7 (CH₂), 21.5 (CH₃).



N-Allyl-*N*-(but-3-yn-2-yl)-4-methylbenzenesulfonamide¹⁷ (**40**) was prepared according to procedure F. Yield: 39%; White solid; **R_f** (PE/Et₂O 15/1) 0.25; Enantiomeric excess: 0.2%, determined by HPLC [Chiralpak AD-H, Heptane/ethanol = 95/5, flow rate = 1 ml/min, λ = 254 nm, t_R = 9.33 min, t_R = 11.47 min];

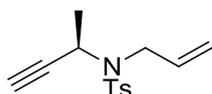


UV Results					
Retention Time	Area	Area %	Capacity factor	Relative RT	Resolution (USP)
9.33	8843300	49.92	2.11	1.00	0.00
11.47	8870267	50.08	2.82	1.34	3.67
Totals		17713567	100.00		

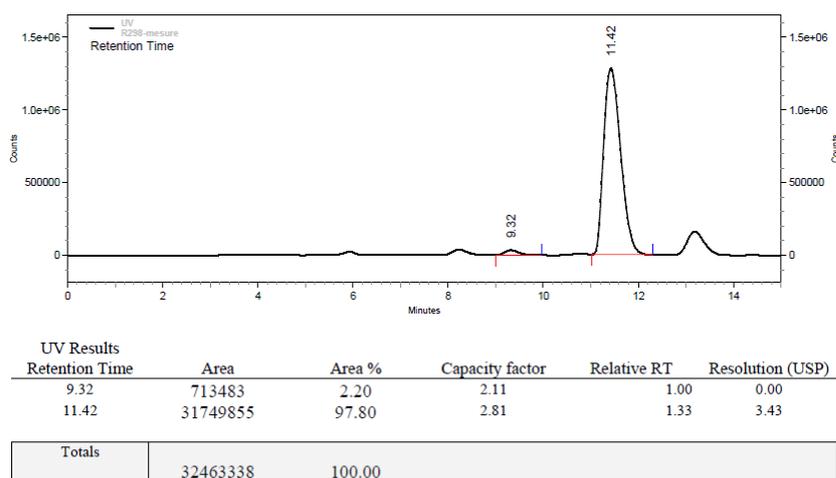
¹H NMR (400 MHz, CDCl₃): δ 7.72 (d, *J* = 8.3 Hz, 2H), 7.28 (d, *J* = 8.0 Hz, 2H), 5.91 (dddd,

¹⁷ Song, H.; Liu, Y.; Wang, Q. *Org. Lett.* **2013**, *15*, 3274-3277.

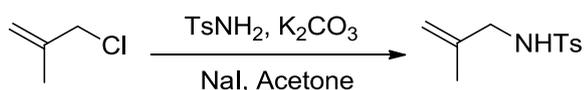
$J = 4.8, 6.9, 10.2, 17.1$ Hz, 1H), 5.26 (ddd, $J = 1.3, 2.9, 17.2$ Hz, 1H), 5.17 (ddd, $J = 1.3, 2.6, 10.2$ Hz, 1H), 4.90 (ddd, $J = 2.3, 7.1, 14.2$ Hz, 1H), 3.97-3.91 (m, 1H), 3.77-3.71 (m, 1H), 2.42 (s, 3H), 2.13 (d, $J = 2.4$ Hz, 1H), 1.44 (d, $J = 7.1$ Hz, 3H); ^{13}C NMR (400 MHz, CDCl_3): δ 143.4 (C), 136.4 (C), 135.8 (CH), 129.4 (CH \times 2), 127.6 (CH \times 2), 117.1 (CH_2), 81.3 (C), 73.3 (CH), 47.3 (CH_2), 46.1 (CH), 22.6 (CH_3), 21.5 (CH_3).



(*R*)-*N*-Allyl-*N*-(but-3-yn-2-yl)-4-methylbenzenesulfonamide (*R*)-**40** was prepared according to procedure F. Yield : 38%; White solid; R_f (PE/ Et_2O 15/1) 0.25; Enantiomeric excess: 96%, determined by HPLC [Chiralpak AD-H, Heptane/ethanol = 95/5, flow rate = 1 ml/min, $\lambda = 254$ nm, $t_R = 9.32$ min (minor), $t_R = 11.42$ min (major)]; $[\alpha]_D^{20} = +135.1^\circ$ ($c = 1.0$, chloroform);



4-Methyl-*N*-(2-methylallyl)benzenesulfonamide¹⁸ (**5**)

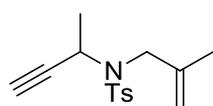


A mixture of 3-chloro-2-methyl-1-propene (0.98 mL, 10.0 mmol), TsNH_2 (3.77 g, 22.0 mmol), K_2CO_3 (5.52 g, 40.0 mmol), NaI (75 mg, 0.5 mmol) and acetone (20 mL) was heated at 60°C . After being stirred for 16 h, the solution was cooled to room temperature and

¹⁸ Onistschenkoi, A.; Buchholz, B.; Stamm, H. *Tetrahedron* **1987**, *43*, 565-576.

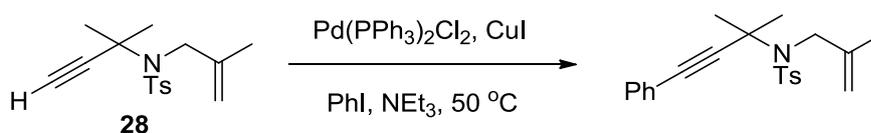
concentrated under reduced pressure. The residue was dissolved in ethyl acetate (20 mL). Water (20 mL) was added to the solution and the aqueous layer was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated in vacuo. The residue was purified by column chromatography over silica gel.

Yield: 62%; White solid; **R_f** (PE/ AcOEt 5/1) 0.30; **¹H NMR** (300 MHz, CDCl₃): δ 7.75 (d, *J* = 8.3 Hz, 2H), 7.29 (d, *J* = 8.2 Hz, 2H), 4.85 (s, 1H), 4.79 (s, 1H), 4.45 (br, 1H), 3.46 (d, *J* = 6.3 Hz, 2H), 2.41 (s, 3H), 1.66 (s, 3H); **¹³C NMR** (300 MHz, CDCl₃): δ 143.4 (C), 140.5 (C), 137.0 (C), 129.7 (CH × 2), 127.1 (CH × 2), 112.7 (CH₂), 49.0 (CH₂), 21.5 (CH₃), 20.1 (CH₃).



N-(*But-3-yn-2-yl*)-*4-methyl-N*-(*2-methylallyl*)benzenesulfonamide³ (**42**) was prepared according to procedure F. Yield: 16%; White solid; **R_f** (PE/Et₂O 10/1) 0.35; **¹H NMR** (300 MHz, CDCl₃): δ 7.72 (d, *J* = 8.3 Hz, 2H), 7.25 (d, *J* = 8.0 Hz, 2H), 5.04 (br s, 1H), 4.92 (br s, 1H), 4.90-4.85 (m, 1H), 3.89 (d, *J* = 16.1 Hz, 1H), 3.65 (d, *J* = 16.1 Hz, 1H), 2.42 (s, 3H), 2.10 (d, *J* = 2.3 Hz, 1H), 1.82 (s, 3H), 1.43 (d, *J* = 7.2 Hz, 3H); **¹³C NMR** (300 MHz, CDCl₃): δ 143.4 (C), 142.4 (C), 136.1 (C), 129.4 (CH × 2), 127.7 (CH × 2), 113.4 (CH₂), 80.8 (CH), 73.5 (C), 50.9 (CH₂), 46.6 (CH), 22.3 (CH₃), 21.5 (CH₃), 20.0 (CH₃).

4-Methyl-N-(*2-methyl-4-phenylbut-3-yn-2-yl*)-*N*-(*2-methylallyl*)benzenesulfonamide (**34**)

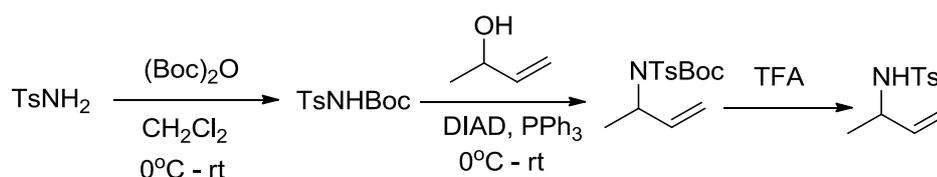


PdCl₂(PPh₃)₂ (35 mg, 0.05 mmol) and CuI (10 mg, 0.05 mol) were added to a solution of **28** (291 mg, 1.0 mmol) and iodobenzene (0.12 mL, 1.1 mmol) in triethylamine (8 mL). The resulting mixture was stirred at 50 °C for 20 h, then cooled to room temperature and concentrated under vacuum. The residue was purified by flash chromatography over silica gel.

Yield: 98%; Colorless oil; **R_f** (PE/Et₂O 10/1) 0.45; **IR** (neat) ν 2991, 2927, 1338, 1150, 1093, 765, 580, 552 cm⁻¹; **¹H NMR** (300 MHz, CDCl₃): δ 7.75 (d, *J* = 8.3 Hz, 2H), 7.28-7.13 (m,

7H), 5.15 (s, 1H), 4.97-4.86 (m, 1H), 4.14 (s, 2H), 2.33 (s, 3H), 1.82 (s, 3H), 1.74 (s, 6H); ^{13}C NMR (300 MHz, CDCl_3): δ 143.1 (C), 142.9 (C), 139.0 (C), 131.5 (CH \times 2), 129.3 (CH \times 2), 128.2 (CH), 128.1 (CH \times 2), 127.6 (CH \times 2), 122.5 (C), 112.0 (CH_2), 91.2 (C), 83.3 (C), 57.1 (C), 54.1 (CH_2), 31.1 ($\text{CH}_3 \times 2$), 21.4 (CH_3), 20.2 (CH_3); HRMS (ESI-MS) calcd. for $\text{C}_{22}\text{H}_{26}\text{NO}_2\text{S}^+$ ($[\text{M}+\text{H}]^+$): 368.1679, found 368.1676.

N-(but-3-en-2-yl)-4-methylbenzenesulfonamide⁵



tert-Butyl tosylcarbamate¹⁹

To a cooled solution (0 °C) of *p*-toluenesulfonamide (1.7 g, 10.0 mmol), triethylamine (1.7 mL, 12.0 mmol), and DMAP (61 mg, 0.5 mmol) in CH_2Cl_2 (20 mL) was added a solution of di-*tert*-butyl dicarbonate (2.6 g, 12.0 mmol) in CH_2Cl_2 (15 mL) and the solution was stirred at room temperature overnight. The solvent was removed under reduced pressure and the residue was dissolved in ethyl acetate (50 mL). The organic layer was washed with water (50 mL) and brine (50 mL), dried over Na_2SO_4 , and then concentrated in vacuo. The residue was purified by recrystallization from AcOEt and petroleum ether to give the desired tosylcarbamate.

Yield: 77%; White solid; ^1H NMR (300 MHz, CDCl_3): δ 7.89 (d, $J = 8.3$ Hz, 2H), 7.88 (br, 1H), 7.31 (d, $J = 8.1$ Hz, 2H), 2.43 (s, 3H), 1.36 (s, 9H); ^{13}C NMR (300 MHz, CDCl_3): δ 149.1 (C=O), 144.7 (C), 135.9 (C), 129.5 (CH \times 2), 128.2 (CH \times 2), 84.1 (C), 27.9 ($\text{CH}_3 \times 3$), 21.7 (CH_3).

tert-butyl but-3-en-2-yl(tosyl)carbamate²⁰

To a cooled solution (0 °C) of *tert*-butyl tosylcarbamate (1.63 g, 6.0 mmol), but-3-en-2-ol (0.52 mL, 6.0 mmol), and triphenylphosphine (2.36 g, 9.0 mmol) in THF (24 mL) was added diisopropyl azodicarboxylate (1.77 mL, 9.0 mmol), and then the reaction mixture was gradually warmed to room temperature, and stirred overnight. The solvent was removed under vacuum and the residue was purified by flash chromatography over silica gel.

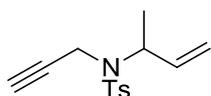
¹⁹ Wu, Q.; Hu, J.; Ren, X.; Zhou, J.(S.) *Chem. Eur. J.* **2011**, *17*, 11553-11558.

²⁰ Garzon, C.; Attolini, M.; Maffei, M. *Eur. J. Org. Chem.* **2013**, 3653-3657.

Yield: 88%; Pale yellow oil; R_f (PE/Et₂O 3/1) 0.45; $^1\text{H NMR}$ (300 MHz, CDCl₃): δ 7.76 (d, $J = 6.8$ Hz, 2H), 7.26 (d, $J = 7.0$ Hz, 2H), 6.16-6.00 (m, 1H), 5.24-5.06 (m, 3H), 2.40 (s, 3H), 1.55 (d, $J = 5.6$ Hz, 3H), 1.30 (s, 9H); $^{13}\text{C NMR}$ (300 MHz, CDCl₃): δ 150.5 (C=O), 143.9 (C), 138.5 (CH), 137.8 (C), 129.2 (CH x 2), 127.7 (CH x 2), 116.1 (CH₂), 84.1 (C), 56.3 (CH), 27.9 (CH₃ x 3), 21.6 (CH₃), 19.5 (CH₃).

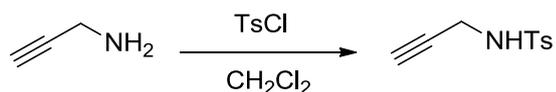
To a cooled solution (0 °C) of *tert*-butyl but-3-en-2-yl(tosyl)carbamate (1.63 g, 5 mmol) in CH₂Cl₂ (5 mL) added trifluoroacetic acid (4.6 mL, 60.0 mmol) at 0 °C. After stirring for 3 h, the mixture was concentrated in vacuum and purified by flash column chromatography over silica gel.

Yield: 76%; Pale yellow oil; R_f (PE/AcOEt 5/1) 0.30; $^1\text{H NMR}$ (300 MHz, CDCl₃): δ 7.75 (d, $J = 8.3$ Hz, 2H), 7.29 (d, $J = 8.0$ Hz, 2H), 5.64 (ddd, $J = 5.7, 10.4, 17.2$ Hz, 1H), 5.06 (d, $J = 17.2$ Hz, 1H), 4.98 (d, $J = 10.4$ Hz, 1H), 4.42 (d, $J = 7.0$ Hz, 1H), 3.97-3.84 (m, 1H), 2.42 (s, 3H), 1.18 (d, $J = 6.8$ Hz, 3H); $^{13}\text{C NMR}$ (300 MHz, CDCl₃): δ 143.3 (C), 139.0 (CH), 138.0 (C), 129.6 (CH x 2), 127.2 (CH x 2), 115.0 (CH₂), 51.6 (CH), 21.5 (CH₃), 21.4 (CH₃).



N-(but-3-en-2-yl)-4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide²¹ (**44**) was prepared according to procedure F. Yield: 39%; White solid; R_f (PE/Et₂O 10/1) 0.45; $^1\text{H NMR}$ (300 MHz, CDCl₃): δ 7.81 (d, $J = 8.3$ Hz, 2H), 7.28 (d, $J = 8.0$ Hz, 2H), 5.76 (ddd, $J = 4.7, 10.8, 17.1$ Hz, 1H), 5.19-5.10 (m, 2H), 4.60-4.48 (m, 1H), 4.14 (dd, $J = 2.5, 18.5$ Hz, 1H), 3.88 (dd, $J = 2.5, 18.5$ Hz, 1H), 2.42 (s, 3H), 2.14 (t, $J = 2.5$ Hz, 1H), 1.27 (d, $J = 7.0$ Hz, 3H); $^{13}\text{C NMR}$ (300 MHz, CDCl₃): δ 143.5 (C), 137.8 (C), 137.3 (CH), 129.4 (CH x 2), 127.5 (CH x 2), 117.1 (CH₂), 80.2 (C), 72.3 (CH), 54.8 (CH), 32.3 (CH₂), 21.5 (CH₃), 17.0 (CH₃).

4-Methyl-*N*-prop-2-ynyl-benzenesulfonamide¹⁷

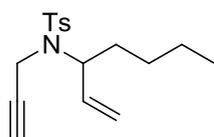


To a solution of propargylamine (2.2 mL, 35.0 mmol) in CH₂Cl₂ (10 mL) was added *p*-toluenesulfonyl chloride (2.0 g, 10.5 mmol) at 0 °C, and the solution was stirred at room

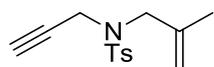
²¹ Pagenkopf, B. L.; Livinghouse, T. *J. Am. Chem. Soc.* **1996**, *118*, 2285-2286.

temperature overnight. The solvent was removed under reduced pressure and the residue was dissolved in ethyl acetate. The organic layer was washed with aqueous 10% HCl and brine, dried over Na₂SO₄, and evaporated. The residue was purified by column chromatography over silica gel.

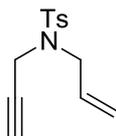
Yield: 72%; White solid; **R_f** (PE/Et₂O 30/10) 0.20; **¹H NMR** (300 MHz, CDCl₃): δ 7.77 (d, *J* = 8.3 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 4.83 (br, 1H), 3.82-3.81 (m, 2H), 2.43 (s, 3H), 2.10 (t, *J* = 2.5 Hz, 1H); **¹³C NMR** (300 MHz, CDCl₃): δ 143.9 (C), 136.5 (C), 129.7 (CH x 2), 127.4 (CH x 2), 78.0 (C), 73.0 (CH), 32.9 (CH₂), 21.6 (CH₃).



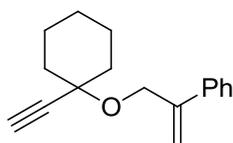
N-(hept-1-en-3-yl)-4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide (**46**) was prepared according to procedure E. Yield: 45%; Colorless oil; **R_f** (PE/Et₂O 3/1) 0.45; **IR** (neat) ν 2955, 1334, 1154, 1093, 1051, 669, 576, 548 cm⁻¹; **¹H NMR** (400 MHz, CDCl₃): δ 7.78 (d, *J* = 8.3 Hz, 2H), 7.26 (d, *J* = 8.0 Hz, 2H), 5.69 (ddd, *J* = 5.9, 10.6, 16.8 Hz, 1H), 5.12-5.06 (m, 2H), 4.33 (dd, *J* = 7.3, 13.6 Hz, 1H), 4.09 (dd, *J* = 2.5, 18.5 Hz, 1H), 3.90 (dd, *J* = 2.5, 18.5 Hz, 1H), 2.41 (s, 3H), 2.13 (t, *J* = 2.5 Hz, 1H), 1.66-1.58 (m, 2H), 1.32-1.18 (m, 4H), 0.83 (t, *J* = 7.0 Hz, 3H); **¹³C NMR** (300 MHz, CDCl₃): δ 143.2 (C), 137.8 (C), 136.0 (CH), 129.3 (CH x 2), 127.6 (CH x 2), 117.7 (CH₂), 79.9 (C), 72.1 (CH), 60.0 (CH), 32.4 (CH₂), 31.4 (CH₂), 28.4 (CH₂), 22.3 (CH₂), 21.5 (CH₃), 13.9 (CH₃); **HRMS** (ESI-MS) calcd. for C₁₇H₂₄NO₂S⁺ ([M+H]⁺): 306.1522, found 306.1523.



4-Methyl-*N*-(2-methylallyl)-*N*-(prop-2-yn-1-yl)benzenesulfonamide⁹ (**49**) was prepared according to procedure C. Yield: 82%; White solid; **R_f** (PE/AcOEt 10/1) 0.30; **¹H NMR** (400 MHz, CDCl₃): δ 7.74 (d, *J* = 8.3 Hz, 2H), 7.29 (d, *J* = 8.1 Hz, 2H), 4.97 (s, 2H), 4.05 (d, *J* = 2.4 Hz, 2H), 3.73 (s, 2H), 2.42 (s, 3H), 1.96 (t, *J* = 2.5 Hz, 1H), 1.76 (s, 3H); **¹³C NMR** (300 MHz, CDCl₃): δ 143.5 (C), 139.1 (C), 136.0 (C), 129.4 (CH x 2), 127.8 (CH x 2), 115.5 (CH₂), 76.3 (C), 73.7 (CH), 52.4 (CH₂), 35.4 (CH₂), 21.5 (CH₃), 19.6 (CH₃).

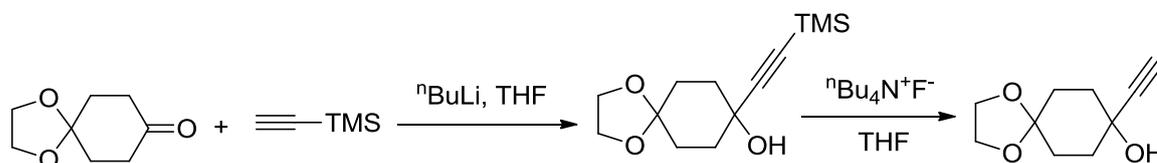


N-allyl-4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide²² (**52**) was prepared according to procedure E. Yield : 63%; White solid; R_f (PE/AcOEt 10/1) 0.30; $^1\text{H NMR}$ (300 MHz, CDCl_3): δ = 7.72 (d, J = 8.1 Hz, 2H), 7.28 (d, J = 8.2 Hz, 2H), 5.79-5.65 (m, 1H), 5.25 (t, J = 14.4 Hz, 2H), 4.08 (d, J = 2.2 Hz, 2H), 3.82 (d, J = 6.5 Hz, 2H), 2.41 (s, 3H), 2.00 (t, J = 2.5 Hz, 1H); $^{13}\text{C NMR}$ (300 MHz, CDCl_3): δ = 143.6 (C), 136.0 (C), 131.9 (CH), 129.5 (CH x 2), 127.7 (CH x 2), 120.0 (CH_2), 76.5 (C), 73.8 (CH), 49.0 (CH_2), 35.8 (CH_2), 21.5 (CH_3).



(3-((1-Ethynylcyclohexyl)oxy)prop-1-en-2-yl)benzene (**56**) was prepared according to procedure D. Yield : 71%; Colorless oil; R_f (PE/Et₂O 20/1) 0.30; IR (neat) ν 2934, 2853, 1447, 1073, 764, 697, 658 cm^{-1} ; $^1\text{H NMR}$ (300 MHz, CDCl_3): δ 7.53-7.50 (m, 2H), 7.38-7.30 (m, 3H), 5.53 (br s, 1H), 5.45 (br d, J = 1.5 Hz, 1H), 4.52 (s, 2H), 2.54 (s, 1H), 2.03-1.97 (m, 2H), 1.73-1.51 (m, 7H), 1.38-1.29 (m, 1H); $^{13}\text{C NMR}$ (300 MHz, CDCl_3): δ 145.0 (C), 139.3 (C), 128.2 (CH x 2), 127.6 (CH), 126.1 (CH x 2), 113.6 (CH_2), 85.2 (C), 74.0 (CH), 73.8 (C), 65.1 (CH_2), 37.2 (CH_2 x 2), 25.4 (CH_2), 22.7 (CH_2 x 2); HRMS (ESI-MS) calcd. for $\text{C}_{17}\text{H}_{20}\text{ONa}^+$ ($[\text{M}+\text{Na}]^+$): 263.1406, found 263.1411.

