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**ECOLE CENTRALE DE MARSEILLE**

*Institut des Sciences Moléculaires de Marseille (UMR 7313)*

**THESE**

Pour obtenir le grade de:

**DOCTEUR DE L'ECOLE CENTRALE DE MARSEILLE**

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**RUTHENIUM(II)-CATALYZED ENYNE  
CARBOCYCLIZATION REACTIONS**

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## *List of Abbreviations*

Ac	acetyl
aq	aqueous
Bn	benzyl
Boc	<i>t</i> -butoxycarbonyl
br	broad (spectroscopy)
brsm	based on recovered starting material
cat.	catalytic
CDCl <sub>3</sub>	deuterated chloroform
cod	1,5-cyclooctadiene
COSY	correlation spectroscopy
Cp	cyclopentadienyl
Cp*	pentamethylcyclopentadienyl
δ	Chemical shift
d	doublet
DCE	dichloroethane
DCM	dichloromethane
DEPT	Distortionless Enhancement by Polarization Transfer
DIAD	diisopropyl azodicarboxylate
DMA	dimethylacetamide
DMAD	dimethyl acetylenedicarboxylate
DMAP	<i>N,N</i> -4-dimethylaminopyridine
DMF	<i>N,N</i> -dimethylformamide
DMSO	dimethylsulfoxide
dppe	1,2-diphenylphosphinoethane
dr	diastereomeric ratio
EA	ethyl acetate

equiv	equivalent
ee	enantiomeric excess
h	hour
Hz	hertz
HMBC	Heteronuclear Multiple Bond Correlation
HMQC	Heteronuclear Multiple-Quantum Correlation
HPLC	High Performance Liquid Chromatography
HRMS	High Resolution Mass Spectroscopy
IR	infrared spectroscopy
J	coupling constant in hertz
LAH	lithium aluminum hydride
m	multiplet
Me	methyl
Ms	methanesulfonyl
NBS	<i>N</i> -bromosuccinimide
NMP	<i>N</i> -methylpyrrolidone
NOESY	Nuclear Overhauser Enhancement Spectroscopy
PE	petroleum ether
Ph	phenyl
ppm	parts per million
q	quartet
rt	room temperature
$R_f$	retention factor value
rt	room temperature
s	singlet
t	triplet
TBAI	<i>tetra-n</i> -butylammonium iodide

TES	triethylsilyl
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl
Ts	<i>para</i> -toluenesulfonyl

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## **General Introduction**

Transition metal-mediated cyclization reactions of 1,6-enynes have attracted considerable attention because of their potential to access a myriad of cyclic compounds in an atom-economic fashion and usually mild reaction conditions.<sup>1</sup> The last decades have witnessed a rapid development in this area. However, the use of expensive transition metal catalysts and ligands has hampered application at industrial scale. Therefore, we described in this manuscript three distinct Ru(II)-catalyzed cyclization reactions of 1,6-enynes, affording functionalized monocyclic/bicyclic compounds.

Chapter I. This chapter summarized the main transition-metal-catalyzed cyclization reactions of enynes with unsaturated coupling partners such as alkenes, alkynes and 1,3-dienes. It outlines access to complex (poly)cyclic molecules according to the nature of the co-reactant. In addition, intramolecular cyclization reactions, as special cases, were also included.

Chapter II. We present a novel ruthenium-catalyzed hydroalkynylative cyclization reaction of 1,6-enynes using bulky-substituted terminal alkynes to provide five-membered cyclic compounds featuring an exocyclic 1,5-enyne motif. On the basis of deuterium-labeling and control experiments, a mechanism involving the key metal-assisted  $\sigma$ -bond metathesis reaction is proposed.

Chapter III. In this chapter, the [2+2+2] cycloaddition reaction of 1,6-enynes and alkynes to give bicyclohexa-1,3-dienes derivatives have been well established through the use of same ruthenium catalyst [Cp\**Ru*(cod)Cl]. Scope investigation exhibited excellent tolerance to a wide range of functional groups, such as free alcohol and sulfonamide. Interestingly, the use of tertiary propargyl alcohols exclusively leads to single regioisomers. The chemo- and regio-selectivity issues are discussed on the basis of steric bulk of substituents and/or inter-ligand interactions through H-bond between the substrates and chloride ligand of the catalyst.

Chapter IV. This chapter put emphasis on the ruthenium-catalyzed cycloisomerization of *N*-tethered 1,6-enynes to provide azabicyclo[4.1.0]heptenes derivatives. The bicyclization

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<sup>1</sup> a) C. Aubert, O. Buisine, M. Malacria, *Chem. Rev.* **2002**, *102*, 813-834; b) S. T. Diver, A. J. Giessert, *Chem. Rev.* **2004**, *104*, 1317-1382; c) P. R. Chopade, J. Louie, *Adv. Synth. Catal.* **2006**, *348*, 2307-2327; d) V. Michelet, P. Y. Toullec, J.-P. Genêt, *Angew. Chem., Int. Ed.* **2008**, *47*, 4268-4315; e) G. Dominguez, J. Perez- Castells, *Chem. Soc. Rev.* **2011**, *40*, 3430-3444.

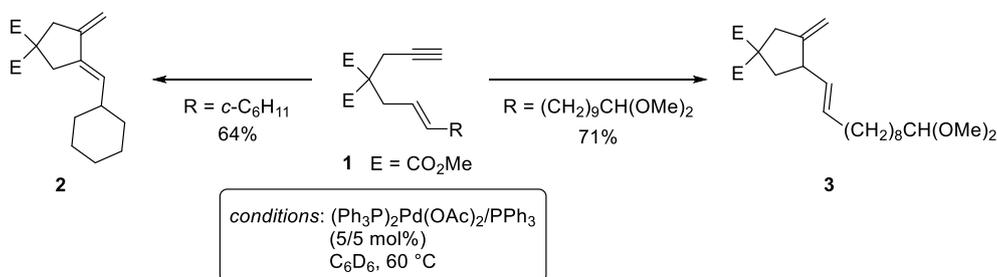
reaction can be achieved by using  $[\text{RuCl}_2(\text{CO})_3]_2$  as an electrophilic and alkynophilic catalyst. On the basis of related cyclizations with other metal catalysts, a mechanism rationale is discussed.

## **Chapter I**

# **Transition-Metal Catalyzed Co-cyclization of Enynes with Carbon-Carbon or Carbon-Heteroatom Unsaturated Motifs**

## Historical background

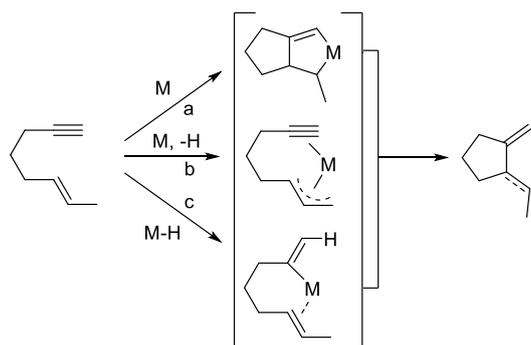
Enynes, and more specifically 1,6-enynes, have been exploited as useful building blocks in a wide range of cyclization reactions since the pioneering report by Trost and Lautens<sup>1</sup> in the mid-eighties entitled "Cyclization via Isomerization: A Palladium(2+)-Catalyzed Carbocyclization of 1,6-Enynes to 1,3- and 1,4-Dienes". It was discovered that heating the simple enyne **1** with a catalytic amount of palladium acetate, or preferably  $(\text{Ph}_3\text{P})_2\text{Pd}(\text{OAc})_2$ , in  $d_6$ -benzene solution resulted in a carbocyclization reaction leading to methylenecyclopentanes featuring a 1,3- or 1,4-diene unit, **2** and **3** respectively, according to the structural patterns of the substrate (Scheme 1).



**Scheme 1.** Palladium-catalyzed carbocyclization of 1,6-enynes

Initially, a palladacyclopentene intermediate followed by a  $\beta$ -H elimination was invoked to explain the mechanism of the cyclization (metallo-cyclopentene pathway) (Scheme 2, a). Further studies demonstrated that other mechanisms might also be operative. The  $\pi$ -allylmetal pathway (Scheme 2, b) initiated through the activation of the allylic C-H bond and the vinylmetal pathway (Scheme 2, c) initiated through *in situ* generation of metal-hydride species and subsequent hydrometalation of the triple bond can also lead to the formation of cycloisomers.

<sup>1</sup> B. M. Trost, M. Lautens, *J. Am. Chem. Soc.* **1985**, *107*, 1781-1783.



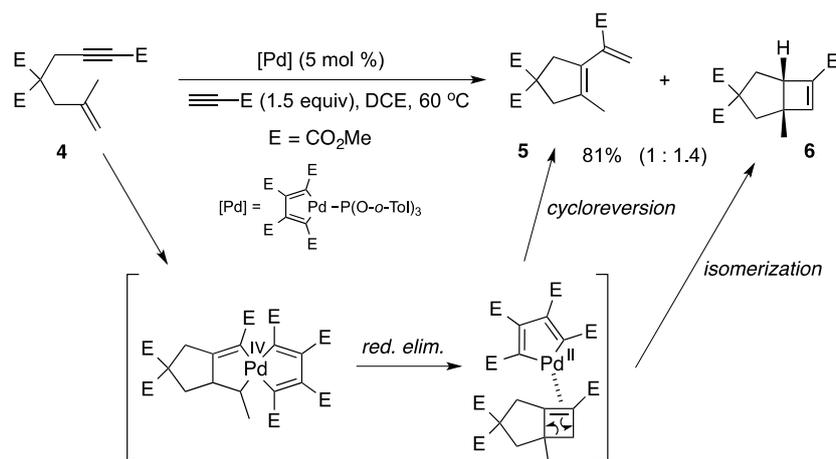
**Scheme 2.** Operating mechanisms for carbocyclization of 1,6-enynes

Afterwards, to define these reactions the term *cycloisomerization*, contraction of "Cyclization via Isomerization" was coined by Trost and various metal catalysts such as Ru, Rh, Co, Ir and Ti displayed similar reactivities. This topic has been reviewed in a number of excellent reports.<sup>2</sup>

While studying new palladium complexes for further developments of cycloisomerization of enynes, Trost and coworkers observed new products which questioned for their formation (Scheme 3). Thus, an electron-poor palladacyclopentadiene catalyzed the cyclization of enynes **4** capped with electron withdrawing substituent at the sp carbon atom to give a bicyclic cyclobutene **6** along with a vinylcyclopentene **5** featuring a structural reorganization.<sup>3</sup>

<sup>2</sup> a) C. Aubert, O. Buisine, M. Malacria, *Chem. Rev.* **2002**, *102*, 813-834; b) G. C. Lloyd-Jones, *Org. Biomol. Chem.* **2003**, *1*, 215-236; c) S. T. Diver, A. J. Giessert, *Chem. Rev.* **2004**, *104*, 1317-1382; d) A. M. Echavarren, C. Nevado, *Chem. Soc. Rev.* **2004**, *33*, 431-436; e) C. Nieto-Oberhuber, S. López, E. Jiménez-Núñez, A. M. Echavarren, *Chem. Eur. J.* **2006**, *12*, 5916-5923; f) L. Zhang, J. Sun, S. A. Kozmin, *Adv. Synth. Catal.* **2006**, *348*, 2271-2296; g) A. Fürstner, P. W. Davies, *Angew. Chem., Int. Ed.* **2007**, *46*, 3410-3449; h) V. Michelet, P. Y. Toullec, J.-P. Genêt, *Angew. Chem., Int. Ed.* **2008**, *47*, 4268-4315; i) E. Jiménez-Núñez, A. M. Echavarren, *Chem. Rev.* **2008**, *108*, 3326-3350; j) S. I. Lee, N. Chatani, *Chem. Commun.* **2009**, 371-384; for enantioselective reactions, see : h) A. Pradal, P. Y. Toullec, V. Michelet, *Synthesis* **2011**, *2011*, 1501-1514; i) I. D. G. Watson, F. D. Toste, *Chemical Science* **2012**, *3*, 2899-2919; j) A. Marinetti, H. Jullien, A. Voitouriez, *Chem. Soc. Rev.* **2012**, *41*, 4884-4908.

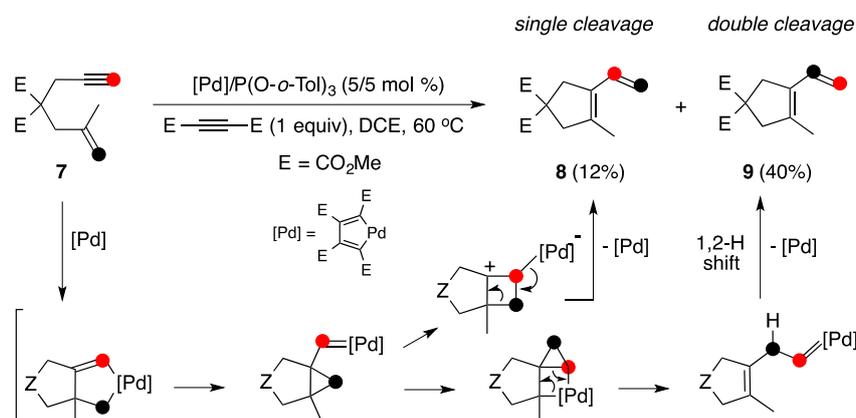
<sup>3</sup> B. M. Trost, G. J. Tanoury, *J. Am. Chem. Soc.* **1988**, *110*, 1636-1638.



**Scheme 3.** Palladacycle-catalyzed unusual cycloisomerization of 1,6-enynes

It was initially proposed the intermediacy of a cyclobutene, which undergo conrotatory ring opening to produce the rearranged diene **5**, and a 1,3-H shift, presumably metal-catalyzed, to form the more stable isomer **6**. These studies provided the first examples of transition-metal catalyzed skeletal reorganization (aka enyne metathesis) of 1,6-enynes.

Further insights to the understanding of the skeletal rearrangement mechanisms were provided by an in-depth studies through  $^2\text{H}$ - and  $^{13}\text{C}$ -labelling experiments<sup>4</sup> (Scheme 4).



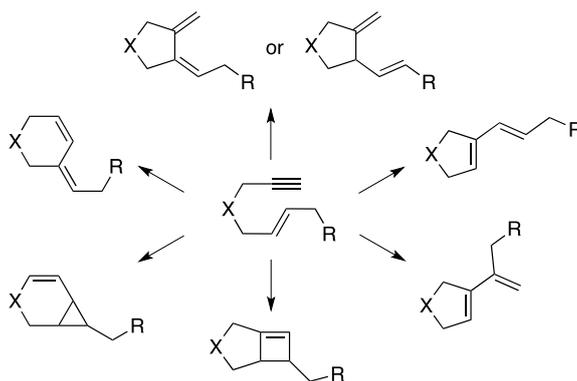
**Scheme 4.** Mechanisms of formation of single and double cleavage metathesis products

It appeared that dienes **8** and **9** arise from either a *single cleavage* of the double bond or a *double cleavage* of both insaturations of the enyne, respectively. The key

<sup>4</sup> a) B. M. Trost, A. S. K. Hashmi, *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1085-1087; b) B. M. Trost, A. S. K. Hashmi, *J. Am. Chem. Soc.* **1994**, *116*, 2183-2184; c) B. M. Trost, A. S. K. Hashmi, R. G. Ball, *Adv. Synth. Catal.* **2001**, *343*, 490-494; d) N. Chatani, N. Furukawa, H. Sakurai, S. Murai, *Organometallics* **1996**, *15*, 901-903.

palladacyclopentene isomerized into the  $\alpha$ -cyclopropyl palladacarbene and further rearrangements as depicted in Scheme 4 might account for the observed products.

Since the 1990s, Fürstner, Echavarren, Malacria and Toste research groups intensified studies on new cycloisomerization paths mainly performed with platinum and gold catalysts. The array of cycloisomers is summarized in Scheme 5 and these methodologies were exploited in natural products synthesis.<sup>5</sup>



**Scheme 5.** Array of enyne cycloisomers

The metal-catalyzed cyclization reactions of enynes incorporating an unsaturated partner were thoroughly investigated in the last decades to construct (poly)cyclic structures with high molecular complexity. This chapter will focused on recent methodologies developed in this area with emphasis on the mechanism aspects of the transformation. Both inter- and intramolecular (when available) reactions will be considered and the selected examples are in line with the atom economy principle. Although in the frame of this chapter, the Pauson-Khand reaction will not be dealt with here.

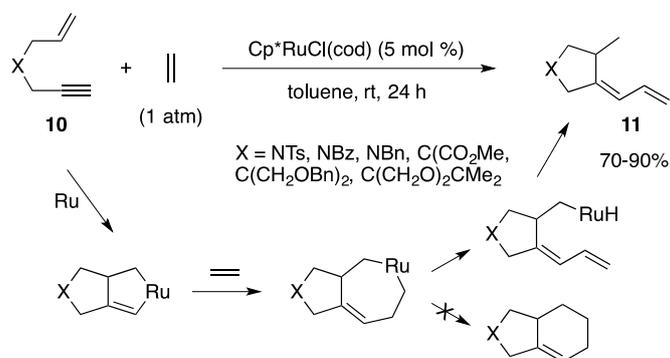
<sup>5</sup> a) Streptorubin B and Metacycloprodigiosin: A. Fürstner, H. Szillat, B. Gabor, R. Mynott, *J. Am. Chem. Soc.* **1998**, *120*, 8305-8314; b) B. M. Trost, G. A. Doherty, *J. Am. Chem. Soc.* **2000**, *122*, 3801-3810; c) (+)-Lycopladyne A: S. T. Staben, J. J. Kennedy-Smith, D. Huang, B. K. Corkey, R. L. LaLonde, F. D. Toste, *Angew. Chem., Int. Ed.* **2006**, *45*, 5991-5994; d) H. Deng, X. Yang, Z. Tong, Z. Li, H. Zhai, *Org. Lett.* **2008**, *10*, 1791-1793; e) Ventricos-7(13)-ene: S. G. Sethofer, S. T. Staben, O. Y. Hung, F. D. Toste, *Org. Lett.* **2008**, *10*, 4315-4318; f) (+)-Orientalol F and Pubinernoid B: E. Jimenez-Nunez, K. Molawi, A. M. Echavarren, *Chem. Commun.* **2009**, 7327-7329; g)  $\Delta^{9(12)}$ -Capnellene: G. Lemièrre, V. Gandon, K. Cariou, A. Hours, T. Fukuyama, A.-L. Dhimane, L. Fensterbank, M. Malacria, *J. Am. Chem. Soc.* **2009**, *131*, 2993-3006; h) (-)-Englerin A: K. Molawi, N. Delpont, A. M. Echavarren, *Angew. Chem., Int. Ed.* **2010**, *49*, 3517-3519; i) E. T. Newcomb, P. C. Knutson, B. A. Pedersen, E. M. Ferreira, *J. Am. Chem. Soc.* **2016**, *138*, 108-111.

## 1.1 Co-cyclizations of Enynes with Alkenes

Since the seminal report by Mitsudo and co-workers in 1976 disclosing the [2+2] cycloaddition of norbornene and alkynes to form norbornane-fused cyclobutenes,<sup>6</sup> ruthenacyclopentenes, generated through the cyclo-oxidative addition of alkyne and alkene to ruthenium, were recognized as important intermediates in modern ruthenium chemistry.

### 1.1.1 Intermolecular reactions

Mori reported an interesting alkenylative cyclization of 1,6-enynes **10** with ethylene gas in the presence of Cp\*RuCl(cod) as the catalyst to produce prop-2-enylidenecyclopentane or heterocyclic analogues **11** under mild conditions (Scheme 6).<sup>7</sup>



**Scheme 6.** Alkenylative cyclization of enynes

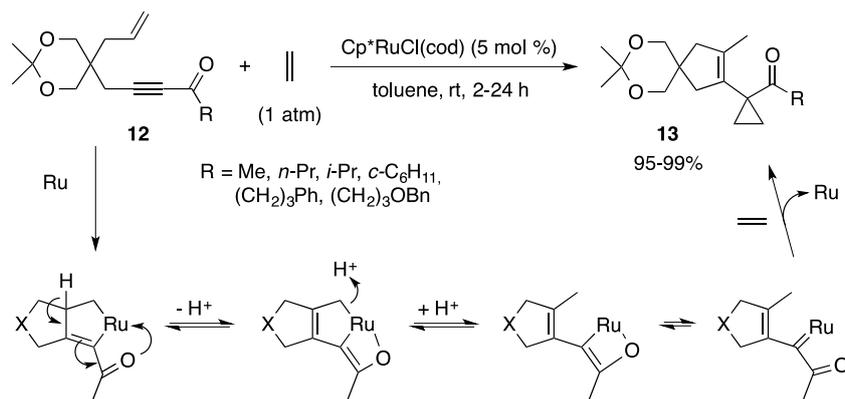
The mechanism of formation of 1,3-dienyl product **11** involved insertion of ethylene into ruthenacyclopentene followed by  $\beta$ -H elimination and subsequent reductive elimination of the metal species. It is quite intriguing that the direct reductive elimination of the ruthenacycloheptene intermediate do not occur to deliver the bicyclic product.

Further developments by the same group focused on reactions of enynes bearing an acyl group on the alkyne moiety. Thus, the electron-poor enyne **12**, compared to the previous ones **10**, completely changed the outcome of the reaction and led to 1-cyclopentenyl-1-acylcyclopropane derivatives **13** (Scheme 7).<sup>8</sup>

<sup>6</sup> T.-A. Mitsudo, K. Kokuryo, Y. Takegami, *J. Chem. Soc., Chem. Commun.* **1976**, 722-723.

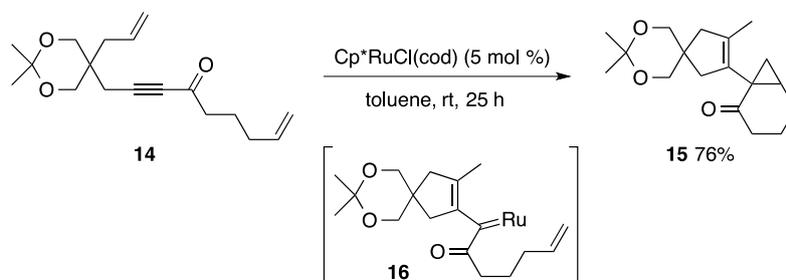
<sup>7</sup> a) M. Mori, N. Saito, D. Tanaka, M. Takimoto, Y. Sato, *J. Am. Chem. Soc.* **2003**, *125*, 5606-5607; b) M. Mori, D. Tanaka, N. Saito, Y. Sato, *Organometallics* **2008**, *27*, 6313-6320.

<sup>8</sup> a) D. Tanaka, Y. Sato, M. Mori, *Organometallics* **2006**, *25*, 799-801.



**Scheme 7.** Ru-catalyzed cyclization of enyn-ones with ethene

Mechanism investigations through deuterium labeling experiments showed that deuterium located on the internal carbon of olefin is completely transferred on the methyl group (as  $\text{CH}_2\text{D}$ ). On the basis of this result, a 1,2-H shift as depicted in Scheme 7 was invoked to form an  $\alpha$ -acyl-ruthenacarbene intermediate which is trapped by ethylene to deliver the final product. The occurrence of such intermediate was supported with the intramolecular variant of the reaction. Thus, under the same reaction conditions diene-ynone **14** was easily converted to the tetracyclic enone **15** through intramolecular cyclopropanation of the putative ruthenacarbene **16** (Scheme 8).

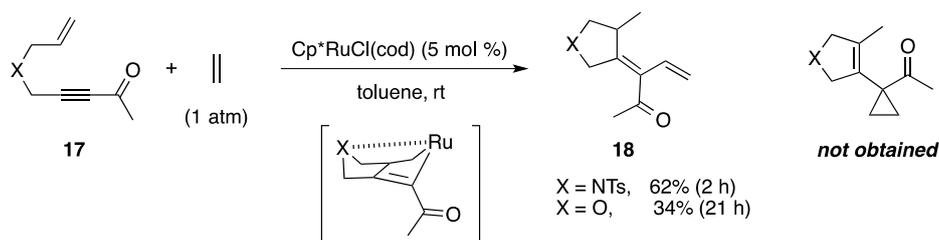


**Scheme 8.** Ru-catalyzed intramolecular cyclization of enyn-ones with alkene

Surprisingly, the reaction extended to heteroatom-tethered enynes **17** resulted into the formation of dienyl heterocycles **18** instead of the expected bicyclic ketones (Scheme 9).<sup>8a,9</sup> A plausible explanation consists in the intracyclic coordination of the heteroatom to the metal centre within the ruthenacycle intermediate which prevented the coordination of the carbonyl group. Therefore, insertion of ethylene might occur to afford the alkenylative cyclization

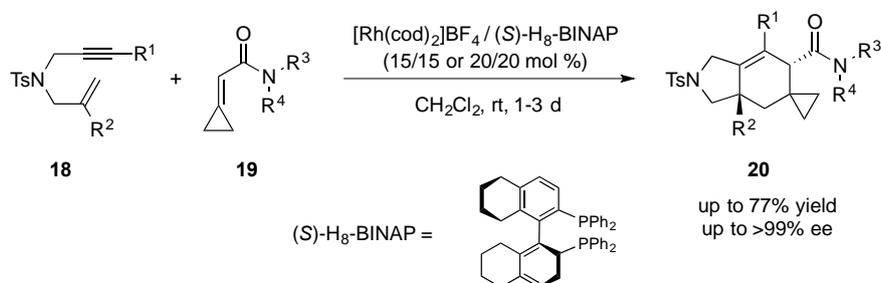
<sup>9</sup> D. Tanaka, Y. Sato, M. Mori, *J. Am. Chem. Soc.* **2007**, *129*, 7730-7731.

products.



**Scheme 9.** Ru-catalyzed cyclization of heteroatom-tethered enyn-ones with ethene

Quite recently, Tanaka and co-workers described the rhodium-catalyzed enantioselective [2+2+2] cycloaddition of enynes **18** with cyclopropylideneacetamides **19** to form spirocyclohexenes derivatives **20** retaining the cyclopropane ring (Scheme 10).<sup>10a</sup> The co-cyclizations proceeded smoothly under the optimized conditions, and excess of alkene decreased the reaction rate and produced adducts in low yields. Pleasingly, the products were formed with high regioselectivity even though the yields were found moderate. The proposed mechanism initiated with the formation of rhodacyclopentene followed by the regioselective insertion of alkene **19** and subsequent reductive elimination of the metal species to release **20**.



**Scheme 10.** Rh-catalyzed [2+2+2] cycloaddition of enynes and cyclopropylideneacetamides

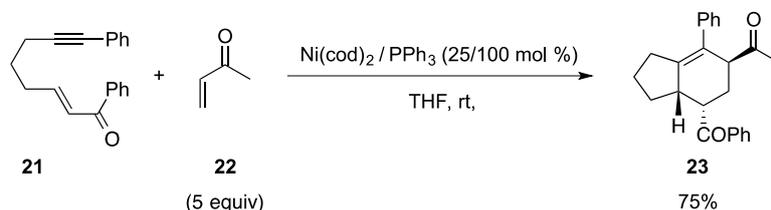
A similar co-cyclization of enynes and  $\alpha,\beta$ -unsaturated ketone catalyzed with a zerovalent nickel catalyst was reported by Montgomery (Scheme 11).<sup>11</sup> The reaction of enyne **21** and methyl vinylketone (**22**) in the presence of substoichiometric amounts of bis(1,5-cyclooctadiene)nickel(0) afforded the bicyclo[4.3.0]non-1-ene derivative **23** as a single regio- and diastereomer. The stereocontrol of three carbon centres in this [2+2+2]

<sup>10</sup> a) S. Yoshizaki, Y. Nakamura, K. Masutomi, T. Yoshida, K. Noguchi, Y. Shibata, K. Tanaka, *Org. Lett.* **2016**, *18*, 388-391;

b) See also: K. Masutomi, N. Sakiyama, K. Noguchi, K. Tanaka, *Angew. Chem., Int. Ed.* **2012**, *51*, 13031-13035.

<sup>11</sup> J. Seo, H. M. P. Chui, M. J. Heeg, J. Montgomery, *J. Am. Chem. Soc.* **1999**, *121*, 476-477.

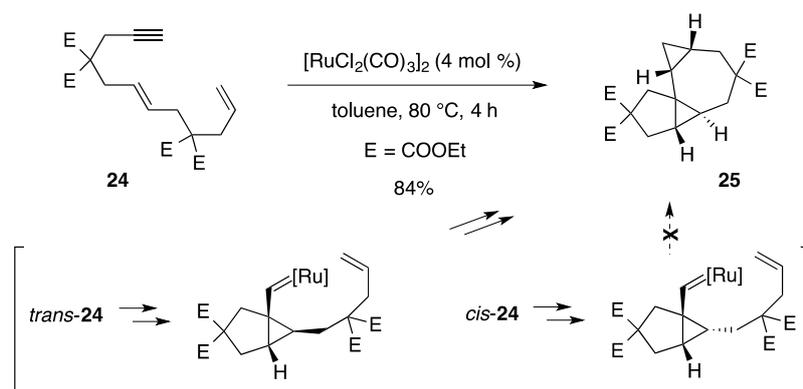
cycloaddition between an alkyne and two electron-deficient alkenes is a notable feature of the reaction.



**Scheme 11.** Ni-catalyzed [2+2+2] cycloaddition of enyne **21** and methyl vinylketone

### 1.1.2 Intramolecular reactions

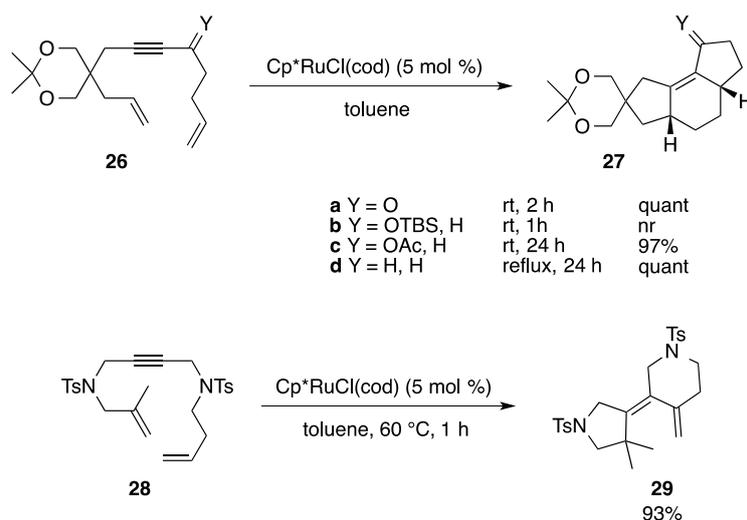
Chatani and Murai reported various metal-catalyzed cycloisomerizations of ene-ene-yne for the construction of complex stereodefined polycyclic ring systems.<sup>12</sup> For instance, treatment of acyclic dienyne *trans*-**24** with  $[\text{RuCl}_2(\text{CO})_3]_2$  (4 mol %) at 80°C in toluene solution produced the unusual tetracyclo [6.4.0.0<sup>1,9</sup>.0<sup>2,4</sup>]undecane derivative **25** as a single diastereomer in 84% isolated yield (Scheme 12). Importantly, the reaction of *cis*-**24** under the same conditions afforded a complex reaction mixture. These results were rationalized on the basis of the stereospecificity of the first cyclopropanation giving rise to carbenoid complexes which are able to undergo cyclopropanation only if the carbenoid moiety is sufficiently close to the double bond for an efficient intramolecular trapping.



**Scheme 12.** Ru-catalyzed enyne-ene cyclization

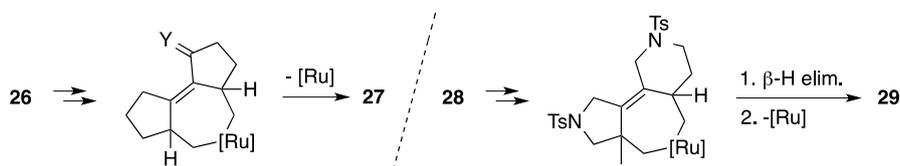
<sup>12</sup> N. Chatani, K. Kataoka, S. Murai, N. Furukawa, Y. Seki, *J. Am. Chem. Soc.* **1998**, *120*, 9104-9105.

Structural modifications of substrates often allow for new assembly of unsaturated partners. Representative examples are given in Scheme 13. For instance, [2+2+2] cycloaddition reactions are observed from dienynes **26**, with the exception of **26b** bearing the bulky OTBS substituent,<sup>9</sup> whereas the related *homo* [2+2+2] cycloaddition of **28** was not observed, instead diene **29** was formed in high yield.<sup>13</sup>



**Scheme 13.** Ru-catalyzed cyclizations of dienynes **26** and **28**

The different reaction outcomes might be ascribed to the formation of more flexible 5/7/6 ring system intermediates compared to the 5/7/5, formed from **28** and **26** respectively, which allows for a coplanarity of H-C-C-Ru required for the  $\beta$ -H elimination, before releasing **29** (Scheme 14). These requirements are not possible in case of the 5/7/5 ring system intermediate, although two hydrogen atoms are available at  $\beta$  carbons, consequently reductive elimination of the metal is favored to release **27**.

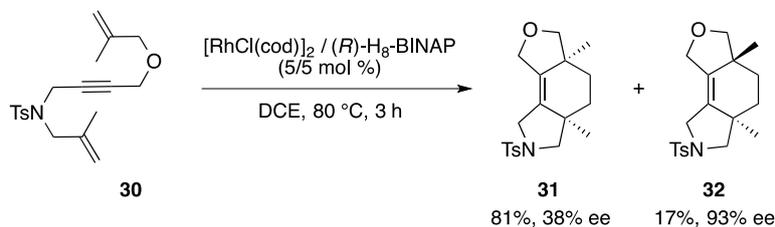


**Scheme 14.** Possible ruthenacycle intermediates from dienynes **26** and **28**

The cationic rhodium(I)/(*R*)-H<sub>8</sub>-BINAP or (*R*)-Segphos complex catalyzes the

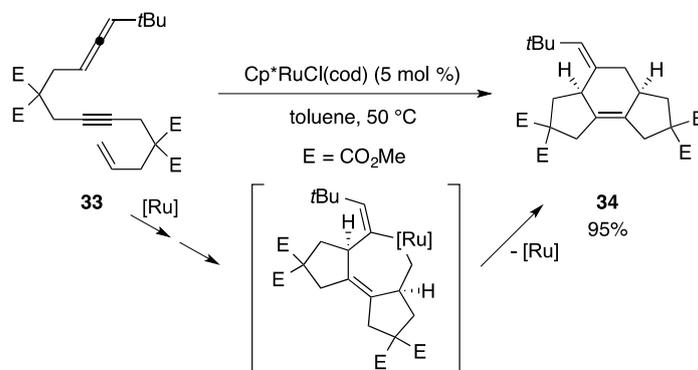
<sup>13</sup> N. Saito, D. Tanaka, M. Mori, Y. Sato, *Chem. Rec.* **2011**, *11*, 186-198.

intramolecular [2 + 2 + 2] cycloaddition of unsymmetrical dienynes, leading to fused tricyclic cyclohexenes bearing two quaternary carbon centers with high enantio- and diastereoselectivity (Scheme 15).<sup>14</sup>



**Scheme 15.** Rh-catalyzed enantioselective [2+2+2] cycloaddition of unsymmetrical dienynes

The ruthenium-catalyzed cyclization of 1,6-enynes tethered to allenes produces 5/6/5 tricyclic systems in moderate to good yields and complete regioselectivity (Scheme 16).<sup>15</sup> According to the initial allene/alkyne or alkene/alkyne oxidative coupling, two different paths ending with a common ruthenacycloheptene intermediate might account for the formation of the products.



**Scheme 16.** Ru-catalyzed intramolecular [2+2+2] cycloaddition of allene-yne-enes

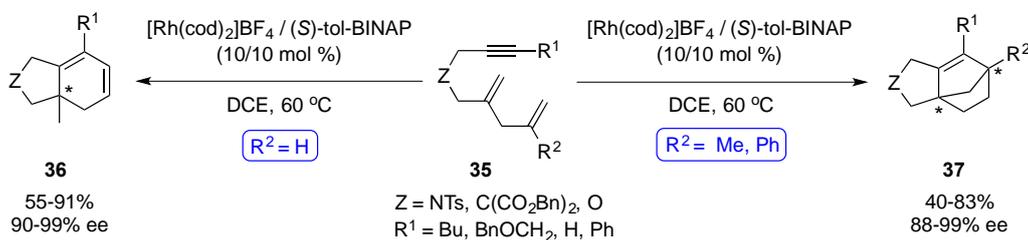
According to the substitution patterns of 1,4-diene-yne, the Shibata group developed a divergent synthetic route to enantioenriched bicyclodienes **36** or bridged tricycloalkenes **37** (Scheme 13).<sup>16</sup> Thus, *C/O/N*-linked substrates **35** provided the corresponding tricyclic adducts **37** in good yields and enantioselectivity up to 99% when R<sup>2</sup> is a methyl or phenyl

<sup>14</sup> H. Sagae, K. Noguchi, M. Hirano, K. Tanaka, *Chem. Commun.* **2008**, 3804-3806.

<sup>15</sup> N. Saito, T. Ichimaru, Y. Sato, *Chem. Asian, J.* **2012**, *7*, 1521-1523.

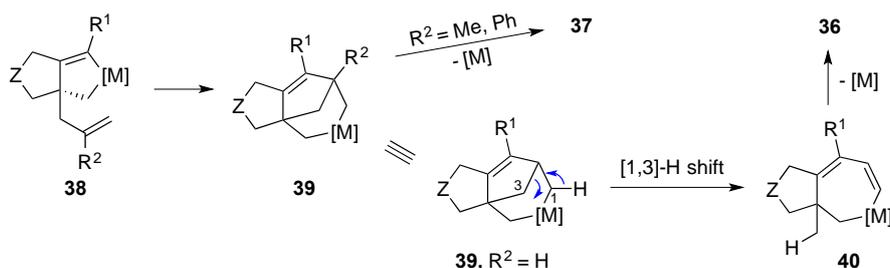
<sup>16</sup> T. Shibata, Y.-k. Tahara, *J. Am. Chem. Soc.* **2006**, *128*, 11766-11767.

group. In contrast, when R<sup>2</sup> is an hydrogen atom, the 1,4-diene-yne **36** gave rise to bicyclohexadienes **36** with excellent ee values.



**Scheme 17.** Rh-catalyzed intramolecular [2+2+2] cycloaddition of 1,4-diene-yne

The two reactions paths can evolve through common intermediates **38** and **39** (Scheme 18). Firstly, the oxidative cyclization of enyne **35** led to intermediate **38** which upon insertion of the terminal alkene generates the metalatricycle intermediate **39**. At this point, the readily reductive elimination yielded tricyclic compounds **37** when R<sup>2</sup> is an alkyl or aryl group. When R<sup>2</sup> is an hydrogen atom, **39** undergo a 1,3-proton shift and concomitant bridge cleavage to form **40** which would release the bicyclic compound **36** through reductive elimination. Extension of this work by elongating the chain between the two double bonds, as for instance 1,5- and 1,6-diene-yne gave tricyclic and bicyclic compounds which included medium-sized ring systems.<sup>17</sup>



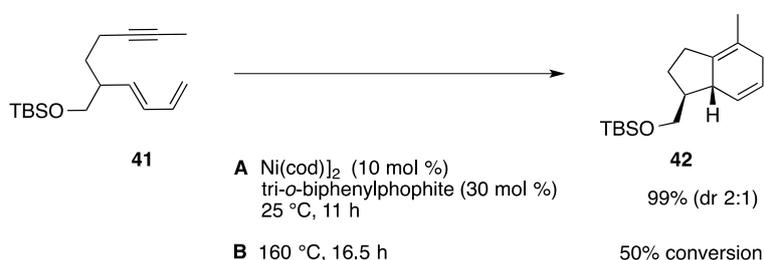
**Scheme 18.** Suggested mechanism for intramolecular [2+2+2] cycloaddition

In 1989, Wender reported the first cases of nickel(0)-catalyzed intramolecular [4+2] cycloaddition of a diene-tethered alkyne.<sup>18a</sup> The cycloaddition proceeded smoothly at room

<sup>17</sup> T. Shibata, Y.-k. Tahara, K. Tamura, K. Endo, *J. Am. Chem. Soc.* **2008**, *130*, 3451-3457.