8-Ethynyl-1,4-dioxaspiro[4.5]decan-8-ol²³



A flame-dried round-bottom flask was charged with 2.5 M $^n\text{BuLi}$ (3.2 mL, 8.0 mmol) and anhydrous THF (25 mL). The resulting solution was cooled to $-78\text{ }^\circ\text{C}$ and ethynyltrimethylsilane (1.7 mL, 12.0 mmol) was added dropwise. After being stirred for 30

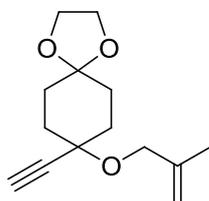
²² Huang, L.; Yang, H.-B.; Zhang, D.-H.; Zhang, Z.; Tang, X.-Y.; Xu, Q.; Shi, M. *Angew. Chem. Int. Ed.* **2013**, *52*, 6767-6771.

²³ Hiller, C.; Kling, R. C.; Heinemann, F. W.; Meyer, K.; Hubner, H.; Gmeiner, P. *J. Med. Chem.* **2013**, *56*, 5130-5141.

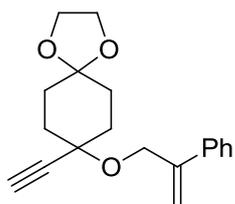
minutes at $-20\text{ }^{\circ}\text{C}$, the solution was cooled again to $-78\text{ }^{\circ}\text{C}$ and then the cyclic ketone (1.25 g, 8.0 mmol) dissolved in anhydrous THF (5 mL) was added dropwise. The reaction mixture was allowed to warm to room temperature and stirred overnight. After completion, saturated NH_4Cl solution was added. The mixture was extracted with Et_2O ($3 \times 50\text{ mL}$), and the organic phases were combined and washed with brine, dried over Na_2SO_4 , filtered and concentrated in vacuo to yield the crude propargylic alcohol which was used in the subsequent step without further purification.

To the above alcohol at $0\text{ }^{\circ}\text{C}$ was added a solution of tetrabutylammonium fluoride (1M in THF) (10 mL, 10.0 mmol) in THF (30 mL) with stirring. The reaction was allowed to warm to room temperature and stirred for 2 h. After completion of the reaction, THF was removed in vacuo, and the residue was purified by column chromatography to afford pure propargyl alcohol.

Overall yield: 84%; Colorless oil; R_f (PE/ Et_2O 1/1) 0.20; $^1\text{H NMR}$ (300 MHz, CDCl_3): δ 3.94 (s, 4H), 2.47 (s, 1H), 2.05 (br, 1H), 2.03-1.74 (m, 8H); $^{13}\text{C NMR}$ (300 MHz, CDCl_3): δ 107.9 (C), 138.9 (C), 87.0 (C), 72.0 (CH), 67.1 (C), 64.3 (CH_2), 64.2 (CH_2), 37.0 ($\text{CH}_2 \times 2$), 31.3 ($\text{CH}_2 \times 2$).

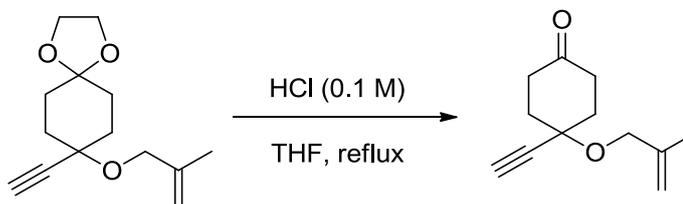


8-Ethynyl-8-((2-methylallyl)oxy)-1,4-dioxaspiro[4.5]decane (**58**) was prepared according to procedure D. Yield: 84%; Colorless oil; R_f (PE/ Et_2O 4/1) 0.40; IR (neat) ν 3292, 2957, 2879, 1372, 1251, 1162, 1102, 1038, 952, 931, 899, 667 cm^{-1} ; $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 5.00 (s, 1H), 4.86 (s, 1H), 3.98 (s, 2H), 3.94 (s, 4H), 2.45 (s, 1H), 1.99 (t, $J = 6.2\text{ Hz}$, 4H), 1.85-1.67 (m, 4H), 1.76 (s, 3H); $^{13}\text{C NMR}$ (400 MHz, CDCl_3): δ 142.6 (C), 111.5 (CH_2), 108.0 (C), 84.6 (C), 73.5 (CH), 71.9 (C), 67.7 (CH_2), 64.3 ($\text{CH}_2 \times 2$), 34.2 ($\text{CH}_2 \times 2$), 30.8 ($\text{CH}_2 \times 2$), 19.8 (CH_3); HRMS (ESI-MS) calcd. for $\text{C}_{14}\text{H}_{21}\text{O}_3^+$ ($[\text{M}+\text{H}]^+$): 237.1485, found 237.1485.



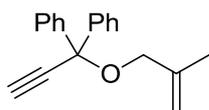
8-Ethynyl-8-((2-phenylallyl)oxy)-1,4-dioxaspiro[4.5]decane (**60**) was prepared according to procedure D. Yield: 75%; Colorless oil; R_f (PE/Et₂O 2/1) 0.40; **IR** (neat) ν 3291, 2995, 2881, 1370, 1257, 1161, 1104, 1073, 1037, 960, 927, 779, 708 cm⁻¹; **¹H NMR** (400 MHz, CDCl₃): δ 7.49-7.46 (m, 2H), 7.35-7.27 (m, 3H), 5.50 (br s, 1H), 5.41 (br d, $J = 1.4$ Hz, 1H), 4.47 (s, 2H), 3.95 (s, 4H), 2.51 (s, 1H), 2.03 (t, $J = 2.0$ Hz, 4H), 1.84 - 1.71 (m, 4H); **¹³C NMR** (300 MHz, CDCl₃): δ 144.7 (C), 139.2 (C), 128.3 (CH \times 2), 127.6 (CH), 126.1 (CH \times 2), 113.8 (CH₂), 108.0 (C), 84.4 (C), 73.9 (CH), 72.3 (C), 65.6 (CH₂), 64.3 (CH₂ \times 2), 34.2 (CH₂ \times 2), 30.9 (CH₂ \times 2); **HRMS** (ESI-MS) calcd. for C₁₉H₂₃O₃⁺ ([M+H]⁺): 299.1642, found 299.1642.

4-Ethynyl-4-((2-methylallyl)oxy)cyclohexanone (**62**)

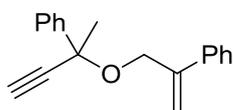


To a stirred solution of 8-ethynyl-8-((2-methylallyl)oxy)-1,4-dioxaspiro[4.5]decane **58** (0.95 g, 4.0 mmol) in THF (80 mL) was added 0.1 M HCl (12 mL). The solution was heated under reflux for 5 h, cooled to room temperature, neutralized with 0.1 M NaOH (12 mL), and extracted with ether (3 \times 15 mL). The combined organic layers were washed with water (50 mL), dried over Na₂SO₄ and concentrated under reduced pressure to yield a yellow oil which was purified by flash chromatography over silica gel.

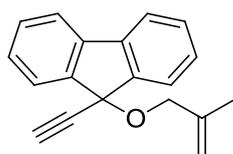
Yield: 52%; Waxy oil; R_f (PE/Et₂O 10/1) 0.35; **IR** (neat) ν 3246, 1713, 1112, 1047, 895, 725, 697 cm⁻¹; **¹H NMR** (400 MHz, CDCl₃): δ 5.03 (s, 1H), 4.90 (s, 1H), 4.07 (s, 2H), 2.60-2.36 (m, 4H), 2.56 (s, 1H), 2.33 - 2.12 (m, 4H), 1.79 (s, 3H); **¹³C NMR** (300 MHz, CDCl₃): δ 209.9 (C=O), 142.2 (C), 111.8 (CH₂), 83.3 (C), 74.6 (CH), 71.1 (C), 68.1 (CH₂), 37.0 (CH₂ \times 2), 36.1 (CH₂ \times 2), 19.8 (CH₃); **HRMS** (ESI-MS) calcd. for C₁₂H₂₀NO₂⁺ ([M+NH₄]⁺): 210.1489, found 210.1488.



(1-((2-methylallyl)oxy)prop-2-yn-1,1-diyl)dibenzene²⁴ (**64**) was prepared according to procedure D. Yield: 39%; Colorless oil; **R_f** (PE/Et₂O 50/1) 0.40; **¹H NMR** (300 MHz, CDCl₃): δ 7.61-7.57 (m, 4H), 7.35-7.23 (m, 6H), 5.11 (s, 1H), 4.91 (s, 1H), 3.93 (s, 2H), 2.90 (s, 1H), 1.80 (s, 3H); **¹³C NMR** (300 MHz, CDCl₃): δ 143.3 (C × 2), 142.3 (C), 128.2 (CH × 4), 127.7 (CH × 2), 126.6 (CH × 4), 111.3 (CH₂), 83.3 (C), 80.0 (C), 77.6 (CH), 68.5 (CH₂), 20.0 (CH₃).



(2-((2-phenylallyl)oxy)but-3-yn-2-yl)benzene (**66**) was prepared according to procedure D. Yield: 58%; Colorless oil; **R_f** (PE/Et₂O 20/1) 0.35; **IR** (neat) ν 3271, 2981, 1140, 1221, 1097, 1076, 906, 761, 708, 680, 609 cm⁻¹; **¹H NMR** (400 MHz, CDCl₃): δ 7.65-7.62 (m, 2H), 7.43-7.27 (m, 8H), 5.51 (br s, 1H), 5.43 (br d, *J* = 1.4, 1H), 4.52 (d, *J* = 12.2 Hz, 1H), 4.01 (d, *J* = 12.3 Hz, 1H), 2.78 (s, 1H), 1.80 (s, 3H); **¹³C NMR** (300 MHz, CDCl₃): δ 144.6 (C), 142.4 (C), 139.1 (C), 128.4 (CH × 2), 128.2 (CH × 2), 128.0 (CH), 127.7 (CH), 126.1 (CH × 2), 126.0 (CH × 2), 113.8 (CH₂), 83.9 (C), 76.1 (C), 75.8 (CH), 66.7 (CH₂), 32.9 (CH₃); **HRMS** (ESI-MS) calcd. for C₁₉H₁₈ONa⁺ ([M+Na]⁺): 285.1250, found 285.1250.

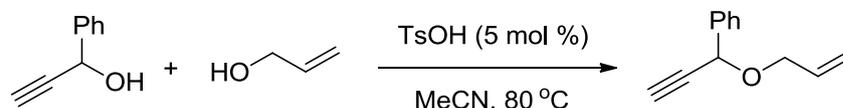


9-Ethynyl-9-((2-methylallyl)oxy)-9H-fluorene (**66**) was prepared according to procedure D. Yield: 56%; Yellow solid; m.p. 86-88 °C; **R_f** (PE/Et₂O 10/1) 0.40; **IR** (neat) ν 3278, 1447, 1207, 1044, 1027, 909, 736, 673, 645 cm⁻¹; **¹H NMR** (400 MHz, CDCl₃): δ 7.69 (d, *J* = 7.4 Hz, 2H), 7.64 (d, *J* = 7.4 Hz, 2H), 7.40 (td, *J* = 1.1, 7.5 Hz, 2H), 7.35 (td, *J* = 1.0, 7.4 Hz, 2H), 4.90 (s, 1H), 4.79 (s, 1H), 3.58 (s, 2H), 2.46 (s, 1H), 1.67 (s, 3H); **¹³C NMR** (300 MHz, CDCl₃): δ 144.0 (C), 141.9 (C × 2), 140.1 (C × 2), 129.8 (CH × 2), 128.3 (CH × 2), 125.0 (CH × 2), 120.1 (CH × 2), 112.2 (CH₂), 83.2 (C), 79.5 (C), 71.6 (CH), 68.1 (CH₂), 19.7

²⁴ Schmid, T. E.; Bantreil, X.; Citadelle, C. A.; Slawin A. M. Z.; Cazin, C. S. J. *Chem. Commun.*, **2011**, 47, 7060-7062.

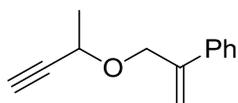
(CH₃); **HRMS** (ESI-MS) calcd. for C₁₉H₁₇O⁺ ([M+H]⁺): 261.1274, found 261.1277.

*(1-(allyloxy)prop-2-yn-1-yl)Benzene*²⁵ (**71**)



1-Phenylprop-2-yn-1-ol (1.4 mL, 10.0 mmol), allyl alcohol (2.1 mL, 30.0 mmol), and TsOH (86 mg, 0.5 mmol) were mixed in CH₃CN (50 mL). After being stirred for 12 h at 80 °C, the reaction mixture concentrated in vacuo. The residue was purified by column chromatography over silica gel.

Yield: 89%; Pale yellow oil; **R_f** (PE) 0.60; **¹H NMR** (300 MHz, CDCl₃): δ 7.53 (d, *J* = 6.9 Hz, 2H), 7.40-7.31 (m, 3H), 6.03-5.90 (m, 1H), 5.34 (ddd, *J* = 1.2, 3.2, 10.3 Hz, 1H), 5.25-5.22 (m, 2H), 4.23-4.09 (m, 2H), 2.64 (d, *J* = 2.2 Hz, 1H); **¹³C NMR** (300 MHz, CDCl₃): δ 138.1 (C), 134.1 (CH), 128.5 (CH × 2), 128.4 (CH), 127.4 (CH × 2), 117.9 (CH₂), 81.6 (C), 75.6 (CH), 70.4 (CH), 69.2 (CH₂).

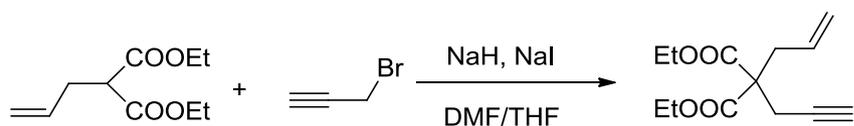


(3-(But-3-yn-2-yloxy)prop-1-en-2-yl)benzene (**72**) was prepared according to procedure D. Yield: 78%; Pale yellow oil; **R_f** (PE/Et₂O 50/1) 0.40; **IR** (neat) ν 3288, 1440, 1104, 1072, 761, 701 cm⁻¹; **¹H NMR** (400 MHz, CDCl₃): δ 7.52-7.46 (m, 2H), 7.37-7.27 (m, 3H), 5.56 (br s, 1H), 5.39 (br d, *J* = 1.2 Hz, 1H), 4.68 (dd, *J* = 0.8, 12.6 Hz, 1H), 4.35 (dd, *J* = 0.6, 12.6 Hz, 1H), 4.27 (dq, *J* = 2.0, 6.7 Hz, 1H), 2.46 (d, *J* = 2.0 Hz, 1H), 1.45 (d, *J* = 6.7 Hz, 3H); **¹³C NMR** (300 MHz, CDCl₃): δ 143.7 (C), 138.7 (C), 128.3 (CH × 2), 127.8 (CH), 126.1 (CH × 2), 114.8 (CH₂), 83.6 (C), 73.1 (CH), 70.4 (CH₂), 64.1 (CH), 22.0 (CH₃); **HRMS** (ESI-MS) calcd. for C₁₃H₁₅O⁺ ([M+H]⁺): 187.1117, found 187.1119.

*Diethyl 2-allyl-2-(prop-2-yn-1-yl)malonate*²⁶ (**76**)

²⁵ Shen, R.; Chen, K.; Deng, Q.; Yang, J.; Zhang, L. *Org. Lett.*, **2014**, *16*, 1208-1211.

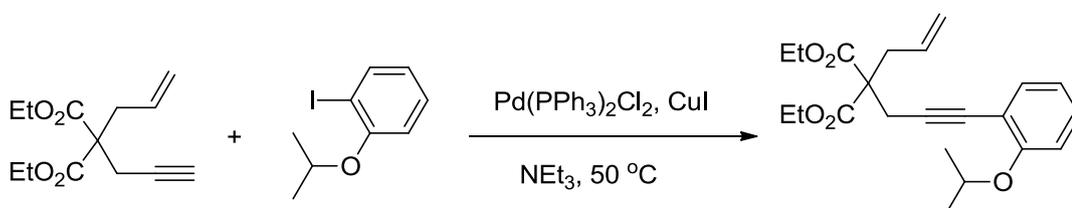
²⁶ Wu, J. Y.; Stanzl, B. N.; Ritter, T. *J. Am. Chem. Soc.* **2010**, *132*, 13214-13216.



To a cooled (0 °C) suspension of NaH (60% oil dispersion washed with PE) (0.45 g, 18.8 mmol) in THF/DMF (1/2, 60 mL) was added diethyl allylmalonate (3.0 mL, 15.2 mmol) dropwise. The resulting mixture was stirred for 1 h at 0 °C, then propargyl bromide (3.20 mL of 80 wt% solution in toluene, 18.6 mmol) and NaI (2.25 g, 15.2 mmol) were added. The mixture was stirred at room temperature for 12 h, then saturated aqueous NH₄Cl was added. The aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated in vacuo. The residue was purified by column chromatography over silica gel.

Yield: 77%; Pale yellow oil; **R_f** ((PE/EtOAc 20/1) 0.30; ¹H NMR (300 MHz, CDCl₃): δ, 5.67-5.56 (m, 1H), 5.18 (br d, *J* = 16.9 Hz, 1H), 5.12 (br d, *J* = 10.1 Hz, 1H), 4.20 (q, *J* = 7.1 Hz, 4H), 2.81-2.78 (m, 4H), 2.00 (t, *J* = 2.7 Hz, 1H), 1.25 (t, *J* = 7.1 Hz, 6H); ¹³C NMR (300 MHz, CDCl₃): δ 169.0 (C=O × 2), 131.7 (CH), 119.8 (CH₂), 78.9 (C), 71.4 (CH), 61.7 (CH₂ × 2), 56.6 (C), 36.3 (CH₂), 22.5 (CH₂), 14.1 (CH₃ × 2).

*Diethyl 2-allyl-2-(3-(2-isopropoxyphenyl)prop-2-yn-1-yl)malonate*²⁷ (**74**)



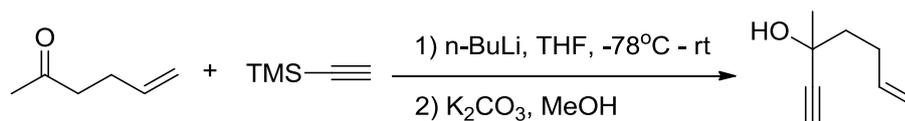
PdCl₂(PPh₃)₂ (35 mg, 0.05 mmol) and CuI (10 mg, 0.05 mol) were added to a solution of diethyl 2-allyl-2-(prop-2-yn-1-yl)malonate (238 mg, 1.0 mmol) and 1-iodo-2-isopropoxybenzene (288 mg, 1.1 mmol) in triethylamine (8 mL). The resulting mixture was stirred at 50 °C for 20 h, then cooled to room temperature and concentrated under vacuum. The residue was purified by flash chromatography over silica gel.

Yield : 98%; Colorless oil; **R_f** (PE/Et₂O 10/1) 0.45; ¹H NMR (300 MHz, CDCl₃): δ 7.32 (dd, *J* = 7.5, 1.6 Hz, 1H), 7.22-7.18 (m, 1H), 6.86-6.82 (m, 2H), 5.80-5.64 (m, 1H), 5.25 (d, *J* = 16.3 Hz, 1H), 5.14 (d, *J* = 10.1 Hz, 1H), 4.61-4.52 (m, 1H), 4.21 (q, *J* = 7.1 Hz, 4H), 3.06 (s,

²⁷ Fürstner, A.; Davies, P. W.; Gress, T. *J. Am. Chem. Soc.* **2005**, *127*, 8244-8245.

2H), 2.93 (d, $J = 7.5$ Hz, 2H), 1.35 (d, $J = 6.1$ Hz, 6H), 1.25 (t, $J = 7.1$ Hz, 6H); ^{13}C NMR (300 MHz, CDCl_3): δ 169.9 (C=O \times 2), 158.8 (C), 133.7 (CH), 132.2 (CH), 129.0 (CH), 120.3 (CH), 119.6 (CH_2), 114.3 (C), 114.2 (CH), 88.0 (C), 80.2 (C), 71.2 (CH), 61.5 ($\text{CH}_2 \times 2$), 57.1 (C), 36.5 (CH_2), 23.8 (CH_2), 22.1 ($\text{CH}_3 \times 2$), 14.1 ($\text{CH}_3 \times 2$).

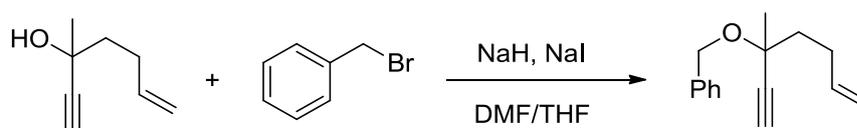
*3-Methylhept-6-en-1-yn-3-ol*²⁸ (**78**)



To a solution of ethynyltrimethylsilane (2.12 mL, 15 mmol) in THF (25 mL) was added 1.6 M $n\text{-BuLi}$ (6.25 mL, 10.0 mmol) at -78°C . The solution was stirred at -78°C for 30 minutes, and then hex-5-en-2-one (1.2 mL, 10.0 mmol) was added. The solution was warmed to room temperature within 2 h. The organic layer was washed with water, brine, dried over Na_2SO_4 , and evaporated. The crude alcohol was dissolved in MeOH (20 mL). To this solution was added potassium carbonate (276 mg, 2 mmol). The reaction was stirred for 6 hours at room temperature and then quenched with saturated NH_4Cl . The resulting mixture was extracted twice with diethyl ether and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography over silica gel.

Yield: 86%; Colorless oil; R_f (PE/ Et_2O 5/1) 0.30; ^1H NMR (300 MHz, CDCl_3): δ 5.94-5.81 (m, 1H), 5.09 (ddd, $J = 1.7, 3.4, 17.2$ Hz, 1H), 4.99 (ddd, $J = 1.3, 3.2, 10.2$ Hz, 1H), 2.46 (s, 1H), 2.39-2.22 (m, 2H), 1.95 (br s, 1H), 1.83-1.72 (m, 2H), 1.51 (s, 3H); ^{13}C NMR (300 MHz, CDCl_3): δ 138.2 (C), 115.0 (CH_2), 87.4 (C), 71.6 (CH), 68.0 (C), 42.4 (CH_2), 29.9 (CH_3), 29.1 (CH_2).

(((3-methylhept-6-en-1-yn-3-yl)oxy)methyl)benzene (**79**)

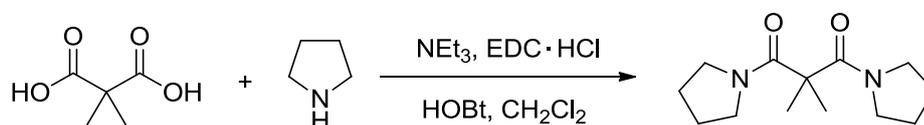


²⁸ Lemière, G.; Gandon, V.; Cariou, K.; Fukuyama, T.; Dhimane, A.-L.; Fensterbank, L.; Malacria, M. *Org. Lett.*, **2007**, 9, 2207-2209.

To a cooled (0 °C) suspension of NaH (60% oil dispersion washed with PE) (0.1 g, 2.5 mmol) in THF/DMF (1/2, 12 mL) was added 3-methylhept-6-en-1-yn-3-ol (0.37g, 3.0 mmol). The resulting mixture was stirred for 1 h at 0 °C, then benzyl bromide (0.36 mL, 3.0 mmol) and NaI (0.18 g, 4.5 mmol) were added. The mixture was stirred at room temperature for 12 h, then saturated aqueous NH₄Cl was added. The aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated in vacuo. The residue was purified by column chromatography over silica gel.

Yield : 55%; Colorless oil; **R_f** (PE/Et₂O 50/1) 0.60; **IR** (neat) ν 3296, 2984, 2927, 1455, 1062, 913, 736, 694, 637 cm⁻¹; **¹H NMR** (400 MHz, CDCl₃): δ 7.39-7.24 (m, 5H), 5.95-5.79 (m, 1H), 5.06 (dq, *J* = 1.7, 17.2 Hz, 1H), 4.89 (ddd, *J* = 1.3, 3.2, 10.2 Hz, 1H), 4.69 (d, *J* = 11.1 Hz, 1H), 4.60 (d, *J* = 11.1 Hz, 1H), 2.51 (s, 1H), 2.42-2.21 (m, 2H), 1.97-1.76 (m, 2H), 1.53 (s, 3H); **¹³C NMR** (300 MHz, CDCl₃): δ 139.0 (C), 138.3 (CH), 128.3 (CH × 2), 127.6 (CH × 2), 127.3 (CH), 114.5 (CH₂), 85.0 (C), 73.6 (CH), 73.3 (C), 66.3 (CH₂), 40.8 (CH₂), 28.6 (CH₂), 26.4 (CH₃); **HRMS** (ESI-MS) calcd. for C₁₅H₁₉O⁺ ([M+H]⁺): 215.1430, found 215.1432.

2,2-Dimethyl-1,3-di(pyrrolidin-1-yl)propane-1,3-dione (82)

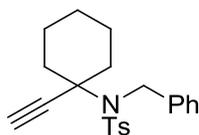


Based on a modification of the procedure reported by Valerio.²⁹ To a solution of 2,2-dimethylmalonic acid (1.06 g, 8.0 mmol) in dichloromethane (50 mL) were added consecutively pyrrolidine (1.34 mL, 16 mmol), triethylamine (2.23 mL, 16 mmol), 1-hydroxybenzotriazole hydrate (2.16 g, 16 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (3.07 g, 16 mmol), and the solution was stirred overnight at room temperature. The reaction was quenched with 0.5 M HCl. The aqueous phase was separated and extracted with dichloromethane. The organic phase was washed consecutively with sat. NaHCO₃ and brine. The combined organic layers were dried over Na₂SO₄, filtered, and concentrated in vacuo. The residue was purified by recrystallization from AcOEt to give the desired compound.

Yield: 75%; Pale yellow crystal; m.p. 170-171 °C; **IR** (neat) ν 2969, 2870, 1607, 1423, 1395;

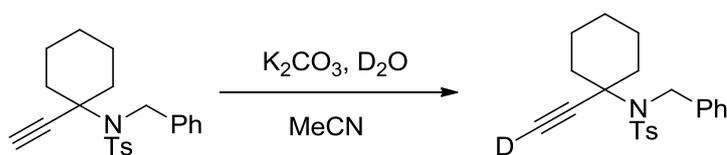
²⁹ Valerio, V.; Petkova, D.; Madelaine, C.; Maulide, N. *Chem. Eur. J.* **2013**, *19*, 2606–2610.

$^1\text{H NMR}$ (300 MHz, CDCl_3): 3.48 (t, $J = 6.8$ Hz, 4H), 3.23 (t, $J = 6.2$ Hz, 4H), 1.82 (m, 8H), 1.39 (s, 6H); $^{13}\text{C NMR}$ (300 MHz, CDCl_3): $\delta = 171.8$ (C \times 2), 49.5 (C), 47.2 ($\text{CH}_2 \times 2$), 46.3 ($\text{CH}_2 \times 2$), 26.7 ($\text{CH}_2 \times 2$), 23.5 ($\text{CH}_2 \times 2$), 23.3 ($\text{CH}_3 \times 2$); **HRMS** (ESI-MS) calcd. for $\text{C}_{13}\text{H}_{23}\text{N}_2\text{O}_2^+$ ($[\text{M}+\text{H}]^+$): 239.1754, found 239.1754.



N-Benzyl-*N*-(1-ethynylcyclohexyl)-4-methylbenzenesulfonamide (**84**) was prepared according to procedure C. Yield: 91%; White solid; m.p. 70-72 °C; **R_f** (PE/Et₂O 10/1) 0.35; **IR** (neat) ν 3274, 2934, 1455, 1331, 1153, 1094, 701, 542 cm^{-1} ; $^1\text{H NMR}$ (300 MHz, CDCl_3): δ 7.75 (d, $J = 8.3$ Hz, 2H), 7.54-7.52 (m, 2H), 7.40-7.35 (m, 2H), 7.31-7.26 (m, 3H), 4.89 (s, 2H), 2.45 (s, 3H), 2.34 (s, 1H), 2.08-2.04 (m, 2H), 1.90 (td, $J = 4.0, 12.5$ Hz, 2H), 1.66-1.49 (m, 5H), 1.16-1.03 (m, 1H); $^{13}\text{C NMR}$ (300 MHz, CDCl_3): δ 143.0 (C), 140.0 (C), 139.3 (C), 129.3 (CH \times 2), 128.3 (CH \times 2), 127.6 (CH \times 2), 127.3 (CH \times 2), 126.9 (CH), 83.4 (C), 75.4 (CH), 62.8 (C), 51.8 (CH_2), 37.9 ($\text{CH}_2 \times 2$), 24.6 (CH_2), 23.5 ($\text{CH}_2 \times 2$), 21.5 (CH_3); **HRMS** (ESI-MS) calcd. for $\text{C}_{22}\text{H}_{26}\text{NO}_2\text{S}^+$ ($[\text{M}+\text{H}]^+$): 368.1679, found 368.1677.

N-Benzyl-*N*-(1-Deutero-ethynylcyclohexyl)-4-methylbenzenesulfonamide (**[D]-84**)



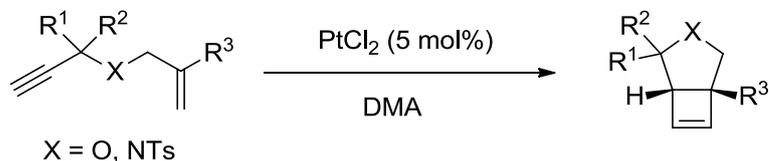
Based on a modification of the procedure reported by Bew.⁶ A flame dried 10 mL round bottomed flask was charged with **13** (37 mg, 1.0 mmol), potassium carbonate (207 mg, 1.5 mmol) and MeCN (4 mL). This was allowed to stir under an atmosphere of argon for 2 h, then D₂O (1 mL, 50.0 mmol) was added and left to stir for 10 h. The resulting crude reaction mixture was diluted with CH₂Cl₂ (10 mL) and transferred to a separating funnel. The organic layer was separated and dried with Na₂SO₄, filtered and concentrated under reduced pressure. The residue was used immediately in the subsequent step without further purification.

Yield: 98%, deuteration: 98%; White solid; m.p. 71-72 °C; **R_f** (PE/Et₂O 10/1) 0.35; **IR** (neat) ν 3030, 2938, 1451, 1331, 1154, 1095, 700, 548 cm^{-1} ; $^1\text{H NMR}$ (300 MHz, CDCl_3): δ 7.75 (d, $J = 8.3$ Hz, 2H), 7.54-7.52 (m, 2H), 7.40-7.35 (m, 2H), 7.31-7.26 (m, 3H), 4.88 (s, 2H),

2.46 (s, 3H), 2.34 (s, 1H), 2.08-2.04 (m, 2H), 1.89 (td, $J = 4.0, 12.5$ Hz, 2H), 1.66-1.49 (m, 5H), 1.16-1.03 (m, 1H); ^{13}C NMR (300 MHz, CDCl_3): δ 143.0 (C), 140.0 (C), 139.3 (C), 129.3 (CH \times 2), 128.3 (CH \times 2), 127.6 (CH \times 2), 127.3 (CH \times 2), 126.9 (CH), 83.1-82.8 (C, t, $J = 7.2$ Hz), 75.7-74.5 (C-D, t, $J = 38.7$ Hz), 62.8 (C), 51.8 (CH₂), 37.9 (CH₂ \times 2), 24.6 (CH₂), 23.5 (CH₂ \times 2), 21.5 (CH₃); HRMS (ESI-MS) calcd. for $\text{C}_{22}\text{H}_{25}\text{DNO}_2\text{S}^+$ ($[\text{M}+\text{H}]^+$): 369.1742, found 369.1741.

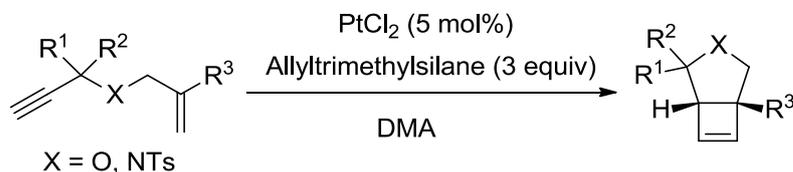
II. PtCl₂-catalyzed enyne cycloisomerizations

General procedure G

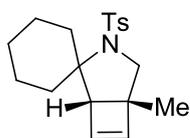


Under a argon atmosphere, PtCl₂ (2.7 mg, 0.01 mmol) was added to a solution of the enyne (0.2 mmol) in DMA (1 mL). The reaction mixture was stirred at 80-105 °C and monitored by TLC. Upon completion, the mixture was poured into water (10 mL), and extracted with diethyl ether (3 × 15 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by column chromatography over triethylamine-treated silica gel (eluent: petroleum ether / diethyl ether).

General procedure H



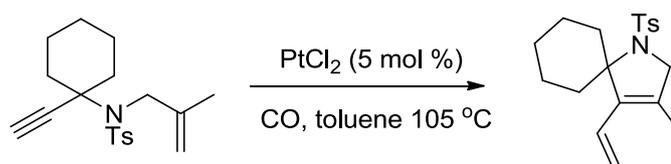
Under a argon atmosphere, PtCl₂ (2.7 mg, 0.01 mmol) was added to a solution of allyltrimethylsilane (69 mg, 0.6 mmol) and the enyne (0.2 mmol) in DMA (1 mL). The reaction mixture was stirred at 80-85 °C and monitored by TLC. Upon completion, the mixture was poured into water (10 mL), and extracted with diethyl ether (3 × 15 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by column chromatography over triethylamine-treated silica gel (eluent: petroleum ether / diethyl ether).



(1*S**,5*R**)-5-Methyl-3-tosyl-3-azaspiro[bicyclo[3.2.0]hept[6]ene-2,1'-cyclohexane] (**3**) was

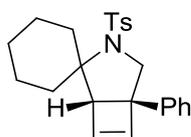
synthesized following the procedure G. Yield: 95%; White solid; m.p. 113-115 °C; R_f (PE/Et₂O 5/1) 0.45; **IR** (neat) ν 2950, 2862, 1321, 1140, 1093, 1056, 960, 815, 736, 657, 581, 543 cm⁻¹; **¹H NMR** (400 MHz, CDCl₃): δ 7.70 (d, J = 8.2 Hz, 2H), 7.22 (d, J = 8.1 Hz, 2H), 6.04 (d, J = 2.8 Hz, 1H), 6.00 (d, J = 2.8 Hz, 1H), 3.50 (d, J = 10.8 Hz, 1H), 3.22 (d, J = 10.8 Hz, 1H), 2.99 (s, 1H), 2.39 (s, 3H), 2.31 (td, J = 3.6, 12.8 Hz, 1H), 1.92-1.84 (m, 1H), 1.71-1.61 (m, 5H), 1.48-1.09 (m, 3H), 1.30 (s, 3H); **¹³C NMR** (400 MHz, CDCl₃): δ 142.34 (CH), 142.31 (C), 140.3 (C), 134.4 (CH), 129.1 (CH \times 2), 126.9 (CH \times 2), 68.7 (C), 58.4 (CH), 53.7 (CH₂), 49.8 (C), 32.9 (CH₂), 32.6 (CH₂), 25.2 (CH₂), 24.1 (CH₂), 23.4 (CH₂), 21.4 (CH₃), 20.8 (CH₃); **HRMS** (ESI-MS) calcd. for C₁₉H₂₆NO₂S⁺ ([M+H]⁺): 332.1679, found 332.1680.

*3-Methyl-1-tosyl-4-vinyl-1-azaspiro[4.5]dec-3-ene*³ (**4**)

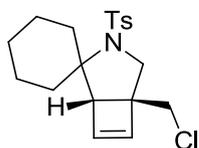


PtCl₂ (5.4 mg, 0.02 mmol) was added to a solution of the *N*-(1-ethynylcyclohexyl)-4-methyl-*N*-(2-methylallyl)benzenesulfonamide (66 mg, 0.2 mmol) in toluene (1 mL), CO was bubbled through the solution for 1 minute and the resulting mixture was stirred at 105 °C under CO atmosphere for 5 h. The solvent was evaporated and the residue purified by flash chromatography.

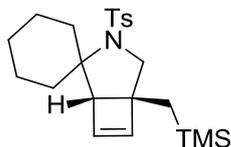
Yield : 65%; Pale yellow oil; R_f (PE/Et₂O 10/1) 0.50; **¹H NMR** (300 MHz, CDCl₃): δ 7.76 (d, J = 8.3 Hz, 2H), 7.29 (d, J = 8.0 Hz, 2H), 6.30 (ddd, J = 1.2, 11.1, 17.4 Hz, 1H), 5.30 (dd, J = 2.3, 11.1 Hz, 1H), 5.06 (dd, J = 2.3, 17.4 Hz, 1H), 3.94 (s, 2H), 2.62 (td, J = 5.9, 13.0 Hz, 2H), 2.40 (s, 3H), 1.83 (d, J = 12.6 Hz, 2H), 1.73-1.57 (m, J = 6H), 1.67 (d, J = 1.1 Hz, 3H); **¹³C NMR** (300 MHz, CDCl₃): δ 142.7 (C), 141.2 (C), 138.7 (C), 132.5 (CH), 129.4 (CH \times 2), 127.2 (CH \times 2), 127.1 (C), 119.4 (CH₂), 76.7 (C), 57.6 (CH₂), 36.3 (CH₂ \times 2), 24.4 (CH₂), 23.7 (CH₂ \times 2), 21.5 (CH₃), 12.7 (CH₃).



(1*S**,5*R**)-5-Phenyl-3-tosyl-3-azaspiro[bicyclo[3.2.0]hept[6]ene-2,1'-cyclohexane] (**8**) was synthesized following the procedure G. Yield : 80%; White solid; m.p. 122-124 °C; **R_f** (PE/Et₂O 5/1) 0.30; **IR** (neat) ν 2945, 2856, 1317, 1150, 1104, 984, 669, 609, 584, 547 cm⁻¹; **¹H NMR** (400 MHz, CDCl₃): δ 7.75 (d, *J* = 8.3 Hz, 2H), 7.35-7.22 (m, 7H), 6.37 (d, *J* = 2.9 Hz, 1H), 6.18 (d, *J* = 2.9 Hz, 1H), 3.79 (d, *J* = 11.0 Hz, 1H), 3.60 (d, *J* = 11.0 Hz, 1H), 3.51 (s, 1H), 2.46-2.37 (m, 1H), 2.41 (s, 3H), 1.91 (m, 1H), 1.79-1.14 (m, 8H); **¹³C NMR** (400 MHz, CDCl₃): δ 142.5 (C), 141.4 (C), 140.3 (CH), 140.0 (C), 136.0 (CH), 129.2 (CH \times 2), 128.5 (CH \times 2), 127.0 (CH \times 2), 126.7 (CH), 126.3 (CH \times 2), 68.4 (C), 59.4 (CH), 56.8 (C), 53.8 (CH₂), 33.1 (CH₂), 32.4 (CH₂), 25.3 (CH₂), 24.1 (CH₂), 23.3 (CH₂), 21.5 (CH₃); **HRMS** (ESI-MS) calcd. for C₂₄H₂₈NO₂S⁺ ([M+H]⁺): 394.1835, found 394.1833.

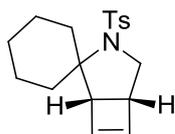


(1*S**,5*S**)-5-(Chloromethyl)-3-tosyl-3-azaspiro[bicyclo[3.2.0]hept[6]ene-2,1'-cyclohexane] (**10**) was synthesized following the procedure G. Yield: 96%; White solid; m.p. 98-100 °C; **R_f** (PE/Et₂O 5/1) 0.25; **IR** (neat) ν 2936, 2861, 1328, 1157, 1100, 984, 731, 662, 583, 547 cm⁻¹; **¹H NMR** (400 MHz, C₆D₆): δ 7.80 (d, *J* = 8.3 Hz, 2H), 6.80 (d, *J* = 8.2 Hz, 2H), 5.71 (d, *J* = 2.9 Hz, 1H), 5.67 (d, *J* = 2.9 Hz, 1H), 3.61 (d, *J* = 11.0 Hz, 1H), 3.43 (d, *J* = 11.0 Hz, 1H), 3.14 (d, *J* = 11.2 Hz, 1H), 3.11 (d, *J* = 11.2 Hz, 1H), 2.67 (s, 1H), 2.62 (m, 1H), 2.06 (td, *J* = 4.3, 13.1 Hz, 1H), 1.90 (s, 3H), 1.57 (dd, *J* = 2.3, 13.1 Hz, 1H), 1.48-0.76 (m, 7H); **¹³C NMR** (400 MHz, C₆D₆): δ 142.2 (C), 141.4 (C), 139.2 (CH), 136.8 (CH), 129.3 (CH \times 2), 127.4 (CH \times 2), 68.3 (C), 55.9 (CH), 54.5 (C), 50.8 (CH₂), 47.9 (CH₂), 33.4 (CH₂), 32.9 (CH₂), 25.5 (CH₂), 24.2 (CH₂), 23.4 (CH₂), 21.1 (CH₃); **HRMS** (ESI-MS) calcd. for C₁₉H₂₅NO₂SCl⁺ ([M+H]⁺): 366.1289, found 366.1290.

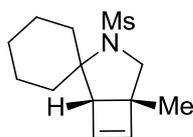


(1*S**,5*S**)-3-Tosyl-5-((trimethylsilyl)methyl)-3-azaspiro[bicyclo[3.2.0]hept[6]ene-2,1'-cyclohexane] (**12**) was synthesized following the procedure G. Yield: 99%; Colorless oil; **R_f** (PE/Et₂O 5/1) 0.30; **IR** (neat) ν 2928, 2861, 1326, 1247, 1154, 1093, 975, 836, 813, 669, 579, 546 cm⁻¹; **¹H NMR** (400 MHz, C₆D₆): δ 7.96 (d, *J* = 8.3 Hz, 2H), 6.88 (d, *J* = 8.0 Hz, 2H),

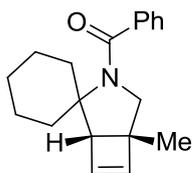
5.95 (d, $J = 2.9$ Hz, 1H), 5.85 (d, $J = 2.9$ Hz, 1H), 3.77 (d, $J = 10.8$ Hz, 1H), 3.36 (d, $J = 10.8$ Hz, 1H), 2.88 (s, 1H), 2.76-2.69 (m, 1H), 2.28-2.18 (m, 1H), 1.96 (s, 3H), 1.72-1.45 (m, 6H), 1.27-1.17 (m, 2H), 0.89 (d, $J = 14.6$ Hz, 1H), 0.81 (d, $J = 14.6$ Hz, 1H), 0.00 (s, 9H); ^{13}C NMR (400 MHz, C_6D_6): δ 142.5 (C), 142.1 (CH), 142.0 (C), 134.5 (CH), 129.3 (CH \times 2), 127.5 (CH \times 2), 68.3 (C), 61.2 (CH), 55.2 (CH₂), 52.7 (C), 33.4(CH₂), 33.0 (CH₂), 25.8 (CH₂), 24.9 (CH₂), 24.6 (CH₂), 23.8 (CH₂), 21.2 (CH₃), 0.0 (CH₃ \times 3); HRMS (ESI-MS) calcd. for $\text{C}_{22}\text{H}_{34}\text{NO}_2\text{SSi}^+$ ($[\text{M}+\text{H}]^+$): 404.2074, found 404.2070.



(*1S^*,5R^**)-3-Tosyl-3-azaspiro[bicyclo[3.2.0]hept[6]ene-2,1'-cyclohexane] (**14**) was synthesized following the procedure G. Yield: 80%; White solid; m.p. 118-120 °C; R_f (PE/Et₂O 5/1) 0.30; IR (neat) ν 2939, 2857, 1319, 1149, 1102, 983, 814, 668, 604, 581, 543 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 7.71 (d, $J = 8.3$ Hz, 2H), 7.23 (d, $J = 8.0$ Hz, 2H), 6.04 (d, $J = 3.0$ Hz, 1H), 6.03(d, $J = 3.0$ Hz, 1H), 3.53 (d, $J = 11.0$ Hz, 1H), 3.47 (d, $J = 3.7$ Hz, 1H), 3.40 (dd, $J = 6.4, 10.9$ Hz, 1H), 3.21 (dd, $J = 3.7, 6.4$ Hz, 1H), 2.40 (s, 3H), 1.85-1.13 (m, 10H); ^{13}C NMR (400 MHz, CDCl_3): δ 142.3 (C), 140.4(C), 138.5 (CH), 137.4 (CH), 129.1 (CH \times 2), 126.9 (CH \times 2), 67.8 (C), 52.8 (CH), 48.1 (CH₂), 42.6 (CH), 32.8 (CH₂), 31.7 (CH₂), 25.3 (CH₂), 24.2 (CH₂), 23.4 (CH₂), 21.4 (CH₃); HRMS (ESI-MS) calcd. for $\text{C}_{18}\text{H}_{24}\text{NO}_2\text{S}^+$ ($[\text{M}+\text{H}]^+$): 318.1522, found 318.1521.

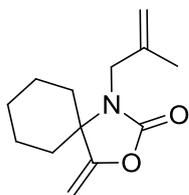


(*1S^*,5R^**)-5-Methyl-3-(methylsulfonyl)-3-azaspiro[bicyclo[3.2.0]hept[6]ene-2,1'-cyclohexane] (**20**) was synthesized following the procedure G. Yield: 96%; Yellow solid; m.p. 80-82 °C; R_f (PE/Et₂O 2/1) 0.25; IR (neat) ν 2931, 1316, 1139, 869, 753, 548, 520 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3): δ 6.13-6.11 (m, 2H), 3.46 (d, $J = 11.0$ Hz, 1H), 3.20 (d, $J = 11.0$ Hz, 1H), 3.02 (s, 1H), 2.89 (s, 3H), 2.41 (td, $J = 3.7, 12.9$ Hz, 1H), 1.93-1.83 (m, 1H), 1.79-1.59 (m, 5H), 1.46-1.35 (m, 1H), 1.32 (s, 3H), 1.27-1.19 (m, 2H); ^{13}C NMR (300 MHz, CDCl_3): δ 142.6 (CH), 134.5 (CH), 68.3 (C), 58.4 (CH), 53.6 (CH₂), 49.9 (C), 42.8 (CH₃), 33.3 (CH₂), 32.6 (CH₂), 25.2 (CH₂), 24.1 (CH₂), 23.5 (CH₂), 20.8 (CH₃); HRMS (ESI-MS) calcd. for $\text{C}_{13}\text{H}_{22}\text{NO}_2\text{S}^+$ ($[\text{M}+\text{H}]^+$): 256.1366, found 256.1366.