<sup>18</sup> For examples of transition-metal-catalyzed [4+2] cycloaddition of 1,3-dien-8-yne derivatives, see: **Ni**: a) P. A. Wender, T. E. Jenkins, *J. Am. Chem. Soc.* **1989**, *111*, 6432-6434; b) P. A. Wender, T. E. Smith, *J. Org. Chem.* **1995**, *60*, 2962-2963; c) P. A. Wender, T. E. Smith, *J. Org. Chem.* **1996**, *61*, 824-825; d) P. A. Wender, T. E. Smith, *Tetrahedron* **1998**, *54*, 1255-1275; **Pd**: e) K. Kumar, R. S. Jolly, *Tetrahedron Lett.* **1998**, *39*, 3047-3048; **Rh**: f) R. S. Jolly, G. Luedtke, D. Sheehan, T. Livinghouse, *J. Am. Chem. Soc.* **1990**, *112*, 4965-4966; g) L. McKinstry, T. Livinghouse, *Tetrahedron* **1994**, *50*, 6145-6154; h) P. A.

temperature with yields ranging from 85 to 99%. Conversely, the thermal reaction required temperatures between 160 °C to 200 °C, and in some cases substantial decomposition of starting materials was observed (Scheme 19). Since then, various other transition metal catalysts<sup>18</sup> were proven efficient to effect these reactions, including in enantioselective variants.<sup>19</sup> Turn-over numbers (TON) beyond 1900 were recorded with NHC-bounded cationic rhodium complexes.<sup>18o</sup> Because dienynes are special cases of enynes, and even though similar intermediates have been involved in mechanisms of formation of bicyclic cyclohexadienes, this section will be not extended herein.



**Scheme 19.** Wender's Ni-catalyzed intramolecular [4+2] cycloaddition of dienynes

## 1.2 Co-cyclization of 1,6-Enynes with 1,3-Dienes

Enynes can be involved in high order [4+2+2] cycloaddition reactions to provide interesting ring-fused cyclooctanoid structures. The first metal-catalyzed intermolecular [4+2+2] cycloaddition reactions involving enynes and dienes were described by the Evans group in 2002.<sup>20</sup> Treatment of 1,6-enynes **43** with a catalytic system combining the Wilkinson's complex [Rh(PPh<sub>3</sub>)<sub>3</sub>Cl] and AgOTf under 1,3-butadiene atmosphere furnished the

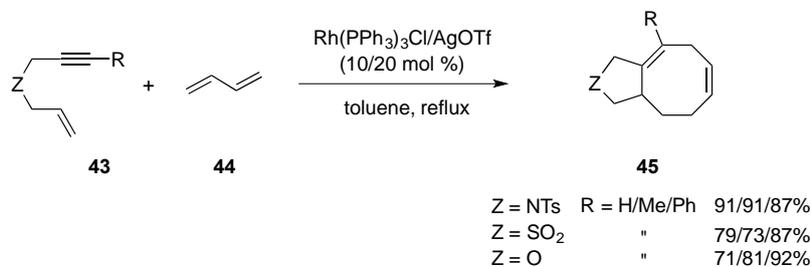
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Wender, T. E. Jenkins, S. Suzuki, *J. Am. Chem. Soc.* **1995**, *117*, 1843-1844; i) S. R. Gilbertson, G. S. Hoge, *Tetrahedron Lett.* **1998**, *39*, 2075-2078; j) S.-J. Paik, S. U. Son, Y. K. Chung, *Org. Lett.* **1999**, *1*, 2045-2047; k) B. Wang, P. Cao, X. Zhang, *Tetrahedron Lett.* **2000**, *41*, 8041-8044; l) D. J. R. O'Mahony, D. B. Belanger, T. Livinghouse, *Org. Biomol. Chem.* **2003**, *1*, 2038-2040; m) D. Motoda, H. Kinoshita, H. Shinokubo, K. Oshima, *Angew. Chem., Int. Ed.* **2004**, *43*, 1860-1862; n) W.-J. Yoo, A. Allen, K. Villeneuve, W. Tam, *Org. Lett.* **2005**, *7*, 5853-5856; o) S. I. Lee, S. Y. Park, J. H. Park, I. G. Jung, S. Y. Choi, Y. K. Chung, B. Y. Lee, *J. Org. Chem.* **2006**, *71*, 91-96; p) A. Saito, M. Hironaga, S. Oda, Y. Hanzawa, *Tetrahedron Lett.* **2007**, *48*, 6852-6855; q) T. Shibata, T. Chiba, H. Hirashima, Y. Ueno, K. Endo, *Angew. Chem., Int. Ed.* **2009**, *48*, 8066-8069; **Au**: r) A. Fürstner, C. C. Stimson, *Angew. Chem., Int. Ed.* **2007**, *46*, 8845-8849; s) H. Kusama, Y. Karibe, Y. Onizawa, N. Iwasawa, *Angew. Chem., Int. Ed.* **2010**, *49*, 4269-4272; **Cu**: ref. 18r. **Fe**: t) A. Fürstner, K. Majima, R. Martín, H. Krause, E. Kattmig, R. Goddard, C. W. Lehmann, *J. Am. Chem. Soc.* **2008**, *130*, 1992-2004; **Ir**: u) A. Tigchelaar, W. Tam, *Beilstein J. Org. Chem.* **2012**, *8*, 1765-1770.

<sup>19</sup> **Rh**: a) L. McKinstry, T. Livinghouse, *Tetrahedron* **1994**, *50*, 6145-6154; b) D. J. R. O'Mahony, D. B. Belanger, T. Livinghouse, *Synlett* **1998**, *1998*, 443-445; c) S. R. Gilbertson, G. S. Hoge, D. G. Genov, *J. Org. Chem.* **1998**, *63*, 10077-10080; d) H. Heath, B. Wolfe, T. Livinghouse, S. K. Bae, *Synthesis* **2001**, *2001*, 2341-2347; e) R. Shintani, Y. Sannohe, T. Tsuji, T. Hayashi, *Angew. Chem., Int. Ed.* **2007**, *46*, 7277-7280; f) **Ir**: T. Shibata, K. Takasaku, Y. Takesue, N. Hirata, K. Takagi, *Synlett* **2002**, *2002*, 1681-1682.

<sup>20</sup> a) P. A. Evans, J. E. Robinson, E. W. Baum, A. N. Fazal, *J. Am. Chem. Soc.* **2002**, *124*, 8782-8783; b) P. A. Evans, J. E. Robinson, E. W. Baum, A. N. Fazal, *J. Am. Chem. Soc.* **2003**, *125*, 14648-14648 (correction).

*cross*-cycloadducts in good to excellent yields (Scheme 20). In this study, only heteroatom-tethered enyne substrates are described in the intermolecular cyclization. The proposed mechanism implies the formation of bicyclic rhodacyclopentene, migratory insertion of butadiene followed by reductive elimination of the metal species.



**Scheme 20.** Rhodium-catalyzed [4+2+2] cycloaddition of 1,6-enynes with butadiene

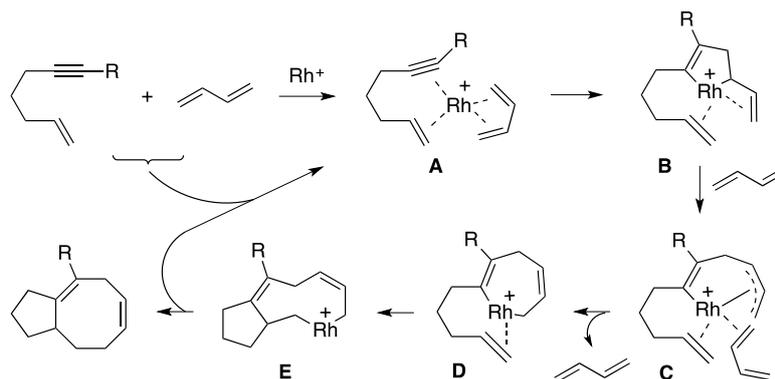
Intramolecular version of the reaction through the temporary silicon tethered substrates allowed the regiospecific and diastereoselective construction of tricyclic eight-membered heterocycles and carbocycles.<sup>21</sup>

High-level density functional theory (DFT) calculations highlighted the occurrence of an unpredictable reaction pathway<sup>22</sup> (Scheme 21) that involves complex **A** which undergo intermolecular oxidative coupling to form the rhodacyclopentene **B** which may evolve to a  $\sigma$ -vinyl, $\pi$ -allyl rhodium intermediate **C** stabilized by complexation with butadiene. By releasing butadiene ligand, **C** gives the rhodacycloheptadiene complex **D** which upon insertion of the pendant olefin and subsequent reductive elimination regenerates the  $\eta$ -diene-Rh complex **A** and releases the *cross*-cycloadduct. This model also demonstrates the origin of the excellent diastereoselectivity in reactions of alkyl-substituted substrates.<sup>23</sup>

<sup>21</sup> P. A. Evans, E. W. Baum, *J. Am. Chem. Soc.* **2004**, *126*, 11150-11151.

<sup>22</sup> M.-H. Baik, E. W. Baum, M. C. Burland, P. A. Evans, *J. Am. Chem. Soc.* **2005**, *127*, 1602-1603.

<sup>23</sup> P. A. Evans, E. W. Baum, A. N. Fazal, M. Pink, *Chem. Commun.* **2005**, 63-65.



**Scheme 21.** Proposed mechanism of rhodium-catalyzed [4+2+2] cycloaddition based on DFT calculations

### 1.3 Co-cyclization of 1,6-Enynes with Alkynes

#### 1.3.1 Intermolecular processes

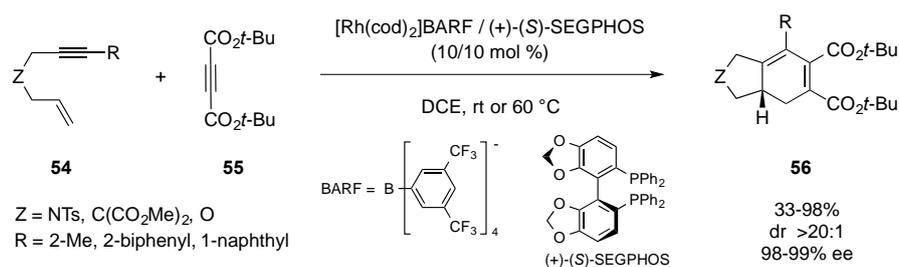
In contrast with studies devoted to the cycloadditions of  $\alpha,\omega$ -diynes with alkynes in presence of transition metal catalysts for the construction of annulated aromatic rings,<sup>24</sup> the parent reactions using enynes instead of diynes were developed quite recently. In 2005, Takeuchi and co-workers reported the Ir-catalyzed cyclization of 1,6-enynes **46** in the presence of alkynes **47** leading to bicyclic cyclohexa-1,3-dienes **48** (Scheme 22).<sup>25</sup> Interestingly, the selectivity issues of the reaction were addressed through the examination of the nature of associated bidentate ligand. For instance, when dppe was combined with  $[\text{Ir}(\text{cod})\text{Cl}]_2$ , the intermolecular [2+2+2] cycloadducts **48** were obtained as major products, whereas using dppf instead of dppe the cycloisomers **49** were predominantly formed. Both products resulted from an iridacyclopentene intermediate. Notably, the insertion of alkyne to metallacyclopentene should take place within the C(sp<sup>2</sup>)-M bond to provide **48**. Diene **49** was formed through  $\beta$ -hydride elimination of the iridacyclopentene followed by reductive elimination.

<sup>24</sup> Y. Yamamoto, in *Transition-Metal-Mediated Aromatic Ring Construction*, John Wiley & Sons, Inc., **2013**, pp. 71-125.

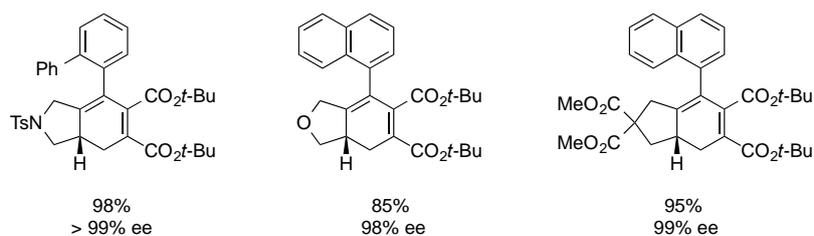
<sup>25</sup> S. Kezuka, T. Okado, E. Niou, R. Takeuchi, *Org. Lett.* **2005**, *7*, 1711-1714.



In 2008, Shibata applied the intermolecular [2 + 2 + 2] cycloaddition of enynes and alkynes to form bicyclohexadienes with both central and axial chiralities in highly diastereo- and enantioselective manner (Scheme 26).<sup>28</sup> Using the cationic Rh/(+)-(S)-SEGPHOS complex, N/C/O-linked enynes **54** and di-*tert*-butyl acetylenedicarboxylate (**55**) provided bicyclic adducts **56** in >20 :1 diastereomeric ratio and ee up to 99%. Regular unactivated alkynes can also be used in the coupling reaction but the diastereomeric ratio is quite poor (1-2 :1).

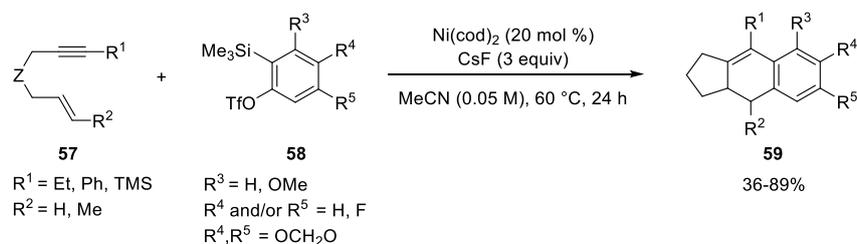


representative examples



**Scheme 26.** Rh-catalyzed [2+2+2] cycloaddition of enynes and electron-deficient alkynes

Candito and Lautens employed *in situ* generated arynes as alkyne surrogates in the coupling reactions with enynes. A stereoselective nickel-catalyzed [2+2+2] cycloaddition of 1,6-enynes **57** with 2-trimethylsilylaryl triflates **58** as arynes precursors to give polycyclic-fused benzene compounds **59** in poor to very good yields (Scheme 27).<sup>29</sup> Interestingly, a ligand free nickel(0) catalyst is operative for the couplings.



**Scheme 27.** Ni(0)-catalyzed [2+2+2] cycloaddition of enynes and arynes

<sup>28</sup> T. Shibata, M. Otomo, Y.-k. Tahara, K. Endo, *Org. Biomol. Chem.* **2008**, *6*, 4296-4298.

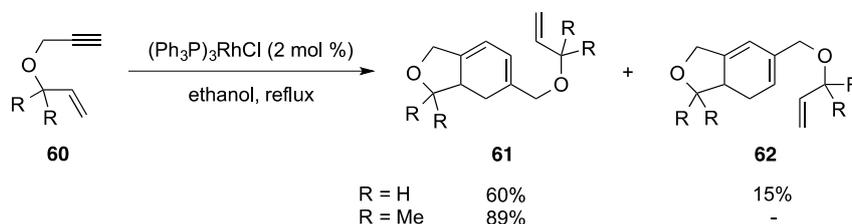
<sup>29</sup> D. A. Candito, M. Lautens, *Synlett* **2011**, *22*, 1987-1992.

### 1.3.2 Self-coupling of enynes

#### Through [2+2+2] Cycloaddition

The past decades have witnessed a rapid development of cycloaddition reactions to prepare a broad range of cyclic compounds. In some instances, investigations involving 1,6-enynes ended up the formation of adducts through the *homo*-[2+2+2] cycloaddition between 2 alkynes and 1 alkene motifs affording undesired bicyclohexadienes.

The first metal-catalyzed dimerization of enynes was reported unexpectedly by the Grigg group.<sup>30</sup> Treatment of enynes **60** with the Wilkinson's catalyst [(Ph<sub>3</sub>P)<sub>3</sub>RhCl] in boiling ethanol furnished bicyclic 1,3-cyclohexadiene derivatives **61/62** in good overall yields as a pair of regioisomers (Scheme 28). It is worth to note that only oxygen-tethered enynes have the ability to give adducts, whereas *N*-tethered or regular enynes were reluctant to undergo the cycloaddition reaction. In addition, the regioselectivity seems to depend on the enyne substitution patterns, but this trend has not been supported by other examples.



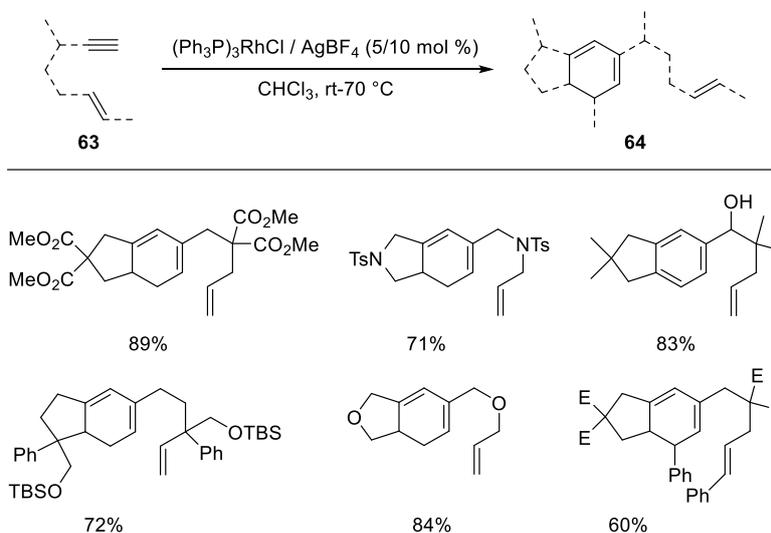
**Scheme 28.** Rhodium-catalyzed *self*-dimerization of 1,6-enynes

In 2001, Oh and co-workers reported the Rh-catalyzed *homo* [2+2+2] cycloaddition of enynes **63** bearing terminal alkynes giving rise to products **64** as single regioisomers (Scheme 29).<sup>31</sup> Addition of silver salt to RhCl(PPh<sub>3</sub>)<sub>3</sub> generates cationic [Rh]<sup>+</sup> species which promotes the cycloaddition in relatively high yields and suppressed the formation of linear dimers. Substituents of enynes, such as ester, sulfonamide, have no deleterious effect for this transformation. However, the enyne bearing OH group underwent the cyclization to form trisubstituted benzene through the dehydration of the expected adduct. On the basis of known rhodium chemistry, oxidative addition of [Rh]<sup>+</sup> species to the C(sp)-H bond forms an

<sup>30</sup> R. Grigg, R. Scott, P. Stevenson, *J. Chem. Soc., Perkin Trans. 1.* **1988**, 1365-1369.

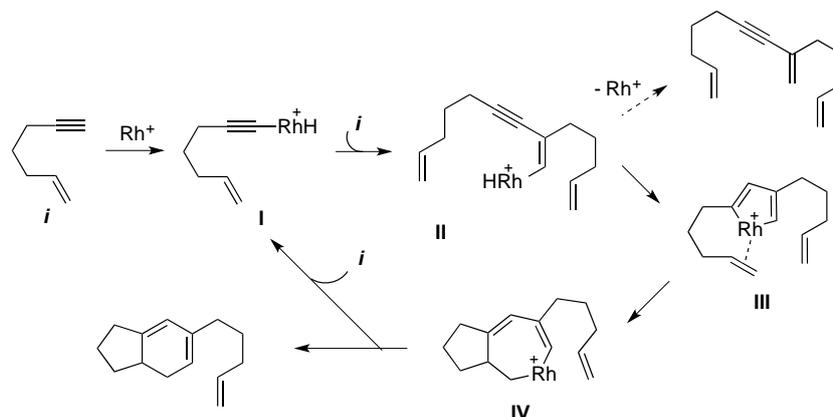
<sup>31</sup> C. H. Oh, H. R. Sung, S. H. Jung, Y. M. Lim, *Tetrahedron Lett.* **2001**, 42, 5493-5495.

alkynylhydridorhodium complex **I** which add intermolecularly to another alkyne (carboration). The resulting vinylrhodium **II** could undergo either reductive elimination to



**Scheme 29.** Rhodium-catalyzed [2+2+2] cycloaddition of 1,6-enynes

form linear dimers or rhodacyclization to generate rhodacyclopentadiene **III** and subsequently rhodacycloheptadiene **IV** from which reductive elimination delivers the cycloadduct (Scheme 30).

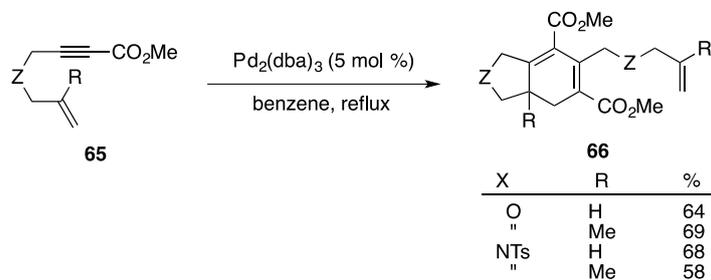


**Scheme 30.** Mechanism of rhodium-catalyzed [2+2+2] cycloaddition of 1,6-enynes

Yamamoto and co-workers reported a related cyclodimerization of 1,6-enynes capped with electron-withdrawing substituents on the triple bond.<sup>32</sup> In the presence of a zerovalent palladium catalyst, electron-deficient enynes **65** were converted into bicyclohexadienes **66**

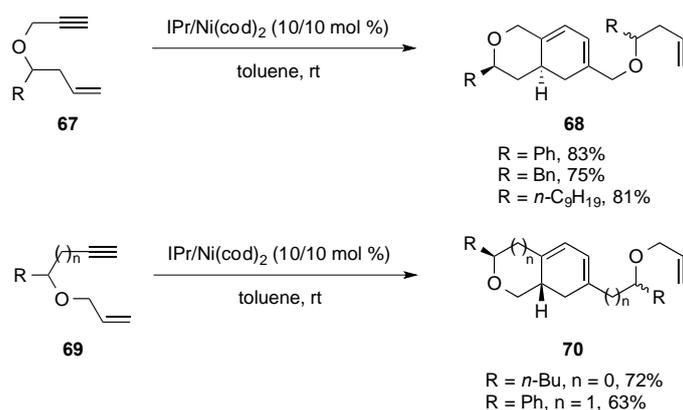
<sup>32</sup> Y. Yamamoto, S. Kuwabara, Y. Ando, H. Nagata, H. Nishiyama, K. Itoh, *J. Org. Chem* **2004**, *69*, 6697-6705.

as single regioisomers in fair yields (Scheme 31). A palladacyclopentadiene intermediate stabilized by intramolecular coordination of double bond resulting from the cyclo-oxidative coupling of two alkynes was proposed on the basis of the regioselectivity of the reaction.



**Scheme 31.** Palladium-catalyzed cyclodimerization of electron-deficient 1,6-enynes

Quite recently, Ho and co-workers reported the room-temperature Ni-catalyzed dimerization of 1,*n*-enynes toward the formation of ring-fused tetrahydropyran and furan derivatives (Scheme 32).<sup>33</sup> NHCs ligands screening showcased IPr as the best ligand to yield *homo* [2+2+2] cycloadducts. Interestingly, the relative position of a substituent R at the  $\alpha$ -carbon of the heteroatom tether allow control of diastereoselectivity. For instance, the substituent at the butenyl side chain favored a *syn*-relative configuration at the 1*H*-2-benzopyran core whereas a substituent at the propargyl side chain provided products with the *anti*-relative configuration.

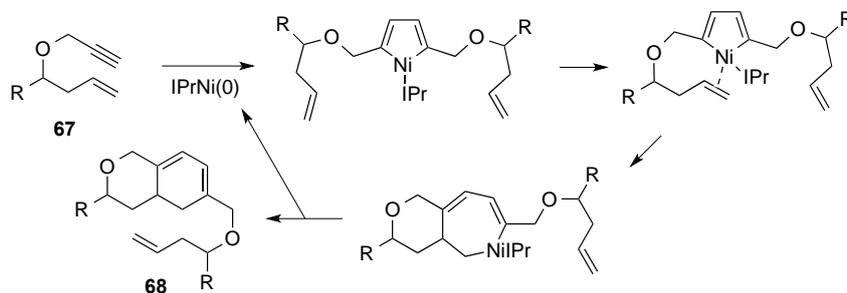


**Scheme 32.** Nickel-catalyzed [2+2+2] dimerization of 1,*n*-enynes

A mechanism rationale, in line with the observed results involves formation of the symmetrical nickelacyclopentadiene intermediate from the regioselective tail-to-tail coupling of two triple bonds, followed by intramolecular insertion of double bond and reductive

<sup>33</sup> J.-P. Zhao, S.-C. Chan, C.-Y. Ho, *Tetrahedron*. **2015**, *71*, 4426-4431.

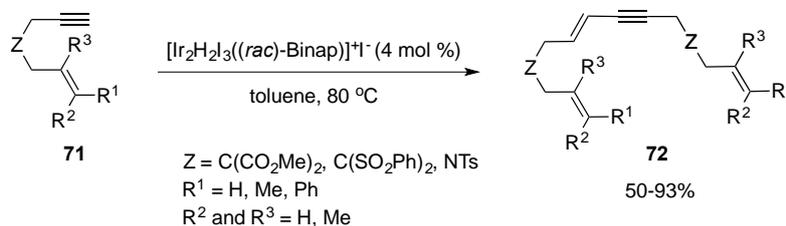
elimination of the metal to deliver the cycloadduct (Scheme 33). However, the origin of the regioselectivity of the coupling still remains unclear.



**Scheme 33.** Mechanism rationale for the nickel-catalyzed [2+2+2] dimerization of 1,n-enynes

### Through Alkyne Coupling

While exploring the potential of cationic dinuclear triply halogen-bridged Ir(III)-atropisomeric ligands complexes in carbon-carbon bond formations, Michelet group found the Ir-catalyzed head-to-head coupling of 1,6-enynes **71** giving polyunsaturated linear dimers **72** with *E* selectivity (Scheme 34).<sup>34</sup>



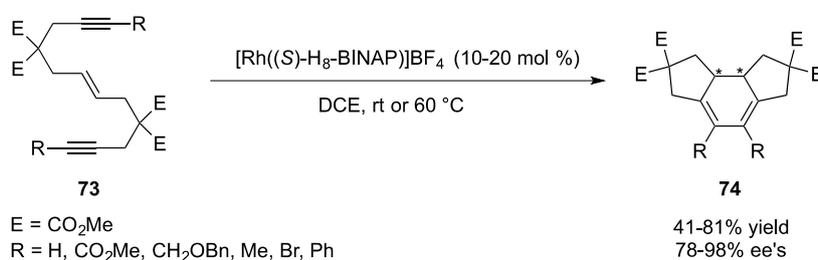
**Scheme 34.** Iridium-catalyzed dimerization of 1,6-enynes

Catalyst screening showed  $[\text{Ir}_2\text{H}_2\text{I}_3((\text{rac})\text{-Binap})]^+\text{T}$  exhibited the best catalytic activity at 80 °C for the selective dimerization of a number of functionalized enynes in 50–93% ranging yields. As the coupling reaction concerns only the alkyne moiety, enynes featuring various substitution patterns on the double bond are well suited for the couplings. Therefore, the above catalyst proved excellent for the *self*-coupling of regular terminal alkynes to give conjugated 1,3-enynes with exclusive *E*-selectivity in good yields.

<sup>34</sup> M. Ez-Zoubir, F. L. B. d'Herouville, J. A. Brown, V. Ratovelomanana-Vidal, V. Michelet, *Chem. Commun.* **2010**, 46, 6332-6334.

### 1.3.3 Intramolecular reactions

In 2006, Shibata and co-workers reported the first enantioselective intramolecular [2+2+2] cycloaddition of enediynes (Scheme 35).<sup>35,36</sup> On exposure to a cationic Rh/((S)-H<sub>8</sub>-BINAP) catalyst, carbon-tethered enediynes **73** were smoothly converted to 5/6/5 tricyclic dienes **74** in good yields and enantiomeric excesses regardless of the substitution at terminal sp carbon atoms. In the case of *N*-tethered enediynes, substituents on the alkyne termini is mandatory to prevent their alkyne-alkyne oxidative couplings. Thus, products can be formed in good yields and high ee values using substrates with specific alkyne substituents groups such as Me, Ph or CO<sub>2</sub>Me.



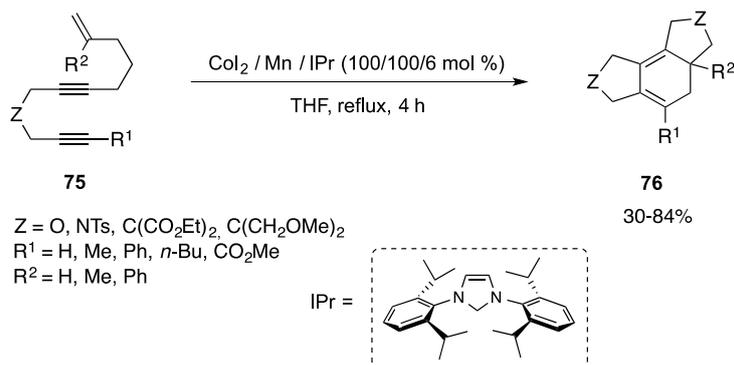
**Scheme 35.** Rh-catalyzed intramolecular [2+2+2] cycloaddition of ene-diyne

Malacria and co-workers reported the cobalt-mediated [2+2+2] cycloaddition of enediynes **75**, which feature a double bond at terminal position, to polycyclic cyclohexadienes **76** with 30-84% yields range (Scheme 36).<sup>37</sup> The authors claim an improvement procedure that uses a catalytic amount (6 mol %) of *in situ* generated *N*-heterocyclic carbene (IPr) instead of PPh<sub>3</sub> (2 equivalents) but the promoter system remains marginal in the context of metal-catalyzed [2+2+2] cycloaddition reactions as the reaction works only with equimolar amounts of Co(II) iodide and manganese as reducing reagent.

<sup>35</sup> T. Shibata, H. Kurokawa, K. Kanda, *J. Org. Chem.* **2007**, *72*, 6521-6525.

<sup>36</sup> T. Shibata, M. Otomo, K. Endo, *Synlett* **2010**, *2010*, 1235-1238.

<sup>37</sup> A. Geny, S. Gaudrel, F. Slowinski, M. Amatore, G. Chouraqui, M. Malacria, C. Aubert, V. Gandon, *Adv. Synth. Catal.* **2009**, *351*, 271-275.

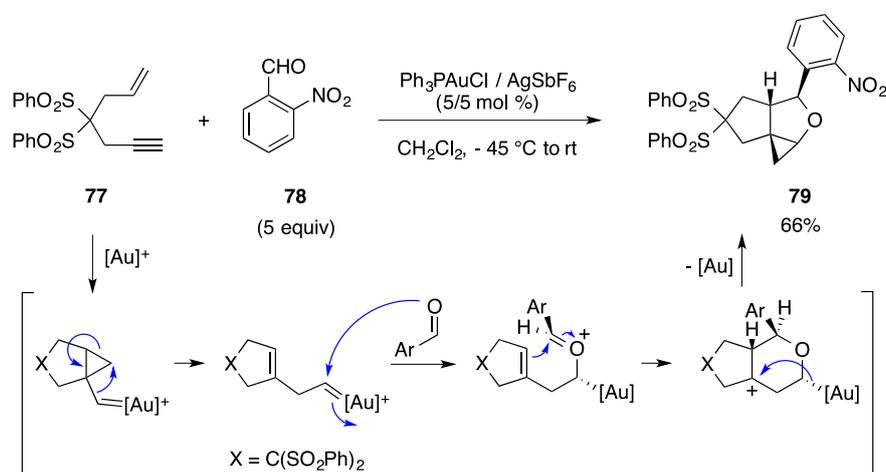


**Scheme 36.** Ni-catalyzed intramolecular [2+2+2] cycloaddition of ene-diyne

## 1.4 Co-cyclization of Enynes with Carbonyl Compounds

### 1.4.1 Intermolecular reactions

Helmchen reported the first examples of intermolecular cyclization of enynes that incorporates aromatic aldehydes in the presence of Ph<sub>3</sub>PAuCl/AgSbF<sub>6</sub> catalyst system to form tricyclic ethers in a diastereoselective fashion (Scheme 37).<sup>38</sup> The cyclization reaction was successfully extended to enolizable aldehydes and ketones.



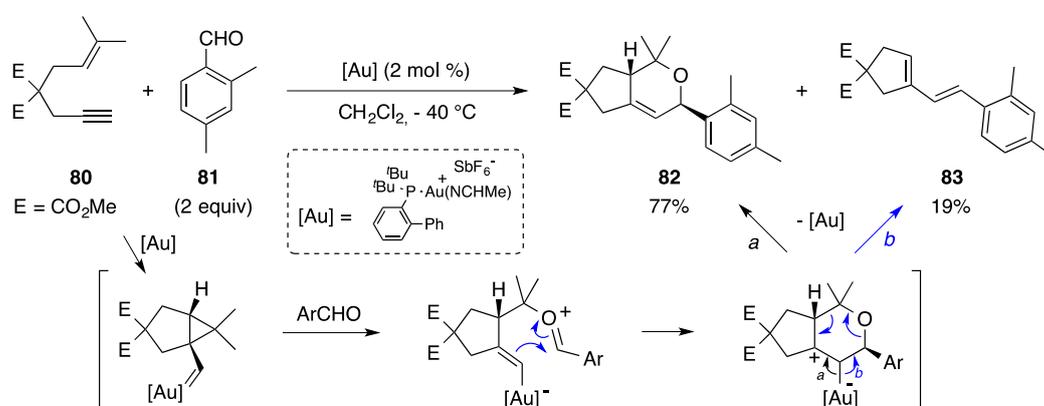
**Scheme 37.** Gold-catalyzed intermolecular addition of carbonyl compounds to 1,6-enynes

The mechanism of formation of **79** involves cyclization of enynes to form auracarbenes which upon nucleophilic attack of oxygen atom of the aldehyde form an oxonium ion. Cyclization through nucleophilic attack of cycloalkene to the oxonium ion generates a tertiary

<sup>38</sup> M. Schelwies, A. L. Dempwolff, F. Rominger, G. Helmchen, *Angew. Chem., Int. Ed.* **2007**, *46*, 5598-5601.

carbonium ion which finally undergo intramolecular attack of the alkylaurate to release the tricyclic ether **79** and the metal species (Scheme 37).

In these reactions, the nature of the ligand plays a significant role in the control of selectivity of the reaction.<sup>39</sup> For instance, in the presence of an electron-rich bulky phosphine-coordinated cationic gold catalyst, enyne **80** and 2,4-dimethyl benzaldehyde (**81**) can be coupled at low temperature to give bicyclic hydroxyprans **82** along with diene **83** as by product. A common cycloalkylaurate(I) intermediate is proposed as precursor of **82** and **83** (Scheme 38).

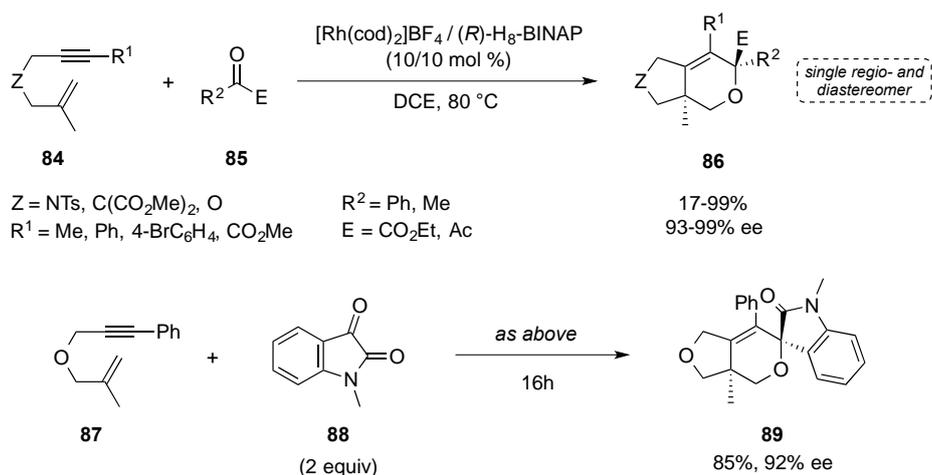


**Scheme 38.** Gold-catalyzed intermolecular addition of carbonyl compounds to 1,6-enynes

In 2008, Tanaka and co-workers described the [2+2+2] cycloaddition of enynes **84** with electron-deficient ketones **85** using the cationic RhI/(*R*)-H<sub>8</sub>-BINAP catalyst to construct bicyclic hydroxyprans derivatives **86** with excellent regio-, diastereo-, and enantioselectivity (Scheme 39).<sup>40</sup> Other chiral ligands, such as (*R*)-tol-BINAP and (*R*)-Segphos provided adducts in high enantioselectivity although the chemical yields dropped dramatically. Interestingly the reaction was useful to synthesize enantiomerically enriched complex spirocyclic compounds. For instance, the coupling reaction of enyne **87** and 1-methylisatin (**88**) provided polyheterocyclic structure **89** with 92% ee.

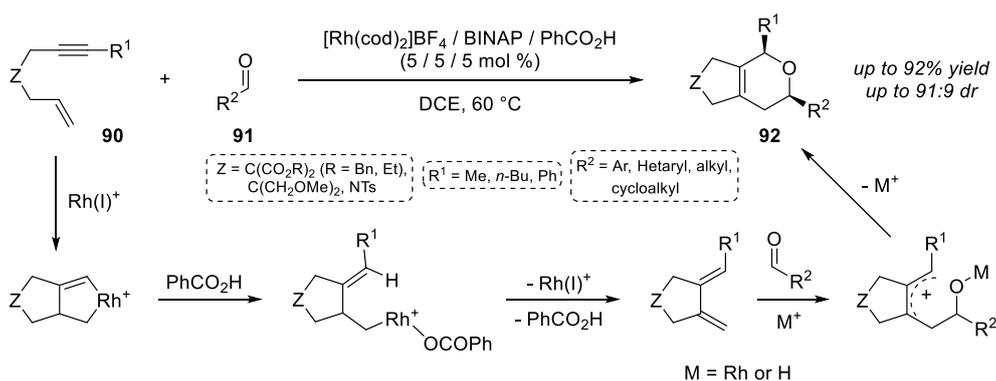
<sup>39</sup> A. Escribano-Cuesta, V. López-Carrillo, D. Janssen, A. M. Echavarren, *Chem. Eur. J.* **2009**, *15*, 5646-5650.

<sup>40</sup> K. Tanaka, Y. Otake, H. Sagae, K. Noguchi, M. Hirano, *Angew. Chem., Int. Ed.* **2008**, *47*, 1312-1316.



**Scheme 39.** Rh-catalyzed [2+2+2] cycloaddition of enynes and electron-deficient ketones

Tanaka and Ishida reported a tandem cycloisomerization/hetero-Diels–Alder reaction of 1,6-enynes **90** with unactivated aldehydes **91** promoted by a cationic rhodium catalyst associated with a carboxylic acid.<sup>41</sup> The co-cyclization produces a variety of cyclopentane-fused dihydropyrans **92** as single regioisomers (Scheme 40). The role of benzoic acid as co-catalyst is ascribed to the cleavage of the rhodacyclopentene intermediate prior to the β-H elimination step. The resulting *s*-cis diene might undergo the coupling with the aldehyde through electrophilic activation by the metal or a proton to generate an allyl cationic species which upon intramolecular *O*-alkylation delivers the heterocycle **92**.