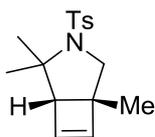


((1*S**,5*R**)-5-Methyl-3-azaspiro[bicyclo[3.2.0]hept[6]ene-2,1'-cyclohexan]-3-yl)(phenyl)methanone (**22**) was synthesized following the procedure G. Yield: 32%; Colorless oil; R_f (PE/Et₂O 5/1) 0.25;

IR (neat) ν 2924, 2857, 1636, 1384, 1114, 753, 723, 699, 663, 611 cm⁻¹; **¹H NMR** (300 MHz, CDCl₃): δ 7.37-7.35 (m, 5H), 6.21 (d, J = 2.8 Hz, 1H), 6.12 (d, J = 2.8 Hz, 1H), 3.51 (d, J = 11.6 Hz, 1H), 3.06 (s, 1H), 3.02 (d, J = 11.8 Hz, 1H), 2.22 (d, J = 12.1 Hz, 1H), 1.79-1.19 (m, 9H), 1.26 (s, 3H); **¹³C NMR** (300 MHz, CDCl₃): δ 172.7 (C=O), 142.1 (CH), 139.6 (C), 135.4 (CH), 129.0 (CH), 128.3 (CH \times 2), 126.6 (CH \times 2), 66.4 (C), 58.6 (CH), 55.9 (CH₂), 50.2 (C), 32.3 (CH₂), 30.4 (CH₂), 25.4 (CH₂), 23.9 (CH₂), 23.2 (CH₂), 21.1 (CH₃); **HRMS** (ESI-MS) calcd. for C₁₉H₂₄NO⁺ ([M+H]⁺): 282.1852, found 282.1851.

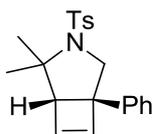


1-(2-methylallyl)-4-methylene-3-oxa-1-azaspiro[4.5]decan-2-one (**24**) was synthesized following the procedure G. Yield: 58%; Pale yellow oil; R_f (PE/Et₂O 1/1) 0.25; **IR** (neat) ν 2936, 1773, 1663, 1401, 1311, 1079, 967, 944, 907, 837, 759, 627, 588 cm⁻¹; **¹H NMR** (300 MHz, CDCl₃): δ 4.89-4.87 (m, 2H), 4.74 (d, J = 3.2 Hz, 1H), 4.51 (d, J = 3.1 Hz, 1H), 3.78 (s, 2H), 1.76-1.60 (m, 13H); **¹³C NMR** (300 MHz, CDCl₃): δ 158.8 (C=O), 154.7 (C), 141.3 (C), 111.9 (CH₂), 87.9 (CH₂), 63.7 (C), 45.5 (CH₂), 33.6 (CH₂ \times 2), 24.1 (CH₂), 21.4 (CH₂ \times 2), 20.0 (CH₃); **HRMS** (ESI-MS) calcd. for C₁₃H₂₀NO₂⁺ ([M+H]⁺): 222.1489, found 222.1491.

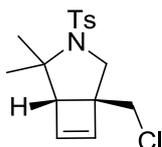


(1*R**,5*S**)-1,4,4-Trimethyl-3-tosyl-3-azabicyclo[3.2.0]hept-6-ene (**27**) was synthesized following the procedure G. Yield: 65%; Colorless oil; R_f (PE/Et₂O 10/1) 0.35; **IR** (neat) ν

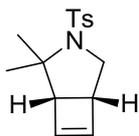
2925, 2866, 1322, 1156, 1092, 962, 713, 682, 654, 584, 550 cm^{-1} ; $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 7.71(d, $J = 8.3$ Hz, 2H), 7.24 (d, $J = 8.1$ Hz, 2H), 6.03 (s, 2H), 3.42 (d, $J = 10.6$ Hz, 1H), 3.09 (d, $J = 10.6$ Hz, 1H), 2.46 (s, 1H), 2.40 (s, 3H), 1.40 (s, 3H), 1.29 (s, 3H), 1.18 (s, 3H); $^{13}\text{C NMR}$ (400 MHz, CDCl_3): δ 142.6 (C), 142.2 (CH), 139.3 (C), 134.7 (CH), 129.2 (CH \times 2), 127.1 (CH \times 2), 64.9 (CH), 64.1 (C), 53.7 (CH_2), 49.9 (C), 24.4 (CH_3), 24.3 (CH_3), 21.5 (CH_3), 20.4 (CH_3); **HRMS** (ESI-MS) calcd. for $\text{C}_{16}\text{H}_{22}\text{NO}_2\text{S}^+$ ($[\text{M}+\text{H}]^+$): 292.1366, found 292.1365.



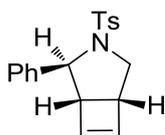
(*1R^*,5S^**)-4,4-Dimethyl-1-phenyl-3-tosyl-3-azabicyclo[3.2.0]hept-6-ene (**29**) was synthesized following the procedure H. Yield: 66%; White solid; m.p. 80-81 $^\circ\text{C}$; R_f (PE/Et₂O 5/1) 0.30; **IR** (neat) ν 2936, 1324, 1157, 1089, 1004, 989, 751, 699, 656, 596, 550 cm^{-1} ; $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 7.75 (d, $J = 8.3$ Hz, 2H), 7.35-7.22 (m, 7H), 6.36 (d, $J = 2.9$ Hz, 1H), 6.22 (d, $J = 2.9$ Hz, 1H), 3.72 (d, $J = 10.8$ Hz, 1H), 3.49 (d, $J = 10.8$ Hz, 1H), 2.98 (s, 1H), 2.42 (s, 3H), 1.51 (s, 3H), 1.31 (s, 3H); $^{13}\text{C NMR}$ (400 MHz, CDCl_3): δ 142.8 (C), 141.1 (C), 140.3 (CH), 139.0 (C), 136.2 (CH), 129.3 (CH \times 2), 128.6 (CH \times 2), 127.2 (CH \times 2), 126.8 (CH), 126.3 (CH \times 2), 66.0 (CH), 63.8 (C), 56.9 (C), 53.7 (CH_2), 24.4 ($\text{CH}_3 \times 2$), 21.5 (CH_3); **HRMS** (ESI-MS) calcd. for $\text{C}_{21}\text{H}_{24}\text{NO}_2\text{S}^+$ ($[\text{M}+\text{H}]^+$): 354.1522, found 354.1521.



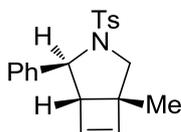
(*1S^*,5S^**)-1-(Chloromethyl)-4,4-dimethyl-3-tosyl-3-azabicyclo[3.2.0]hept-6-ene (**31**) was synthesized following the procedure G. Yield: 64%; Yellow solid; m.p. 70-71 $^\circ\text{C}$; R_f (PE/Et₂O 5/1) 0.30; **IR** (neat) ν 2925, 2870, 1324, 1149, 975, 719, 658, 591, 545 cm^{-1} ; $^1\text{H NMR}$ (400 MHz, C_6D_6): δ 7.78 (d, $J = 8.3$ Hz, 2H), 6.77 (d, $J = 8.0$ Hz, 2H), 5.68 (d, $J = 2.9$ Hz, 1H), 5.67 (d, $J = 2.9$ Hz, 1H), 3.51 (d, $J = 10.8$ Hz, 1H), 3.27 (d, $J = 10.8$ Hz, 1H), 3.09 (s, 2H), 2.01 (s, 1H), 1.88 (s, 3H), 1.37 (s, 3H), 1.06 (s, 3H); $^{13}\text{C NMR}$ (400 MHz, C_6D_6): δ 142.4 (C), 140.3 (C), 139.0 (CH), 136.9 (CH), 129.4 (CH \times 2), 127.5 (CH \times 2), 63.6 (C), 62.2 (CH), 54.5 (C), 50.8 (CH_2), 47.8 (CH_2), 24.6 (CH_3), 24.5 (CH_3), 21.1 (CH_3); **HRMS** (ESI-MS) calcd. for $\text{C}_{16}\text{H}_{20}\text{NO}_2\text{SClNa}^+$ ($[\text{M}+\text{Na}]^+$): 348.0795, found 348.0797.



(1*S**,5*R**)-2,2-Dimethyl-3-tosyl-3-azabicyclo[3.2.0]hept-6-ene (**33**) was synthesized following the procedure G. Yield: 85%; White solid; m.p. 87-89 °C; R_f (PE/Et₂O 5/1) 0.30; **IR** (neat) ν 2939, 2857, 1319, 1149, 983, 705, 668, 581, 543 cm⁻¹; **¹H NMR** (400 MHz, CDCl₃): δ 7.71 (d, J = 8.3 Hz, 2H), 7.24 (d, J = 8.1 Hz, 2H), 6.06 (d, J = 2.8 Hz, 1H), 6.03 (d, J = 2.8 Hz, 1H), 3.45 (d, J = 10.6 Hz, 1H), 3.27 (dd, J = 6.4, 10.6 Hz, 1H), 3.19 (dd, J = 3.7, 6.4 Hz, 1H), 2.93 (d, J = 3.6 Hz, 1H), 2.40 (s, 3H), 1.44 (s, 3 H), 1.14 (s, 3H); **¹³C NMR** (400 MHz, CDCl₃): δ 142.6 (C), 139.3 (C), 138.3 (CH), 137.6 (CH), 129.2 (CH \times 2), 127.1 (CH \times 2), 63.2 (C), 59.6 (CH), 48.0 (CH₂), 42.6(CH), 24.1 (CH₃), 23.7 (CH₃), 21.5 (CH₃); **HRMS** (ESI-MS) calcd. for C₁₅H₂₀NO₂S⁺ ([M+H]⁺): 278.1209, found 278.1209.



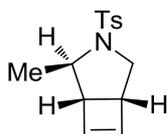
(1*S**,2*S**,5*R**)-2-Phenyl-3-tosyl-3-azabicyclo[3.2.0]hept-6-ene ³⁰ (**37**) was synthesized following the procedure G. Yield: 81%; White solid; m.p. 105-106 °C; R_f (PE/Et₂O 5/1) 0.25; **IR** (neat) ν 2919, 1339, 1155, 1105, 993, 700, 661, 588, 545 cm⁻¹; **¹H NMR** (400 MHz, CDCl₃): δ 7.53 (d, J = 8.3 Hz, 2H), 7.30-7.15 (m, 7H), 5.87 (d, J = 2.7 Hz, 1H), 5.75 (d, J = 2.7 Hz, 1H), 4.99 (s, 1H), 3.67 (d, J = 11.5 Hz, 1H), 3.46-3.42 (m, 2H), 3.31 (dd, J = 5.7, 11.7 Hz, 1H), 2.38 (s, 3H); **¹³C NMR** (400 MHz, CDCl₃): δ 142.6 (C), 140.9 (C), 138.4 (CH), 138.1 (CH), 137.6 (C), 129.1 (CH \times 2), 128.5 (CH \times 2), 127.2 (CH), 127.1 (CH \times 2), 126.7 (CH \times 2), 63.3 (CH), 55.1 (CH), 47.94 (CH₂), 47.91 (CH) 53.5 (CH₂), 21.5 (CH₃); **HRMS** (ESI-MS) calcd. for C₁₉H₁₉NO₂SNa⁺ ([M+Na]⁺): 348.1029, found 348.1030.



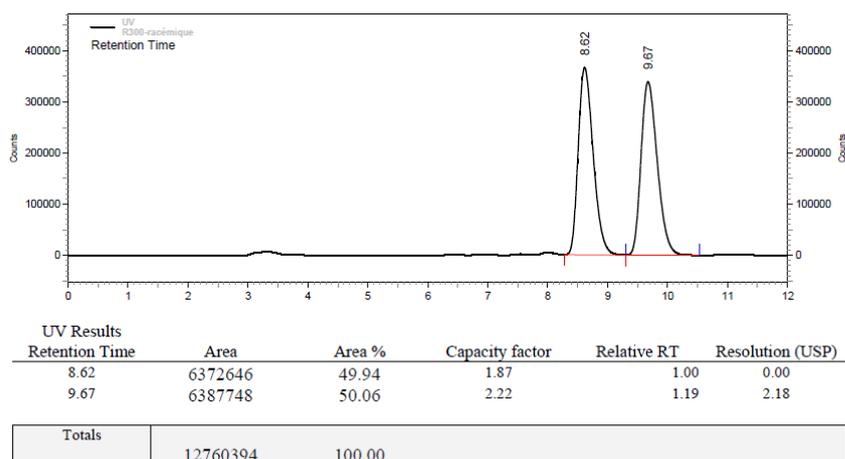
(1*R**,4*S**,5*S**)-1-Methyl-4-phenyl-3-tosyl-3-azabicyclo[3.2.0]hept-6-ene (**39**) was synthesized following the procedure G. Yield: 57%; Pale yellow oil; R_f (PE/Et₂O 3/1) 0.35; **IR** (neat) ν 2957, 2866, 1339, 1157, 1091, 1036, 957, 815, 749, 700, 662, 583, 542 cm⁻¹; **¹H NMR** (300 MHz, CDCl₃): δ 7.49 (d, J = 8.3 Hz, 2H), 7.28-7.13 (m, 7H), 5.87 (d, J = 2.8 Hz,

³⁰ Xia, J.-B.; Liu, W.-B.; Wang, T.-M.; You, S.-L. *Chem. Eur. J.* **2010**, *16*, 6442-6446.

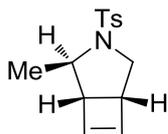
1H), 5.79 (d, $J = 2.8$ Hz, 1H), 4.96 (s, 1H), 3.66 (d, $J = 11.5$ Hz, 1H), 3.08 (d, $J = 11.5$ Hz, 1H), 2.97 (s, 1H), 2.37 (s, 3H), 1.30 (s, 3H); ^{13}C NMR (300 MHz, CDCl_3): δ 142.6 (C), 142.2 (CH), 140.9 (C), 137.6 (C), 135.8 (CH), 129.1 ($\text{CH} \times 2$), 128.6 ($\text{CH} \times 2$), 127.2 (CH), 127.1 ($\text{CH} \times 2$), 126.8 ($\text{CH} \times 2$), 64.4 (CH), 60.2 (CH), 55.7 (C), 53.5 (CH_2), 21.5 (CH_3), 20.1 (CH_3); HRMS (ESI-MS) calcd. for $\text{C}_{20}\text{H}_{22}\text{NO}_2\text{S}^+$ ($[\text{M}+\text{H}]^+$): 340.1366, found 340.1366.



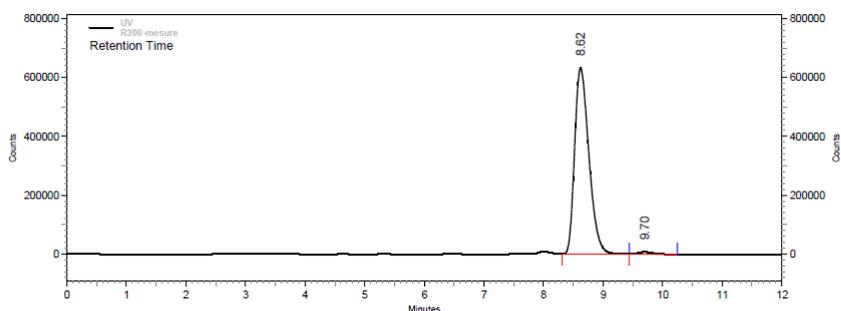
($1S^*,2R^*,5R^*$)-2-Methyl-3-tosyl-3-azabicyclo[3.2.0]hept-6-ene³⁰ (**41**) was synthesized following the procedure G. Yield: 68% ; White solid; m.p. 82-83 °C; R_f (PE/Et₂O 5/1) 0.30; Enantiomeric excess: 0.02%, determined by HPLC [Chiralpak AD-H, Heptane/ethanol = 80/20, flow rate = 1 ml/min, $\lambda = 254$ nm, $t_R = 8.62$ min, $t_R = 9.67$ min];



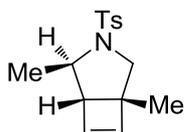
IR (neat) ν 2968, 2882, 1327, 1151, 1004, 657, 589, 545 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 7.68 (d, $J = 8.3$ Hz, 2H), 7.25 (d, $J = 8.6$ Hz, 2H), 5.70 (d, $J = 2.7$ Hz, 1H), 5.65 (d, $J = 2.7$ Hz, 1H), 3.94 (q, $J = 6.7$ Hz, 1H), 3.47 (d, $J = 11.6$ Hz, 1H), 3.30 (dd, $J = 3.3, 5.7$ Hz, 1H), 3.18 (dd, $J = 6.0, 11.6$ Hz, 1H), 2.95 (d, $J = 3.4$ Hz, 1H), 2.40 (s, 3H), 1.07 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (400 MHz, CDCl_3): δ 142.7 (C), 138.4 (CH), 138.2 (C), 137.6 (CH), 129.3 ($\text{CH} \times 2$), 127.1 ($\text{CH} \times 2$), 55.9 (CH), 54.2 (CH), 46.9 (CH), 46.0 (CH_2), 21.5 (CH_3), 18.6 (CH_3); HRMS (ESI-MS) calcd. for $\text{C}_{14}\text{H}_{18}\text{NO}_2\text{S}^+$ ($[\text{M}+\text{H}]^+$): 264.1053, found 264.1052.



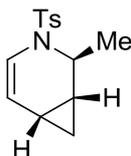
(1*S*, 2*R*, 5*R*)-2-Methyl-3-tosyl-3-azabicyclo[3.2.0]hept-6-ene³⁰ (1*S*, 2*R*, 5*R*)-**41** was synthesized following the procedure G. Yield: 62%; White solid; m.p. 82-83 °C; **R_f** (PE/Et₂O 5/1) 0.30; Enantiomeric excess: 98%, determined by HPLC [Chiralpak AD-H, Heptane/ethanol = 80/20, flow rate = 1 ml/min, λ = 254 nm, t_R = 8.62 min (major), t_R = 9.70 min (minor)]; [α]_D²⁰ = -31.7° (c = 1.0, chloroform);



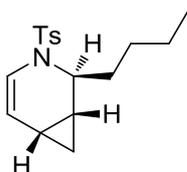
UV Results						
Retention Time	Area	Area %	Capacity factor	Relative RT	Resolution (USP)	
8.62	10534709	98.81	1.87	1.00	0.00	
9.70	126621	1.19	2.23	1.19	2.36	
Totals		10661330	100.00			



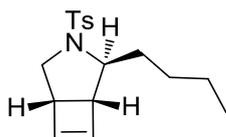
(1*R**, 4*R**, 5*S**)-1,4-Dimethyl-3-tosyl-3-azabicyclo[3.2.0]hept-6-ene (**43**) was synthesized following the procedure G. Yield: 23%; White solid; m.p. 110-112 °C; **R_f** (PE/Et₂O 10/1) 0.25; **IR** (neat) ν 2929, 1330, 1161, 1144, 1092, 1033, 661, 582, 548 cm⁻¹; **¹H NMR** (400 MHz, CDCl₃): δ 7.68 (d, *J* = 8.3 Hz, 2H), 7.25 (d, *J* = 8.0 Hz, 2H), 5.68 (s, 2H), 3.93 (q, *J* = 6.8 Hz, 1H), 3.45 (d, *J* = 11.4 Hz, 1H), 2.99 (d, *J* = 11.4 Hz, 1H), 2.48 (s, 1H), 2.41 (s, 3H), 1.29 (s, 3H), 1.10 (d, *J* = 6.7 Hz, 3H); **¹³C NMR** (300 MHz, CDCl₃): δ 142.7 (C), 141.4 (CH), 138.3 (C), 135.6 (CH), 129.3 (CH × 2), 127.1 (CH × 2), 59.7 (CH), 56.7 (CH), 54.8 (C), 51.6 (CH₂), 21.5 (CH₃), 20.4 (CH₃), 19.2 (CH₃); **HRMS** (ESI-MS) calcd. for C₁₅H₂₀NO₂S⁺ ([M+H]⁺): 278.1209, found 278.1209.



(1*R**,2*S**,6*R**)-2-methyl-3-tosyl-3-azabicyclo[4.1.0]hept-4-ene (**45**) was synthesized following the procedure G. Yield: 78%; White solid; m.p. 81-83 °C; R_f (PE/Et₂O 10/1) 0.50; **IR** (neat) ν 2966, 1341, 1168, 994, 707, 683, 545 cm⁻¹; **¹H NMR** (300 MHz, CDCl₃): δ 7.64 (d, J = 8.3 Hz, 2H), 7.29 (d, J = 8.1 Hz, 2H), 6.14 (d, J = 7.8 Hz, 1H), 5.50 (dd, J = 5.8, 7.8 Hz, 1H), 4.25 (d, J = 6.4 Hz, 1H), 2.42 (s, 3H), 1.39-1.32 (m, 1H), 1.26 (d, J = 6.5 Hz, 3H), 1.14-1.08 (m, 1H), 0.60 (ddd, J = 4.6, 8.3, 12.9 Hz, 1H), -0.32 (dd, J = 4.5, 10.0 Hz, 1H); **¹³C NMR** (300 MHz, CDCl₃): δ 143.2 (C), 136.3 (C), 129.6 (CH x 2), 126.7 (CH x 2), 118.0 (CH), 114.8 (CH), 46.7 (CH), 27.7 (CH₃), 21.5 (CH₃), 20.6 (CH), 14.1 (CH₂), 7.0 (CH); **HRMS** (ESI-MS) calcd. for C₁₄H₁₈NO₂S⁺ ([M+H]⁺): 264.1053, found 264.1055.

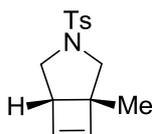


(1*R**,2*S**,6*R**)-2-butyl-3-tosyl-3-azabicyclo[4.1.0]hept-4-ene (**47**) was synthesized following the procedure G. Yield: 33%; white solid; m.p. 60-62 °C; R_f (PE/Et₂O 10/1) 0.45; **IR** (neat) ν 2930, 2850, 1345, 1161, 1097, 1034, 952, 715, 690, 661, 559, 545 cm⁻¹; **¹H NMR** (400 MHz, CDCl₃): δ 7.62 (d, J = 8.3 Hz, 2H), 7.29 (d, J = 8.0 Hz, 2H), 6.12 (m, 1H), 5.52 (dd, J = 5.8, 7.7 Hz, 1H), 4.10 (t, J = 6.6 Hz, 1H), 2.41 (s, 3H), 1.65-1.28 (m, 7H), 1.13-1.03 (m, 1H), 0.91 (t, J = 7.2 Hz, 3H), 0.54 (ddd, J = 4.6, 8.3, 12.9 Hz, 1H), -0.60 (dd, J = 4.4, 10.0 Hz, 1H); **¹³C NMR** (300 MHz, CDCl₃): δ 143.2 (C), 136.2 (C), 129.6 (CH x 2), 126.8 (CH x 2), 118.5 (CH), 116.4 (CH), 51.1 (CH), 34.4 (CH₂), 28.5 (CH₂), 26.5 (CH), 22.7 (CH₂), 21.5 (CH₃), 14.2 (CH₂), 14.0 (CH₃), 7.2 (CH); **HRMS** (ESI-MS) calcd. for C₁₇H₂₄NO₂S⁺ ([M+H]⁺): 306.1522, found 306.1523.