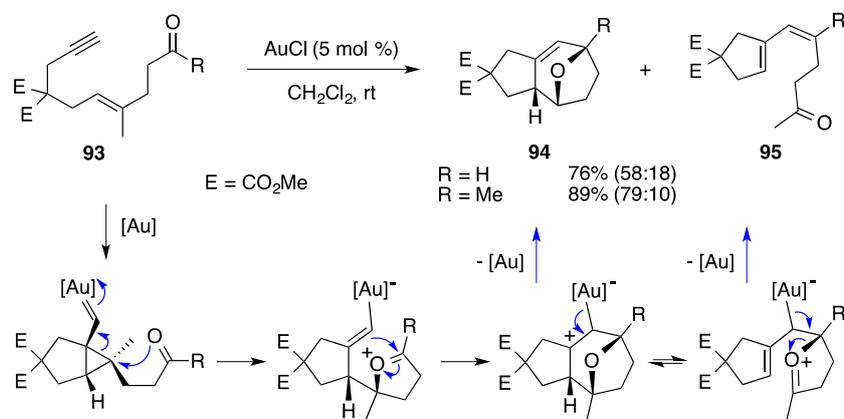
**Scheme 40.** Rh-catalyzed tandem cycloisomerization/hetero Diels-Alder of enynes with aldehydes

<sup>41</sup> M. Ishida, K. Tanaka, *Org. Lett.* **2013**, *15*, 2120-2123.

The tandem reaction can be applied to aldimines in place of aldehydes to produce bicyclic tetrahydropyridines, but in these cases a Brønsted acid such as *p*-toluenesulfonic acid is required as the co-catalyst.

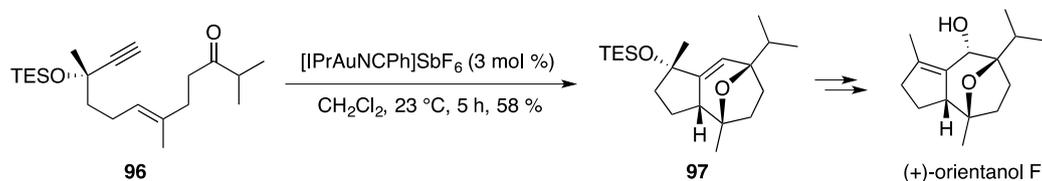
### 1.4.2 Intramolecular reactions

Echavarren group developed the synthesis of fused 5,7-ring systems using 1,6-enynes with a pendant carbonyl group at the alkenyl side chain in the presence of Au(I) catalysts to give bridged oxatricyclic skeletons by a domino process in which two C–C and one C–O bonds are assembled by a formal [2 + 2 + 2] alkyne/alkene/carbonyl cycloaddition (Scheme 41).<sup>42</sup>



**Scheme 41.** AuCl<sub>3</sub>-catalyzed intramolecular [2+2+2] cycloaddition of keto-yne-enes

Using this method as the key step, Echavarren and co-workers have completed the total synthesis of (+)-orientanol F,<sup>5f</sup> corrected the structure of pubinernoid B,<sup>5f</sup> and achieved an asymmetric total synthesis of (–)-englerin A<sup>5h</sup> (Scheme 42). This last target has also been synthesized by the Ma group through a similar strategy.<sup>43</sup>



<sup>42</sup> E. Jiménez-Núñez, C. K. Claverie, C. Nieto-Oberhuber, A. M. Echavarren, *Angew. Chem., Int. Ed.* **2006**, *45*, 5452-5455.

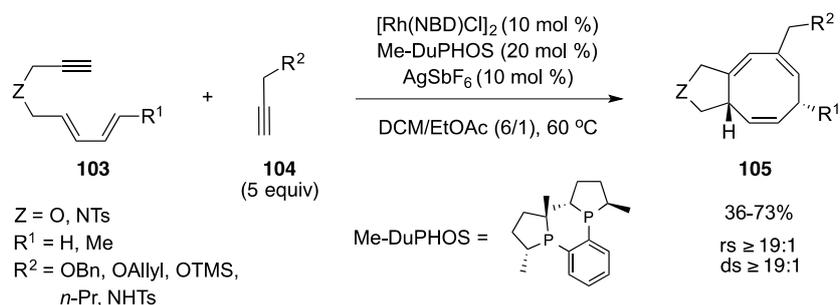
<sup>43</sup> Q. Zhou, X. Chen, D. Ma, *Angew. Chem., Int. Ed.* **2010**, *49*, 3513-3516.



## 1.5 Enynes Variants in Co-cyclization Reaction

### 1.5.1 Co-cyclization of dienynes and alkynes

Gilbertson and DeBoef disclosed a complementary approach to the Evans' Rh-catalyzed [4+2+2] cycloaddition (see § 1.2) using 1,3,8-dienynes and alkynes for the stereoselective elaboration of bicyclooctatrienes (Scheme 44).<sup>45</sup> Thus, a catalyst system combining [Rh(nbd)Cl]<sub>2</sub>, AgSbF<sub>6</sub> and Me-DuPHOS proved to be efficient for the coupling of dienynes **103** with terminal alkynes **104** giving rise to the formation of bicyclic [6.3.0] adducts **105** featuring the cycloocta-1,3,6-triene ring in high regio- and diastereoselectivity. Functional group tolerance to ethers and sulfonamides groups both in propargyl position of the reactants is noteworthy. Optimization of reaction catalyst revealed that the amount of silver salt AgSbF<sub>6</sub> should be less than one half of one equivalent, or less (on the basis of Rh). To date the asymmetric induction level remains modest.



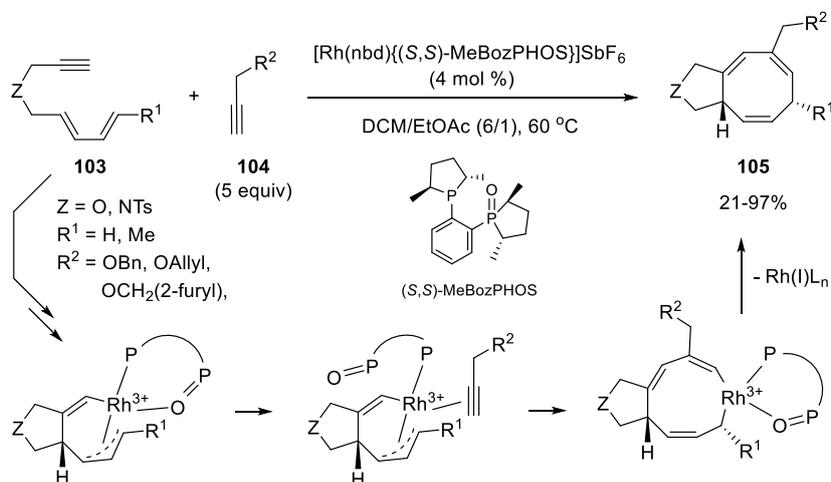
**Scheme 44.** Rhodium-catalyzed [4+2+2] cycloaddition of dienynes

Recently, the Gilbertson group designed a novel Rh-based bisphosphine monooxide complex ([Rh(nbd){(*S,S*)-MeBozPHOS}]SbF<sub>6</sub>) displaying applicability and good level of catalytic activity in the above reaction (Scheme 45).<sup>46</sup> As previously observed, the reaction can be carried out in the absence of alkynes, and hence *homo* adducts were produced. Despite the chiral catalytic system failed to give high ee's, the adducts were obtained with high diastereomeric excess (>20:1). According to the proposed mechanism, oxidative cyclization of dienyne over the metal promotes the formation of a vinylrhodium  $\pi$ -allyl intermediate. Due

<sup>45</sup> a) S. R. Gilbertson, B. DeBoef, *J. Am. Chem. Soc.* **2002**, *124*, 8784-8785; b) For detailed studies, see : B. DeBoef, W. R. Counts, S. R. Gilbertson, *J. Org. Chem.* **2007**, *72*, 799-804.

<sup>46</sup> G. M. R. Canlas, S. R. Gilbertson, *Chem. Commun.* **2014**, *50*, 5007-5010.

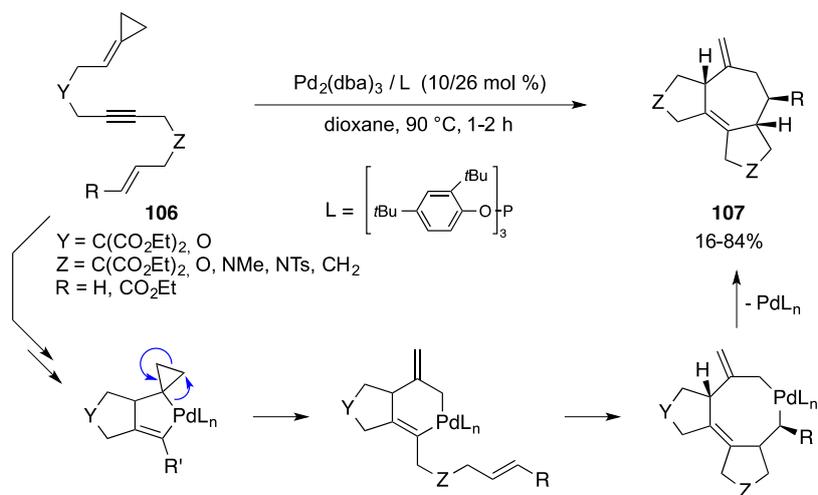
to the weakly coordinating phosphine oxide, its displacement allow for the release of a coordination site to promote the migratory insertion of alkyne prior to reductive elimination to yield the cyclotriene product.



**Scheme 45.** Improved rhodium-catalyzed [4+2+2] cycloaddition of dienynes with alkynes

### 1.5.2 Intramolecular [3+2+2] carbocyclization of dienynes

Mascarenas and co-workers took advantage of the opportunity to use alkylidenecyclopropanes (ACP) units as 3C partners in cycloaddition reactions to develop the [3+2+2] carbocyclization of dienynes leading to the synthetically relevant angular 5/7/5 tricyclic structures (Scheme 46).<sup>47</sup> Dienynes **106**, having a central alkyne unit, subjected to a

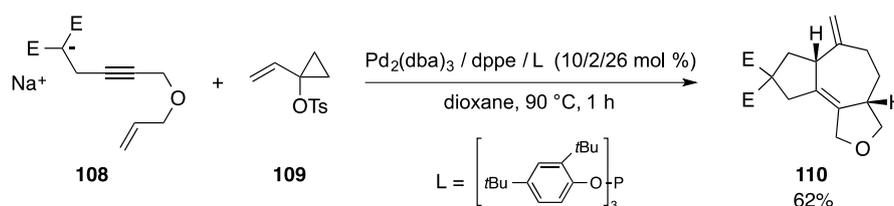


**Scheme 46.** Pd-catalyzed [3+2+2] carbocyclization of dienynes

<sup>47</sup> G. Bhargava, B. Trillo, M. Araya, F. Lopez, L. Castedo, J. L. Mascarenas, *Chem. Commun.* **2010**, 46, 270-272.

catalyst generated from a mixture of  $\text{Pd}_2(\text{dba})_3$  and a bulky phosphite, were converted to tricyclo[8.3.0.0<sup>2,6</sup>]tridec-1-enes **107** with good chemoselectivity and complete diastereoselectivity.

The mechanism of formation of **107** might involve first the oxidative coupling on the most strained double bond (ACP). The resulting spirometalacycle, viewed as a  $\pi$ -allylpalladium, can rearranges to the palladacyclohexene ( $\sigma$ -allylpalladium) which upon olefin insertion and reductive elimination affords the tricycle **107**. The authors performed successfully a tandem palladium-catalyzed allylic alkylation of a well-defined malonate **108** with 1-vinyl-cyclopropyl tosylate **109**, and carbocyclization of the resulting dienyne (not shown) to the 5/7/5 tricycle **110** (Scheme 47).



**Scheme 47.** Tandem Pd-catalyzed allylic alkylation/[3+2+2] carbocyclization reaction

## 1.6 Conclusion

The readily access to complex polycyclic scaffolds from simple acyclic precursors has aroused a growing interest of the chemist community as evidenced by the large number of publications. This chapter outlines the main developments on the transition metal-catalyzed cyclization of enynes with a multi-bonded coupling partner. This topic poses a number of challenges that includes regio-, stereo-, and enantiomeric control of the cyclization reactions. It can be seen by the references dates that this exciting area of research is still in expansion and future prospects devoted on asymmetric catalysis are desirable to provide addition of useful synthetic methods to the organic chemist's arsenal.

## **Chapter II**

# **Ruthenium-Catalyzed Hydroalkynylation Cyclization of 1,6-Enynes with Alkynes**

## 2.1 Introduction

Transition-metal-catalyzed cyclizations of enynes have been widely investigated and provided useful synthetic methodologies for the construction of carbo- and heterocycles which have been applied in total synthesis of natural compounds.<sup>1</sup> These reactions present significant advantages such as atom economical transformations that are carried out, most of the time, under mild reaction conditions, efficiency considering that several chemical bonds can be formed in a single step, and last but not least structural complexity of the cyclized products. In parallel, selectivity (stereo, regio, and enantioselectivity), catalyst loading as low as possible (< 5 mol %) and recycling of the catalyst are important challenges to be solved in order to gain synthetic utility. Among the wide range of enyne transformations, the propensity to undergo a *self-coupling*<sup>2</sup> could hamper the developments of the new reactions. From the synthetic point of view, the *cross-coupling* between enynes and an unsaturated partner make such an event more interesting, as the introduction of new functional groups offers opportunities for further synthetic elaborations through functional group manipulations. Based on this principle, the cyclization reactions of 1,6-enynes incorporating an external pronucleophile, an unsaturated partner or even an organometallic reagent provide useful (poly)cycles with synthetic potentialities. A general overview of transition-metal catalyzed *cross* cyclization of enynes with an unsaturated coupling partner have been summarized in the first chapter. Therefore, we here briefly list some representative transformations according to the key organometallic intermediate involved in these processes.

## 2.2 Transition Metal-Catalyzed Cyclizations of 1,6-Enynes with Pronucleophiles

### 2.2.1 Cyclizations of 1,6-enynes with pronucleophiles through metal carbene intermediates

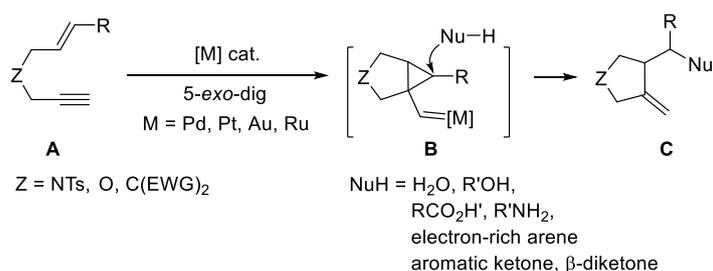
The co-cyclization reactions of 1,6-enynes with pronucleophiles were developed on the basis

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<sup>1</sup> a) C. Aubert, O. Buisine, M. Malacria, *Chem. Rev.* **2002**, *102*, 813-834; b) L. Zhang, J. Sun, S. A. Kozmin, *Adv. Synth. Catal.* **2006**, *348*, 2271-2296; c) V. Michelet, P. Y. Toullec, J.-P. Genêt, *Angew. Chem. Int. Ed.* **2008**, *47*, 4268-4315.

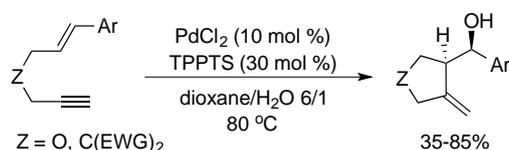
<sup>2</sup> a) P. A. Evans, J. R. Sawyer, K. W. Lai, J. C. Huffman, *Chem. Commun.* **2005**, 3971-3973; b) M. Ez-Zoubir, F. L. B. d'Herouville, J. A. Brown, V. Ratovelomanana-Vidal, V. Michelet, *Chem. Commun.* **2010**, *46*, 6332-6334.

of metal-carbene intermediates as outlined in Scheme 1. It has been showed that in the presence of  $\pi$ -acidic, alkynophilic metal complexes, 1,6-enynes **A** undergo the 5-*exo*-dig cyclization to give metal carbene intermediates **B** which can be trapped by a pronucleophile such as H<sub>2</sub>O, alcohol, carboxylic acid, amine and electron-rich aromatics leading to functionalized five-membered cyclic compounds. Within these lines, Pd-, Pt-, Au- and Ru-based complexes proved to be active catalysts of these cyclizations.



**Scheme 1.** Cyclization of 1,6-enynes incorporating pronucleophiles through metal carbene intermediates

Pioneering works by Genêt and co-workers disclosed the first hydroxycyclization of 1,6-enynes using water soluble PdCl<sub>2</sub>/TPPTS catalytic system as depicted in Scheme 2.<sup>3</sup> In these studies, *O*-linked 1,6-enynes gave rise to *homoallylic* alcohols as single diastereoisomers in good yields. The hydroxycyclization of *C*-linked 1,6-enynes could also be achieved, albeit with relatively lower yields. Notably, an aromatic group on the double bond of 1,6-enynes is mandatory in order to stabilize a putative benzylic cation intermediate. Mechanism investigations by Genêt and Echavarren focusing on intermediates **B** nicely explain the stereochemical outcome of the cyclization/functionalization of 1,6-enynes.<sup>4</sup>



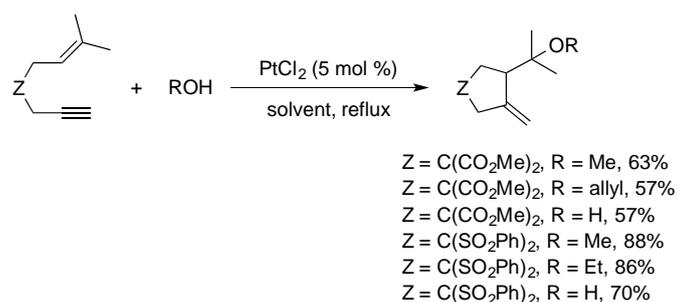
**Scheme 2.** Pd-catalyzed hydroxycyclization of 1,6-enynes

In 2001, Echavarren and co-workers described related cyclizations of enynes catalyzed by PtCl<sub>2</sub>. Thus, Pt-catalyzed cycloisomerization of 1,6-enynes carried out in nucleophilic protic

<sup>3</sup> J.-C. Galland, M. Savignac, J.-P. Genêt, *Tetrahedron Lett.* **1997**, 38, 8695-8698.

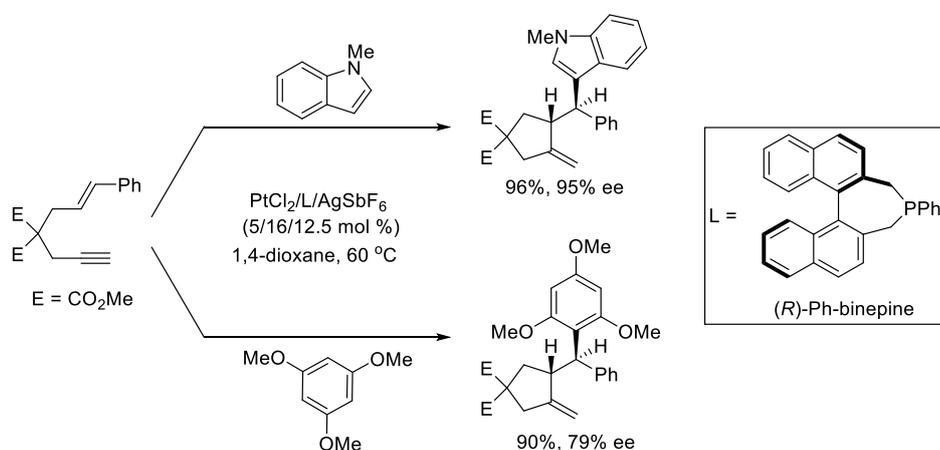
<sup>4</sup> a) C. Nevado, L. Charruault, V. Michelet, C. Nieto-Oberhuber, M. P. Muñoz, M. Méndez, M.-N. Rager, J.-P. Genêt, Antonio M. Echavarren, *Eur. J. Org. Chem.* **2003**, 2003, 706-713; b) L. Charruault, V. Michelet, J.-P. Genêt, *Tetrahedron Lett.* **2002**, 43, 4757-4760.

solvents afforded hydroxy/alkoxycyclization adducts in good to excellent yields (Scheme 3).<sup>5</sup> In these studies, several alcohols such as methanol, ethanol, and allyl alcohol were incorporated to give cyclized *homoallylic* ethers. Further insights into the mechanisms were provided by DFT calculations and deuterium labeling experiments. Afterwards, on the basis of these results, various designed Pt complexes proved efficient in the alkoxy cyclization reactions.



**Scheme 3.** Pt-catalyzed hydroxy/alkoxycyclization of 1,6-enynes

Interestingly, the nucleophilic reagents can also be extended to electron-rich aromatic and heteroaromatic compounds that behave as carbon nucleophiles.<sup>6</sup> As shown in Scheme 4,



**Scheme 4.** Pt-catalyzed hydroarylation of 1,6-enynes

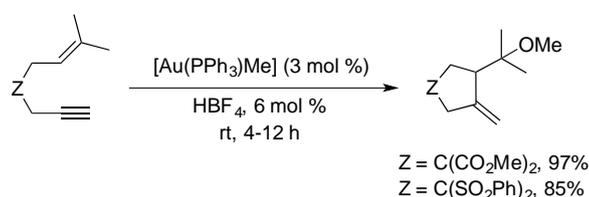
Michelet and co-workers reported the hydroarylation cyclization of 1,6-enynes with 1-methylindole/1,3,5-trimethoxybenzene using chiral dicationic platinum catalysts. These adducts were isolated as single diastereoisomers in good yields and ee's. Remarkably, control

<sup>5</sup> M. Méndez, M. P. Muñoz, C. Nevado, D. J. Cárdenas, A. M. Echavarren, *J. Am. Chem. Soc.* **2001**, *123*, 10511-10520.

<sup>6</sup> a) P. Y. Toullec, C.-M. Chao, Q. Chen, S. Gladiali, J.-P. Genêt, V. Michelet, *Adv. Synth. Catal.* **2008**, *350*, 2401-2408; b) C.-M. Chao, M. R. Vitale, P. Y. Toullec, J.-P. Genêt, V. Michelet, *Chem. Eur. J.* **2009**, *15*, 1319-1323.

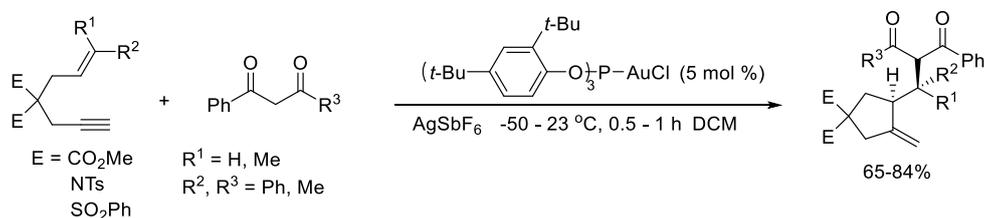
experiments strongly supported that active  $L_3Pt^{2+}$  species should be responsible for the high enantioselectivity.

Gold-catalyzed alkoxy cyclizations of 1,6-enynes were developed by the Echavarren group in 2004. Treatment of regular 1,6-enynes with cationic species  $[Au(PPh_3)MeOH]^+$  in situ generated from  $[Au(PPh_3)Me]$  and a protic acid  $HBF_4$ , afforded alkoxy cyclization adducts in excellent yields. Scope investigation (not shown) indicated that Au-catalyzed alkoxy cyclizations proceeded relatively readily at room temperature compared to the related Pt-catalyzed ones.<sup>7</sup>  $AuCl_3/AgSbF_6/PPh_3$  catalytic system also proved to be effective for such cyclizations.<sup>8</sup>



**Scheme 5.** Au-catalyzed hydroxy/alkoxy cyclization of 1,6-enynes

In 2008, Echavarren group found that 1,3-dicarbonyl compounds are suitable to participate as carbonucleophiles in the cyclization/alkylation reactions of 1,6-enynes, thus providing monoalkylated  $\beta$ -diketone as single diastereoisomers in good yields (Scheme 6).<sup>9</sup> However, reactions involving cyclohexane-1,3-dione, cyclopentane-1,3-dione, dimethyl malonate and Meldrum acid failed under the optimized reaction conditions.



**Scheme 6.** Au-catalyzed cyclization of 1,6-enynes with  $\beta$ -diketones

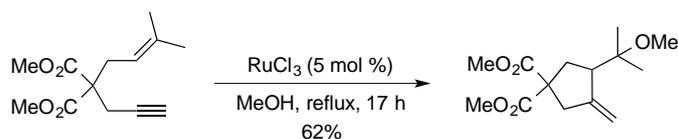
1,6-Enynes bearing trisubstituted double bonds can be converted into methoxycyclization

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

<sup>8</sup> E. Genin, L. Leseurre, P. Y. Toullec, J.-P. Genêt, V. Michelet, *Synlett* **2007**, 2007, 1780-1784.

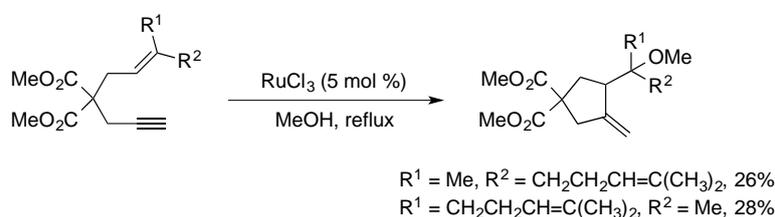
<sup>9</sup> C. H. M. Amijs, V. López-Carrillo, M. Raducan, P. Pérez-Galán, C. Ferrer, A. M. Echavarren, *J. Org. Chem* **2008**, *73*, 7721-7730.

products in the presence of catalytic amounts of  $\text{RuCl}_3$  in MeOH under reflux conditions (Scheme 7).<sup>5</sup>



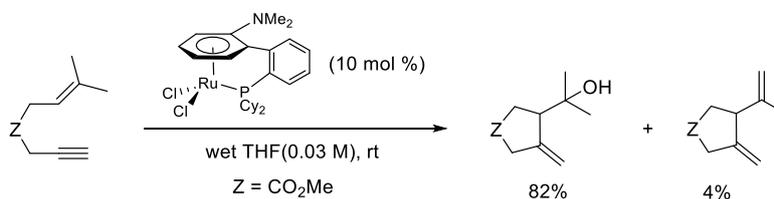
**Scheme 7.** Ru-catalyzed methoxycyclization of 1,6-enynes

The efficiency of the methoxy/cycloisomerization reaction does not depend on the starting olefin geometry as illustrated in Scheme 8.



**Scheme 8.** Ru-catalyzed alkoxy cyclization of 1,6-enynes

In 2006, Faller and co-workers reported a well-defined arene-Ru(II) complex as catalyst of hydroxycyclizations of 1,6-enynes in wet THF as outlined in Scheme 9.<sup>10</sup> It is worth to note that the enyne concentration has a significant influence on the hydroxycyclizations. Concentrations higher to 0.03 M are detrimental to the reaction and resulted in catalyst decomposition, whereas concentrations lower to 0.03 M increased the yields of Alder-ene product to the detriment of hydroxycyclization product.

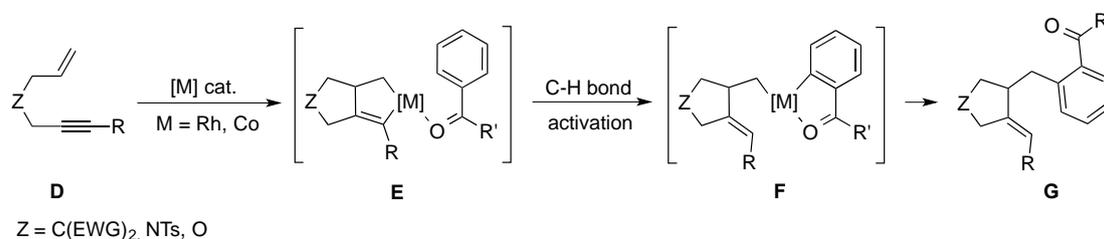


**Scheme 9.** Ru-catalyzed hydroxycyclization of 1,6-enynes

<sup>10</sup> J. W. Faller, P. P. Fontaine, *J. Organomet. Chem.* **2006**, *691*, 1912-1918.

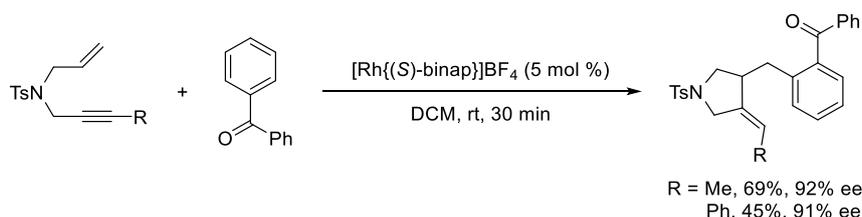
## 2.2.2 Cyclizations of 1,6-enynes with aromatic carbonyl compounds through C-H activation pathway

Cyclizations of 1,6-enynes involving functionalized aromatic compounds which proceeded through C-H activation have appeared quite recently. A general mechanism is summarized in Scheme 10. Oxidative cyclization of 1,6-enynes **D** in the presence of metal complex led to metallacyclopentene intermediate **E** which can coordinate the aromatic carbonyl group. Upon C(sp<sup>2</sup>)-H bond activation and H-transfer to the double bond, **E** led to the aryl-alkyl intermediate **F**. Subsequent reductive elimination released the coupling product **G** and regenerated the active catalytic species.



**Scheme 10.** Cyclization of 1,6-enynes through C-H bond activation of aromatic compounds

The first examples of the above entitled reactions were reported by Shibata and co-workers using a cationic rhodium complex as illustrated with the enantioselective cyclization of enynes with aromatic ketones (Scheme 11).<sup>11</sup> The reactions were best performed within 30



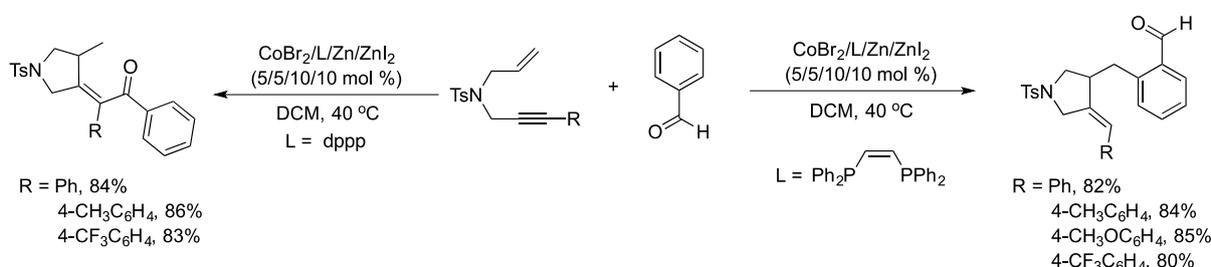
**Scheme 11.** Rhodium-catalyzed cyclization of 1,6-enynes with benzophenone

minutes at room temperature through the slow addition of enynes to a solution of benzophenone in dichloromethane in the presence of [Rh{(S)-binap}]BF<sub>4</sub>. Under these conditions, the hydroarylated products are formed in good to moderate yield with high ee value (> 90%). Quite recently, cobalt-catalyzed hydroarylated cyclization of 1,6-enynes with

<sup>11</sup> K. Tsuchikama, Y. Kuwata, Y.-k. Tahara, Y. Yoshinami, T. Shibata, *Org. Lett.* **2007**, *9*, 3097-3099.

aromatic ketones through C-H activation was reported by Cheng.<sup>12</sup>

In 2015, Cheng and co-workers described a divergent ligand-controlled C-H functionalization of 1,6-enynes with aldehydes in the presence of cobalt catalysts to synthesize functionalized pyrrolidines and furans with high chemo- and stereoselectivity (Scheme 12).<sup>13</sup> From a common cobaltacyclopentene, the metal-catalyzed *ortho* C-H functionalization of aldehydes is favored in the presence of dppp [1,2-bis(diphenylphosphino)propane] to form hydroacylative cyclized products. In deep contrast, the use of dppe (*Z*-1,2-bis(diphenylphosphino)ethane) promotes the hydroarylyative adducts. The reasons for the observed chemoselectivity remain unclear at the present time.



**Scheme 12.** Divergent Co-catalyzed cyclization of 1,6-enynes using aromatic aldehyde

While various cyclizations/functionalizations of 1,6-enynes with pronucleophiles, electron-rich aromatics or aromatic carbonyl compounds are well established, a similar reaction involving terminal alkynes remains still unexplored to date.

### 2.3 Ruthenium-Catalyzed Hydroalkynylyative Cyclization of 1,6-Enynes with Alkynes

Previous studies in our laboratories have shown that hydroalkynylation of strained double bonds such as in norbornadiene or cyclopropene derivatives were achieved under mild and neutral conditions using the Herrmann-Beller phosphapalladacycle<sup>14</sup> (Scheme 13).

<sup>12</sup> R. Santhoshkumar, S. Mannathan, C.-H. Cheng, *Org. Lett.* **2014**, *16*, 4208-4211.

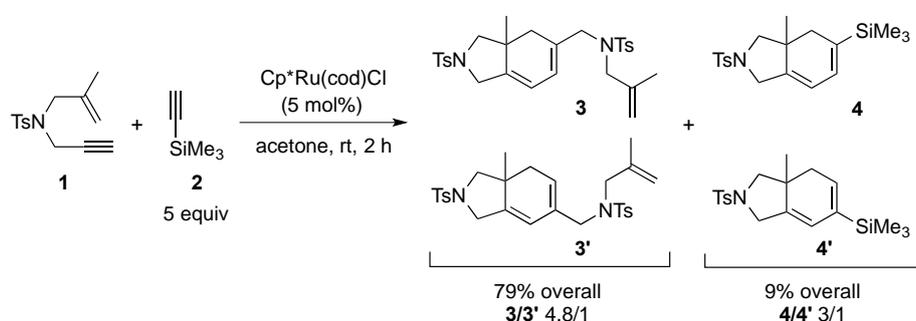
<sup>13</sup> R. Santhoshkumar, S. Mannathan, C.-H. Cheng, *J. Am. Chem. Soc.* **2015**, *137*, 16116-16120.

<sup>14</sup> A) A. Tenaglia, L. Giordano, G. Buono, *Org. Lett.* **2006**, *8*, 4315-4318; b) A. Tenaglia, K. Le Jeune, L. Giordano, G. Buono, *Org. Lett.* **2011**, *13*, 636-639.



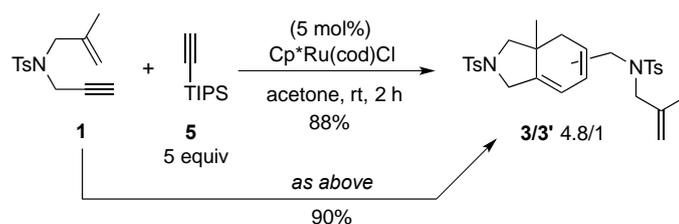
### 2.3.1 Initial experiments

At the outset of our studies, 1,6-enyne **1** and commercially available trimethylsilylacetylene (**2**), as a surrogate of ethyne for further synthetic transformations, were chosen as coupling partners. From a survey of literature, we focused on ruthenium catalysts which have been successfully utilized in a number of enyne cycloisomerizations that involve ruthenacycles as intermediates and especially chloro(pentamethylcyclopentadienyl)-(cyclooctadiene)ruthenium (II) [Cp\*Ru(cod)Cl] was selected for its catalytic performances. Thus, treatment of enyne **1** and excess trimethylsilylacetylene **2** (5 equiv) in the presence of



**Scheme 15.** Ru(II)-catalyzed [2+2+2] cycloaddition of 1,6-enynes and alkynes

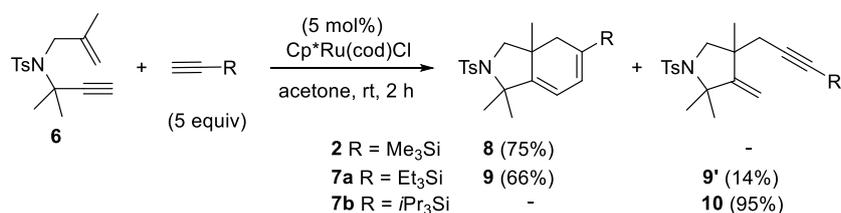
Cp\*Ru(cod)Cl (5 mol %) in acetone at room temperature afforded an unseparated mixture of *homo*-[2+2+2] cycloadducts **3/3'** (**3/3'** 4.8/1, major regioisomer **3** as depicted in Scheme 15) in 79% yield and *cross*-[2+2+2] cycloadducts **4/4'** (**4/4'** 3/1) in 9% yield. Disappointingly, none of the expected hydroalkynylative cyclization adduct was detected. Considering that the formation of [2+2+2] adducts should result through the insertion of alkyne to the ruthenacyclopentene intermediate, we hypothesized that increasing the bulkiness of alkyne substituent would prevent the insertion step as a consequence of repulsive non-bonded interactions between the substitution patterns of the reactants, and therefore reduce or inhibit the *cross*-[2+2+2] cycloaddition. Therefore, we tested this hypothesis with the reaction of enyne **1** and (triisopropylsilyl)acetylene **5** under the conditions employed above. In this case, *homo*-[2+2+2] cycloadducts **3/3'** (**3/3'** 4.8/1, as above) were obtained exclusively in 88% overall yield. As (triisopropylsilyl)acetylene **5** did not participated in *homo*-coupling adducts, a parallel reaction performed without addition of **5** lead to similar results.



**Scheme 16.** Ru(II)-catalyzed [2+2+2] cycloaddition of 1,6-enyne **1**

These results suggested that the formation of *cross*-[2+2+2] cycloadducts can be prevented by making use of steric hindrance. Hence, bulky enynes featuring substitution at the propargyl carbon atom were considered in order to suppress the *homo*-[2+2+2] cycloaddition reaction.

According to our previous work, a relatively bulky 1,6-enyne **6** bearing two methyl groups at the propargylic position was used in the hydroalkynylative cyclization of enynes and alkynes. As shown in Scheme 17, exposure of **6** and trimethylsilylacetylene **2** to Cp\*Ru(cod)Cl in acetone at room temperature, afforded *cross*-[2+2+2] adduct **8** in 75% yield. *Importantly, self* [2+2+2] adduct of **6** was not observed. Gradually increasing the bulkiness of alkyne, triethylsilylacetylene **7a** allowed the formation of hydroalkynylative cyclization adduct **9'** in 14% yield and *cross*-[2+2+2] cycloadduct in 66% yield, respectively. Gratifyingly, the use of the more bulkier triisopropylsilylacetylene **7b** suppressed the formation of the corresponding *cross*-[2+2+2] cycloadduct and only led to the desired product **10** in almost quantitative yield (95%) within 2 h at room temperature.

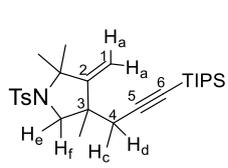


**Scheme 17.** Ru(II)-catalyzed cyclization of 1,6-enynes with alkynes

### 2.3.2 Determination structural characterization of **10**

The structure of cyclic adduct **10** was established with the data of  $^1\text{H}$  NMR,  $^{13}\text{C}$  NMR as well as HRMS analysis (Scheme 18). Three distinct singlets at  $\delta$  1.56, 1.52 and 1.20 are observed for the methyl substituents of the pyrrolidine ring. Two doublets at  $\delta$  3.37 and 3.12 with a

geminal coupling constant of 9.7 Hz are characteristic of the methylene  $\alpha$  to nitrogen atom. The *exo*-methylene group was observed at  $\delta$  4.86 as a singlet peak. The propargylic protons H<sub>c</sub> [2.32 (d,  $J$  = 16.9 Hz, 1H)] and H<sub>d</sub> [2.24 (d,  $J$  = 16.9 Hz, 1H)] are fully consistent with the suggested structure. In addition, the normal <sup>13</sup>C NMR and DEPT-135 spectra also provided enough evidence for the structural subunits of the pyrrolidine ring and its substituents. For instance, the *exo*-methylene carbon and the propargyl methylene were observed at  $\delta$  105.2 and 31.3, respectively.

	<sup>1</sup> H NMR	<sup>13</sup> C NMR
	H <sub>a</sub> 4.86 (s, 2H)	C <sub>1</sub> 105.2 (CH <sub>2</sub> )
	H <sub>c</sub> 2.32 (d, $J$ = 16.9 Hz, 1H)	C <sub>2</sub> 163.7 (C)
	H <sub>d</sub> 2.24 (d, $J$ = 16.9 Hz, 1H)	C <sub>3</sub> 44.1 (C)
	H <sub>e</sub> 3.37 (d, $J$ = 9.7 Hz, 1H)	C <sub>4</sub> 31.3 (CH <sub>2</sub> )
H <sub>e</sub> 3.12 (d, $J$ = 9.7 Hz, 1H)	C <sub>5</sub> 81.0 (C)	
	C <sub>6</sub> 105.3 (C)	

HRMS (ESI-MS): C<sub>27</sub>H<sub>44</sub>NO<sub>2</sub>SSi<sup>+</sup> ([M+H]<sup>+</sup>):  
 Calcd. 474.2857  
 Found 474.2855

**Scheme 18.** Typical NMR data and HRMS of **10**

### 2.3.3 Results and discussion

Selecting the *cross*-coupling reaction of **6** and triisopropylsilylacetylene **5** as a model reaction, a systematic study of the reaction conditions on the outcome of the reaction was undertaken (Table 1).

#### 2.3.3.1 Screening of reaction conditions

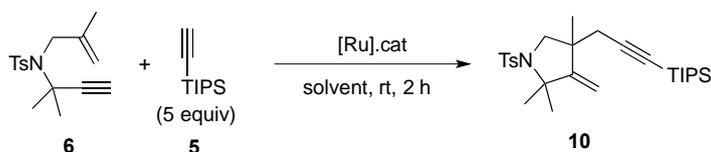
We first focused on the screening of solvents and showed that a wide range of solvents, including polar/apolar, protic/aprotic and even those with coordinating abilities were suitable although the best result was observed for the reaction performed in acetone (entries 1-8). For instance, acetonitrile, which in our hands retarded some catalytic reactions studied in our laboratories,<sup>18</sup> proved to be compatible with Cp\*Ru(cod)Cl affording **10** in 85% yield (entry 2). The reaction carried out in methanol was also effective (entry 4) although protic solvents participate as nucleophiles in ruthenium-catalyzed reactions.<sup>5,10</sup> Interestingly, water

<sup>18</sup> a) A. Tenaglia, S. Gaillard, *Angew. Chem. Int. Ed.* **2008**, *47*, 2454-2457; b) M. Achard, A. Tenaglia, G. Buono, *Org. Lett.* **2005**, *7*, 2353-2356.

as co-solvent (H<sub>2</sub>O/acetone, 85/15) was also well tolerated (entry 6). Halogenated solvent such as 1,2-dichloroethane was the less efficient among the examined solvents affording **10** in fair yield (entry 8).

We next examined the activity of structurally similar Ru(II) complexes for a better understanding of the structural features favoring the hydroalkynylative cyclization (entries 9-15). Phosphine-coordinated complexes Cp\*Ru(PPh<sub>3</sub>)<sub>2</sub>Cl and CpRu(PPh<sub>3</sub>)<sub>2</sub>Cl failed to provide **10**, presumably because ligand(s) dissociation from the metal center to generate free coordination site(s) is prevented under the used conditions (room temperature) (entry 9-10). The indenyl ligand-containing (Ind)Ru(PPh<sub>3</sub>)<sub>2</sub>Cl follows the same trend although a coordination site can be released through the haptophilicity of the indenyl ligand<sup>19</sup> (entry 11).

**Table 1.** Screening of reaction conditions for the *cross*-coupling of **6** and **5**<sup>[a]</sup>



Entry	Catalyst	Solvent	Yield [%] <sup>[b]</sup>
<b>1</b>	<b>Cp*Ru(cod)Cl</b>	<b>acetone</b>	<b>95</b>
2	"	MeCN	85
3	"	AcOEt	81
4	"	MeOH	79
5	"	toluene	77
6	"	H <sub>2</sub> O/acetone (85/15)	71
7	"	THF	61
8	"	DCE	51
9	Cp*Ru(PPh <sub>3</sub> ) <sub>2</sub> Cl	acetone	0
10	CpRu(PPh <sub>3</sub> ) <sub>2</sub> Cl	"	0
11	IndRu(PPh <sub>3</sub> ) <sub>2</sub> Cl	"	0
12	CpRu(MeCN) <sub>3</sub> PF <sub>6</sub>	"	0
13	Cp*Ru(MeCN) <sub>3</sub> PF <sub>6</sub>	"	56
14	Cp*Ru(MeCN) <sub>3</sub> PF <sub>6</sub> / <i>n</i> -Bu <sub>4</sub> NCl <sup>[c]</sup>	"	90
15	Cp*Ru(cod)Cl	"	78 <sup>[d]</sup>

<sup>[a]</sup> Reaction conditions: **6** (0.2 mmol), **5** (1.0 mmol), catalyst (0.01 mmol), solvent (1 mL), rt, 2 h. <sup>[b]</sup> Yields of isolated product. <sup>[c]</sup> 5/10 mol%. cod = 1,5-cyclooctadiene, Cp\* = pentamethylcyclopentadienyl, Cp = cyclopentadienyl, Ind = indenyl. <sup>[d]</sup> 1 mol % of catalyst and 24 h.

<sup>19</sup> B.M. Trost, M. C. Ryan, *Angew. Chem. Int. Ed.* **2017**, *56*, 2862-2879.

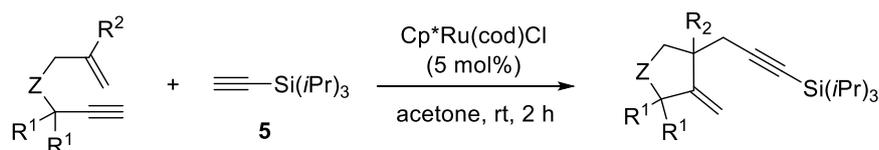
The cationic complex  $\text{Cp}^*\text{Ru}(\text{MeCN})_3\text{PF}_6$  exhibited relatively lower catalytic activity in terms of the yield (56%) compared to  $\text{Cp}^*\text{Ru}(\text{cod})\text{Cl}$  (entries 13 and 1). Compared to  $\text{Cp}^*\text{Ru}(\text{MeCN})_3\text{PF}_6$ , the less electron-rich complex  $\text{CpRu}(\text{MeCN})_3\text{PF}_6$  failed to produce **10** (entry 12). These results showed that the  $\text{Cp}^*$  ligand is crucial for the catalytic activity of ruthenium catalyst. More importantly, the reaction carried out with a mixture of  $\text{Cp}^*\text{Ru}(\text{MeCN})_3\text{PF}_6$  with  $n\text{Bu}_4\text{NCl}$  in acetone solution afforded **10** in 90% yield (entry 14). The recovery of the catalytic performance can be attributed to the *in situ* generation of neutral ruthenium species.<sup>20</sup> Scaling-up the reaction to 1g of enyne was conducted without loss of the yield (not shown in Table 1) thus making these transformations useful for further synthetic purposes. In addition, the loading of catalyst can be reduced to 1 mol % to afford **10** in a satisfactory 78% yield, albeit a longer reaction time (24 h) was required (entry 15).

### 2.3.3.2 Scope of substrates

#### Investigation of 1,6-Enynes

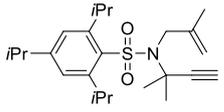
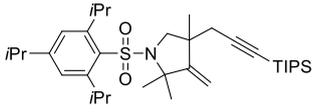
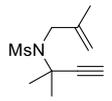
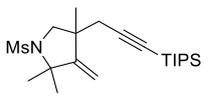
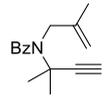
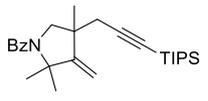
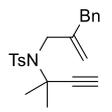
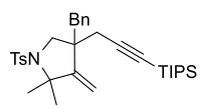
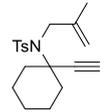
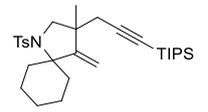
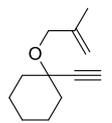
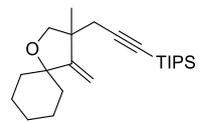
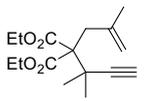
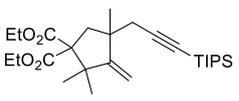
With the optimized conditions in hand, we next investigated the applicability of various 1,6-enynes to the ruthenium-catalyzed hydroalkynylation cyclization with alkyne **5** (Table 2).

**Table 2.** Hydroalkynylation cyclization reactions of various 1,6-enynes and **5**.<sup>[a]</sup>



Entry	1,6-Enynes	Product	Yields (%) <sup>[b]</sup>
1			87
2			83

<sup>20</sup> J. A. Varela, S. G. Rubín, C. González-Rodríguez, L. Castedo, C. Saá, *J. Am. Chem. Soc.* **2006**, *128*, 9262-9263.

3			95
	<b>13</b>	<b>22</b>	
4			71
	<b>14</b>	<b>23</b>	
5			73
	<b>15</b>	<b>24</b>	
6			71
	<b>16</b>	<b>25</b>	
7			86
	<b>17</b>	<b>26</b>	
8			82
	<b>18</b>	<b>27</b>	
9			83
	<b>19</b>	<b>28</b>	

<sup>[a]</sup> Reaction conditions: enyne (0.2 mmol), **5** (1.0 mmol), catalyst (0.01 mmol), acetone (1 mL), rt, 2 h. <sup>[b]</sup> Yields of isolated product.

*N*-tethered 1,6-enynes bearing various groups attached to the nitrogen atom reacted smoothly to provide the expected coupling adducts in good to excellent yields (entry 1-7). Electron-rich or poor arylsulfonyl groups attached to the nitrogen atom have only little influence on the outcome of catalytic reactions, as for adducts **20** and **21** which were isolated with 87% and 83% yield, respectively (entry 1, 2). Increasing both the steric and electronic parameters of the aryl group has a positive impact on the reaction. For instance, enyne **13** exhibited high reactivity, and was converted into **22** with 95% yield (entry 3). Besides sulfonamides, amides groups such as for **15** are also tolerated however the yield of cyclized enyne **24** dropped to 73%. Variation of substitution at the olefin or propargyl carbon atom has

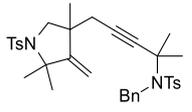
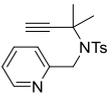
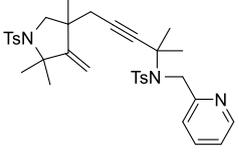
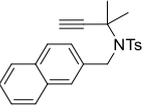
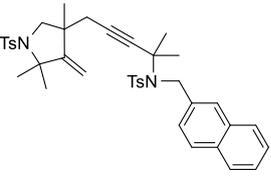
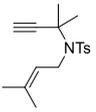
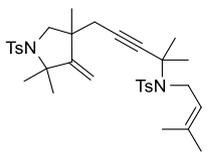
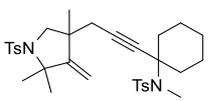
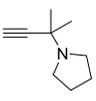
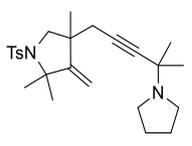
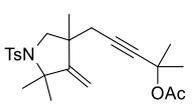
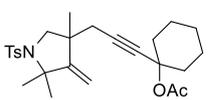
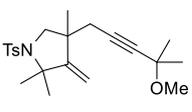
no deleterious effect on the overall outcome (entry 6-7). Thus, cross adducts **25** (71%) and **26** (86%) were obtained from enynes **16** and **17**, respectively. Gratifyingly, the reaction was not limited to *N*-containing substrates and it can be easily extended to oxygen- and carbon-linked enynes to provide *cross*-adducts **27** (82%) and **28** (83%), respectively (entry 8-9).

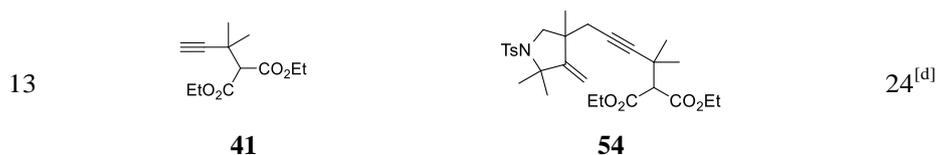
### Investigation of Alkynes

The next scope investigations focused on the structural modification of acetylene derivatives by changing the substituent of ethyne. Based on our initial discoveries, alkynes substituted with bulky groups might favor the hydroalkynylation cyclization reactions. Therefore, mimicking alkyne **5** we firstly selected bulky tertiary propargyl sulfonamide-based substrates easily available from commercial 2-methylbut-3-yn-2-amine. As shown in Table 3, *N*-alkyl, *N*-benzyl and *N*-methallyl substituted tertiary propargyl sulfonamides proved to be excellent substrates to provide the expected cyclized 1,5-enynes **42-49** in very good yields (entries 1-8).

**Table 3.** Hydroalkynylation cyclization reactions of **6** and various alkynes<sup>[a]</sup>

Entry	1,6-Enynes	Product	Yields (%) <sup>[b]</sup>
1	 <b>29</b>	 <b>42</b>	78
2	 <b>30</b>	 <b>43</b>	91
3	 <b>31</b>	 <b>44</b>	81

4	 <b>32</b>	 <b>45</b>	83
5	 <b>33</b>	 <b>46</b>	80
6	 <b>34</b>	 <b>47</b>	82
7	 <b>35</b>	 <b>48</b>	81
8	 <b>36</b>	 <b>49</b>	86
9	 <b>37</b>	 <b>50</b>	80
10	 <b>38</b>	 <b>51</b>	42 <sup>[c]</sup>
11	 <b>39</b>	 <b>52</b>	37 <sup>[c]</sup>
12	 <b>40</b>	 <b>53</b>	24 <sup>[c]</sup>



<sup>[a]</sup> Reaction conditions: **6** (0.2 mmol), alkyne (1.0 mmol), catalyst (0.01 mmol), acetone (1 mL), rt, 2 h. <sup>[b]</sup> Yields of isolated product. <sup>[c]</sup> Major products are [2+2+2] cycloadducts. <sup>[d]</sup> Unidentified products were also detected.

Interestingly, enyne **33** featuring the pyridine ring, which is an excellent ligand in a number of ruthenium complexes,<sup>21</sup> was not detrimental to the reaction outcome and provided **46** 80% yield. It is worth to note that the reaction between **6** and enyne **35** exhibits excellent chemoselectivity, as two distinct enyne partners were involved at the same time and we surmised that the most substituted enyne would not undergo the cyclization. Indeed, a single coupling product **48** was obtained in 81% yield (entry 7). Interestingly, the *N*-tosyl group within the alkyne is not mandatory and the pyrrolidyl-containing alkyne **37** exhibited sufficient bulkiness to undergo the coupling reaction, thus providing the bicyclic product **50** in a satisfactory 80% yield (entry 9). These couplings are not restricted to *N*-containing alkynes and tertiary propargyl carboxylates or ethers **38-40** equally participate to the hydroalkynylation cyclization but were less prone to undergo the desired coupling (entries 10-12). In these cases, the major products were identified as [2+2+2] cycloadducts and will be presented in the next chapter. The same trend was observed with *C*-substituted alkyne 1,6-enyne **41** giving **54** with only 24% yield (entry 13) and an intractable mixture of products.

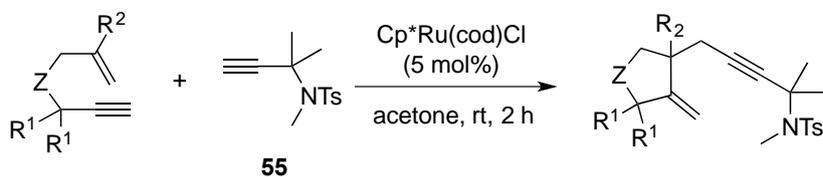
### Investigation of various 1,6-enynes with propargyl sulfonamide **55**

To further extend the applicability of the hydroalkynylation cyclization, we also investigated the coupling of various 1,6-enynes by replacing the triisopropylsilylethyne **5** with the tertiary propargyl sulfonamide **55**. As these coupling partners proved to be suitable for our purposes, it was anticipated that the reaction

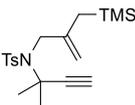
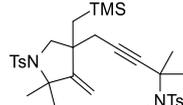
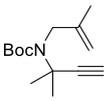
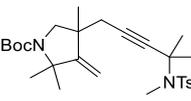
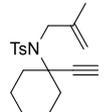
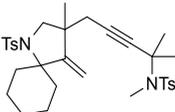
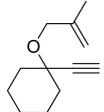
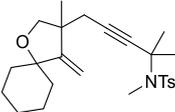
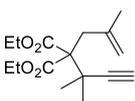
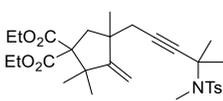
<sup>21</sup> a) V. T. Annibale, R. Batcup, T. Bai, S. J. Hughes, D. Song, *Organometallics* **2013**, 32, 6511-6521; b) M. Jiménez-Tenorio, M. C. Puerta, P. Valerga, M. A. Ortuño, G. Ujaque, A. Lledós, *Organometallics* **2014**, 33, 2549-2560; G. Gupta, G. P. A. Yap, B. Therrien, K. Mohan Rao, *Polyhedron* **2009**, 28, 844-850.

might be successfully carried out. To our delight, similar results as those previously reported in Table 2, were observed and summarized in Table 4.

**Table 4.** Hydroalkynylative cyclization reactions of enynes and alkyne **55**.<sup>[a]</sup>



Entry	1,6-Enynes	Product	Yields (%) <sup>[b]</sup>	Yields (%) <sup>[d]</sup>
1			78	95
	<b>6</b>	<b>59</b>		
2			75	87
	<b>11</b>	<b>60</b>		
3			79	83
	<b>12</b>	<b>61</b>		
4			61	95
	<b>13</b>	<b>62</b>		
5			65	71
	<b>14</b>	<b>63</b>		
6			81	73
	<b>15</b>	<b>64</b>		
7			24 <sup>[c]</sup>	--
	<b>56</b>	<b>65</b>		

8			71	--
	<b>57</b>	<b>66</b>		
9			83	--
	<b>58</b>	<b>67</b>		
10			63	87
	<b>17</b>	<b>68</b>		
11			84	82
	<b>18</b>	<b>69</b>		
12			71	83
	<b>19</b>	<b>70</b>		

<sup>[a]</sup> Reaction conditions: enyne (0.2 mmol), **58** (1.0 mmol), catalyst (0.01 mmol), acetone (1 mL), rt, 2 h. <sup>[b]</sup> Yields of isolated product. <sup>[c]</sup> 20 mol % catalyst was used, and 65% of **56** was recovered. <sup>[d]</sup> Yield of coupling reaction between 1,6-enynes and **5**.

For comparative purposes, in the ending column of Table 4 are reported the related couplings of enynes with triisopropylsilylethyne **5**. At a first glance, the observed yields are lower compared to those obtained in the coupling reactions with **55** but still remain between fair to very good (entries 1-6, 10-12). New compatible functional groups such as halide and silane are presented in entries 7-8. In contrast with a nucleophilic function which is well tolerated (entry 8), an electrophilic function such as allyl chloride **56** poses problem (entry 7). Indeed the coupling product **65** was obtained at best with 24% yield along with unreacted enyne **56** by using 20 mol % of the ruthenium catalyst. Accordingly, the coupling reaction is achieved under stoichiometric conditions and we presume that a stable  $[\text{Cp}^*\text{Ru}(\text{allyl})]^+\text{Cl}^-$  complex<sup>22</sup> might be formed shutting down the catalytic cycle. Carbamate **58** also reacted smoothly to provide **67** in 83%. This result singularly contrasts with the behavior of

<sup>22</sup> a) B. M. Trost, P. L. Fraisse, Z. T. Ball, *Angew. Chem.* **2002**, *114*, 1101-1103; b) R. Hermatschweiler, I. Fernandez, P. S. Pregosin, *Organometallics* **2006**, *25*, 1440-1447; c) B. M. Trost, T. Zhang, J. D. Sieber, *Chem. Sci.* **2010**, *1*, 427-440.

*tert*-butylcarbamates as heteronucleophiles toward  $\pi$ -activated alkyne-gold complexes to deliver 5-methylene-1,3-oxazolidin-2-ones.<sup>23</sup> Oxygen-tethered and carbon-linked enynes also reacted satisfactorily affording cross adducts **69** (84%) and **70** (71%), respectively (entry 11-12).

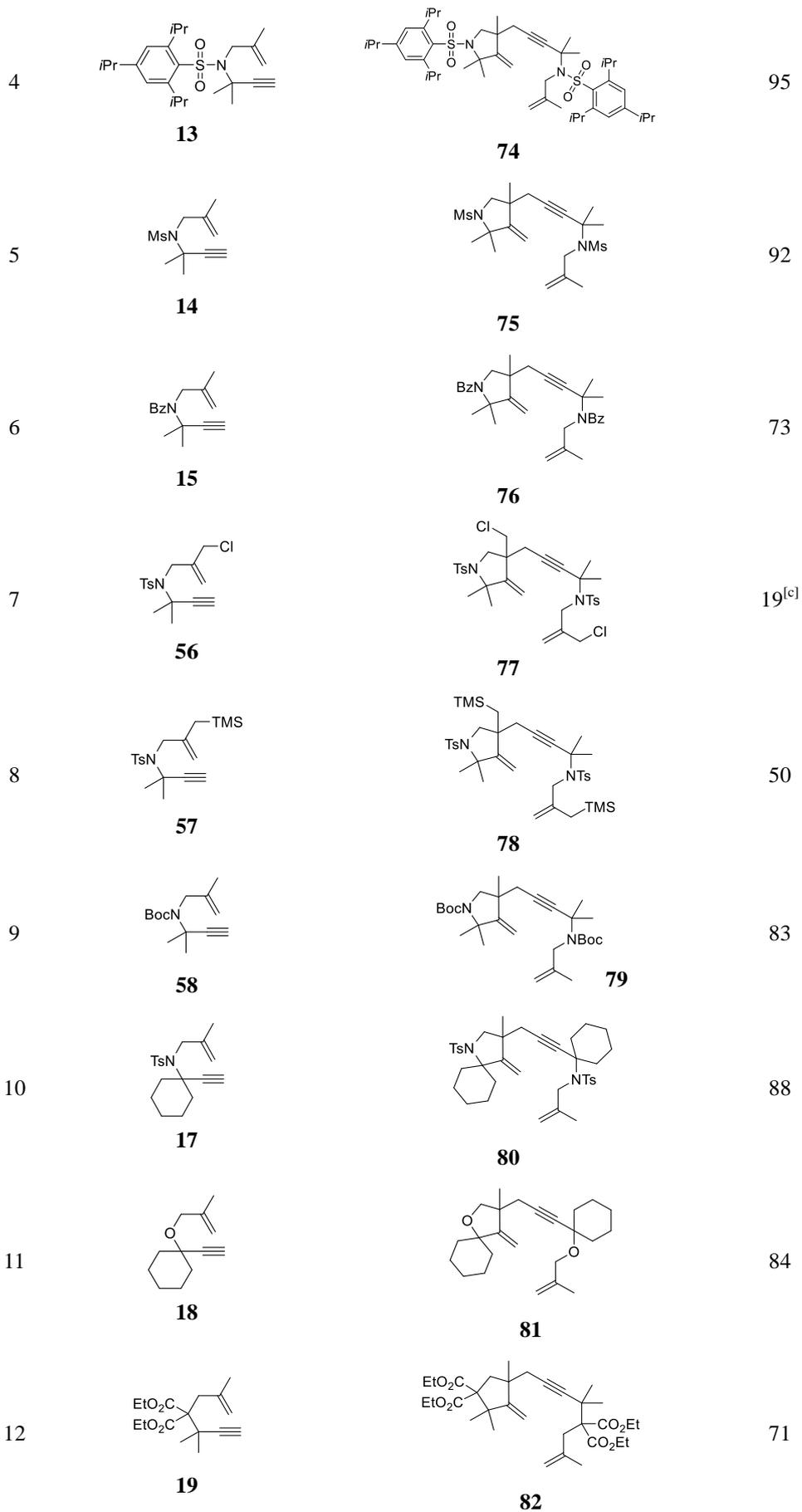
### Self hydroalkynylation reactions of various 1,6-enynes

In the course of previous studies dealing with the cross hydroalkynylation cyclization reaction, byproducts (< 5-10%), presumably enyne dimers, were observed in some instances. To ascertain our assumptions, we next performed the catalytic reactions involving solely the 1,6-enynes as substrates. As expected, all the enynes tested were prone to undergo the *self*-coupling thus forming dienyne in good to excellent yields (Table 5).

**Table 5.** *Self*-hydroalkynylation reactions of various alkynes.<sup>[a]</sup>

Entry	1,6-Enyne	Dienyne	Yield (%) <sup>[b]</sup>
1	<p style="text-align: center;"><b>6</b></p>	<p style="text-align: center;"><b>71</b></p>	91
2	<p style="text-align: center;"><b>11</b></p>	<p style="text-align: center;"><b>72</b></p>	91
3	<p style="text-align: center;"><b>12</b></p>	<p style="text-align: center;"><b>73</b></p>	87

<sup>23</sup> a) R. Robles-Machín, J. Adrio, J. C. Carretero, *J. Org. Chem.* **2006**, *71*, 5023-5026; b) A. Buzas, F. Gagosz, *Synlett* **2006**, 2727-2730.



<sup>[a]</sup> Reaction conditions: enyne (0.2 mmol), catalyst (0.01 mmol), acetone (1 mL), rt, 3 h. <sup>[b]</sup> Yields of isolated product. <sup>[c]</sup> 20 mol % catalyst was used, and 58% of **56** was recovered.

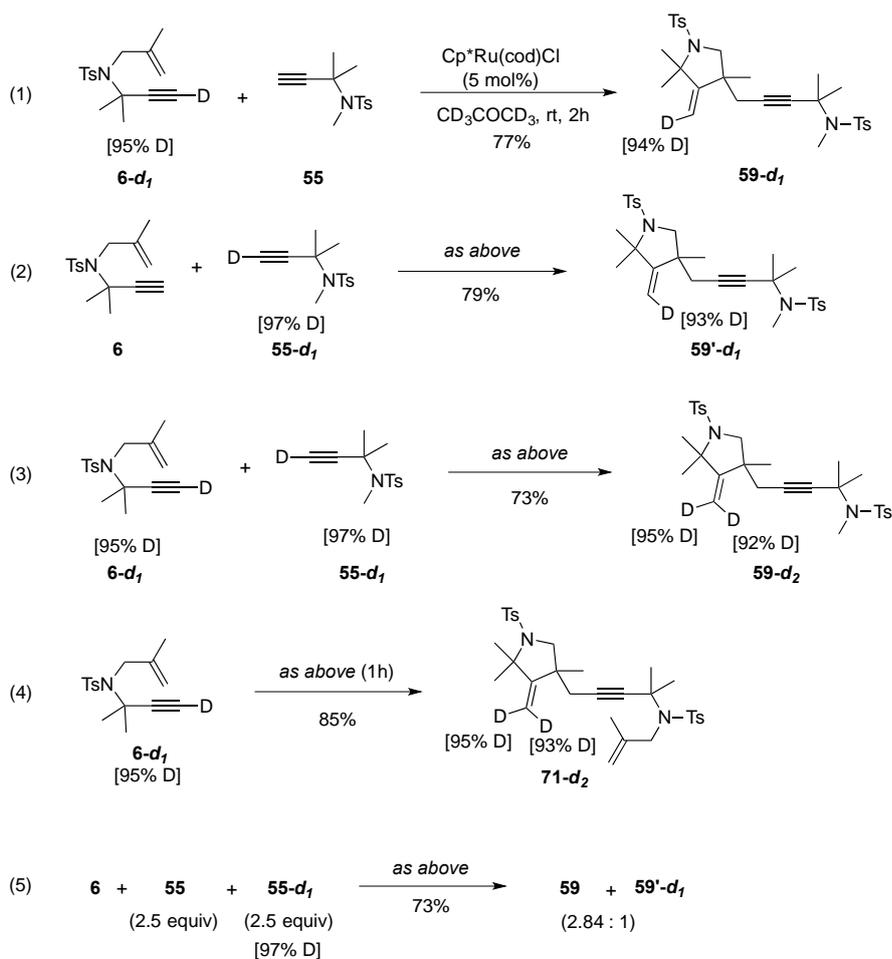
The reactions were achieved with the same features as previously described such as substitution patterns at nitrogen atom (entries 1-6, 9), as well as at olefin (entries 7-8) and propargyl carbon atoms (entries 10-11). Here again, the *self*-coupling of enyne **56** required a stoichiometric amount of catalyst (entry 7) and oxygen- and carbon-linked enynes reacted satisfactorily to provide dienyne **81** (84%) and **82** (71%), respectively (entry 11-12).

### 2.3.4 Mechanism studies

#### 2.3.4.1 Deuterium labeling experiments

In order to gain mechanistic insight into the hydroalkynylative cyclization reaction of enynes, a series of deuterium-labeling experiments was designed and conducted in deuterated acetone under the optimized reaction conditions (Scheme 19). First, deuterated 1,6-enyne **6-d<sub>1</sub>** and alkyne **55-d<sub>1</sub>** were prepared through H/D exchange of alkynes in a mixed solution of D<sub>2</sub>O and dichloromethane in the presence of K<sub>2</sub>CO<sub>3</sub>.<sup>24</sup> Labeling either the enyne or the alkyne partner in *cross*-coupling reactions allowed location of deuterium in **59-d<sub>1</sub>** and **59'-d<sub>1</sub>** (eqs 1 and 2) (the proton relative position of *exo*-methylene motif was determined by NOESY experiments). On the other hand, the *cross*-coupling of **6-d<sub>1</sub>** with **55-d<sub>1</sub>** (eq 3) as well as the dimerization of **6-d<sub>1</sub>** (eq 4) led exclusively to **59-d<sub>2</sub>** and **71-d<sub>2</sub>**, respectively whereas the *homo*-coupling of **6** carried out in a 9/1 mixture of D<sub>2</sub>O/d<sub>6</sub>-acetone delivered **71** with no deuterium incorporation (not shown in Scheme 19). Furthermore, the kinetic isotopic effect (KIE) experiment investigated with the competitive reaction of **6** with an equimolar mixture of **55/55-d<sub>1</sub>** ( $k_H/k_D = 2.84$ ) (eq 5) suggested that the cleavage of the C–H bond of alkyne may have been involved in the rate-determining step. *As no deuterium scrambling was observed from these experiments, a mechanism involving formation of ruthenium hydride species followed by sequential insertions of the triple bonds (hydroruthenation) and double bonds (carboruthenation) of the enyne was ruled out.*

<sup>24</sup> Z. Ni, L. Giordano, A. Tenaglia, *Chem. Eur. J.* **2014**, *20*, 11703-11706.

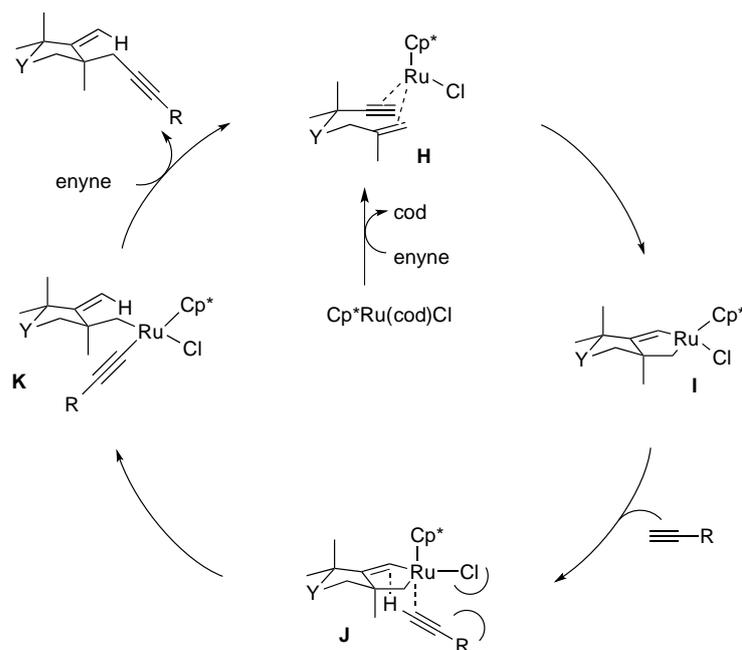


**Scheme 19.** Deuterium-labeling experiments

### 2.3.4.2 Proposed mechanism for the hydroalkynylation of 1,6-enynes

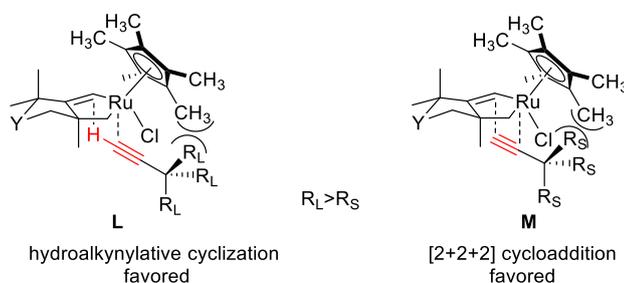
Taking into account the deuterium labelling experiments, a plausible mechanism for the hydroalkynylation that involves ruthenacycles intermediates is depicted in Scheme 20. Cyclooctadiene ligand dissociation from  $\text{Cp}^*\text{Ru}(\text{cod})\text{Cl}$  generated two vacant coordination sites which allowed coordination of both triple and double bonds of 1,6-enyne and subsequent oxidative cyclization to form the ruthenacyclopentene intermediate **I**. Then, coordination of the bulky-substituted alkyne as  $\eta^2$  ligand to the ruthenium center of intermediate **J** might be partly prevented due to the severe non-bonded repulsive interactions between the substituents of alkyne and metal ligands. Therefore, the ruthenacycle **J** might undergo an unprecedented metal-assisted  $\sigma$ -bond metathesis reaction<sup>25</sup> generating the alkyl, alkynylruthenium(II) intermediate **K**. Upon reductive elimination of intermediate **K**, the 1,5-enyne adduct is delivered and the active metal species regenerated.

<sup>25</sup> J. F. Hartwig, S. Bhandari, P. R. Rablen, *J. Am. Chem. Soc.* **1994**, *116*, 1839-1844.



**Scheme 20.** Proposed reaction mechanism for the hydroalkynylation cyclization

In this catalytic reaction, the cleavage of the C-H bond of alkyne should be involved in rate-determining step. The repulsion between the alkyne substituent (R) and methyl groups of cyclopentadienyl ligand greatly weakens the coordination of alkyne to the metal centre as outlined in Scheme 21 (intermediate **L**), thus favoring the ruthenium-assisted  $\sigma$ -bond metathesis step. In contrast, when a less bulky-substituted or even an unsubstituted alkyne was used as the coupling partner, the alkyne triple bond can coordinate to ruthenium (intermediate **M**), favoring the alkyne insertion for [2+2+2] cycloaddition (in-deep discussion will be presented in the next chapter). In summary, the steric hindrance of the coupling partners, and particularly the alkyne, play a key role for the hydroalkynylation cyclization process.



**Scheme 21.** Possible intermediates of hydroalkynylation cyclization and [2+2+2] cycloaddition reaction

As a matter of fact, this unprecedented Ru(II)-assisted  $\sigma$ -bond metathesis reaction offers an

entry for late transition metals.  $\sigma$ -Bond metathesis reactions have been well established on the basis of early metals with  $d^0$  electronic configurations,<sup>26</sup> for instance Sc,<sup>27</sup> which does not undergo oxidative addition and reductive elimination processes due to their highest permissible oxidation state. On the other hand, the electron-deficient metal center equipped with vacant orbitals would provide a low-energy means of approach for  $\sigma$ -bond, such as C-H bond and H-H bond. A number of experimental and theoretical studies have successfully developed the concept of the four-center transition state for such an event. However, the late transition metal-promoted  $\sigma$ -bond metathesis reactions are quite rare.<sup>28</sup> Hartwig and co-workers in 1994 provided an early example of ruthenium-assisted  $\sigma$ -bond metathesis for the exchange of methyl and hydrogen between CpRu(PPh<sub>3</sub>)<sub>2</sub>Me and HBcat (cat = catechol) to provide CpRu(PPh<sub>3</sub>)<sub>2</sub>H and MeBcat.<sup>29</sup> To the best of our knowledge, the  $\sigma$ -bond metathesis reactions of C(sp)-H bond in the presence of late transition metal have never been described. In our project, taking advantage of the steric repulsion of reactants, opportunity is given for the reaction to evolve through ruthenium-assisted  $\sigma$ -bond metathesis rather than regular insertion of C-C triple bond.

### 2.3.5 Synthetic applications of hydroalkynylative cyclization products

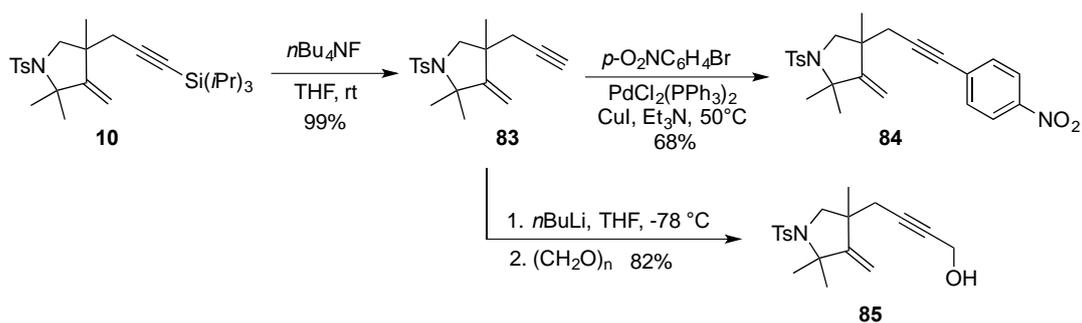
To illustrate the synthetic utility of the 1,5-enyne-containing cyclized product into useful building blocks, we examined organic transformations of compounds **10**, **51** and **71**. First, we took advantage of the trialkylsilyl-substituted adducts as terminal alkynes surrogates. Thus, enyne **10** was quantitatively protodesilylated with *n*Bu<sub>4</sub>NF solution in THF at room temperature and subsequent hydrolysis (Scheme 22). Sonogashira *cross*-coupling reaction of **83** with 1-bromo-4-nitrobenzene allowed the installation of an aryl group at terminal carbon of alkyne and provided **84** in 68% yield. Treatment of **83** with *n*-butyllithium and subsequent slow addition of powdered paraformaldehyde at -78 °C afforded enynol **85** in 82% yield. *In such a way, a wide variety of terminal alkynes not suitable for the intermolecular cross coupling reaction can indirectly be used.*

<sup>26</sup> R. Waterman, *Organometallics* 2013, 32, 7249-7263.

<sup>27</sup> a) M. L. Steigerwald, W. A. Goddard III, *J. Am. Chem. Soc.* **1984**, 106, 308-311; b) M. E. Thompson, S. M. Baxter, A. R. Bulls, B. J. Burger, M. C. Nolan, B. D. Santarsiero, W. P. Schaefer, J. E. Bercaw, *J. Am. Chem. Soc.* **1987**, 109, 203-219.