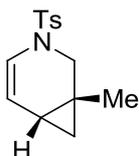


(1*R**,2*S**,5*S**)-2-butyl-3-tosyl-3-azabicyclo[3.2.0]hept-6-ene (**48**) was synthesized following the procedure G. Yield: 16%; Pale yellow oil; R_f (PE/Et₂O 10/1) 0.30; **IR** (neat) ν 2952, 2870, 1342, 1189, 1150, 1101, 1055, 984, 814, 682, 595, 552 cm⁻¹; **¹H NMR** (400 MHz, CDCl₃): δ

7.67 (d, $J = 8.3$ Hz, 2H), 7.24 (d, $J = 8.0$ Hz, 2H), 5.58 (d, $J = 2.7$ Hz, 1H), 5.50 (d, $J = 2.7$ Hz, 1H), 3.81 (t, $J = 6.8$ Hz, 1H), 3.50 (d, $J = 12.0$ Hz, 1H), 3.25 (dd, $J = 3.4, 5.9$ Hz, 1H), 3.18 (dd, $J = 6.0, 12.0$ Hz, 1H), 3.04 (d, $J = 3.4$ Hz, 1H), 2.40 (s, 3H), 1.40-1.25 (m, 6H), 0.89-0.85 (m, 3H); ^{13}C NMR (400 MHz, CDCl_3): δ 142.6 (C), 138.5 (CH), 138.4 (C), 137.6 (CH), 129.2 (CH x 2), 127.2 (CH x 2), 60.8 (CH), 52.4 (CH), 47.3 (CH), 47.0 (CH_2), 33.1 (CH_2), 28.2 (CH_2), 22.6 (CH_2), 21.5 (CH_3), 14.0 (CH_3); HRMS (ESI-MS) calcd. for $\text{C}_{17}\text{H}_{24}\text{NO}_2\text{S}^+$ ($[\text{M}+\text{H}]^+$): 306.1522, found 306.1522.

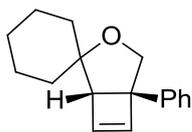


($1R^*,5S^*$)-1-methyl-3-tosyl-3-azabicyclo[3.2.0]hept-6-ene (**50**) was synthesized following the procedure G. Yield: 17%; White solid; m.p. 77-79°C; R_f (PE/Et₂O 5/1) 0.40; IR (neat) ν 2852, 1341, 1160, 1027, 1005, 809, 660, 583, 547 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 7.68 (d, $J = 8.2$ Hz, 2H), 7.32 (d, $J = 8.0$ Hz, 2H), 6.00 (d, $J = 2.8$ Hz, 1H), 5.95 (d, $J = 2.8$ Hz, 1H), 3.44 (dd, $J = 1.8, 10.0$ Hz, 2H), 2.75 (d, $J = 6.0$ Hz, 1H), 2.54 (dd, $J = 6.0, 10.0$ Hz, 1H), 2.43 (s, 3H), 2.24 (d, $J = 10.0$ Hz, 1H), 1.21 (s, 3H); ^{13}C NMR (400 MHz, CDCl_3): δ 143.2 (C), 141.9 (CH), 134.9 (CH), 133.4 (C), 129.5 (CH x 2), 127.8 (CH x 2), 54.1 (C), 53.8 (CH_2), 51.8 (CH), 48.4 (CH_2), 21.5 (CH_3), 19.7 (CH_3); HRMS (ESI-MS) calcd. for $\text{C}_{14}\text{H}_{18}\text{NO}_2\text{S}^+$ ($[\text{M}+\text{H}]^+$): 264.1053, found 264.1053.

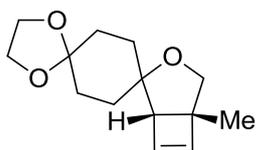


($1R^*,6R^*$)-1-methyl-3-tosyl-3-azabicyclo[4.1.0]hept-4-ene³¹ (**51**) was synthesized following the procedure G. Yield: 76%; White solid; R_f (PE/Et₂O 5/1) 0.25; ^1H NMR (300 MHz, CDCl_3): δ 7.65 (d, $J = 8.3$ Hz, 2H), 7.31 (d, $J = 8.1$ Hz, 2H), 6.28 (d, $J = 7.9$ Hz, 1H), 5.40 (dd, $J = 5.6, 7.9$ Hz, 1H), 3.84 (d, $J = 11.3$ Hz, 1H), 2.72 (d, $J = 11.3$ Hz, 1H), 2.42 (s, 3H), 1.11 (s, 3H), 0.95-0.90 (m, 1H), 0.62 (ddd, $J = 1.0, 4.4, 8.1$ Hz, 1H), 0.56 (t, $J = 4.3$ Hz, 1H); ^{13}C NMR (300 MHz, CDCl_3): δ 143.6 (C), 135.0 (C), 129.7 (CH x 2), 127.0 (CH x 2), 120.3 (CH), 112.7 (CH), 46.0 (CH_2), 25.7 (C), 21.9 (CH), 21.5 (CH_3), 20.2 (CH_2), 15.9 (CH_3).

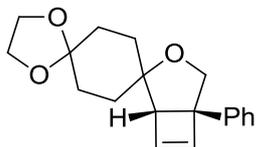
³¹ Benedetti, E.; Simonneau, A.; Hours, A.; Amouri, H.; Penoni, A.; Palmisano, G.; Malacria, M.; Goddard, J.-P.; Fensterbank, L.; *Adv. Synth. Catal.* **2011**, 353, 1908-1902.



(1*S**,5*R**)-5-Phenyl-3-oxaspiro[bicyclo[3.2.0]hept[6]ene-2,1'-cyclohexane] (**57**) was synthesized following the procedure H. Yield: 75%; yellow solid; m.p. 48-50 °C; **R_f** (PE/Et₂O 10/1) 0.35; **IR** (neat) ν 2929, 2854, 1497, 1448, 1037, 956, 804, 740, 701, 552, 524 cm⁻¹; **¹H NMR** (400 MHz, C₆D₆): δ 7.19-7.15 (m, 4H), 7.10-7.05 (m, 1H), 6.23 (d, *J* = 2.7 Hz, 1H), 6.07 (d, *J* = 3.0 Hz, 1H), 3.86 (d, *J* = 9.7 Hz, 1H), 3.71 (d, *J* = 9.7 Hz, 1H), 2.92 (s, 1H), 1.78-1.65 (m, 4H), 1.49-1.21 (m, 6H); **¹³C NMR** (300 MHz, C₆D₆): δ 141.8 (C), 140.7 (CH), 135.7 (CH), 128.3 (CH \times 2), 126.6 (CH \times 2), 126.2 (CH), 79.3 (C), 69.4 (CH₂), 62.9 (C), 62.0 (CH), 34.2 (CH₂), 32.6 (CH₂), 25.9 (CH₂), 23.4 (CH₂), 22.4 (CH₂); **HRMS** (ESI-MS) calcd. for C₁₇H₂₀ONa⁺ ([M+Na]⁺): 263.1406, found 263.1405.

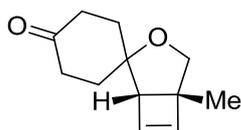


(11*S**,14*R**)-11-Methyl-1,4,9-trioxadispiro[4.2.6.2.0^{11,14}]hexadec-12-ene (**59**) was synthesized following the procedure H. Yield: 55%; yellow solid; m.p. 42-44 °C; **R_f** (PE/Et₂O 2/1) 0.50; **IR** (neat) ν 2951, 2929, 1372, 1107, 1094, 1036, 938, 809, 746, 664 cm⁻¹; **¹H NMR** (400 MHz, CDCl₃): δ 6.13 (d, *J* = 2.9 Hz, 1H), 6.08 (d, *J* = 2.9 Hz, 1H), 3.93 (dd, *J* = 2.6, 4.9 Hz, 4H), 3.64 (d, *J* = 9.7 Hz, 1H), 3.34 (d, *J* = 9.7 Hz, 1H), 2.60 (s, 1H), 1.88-1.43 (m, 8H), 1.32 (s, 3H); **¹³C NMR** (400 MHz, CDCl₃): δ 142.9 (CH), 134.3 (CH), 108.7 (C), 78.5 (C), 69.7 (CH₂), 64.3 (CH₂), 64.2 (CH₂), 60.3 (CH), 55.5 (C), 31.7 (CH₂), 31.4 (CH₂), 30.7 (CH₂), 29.4 (CH₂), 19.2 (CH₃); **HRMS** (ESI-MS) calcd. for C₁₄H₂₁O₃⁺ ([M+H]⁺): 237.1485, found 237.1484.

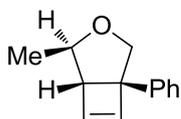


(11*S**,14*R**)-11-Phenyl-1,4,9-trioxadispiro[4.2.6.2.0^{11,14}]hexadec-12-ene (**61**) was synthesized following the procedure H. Yield: 55%; colorless oil; **R_f** (PE/Et₂O 3/1) 0.30; **IR** (neat) ν 2940, 2876, 1376, 1167, 1101, 1036, 941, 815, 741, 699 cm⁻¹; **¹H NMR** (400 MHz, C₆D₆): δ 7.15-7.12 (m, 4H), 7.09-7.05 (m, 1H), 6.19 (d, *J* = 2.9 Hz, 1H), 6.00 (d, *J* = 2.9 Hz, 1H), 3.82 (d, *J* = 9.7 Hz, 1H), 3.62 (d, *J* = 9.7 Hz, 1H), 3.58-3.52 (m, 4H), 2.88 (s, 1H),

2.22-2.06 (m, 2H), 1.94-1.82 (m, 3H), 1.72-1.60 (m, 3H); ^{13}C NMR (300 MHz, C_6D_6): δ 141.5 (C), 140.8 (CH), 135.7 (CH), 128.3 ($\text{CH} \times 2$), 126.6 ($\text{CH} \times 2$), 126.2 (CH), 108.6 (C), 78.2 (C), 69.4 (CH_2), 64.0 (CH_2), 63.9 (CH_2), 62.9 (C), 62.0 (CH), 32.0 (CH_2), 31.5 (CH_2), 31.0 (CH_2), 29.6 (CH_2); **HRMS** (ESI-MS) calcd. for $\text{C}_{19}\text{H}_{23}\text{O}_3^+$ ($[\text{M}+\text{H}]^+$): 299.1642, found 299.1641.



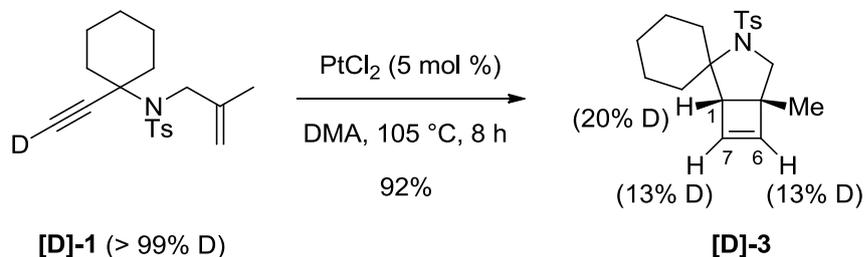
(*1S^*,5R^**)-5-Methyl-3-oxaspiro[bicyclo[3.2.0]hept[6]ene-2,1'-cyclohexan]-4'-one (**63**) was synthesized following the procedure H. Yield: 73%; Pale yellow oil; R_f (PE/Et₂O 3/1) 0.30; **IR** (neat) ν 2926, 2863, 1713, 1438, 1311, 1136, 1032, 912, 812, 745, 676 cm^{-1} ; ^1H NMR (300 MHz, C_6D_6): δ 5.86 (d, $J = 2.9$ Hz, 1H), 5.76 (d, $J = 2.9$ Hz, 1H), 3.46 (d, $J = 9.6$ Hz, 1H), 2.98 (d, $J = 9.6$ Hz, 1H), 2.64-2.38 (m, 2H), 2.19-2.01 (m, 2H), 2.10 (s, 1H), 1.78- 1.68 (m, 1H), 1.59-1.50 (m, 1H), 1.41-1.35 (m, 1H), 1.09-0.98 (m, 1H), 1.01 (s, 3H); ^{13}C NMR (300 MHz, C_6D_6): δ 208.5 (C=O), 142.7 (CH), 133.9 (CH), 77.4 (C), 69.2 (CH_2), 60.3 (CH), 55.3 (C), 38.0 (CH_2), 36.7 (CH_2), 33.4 (CH_2), 31.2 (CH_2), 18.7 (CH_3); **HRMS** (ESI-MS) calcd. for $\text{C}_{12}\text{H}_{17}\text{O}_2^+$ ($[\text{M}+\text{H}]^+$): 193.1223, found 193.1221.



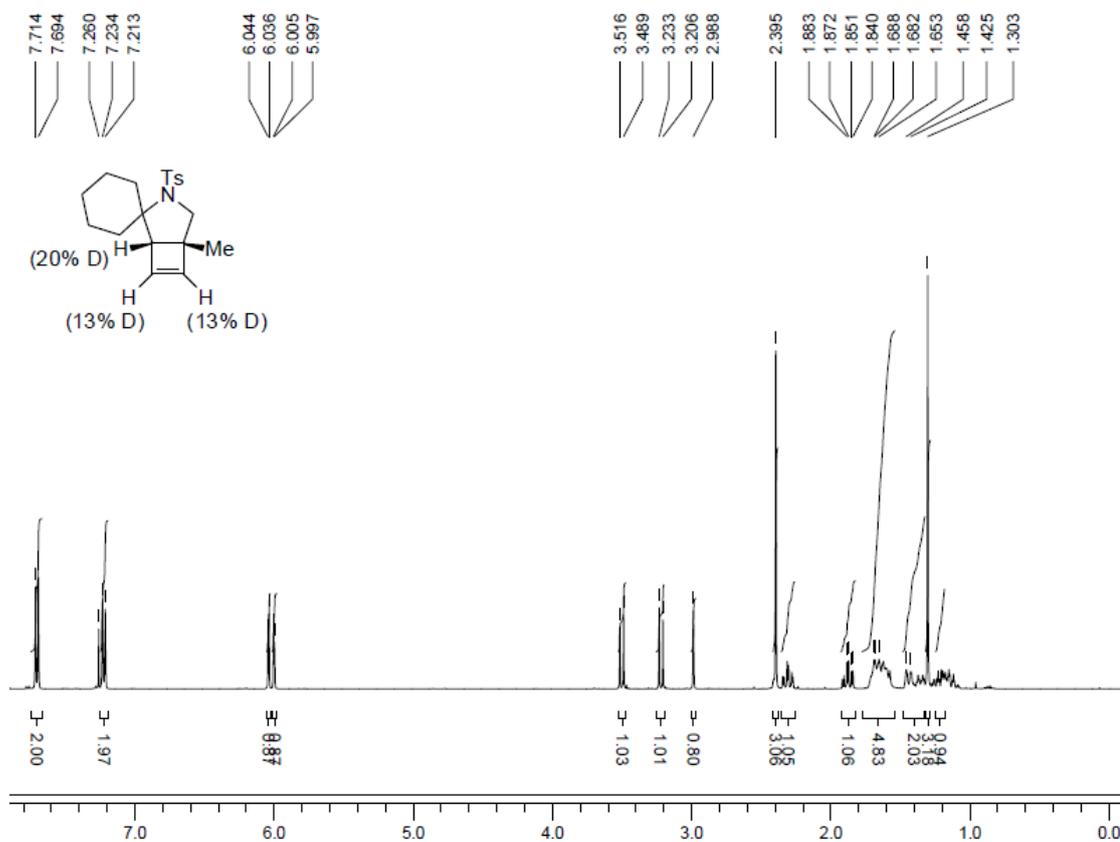
(*1R^*,4R^*,5S^**)-4-Methyl-1-phenyl-3-oxabicyclo[3.2.0]hept-6-ene (**73**) was synthesized following the procedure H. Yield: 32%; Pale yellow oil; R_f (PE/Et₂O 20/1) 0.30; **IR** (neat) ν 2972, 2846, 1493, 1446, 1381, 1104, 828, 777, 755, 700, 522 cm^{-1} ; ^1H NMR (300 MHz, C_6D_6): δ 7.28-7.18 (m, 5H), 6.31 (d, $J = 2.9$ Hz, 1H), 6.07 (d, $J = 2.9$ Hz, 1H), 3.98 (d, $J = 9.5$ Hz, 1H), 3.73 (m, 1H), 3.62 (d, $J = 9.5$ Hz, 1H), 3.00 (d, $J = 4.5$ Hz, 1H), 1.30 (d, $J = 6.2$ Hz, 3H); ^{13}C NMR (300 MHz, C_6D_6): δ 141.7 (C), 140.2 (CH), 134.1 (CH), 128.2 ($\text{CH} \times 2$), 126.6 ($\text{CH} \times 2$), 126.2 (CH), 73.8 (CH), 73.0 (CH_2), 63.0 (C), 59.8 (CH), 16.0 (CH_3); **HRMS** (ESI-MS) calcd. for $\text{C}_{13}\text{H}_{15}\text{O}^+$ ($[\text{M}+\text{H}]^+$): 187.1117, found 187.1119.

III. Deuterium labeling experiments

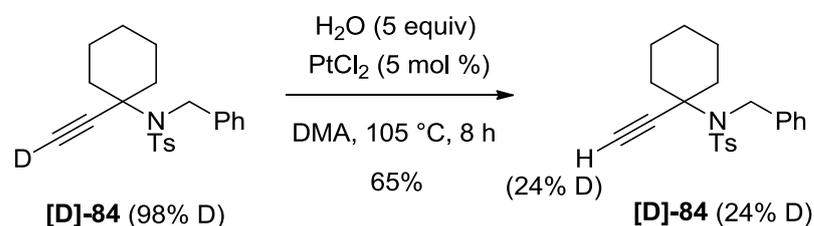
PtCl₂-catalyzed cycloisomerization of [D]-1



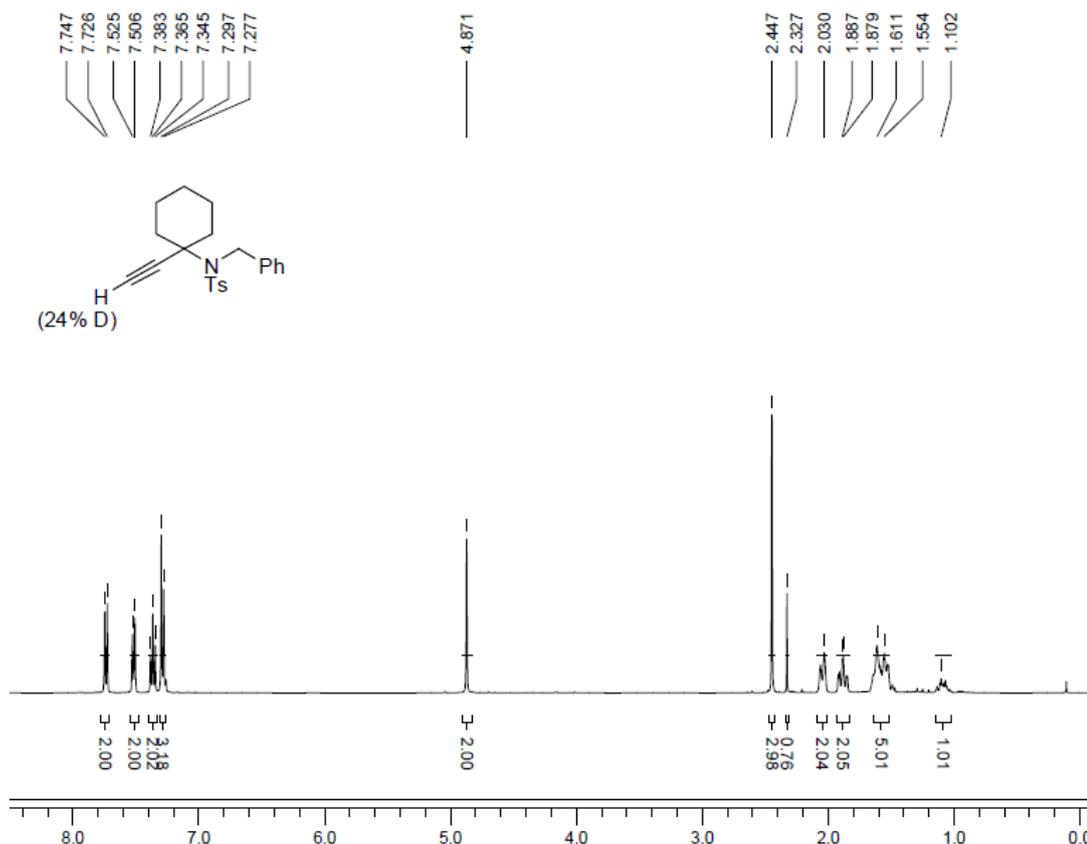
Under an argon atmosphere, PtCl₂ (2.7 mg, 0.01 mmol) was added to a solution of [D]-1 (66.5 mg, 0.2 mmol) in DMA (1 mL). The reaction mixture was stirred at 105 °C for 8 h. Then the mixture was poured into water (10 mL), and extracted with diethyl ether (3 × 15 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by column chromatography over triethylamine-treated silica gel to give a white solid (61.1 mg, 92% yield).



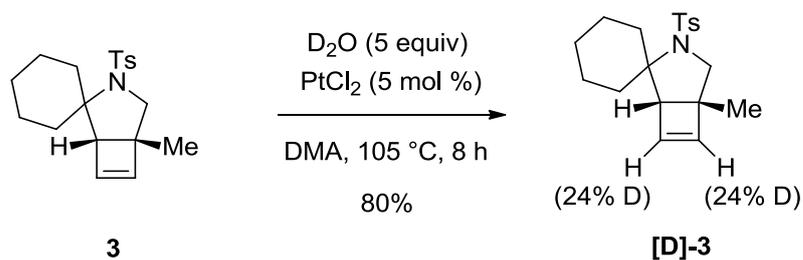
Deuterium to hydrogen exchange of [D]-84 in the presence of PtCl₂



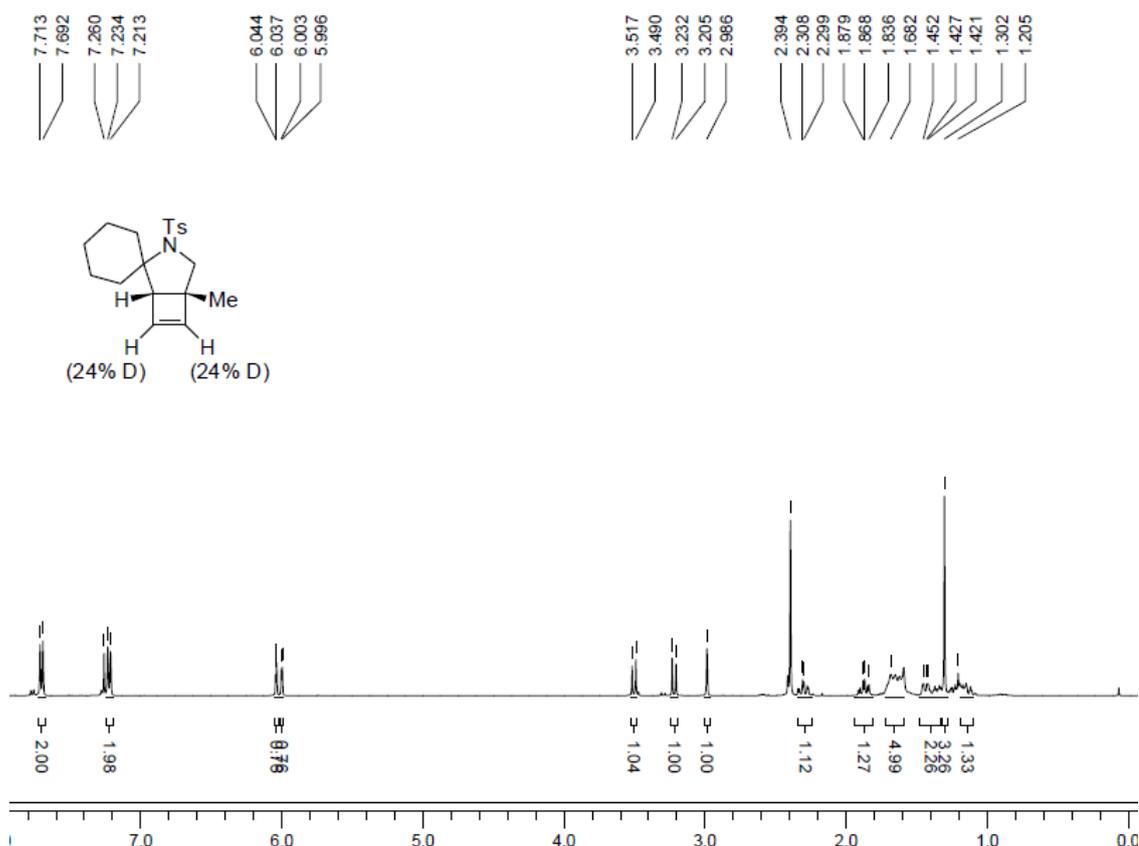
Under an argon atmosphere, PtCl₂ (2.7 mg, 0.01 mmol) was added to a solution of [D]-84 (73.7 mg, 0.2 mmol) and H₂O (18 mg, 1 mmol) in DMA (1 mL). The reaction mixture was stirred at 105 °C for 8 h. Then the mixture was poured into water (10 mL), and extracted with diethyl ether (3 × 15 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by column chromatography over triethylamine-treated silica gel to give a white solid (47.8 mg, 65% yield).



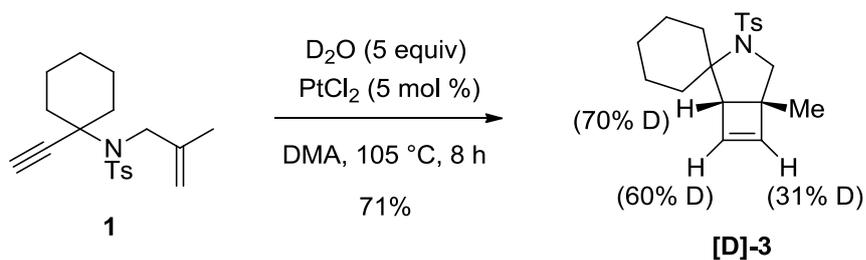
Deuterium to hydrogen exchange of **3** in the presence of PtCl₂



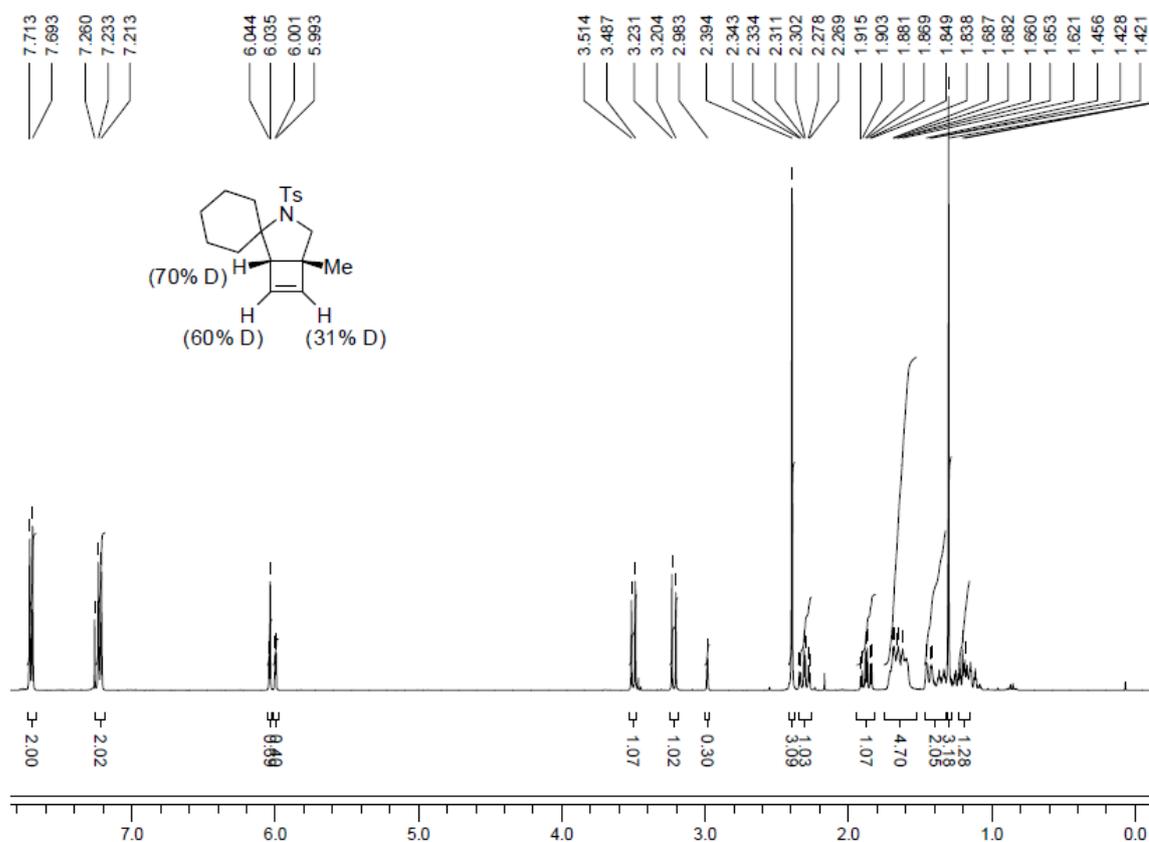
Under an argon atmosphere, PtCl₂ (2.7 mg, 0.01 mmol) was added to a solution of **3** (66.3 mg, 0.2 mmol) and D₂O (20 mg, 1 mmol) in DMA (1 mL). The reaction mixture was stirred at 105 °C for 8 h. Then the mixture was poured into water (10 mL), and extracted with diethyl ether (3 × 15 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by column chromatography over triethylamine-treated silica gel to give a white solid (52.8 mg, 80% yield).



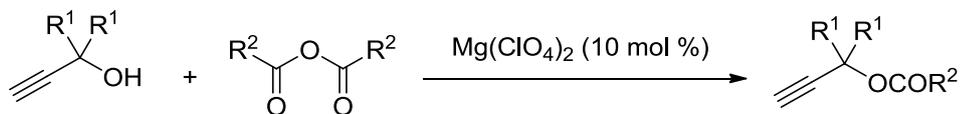
PtCl₂-catalyzed cycloisomerization of **1** in the presence of D₂O



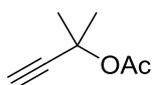
Under an argon atmosphere, PtCl₂ (2.7 mg, 0.01 mmol) was added to a solution of **1** (66.3 mg, 0.2 mmol) and D₂O (20 mg, 1 mmol) in DMA (1 mL). The reaction mixture was stirred at 105 °C for 8 h. Then the mixture was poured into water (10 mL), and extracted with diethyl ether (3 × 15 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by column chromatography over triethylamine-treated silica gel to give a white solid (47.1 mg, 71% yield).



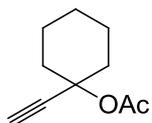
IV. Preparation of tertiary propargyl carboxylates



General Procedure I.³² To a cooled solution (0 °C) of propargyl alcohol (23 mmol) was added the acid anhydride (23 mmol) and magnesium perchlorate (513 mg, 2.3 mmol). The reaction mixture was allowed to stir at room temperature (unless otherwise stated). Then, a saturated solution of NaHCO₃ (10 mL) was added and the resulting mixture was stirred overnight. After extraction with Et₂O (2 × 25 mL), the organic phases were washed with sat. NaHCO₃, brine, dried over Na₂SO₄, filtered and the volatiles were removed under reduced pressure. The crude mixture was purified by bulb-to-bulb distillation to give the desired product.



*2-Methylbut-3-yn-2-yl acetate*³³ (**85**) was prepared following the procedure I for 30 minutes and purified by bulb-to-bulb distillation (T = 35 °C @ 20 mbar) to give **85** as a colorless liquid. Yield: 75%; ¹H NMR (300 MHz, CDCl₃): δ 2.48 (s, 1H), 1.96 (s, 3H), 1.61 (s, 6H); ¹³C NMR (75 MHz, CDCl₃): δ 169.1 (C=O), 84.5 (CH), 72.2 (C), 71.4 (C), 28.7 (CH₃ × 2), 21.7 (CH₃).



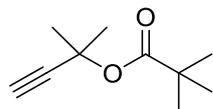
*1-Ethynylcyclohexyl acetate*³⁴ (**97**) was prepared following the procedure I for 1 h and purified by bulb-to-bulb distillation (T = 77 °C @ 0.2 mbar) to give **97** as a colorless liquid. Yield: 85%; ¹H NMR (400 MHz, CDCl₃): δ 2.56 (s, 1H), 2.15-2.10 (m, 2H), 2.04 (s, 3H), 1.88-1.181 (m, 2H), 1.65-1.59 (m, 4H), 1.56-1.47 (m, 1H), 1.36-1.29 (m, 1H); ¹³C NMR (100 MHz, CDCl₃): 169.0 (C=O), 83.5 (CH), 74.9 (C), 74.1 (C), 36.8 (CH₂ × 2), 24.9 (CH₂).

³² a) Chakraborti, A. S.; Sharma, L.; Shivani, R. G. *Tetrahedron*, **2003**, *59*, 7661-7668. b) Bartoli, G.; Bosco, M.; Dalpozzo, R.; Marcantoni, E.; Massaccesi, M.; Rinaldi, S.; Sambri, L. *Synlett*, **2003**, 39-42.

³³ Bartels, A.; Mahrwald, R.; Müller, K. *Adv. Synth. Cat.*, **2004**, *346*, 483-485.

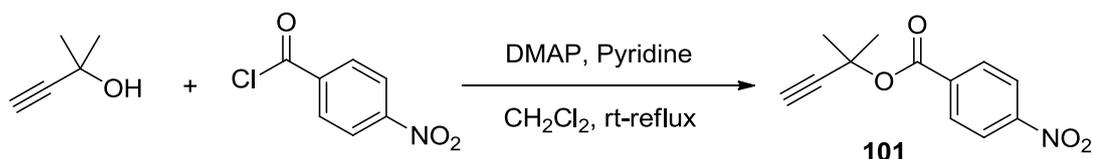
³⁴ Ishihara, K.; Kubota, M.; Kurihara, H.; Yamamoto, H. *J. Org. Chem.*, **1996**, *61*, 4560-4567.

22.4 (CH₂ × 2), 21.8 (CH₃).



2-Methylbut-3-yn-2-yl pivalate³⁵ (**99**) was prepared following the procedure I at 80 °C for 1 h and purified by bulb-to-bulb distillation (T = 75 °C @ 11 mbar) to give **99** as a colorless liquid. Yield: 81%; ¹H NMR (400 MHz, CDCl₃): δ 2.49 (s, 1H), 1.66 (s, 6H), 1.18 (s, 9H); ¹³C NMR (100 MHz, CDCl₃): δ 176.7 (C=O), 84.9 (C), 71.8 (CH), 71.1 (C), 38.4 (C), 28.7 (CH₃ × 2), 26.9 (CH₃ × 3).

2-methylbut-3-yn-2-yl 4-nitrobenzoate³⁶ (**101**)



To a solution of 2-methyl-3-butyn-2-ol (2.0 g, 23.8 mmol) in CH₂Cl₂ (24.0 mL) was added DMAP (150 mg, 1.2 mmol) and pyridine (19.0 mL). The mixture was stirred for 30 minutes at room temperature and 4-nitrobenzoyl chloride (8.8 g, 47.4 mmol) was added dropwise and then heated to reflux overnight. After being cooled to room temperature, the mixture was diluted with Et₂O (200 mL), and quenched with 1N HCl (250 mL). The aqueous layer was extracted with Et₂O (3 × 60 mL) and the combined organic layers were washed with sat. Na₂CO₃ and brine, dried over Na₂SO₄, and concentrated in vacuo. The residue was purified by column chromatography over silica gel.

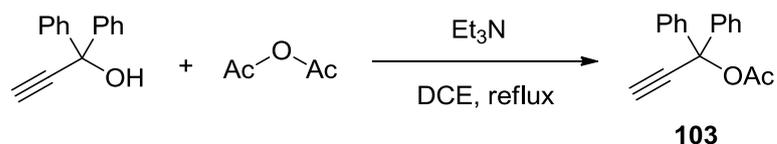
Yield: 43%; Yellow solid; ¹H NMR (300 MHz, CDCl₃): δ 8.28 (d, *J* = 8.9 Hz, 2H), 8.18 (d, *J* = 8.9 Hz, 2H), 2.62 (s, 1H), 1.85 (s, 6H); ¹³C NMR (300 MHz, CDCl₃): δ 162.9 (C=O), 150.5 (C), 136.2 (C), 130.7 (CH), 123.5 (CH), 84.0 (CH), 73.6 (C), 73.2 (C), 28.9 (CH₃ × 2).

1,1-Diphenylprop-2-ynyl acetate³⁷ (**103**)

³⁵ Pagar, V. V.; Jadhav, A. M.; Liu, R.-S. *J. Am. Chem. Soc.*, **2011**, *133*, 20728-20731.

³⁶ Gung, B. W.; Bailey, L. N.; Wonser, J. *Tetrahedron Lett.* **2010**, *51*, 2251-2253.

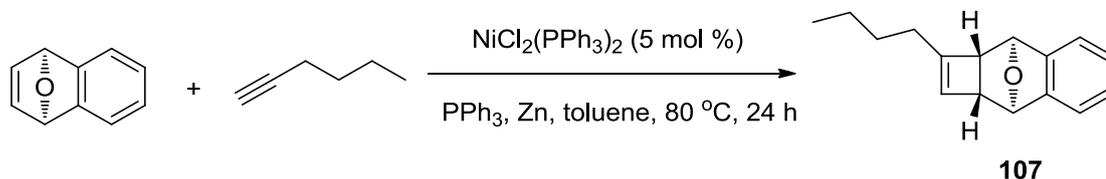
³⁷ Marion, N.; Carlqvist, P.; Gealageas, R.; de Frémont, P.; Maseras, F.; Nolan, S. P. *Chem. Eur. J.*, **2007**, *13*, 6437-6451.



To a solution of 1,1-diphenylprop-2-yn-1-ol (2.08 g, 10 mmol) in dichloroethane (30 mL) was added triethylamine (5.6 mL, 40 mmol), and acetic anhydride (1.9 mL, 20 mmol). The resulting mixture was refluxed for 16 h, cooled to room temperature and quenched with a saturated solution of NH_4Cl . The aqueous layer was extracted with Et_2O (2×30 mL) and the combined organic layers were washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel chromatography. Yield: 95%; Yellow solid; $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 7.54-7.51 (m, 4H), 7.35-7.31 (m, 4H), 7.29-7.27 (m, 2H), 2.99 (s, 1H), 2.17 (s, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 168.1 (C=O), 141.9 (C), 128.3 (CH), 127.9 (CH), 126.0 (CH), 82.3 (C), 78.9 (C), 78.0 (CH), 21.7 (CH_3).

V. Preparation of cyclobutenes 107, 113, 117 and 122

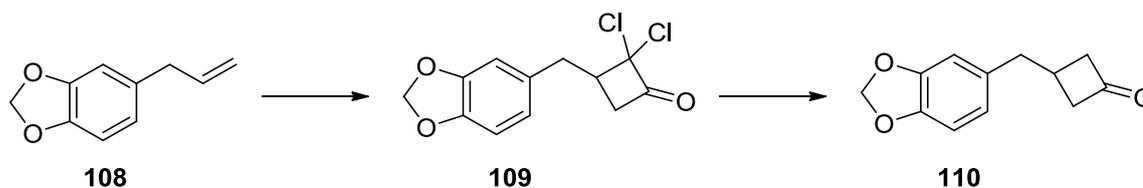
(2*aR**,8*aR**)-1-butyl-2*a*,3,8,8*a*-tetrahydro-3,8-epoxycyclobuta[*b*]naphthalene³⁸ (**107**)



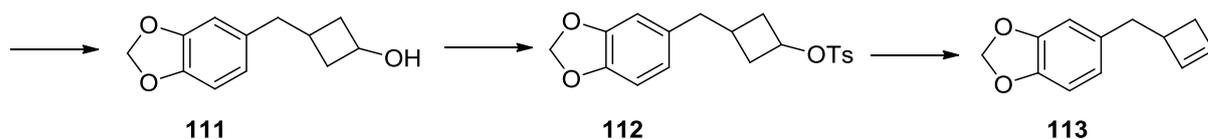
To a solution of 1,4-dihydro-1,4-epoxynaphthalene (0.144 g, 1.0 mmol) and hex-1-yne (0.23 mL, 2 mmol) in toluene (2.0 mL) was added $\text{NiCl}_2(\text{PPh}_3)_2$ (32.7 mg, 0.05 mmol), PPh_3 (0.21 g, 0.8 mmol) and Zn powder (0.18 g, 2.75 mmol). The reaction mixture was stirred at 70 °C for 24 h and monitored by TLC. Upon completion, the reaction mixture was stirred under air for 15 min at room temperature, filtered through Celite[®] and silica gel, and eluted with dichloromethane. The filtrate was concentrated, and the residue was purified by column chromatography over silica gel. (eluent: petroleum ether / diethyl ether).

Yield: 36%; Pale yellow oil; R_f (PE/Et₂O 10/1) 0.50; **IR** (neat) ν 2956, 2927, 2864, 1455, 1196, 966, 899, 842, 814, 756, 660, 547 cm^{-1} ; **¹H NMR** (300 MHz, CDCl₃): δ 7.29-7.22 (m, 2H), 7.17-7.11 (m, 2H), 5.89 (s, 1H), 4.95 (s, 1H), 4.89 (s, 1H), 2.63 (d, $J = 3.2$ Hz, 1H), 2.56-2.55 (m, 1H), 2.21-2.07 (m, 2H), 1.56-1.34 (m, 4H), 0.93 (t, $J = 7.2$ Hz, 3H); **¹³C NMR** (300 MHz, CDCl₃): δ 151.6 (C), 145.3 (C), 144.6 (C), 127.1 (CH), 126.4 (CH \times 2), 119.5 (CH \times 2), 76.6 (CH), 75.5 (CH), 48.7 (CH), 44.4 (CH), 29.2 (CH₂), 28.9 (CH₂), 22.6 (CH₂), 13.9 (CH₃); **HRMS** (ESI-MS) calcd. for C₁₆H₁₉O⁺ ($[\text{M}+\text{H}]^+$): 227.1430, found 227.1430.

5-(cyclobut-2-en-1-ylmethyl)benzo[*d*][1,3]dioxole (**113**) was prepared through the following five-step procedure.



³⁸ Huang, D.-J.; Rayabarapu, D. K.; Li, L.-P.; Sambaiah, T.; Cheng, C.-H. *Chem. Eur. J.* **2000**, *6*, 3706-3713.



3-(benzo[*d*][1,3]dioxol-5-ylmethyl)cyclobutanone (**110**)

Based on a procedure reported by Xu.³⁹ To a solution of safrole **108** (2.96 mL, 20 mmol) in anhydrous ether (40 mL) was added the zinc-copper couple (3.9 g, 60 mmol). To the stirred suspension was added a solution of trichloroacetyl chloride (4.48 mL, 40 mmol) and phosphorus oxychloride (2.04 mL, 22 mmol) in ether (15 mL) over 1 h. The reaction mixture was stirred overnight at reflux. Upon completion (TLC monitoring), the mixture was cooled to room temperature, filtered through a short pad of Celite[®] with ether washings. The filtrate was washed with water, sat. NaHCO₃, brine, dried over Na₂SO₄, and then concentrated under vacuum. Purification with column chromatography over silica gel afforded the desired cyclobutanone **109** for the next step.

The above 3-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-2,2-dichlorocyclobutanone **109** and Zn powder (5.2 g, 79.5 mmol) were mixed in acetic acid (30 mL). The suspension was stirred at room temperature for 2 h and then heated at 70 °C for 6 h. Upon completion (TLC monitoring), the mixture was cooled to room temperature, diluted with water and extracted with ether. The combined organic layers were washed with water, sat. NaHCO₃, brine, dried over Na₂SO₄ and filtered. The filtrate was concentrated and the residue was purified by column chromatography over silica gel to give cyclobutanone **110** (eluent: petroleum ether / diethyl ether).

Yield (over the two steps): 22%; Colorless oil; **R_f** (PE/Et₂O 3/1) 0.35; **IR** (neat) ν 2913, 1777, 1487, 1444, 1253, 1235, 1189, 1101, 1034, 924, 811, 775, 520 cm⁻¹; **¹H NMR** (300 MHz, CDCl₃): δ 6.75 (d, *J* = 7.9 Hz, 1H), 6.68 (s, 1H), 6.63 (d, *J* = 7.9 Hz, 1H), 5.93 (s, 2H), 3.16-3.08 (m, 2H), 2.82-2.62 (m, 5H); **¹³C NMR** (300 MHz, CDCl₃): δ 207.8 (C=O), 147.8 (C), 146.1 (C), 133.8 (C), 121.4 (CH), 108.9 (CH), 108.3 (CH), 100.9 (CH₂), 52.2 (CH₂ × 2), 41.6 (CH₂), 25.2 (CH); **HRMS** (ESI-MS) calcd. for C₁₂H₁₃O₃⁺ ([M+H]⁺): 205.0859, found 205.0858.

3-(benzo[*d*][1,3]dioxol-5-ylmethyl)cyclobutanol (**111**)

To a cooled (0 °C) suspension of NaBH₄ (51.9 mg, 1.4 mmol) in MeOH (10 mL) was added 3-(benzo[*d*][1,3]dioxol-5-ylmethyl)cyclobutanone **110** (715 mg, 3.5 mmol) in MeOH (5 mL).