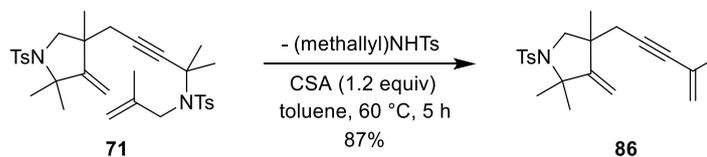
<sup>28</sup> For a Rh-assisted  $\sigma$ -bond metathesis, see: G. Huang, *Org. Lett.* **2015**, 17, 1994-1997.

<sup>29</sup> J. F. Hartwig, S. Bhandari, P. R. Rablen, *J. Am. Chem. Soc.* **1994**, 116, 1839-1844.



**Scheme 22.** Transformations of *cross*-adduct **10** to arylalkyne **84** and enyn-ol **85**

Complementarily, treatment of the dimer **71** with camphorsulfonic acid (CSA) in toluene solution at 60 °C resulted in the elimination of *N*-methallyl,*N*-tosylamine so as to provide the conjugated enyne **86** in 87% yield.



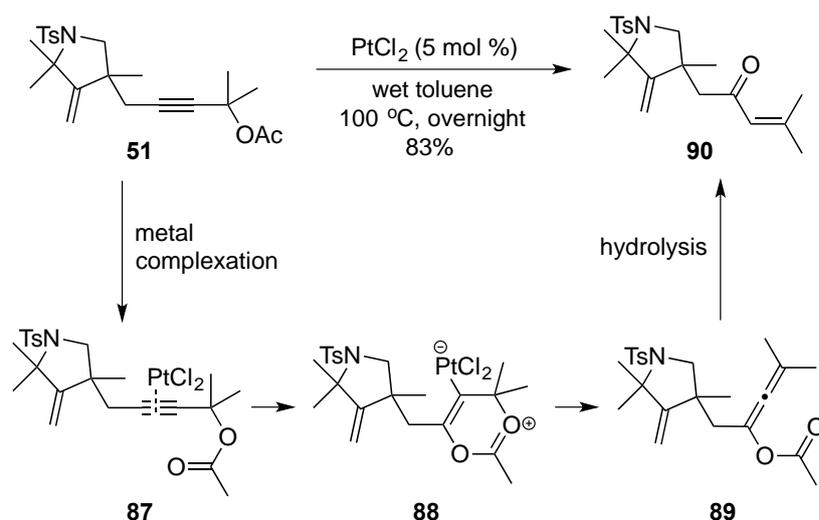
**Scheme 23.** Acid promoted conversion of *cross*-adduct **71** to dienyne **86**

We also examined other functional groups transformations and typically the conversion of tertiary propargyl carboxylates into conjugated enone through gold chemistry.<sup>30</sup> In our hands, platinum(II) chloride proved to be also effective for this reaction. Heating a solution of acetate **51** in the presence of a catalytic amount of PtCl<sub>2</sub> in wet toluene, afforded the conjugated enone **90** in 83% yield (Scheme 24).

The mechanism proposed involve activation of the triple bond of **51** through complexation with PtCl<sub>2</sub>. Then, the possible 1,3-acyloxy migration which is usually favored for internal alkyne<sup>31</sup> generated the metallic zwitterion species **88** which upon demetallation gave rise to the acetoxy-allene **89**. The final hydrolysis step releases the allenol (not shown) which spontaneously tautomerizes to the more stable  $\alpha,\beta$ -unsaturated ketone **90**.

<sup>30</sup> A. Simonneau. *Gold-Catalyzed Cycloisomerization Reactions Through Activation of Alkynes: New Developments and Mechanistic Studies*, Springer International Publishing, Cham, **2014**, pp. 85-117; b) R. K. Shiroodi, V. Gevorgyan, *Chem. Soc. Rev.* **2013**, *42*, 4991-5001.

<sup>31</sup> X.-Z. Shu, D. Shu, C. M. Schienebeck, W. Tang, *Chem. Soc. Rev.* **2012**, *41*, 7698-7711.



**Scheme 24.** Transformations of *cross*-adduct **51** into enone **90**

## 2.4 Conclusion

In summary, we have successfully developed an unprecedented hydroalkynylative cyclization of 1,6-enynes to highly substituted five-membered cyclic compounds containing 1,5-enyne motif by using a commercially available neutral ruthenium(II) complex as catalyst. A wide range of 1,6-enynes and alkynes both bulky-substituted at the propargyl position proved to be the substrates of choice for this transformation. The benefit of these features is to suppress the *homo*- and *cross*-[2+2+2] cycloaddition products. The hydroalkynylative *cross*-coupling cyclization was observed in good to excellent yields using a 1/5 enyne/alkyne as optimal ratio. In the absence of alkyne, 1,6-enynes can undergo the *self*-coupling reaction to provide polyunsaturated cyclodimers in very good yields. Based on deuterium labeling and control experiments, a plausible mechanism through the metal-assisted C(sp)-H  $\sigma$ -bond metathesis pathway rests on the repulsive non-bonded interactions between the ruthenacyclopentene intermediate and the bulky-substituted was proposed.

## **Chapter III**

# **Ruthenium-Catalyzed [2+2+2] Cycloaddition of 1,6-Enynes with Alkynes**

### 3.1 Introduction

In the past decades, significant advances have been achieved in the area of transition-metal catalyzed [2+2+2] cycloaddition reactions.<sup>1</sup> As a powerfully synthetic tool in organic field and a complementary method of pericyclic reactions, [2+2+2] carbocyclization have been widely exploited to construct aromatic rings or cyclohexadiene derivatives. These cycloaddition reactions were successfully achieved in both intramolecular and intermolecular modes. Generally, a broad variety of substrates classes including alkynes, allenes, alkenes, isocyanates, and electron-poor carbonyl derivatives participate well in these catalytic processes leading to useful carbo- and heterocycles. A number of reviews stating the historical context and important contributions and applications bear witness to this broad area of research.<sup>2</sup>

The discovery by Reppe in 1948 that nickel complexes are capable of trimerizing ethyne gas to benzene established a major breakthrough, but did not arouse immediate interest.<sup>3</sup> A few decades later, the progress achieved in organic synthesis by means of metallic mediators enabled to carry out various [2+2+2] cycloaddition reactions of acetylenes as straightforward means for the construction of aromatic rings including hetarenes. Not only group VIII transition metals but also others such as Nb<sup>4</sup> proved efficient catalysts in these types of reactions. Variation of the reactants has greatly expanded the reaction scope and the array of six-membered carbo- and heterocycles available through [2+2+2] cycloadditions. Despite myriads of well-known protocols of metal catalyzed reactions to build complex polycyclic structures,<sup>5</sup> the *intermolecular* carbocyclization between enynes and alkynes has been scarcely reported to date. The coupling of enynes with alkynes conceptually represents a

<sup>1</sup> a) S. Saito, Y. Yamamoto, *Chem. Rev.* **2000**, *100*, 2901-2916; b) J. A. Varela, C. Saá, *Chem. Rev.* **2003**, *103*, 3787-3802; c) P. R. Chopade, J. Louie, *Adv. Synth. Catal.* **2006**, *348*, 2307-2327; d) A. P. Quintana, A. Roglans, *Molecules* **2010**, *15*, 9230-9251; e) X. F. Wu, M. Beller, in *Economic Synthesis of Heterocycles: Zinc, Iron, Copper, Cobalt, Manganese and Nickel Catalysts*, The Royal Society of Chemistry, **2014**, pp. 435-498; f) G. Domínguez, J. Pérez-Castells, *Chem. Eur. J.* **2016**, *22*, 6720-6739; g) A. Lledo, A. Pla-Quintana, A. Roglans, *Chem. Soc. Rev.* **2016**, *45*, 2010-2023.

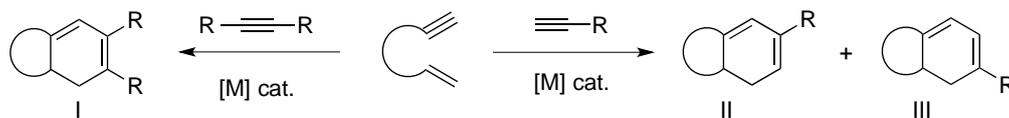
<sup>2</sup> a) S. Kotha, E. Brahmachary, K. Lahiri, *Eur. J. Org. Chem.* **2005**, *2005*, 4741-4767; b) G. Dominguez, J. Perez-Castells, *Chem. Soc. Rev.* **2011**, *40*, 3430-3444.

<sup>3</sup> a) W. Reppe, O. Schichting, K. Klager, T. Toepel, *Justus Liebigs, Ann. Chem.* **1948**, *560*, 1-92; b) V. W. Reppe, W. J. Schweckendeik, *Justus Leibigs Ann. Chem.* **1948**, *560*, 104-116.

<sup>4</sup> C. Simon, M. Amatore, C. Aubert, M. Petit, *Org. Lett.* **2015**, *17*, 844-847.

<sup>5</sup> a) C.-A. Chang, J. A. King, K. P. C. Vollhardt, *J. Chem. Soc., Chem. Commun.* **1981**, 53-55; b) R. Grigg, R. Scott, P. Stevenson, *J. Chem. Soc., Perkin Trans 1.* **1988**, 1357-1364; c) B. M. Trost, G. J. Tanoury, *J. Am. Chem. Soc.* **1987**, *109*, 4753; d) C. H. Oh; H. R. Sung; S. H. Jung; Y. M. Lim, *Tetrahedron Lett.* **2001**, *42*, 5493.

straightforward access to bicyclic cyclohexadienes as outlined in Scheme 1.



**Scheme 1.** Intermolecular carbocyclization reaction of enynes with alkynes

Although these simple sketches are appealing, significant challenges such as chemoselectivity (for instance *self* versus intramolecular coupling of reactants, di- and trimerisation processes, ...) and regioselectivity (Type II and III products) should be controlled in order to make these reactions synthetically useful. Major advances involving cationic rhodium catalysts have appeared in 2005 by the groups of Shibata and Evans.

The group of Shibata reported the enantioselective intermolecular carbocyclization of enynes and alkynes through the use of a catalyst combining bis(1,5-cyclooctadiene)rhodium(I) tetrafluoroborate and tolBINAP to give bicyclic 1,3-diene derivatives with enantiomeric excesses up to 98% (Scheme 2).<sup>6</sup> Although high *ee*'s are achieved, the absolute configuration of tolBINAP is not specified in the Shibata's report. These reactions were satisfactory achieved using high catalyst loading and ligand (10 mol %) and large excess of alkynes (10 equiv with respect to enynes). In the case of propargyl alcohol as the coupling partner, a pair of regioisomers (7/1 ratio) was observed.



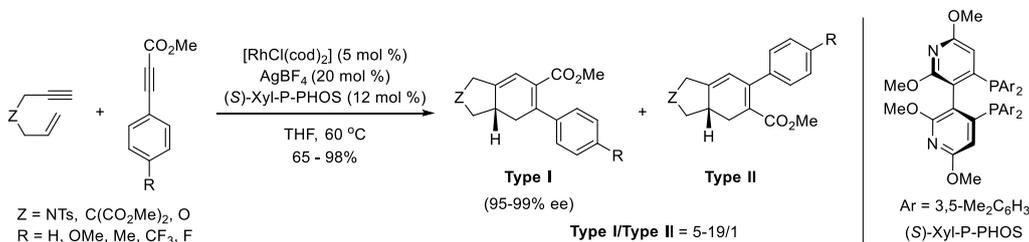
**Scheme 2.** Rhodium-catalyzed [2+2+2] cycloaddition of enynes and alkynes

Evans and co-workers reported similar results with methyl arylpropiolates as partners to form chiral bicyclohexadiene compounds as outlined in Scheme 3.<sup>7</sup> In this process, type I products were produced as major regioisomers in satisfied yields and excellent enantioselectivities.

<sup>6</sup> T. Shibata, Y. Arai, Y.-k. Tahara, *Org. Lett.* **2005**, *7*, 4955-4957.

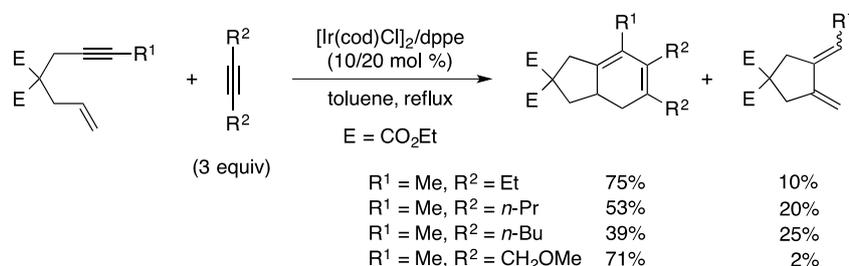
<sup>7</sup> P. A. Evans, K. W. Lai, J. R. Sawyer, *J. Am. Chem. Soc.* **2005**, *127*, 12466-12467.

The reaction is however narrow in substrate scope as only electron-poor alkynes were described in these couplings. Although high regio- and enantioselectivities are achieved, the regioisomers cannot be separated for further synthetic transformations.



**Scheme 3.** Rhodium-catalyzed [2+2+2] cycloaddition of enynes and methyl arylpropiolates

In the same year, Takeuchi and co-workers also reported similar results using [Ir(cod)Cl]<sub>2</sub> and dppe as the catalyst (Scheme 4).<sup>8</sup> The reaction was restricted to enynes capped with alkyl substituents at sp carbon atom and internal alkynes. The reactions carried out with terminal alkynes failed to give any of the expected adducts. The formation of undesired 1,3-diene cycloisomers as byproducts and high cost and charge (10 mol %) of catalyst constitute major drawbacks for applications of this protocol to elaborate organic scaffolds.



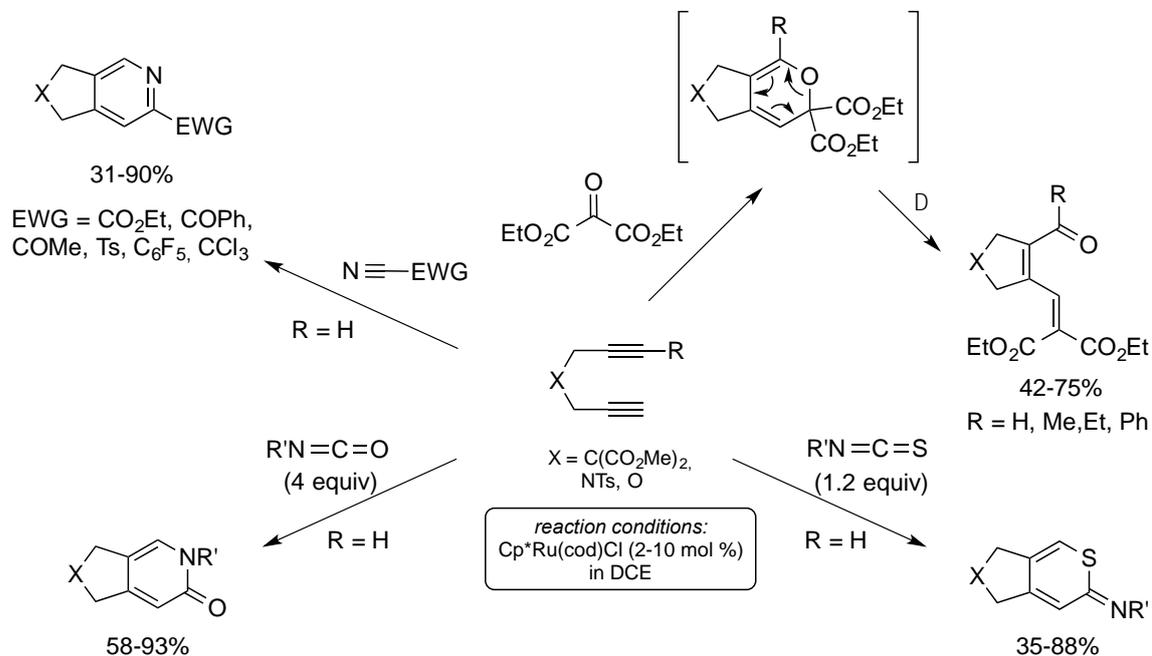
**Scheme 4.** Iridium-catalyzed [2+2+2] cycloaddition of enynes and internal alkynes

The ability of ruthenium complexes to catalyze a wide variety of [2+2+2] cycloaddition reactions,<sup>9</sup> including those involving  $\alpha,\omega$ -diynes with electron-deficient carbon-heteroatom multiple bonds leading to heterocycles (Scheme 5), suggested that the coupling of 1,6-enynes with alkynes in a related cycloaddition should be feasible to build up cyclohexadiene structures provided major challenges such as chemoselectivity and regioselectivity are solved

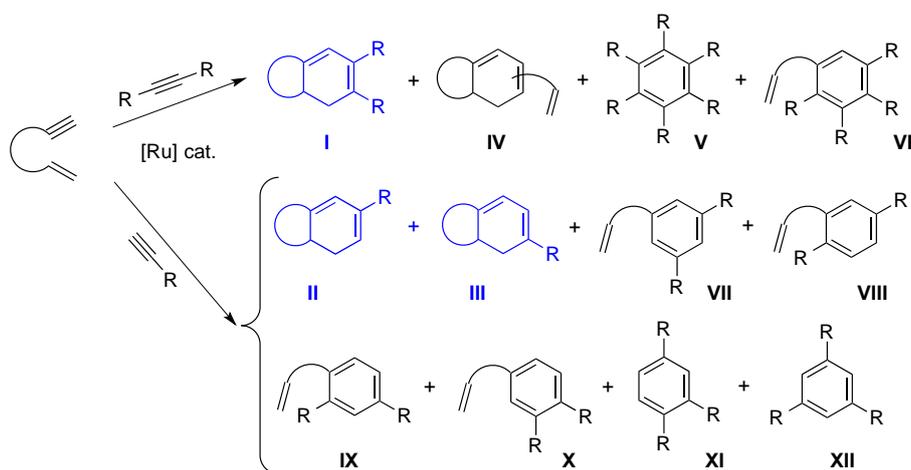
<sup>8</sup> S. Kezuka, T. Okado, E. Niou, R. Takeuchi, *Org. Lett.* **2005**, *7*, 1711-1714.

<sup>9</sup> Y. Yamamoto, K. Kinpara, T. Saigoku, H. Takagishi, S. Okuda, H. Nishiyama, K. Itoh, *J. Am. Chem. Soc.* **2005**, *127*, 605-613.

as emphasized above (*vide supra*). For instance, the [2+2+2] cycloadditions between enynes and symmetric alkynes are supposed to give the desired adduct **I** along with the *homodimer* **IV**, *homotrimer* **V** and *cotrimer* **VI** (Scheme 6).



**Scheme 5.** Heterocycles synthesis through ruthenium-catalyzed [2+2+2] cycloadditions of 1,6-diynes and carbon-heteroatom multibonded compounds



**Scheme 6.** Possible cycloadducts expected from [2+2+2] cycloaddition reactions of enynes and alkynes

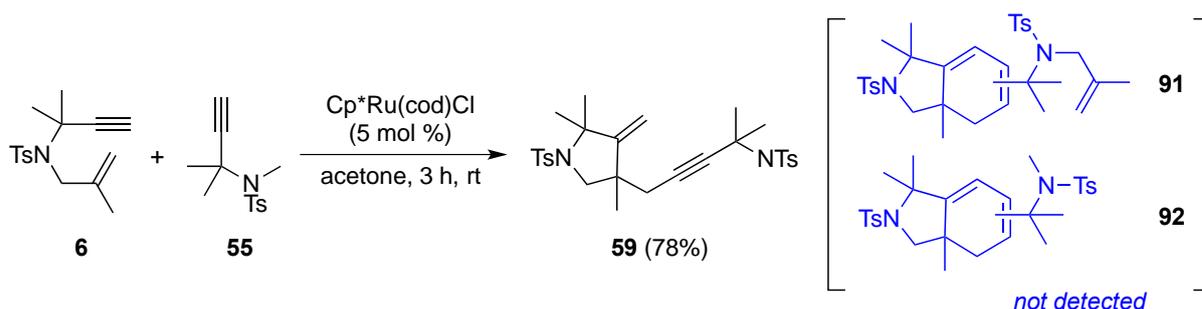
In reactions involving terminal alkynes, one would consider both the chemo- and regioselectivity of the reaction, and therefore the number of adducts significantly increases,

even though the formation of structures suffering from steric constraints should be less favorable (Scheme 6). Thus, *cross*-adducts leading to cyclohexadienes **II** and **III**, and aromatic structures from co-trimerization (**VII-X**) and trimerization (**XI-XII**) reactions are likely to form. Herein we disclose our results of studies dealing with these issues for the development of the ruthenium-catalyzed *cross*-carbocyclization of 1,6-enynes with alkynes.

### 3.2 Ruthenium-Catalyzed [2+2+2] Cycloaddition of 1,6-Enynes with Alkynes

#### 3.2.1 Initial experiments

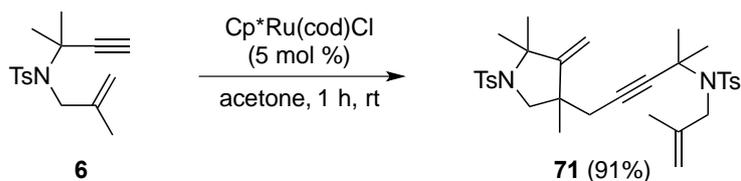
In the previous chapter, we reported the ruthenium-catalyzed hydroalkynylative cyclization of 1,6-enynes using terminal alkynes which occurred through a ruthenacyclopentene intermediate followed by a metal-assisted C(sp)-H  $\sigma$ -bond metathesis reaction.<sup>10</sup> These unusual *cross*-coupling reactions were successfully achieved employing both enynes and alkynes bearing substituents at propargyl carbon atom. For instance, the ruthenium-catalyzed *cross*-coupling of enyne **6** and alkyne **55** provided highly substituted five-membered cyclic compound **59** (Scheme 7). Under these conditions, [2+2+2] cycloadducts **91** and **92**, arising from *self*-coupling of enyne **6** and *cross*-coupling of enyne **6** and alkyne **55** respectively, were not detected during this catalytic process.



**Scheme 7.** Ru(II)-catalyzed *cross*-coupling reaction of enyne **6** and alkyne **55**

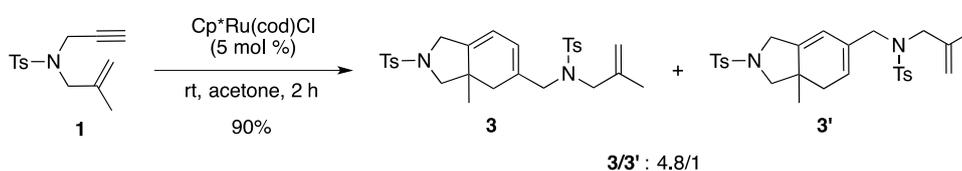
On the other hand, the reaction performed in the absence of **55** provided the monocyclic dimer **71** as the sole product in 91% isolated yield (Scheme 8).

<sup>10</sup> R. Liu, Z. Ni, L. Giordano, A. Tenaglia, *Org. Lett.* **2016**, *18*, 4040-4043.



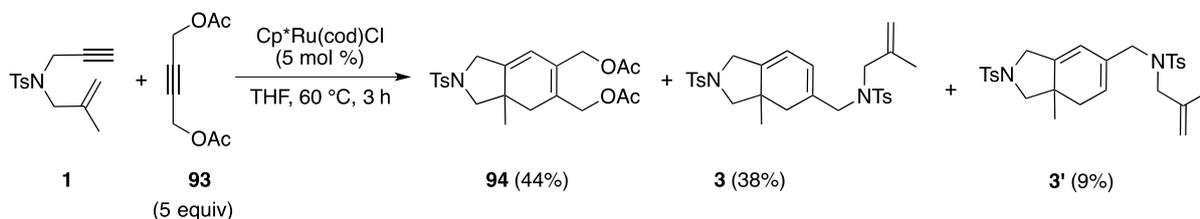
**Scheme 8.** Ru(II)-catalyzed *homo*-coupling reaction of enyne **7**

In deep contrast, treatment of unsubstituted enyne **1** with Cp\*Ru(cod)Cl in acetone at room temperature furnished selectively [2+2+2] cycloadducts as a 4.8/1 inseparable pair of regioisomers in 90% overall yield (Scheme 9).



**Scheme 9.** *Self*-[2+2+2] cycloaddition of enyne **1**

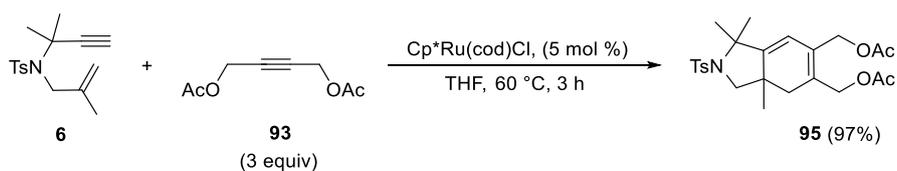
The above results prompted us to investigate the *intermolecular* [2+2+2] cycloaddition between enynes and alkynes. At the outset of these studies, the enyne **1** and symmetric alkyne **93** which can simplify our initial research were selected to perform the reaction test. In addition, excess alkyne **93** was employed in the catalytic reaction in order to disfavour the cyclodimerization of enyne **1** (Scheme 9). As shown in Scheme 10, exposure of enyne **1** (1 equiv) and alkyne **93** (5 equiv) to catalytic amount of Cp\*Ru(cod)Cl (5 mol %) at 60 °C in THF afforded the desired *cross*-adduct **94** in 44% yield along with cyclodimers **3** (38%) and **3'** (9%) as non separated regioisomers.



**Scheme 10.** [2+2+2] Cycloaddition reaction of 1,6-enyne **1** and alkyne **93**

As mentioned earlier, the use of enyne **6** failed to produce the corresponding [2+2+2]

cycloadduct in the presence of catalytic amount of Cp\**Ru*(cod)Cl (Scheme 7). Consequently, the [2+2+2] *intermolecular* carbocyclization reaction was attempted with enyne **6**. Gratifyingly, the ruthenium-catalyzed coupling reaction of enyne **6** (1 equiv) and alkyne **93** (5 equiv) led to the expected adduct **95** as the sole product in 97% yield (Scheme 11). Further investigations showed that the amount of alkyne **93** can be reduced to 3 equivalents with respect to the corresponding enyne while preserving the yield of **95**.



**Scheme 11.** [2+2+2] Cycloaddition reaction of 1,6-enyne **6** and alkyne **93**

### 3.2.2 Structural identification of adduct **95**

The structure of *cross*-adduct **95** was ascertained by  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectroscopy with typical data given in Scheme 12, and the molecular mass was determined by HRMS analysis. The proton nmr data clearly showed 5 distinct methyl groups, 2 allylic protons as a multiplet, 2 distincts germinal protons at  $\delta$  3.40 and 3.01 with a germinal coupling constant  $J_{gem} = 9.2$  Hz characteristic of the methylene group of pyrrolidine ring,<sup>10</sup> and 1 vinylic proton as a singlet at  $\delta$  5.65 ppm which accommodate with the proposed structure. Additionally, the normal  $^{13}\text{C}$  NMR and DEPT-135 spectra were fully consistent with the nature and multiplicity of the carbon atoms. Of note, the  $^{13}\text{C}$  NMR displayed 21 instead of 22 lines; the two carbonyls are visible within a common signal at 171.0.

<p style="text-align: center;"><b>95</b></p>	$^1\text{H NMR (ppm)}$	$^{13}\text{C NMR (ppm)}$
	H <sub>7</sub> 5.65 (s, 1H)	C <sub>4</sub> 38.3
	H <sub>3</sub> 3.40 (d, $J = 9.2$ Hz, 1H)	C <sub>5</sub> 129.4
	H <sub>3</sub> 3.01 (d, $J = 9.2$ Hz, 1H)	C <sub>6</sub> 128.7
	H <sub>4</sub> 2.14-2.20 (m, 2H)	C <sub>7</sub> 115.3
		C <sub>7a</sub> 156.6
	C <sub>3a</sub> 39.5	

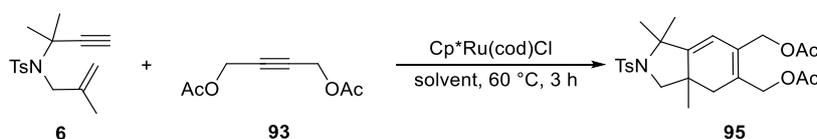
HRMS (ESI-MS): C<sub>24</sub>H<sub>32</sub>NO<sub>6</sub>S<sup>+</sup> ([M+H]<sup>+</sup>)  
*th.* 462.1945, *exp.* 462.1947

**Scheme 12.** Typical NMR data and HRMS for compound **95**

### 3.2.3 Optimization of the ruthenium-catalyzed [2+2+2] cycloaddition of 1,6-enyne **6** with alkyne **93**

Further studies focused on the screening of reaction conditions for the carbocyclization reaction of **6** and **93** as the model reaction (Table 1). The overall efficiency was firstly optimized by systematically changing the solvent properties, including polarity and coordinating ability. MeOH, as a typical protic solvent, was proved to be less effective for

**Table 1.** Screening of solvents and ruthenium catalysts<sup>[a]</sup>



Entry	Conditions	Yield (%) <sup>[b]</sup>
1	tetrahydrofuran	97
2	acetone	90
3	ethyl acetate	92
4	dichloroethane	88
5	1, 4-dioxane	78
6	methanol	61
7	toluene	86
8	H <sub>2</sub> O/ tetrahydrofuran 85/15	95
9	chloroform	82
10	diethyl ether	78
11 <sup>c</sup>	$\text{CpRu}(\text{PPh}_3)_2\text{Cl}$ instead of $\text{Cp}^*\text{Ru}(\text{cod})\text{Cl}$	15 (70) <sup>d</sup>
12 <sup>c</sup>	$\text{Cp}^*\text{Ru}(\text{PPh}_3)_2\text{Cl}$ instead of $\text{Cp}^*\text{Ru}(\text{cod})\text{Cl}$	85
13 <sup>c</sup>	$\text{CpRu}(\text{MeCN})_3\text{PF}_6$ instead of $\text{Cp}^*\text{Ru}(\text{cod})\text{Cl}$	9 (62) <sup>d</sup>
14 <sup>c</sup>	$\text{Cp}^*\text{Ru}(\text{MeCN})_3\text{PF}_6$ instead of $\text{Cp}^*\text{Ru}(\text{cod})\text{Cl}$	61
15 <sup>c</sup>	$\text{Cp}^*\text{Ru}(\text{MeCN})_3\text{PF}_6/n\text{Bu}_4\text{NCl}$ <sup>e</sup> instead of $\text{Cp}^*\text{Ru}(\text{cod})\text{Cl}$	90

<sup>[a]</sup> Reaction conditions: enyne **6** (0.2 mmol), alkyne **2** (0.6 mmol),  $\text{Cp}^*\text{Ru}(\text{cod})\text{Cl}$  (0.01 mmol), solvent (1 mL),  $60\text{ }^\circ\text{C}$ , 3 h. <sup>[b]</sup> Isolated yield. <sup>[c]</sup> Reactions conducted in THF. <sup>[d]</sup> Yields of recovered enyne **6**. <sup>[e]</sup> 10 mol % of  $n\text{Bu}_4\text{NCl}$  was used.

this transformation in terms of yield which decreased to 61% (entry 6). Other polar solvents such as 1,4-dioxane (entry 5), Et<sub>2</sub>O (entry 10) and CHCl<sub>3</sub> (entry 9) afforded the desired adduct in relatively higher yield compared with MeOH. Among the various polar solvents examined, it turns out that ethyl acetate (entry 3) and acetone (entry 2) provided **95** with the highest yields (90% and 92%, respectively). Further screening of solvents showed that the carbocyclization reaction in THF at 60 °C provided the *cross*-adduct **95** in almost quantitative yield (97%) when Cp\*Ru(cod)Cl was selected as the catalyst (entry 1). Notably, the reaction can be performed in a mixed solvent system such as H<sub>2</sub>O/THF (85/15) without significant decrease of the yield (entry 8).

We also examined the catalytic performances of structurally similar ruthenium complexes on the outcome of the [2+2+2] cycloaddition reaction. First, the results showed that the reaction was best performed using electron-rich ruthenium complexes containing a pentamethylcyclopentadienyl (Cp\*) ligand rather than the cyclopentadienyl (Cp) one (compare entries 11/12 and 13/14). Second, unlike similar reactions described with rhodium complexes,<sup>6,7,11</sup> neutral complexes exhibited a better activity compared to the cationic catalysts (compare entries 11/13 and 12/14). This observation was supported by the following experiment. The reaction of enyne **6** and alkyne **93** was conducted in the presence of Cp\*Ru(MeCN)<sub>3</sub>PF<sub>6</sub> and *n*Bu<sub>4</sub>NCl (entry 15). This catalyst combination was used by the Varela and co-workers to *in situ* generate the neutral complex Cp\*Ru(MeCN)<sub>3</sub>Cl precursor of the coordinatively unsaturated neutral active species [Cp\*RuCl].<sup>12</sup> Under these conditions, the reaction provided **95** with the restored yield (90%). Third, owing to the more labile bidentate cod ligand compare to the triphenylphosphine, Cp\*Ru(cod)Cl gave the best result (compare entry 1 with entries 11-14).

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<sup>11</sup> a) Y. Aida, H. Sugiyama, H. Uekusa, Y. Shibata, K. Tanaka, *Org. Lett.* **2016**, *18*, 2672-2675; b) T. Yoshida, Y. Tajima, M. Kobayashi, K. Masutomi, K. Noguchi, K. Tanaka, *Angew. Chem.* **2015**, *127*, 8359-8362.

<sup>12</sup> J. A. Varela, S. G. Rubín, C. González-Rodríguez, L. Castedo, C. Saá, *J. Am. Chem. Soc.* **2006**, *128*, 9262-9263.

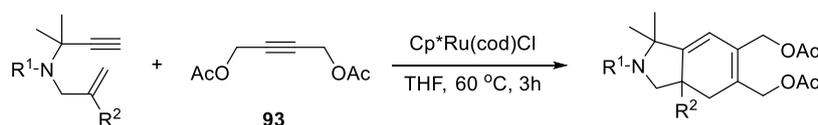
### 3.2.4 Scope of substrates

With the best reaction conditions in hand, the applicability of the ruthenium-catalyzed [2+2+2] cycloaddition reactions was studied according to the structural variation of either enynes or alkynes.

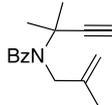
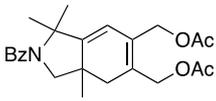
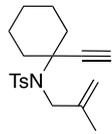
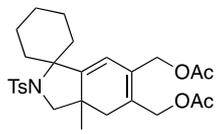
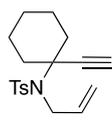
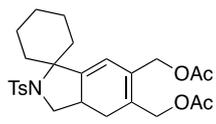
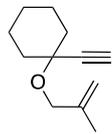
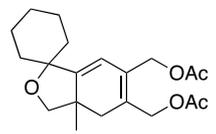
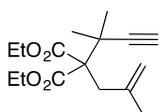
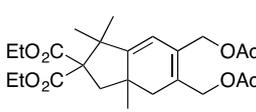
#### Scope of enyne substrates

The carbocyclization of various substituted 1,6-enynes was investigated with but-2-yne-1,4-diyl diacetate **93** and the results are summarized in Table 2.

**Table 2.** Cp\*Ru(cod)Cl-catalyzed cycloaddition of 1,6-enynes and alkyne **93**



Entry	1,6-Enyne	Product	Yield (%) <sup>[b]</sup>
1	 <b>56</b>	 <b>99</b>	98
2	 <b>57</b>	 <b>100</b>	73
3	 <b>96</b>	 <b>101</b>	62
4	 <b>97</b>	 <b>102</b>	92
5	 <b>14</b>	 <b>103</b>	93

6	 <b>15</b>	 <b>104</b>	91
7	 <b>17</b>	 <b>105</b>	93
8	 <b>98</b>	 <b>106</b>	87
9	 <b>18</b>	 <b>107</b>	85
10	 <b>19</b>	 <b>108</b>	88

<sup>[a]</sup> Reaction conditions: enyne (0.2 mmol), alkyne **91** (0.6 mmol), Cp\**Ru*(cod)Cl (0.01 mmol), solvent (1 mL), 60 °C, 3 h. <sup>[b]</sup> Isolated yield.

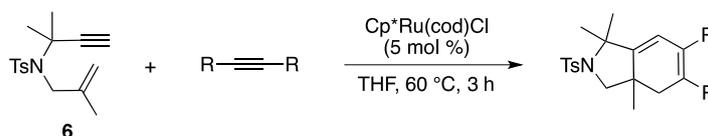
We firstly examined the [2+2+2] cycloaddition reactions using enynes featuring substitution on the internal carbon of the double bond. This peculiar substitution was selected in order to install a quaternary carbon atom at the ring junction of the cycloadducts. Interestingly, enynes **56** and **57** featuring an electrophilic or nucleophilic double bond, respectively reacted satisfactorily to provide the corresponding azabicycles **99** (98%) and **100** (73%) (entries 1-2). It is worth to note that the reactivity of enyne **56** deeply contrasted with the hydroalkynylation cyclization which required stoichiometric amount of the same catalyst (see Chapter II, entry 7 of Table 4, entry 7 of Table 5). Enyne **96** with the bulkier phenyl substituent also provided the corresponding adduct **101** although the yield dropped to 62% (entry 3). This yield is quite good considering severe non-bonded 1,3 interaction between phenyl and methyl

groups in the rigid conformation of the bicycle **101**. Interestingly, enyne **97**, without substituent on the double bond, proved suitable substrate to undergo the cycloaddition reaction thus affording **102** in excellent yield (92%) (entry 4). This result established that insertion step of the alkyne within the ruthenacyclopentene intermediate is faster compared to the  $\beta$ -H elimination. A similar result was observed with enyne **98** which provided cycloadduct **106** in 87% yield (entry 8). Variation of substitution at the nitrogen atom of the enyne, namely replacing the tosyl group with mesyl or benzoyl group, as in enynes **14** and **15** respectively, is well tolerated and provided **103** and **104** in excellent yields (entry 5-6). Variation of substitution at the propargyl position of enynes did not impact significantly the formation of cycloadducts (entries 7-9). Gratifyingly, the reaction can be successfully extended to oxygen- (**18**) and carbon-tethered (**19**) enynes providing oxabicyclic **107** (85%) and bicyclo[4.3.0]nonadiene **108** (88%) respectively (entry 9-10).

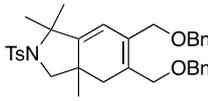
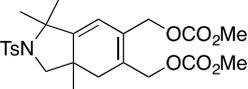
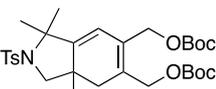
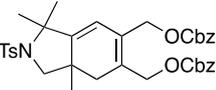
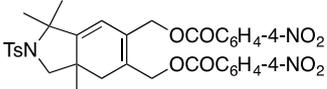
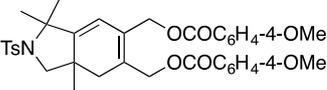
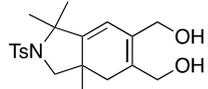
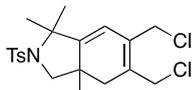
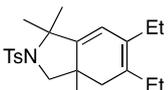
### Scope of alkyne substrates

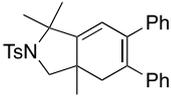
To extend the scope of the intermolecular carbocyclization, the reaction of enyne **6** with various functionalized internal alkynes was performed under the optimal conditions. The results are summarized in Table 3.

**Table 3.** Scope of Cp\**Ru*(cod)Cl-catalyzed cycloaddition of **6** and alkynes<sup>[a]</sup>



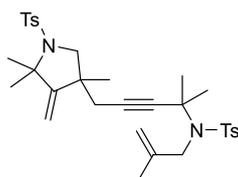
Entry	R	Product	Yield(%) <sup>[b]</sup>
1	CH <sub>2</sub> OMe <b>109</b>	 <b>122</b>	89

2	<p>CH<sub>2</sub>OBn</p> <p><b>110</b></p>	 <p><b>123</b></p>	93
3	<p>CH<sub>2</sub>OCO<sub>2</sub>Me</p> <p><b>111</b></p>	 <p><b>124</b></p>	95
4	<p>CH<sub>2</sub>OBoc</p> <p><b>112</b></p>	 <p><b>125</b></p>	94
5	<p>CH<sub>2</sub>OCbz</p> <p><b>113</b></p>	 <p><b>126</b></p>	87
6	<p>CH<sub>2</sub>OCOC<sub>6</sub>H<sub>4</sub>-4-NO<sub>2</sub></p> <p><b>114</b></p>	 <p><b>127</b></p>	83
7	<p>CH<sub>2</sub>OCOC<sub>6</sub>H<sub>4</sub>-4-OMe</p> <p><b>115</b></p>	 <p><b>128</b></p>	94
8	<p>CH<sub>2</sub>OH</p> <p><b>116</b></p>	 <p><b>129</b></p>	86
9	<p>CH<sub>2</sub>Cl</p> <p><b>117</b></p>	 <p><b>130</b></p>	86
10	<p>Et</p> <p><b>118</b></p>	 <p><b>131</b></p>	98

11	Ph <b>119</b>		21
12	SiMe <sub>3</sub> <b>120</b>	---	0
13	CO <sub>2</sub> Me <b>121</b>	---	0

<sup>[a]</sup> Reaction condition: enyne **6** (0.2 mmol), alkyne (0.6 mmol), Cp\*Ru(cod)Cl (0.01 mmol), solvent (1 mL), 60 °C, 3 h. <sup>[b]</sup> Isolated yield.

Bicyclic dienes **122-131** were obtained in very good to excellent yields (entries 1-10) and protecting groups of alcohols such as ethers (entry 1-2), mixed carbonates (entries 3-5) or esters (entry 6-7) are well compatible with our conditions. Even functional groups such as alcohol (entry 8) and chloride (entry 9) are well tolerated and unactivated alkyne such as hex-3-yne **118** afforded **131** in an almost quantitative yield. Interestingly, diphenylacetylene **119** allowed the formation of **132**, albeit in modest yield (21%), which contrasts with the failure of the related rhodium-catalyzed carbocyclization reaction.<sup>13</sup> In this case, the major product (61%) was the alkynylative cyclodimer **71**.<sup>10</sup> Similarly, bistrimethylsilylethyne **120**, which is an excellent partner in cobalt-catalyzed cycloadditions,<sup>14</sup> did not afford the expected adduct, instead **71** was obtained as the sole product in 86% yield. As an electron-poor alkyne, dimethyl acetylenedicarboxylate (DMAD) **121** proved reactive but disappointingly led an intractable mixture of products.

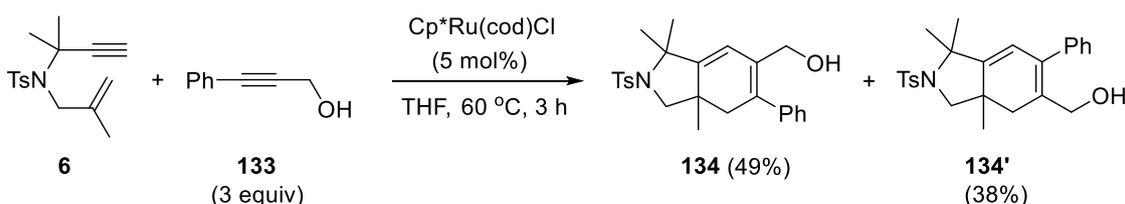


**Scheme 13.** Structure of dimer **71**

<sup>13</sup> P. A. Evans, J. R. Sawyer, K. W. Lai, J. C. Huffman, *Chem. Commun.* **2005**, 3971-3973.

<sup>14</sup> K. P. C. Vollhardt, *Angew. Chem. Int. Ed. Engl.* **1984**, 23, 539-556.

We also examined the behaviour of internal, asymmetric alkynes to evaluate the regioselectivity of the cycloaddition. As an illustrative example, the coupling reaction of **6** and 3-phenylprop-2-yn-1-ol **133** under the typical conditions led as expected to cycloadduct **134** and **134'** in very good overall yield but with a poor regioselectivity. The two regioisomers were separated by column chromatography for identification purposes, and their structures were established by NOESY experiments.



**Scheme 14.** [2+2+2] cycloaddition reaction of **6** with internal alkyne **133**

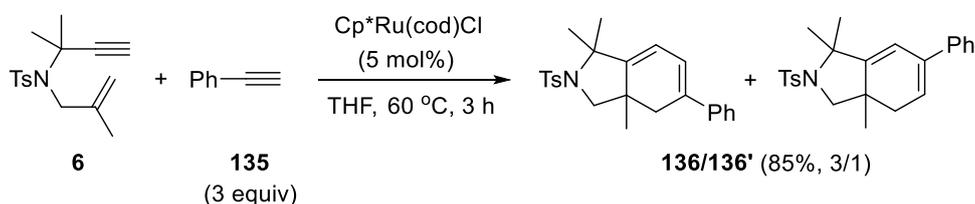
In summary, internal alkynes featuring electrophilic or nucleophilic functional groups are suitable to perform the intermolecular carbocyclization reaction with enynes partners to provide an easy access to a wide range of bicyclic dienes. However, the reaction is sensitive to steric and/or electronic properties of alkynes as exemplified with the failure of reactions involving alkynes **120** and **121**. Non-symmetric alkynes should also be considered in these reactions, provided that a delicate balance between steric and electronic factors is found to control efficiency and regioselectivity.

### 3.2.5 Carbocyclizations involving terminal alkynes — achievements in regioselectivity

Then, to make this carbocyclization reaction more attractive, we have turned our attention to the use of terminal alkynes and the control of regioselectivity. Evans and co-workers achieved the [2+2+2] cycloaddition reaction between enynes and methyl arylpropiolates to give a pair of regioisomers with high regiocontrol (up to >20:1).<sup>7</sup> However the alkyne scope is rather restricted to electron-poor alkynes.

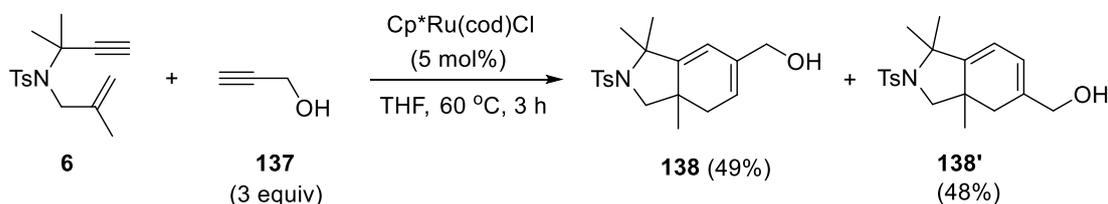
Initial investigation focused on the cycloaddition reaction of **6** and phenylacetylene **135**, which afforded a pair of regioisomers **136/136'** as an inseparable mixture in 85%

overall yield. The major isomer **136** is in line with the highest conjugation of the  $\pi$ -system.



**Scheme 15.** [2+2+2] cycloaddition reaction of **6** with terminal alkyne **135**

Propargyl alcohols have proven to be excellent substrates in ruthenium chemistry for a number of useful synthetic transformations.<sup>15</sup> Moreover, functional group manipulations can be envisaged for further applications of the expected cycloadducts. Therefore, we began to examine the carbocyclization reaction of enyne **6** and propargyl alcohol **137** under the usual conditions. Disappointingly, the reaction provided a pair of regioisomers **138** and **138'** in nearly equal amounts and almost quantitative yield.

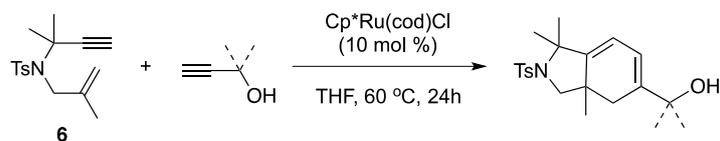


**Scheme 16.** Carbocyclization of enyne **6** and propargyl alcohol **137**

Because hydroxyl group may coordinate to the ruthenium center<sup>16</sup> and bulky substituents at the propargyl carbon of enynes plays an important role on the outcome of our ruthenium-catalyzed reactions, it was tempting to examine the behavior of tertiary propargyl alcohols in the carbocyclization reaction. Thus a series of commercially available tertiary propargyl alcohols **139-142** was selected and the results obtained are summarized in Table 4.

<sup>15</sup> a) B. M. Trost, M. T. Rudd, *Org. Lett.* **2003**, *5*, 1467-1470; b) B. M. Trost, A. Breder, B. M. O'Keefe, M. Rao, A. W. Franz, *J. Am. Chem. Soc.* **2011**, *133*, 4766-4769; c) F. Jerome, F. Monnier, H. Lawicka, S. Derien, P. H. Dixneuf, *Chem. Commun.* **2003**, 696-697; d) R. Malacea, P. H. Dixneuf, *Metal Vinylidenes and Allenylidenes in Catalysis*, Wiley-VCH Verlag GmbH & Co. KGaA, **2008**, pp. 251-277.

<sup>16</sup> a) B. M. Trost, R. C. Livingston, *J. Am. Chem. Soc.* **2008**, *130*, 11970-11978; b) B. M. Trost, N. Maulide, R. C. Livingston, *J. Am. Chem. Soc.* **2008**, *130*, 16502-16503; c) B. M. Trost, A. C. Gutierrez, R. C. Livingston, *Org. Lett.* **2009**, *11*, 2539-2542;

**Table 4.** Ru-catalyzed carbocyclization of **6** with bulky substituted terminal alkynes<sup>[a]</sup>

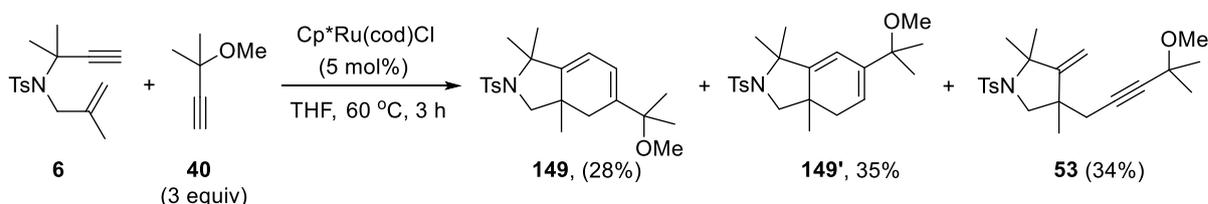
Entry	Alkynes	Product	Yield (%) <sup>[b]</sup>
1	 <b>139</b>	 <b>144</b>	86
2	 <b>140</b>	 <b>145</b>	85 (dr 1/1) <sup>[c]</sup>
3	 <b>141</b>	 <b>146</b>	91
4	 <b>142</b>	 <b>147</b>	70
5	 <b>143</b>	 <b>148</b>	64

<sup>[a]</sup> Reaction conditions: **6** (0.2 mmol), alkyne (0.6 mmol), THF (1 mL), Cp<sup>\*</sup>Ru(cod)Cl (0.02 mmol), solvent (1 mL), 60 °C, 24 h. <sup>[b]</sup> Isolated yield. <sup>[c]</sup> Ratio of diastereomers determined by <sup>1</sup>H NMR of the crude reaction.

As the reactions proceeded slowly, a catalyst charge of 10 mol % and a reaction time of 24 h were required for completion. Under these modified conditions, we were pleased to observe the formation of adducts **144-148** as single regioisomers, as judged by <sup>1</sup>H NMR, in good to excellent yields. This excellent regioselectivity was not restricted to the tertiary alcohols. Indeed, the bulky tertiary propargylic sulfonamide

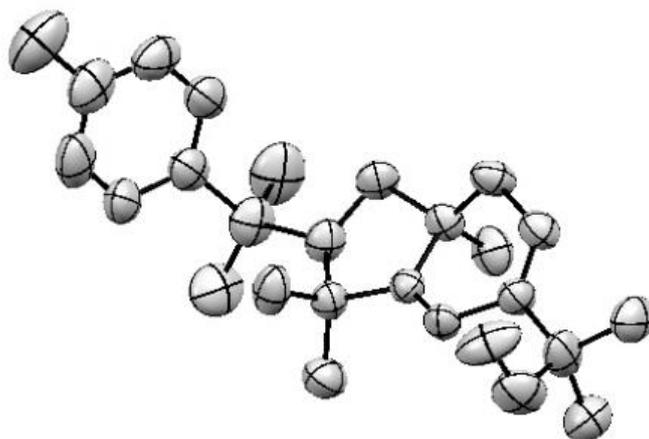
**143** provided the ring-fused cyclohexadiene **148** in 64% yield as a single isomer.

We questioned about the regioselectivity observed within the reactions of tertiary propargyl alcohols and we wonder about the ability of the free hydroxyl group to coordinate the ruthenium, and to play a major role in the regiocontrol of the reaction. Indeed, such properties have been highlighted in a number of ruthenium-catalyzed reactions involving this class of substrates.<sup>17</sup> Thus, performing the reaction of 3-methoxy-3-methylbut-1-yne (**40**) with **6** resulted in loss of both regio- and chemoselectivity providing bicyclic dienes **149/149'** (63%, 0.83/1 ratio of regioisomers) and 1,5-enyne **53** (34%) arising from the alkynylative coupling reaction (Scheme 17).<sup>10</sup> The structure of **149'** was confirmed by single crystal X-ray diffraction analysis (Scheme 18). This result indicated that: a) the relative bulk of the methoxy group compared to the hydroxyl one could modify the coordinating ability of oxygen atom as an element of regiocontrol; b) the free alcohol function appears to be a better directing group to improve the regioselectivity. Therefore, the orientation of insertion of alkyne **40** into the ruthenacycle is no longer secured. In addition, a competitive cyclization through the metal-assisted  $\sigma$ -bond metathesis occurred to give **53**.



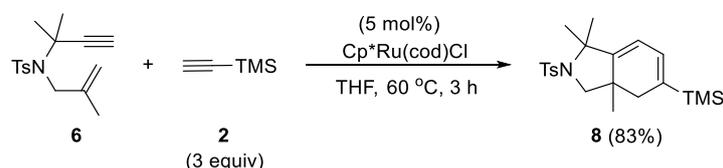
**Scheme 17.** Cross-carbocyclization of **6** and tertiary propargyl ether **40**

<sup>17</sup> a) B. M. Trost, A. Breder, *Org. Lett.* **2011**, *13*, 398-401; b) B. M. Trost, A. Breder, B. M. O'Keefe, M. Rao, A. W. Franz, *J. Am. Chem. Soc.* **2011**, *133*, 4766-4769; c) B. M. Trost, A. Breder, B. Kai, *Org. Lett.* **2012**, *14*, 1708-1711; d) B. M. Trost, M. C. Ryan, M. Rao, T. Z. Markovic, *J. Am. Chem. Soc.* **2014**, *136*, 17422-17425.



**Scheme 18.** ORTEP representation of **149'**<sup>18</sup>

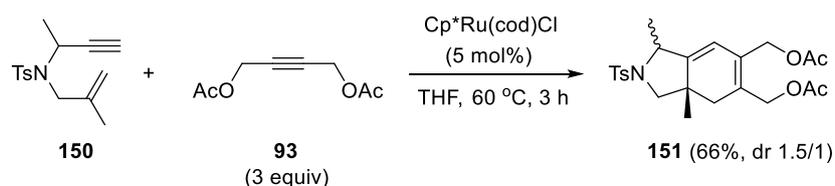
In the previous chapter, we already observed a single example of regiocontrol of the carbocyclization of **6** with trimethylsilylacetylene **2** thus forming **8** in 75% yield. Under slightly modified conditions (THF in place of acetone, 60 °C), **8** has been obtained in 83% yield (Scheme 19). It is believed that a good balance between steric and electronic properties of the alkyne could control the regioselectivity of these reactions.



**Scheme 19.** Cross-carbocyclization of **6** and trimethylsilylacetylene **2**

Lastly, we examined the influence of a substituent at the propargyl side chain on the reaction diastereoselectivity. The coupling reaction of 1,6-enyne **150** featuring monosubstitution at the propargyl position with **93** gave the cycloadduct **151** in 66% yield with 1.5/1 diastereomeric ratio (Scheme 20).

<sup>18</sup> Crystal data: C<sub>22</sub>H<sub>31</sub>NO<sub>3</sub>S, FW = 389.54, monoclinic, *P* 1 21 1, *a* = 6.4533(5) Å, *b* = 8.1500(5) Å, *c* = 20.626(2) Å,  $\beta$  = 93.939(8)°, *V* = 1082.25(16) Å<sup>3</sup>, *Z* = 2, *D*<sub>calcd</sub> = 1.195 g cm<sup>-3</sup>, *R* = 0.0684 (*R*<sub>w</sub> = 0.1905) for 3537 reflections with *I* > 2.00σ(*I*) and 251 variable parameters. CCDC 1535396 (**149'**) contains supplementary crystallographic data for this compound. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via [www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif).



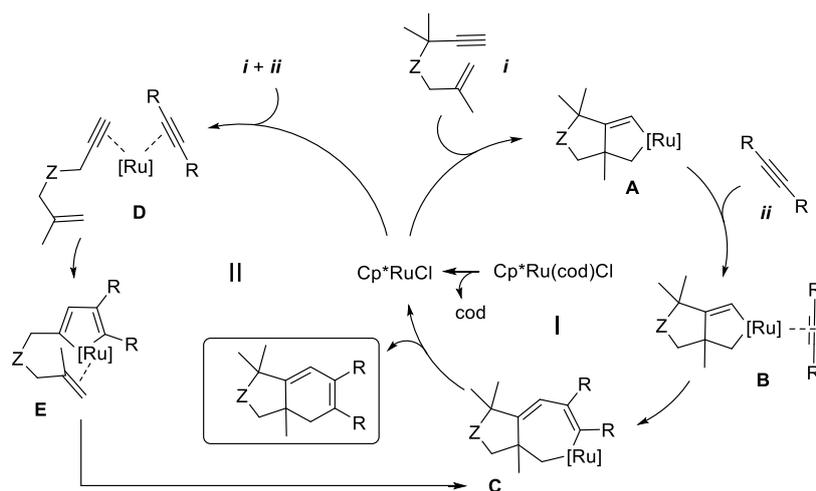
**Scheme 20.** Cross-coupling reaction of **150** and **93**

### 3.2.6 Mechanism proposal

#### Catalytic cycle of the carbocyclization reaction

Based on previous reports of related metal-catalyzed [2+2+2] cycloaddition reactions,<sup>19</sup> two plausible mechanisms involving ruthenacycles as intermediates should be considered (Scheme 21). Both catalytic cycle **I** and **II** starts with the cod ligand dissociation of Cp\*Ru(cod)Cl. Intramolecular coordination of both triple and double bonds of enynes *i* to ruthenium centre followed by oxidative cyclization allow the formation of the ruthenacyclopentene **A**. Upon coordination of the alkyne partner *ii* to the ruthenium centre, complex **B** undergoes the migratory insertion to generate the ruthenacycloheptadiene **C**. Finally, reductive elimination released the bicyclic product and regenerated the active metal species. An alternative mechanism (**II**) leading to intermediate **C** might involve first intermolecular coordination of the two alkyne partners (**D**) to afford ruthenacyclopentadiene **E** and subsequent insertion of the alkene motif. At this stage, it appears quite difficult to select the catalytic cycle responsible for the formation of the product. On the basis of the hydroalkynylative cyclization (see chapter II) that involved ruthenacyclopentene intermediate **A**, and excellent regioselectivity observed with certain terminal alkynes we are inclined to favor mechanism path **I**.

<sup>19</sup> a) P. R. Chopade, J. Louie, *Adv. Synth. Catal.* **2006**, *348*, 2307-2327; b) S. Saito, Y. Yamamoto, *Chem. Rev.* **2000**, *100*, 2901-2916.



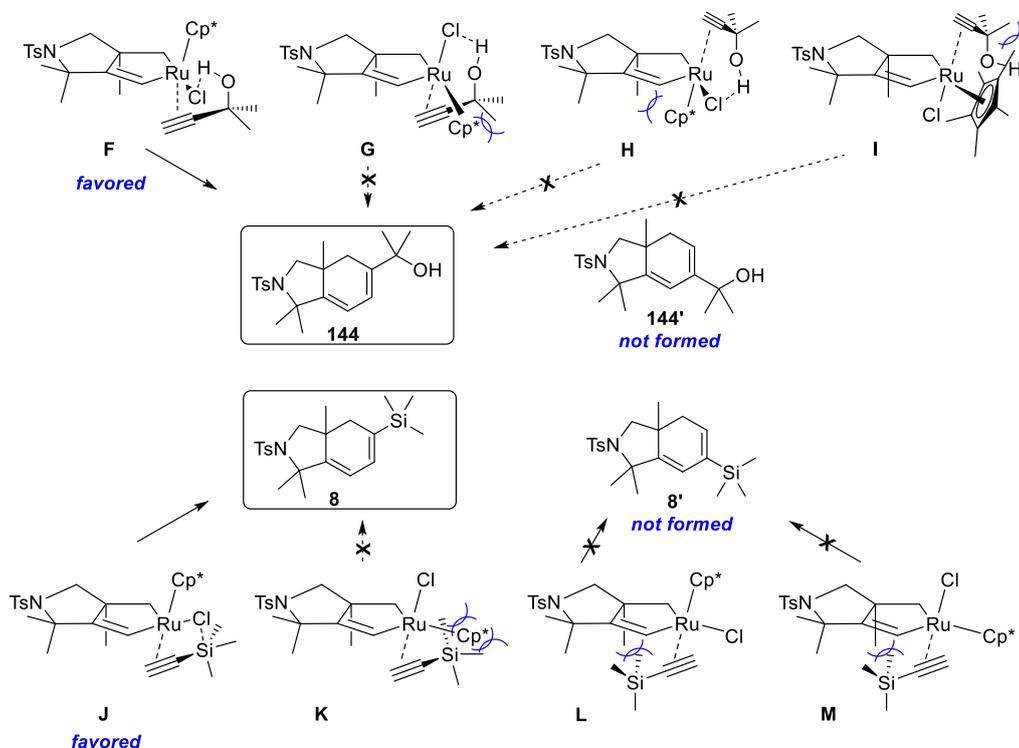
**Scheme 21.** Mechanism of the [2+2+2] intermolecular carbocyclization

### Origin of the regioselectivity

To explain the observed regioselectivity within reactions involving tertiary propargyl alcohols and ethynyltrimethylsilane **2**, we considered different approaches between the ruthenacycle and alkyne using molecular models. As depicted in Scheme 22, we selected eight possible sketches (**F-M**) involving alkyne as a ligand. In the presence of tertiary terminal alkynol, the interligand interactions, concept recently introduced by Fürstner group,<sup>20</sup> through H-bonding between the hydroxyl group and chloride ligand of the ruthenacycle was therefore considered. Complex **F** in line with interligand interactions might favor formation of **144**. It appears that intermediate **G** is less favored to release **144** due to steric hindrance that prevent insertion of alkyne, even though interligand interactions are possible. Intermediate **H** and **I** not suitable to give **144** can be easily ruled out. These interactions are equally operative with other protic functions at the propargyl carbon as illustrated in the reaction of secondary sulfonamide **143**. In case of trimethylsilylacetylene as coupling partner (intermediate **J**), interligand interactions through halophilicity of the silicon atom nicely explain the regioselectivity observed in the formation of **8**. Complexes **K**, **L** and **M** appear unlikely as a consequence of severe steric interactions. Therefore, it is suggested that

<sup>20</sup> a) S. M. Rummelt, K. Radkowski, D.-A. Roşca, A. Fürstner *J. Am. Chem. Soc.* **2015**, *137*, 5506–5519; b) D.-A. Roşca, K. Radkowski, L. M. Wolf, M. Wagh, R. Goddard, W. Thiel, A. Fürstner, *J. Am. Chem. Soc.* **2017**, *139*, 2443–2455; c) S. M. Rummelt, G.-J. Cheng, P. Gupta, W. Thiel, A. Fürstner, *Angew. Chem. Int. Ed.* **2017**, *56*, 3599–3604.

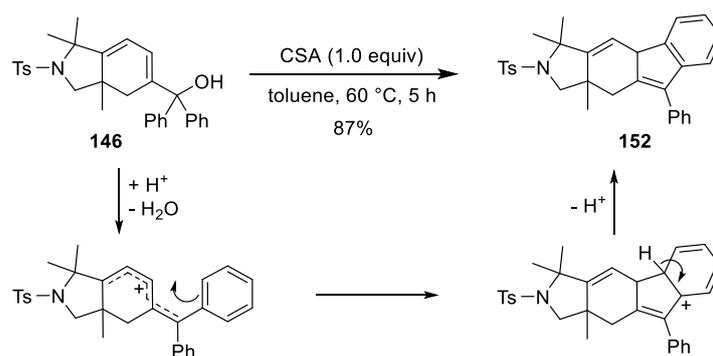
both interligand interactions and steric hindrance equally affect the regioselectivity of this [2+2+2] cycloaddition reaction.



**Scheme 22.** Possible intermediate complexes

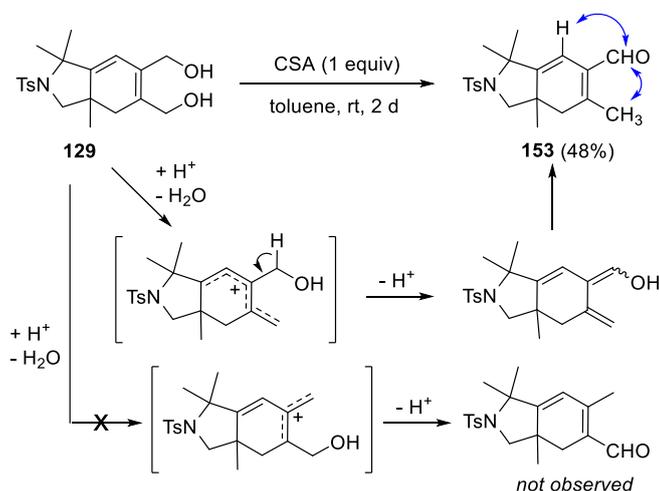
### 3.2.7 Synthetic applications of cycloadducts

To demonstrate the synthetic utility of this protocol, chemical transformations into more complex ring-fused polycycles were briefly examined. Cycloadduct **146** was first selected as representative product to explore potential transformations through carbocation intermediates. Thus, treatment of **146** with camphorsulfonic acid (CSA) in toluene at 60 °C provided the tetracyclic structure **152** in 87% isolated yield through the acid-promoted dehydrative cyclization (Scheme 20). We assume that the highly stabilized pentadienyl-like cation intermediate generated after dehydration undergo a Nazarov-like reaction involving the participation of a phenyl group followed by the loss of proton to restore the aromatic ring.



**Scheme 23.** CSA-promoted dehydrative cyclization of cycloadduct **146**

On the other hand, upon exposure to a CSA solution in toluene, diol **129** was smoothly converted at room temperature to aldehyde **153** in 48% yield (Scheme 21).



**Scheme 24.** CSA-promoted dehydration of cycloadduct **129**

The yield could not be improved by elevating the temperature and the reaction resulted into an inextricable mixture of products. The structure of **153** was confirmed by NOESY experiment displaying correlation between the formyl and ethylenic protons as well as between the formyl and allylic methyl protons. Interestingly, the dehydration reaction led solely to the regioisomer **153** which presumably arise from the more stabilized pentadienyl cation intermediate versus the allylic one as depicted in Scheme 24.

### 3.3 Conclusion

In conclusion, we have successfully developed the ruthenium-catalyzed [2+2+2]

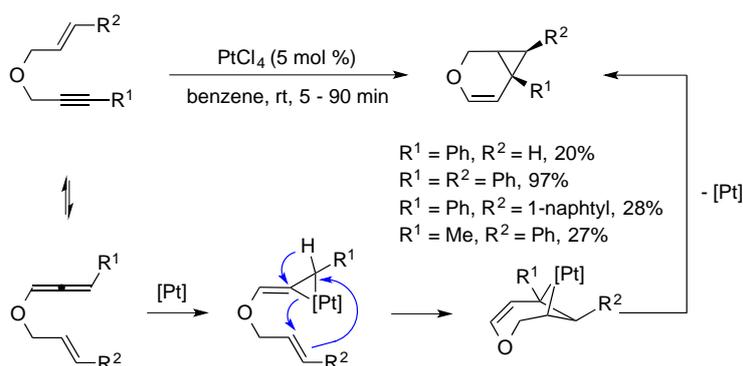
cycloaddition of 1, 6-enynes with alkynes. Formation of undesired byproducts is significantly reduced or suppressed using an optimal ratio enyne/alkyne 1/3. Scope investigation indicated that a number of *N/O/C*-linked 1,6-enynes reacted with various internal alkynes to provide bicyclohexadienes in good to excellent yields under mild reaction conditions. Interestingly, tertiary propargyl alcohols can also be incorporated in the present catalytic process to release desired adducts as single regioisomers. The reaction might proceed through either ruthenacyclopentene or ruthenacyclopentadiene intermediates. Experimental results and examination of molecular models supported the hypothesis that *interligand interaction* (repulsion or association) between the ligands of [Cp\**Ru*Cl] and the substituents of tertiary propargyl alcohols might explain the formation of adducts as single regioisomers. Importantly, the non-bonded interactions between substituents within the reaction intermediates play an important role on the regioselectivity of [2+2+2] cycloaddition.

## **Chapter IV**

# **Ruthenium-Catalyzed Cycloisomerization of *N*-Tethered 1,6-Enynes: Access to Aza-Bicyclo[4.1.0]heptenes**

## 4.1 Introduction

The past thirty years have witnessed a rapid growth of transition metal-catalyzed cycloisomerization reactions of 1,6-enynes as they allowed a straightforward access to a wide array of cyclic products featuring among others 1,3- or 1,4-diene and cyclobutene moieties.<sup>1</sup> Among the arsenal of cycloisomerization reactions available, those involving heteroatom-tethered 1,6-enynes are characterized with a unique class of reaction allowing construction of heterobicycles featuring the cyclopropane ring in a single step.<sup>2</sup> Pioneering work by the Blum group in 1995 reported the conversion of allyl propargyl ethers into 3-oxabicyclo[4.1.0]hept-4-enes on exposure to catalytic amounts of platinum(IV) tetrachloride. Due to the sensitivity of the bicyclic ether structures, the cycloisomers were observed in most of cases with poor yields (Scheme 1).<sup>3</sup> Interestingly, it was showed that the stereochemical information of the double bond was retained in the product formed.



**Scheme 1.** Blum's PtCl<sub>4</sub>-catalyzed cycloisomerization of allyl propargyl ethers

At that time, the mechanism of this intriguing cyclization was not clearly understood. Blum proposed the tautomerization of alkyne to allene followed by complexation with Pt. Intramolecular cyclization involving a 1,2-*H* shift resulted in the formation of a bridged platinumacyclic which upon metal elimination released the oxabicyclic. The main raised

<sup>1</sup> a) V. Michelet, P. Y. Toullec, J.-P. Genêt, *Angew. Chem., Int. Ed.* **2008**, *47*, 4268-4315; b) C. I. Stathakis, P. L. Gkizis, A. L. Zografos, *Nat. Prod. Rep.* **2016**, *33*, 1093-1117; c) P. Cao, X. Zhang, *Angew. Chem., Int. Ed.* **2000**, *39*, 4104-4106; d) G. C. Lloyd-Jones, *Org. Biomol. Chem.* **2003**, *1*, 215-236.

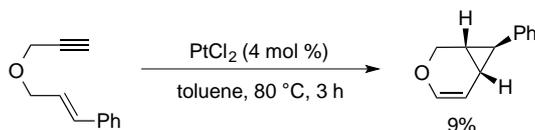
<sup>2</sup> a) C. Bruneau, *Angew. Chem., Int. Ed.* **2005**, *44*, 2328-2334; b) J. Marco-Contelles, N. Arroyo, S. Anjum, E. Mainetti, N. Marion, K. Cariou, G. Lemièrre, V. Mouriès, L. Fensterbank, M. Malacria, *Eur. J. Org. Chem.* **2006**, *2006*, 4618-4633; c) L. Zhang, J. Sun, S. A. Kozmin, *Adv. Synth. Catal.* **2006**, *348*, 2271-2296; d) H. Teller, M. Corbet, L. Mantilli, G. Gopakumar, R. Goddard, W. Thiel, A. Fürstner, *J. Am. Chem. Soc.* **2012**, *134*, 15331-15342.

<sup>3</sup> Blum, J.; Beer-Kraft, H.; Badrieh, Y., *J. Org. Chem.* **1995**, *60*, 5567-5569.

question rests upon the oxidation state regarding the metalacycle intermediates.

### Cycloisomerization of Heteroatom-tethered 1,6-Enynes — A Brief Overview

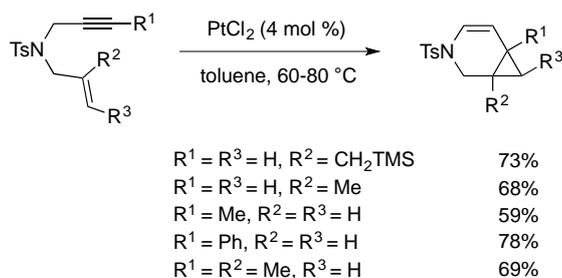
Shortly later the Blum's report, Murai and co-workers<sup>4</sup> described a single example of cycloisomerization of cinnamyl propargyl ether to 7-phenyl-3-oxabicyclo[4.1.0]hept-4-ene in 9% yield as most of the enyne being polymerized (Scheme 2). This confirmed the sensitivity of the enyne and/or cycloisomer thereof and the observed poor yields.



**Scheme 2.** Murai's PtCl<sub>2</sub>-catalyzed cycloisomerization of cinnamyl propargyl ether

The reaction was extended to enynes featuring enol ethers as the alkene component by Echavarren and co-workers.<sup>5</sup>

Fürstner later reported a similar transformation utilizing a sulfonamide group in the tether of 1,6-enynes and replacing the moist sensitive PtCl<sub>4</sub> with the robust PtCl<sub>2</sub>.<sup>6</sup>



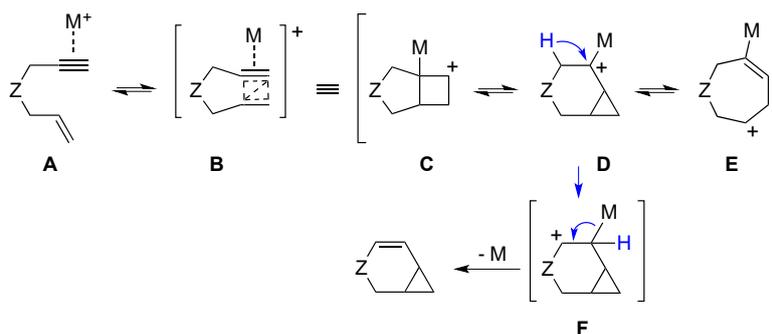
**Scheme 3.** Fürstner's PtCl<sub>2</sub>-catalyzed cycloisomerization of *N*-tethered 1,6-enynes

On the basis of deuterium labeling experiments which showed an intramolecular 1,2-*H(D)* shift, a mechanism rationale involving cationic intermediates was presented.<sup>6b-c</sup>

<sup>4</sup> N. Chatani, N. Furukawa, H. Sakurai, S. Murai, *Organometallics* **1996**, *15*, 901-903.

<sup>5</sup> C. Nevado, C. Ferrer, A. M. Echavarren, *Org. Lett.* **2004**, *6*, 3191-3194.

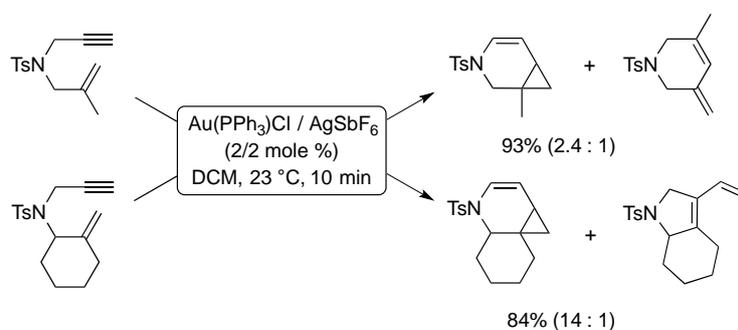
<sup>6</sup> a) A. Fürstner, H. Szillat, F. Stelzer, *J. Am. Chem. Soc.* **2000**, *122*, 6785-6786; b) A. Fürstner, F. Stelzer, H. Szillat, *J. Am. Chem. Soc.* **2001**, *123*, 11863-11869; c) M. Mendez, V. Mamane, A. Fürstner, *Chemtracts—Organic Chemistry* **2003**, *16*, 397-425.



**Scheme 4.** Mechanism rationale of cycloisomerization of heteroatom-tethered 1,6-enynes

The highly electrophilic entities generated through alkyne coordination to the metal center (**A**) are readily attacked by the tethered alkene moiety to form cationic complex **B** which can evolve to cyclobutyl cation **C** also represented by the forms **D** and **E**. Specifically, the cyclopropyl-methyl cation resonance in **D**, carbenoid in nature, suffered a rapid 1,2-hydrogen shift to give **F** which upon metal elimination give the bicyclo[4.1.0]heptene derivative.

On the course of studies on gold(I) complexes-catalyzed cyclization of enynes, Echavarren and co-workers found that *N*-tethered 1,6-enynes undergo a similar cyclization in the presence of cationic gold species  $[\text{Au}(\text{PPh}_3)]\text{SbF}_6$  generated from  $[\text{Au}(\text{PPh}_3)\text{Cl}]$  and  $\text{AgSbF}_6$ .<sup>7</sup>



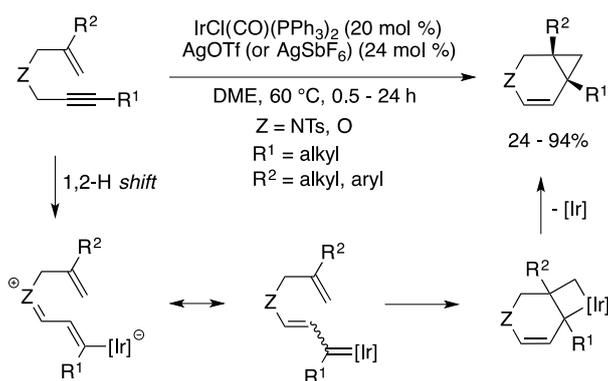
**Scheme 5.** Au-catalyzed cycloisomerization of allyl propargyl sulfonamides

Shibata group<sup>8</sup> make use of cationic iridium species generated from  $\text{IrCl}(\text{CO})(\text{PPh}_3)_2$  and  $\text{AgSbF}_6$  (or  $\text{AgOTf}$ ) for the conversion of heteroatom-linked 1,6-enynes to

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

<sup>8</sup> a) T. Shibata, Y. Kobayashi, S. Maekawa, N. Toshida, K. Takagi, *Tetrahedron* **2005**, *61*, 9018-9024. See also: b) M. Barbazanges, M. Augé, J. Moussa, H. Amouri, C. Aubert, C. Desmarets, L. Fensterbank, V. Gandon, M. Malacria, C. Ollivier, *Chem Eur. J.*, **2011**, *17*, 13789-13794; c) E. Benedetti, A. Simmoneau, A. Hours, H. Amouri, A. Penoni, G. Palmisano, M. Malacria, J.-P. Goddard, L. Fensterbank, *Adv. Synth. Catal.* **2011**, *353*, 1908-1912; d) M. Dieckmann, Y.-S. Jang, N. Cramer, *Angew. Chem. Int. Ed.* **2015**, *54*, 12149-12152.