³⁹ Xu, H.-J.; Zhu, F.-F.; Shen, Y.-Y.; Wan, X.; Feng, Y.-S. *Tetrahedron*, **2012**, 68, 4145-4151.

The solution was stirred at 0 °C for 1 h and then concentrated in vacuo. The residue was purified by column chromatography over silica gel to give the cyclobutanol **111** (99% yield) which was used in the next step.

3-(benzo[d][1,3]dioxol-5-ylmethyl)cyclobutyl 4-methylbenzenesulfonate (112)

To a cooled (0 °C) solution of cyclobutanol **111** (720 mg, 3.5 mmol) in pyridine (25 mL) was added TsCl (692 mg, 3.6 mmol). The solution was stirred at room temperature for 24 h, then cooled to 0 °C and poured into concentrated HCl (26 mL) in crushed ice (80 g). The mixture was extracted with Et₂O (3 × 50 mL). The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated in vacuo. The residue was purified by column chromatography over silica gel to give tosylate **112** (85% yield) which was used in the next step.

5-(cyclobut-2-en-1-ylmethyl)benzo[d][1,3]dioxole (113) was prepared according to procedure reported by Salaün and Bassindale.⁴⁰

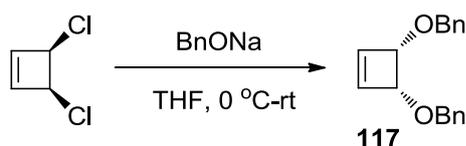
To a suspension of ^tBuOK (673 mg, 6 mmol) in DMSO (12 mL) heated at 70 °C was added dropwise (over a 10 minutes period) a solution of **112** (720 mg, 2 mmol) in DMSO (6 mL). The mixture was stirred at 70 °C for 2 h, cooled to room temperature, diluted with water, and extracted with Et₂O (3 × 20 mL). The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated in vacuo. The residue was purified by column chromatography over silica gel.

Yield (over the five steps): 11%; Colorless oil; **R_f** (PE/Et₂O 4/1) 0.30; **IR** (neat) ν 3044, 2913, 2864, 1487, 1441, 1250, 1189, 1041, 938, 811, 690, 524, 421 cm⁻¹; **¹H NMR** (300 MHz, CDCl₃): δ 6.74 (d, *J* = 7.9 Hz, 1H), 6.69 (s, 1H), 6.63 (d, *J* = 7.9 Hz, 1H), 6.11 (d, *J* = 2.5 Hz, 1H), 6.08 (d, *J* = 2.5 Hz, 1H), 5.92 (s, 2H), 3.04-2.99 (m, 1H), 2.69 (d, *J* = 7.7 Hz, 2H), 2.65 (dd, *J* = 4.1, 13.6 Hz, 1H), 2.16 (d, *J* = 13.5 Hz, 1H); **¹³C NMR** (300 MHz, CDCl₃): δ 147.4 (C), 145.6 (C), 140.5 (CH), 135.5 (CH), 135.2 (C), 121.2 (CH), 109.0 (CH), 108.1 (CH), 100.7 (CH₂), 45.2 (CH), 40.6 (CH₂), 36.5 (CH₂); **HRMS** (ESI-MS) calcd. for C₁₂H₁₂O₂Ag⁺ ([M+Ag]⁺): 294.9883, found 294.9883.

(3R,4S*)-3,4-bis(benzyloxy)cyclobut-1-ene⁴¹ (117)*

⁴⁰ a) Salaün, J.; Fadel, A. *Organic Syntheses, Coll. Vol. 7, p. 117 (1990); Vol. 64, p. 50 (1986)*. b) Bassindale, M. J.; Hamley, P.; Harrity, J.P.A. *Tetrahedron Lett.*, **2001**, 42, 9055-9057.

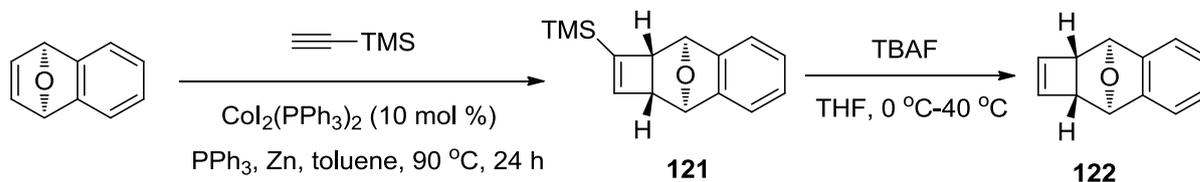
⁴¹ Hoveyda, A. H.; Lombardi, P. J.; O'Brien, R. V.; Zhugralin A. R. *J. Am. Chem. Soc.*, **2009**, 131, 8378-8379.



To a cooled (0 °C) suspension of NaH (60% oil dispersion washed with PE) (53.7 mg, 2.24 mmol) in THF (10.0 mL) was added benzyl alcohol (567.7 mg, 5.25 mmol). The solution was stirred at 0 °C for 1 h, then *cis*-3,4-dichlorocyclobutene (123 mg, 1.0 mmol) was added. The solution was stirred at room temperature for 12 h, diluted with saturated aqueous NH₄Cl and extracted with Et₂O (3 × 10 mL). The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated in vacuo. The residue was purified by column chromatography over silica gel.

Yield: 67%; Colorless oil; *R_f* (PE/Et₂O 10/1) 0.25; ¹H NMR (300 MHz, CDCl₃): δ 7.43-7.29 (m, 10H), 6.41-6.40 (m, 2H), 4.78 (d, *J* = 11.7 Hz, 2H), 4.78-4.72 (m, 2H), 4.67 (d, *J* = 11.7 Hz, 2H); ¹³C NMR (300 MHz, CDCl₃): δ 142.1 (CH × 2), 138.6 (C × 2), 128.3 (CH × 4), 127.9 (CH × 4), 127.5 (CH × 2), 81.4 (CH × 2), 71.0 (CH₂ × 2).

(2*aR**,8*aS**)-2*a*,3,8,8*a*-tetrahydro-3,8-epoxycyclobuta[*b*]naphthalene⁴² (**122**) was prepared from benzoxanorbornadiene and trimethylsilylethyne.



Based on a modification of the procedure reported by Cheng.⁴³ To a solution of the 1,4-dihydro-1,4-epoxynaphthalene (288.3 mg, 2.0 mmol) and hex-1-yne (2.8 mL, 20.0 mmol) in toluene (20.0 mL) were added CoI₂ (62.6 mg, 0.2 mmol), PPh₃ (419.7 mg, 1.6 mmol) and Zn powder (1.31 g, 20.0 mmol). The reaction mixture was stirred at 90 °C for 24 h. Upon completion (TLC monitoring), the reaction mixture was cooled to room temperature and stirred under air for 15 min, filtered through Celite[®] and silica gel, and eluted with dichloromethane. The filtrate was concentrated, and the residue was purified by column chromatography over silica gel.

⁴² Pitt, I. G.; Russell, R. A.; Warrenner, R. N. *J. Am. Chem. Soc.*, **1985**, *107*, 7176-7178.

⁴³ Chao, K. C.; Rayabarapu, D. K.; Wang, C.-C.; Cheng, C.-H. *J. Org. Chem.* **2001**, *66*, 8804-8810.

Trimethyl((2aR,8aS*)-2a,3,8,8a-tetrahydro-3,8-epoxycyclobuta[b]naphthalen-1-yl)silane* (**121**) Yield: 65%; R_f (PE/Et₂O 20/1) 0.45; $^1\text{H NMR}$ (300 MHz, CDCl₃): δ 7.32-7.25 (m, 2H), 7.19-7.15 (m, 2H), 6.68 (s, 1H), 4.94 (s, 1H), 4.92 (s, 1H), 2.81 (d, $J = 3.3$ Hz, 1H), 2.72 (d, $J = 3.2$ Hz, 1H), 0.19 (s, 9H); $^{13}\text{C NMR}$ (300 MHz, CDCl₃): δ 155.6 (C), 147.1 (CH), 144.6 (C \times 2), 126.44 (CH), 126.40 (CH), 119.6 (CH \times 2), 76.5 (CH), 75.9 (CH), 48.8 (CH), -1.8 (CH₃ \times 3).

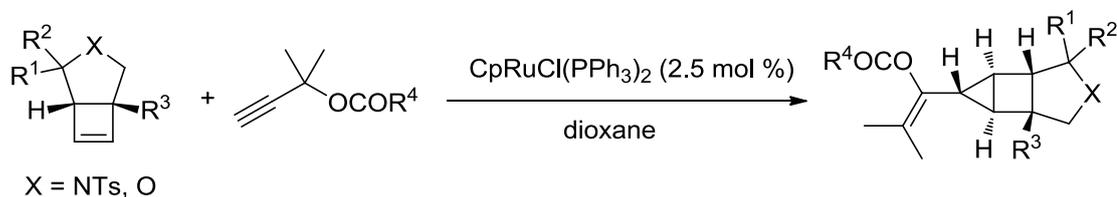
(2aR,8aS*)-2a,3,8,8a-tetrahydro-3,8-epoxycyclobuta[b]naphthalene* (**122**) was prepared using a procedure reported by Day.⁴⁴ To a solution of silylcyclobutene **121** (183.0 mg, 0.75 mmol) in THF (15 mL) was added 1.0 M TBAF in THF (2 mL, 2.0 mmol). The mixture was heated to 50 °C. Upon completion (TLC monitoring), the solution was cooled to room temperature and concentrated in vacuo. The residue was purified by column chromatography over silica gel.

(2aR,8aS*)-2a,3,8,8a-tetrahydro-3,8-epoxycyclobuta[b]naphthalene* (**122**). Yield: 90%; R_f (PE/Et₂O 10/1) 0.30; $^1\text{H NMR}$ (300 MHz, CDCl₃): δ 7.29-7.25 (m, 2H), 7.19-7.13 (m, 2H), 6.26 (s, 2H), 4.95 (s, 2H), 2.77 (s, 2H); $^{13}\text{C NMR}$ (300 MHz, CDCl₃): δ 144.5 (C \times 2), 137.3 (CH \times 2), 126.5 (CH \times 2), 119.7 (CH \times 2), 76.0 (CH \times 2), 48.4 (CH \times 2).

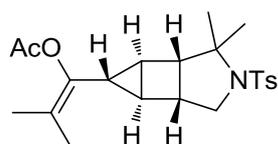
⁴⁴ Day, J. J.; McFadden, R. M.; Virgil, S. C.; Kolding, H.; Alleva, J. L.; Stoltz, B. M. *Angew. Chem. Int. Ed.* **2011**, *50*, 6814-6818.

VI. CpRuCl(PPh₃)₂-catalyzed cyclopropanation of cyclobutenes

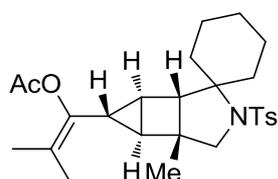
General Procedure J



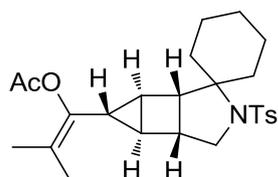
Under a argon atmosphere, CpRuCl(PPh₃)₂ (3.6 mg, 0.005 mmol) was added to a solution of the cyclobutene (0.20 mmol) and propargyl carboxylate (0.20 mmol) in dioxane (2 mL). The reaction mixture was stirred at room temperature and monitored by TLC. Upon completion, the solvent was removed under reduced pressure and the residue purified by column chromatography over silica gel (eluent: petroleum ether / diethyl ether).



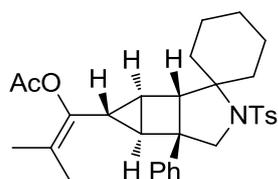
1-((1R,2S*,3S*,4R*,5S*)-6,6-Dimethyl-7-tosyl-7-azatricyclo[3.3.0.0^{2,4}]octan-3-yl)-2-methylprop-1-en-1-yl acetate (86)* was synthesized following the general procedure J. Yield: 94%; Yellow oil; **R_f** (PE/Et₂O 3/1) 0.25; **IR** (neat) ν 2927, 1752, 1327, 1211, 1161, 1094, 701, 658, 605, 556 cm⁻¹; **¹H NMR** (300 MHz, CDCl₃): δ 7.77 (d, *J* = 8.3 Hz, 2H), 7.27 (d, *J* = 8.0 Hz, 2H), 3.63 (d, *J* = 10.7 Hz, 1H), 3.44 (dd, *J* = 6.3, 10.7 Hz, 1H), 2.41 (s, 3H), 2.33 (ddd, *J* = 1.8, 4.4, 6.1 Hz, 1H), 2.07 (s, 3H), 2.04 (dd, *J* = 1.6, 4.3 Hz, 1H), 1.83 (br s, 1H), 1.82 (s, 3H), 1.68-1.66 (m, 1H), 1.53 (s, 3H), 1.51 (s, 3H), 1.51-1.49 (m, 1H), 1.01 (s, 3H); **¹³C NMR** (300 MHz, CDCl₃): δ 169.1 (C=O), 142.8 (C), 139.0 (C), 138.8 (C), 129.4 (CH \times 2), 127.2 (CH \times 2), 120.5 (C), 64.5 (C), 55.9 (CH), 52.2 (CH₂), 38.1 (CH), 26.3 (CH), 24.5 (CH₃), 23.7 (CH), 23.6 (CH₃), 21.5 (CH₃), 21.2 (CH), 20.4 (CH₃), 18.7 (CH₃), 18.0 (CH₃); **HRMS** (ESI-MS) calcd. for C₂₂H₃₀NO₄S⁺ ([M+H]⁺): 404.1890, found 404.1890.



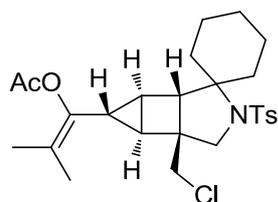
2-Methyl-1-((1*R**,2*R**,3*R**,4*R**,5*S**)-1'-methyl-7'-tosyl-7'-azaspiro[cyclohexane-1,6'-tricyclo[3.3.0.0^{2,4}]octan]-3'-yl)prop-1-en-1-yl acetate (**87**) was synthesized following the general procedure J. Yield: 98%; Colorless oil; **R_f** (PE/Et₂O 3/1) 0.25; **IR** (neat) ν 2924, 1749, 1338, 1210, 1158, 1148, 1087, 818, 722, 669, 591, 552 cm⁻¹; **¹H NMR** (300 MHz, CDCl₃): δ 7.77 (d, *J* = 8.3 Hz, 2H), 7.25 (d, *J* = 8.0 Hz, 2H), 3.75 (d, *J* = 10.6 Hz, 1H), 3.40 (d, *J* = 10.6 Hz, 1H), 2.40 (s, 3H), 2.32-2.22 (m, 1H), 2.15 (br s, 1H), 2.06 (s, 3H), 2.00 (br s, 1H), 1.85 (s, 3H), 1.79-1.60 (m, 6H), 1.52 (s, 3H), 1.50-1.48 (m, 2H), 1.28-1.08 (m, 3H), 1.02 (s, 3H); **¹³C NMR** (300 MHz, CDCl₃): δ 169.0 (C=O), 142.6 (C), 140.3 (C), 139.0 (C), 129.3 (CH \times 2), 126.9 (CH \times 2), 120.5 (C), 69.7 (C), 58.7 (CH₂), 52.4 (CH), 42.8 (C), 32.7 (CH₂), 31.6 (CH₂), 27.2 (CH), 25.2 (CH₂), 24.5 (CH₂), 23.9 (CH₂), 23.4 (CH₂), 21.5 (CH₃), 20.4 (CH₃), 20.2 (CH₃), 18.8 (CH₃), 18.0 (CH₃), 16.7 (CH); **HRMS** (ESI-MS) calcd. for C₂₆H₃₆NO₄S⁺ ([M+H]⁺): 458.2360, found 458.2361.



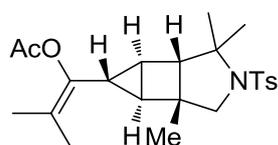
2-Methyl-1-((1*R**,2*S**,3*S**,4*R**,5*S**)-7'-tosyl-7'-azaspiro[cyclohexane-1,6'-tricyclo[3.3.0.0^{2,4}]octan]-3'-yl)prop-1-en-1-yl acetate (**88**) was synthesized following the general procedure J. Yield: 98%; Colorless oil; **R_f** (PE/Et₂O 3/1) 0.25; **IR** (neat) ν 2927, 1749, 1211, 1161, 1147, 1097, 719, 665, 581, 545 cm⁻¹; **¹H NMR** (300 MHz, CDCl₃): δ 7.77 (d, *J* = 8.3 Hz, 2H), 7.24 (d, *J* = 8.1 Hz, 2H), 3.70 (d, *J* = 10.9 Hz, 1H), 3.55 (dd, *J* = 6.3, 10.9 Hz, 1H), 2.55 (dd, *J* = 1.1, 4.4 Hz, 1H), 2.40 (s, 3H), 2.39-2.30 (m, 2H), 2.06 (s, 3H), 1.90 (br s, 1H), 1.83 (s, 3H), 1.80-1.50 (m, 7H), 1.51 (s, 3H), 1.44 (br d, *J* = 13.0 Hz, 1H), 1.27-1.02 (m, 3H); **¹³C NMR** (300 MHz, CDCl₃): δ 169.0 (C=O), 142.6 (C), 140.4 (C), 138.9 (C), 129.3 (CH \times 2), 126.9 (CH \times 2), 120.5 (C), 68.9 (C), 52.0 (CH₂), 48.2 (CH), 37.9 (CH), 32.2 (CH₂), 31.6 (CH₂), 26.6 (CH), 25.2 (CH₂), 23.93 (CH₂), 23.91 (CH), 23.4 (CH₂), 21.5 (CH₃), 20.3 (CH₃), 20.1 (CH), 18.8 (CH₃), 18.0 (CH₃); **HRMS** (ESI-MS) calcd. for C₂₅H₃₄NO₄S⁺ ([M+H]⁺): 444.4403, found 444.4402.



2-Methyl-1-((1*R**,2*R**,3*R**,4*R**,5*S**)-1'-phenyl-7'-tosyl-7'-azaspiro[cyclohexane-1,6'-tricyclo[3.3.0.0^{2,4}]octan]-3'-yl)prop-1-en-1-yl acetate (**89**) was synthesized following the general procedure J. Yield: 12%; Pale yellow oil; **R_f** (PE/Et₂O 2/1) 0.25; **IR** (neat) ν 2930, 1752, 1327, 1211, 1158, 814, 719, 697, 665, 584, 549 cm⁻¹; **¹H NMR** (300 MHz, CDCl₃): δ 7.78 (d, J = 8.3 Hz, 2H), 7.35-7.16 (m, 5H), 7.10 (d, J = 8.0 Hz, 2H), 3.98 (d, J = 10.9 Hz, 1H), 3.47 (d, J = 10.9 Hz, 1H), 2.82 (br d, J = 1.2 Hz, 1H), 2.42 (br s, 1H), 2.41 (s, 3H), 2.10 (s, 3H), 2.01-1.97 (m, 1H), 1.84-1.67 (m, 7H), 1.65 (s, 3H), 1.49 (s, 3H), 1.43 (br s, 1H), 1.29-1.14 (m, 3H); **¹³C NMR** (300 MHz, CDCl₃): δ 169.0 (C=O), 142.7 (C \times 2), 140.0 (C), 138.7 (C), 129.4 (CH \times 2), 128.5 (CH \times 2), 127.1 (CH \times 2), 126.5 (CH), 126.2 (CH \times 2), 120.8 (C), 69.4 (C), 59.4 (CH₂), 52.7 (CH), 51.3 (C), 32.7 (CH₂), 32.2 (CH₂), 27.1 (CH), 25.4 (CH), 25.3 (CH₂), 23.9 (CH₂), 23.3 (CH₂), 21.5 (CH₃), 20.4 (CH₃), 18.6 (CH₃), 18.0 (CH₃), 17.7 (CH); **HRMS** (ESI-MS) calcd. for C₃₁H₃₈NO₄S⁺ ([M+H]⁺): 520.2516, found 520.2517.

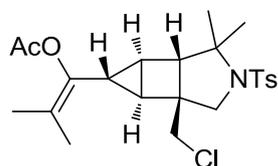


1-((1*S**,2*R**,3*R**,4*R**,5*S**)-1'-(chloromethyl)-7'-Tosyl-7'-azaspiro[cyclohexane-1,6'-tricyclo[3.3.0.0^{2,4}]octan]-3'-yl)-2-methylprop-1-en-1-yl acetate (**90**) was synthesized following the general procedure J. Yield: 33%; Pale yellow oil; **R_f** (PE/Et₂O 2/1) 0.30; **IR** (neat) ν 2924, 1745, 1331, 1214, 1161, 1101, 814, 726, 662, 584, 549 cm⁻¹; **¹H NMR** (300 MHz, CDCl₃): δ 7.77 (d, J = 8.3 Hz, 2H), 7.27 (d, J = 8.0 Hz, 2H), 3.82 (d, J = 10.9 Hz, 1H), 3.60 (d, J = 10.9 Hz, 1H), 3.55 (d, J = 11.1 Hz, 1H), 3.30 (d, J = 11.1 Hz, 1H), 2.41 (s, 3H), 2.37-2.25 (m, 2H), 2.08 (s, 3H), 2.00 (br s, 1H), 1.84 (s, 3H), 1.78-1.54 (m, 8H), 1.54 (s, 3H), 1.30-1.01 (m, 3H); **¹³C NMR** (300 MHz, CDCl₃): δ 169.0 (C=O), 142.8 (C), 139.9 (C), 138.2 (C), 129.4 (CH \times 2), 127.0 (CH \times 2), 121.9 (C), 69.5 (C), 55.9 (CH₂), 50.5 (CH), 47.4 (C), 46.3 (CH₂), 32.8 (CH₂), 31.8 (CH₂), 25.1 (CH₂), 24.8 (CH), 24.3 (CH), 23.9 (CH₂), 23.2 (CH₂), 21.5 (CH₃), 20.4 (CH₃), 18.9 (CH₃), 17.9 (CH₃), 16.7 (CH); **HRMS** (ESI-MS) calcd. for C₂₆H₃₅NO₄SCl⁺ ([M+H]⁺): 492.1970, found 492.1971.

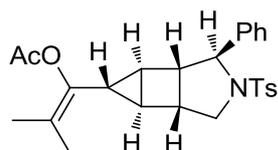


2-Methyl-1-((1*R**,2*R**,3*R**,4*R**,5*S**)-1,6,6-trimethyl-7-tosyl-7-azatricyclo[3.3.0.0^{2,4}]octan-3-

-yl)prop-1-en-1-yl acetate (**91**) was synthesized following the general procedure J. Yield: 99%; Pale yellow oil; R_f (PE/Et₂O 2/1) 0.35; **IR** (neat) ν 2920, 1752, 1320, 1214, 1161, 1152, 1098, 811, 715, 658, 602, 552 cm⁻¹; **¹H NMR** (300 MHz, CDCl₃): δ 7.76 (d, J = 8.3 Hz, 2H), 7.26 (d, J = 8.0 Hz, 2H), 3.66 (d, J = 10.4 Hz, 1H), 3.27 (d, J = 10.4 Hz, 1H), 2.40 (s, 3H), 2.06 (s, 3H), 1.93 (br s, 1H), 1.82 (s, 3H), 1.62 (br s, 1H), 1.60 (br s, 1H), 1.51 (s, 3H), 1.47 (s, 3H), 1.46 (m, 1H), 1.04 (s, 3H), 1.01 (s, 3H); **¹³C NMR** (300 MHz, CDCl₃): δ 169.0 (C=O), 142.8 (C), 139.0 (C), 138.9 (C), 129.4 (CH \times 2), 127.2 (CH \times 2), 120.5 (C), 65.3 (C), 60.0 (CH), 58.9 (CH₂), 43.2 (C), 27.0 (CH), 24.6 (CH₃), 24.2 (CH), 23.6 (CH₃), 21.5 (CH₃), 20.4 (CH₃), 19.9 (CH₃), 18.7 (CH₃), 17.9 (CH₃), 17.8 (CH); **HRMS** (ESI-MS) calcd. for C₂₃H₃₂NO₄S⁺ ([M+H]⁺): 418.2047, found 418.2047.

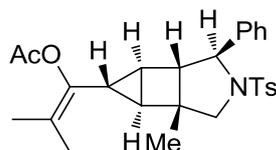


1-((1*S**,2*R**,3*R**,4*R**,5*S**)-1-(chloromethyl)-6,6-Dimethyl-7-tosyl-7-azatricyclo[3.3.0.0^{2,4}]octan-3-yl)-2-methylprop-1-en-1-yl acetate (**92**) was synthesized following the general procedure J. Yield: 46%; Colorless oil; R_f (PE/Et₂O 2/1) 0.30; **IR** (neat) ν 2924, 1749, 1327, 1214, 1154, 1101, 814, 732, 715, 661, 598, 552 cm⁻¹; **¹H NMR** (300 MHz, CDCl₃): δ 7.77 (d, J = 8.3 Hz, 2H), 7.29 (d, J = 8.0 Hz, 2H), 3.75 (d, J = 10.8 Hz, 1H), 3.56 (d, J = 11.1 Hz, 1H), 3.47 (d, J = 10.8 Hz, 1H), 3.29 (d, J = 11.1 Hz, 1H), 2.42 (s, 3H), 2.09 (s, 3H), 1.93 (br s, 1H), 1.83 (s, 3H), 1.75 (d, J = 1.3 Hz, 1H), 1.72 (br d, J = 5.0 Hz, 1H), 1.65 (d, J = 5.0 Hz, 1H), 1.52 (s, 6H), 1.07 (s, 3H); **¹³C NMR** (300 MHz, CDCl₃): δ 169.1 (C=O), 143.1 (C), 138.6 (C), 138.1 (C), 129.5 (CH \times 2), 127.2 (CH \times 2), 120.0 (C), 65.1 (C), 58.0 (CH), 56.2 (CH₂), 47.7 (C), 46.2 (CH₂), 24.9 (CH), 24.7 (CH₃), 24.0 (CH), 23.8 (CH₃), 21.5 (CH), 20.4 (CH₃), 18.8 (CH₃), 17.91 (CH₃), 17.87 (CH₃); **HRMS** (ESI-MS) calcd. For C₂₃H₃₁NO₄SCl⁺ ([M+H]⁺): 452.1657, found 452.1657.

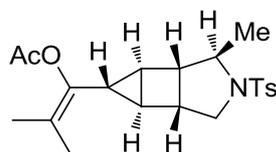


2-Methyl-1-((1*R**,2*S**,3*S**,4*R**,5*S**,6*S**)-6-phenyl-7-tosyl-7-azatricyclo[3.3.0.0^{2,4}]octan-3-yl)prop-1-en-1-yl acetate (**93**) was synthesized following the general procedure J. Yield: 90%; Yellow oil; R_f (PE/Et₂O 2/1) 0.30; **IR** (neat) ν 2938, 1752, 1345, 1211, 1165, 1094, 658, 602,

549 cm^{-1} ; $^1\text{H NMR}$ (300 MHz, CDCl_3): δ 7.50 (d, $J = 8.3$ Hz, 2H), 7.21-7.02 (m, 7H), 5.10 (s, 1H), 3.82 (d, $J = 11.4$ Hz, 1H), 3.42 (dd, $J = 6.0, 11.4$ Hz, 1H), 2.60-2.56 (m, 1H), 2.54-2.52 (m, 1H), 2.34 (s, 3H), 2.09 (s, 3H), 1.91 (br s, 1H), 1.80 (s, 3H), 1.61 (br d, $J = 4.4$ Hz, 1H), 1.51 (s, 3H), 1.44 (br d, $J = 4.3$ Hz, 1H); $^{13}\text{C NMR}$ (300 MHz, CDCl_3): δ 169.1 (C=O), 142.7 (C), 140.9 (C), 138.6 (C), 137.3 (C), 129.1 (CH \times 2), 128.5 (CH \times 2), 127.3 (CH), 127.1 (CH \times 2), 126.6 (CH \times 2), 120.8 (C), 67.0 (CH), 51.1 (CH_2), 50.9 (CH), 43.1 (CH), 27.0 (CH), 24.7 (CH), 24.1 (CH), 21.4 (CH_3), 20.5 (CH_3), 18.8 (CH_3), 17.9 (CH_3); **HRMS** (ESI-MS) calcd. for $\text{C}_{26}\text{H}_{30}\text{NO}_4\text{S}^+$ ($[\text{M}+\text{H}]^+$): 452.1890, found 452.1892.

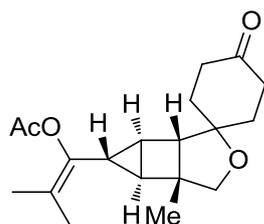


2-Methyl-1-((1R,2R*,3R*,4R*,5S*,6S*)-1-methyl-6-phenyl-7-tosyl-7-azatricyclo[3.3.0.0^{2,4}]octan-3-yl)prop-1-en-1-yl acetate (94)* was synthesized following the general procedure J. Yield: 88%; Pale yellow oil; R_f (PE/Et₂O 1/1) 0.30; **IR** (neat) ν 2927, 1749, 1338, 1211, 1164, 1097, 701, 673, 662, 595, 556 cm^{-1} ; $^1\text{H NMR}$ (300 MHz, CDCl_3): δ 7.51 (d, $J = 8.3$ Hz, 2H), 7.22-7.02 (m, 7H), 5.10 (s, 1H), 3.86 (d, $J = 11.2$ Hz, 1H), 3.24 (d, $J = 11.2$ Hz, 1H), 2.35 (s, 3H), 2.12 (br d, $J = 1.2$ Hz, 1H), 2.10 (s, 3H), 2.00 (br s, 1H), 1.80 (s, 3H), 1.52 (s, 3H), 1.52-1.50 (m, 1H), 1.47-1.44 (m, 1H), 1.02 (s, 3H); $^{13}\text{C NMR}$ (300 MHz, CDCl_3): δ 169.1 (C=O), 142.7 (C), 140.7 (C), 138.7 (C), 137.4 (C), 129.1 (CH \times 2), 128.5 (CH \times 2), 127.2 (CH), 127.1 (CH \times 2), 126.6 (CH \times 2), 120.8 (C), 68.0 (CH), 57.8 (CH_2), 54.6 (CH), 48.6 (C), 27.9 (CH), 24.9 (CH), 24.42 (CH), 21.37 (CH_3), 20.5 (CH_3), 19.3 (CH_3), 18.8 (CH_3), 17.9 (CH_3); **HRMS** (ESI-MS) calcd. for $\text{C}_{27}\text{H}_{32}\text{NO}_4\text{S}^+$ ($[\text{M}+\text{H}]^+$): 466.2047, found 466.2046.

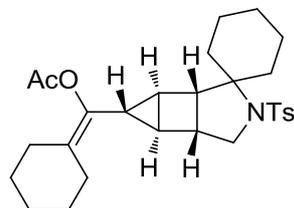


2-Methyl-1-((1R,2S*,3S*,4R*,5S*,6R*)-6-methyl-7-tosyl-7-azatricyclo[3.3.0.0^{2,4}]octan-3-yl)prop-1-en-1-yl acetate (95)* was synthesized following the general procedure J. Yield: 85%; Pale yellow oil; R_f (PE/Et₂O 2/1) 0.30; **IR** (neat) ν 2934, 1745, 1342, 1207, 1168, 1147, 1090, 1048, 1019, 662, 598, 549 cm^{-1} ; $^1\text{H NMR}$ (300 MHz, CDCl_3): δ 7.77 (d, $J = 8.2$ Hz, 2H), 7.26 (d, $J = 8.2$ Hz, 2H), 4.09 (q, $J = 6.7$ Hz, 1H), 3.60 (d, $J = 11.4$ Hz, 1H), 3.31 (dd, J

= 5.9, 11.4 Hz, 1H), 2.44-2.39 (m, 1H), 2.39 (s, 3H), 2.07 (br d, $J = 3.9$ Hz, 1H), 2.04 (s, 3H), 1.82 (br s, 1H), 1.77 (s, 3H), 1.48 (s, 3H), 1.32 (br d, $J = 4.0$ Hz, 1H), 1.25 (br d, $J = 4.0$ Hz, 1H), 1.00 (br d, $J = 6.7$ Hz, 3H); ^{13}C NMR (300 MHz, CDCl_3): δ 169.0 (C=O), 142.9 (C), 138.7 (C), 138.2 (C), 129.4 (CH \times 2), 127.1 (CH \times 2), 120.6 (C), 59.4 (CH), 49.9 (CH), 49.3 (CH₂), 42.1 (CH), 26.7 (CH), 24.1 (CH), 24.0 (CH), 21.5 (CH₃), 20.4 (CH₃), 19.5 (CH₃), 18.7 (CH₃), 17.8 (CH₃); **HRMS** (ESI-MS) calcd. for $\text{C}_{21}\text{H}_{28}\text{NO}_4\text{S}^+$ ($[\text{M}+\text{H}]^+$): 390.1734, found 390.1734.

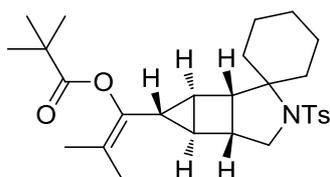


2-Methyl-1-((1'R,2'R*,3'R*,4'S*,5'S*)-1'-methyl-4-oxo-7'-oxaspiro[cyclohexane-1,6'-tricyclo[3.3.0.0^{2,4}]octan]-3'-yl)prop-1-en-1-yl acetate (96)* was synthesized following the general procedure J. Yield: 88%; Pale yellow oil; R_f (PE/Et₂O 1/1) 0.25; **IR** (neat) ν 2929, 1749, 1720, 1372, 1212, 1173, 1045, 917, 792 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3): δ 4.01 (d, $J = 9.7$ Hz, 1H), 3.62 (d, $J = 9.7$ Hz, 1H), 2.76-2.57 (m, 2H), 2.42-2.14 (m, 3H), 2.09 (s, 3H), 2.06 (br s, 1H), 2.00-1.89 (m, 2H), 1.87 (m, 3H), 1.83 (br s, 1H), 1.68-1.63 (m, 2H), 1.59 (br s, 1H), 1.52 (s, 3H), 1.08 (s, 3H); ^{13}C NMR (300 MHz, CDCl_3): δ 211.4 (C=O), 169.2 (C=O), 139.0 (C), 120.2 (C), 80.7 (C), 75.6 (CH₂), 55.1 (CH), 48.8 (C), 38.0 (CH₂), 36.5 (CH₂), 32.5 (CH₂), 32.2 (CH₂), 27.4 (CH), 24.9 (CH), 20.5 (CH₃), 18.84 (CH₃), 18.76 (CH₃), 18.0 (CH₃), 16.9 (CH); **HRMS** (ESI-MS) calcd. for $\text{C}_{19}\text{H}_{30}\text{NO}_4^+$ ($[\text{M}+\text{NH}_4]^+$): 336.2169, found 336.2170.

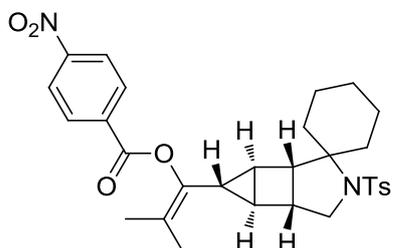


Cyclohexylidene((1'R,2'S*,3'S*,4'R*,5'S*)-7'-tosyl-7'-azaspiro[cyclohexane-1,6'-tricyclo[3.3.0.0^{2,4}]octan]-3'-yl)methyl acetate (98)* was synthesized following the general procedure J. Yield: 97%; Colorless oil; R_f (PE/Et₂O 3/1) 0.25; **IR** (neat) ν 2928, 2858, 1749, 1204, 1161, 1147, 1094, 818, 736, 658, 584, 542 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3): δ 7.78 (d, $J = 8.3$ Hz, 2H), 7.25 (d, $J = 8.0$ Hz, 2H), 3.70 (d, $J = 10.9$ Hz, 1H), 3.55 (dd, $J = 6.3, 10.9$ Hz,

1H), 2.54 (br d, $J = 4.3$ Hz, 1H), 2.40 (s, 3H), 2.35-2.31 (m, 3H), 2.05 (s, 3H), 1.97-1.92 (m, 3H), 1.81-1.46 (m, 15H), 1.31-0.97 (m, 3H); ^{13}C NMR (300 MHz, CDCl_3): δ 169.2 (C=O), 142.6 (C), 140.3 (C), 136.1 (C), 129.3 (CH \times 2), 128.1 (C), 126.9 (CH \times 2), 68.9 (C), 52.0 (CH₂), 48.2 (CH), 37.9 (CH), 32.3 (CH₂), 31.6 (CH₂), 29.1 (CH₂), 28.1 (CH₂), 27.3 (CH₂), 26.8 (CH₂), 26.4 (CH₂), 26.3 (CH), 25.2 (CH₂), 24.1 (CH), 23.9 (CH₂), 23.4 (CH₃), 21.5 (CH₃), 20.4 (CH₂), 20.2 (CH); HRMS (ESI-MS) calcd. for $\text{C}_{28}\text{H}_{38}\text{NO}_4\text{S}^+$ ($[\text{M}+\text{H}]^+$): 484.2516, found 484.2517.

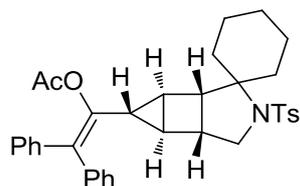


2-Methyl-1-((1'R*,2'S*,3'S*,4'R*,5'S*)-7'-tosyl-7'-azaspiro[cyclohexane-1,6'-tricyclo[3.3.0.0^{2,4}]octan]-3'-yl)prop-1-en-1-yl pivalate (**100**) was synthesized following the general procedure J. Yield: 93%; Colorless oil; R_f (PE/Et₂O 3/1) 0.35; IR (neat) ν 3051, 2930, 2863, 1742, 1458, 1327, 1154, 1122, 1094, 715, 669, 581, 545 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3): δ 7.76 (d, $J = 8.2$ Hz, 2H), 7.24 (d, $J = 8.1$ Hz, 2H), 3.61-3.52 (m, 2H), 2.55 (br d, $J = 4.2$ Hz, 1H), 2.39 (s, 3H), 2.38-2.30 (m, 1H), 1.90 (br s, 1H), 1.83 (s, 3H), 1.80-1.43 (m, 8H), 1.48 (s, 3H), 1.29-1.00 (m, 4H), 1.18 (s, 9H); ^{13}C NMR (300 MHz, CDCl_3): δ 176.3 (C=O), 142.5 (C), 140.2 (C), 138.7 (C), 129.4 (CH \times 2), 126.9 (CH \times 2), 120.3 (C), 69.1 (C), 51.9 (CH₂), 48.2 (CH), 38.9 (C), 37.8 (CH), 32.4 (CH₂), 31.8 (CH₂), 27.2 (CH₃ \times 3), 26.8 (CH), 25.2 (CH₂), 24.1 (CH), 23.9 (CH₂), 23.4 (CH₂), 21.5 (CH₃), 19.8 (CH), 18.8 (CH₃), 17.7 (CH₃); HRMS (ESI-MS) calcd. for $\text{C}_{28}\text{H}_{40}\text{NO}_4\text{S}^+$ ($[\text{M}+\text{H}]^+$): 486.2673, found 486.2671.

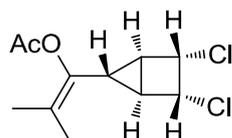


2-Methyl-1-((1'R*,2'S*,3'S*,4'R*,5'S*)-7'-tosyl-7'-azaspiro[cyclohexane-1,6'-tricyclo[3.3.0.0^{2,4}]octan]-3'-yl)prop-1-en-1-yl 4-nitrobenzoate (**102**) was synthesized following the general procedure J. Yield: 94%; Yellow oil; R_f (PE/Et₂O 2/1) 0.25; IR (neat) ν 3055, 2930, 2864, 1742, 1529, 1239, 1165, 1100, 814, 722, 676, 588, 546 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3): δ 8.35 (d, $J = 8.9$ Hz, 2H), 8.22 (d, $J = 8.9$ Hz, 2H), 7.69 (d, $J = 8.3$ Hz, 2H), 7.02 (d, $J = 8.0$

Hz, 2H), 3.68 (d, $J = 10.9$ Hz, 1H), 3.53 (dd, $J = 6.3, 10.9$ Hz, 1H), 2.59 (br d, $J = 4.3$ Hz, 1H), 2.36-2.23 (m, 2H), 2.30 (s, 3H), 2.04 (br s, 1H), 1.92 (s, 3H), 1.76-1.60 (m, 7H), 1.56 (s, 3H), 1.43-1.36 (s, 1H), 1.33-1.03 (m, 3H); ^{13}C NMR (300 MHz, CDCl_3): δ 162.8 (C=O), 150.8 (C), 142.5 (C), 140.1 (C), 139.1 (C), 134.8 (C), 131.1 (CH \times 2), 129.2 (CH \times 2), 126.9 (CH \times 2), 123.8 (CH \times 2), 121.6 (C), 68.7 (C), 51.9 (CH₂), 48.3 (CH), 37.9 (CH), 31.9 (CH₂), 31.7 (CH₂), 26.7 (CH), 25.2 (CH₂), 24.2 (CH), 23.9 (CH₂), 23.3 (CH₂), 21.4 (CH₃), 20.5 (CH), 18.9 (CH₃), 18.1 (CH₃); HRMS (ESI-MS) calcd. for $\text{C}_{30}\text{H}_{35}\text{N}_2\text{O}_6\text{S}^+$ ($[\text{M}+\text{H}]^+$): 551.2210, found 551.2210.

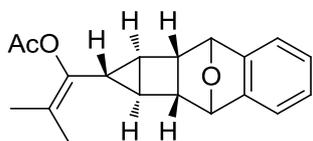


2,2-Diphenyl-1-((1'*R**,2'*S**,3'*S**,4'*R**,5'*S**)-7'-tosyl-7'-azaspiro[cyclohexane-1,6'-tricyclo[3.3.0.0^{2,4}]octan]-3'-yl)vinyl acetate (**104**) was synthesized following the general procedure J. Yield: 43%; Yellow oil; R_f (PE/Et₂O 1/1) 0.25; IR (neat) ν 3056, 2929, 2862, 1759, 1324, 1179, 1154, 1094, 704, 665, 580, 545 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3): δ 7.77 (d, $J = 8.3$ Hz, 2H), 7.43-7.12 (m, 12H), 3.73 (d, $J = 11.0$ Hz, 1H), 3.53 (dd, $J = 6.3, 11.0$ Hz, 1H), 2.45 (br d, $J = 4.0$ Hz, 1H), 2.39 (s, 3H), 2.33-2.24 (m, 1H), 1.96 (br s, 1H), 1.77 (s, 3H), 1.69-0.99 (m, 12H); ^{13}C NMR (300 MHz, CDCl_3): δ 168.6 (C=O), 143.1 (C), 142.6 (C), 140.3 (C), 139.6 (C), 139.4 (C), 130.8 (C), 130.3 (CH \times 2), 129.31 (CH \times 2), 129.27 (CH \times 2), 128.2 (CH \times 2), 128.0 (CH \times 2), 127.3 (CH), 127.0 (CH \times 2), 126.9 (CH), 68.7 (C), 51.9 (CH₂), 48.1 (CH), 37.8 (CH), 32.1 (CH₂), 31.6 (CH₂), 28.3 (CH), 25.2 (CH₂), 25.0 (CH), 24.0 (CH₂), 23.3 (CH₂), 21.5 (CH₃), 21.3 (CH), 20.5 (CH₃); HRMS (ESI-MS) calcd. for $\text{C}_{35}\text{H}_{38}\text{NO}_4\text{S}^+$ ($[\text{M}+\text{H}]^+$): 568.2516, found 568.2517.



1-((1'*R**,2'*S**,3'*R**,4'*S**,5'*S**)-2,3-Dichlorobicyclo[2.1.0]pentan-5-yl)-2-methylprop-1-en-1-yl acetate (**115**) was synthesized following the general procedure J. Yield: 25%; Pale yellow oil; R_f (PE/Et₂O 10/1) 0.30; IR (neat) ν 2915, 1749, 1368, 1212, 1127, 963, 792, 611 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3): δ 4.84-4.74 (m, 2H), 2.82 (s, 1H), 2.44 (dd, $J = 1.8, 4.2$ Hz, 2H), 2.09 (s, 3H), 1.90 (s, 3H), 1.54 (s, 3H); ^{13}C NMR (300 MHz, CDCl_3): δ 168.9 (C=O), 136.3

(C), 123.2 (C), 59.2 (CH × 2), 28.1 (CH × 2), 25.1 (CH), 20.3 (CH₃), 18.7 (CH₃), 18.1 (CH₃); **HRMS** (ESI-MS) calcd. for C₁₁H₁₈NO₂Cl₂⁺ ([M+NH₄]⁺): 266.0709, found 266.0707.



1-((1S,1aR*,1bS*,7aR*,7bS*)-1a,1b,2,7,7a,7b-hexahydro-1H-2,7-epoxycyclopropa[3,4]cyclobuta[1,2-b]naphthalen-1-yl)-2-methylprop-1-en-1-yl acetate (123)* was synthesized following the general procedure J. Yield: 91%; White solid; m.p. 153-155 °C; **R_f** (PE/Et₂O 3/1) 0.35; **IR** (neat) ν 2666, 2332, 1375, 1290, 973, 757 cm⁻¹; **¹H NMR** (300 MHz, CDCl₃): δ 7.24-7.20 (m, 2H), 7.16-7.12 (m, 2H), 5.25 (s, 2H), 2.10 (s, 3H), 2.01 (br s, 2H), 1.98 (br s, 1H), 1.83 (s, 3H), 1.80 (br s, 2H), 1.52 (s, 3H); **¹³C NMR** (300 MHz, CDCl₃): δ 169.3 (C=O), 144.2 (C × 2), 139.1 (C), 126.7 (CH × 2), 119.8 (C), 119.4 (CH × 2), 80.4 (CH × 2), 45.5 (CH × 2), 26.3 (CH), 23.4 (CH × 2), 20.5 (CH₃), 18.7 (CH₃), 18.0 (CH₃); **HRMS** (ESI-MS) calcd. for C₁₉H₂₄NO₃⁺ ([M+NH₄]⁺): 314.1751, found 314.1750.