3-aza(oxa)bicyclo[4.1.0]heptenes compounds in moderate to excellent yields (Scheme 6). However, enynes capped with a phenyl group at alkyne failed to react even in refluxed dimethoxyethane. A mechanism involving iridacarbene intermediates was suggested on the basis of related Pt(II)-catalyzed cycloisomerization<sup>9</sup> (Scheme 3). However, the high catalyst and silver salts loadings limited further interest to use iridium catalysts for synthetic applications.



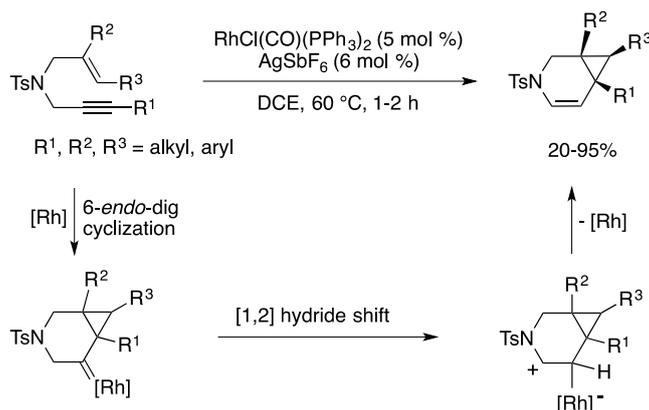
**Scheme 6.** Ir-catalyzed cycloisomerization of heteroatom-tethered 1,6-enynes

Kim and Chung reported a systematic study on cycloisomerization reactions of allyl propynyl tosylamides promoted by rhodium complexes.<sup>10</sup> Various 3-azabicyclo[4.1.0]heptene derivatives were easily synthesized through *in situ* generated cationic rhodium species  $[\{\text{Rh(CO)(PPh}_3)_2\}\text{SbF}_6]$  (Scheme 7). Despite large scope of enyne substrates, it was showcased that the substitution patterns at both alkyne and alkene moieties have a major influence on the efficiency of the bicycloannulation. On the basis of related investigations with group VIII transition metals,<sup>11</sup> a mechanism involving a rhodium-mediated 6-*endo*-dig cyclization, followed by [1,2]-hydride shift was suggested.

<sup>9</sup> M. Méndez, M. P. Muñoz, C. Nevado, D. J. Cárdenas, A. M. Echavarren, *J. Am. Chem. Soc.* **2001**, *123*, 10511-10520.

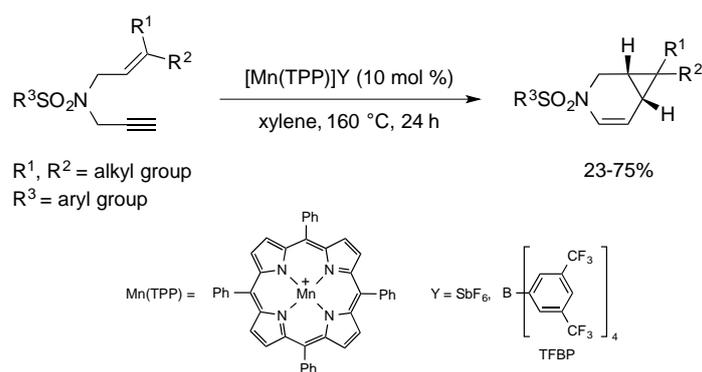
<sup>10</sup> S. Y. Kim, Y. K. Chung, *J. Org. Chem.* **2010**, *75*, 1281-1284.

<sup>11</sup> L. Zhang, J. Sun, S. A. Kozmin, *Adv. Synth. Catal.* **2006**, *348*, 2271-2296.



**Scheme 7.** Rh-catalyzed cycloisomerization of *N*-tethered 1,6-enynes

In 2012, Kurahashi and co-workers introduced cationic manganese(III) porphyrins  $[\text{Mn}(\text{TPP})]^+$  as new catalysts for these cycloisomerization reactions under harsh conditions<sup>12</sup> (Scheme 8). The use of a weakly coordinated axial counteranion ligand is crucial to enhance the electrophilicity of manganese, and hence to activate the triple bond. The product selectivity depends on the nature of the counteranion, for instance TFPB or  $\text{SbF}_6$  tend to promote the formation of cyclopropanation adducts whereas metathesis product was preferentially formed with OTf as ligand (now showed). Interestingly, the sulfonyl motif is mandatory to achieve bicycloannulation. In contrast, aniline-tethered enynes release metathesis adducts regardless of the choice of catalysts.



**Scheme 8.** Mn-catalyzed cycloisomerization of 1,6-enynes

Theoretical studies by DFT calculations conducted by Echavarren<sup>7</sup> Soriano<sup>13</sup> and

<sup>12</sup> T. Ozawa, T. Kurahashi, S. Matsubara, *Org. Lett.* **2012**, *14*, 3008-3011.

<sup>13</sup> E. Soriano, P. Ballesteros, J. Marco-Contelles, *Organometallics* **2005**, *24*, 3172-3181.

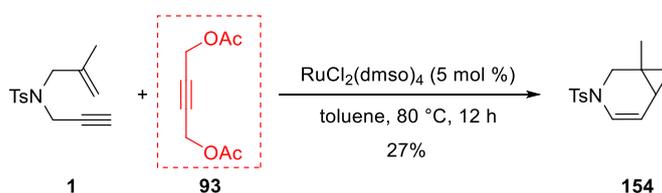
Marco-Contelles<sup>14</sup> supported a unified mechanistic sketch based on the metal-promoted electrophilic activation of the alkyne triggering the intramolecular nucleophilic attack of the alkene to form the vinylcyclopropane intermediate in line with the Fürstner<sup>6b</sup> proposal.

Synthetic applications using these bicyclo[4.1.0]heptenes for complex (poly)oxacycle,<sup>15a</sup> medium to large ring fused carbocycles and macrolactones<sup>15b</sup> as well as medium-sized ketone synthesis<sup>15c</sup> appeared but still remains scarce.

## 4.2 Ruthenium-Catalyzed Cycloisomerization of *N*-Tethered 1,6-Enynes: Access to Aza-Bicyclo[4.1.0]heptenes

### 4.2.1 Initial exploratory experiments

During the screening of Ru(II) catalysts involved in [2+2+2] cycloaddition reaction of enynes and alkynes (see Chapter III), we found that RuCl<sub>2</sub>(dmsO)<sub>4</sub> was able to cycloisomerize 1,6-enyne **1** into azabicyclic[4.1.0]heptene adduct **154** in 27% yield, while leaving intact the alkyne partner **93** (Scheme 9).



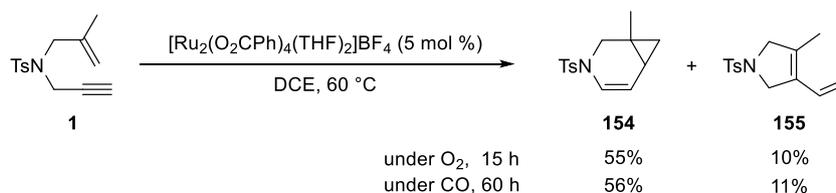
**Scheme 9.** Ru-catalyzed cycloisomerization of 1,6-enyne

Although interesting, this unexpected result could not be improved by changing the reaction conditions. A survey of the literature showed that Pt- and Au-based complexes are, among others, far better catalysts for these cycloisomerizations which are unique for heteratom-tethered 1,6-enynes. Chatani and co-workers described a *single example* of such cycloisomerization by using a well-defined cationic ruthenium dimer complex (Scheme 10).<sup>16</sup>

<sup>14</sup> E. Soriano, J. Marco-Contelles, *J. Org. Chem.* **2005**, *70*, 93345-9353.

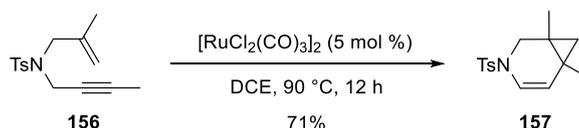
<sup>15</sup> a) C. Nevado, C. Ferrer, A. M. Echavarren, *Org. Lett.*, **2004**, *6*, 3191-3194; b) S. M. Stevenson, E. T. Newcomb, M. Ferreira, *Chem. Commun.*, **2014**, *50*, 5239-5241; c) S. Y. Kim, S. I. Lee, S. Y. Choi, Y. K. Chung, *Angew. Chem. Int. Ed.* **2008**, *47*, 4914-4917.

<sup>16</sup> N. Takahiro, Y. Tomohiko, K. Motonobu, F. Yoshiya, C. Naoto, *Chem. Lett.* **2013**, *42*, 1565-1567.



**Scheme 10.** Ru-catalyzed cycloisomerization of 1,6-enyne

Considering that these reactions are best performed with highly electrophilic and alkynophilic metal complexes, we looked for ruthenium complexes showing such properties. Therefore, the commercially available dimer complex  $[\text{RuCl}_2(\text{CO})_3]_2$  was selected because it contains good  $\pi$  acceptor CO ligands<sup>17</sup> and halide ligands as both good  $\sigma$ - and  $\pi$ -donors which ensure through their electronegativity an electrophilic character. We were however aware that  $[\text{RuCl}_2(\text{CO})_3]_2$  was reported to be effective for metathesis of regular enynes to produce 1-vinyl cycloalkenes.<sup>18</sup> This event can be overcome if enynes are capped with a substituent at the alkyne. Thus, 1,6-enyne **156** with a methyl group on its alkyne terminus was selected as the benchmark substrate for our investigations. To our delight, treatment of 1,6-enyne **156** with a catalytic amount of  $[\text{RuCl}_2(\text{CO})_3]_2$  in DCE at 90 °C afforded the expected heterobicyclic **157** in 71% isolated yield (Scheme 11).



**Scheme 11.**  $[\text{RuCl}_2(\text{CO})_3]_2$ -catalyzed cycloisomerization of 1,6-enyne **156**

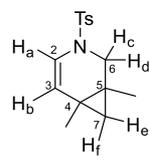
#### 4.2.2 Structural identification of bicyclic **157**

The structure characterization of **157** was established by  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectroscopy and the data matched with those reported by Fürstner.<sup>6</sup> Pertinent NMR data are compiled in Scheme 12. The 3 methyl groups resonate as singlets at  $\delta$  1.10 (6H, cyclopropyl) and 2.41 (Ts) and 2 distinct geminal protons ( $\text{H}_c$  and  $\text{H}_d$ ) were observed as doublets with a coupling constant  $J_{gem} = 11.3$  Hz at  $\delta$  3.76 and 2.68 respectively. Two distinct doublets at  $\delta$  0.72 and

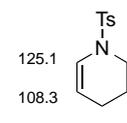
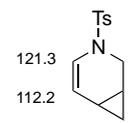
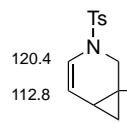
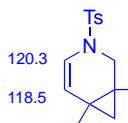
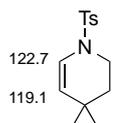
<sup>17</sup> R. H. Crabtree, in *The Organometallic Chemistry of the Transition Metals*, John Wiley & Sons, Inc., **2014**, pp. 98-133.

<sup>18</sup> N. Chatani, T. Morimoto, T. Muto, S. Murai, *J. Am. Chem. Soc.* **1994**, *116*, 6049-6050.

0.31 with coupling constant  $J_{gem} = 3.8$  Hz accommodate with the cyclopropane protons and the ethylenic protons are in a *cis* relationship ( $J = 7.8$  Hz) at  $\delta$  6.25 and 5.17. The normal  $^{13}\text{C}$  NMR and DEPT-135 data proved to be fully consistent with the bicyclic structure. We noticed close values of the chemical shifts of double bond carbons, which resulted from antagonist effects between an electron-withdrawing substituent (NTs) and an electron-rich quaternary carbon substituent C(4). More specifically,  $\beta$ -substituents effects of alkyl groups at C(4) cause substantial downfield shift of C(3).<sup>19</sup> Similar effects observed on related cyclic enesulfonamides<sup>6b, 20-21</sup> are compiled in Scheme 13.

	$^1\text{H}$ NMR	$^{13}\text{C}$ NMR
		H <sub>a</sub> 6.25 (d, $J = 7.8$ Hz, 1H) H <sub>b</sub> 5.17 (d, $J = 7.8$ Hz, 1H) H <sub>c</sub> 3.76 (d, $J = 11.3$ Hz, 1H) H <sub>d</sub> 2.68 (d, $J = 11.3$ Hz, 1H) H <sub>e</sub> 0.72 (d, $J = 3.8$ Hz, 1H) H <sub>f</sub> 0.31 (d, $J = 3.8$ Hz, 1H)

**Scheme 12.** Typical NMR data for compound **157**

				
Dd	16.8 <sup>[20]</sup>	9.1 <sup>[7b]</sup>	1.8	3.6 <sup>[21]</sup>

**Scheme 13.**  $^{13}\text{C}$  NMR data for cyclic enesulfonamides related to **157**

#### 4.2.3 Optimization of the ruthenium-catalyzed cycloisomerization of 1,6-enynes

The reaction conditions of the cycloisomerization of **156** as model substrate, including solvent, temperature and additives, were screened for optimization and the results are summarized in Table 1. *The reaction temperature was set up at 90 °C since the rate of reaction drop down at lower temperatures and no conversion was observed at 60 °C.* First, we examined the solvent ability, with emphasis on polarity and coordination properties, to effect the reaction. Toluene, as a typical solvent in cycloisomerization reactions, proved to be effective for this transformation and **157** was isolated in 66% yield at 90 °C (entry 2). Polar

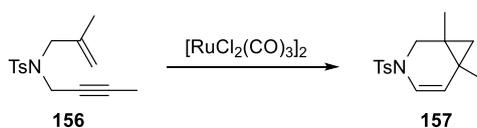
<sup>19</sup> H. O. Kalinowski, S. Berge, S. Braun, in *Carbon-13 NMR Spectroscopy*, John Wiley & Sons, Inc., **1988**, p. 109.

<sup>20</sup> M. Shao, L. Zheng, W. Qiao, J. Wang, J. Wang, *Adv. Synth. Catal.* **2012**, 354, 2743 – 2750.

<sup>21</sup> M. Lecomte, G. Evano, *Angew. Chem. Int. Ed.* **2016**, 55, 4547–4551.

and coordinating solvents of ruthenium, such as DMA<sup>22</sup> and CH<sub>3</sub>CN, as well as protic ones (EtOH) shut down the reaction (entry 3-5). Gratifyingly, 1,4-dioxane proved the best to yield 80% of **5** (entry 6). Increasing the reaction temperature at 110 °C did not enhance the yield of **5** (entry 7) and showed that the cycloisomer is stable under harsh conditions. This turned to be advantageous in substrate scope studies for cases which required higher temperatures.

**Table 1.** Screening of reaction conditions<sup>[a]</sup>



Entry	Solvent	Additive	Temperature (°C)	Yield <sup>[b]</sup>
1	dichloroethane	-	90	71
2	toluene	-	"	66
3	dimethylacetamide	-	"	NR
4	acetonitrile	-	"	NR
5	ethanol	-	"	NR
6	1,4-dioxane	-	"	80
7	"	-	110	81
8	"	PPh <sub>3</sub> (0.04 mmol)	"	76
9	"	CO atmosphere	"	69
10	"	AgSbF <sub>6</sub> (10 mol %)	"	39
11	"	NMO <sup>[c]</sup> (10 mol%)	"	29
12 <sup>[d]</sup>	"	CO atmosphere	"	56 <sup>[e]</sup> (74) <sup>[f]</sup>

<sup>[a]</sup> Reaction conditions: **156** (0.4 mmol), [RuCl<sub>2</sub>(CO)<sub>3</sub>]<sub>2</sub> (0.02 mmol), solvent (1 mL), 12 h; <sup>[b]</sup> Yields of isolated product; <sup>[c]</sup> NMO = trimethylamine *N*-oxide; <sup>[d]</sup> 2.5 mol % of catalyst; <sup>[e]</sup> 23 % of **156** recovered; <sup>[f]</sup> brsm yield. NR = no reaction, brsm = based on recovered starting material.

We then examined the effects of additives. The addition of external ligand, such as PPh<sub>3</sub>, had no significant influence on this catalytic reaction, as 76% of **157** was isolated (entry 8). On

<sup>22</sup> B. R. James, L. D. Markham, B. C. Hui, G. L. Rempel, *J. Chem. Soc. Dalton*, **1973**, 2247-2252.

the basis of Chatani reports,<sup>18</sup> testifying that  $[\text{RuCl}_2(\text{CO})_3]_2$ -catalyzed reactions carried out under CO atmosphere can be significantly improved, such an effect was not beneficial in our hands, and conversely, a slightly decreased yield of **157** was recorded (entry 9). The *in situ* generation of cationic ruthenium species from  $[\text{RuCl}_2(\text{CO})_3]_2$  and  $\text{AgSbF}_6$  proved less efficient to give **157** with a dropped yield of 39% yield (entry 10).

We also combined  $[\text{RuCl}_2(\text{CO})_3]_2$  with trimethylamine *N*-oxide (NMO) to generate active species. NMO has been used as efficient promoter of the Pauson-Khand reaction.<sup>23</sup> It is presumed that this reagent oxidizes a coordinated CO ligand to  $\text{CO}_2$ .<sup>24</sup> As a result,  $\text{CO}_2$  is a very poor sigma donor compared to CO, and its ability to function as a ligand is rather weak, thus providing free coordination site for an incoming unsaturated ligand. This turned out to be quite disappointing with the ruthenium carbonyl complex/NMO system which provided **157** with only 29% yield (entry 11). It is possible that the NMO partially oxidizes the ruthenium, thus rendering it inactive. The yield of **157** remains quite fair (56%) using a catalyst charge of 2.5 mol % and carrying out the reaction under CO atmosphere at 110 °C (entry 12).

#### 4.2.4 Scope of substrates

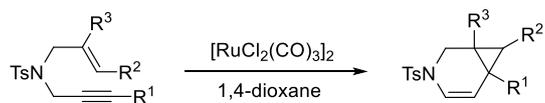
Having in hand a satisfactory set of reaction conditions ( $[\text{RuCl}_2(\text{CO})_3]_2$ , 1,4-dioxane, 90-110 °C), we then investigated the scope of the present ruthenium-catalyzed cycloisomerization of nitrogen-tethered 1,6-enynes with emphasis on the substitution patterns of substrates.

##### Scope of 1,6-enynes featuring internal alkynes

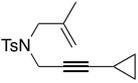
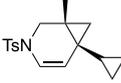
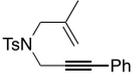
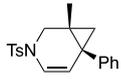
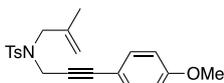
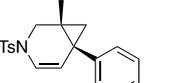
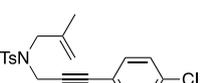
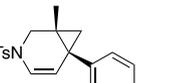
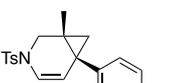
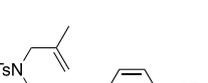
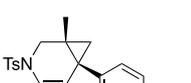
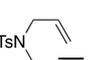
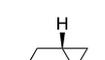
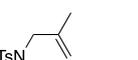
The Ru-catalyzed cycloisomerization of 1,6-enynes capped with alkyl, cycloalkyl or aryl substituents at sp carbon atom was primarily investigated under the optimized reaction conditions; the results are shown in Table 2.

<sup>23</sup> S. Shambayati, W. E. Crowe, S. L. Schreiber, *Tetrahedron Lett.* **1990**, *31*, 5289-5292.

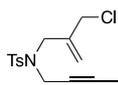
<sup>24</sup> a) M. O. Albers, N. J. Coville, *Coord. Chem. Rev.* **1984**, *53*, 227-259; b) J.-K. Shen, Y.-C. Gao, Q.-Z. Shi, F. Basolo, *Organometallics* **1989**, *8*, 2144-2147.

**Table 2.** [RuCl<sub>2</sub>(CO)<sub>3</sub>]<sub>2</sub>-catalyzed cycloisomerization of 1,6-enynes featuring internal alkynes

Entry	1,6-Enyne	T (°C), t (h/d)	Product	Yield (%) <sup>[b]</sup>
1	 <b>158</b>	90 °C, 12 h	 <b>173</b>	67
2	 <b>159</b>	90 °C, 2.5 d	 <b>174</b>	84
3	 <b>160</b>	110 °C, 2 d	 <b>175</b>	74
4	 <b>161</b>	110 °C, 2.5 d	 <b>176</b>	92
5	 <b>162</b>	90 °C, 36 h	 <b>177</b>	65
6	 <b>163</b>	90 °C, 1.5 d	 <b>178</b>	78

7		110 °C, 5 d		51
	<b>164</b>		<b>179</b>	
8		110 °C, 2 d		80
	<b>165</b>		<b>180</b>	
9		110 °C, 2 d		85
	<b>166</b>		<b>181</b>	
10		110 °C, 3 d		84
	<b>167</b>		<b>182</b>	
11		110 °C, 4 d		73
	<b>168</b>		<b>183</b>	
12		110 °C, 4 d		71
	<b>169</b>		<b>184</b>	
13		90 °C, 12 h		trace
	<b>170</b>		<b>185</b>	
14		110 °C, 4 d	-	-
	<b>171</b>			

15



110 °C, 4 d

decomposition

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**172**

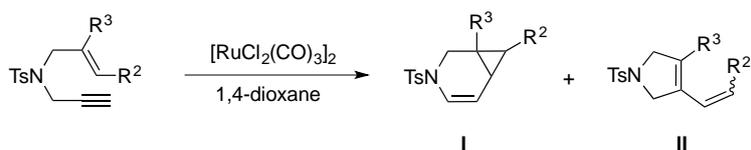
<sup>[a]</sup> Reaction conditions: enyne (0.4 mmol), [RuCl<sub>2</sub>(CO)<sub>3</sub>]<sub>2</sub> (0.02 mmol), 1,4-dioxane (1 mL). <sup>[b]</sup> Isolated yield.

In most of the cases, the reactions are quite slow and the temperature has been adjusted for optimal conversion. Firstly, 1,6-enynes bearing a methyl group on the triple bond were satisfactorily converted to the bicycloisomers **173-178** in good to excellent yields (entries 1-6). Of note, the highest yields was observed for enyne **161** featuring an intracyclic double bond (entry 4). Interestingly, enyne **158** with the nucleophilic allylsilane subunit was well tolerated thus giving cycloisomer **173** in 67% isolated yield (entry 1). As previously noticed for cycloisomerization with different transition metal catalysts,<sup>6b,8c</sup> the stereochemical information of the double bond of enynes **162** and **163** is integrally transmitted on the formed cycloisomers **177** (65%) and **178** (78%), respectively (entries 5-6). It is worth noting that the enyne **164** capped with a cyclopropyl group on the triple bond reacted very sluggishly and released the tricyclic compound **179** in fair yield (entry 7). This compound has been used as precursor of medium-sized ketones through rhodium-catalyzed carbonylation reaction.<sup>15c</sup> Enynes bearing an aromatic group on the alkyne motif reacted satisfactorily giving the expected products with good to very good yields (entry 8-12). It is worth to emphasize that an electron-donating or electron-withdrawing substituent attached to the aryl group has little influence on the efficiency of reaction (entries 9-12). For instance, the reactions are retarded for enynes **167-169** compared to **165-166**, the latter being formed in slightly better yields. Functional groups such as ether, halide, and nitro are well tolerated with the ruthenium carbonyl catalyst (entries 9-11). The cycloisomerization has some limitations. For instance the TMS-substituted enyne **171** was recovered unchanged, even under prolonged reaction time (entry 14) and enyne **172** with an electrophilic subunit is not tolerated under the reaction conditions, and led to decomposition products (entry 15). We presumed that the bulky trimethylsilyl group of **171**, compared to the methyl, prevents the coordination of the alkyne to the ruthenium center.

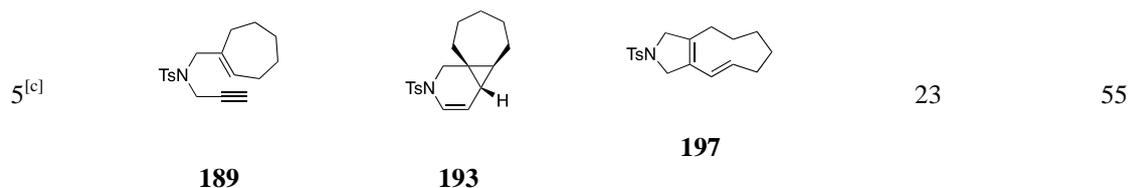
## Scope of enynes featuring a terminal alkyne subunit

To expand the scope of the present cycloisomerization, various enynes without substitution at the propynyl side chain were afterwards examined. In contrast with the cycloisomerization of enynes bearing internal alkynes (Table 2), these substrates provided both azabicyclo[4.1.0]heptene (**I**) and metathesis products (**II**).

**Table 3.** [RuCl<sub>2</sub>(CO)<sub>3</sub>]<sub>2</sub>-catalyzed cycloisomerization of ‘terminal’1,6-enynes



Entry	Enyne	Product (I)	Product (II)	Yield (%) <sup>[b]</sup>	
				I	II
1				9	traces
	<b>186</b>	<b>190</b>	<b>194</b>		
2				40	26
	<b>187</b>	<b>191</b>	<b>195</b>		
3				41	8
	<b>188</b>	<b>192</b>	<b>196</b>		
4				51	27
	<b>1</b>	<b>154</b>	<b>155</b>		



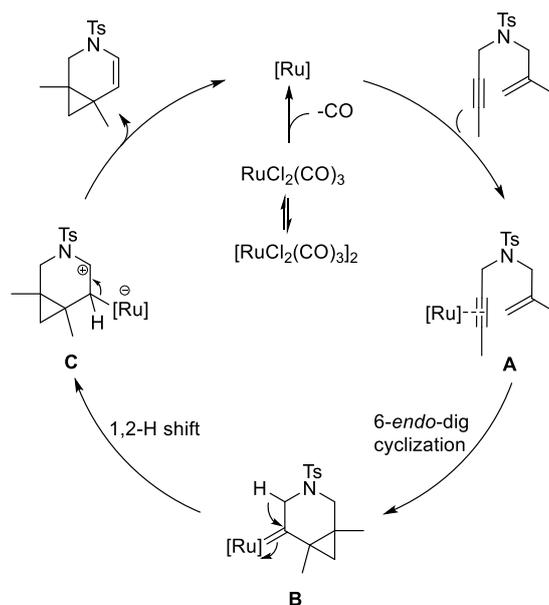
<sup>[a]</sup> Reaction condition: enyne (0.4 mmol), [RuCl<sub>2</sub>(CO)<sub>3</sub>]<sub>2</sub> (0.02 mmol), 1,4-dioxane (1 mL), 90 °C, 12 h. <sup>[b]</sup> Isolated yield. <sup>[c]</sup> Reaction time: 24 h.

The unsubstituted 1,6-enyne **186** proved to be a poorly reactive substrate in cycloisomerization reaction forming **190** in only 9% yield and trace amounts of diene **194** (entry 1). Enynes with substitution on either the external or internal carbon atom of double bond give the bicyclic compounds type **I** as major products along with type **II** products (entries 2-4). At the contrary, enyne **189** with an intracyclic double bond behaves differently since metathesis product **197** was observed as major product (entry 5). On the basis of above catalytic results, it can be seen that “internal” enynes are prone to undergo 6-*endo*-dig cyclization, whilst “terminal” enynes undergo 6-*endo*-dig and 5-*exo*-dig cyclizations.

#### 4.2.5 Mechanism proposal

##### Typically catalytic cycle of the cycloisomerization reaction

On the basis of reports on cycloisomerization with platinum<sup>6</sup> and gold<sup>7</sup> catalysts and DFT calculations,<sup>7</sup> a similar mechanism involving ruthenacarbene intermediates can be proposed as outlined in Scheme 14.

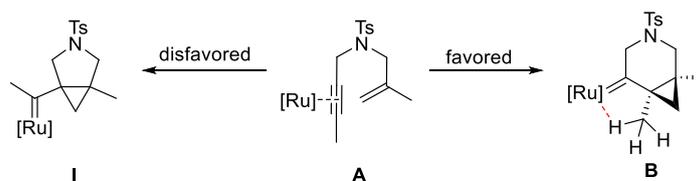


**Scheme 14.** Mechanism of the cycloisomerization of 1,6-enynes

Solvent-induced dissociation of dimeric  $[\text{RuCl}_2(\text{CO})_3]_2$  to the monomeric form  $\text{RuCl}_2(\text{CO})_3$ , and subsequent release of a CO ligand might generate the coordinatively unsaturated species  $[\text{RuCl}_2(\text{CO})_2]$ , represented as  $[\text{Ru}]$ . Coordination of the alkyne to the  $[\text{Ru}]$  species could give  $\pi$ -complex **A**, which upon 6-*endo*-dig cyclization would release ruthenacarbene intermediate **B**. Finally, **B** would undergo a 1,2-hydride shift and then metal elimination to yield the azabicyclic structure. It has been observed that the reaction rate of enynes bearing methyl group is relatively faster compared with enynes bearing aromatic group. A plausible explanation could be ascribed to the conjugation of alkyne with the aromatic group, which can stabilize the  $\pi$ -complex intermediate **A**.

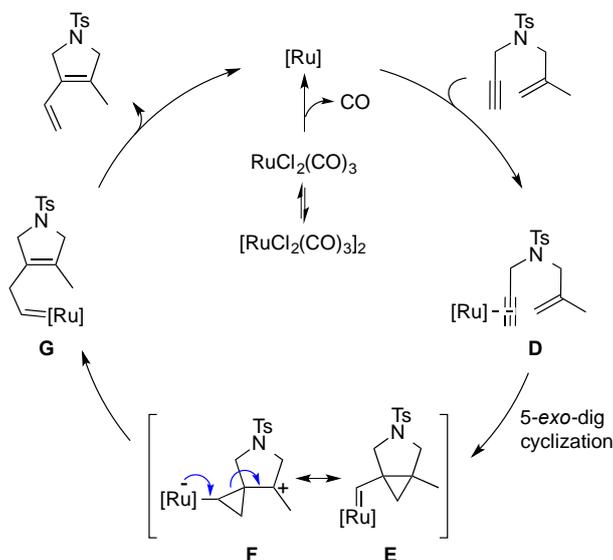
Thus, the formation of ruthenium carbene **B** could be favored considering agostic interaction between the ruthenium and C-H bond,<sup>25</sup> which might stabilize **B**, as outlined in Scheme 15. Therefore, the cycloisomerization proceeded smoothly toward the formation of azabicyclo[4.1.0]heptenes, and metathesis pathway can be prevented.

<sup>25</sup> S. J. La Placa, J. A. Ibers, *Inorg. Chem.* **1965**, *4*, 778-783.



**Scheme 15.** Plausible intermediates formed in Ru-catalyzed cycloisomerization of 1,6-enynes

In addition to the above mechanistic analysis of formation of bicyclic [4.1.0]heptenes, the formation of metathesis adducts observed from enynes featuring terminal alkynes should be considered (Scheme 16). With the same initially generated ruthenium species, 5-*exo*-dig cyclization of enyne can form the cyclopropyl ruthenacarbene intermediate **E** which might undergo rearrangement to generate **F**, represented under its canonical (zwitterionic) structure **F**. Further rearrangement through metal assistance and cyclopropane cleavage produces the ruthenacarbene **G**. Finally, metal elimination releases the metathesis product which arises through the single C-C bond cleavage mechanism.



**Scheme 16.** Mechanism of the cycloisomerization of 1,6-enynes to give metathesis product

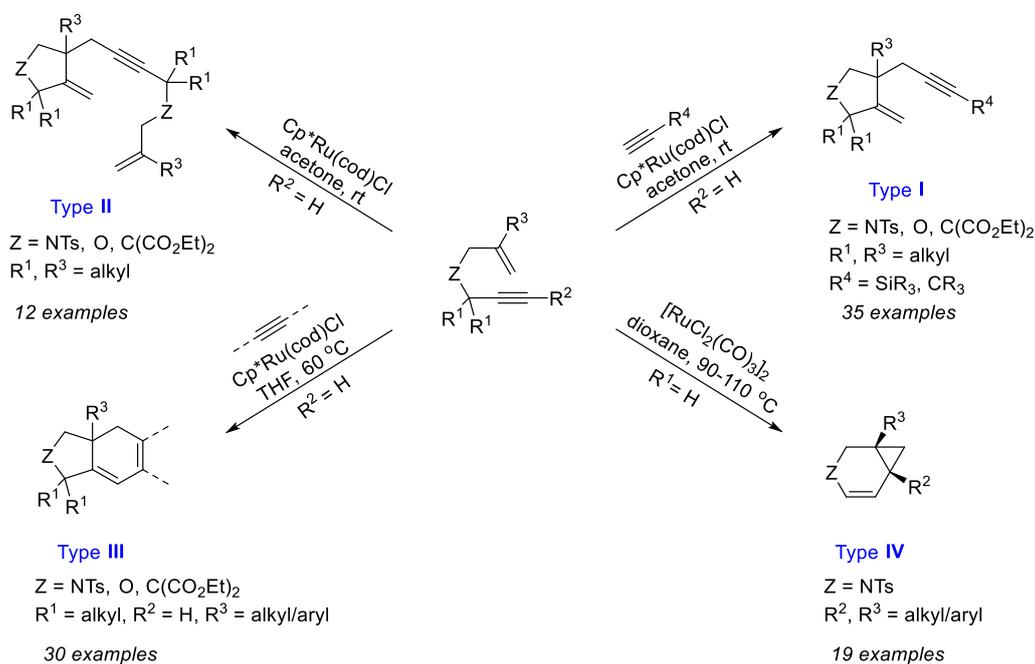
### 4.3 Conclusion

In summary, the ruthenium-catalyzed cycloisomerization of *N*-tethered 1,6-enynes to form azabicyclo[4.1.0]heptenes derivatives was successfully achieved through the use of the commercially available  $[\text{RuCl}_2(\text{CO})_3]_2$  complex. Compared to related cycloisomerizations

mostly described with cationic Pt or Au catalysts, the reactions with  $[\text{RuCl}_2(\text{CO})_3]_2$  require higher temperatures and longer reaction times. However, a higher yield was observed in the presence of cheaper ruthenium complex. Scope investigations indicated that *N*-linked enynes with terminal/internal alkyne unit could be tolerated in such an event. Substitution pattern on either alkyne or alkene have no major influence on the yield of cycloisomers. A plausible mechanism involving the formation of cyclopropyl ruthenacarbenes is proposed. In addition, the different behavior of terminal enynes rests on two competitive initial cyclizations.

## **General Conclusion**

In summary, we have developed three cyclization reactions of 1,6-enynes promoted by commercially available ruthenium complexes as catalysts. We investigated the co-cyclization reaction of 1,6-enynes with alkynes using an electron-rich ruthenium complex  $\text{Cp}^*\text{Ru}(\text{cod})\text{Cl}$  as the catalyst. The structure of cyclized products depends on the nature and structural patterns of the alkyne units. We also described the cycloisomerization of *N*-tethered 1,6-enynes to access 3-azabicyclo[4.1.0]hept-1-enes in the presence of the alkynophilic  $\pi$ -acidic ruthenium complex  $[\text{RuCl}_2(\text{CO})_3]_2$ .



The coupling reaction of 1,6-enynes and bulky-substituted alkynes catalyzed by the neutral ruthenium complex  $\text{Cp}^*\text{Ru}(\text{cod})\text{Cl}$  under mild conditions affords five-membered cyclic compounds featuring a 1,5-enyne motif (type **I**) in moderate to excellent yields. Control and deuterium labelling experiments suggested that this reaction proceeds through ruthenacyclopentene intermediate which might be followed by metal-assisted  $\sigma$ -bond metathesis as the key step. The cyclization/coupling reaction is controlled by the steric hindrance of alkyne that prevents its insertion into the ruthenacycle intermediate, thus disfavoring the *cross*-[2+2+2] cycloaddition pathway. Interestingly, in the absence of alkyne partners, 1,6-enynes can undergo the *self*-hydroalkynylation cyclization to release type **II** adducts. This unprecedented

cyclization reaction illustrates a rare example of late transition metal-assisted  $\sigma$ -bond metathesis as a key step.

Using the same catalyst  $\text{Cp}^*\text{Ru}(\text{cod})\text{Cl}$ , 1,6-enynes are capable to undergo the *cross*-[2+2+2] cycloaddition reaction when relatively less bulky alkynes were employed as co-reactants. Alkynes featuring various functional groups, such as ester, ether, carbamates, halides and even free alcohol, are compatible for the present [2+2+2] carbocyclization reactions. The use of tertiary propargyl alcohol which provided [2+2+2] cycloadducts as single regioisomers is a noteworthy achievement of these cycloadditions. The observed regioselectivity can be rationalized on the basis of interligand interactions through H-bonding between the hydroxyl proton and halogen of the complex and/or non-bonded interactions between the alkyl groups of substrates. The mechanism of formation of cycloadducts might involve either ruthenacyclopentene or ruthenacyclopentadiene intermediates according to the mode of coupling of the unsaturated motifs. The observed results inclined us to favor the former intermediate.

In the presence of electrophilic and alkynophilic ruthenium complex  $[\text{RuCl}_2(\text{CO})_3]_2$  as catalyst, *N*-tethered 1,6-enynes can be easily converted into 3-azabicyclo[4.1.0]hept-1-enes. These cycloisomerizations are well documented with gold and platinum catalyst, but not described with a ruthenium catalyst able to display similar requirements of electro- and alkynophilicity. The reactions utilizing 1,6-enynes bearing a substituent at its alkyne terminus exclusively lead to the bicyclic adducts in high yields, whereas 1,6-enynes integrating terminal alkyne yielded both 3-azabicyclo[4.1.0]hept-1-enes and vinylcyclopentenenes as metathesis products.

## **Experimental Part**

## General Information

All reactions, unless otherwise stated, were carried out under argon atmosphere using oven-dried (120 °C) glasswares. Reaction solvents were degassed and purified according to the standard procedures.<sup>1</sup> Toluene was distilled from lithium aluminum hydride. Diethyl ether and THF 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. All ruthenium complexes were purchased and used as received. Analytical TLC was performed on ready-made plates coated with silica gel on aluminum (Merck 60 F<sub>254</sub>) using UV light and *p*-anisaldehyde with heating as developing agent.

Flash chromatography was performed using E. Merck silica gel 60 (230-400 mesh) according to the protocol of Still, Khan and Mitra.<sup>2</sup> <sup>1</sup>H NMR spectra were recorded on either a Bruker Avance DPX-300 or DPX-400 spectrometer as solutions in Chloroform-*d* (CDCl<sub>3</sub>), unless otherwise indicated. Chemical shifts are given in parts per million ( $\delta$  units) downfield from tetramethylsilane using the residual solvent signal (CHCl<sub>3</sub> 7.26, benzene 7.15) as internal standard. <sup>1</sup>H 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 broadened. Carbon (<sup>13</sup>C) NMR spectra are reported in ppm ( $\delta$ ) relative to residual CHCl<sub>3</sub> ( $\delta$  77.36) unless otherwise noted. High-resolution mass spectra (HRMS) were performed at the “Spectropôle” of Aix Marseille Université.

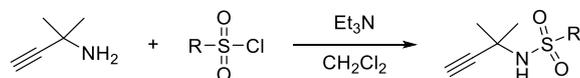
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<sup>1</sup> Armarego, W. L. F.; Chai, C. L. L. *Purification of Laboratory Chemicals, 5th Ed*; Butterworth Heinemann: New York, 2003.

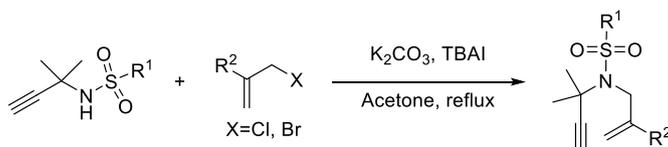
<sup>2</sup> Still, W. C.; Khan, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923-2925.

## Part I. Ruthenium-Catalyzed Hydroalkynylative Cyclization of 1,6-Enynes with Alkynes

### Procedure A<sup>3</sup>

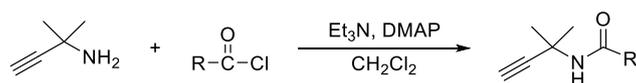


To a solution of 2-methyl-3-butyn-2-amine (10 mmol) and Et<sub>3</sub>N (20 mmol) in dry dichloromethane (30 mL) was added gradually the sulfonyl chloride (12 mmol) at 0 °C. Upon the completion of addition, the reaction solution was stirred overnight. Then the reaction mixture was washed with 10% HCl solution (50 mL), brine (30 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and evaporated under vacuum. Purification by flash chromatography over silica gel afforded the desired sulfonamide.



To a solution of sulfonamide (2 mmol) in acetone was added the allylic halide (4 mmol), potassium carbonate (4 mmol) and tetrabutylammonium iodide (0.2 mmol). The reaction solution was stirred overnight at 60 °C. The solvent was evaporated under vacuo. The residue was taken up in ethyl acetate, washed with distilled water (50 mL), brine (30 mL) and then dried over Na<sub>2</sub>SO<sub>4</sub>, concentrated under vacuo. The crude product was purified by flash chromatography.

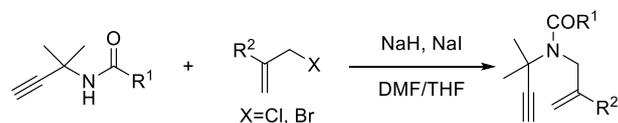
### Procedure B<sup>3</sup>



To a solution of 2-methyl-3-butyn-2-amine (10 mmol), Et<sub>3</sub>N (20 mmol) and DMAP (1 mmol) in dry dichloromethane (30 mL) was gradually added the alkanoyl chloride (12 mmol) at 0 °C. The reaction solution was stirred overnight at room temperature, and then was washed with

<sup>3</sup> Z. Ni, L. Giordano, A. Tenaglia, *Chem. Eur. J.* **2014**, *20*, 11703-11706.

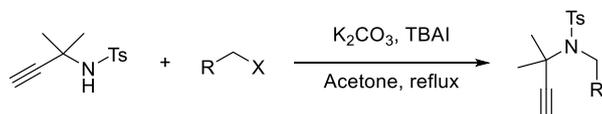
10% HCl (50 mL), brine (30 mL), and dried over Na<sub>2</sub>SO<sub>4</sub>. After evaporation of the solvent under vacuum, the residue was purified by flash chromatography.



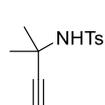
To a cooled (0 °C) suspension of sodium hydride (2 mmol) in THF/DMF (1/2, 20 mL) was slowly added the amide (2 mmol). The mixture was stirred for 1 h at 0 °C. Then, NaI (0.2 mmol) and allylic halide (2.2 mmol) were added. The mixture was warmed to rt and stirred until completion of the reaction (TLC monitoring). Saturated aqueous NH<sub>4</sub>Cl (30 mL) was added at 0 °C and the resulting mixture was extracted with Et<sub>2</sub>O (3 × 15 mL), washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated under vacuo. The crude residue was purified by column chromatography.

### Procedure C

#### *N*-Alkylation of 4-methyl-*N*-(2-methylbut-3-yn-2-yl)benzenesulfonamide



To a solution of 4-methyl-*N*-(2-methylbut-3-yn-2-yl)benzenesulfonamide (474.6 mg, 2 mmol) in acetone (20 mL) was added the alkyl halide (4 mmol), potassium carbonate (552.8 mg, 4 mmol) and tetrabutylammonium iodide (73.9 mg, 0.2 mmol). The resulting mixture was stirred overnight at 60 °C and then evaporated under vacuo. The residue was taken up in ethyl acetate (30 mL), washed with brine (30 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated under vacuo. The crude product was purified by flash chromatography.

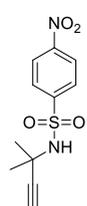


**4-Methyl-*N*-(2-methylbut-3-yn-2-yl)benzenesulfonamid** was prepared according to procedure **A**; obtained: 1.73 g (73%), white solid; *R<sub>f</sub>* (PE/Et<sub>2</sub>O =5: 5) 0.3.

<sup>1</sup>H NMR (400 MHz, Chloroform-*d*) δ 7.83 (d, *J* = 8.3 Hz, 2H), 7.30 (d, *J* = 8.1 Hz, 2H), 5.08 (br s, 1H), 2.44 (s, 3H), 2.11 (s, 1H), 1.56 (s, 6H).

$^{13}\text{C}$  NMR (75 MHz, Chloroform-*d*)  $\delta$  143.3 (C), 139.1 (C), 129.4 (CH x 2), 127.8 (CH x 2), 85.6 (C), 71.5 (CH), 50.0 (C), 31.0 (CH<sub>3</sub>), 21.8 (CH<sub>3</sub> x 2)

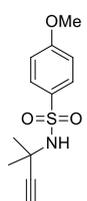
***N*-(2-Methylbut-3-yn-2-yl)-4-nitrobenzenesulfonamide** was prepared according to



procedure **A**; obtained: 1.45 g (54%), faint yellow solid;  $R_f$  (PE/Et<sub>2</sub>O =6: 4) 0.4.

$^1\text{H}$  NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  8.34 (d,  $J$  = 8.8 Hz, 2H), 8.11 (d,  $J$  = 8.8 Hz, 2H), 5.15 (s, 1H), 2.10 (s, 1H), 1.59 (s, 6H).

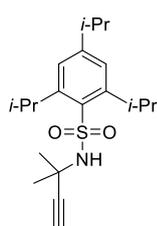
$^{13}\text{C}$  NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  150.3 (C), 147.6 (C), 129.2 (CH x 2), 124.2 (CH x 2), 84.8 (C), 72.5 (CH), 50.7 (C), 31.2 (CH<sub>3</sub> x 2).



**4-Methoxy-*N*-(2-methylbut-3-yn-2-yl)benzenesulfonamide** was prepared according to procedure **A**; obtained: 2.13 g (84%), white solid;  $R_f$  (PE/Et<sub>2</sub>O =6: 4) 0.2.

$^1\text{H}$  NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.84 (d,  $J$  = 8.9 Hz, 2H), 6.95 (d,  $J$  = 8.9 Hz, 2H), 4.82 (s, 1H), 3.86 (s, 3H), 2.10 (s, 1H), 1.54 (s, 6H).

$^{13}\text{C}$  NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  163.0 (C), 133.8 (C), 130.0 (CH x 2), 114.0 (CH x 2), 85.8 (C), 71.5 (CH), 55.9 (CH<sub>3</sub>), 50.0 (C), 31.0 (CH<sub>3</sub> x 2).

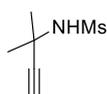


**2,4,6-Triisopropyl-*N*-(2-methylbut-3-yn-2-yl)benzenesulfonamide** was prepared according to procedure **A**; obtained: 1.47 g (42%), white solid;  $R_f$  (PE/Et<sub>2</sub>O =8: 2) 0.3.

$^1\text{H}$  NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.13 (s, 2H), 4.59 (s, 1H), 4.20 (hept,  $J$  = 6.7 Hz, 2H), 2.89 (hept,  $J$  = 6.9 Hz, 1H), 2.07 (s, 1H), 1.56 (s, 6H), 1.28 (d,  $J$  = 6.8 Hz, 12H), 1.24 (d,  $J$  = 6.9 Hz, 6H).

$^{13}\text{C}$  NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  152.9 (C), 150.2 (C x 2), 135.0 (C), 123.9 (CH x 2), 86.0 (C), 71.3 (CH), 50.6 (C), 34.5 (CH x 2), 31.1 (CH<sub>3</sub> x 2), 29.8 (CH), 25.1 (CH<sub>3</sub> x 4), 24.0 (CH<sub>3</sub> x 2).

**MS**  $m/z$  (ESI-MS) calcd. for ([M+Na<sup>+</sup>]): C<sub>20</sub>H<sub>31</sub>NO<sub>2</sub>SN<sup>+</sup> 372.20, Found 372.23.

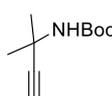


***N*-(2-Methylbut-3-yn-2-yl)methanesulfonamide** was prepared according to

procedure **A**; obtained: 1.45 g (90%), colorless oil;  $R_f$  (PE/Et<sub>2</sub>O =6: 4) 0.4.

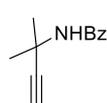
<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 4.72 (br s, 1H), 3.16 (s, 3H), 2.50 (s, 1H), 1.63 (s, 6H).

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 86.2 (C), 72.1 (CH), 50.1 (C), 42.9 (CH<sub>3</sub>), 31.4 (CH<sub>3</sub> x 2).

 **tert-Butyl (2-methylbut-3-yn-2-yl)carbamate** was prepared according to procedure **B**; obtained: 1.78 g (97%), colorless oil;  $R_f$  (PE/Et<sub>2</sub>O =6: 4) 0.2.

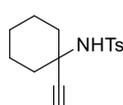
<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 4.75 (br s, 1H), 2.23 (s, 1H), 1.51 (s, 6H), 1.38 (s, 9H).

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 154.3 (C), 87.7 (C), 79.8 (CH), 68.9 (C), 47.2 (C), 29.7 (CH<sub>3</sub> x 2), 28.6 (CH<sub>3</sub> x 3).

 **N-(2-Methylbut-3-yn-2-yl)benzamine** was prepared according to procedure **B**; obtained: 1.69 g (90%), white solid;  $R_f$  (PE/Et<sub>2</sub>O =6: 4) 0.3.

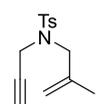
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.75 – 7.73 (m, 2H), 7.48 – 7.43 (m, 1H), 7.39 – 7.35 (m, 2H), 6.35 (brs, 1H), 2.37 (s, 1H), 1.74 (s, 6H).

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 166.8 (C), 135.0 (C), 131.7 (CH), 128.7 (CH x 2), 127.2 (CH x 2), 87.4 (C), 69.6 (CH), 48.2 (C), 29.3 (CH<sub>3</sub> x 2).

 **N-(1-Ethynylcyclohexyl)-4-methylbenzenesulfonamide** was prepared according to procedure **A**; obtained: 1.61 g (58%), white solid;  $R_f$  (PE/Et<sub>2</sub>O =6: 4) 0.3.

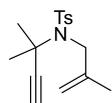
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.80 (d,  $J$  = 8.3 Hz, 2H), 7.26 (d,  $J$  = 8.0 Hz, 2H), 5.14 (s, 1H), 2.41 (s, 3H), 2.11 (s, 1H), 2.02 – 1.98 (m, 2H), 1.67 – 1.51 (m, 7H), 1.19 – 1.16 (m, 1H).

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 143.1 (C), 139.5 (C), 129.3 (CH x 2), 127.8 (CH x 2), 83.9 (C), 74.0 (CH), 54.4 (C), 38.9 (CH<sub>2</sub> x 2), 25.1 (CH<sub>2</sub>), 22.5 (CH<sub>2</sub> x 2), 21.7 (CH<sub>3</sub>).

 **4-Methyl-N-(2-methylallyl)-N-(prop-2-yn-1-yl)benzenesulfonamide(1)** was prepared according to Procedure **A**, obtained: 479 mg (91%), white solid;  $R_f$  (PE/Et<sub>2</sub>O =8: 2) 0.60.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.77 (d,  $J$  = 8.2 Hz, 2H), 7.32 (d,  $J$  = 8.1 Hz, 2H), 5.00 (s, 2H), 4.07 (d,  $J$  = 2.4 Hz, 2H), 3.76 (s, 2H), 2.45 (s, 3H), 1.98 (t, 1H), 1.78 (s, 3H).

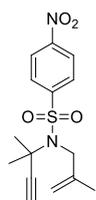
$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  143.5 (C), 139.2 (C), 136.1 (C), 129.4 (CH x 2), 127.8 (CH x 2), 115.5 ( $\text{CH}_2$ ), 76.3 (C), 73.7 (CH), 52.4 ( $\text{CH}_2$ ), 35.5 ( $\text{CH}_2$ ), 21.5 ( $\text{CH}_3$ ), 19.7 ( $\text{CH}_3$ ).



**4-Methyl-N-(2-methylallyl)-N-(2-methylbut-3-yn-2-yl) benzenesulfonamide (6)** was prepared according to procedure A; obtained: 542 mg (93%), white solid;  $R_f$  (PE/ $\text{Et}_2\text{O}$  =8: 2) 0.5.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.73 (d,  $J$  = 8.4 Hz, 2H), 7.26 (d,  $J$  = 8.4 Hz, 2H), 5.09 (s, 1H), 4.94 – 4.93 (m, 1H), 4.10 (s, 2H), 2.41 (s, 3H), 2.19 (s, 1H), 1.79 (s, 3H), 1.65 (s, 6H).

$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  143.3 (C), 143.2 (C), 139.4 (C), 129.5 (CH x 2), 127.8 (CH x 2), 112.5 ( $\text{CH}_2$ ), 86.1 (C), 72.0 (CH), 56.6 (C), 54.1 ( $\text{CH}_2$ ), 31.1 ( $\text{CH}_3$  x 2), 21.8 ( $\text{CH}_3$ ), 20.5 ( $\text{CH}_3$ ).



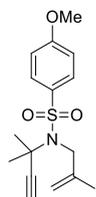
**N-(2-Methylallyl)-N-(2-methylbut-3-yn-2-yl)-4-nitrobenzenesulfonamide (11)** was prepared according to procedure A; obtained: 554 mg (86%), white solid;  $R_f$  (PE/ $\text{Et}_2\text{O}$  =8: 2) 0.5.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.32 (d,  $J$  = 8.9 Hz, 2H), 8.04 (d,  $J$  = 8.9 Hz, 2H), 5.06 (s, 1H), 4.98 (s, 1H), 4.16 (s, 2H), 2.24 (s, 1H), 1.80 (s, 3H), 1.68 (s, 6H).

$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  149.9 (C), 147.8 (C), 142.4 (C), 128.9 (CH x 2), 124.1 (CH x 2), 113.1 ( $\text{CH}_2$ ), 85.3 (C), 72.9 (CH), 56.8 (C), 54.0 ( $\text{CH}_2$ ), 30.9 ( $\text{CH}_3$  x 2), 20.3 ( $\text{CH}_3$ ).

IR (neat)  $\nu$ : 3282, 2988, 2945, 2112, 1528, 1347, 1088, 854, 737, 564  $\text{cm}^{-1}$ .

MS  $m/z$  (ESI-MS) calcd. for ( $[\text{M}+\text{H}^+]$ ):  $\text{C}_{15}\text{H}_{19}\text{N}_2\text{O}_4\text{S}^+$  323.11, Found 323.12.



**4-Methoxy-N-(2-methylallyl)-N-(2-methylbut-3-yn-2-yl)benzenesulfonamide (12)** was prepared according to procedure A; obtained: 553 mg (90%), white solid;  $R_f$  (PE/ $\text{Et}_2\text{O}$  =7: 3) 0.3.

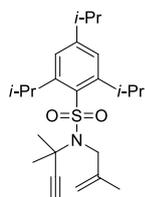
$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.78 (d,  $J$  = 8.9 Hz, 2H), 6.93 (d,  $J$  = 8.9 Hz, 2H), 5.08 (s, 1H), 4.93 (s, 1H), 4.07 (s, 2H), 3.86 (s, 3H), 2.19 (s, 1H), 1.78 (s, 3H), 1.65 (s, 6H).

$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  162.9 (C), 143.3 (C), 134.1 (C), 130.0 (CH x 2), 114.1 (CH x 2), 112.4 ( $\text{CH}_2$ ), 86.3 (C), 71.8 (CH), 56.6 (C), 55.9 ( $\text{CH}_3$ ), 54.1 ( $\text{CH}_2$ ), 31.2 ( $\text{CH}_3$  x 2), 20.6

(CH<sub>3</sub>).

**IR** (neat) v: 3273, 3077, 2985, 2841, 2113, 1659, 1579, 1442, 1258, 1091, 992, 833, 776, 627, 573 cm<sup>-1</sup>.

**MS** m/z (ESI-MS) calcd. for ([M+H<sup>+</sup>]): C<sub>16</sub>H<sub>22</sub>NO<sub>3</sub>S<sup>+</sup> 308.13, Found 308.18.



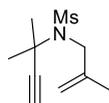
**2,4,6-Triisopropyl-N-(2-methylallyl)-N-(2-methylbut-3-yn-2-yl)benzenesulfonamide (13)** was prepared according to procedure **A**; obtained: 743 mg (92%), white solid; R<sub>f</sub> (PE/Et<sub>2</sub>O =9: 1) 0.6.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.11 (s, 2H), 5.06 (s, 1H), 4.87 (s, 1H), 4.18 (s, 2H), 4.12 (hept, *J* = 6.9 Hz, 2H), 2.88 (hept, *J* = 6.9 Hz, 1H), 2.38 (s, 1H), 1.78 (s, 3H), 1.66 (s, 6H), 1.26 (d, *J* = 6.7 Hz, 12H), 1.24 (d, *J* = 6.9 Hz, 6H).

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 152.9 (C), 150.4 (C x 2), 143.6 (C), 136.7 (C), 124.1 (CH x 2), 114.1 (CH<sub>2</sub>), 87.0 (C), 72.4 (CH), 57.1 (C), 53.5 (CH<sub>2</sub>), 34.4 (CH x 2), 30.4 (CH<sub>3</sub> x 2), 29.3 (CH), 25.1 (CH<sub>3</sub> x 4), 24.0 (CH<sub>3</sub> x 2), 20.8 (CH<sub>3</sub>).

**IR** (neat) v: 3301, 3055, 2963, 2118, 1600, 1422, 1315, 1264, 991, 731, 703, 571 cm<sup>-1</sup>.

**MS** m/z (ESI-MS) calcd. for ([M+H<sup>+</sup>]): C<sub>24</sub>H<sub>38</sub>NO<sub>2</sub>S<sup>+</sup> 404.26, Found 404.32.

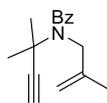


**N-(2-Methylallyl)-N-(2-methylbut-3-yn-2-yl)methanesulfonamide (14)** was prepared according to procedure **A**; obtained: 396 mg (92%), colorless oil; R<sub>f</sub> (PE/Et<sub>2</sub>O =6: 4) 0.4.

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 5.07 (s, 1H), 4.94 (s, 1H), 3.91 (s, 2H), 3.04 (s, 3H), 2.48 (s, 1H), 1.77 (s, 3H), 1.71 (s, 6H).

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 143.0 (C), 111.9 (CH<sub>2</sub>), 86.5 (C), 72.3 (CH), 56.1 (C), 52.8 (CH<sub>2</sub>), 41.1 (CH<sub>3</sub>), 31.1 (CH<sub>3</sub> x 2), 20.4 (CH<sub>3</sub>).

**MS** m/z (ESI-MS) calcd. for ([M+Na<sup>+</sup>]): C<sub>10</sub>H<sub>17</sub>NO<sub>2</sub>SNa<sup>+</sup> 238.09, Found 238.10.



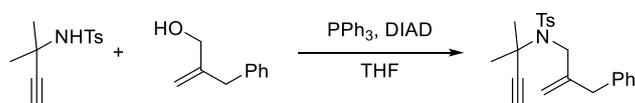
**N-(2-Methylallyl)-N-(2-methylbut-3-yn-2-yl)benzamide (15)** was prepared according to procedure **B**; obtained: 348 mg (72%), colorless oil; R<sub>f</sub> (PE/Et<sub>2</sub>O =6: 4) 0.5.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.44 – 7.43 (m, 2H), 7.36 – 7.32 (m, 3H), 5.11 (s, 1H), 5.00 (s, 1H), 3.95 (s, 2H), 2.44 (s, 1H), 1.89 (s, 6H), 1.55 (s, 3H).

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 173.0 (C), 143.5 (C), 138.6 (C), 129.6 (CH), 128.4 (CH x 2), 126.5 (CH x 2), 112.5 (CH<sub>2</sub>), 87.8 (C), 71.6 (CH), 55.5 (C), 54.7 (CH<sub>2</sub>), 28.6 (CH<sub>3</sub> x 2), 20.4 (CH<sub>3</sub>).

**MS** m/z (ESI-MS) calcd. for ([M+H<sup>+</sup>]): C<sub>16</sub>H<sub>20</sub>NO<sup>+</sup> 242.15, Found 242.13.

***N*-(2-Benzylallyl)-4-methyl-*N*-(2-methylbut-3-yn-2-yl)benzenesulfonamide (16)**



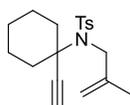
To a stirred and cooled (0 °C) solution of 4-methyl-*N*-(2-methylbut-3-yn-2-yl)benzenesulfonamide (474.6 mg, 2.0 mmol), 2-benzylprop-2-en-1-ol (296.4 mg, 2.0 mmol) and PPh<sub>3</sub> (524.6 mg, 2.0 mmol) in THF (10 mL) was slowly added diisopropylazodicarboxylate (404.4 mg, 2.0 mmol). The resulting mixture was warmed to room temperature and stirred for 12 h. Then the solvent was removed under vacuo and the residue was purified by flash chromatography to give 338 mg (46%) of **16** as a white solid, *R<sub>f</sub>* (PE/Et<sub>2</sub>O = 7: 3) 0.5.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.68 (d, *J* = 8.3 Hz, 2H), 7.32 – 7.27 (m, 2H), 7.25 – 7.19 (m, 5H), 5.27 (s, 1H), 4.92 (h, *J* = 1.5 Hz, 1H), 4.06 (s, 2H), 3.40 (s, 2H), 2.41 (s, 3H), 2.11 (s, 1H), 1.62 (s, 6H).

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>) δ 146.0 (C), 139.1 (C), 139.1 (C), 139.0 (C), 129.6 (CH x 2), 129.5 (CH x 2), 128.7 (CH x 2), 128.0 (CH x 2), 126.6 (CH<sub>2</sub>), 113.6 (CH<sub>2</sub>), 86.2 (C), 71.86 (C), 56.79 (C), 52.87 (CH<sub>2</sub>), 41.18 (CH<sub>2</sub>), 31.12 (CH<sub>3</sub> x 2), 21.84 (CH<sub>3</sub>).

**IR** (neat) *v*: 3280, 3061, 2988, 2925, 2114, 1655, 1494, 1387, 1264, 1149, 1089, 813, 775, 543 cm<sup>-1</sup>.

**MS** m/z (ESI-MS) calcd. for ([M+Na<sup>+</sup>]): C<sub>22</sub>H<sub>26</sub>NO<sub>2</sub>S<sup>+</sup> 368.17, Found 368.20.



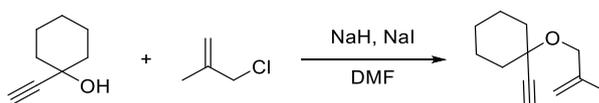
***N*-(1-Ethynylcyclohexyl)-4-methyl-*N*-(2-methylallyl)benzenesulfonamide (17)**

was prepared according to procedure **A**; obtained: 650 mg (98%), white solid;  $R_f$  (PE/Et<sub>2</sub>O =8:2) 0.5.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.72 (d,  $J$  = 8.4 Hz, 2H), 7.25 (d,  $J$  = 8.4 Hz, 2H), 5.12 (s, 1H), 4.94 (p,  $J$  = 1.5 Hz, 1H), 4.11 (s, 2H), 2.41 (s, 3H), 2.24 (s, 1H), 2.07 (d,  $J$  = 11.2 Hz, 2H), 1.88 (td,  $J$  = 12.6, 3.6 Hz, 2H), 1.80 (s, 3H), 1.67 – 1.57 (m, 3H), 1.55 – 1.51 (m, 2H), 1.16 – 1.04 (m, 1H).

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>)  $\delta$  143.6 (C), 143.2 (C), 139.7 (C), 129.5 (CH x 2), 127.8 (CH x 2), 112.2 (CH<sub>2</sub>), 83.5 (C), 75.3 (CH), 62.6 (C), 53.8 (CH<sub>2</sub>), 38.0 (CH<sub>2</sub> x 2), 25.0 (CH<sub>2</sub>), 23.8 (CH<sub>2</sub> x 2), 21.8 (CH<sub>3</sub>), 20.7 (CH<sub>3</sub>).

### 1-Ethynyl-1-((2-methylallyl)oxy)cyclohexane (**18**)<sup>4</sup>



To a stirred and cooled (0 °C) suspension of NaH (400 mg, 10 mmol, 60% oil dispersion) in *N,N*-dimethylformamide (30 mL) was added 1-ethynylcyclohexanol (1.24, 10 mmol) portionwise. After 30 min, NaI (149.9 mg, 1 mmol) and methallyl chloride (1.1 g, 12 mmol) were added. The resulting mixture was stirred overnight at room temperature, and then carefully treated with aqueous NH<sub>4</sub>Cl solution (30 mL). The solution was extracted with Et<sub>2</sub>O (3 × 10 mL), and the combined extracts were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated in vacuo. The crude residue was purified by column chromatography to afford 1.13 g (63%) of **18** as a colorless oil,  $R_f$  (PE) 0.3.

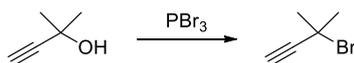
**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>)  $\delta$  5.01 (s, 1H), 4.86 (s, 1H), 4.01 (s, 2H), 2.45 (s, 1H), 1.95 – 1.87 (m, 2H), 1.77 (s, 3H), 1.71 – 1.48 (m, 7H), 1.34 – 1.28 (m, 1H).

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>)  $\delta$  143.3 (C), 111.7 (CH<sub>2</sub>), 85.7 (C), 73.9 (C), 73.5 (CH), 67.5 (CH<sub>2</sub>), 37.4 (CH<sub>2</sub> x 2), 25.7 (CH<sub>2</sub>), 23.0 (CH<sub>2</sub> x 2), 20.14 (CH<sub>3</sub>).

### 3-Bromo-3-methylbut-1-yne<sup>5</sup>

<sup>4</sup> A Gansäuer, M Pierobon, *Synlett*. **2000**, 9, 1357-1359.

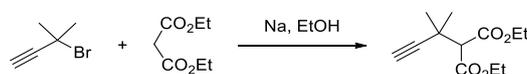
<sup>5</sup> B. M. Trost, Y. Hu, D. B. Horne, *J. Am. Chem. Soc.* **2007**, 129, 11781-11790.



To a flame-dried round flask containing 2-methyl-3-butyn-2-ol (84 g, 1.03 mol) cooled at 0 °C was added PBr<sub>3</sub> (92.0 g, 0.34 mol) dropwise over a 3 h period time. The reaction was warmed to rt and stirred for an additional 30 min. Distillation of the light green solution using a 10 cm Vigreux column gave 41.2 g (28%) of desired product as a colorless oil (bp. 25-30°C/55 mm Hg). <sup>1</sup>H NMR matched the reported data.

<sup>1</sup>H NMR (300 MHz, Chloroform-*d*) δ 2.73 (s, 1H), 2.04 (s, 6H).

#### Diethyl 2-(2-methylbut-3-yn-2-yl)malonate(41)<sup>6</sup>



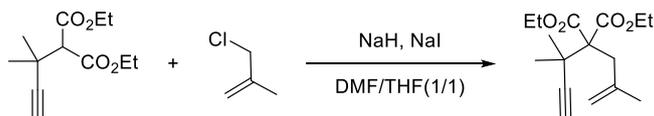
To a freshly prepared solution of sodium ethylate [sodium (460 mg, 0.02 mol)] in EtOH (50 mL) warmed at 60 °C was added dimethyl malonate (3.2 g, 0.02 mol). After 1h, 3-bromo-3-methylbut-1-yne (2.9 g, 0.02 mol) was added and the mixture was stirred for 1 h at 65 °C, 30 min at 80 °C and finally 15 h at 50 °C. The resulting mixture was filtered and concentrated under vacuo. The residue was treated with ice-cooled conc. hydrochloric acid (20 mL) and extracted with Et<sub>2</sub>O (6 x 15 mL). The combined organic layers were washed with water (2 x 30 mL) and a saturated NaHCO<sub>3</sub> solution (2 x 30 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated in vacuo. Distillation under reduced pressure using a 10 cm Vigreux column provided 1.89 g (42%) of desired product as a colorless oil (b.p. 98-101 °C/2-4 Torr). <sup>1</sup>H NMR matched the reported data.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 4.21 (q, *J* = 7.1 Hz, 4H), 3.45 (s, 1H), 2.19 (s, 1H), 1.46 (s, 6H), 1.27 (t, *J* = 7.1 Hz, 6H).

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 166.5 (C x 2), 88.1 (C), 68.6 (CH), 60.6 (CH<sub>2</sub> x 2), 59.7 (C), 31.8 (C), 26.8 (CH<sub>3</sub> x 2), 13.4 (CH<sub>3</sub> x 2).

#### Diethyl 2-(2-methylallyl)-2-(2-methylbut-3-yn-2-yl)malonate (19)

<sup>6</sup> B. Stulgies, P. Prinz, J. Magull, K. Rauch, K. Meindl, S. Rühl, A. de Meijere, *Chem. Eur. J.* **2005**, *11*, 308-320.



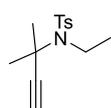
To a cooled (0 °C) solution of sodium hydride (80 mg, 2 mmol, 60% oil dispersion) in THF/DMF (1/1, 20 mL) was slowly added diethyl 2-(2-methylbut-3-yn-2-yl)malonate (452.5 mg, 2 mmol). The mixture was stirred for 1 h at 0 °C. Then, NaI (30.0 mg, 0.2 mmol) and methallyl chloride (199.2 mg, 2.2 mmol) were added. The mixture was warmed to room temperature and stirred overnight. Saturated aqueous NH<sub>4</sub>Cl (20 mL) was added at 0 °C, and the resulting mixture was extracted with Et<sub>2</sub>O (3 × 10 mL). The combined extracts were washed with brine (20 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated in vacuo. The residue was purified by column chromatography to give 291.6 mg (52%) of **19** as a colorless oil, R<sub>f</sub> (PE/Et<sub>2</sub>O =19: 1) 0.5.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 4.78 (p, *J* = 1.6 Hz, 1H), 4.74 (dt, *J* = 2.0, 1.0 Hz, 1H), 4.18 (q, *J* = 7.1 Hz, 4H), 2.98 (s, 2H), 2.25 (s, 1H), 1.74 (s, 3H), 1.43 (s, 6H), 1.27 (t, *J* = 7.1 Hz, 6H).

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 169.8 (C x 2), 143.1 (C), 114.9 (CH<sub>2</sub>), 89.7 (C), 70.6 (CH), 63.9 (C), 61.2 (CH<sub>2</sub> x 2), 40.6 (CH<sub>2</sub>), 38.1 (C), 27.3 (CH<sub>3</sub> x 2), 24.1 (CH<sub>3</sub>), 14.2 (CH<sub>3</sub> x 2).

**IR** (neat) v: 3307, 3273, 2981, 2935, 2358, 2164, 1882, 1303, 1242, 1067, 644 cm<sup>-1</sup>.

**MS** m/z (ESI-MS) calcd. for ([M+H<sup>+</sup>]): C<sub>16</sub>H<sub>25</sub>O<sub>4</sub><sup>+</sup> 281.17, Found 281.22.



**N-Ethyl-4-methyl-N-(2-methylbut-3-yn-2-yl)benzenesulfonamide (29)** was prepared according to procedure C, obtained: 510 mg (96%), colorless oil; R<sub>f</sub> (PE/Et<sub>2</sub>O =9: 1) 0.5.

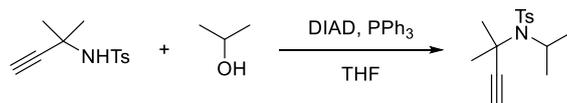
**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 7.74 (d, *J* = 8.3 Hz, 2H), 7.27 (d, *J* = 8.2 Hz, 2H), 3.59 (q, *J* = 7.0 Hz, 2H), 2.41 (s, 3H), 2.28 (s, 1H), 1.67 (s, 6H), 1.36 (t, *J* = 7.0 Hz, 3H).

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 143.1 (C), 140.2 (C), 129.6 (CH x 2), 127.4 (CH x 2), 86.6 (C), 71.7 (CH), 56.3 (C), 43.8 (CH<sub>2</sub>), 30.9 (CH<sub>2</sub> x 2), 21.8 (CH<sub>3</sub>), 17.9 (CH<sub>3</sub>).

**IR** (neat) v: 3257, 3027, 2925, 2103, 1597, 1414, 1289, 1068, 811, 639, 521 cm<sup>-1</sup>.

**MS** m/z (ESI-MS) calcd. for ([M+H<sup>+</sup>]): C<sub>14</sub>H<sub>20</sub>NO<sub>2</sub>S 266.12 Found 266.10.

***N*-isopropyl-4-methyl-*N*-(2-methylbut-3-yn-2-yl)benzenesulfonamide (30)**



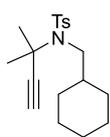
To a solution of 4-methyl-*N*-(2-methylbut-3-yn-2-yl) benzenesulfonamide (474.6 mg, 2.0 mmol), isopropanol (120.2 mg, 2.0 mmol) and PPh<sub>3</sub> (524.4 mg, 2.0 mmol) in dry THF (20 mL) was slowly added diisopropyl azodicarboxylate (404.4 mg, 2.0 mmol) at 0 °C. The resulting mixture was warmed to room temperature and stirred for 12 h. Then the solvent was removed under vacuo and the crude product was purified by flash chromatography to give 262.6 mg (47 %) of **30** as a white solid; *R<sub>f</sub>* (PE/Et<sub>2</sub>O =8: 2) 0.50.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.76 (d, *J* = 8.3 Hz, 2H), 7.26 (d, *J* = 8.1 Hz, 2H), 4.18 (hept, *J* = 6.9 Hz, 1H), 2.41 (s, 3H), 2.36 (s, 1H), 1.64 (s, 3H), 1.62 (s, 3H), 1.60 (s, 6H).

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 142.8 (C), 129.7 (CH x 2), 127.1 (CH x 2), 87.6 (C), 71.3 (CH), 57.2 (C), 54.4 (CH), 30.2 (CH<sub>3</sub> x 2), 23.6 (CH<sub>3</sub> x 2), 21.7 (CH<sub>3</sub>). (The quaternary atom attached to the methyl group of tosylate was not detected).

**IR** (neat) v: 3267, 2976, 2937, 2113, 1599, 1456, 1233, 1117, 778, 636, 530 cm<sup>-1</sup>.

**MS** m/z (ESI-MS) calcd. for ([M+H<sup>+</sup>]): C<sub>15</sub>H<sub>22</sub>NO<sub>2</sub>S<sup>+</sup> 280.14, Found 280.20.



***N*-(Cyclohexylmethyl)-4-methyl-*N*-(2-methylbut-3-yn-2-yl)benzenesulfonamide (31)** was prepared according to procedure **C** using (bromomethyl)cyclohexane, obtained: 480 mg (72%), white solid; *R<sub>f</sub>* (PE/Et<sub>2</sub>O =9: 1) 0.4.

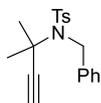
**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 7.69 (d, *J* = 8.3 Hz, 2H), 7.25 (d, *J* = 7.2 Hz, 2H), 3.43 (d, *J* = 6.7 Hz, 2H), 2.40 (s, 3H), 2.28 (s, 1H), 1.89 – 1.67 (m, 6H), 1.65 (s, 6H), 1.26 – 1.18 (m, 3H), 1.06 – 0.86 (m, 2H).

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 142.0 (C), 140.1 (C), 128.6 (CH x 2), 126.4 (CH x 2), 85.8 (C), 71.4 (CH), 55.5 (C), 54.6 (CH<sub>2</sub>), 38.1 (CH), 30.28 (CH<sub>3</sub> x 2), 30.25 (CH<sub>2</sub> x 2), 25.9 (CH<sub>2</sub>), 25.6 (CH<sub>2</sub> x 2), 20.8 (CH<sub>3</sub>).

**IR** (neat) v: 3267, 2984, 2924, 2850, 2111, 1495, 1329, 1154, 1144, 991, 902, 812, 647, 542

cm<sup>-1</sup>.

**MS** m/z (ESI-MS) calcd. for ([M+H<sup>+</sup>]): C<sub>19</sub>H<sub>28</sub>NO<sub>2</sub>S<sup>+</sup> 334.18, Found 334.25.



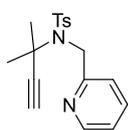
**N-Benzyl-4-methyl-N-(2-methylbut-3-yn-2-yl)benzenesulfonamide (32)** was prepared according to procedure **C** using (bromomethyl)benzene, obtained: 616 mg (94%), white solid; R<sub>f</sub> (PE/Et<sub>2</sub>O =9: 1) 0.6.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.66 (d, *J* = 8.1 Hz, 2H), 7.48 (d, *J* = 7.5 Hz, 2H), 7.32 (d, *J* = 7.8 Hz, 2H), 7.27 – 7.23 (m, 3H), 4.82 (s, 2H), 2.40 (s, 3H), 2.26 (s, 1H), 1.61 (s, 6H).

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 143.3 (C), 139.7 (C), 139.6 (C), 129.6 (CH x 2), 128.6 (CH x 2), 127.9 (CH x 2), 127.7 (CH x 2), 127.3 (CH), 86.4 (C), 72.5 (CH), 57.2 (C), 52.4 (CH<sub>2</sub>), 31.2 (CH<sub>3</sub> x 2), 21.8 (CH<sub>3</sub>).

**IR** (neat) v: 3297, 3086, 3028, 2845, 2102, 1603, 1496, 1437, 1203, 1072, 912, 739, 639, 548 cm<sup>-1</sup>.

**MS** m/z (ESI-MS) calcd. for ([M+H<sup>+</sup>]): C<sub>19</sub>H<sub>22</sub>NO<sub>2</sub>S<sup>+</sup> 328.14, Found 328.29.



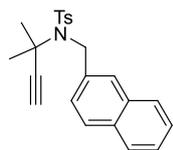
**4-Methyl-N-(2-methylbut-3-yn-2-yl)-N-(pyridin-2-ylmethyl)benzenesulfonamide (33)** was prepared according to procedure **C** using 2-(bromomethyl)pyridine, obtained: 611 mg (93%), white solid; R<sub>f</sub> (PE/Et<sub>2</sub>O =7: 3) 0.3.

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 8.50 (dt, *J* = 4.9, 1.2 Hz, 1H), 7.80 – 7.77 (m, 2H), 7.74 – 7.66 (m, 2H), 7.30 – 7.26 (m, 2H), 7.16 (ddd, *J* = 6.9, 4.9, 1.9 Hz, 1H), 4.88 (s, 2H), 2.42 (s, 3H), 2.12 (s, 1H), 1.60 (s, 6H).

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 160.0 (C), 148.9 (CH), 143.6 (C), 138.6 (C), 136.9 (CH), 129.7 (CH x 2), 127.9 (CH x 2), 122.21 (CH), 122.16 (CH), 85.5 (C), 72.3 (CH), 56.8 (C), 54.3 (CH<sub>2</sub>), 31.2 (CH<sub>3</sub> x 2), 21.8 (CH<sub>3</sub>).

**IR** (neat) v: 3286, 3054, 2939, 2115, 1632, 1509, 1494, 1305, 1233, 1089, 951, 813, 705, 572 cm<sup>-1</sup>.

**MS** m/z (ESI-MS) calcd. for ([M+H<sup>+</sup>]): C<sub>18</sub>H<sub>21</sub>N<sub>2</sub>O<sub>2</sub>S<sup>+</sup> 329.13, Found 329.17.



**4-Methyl-N-(2-methylbut-3-yn-2-yl)-N-(naphthalen-2-ylmethyl)benzenesulfonamide (34)** was prepared according to procedure C using 2-(bromomethyl)naphthalene, obtained: 732 mg (97%), white solid;  $R_f$

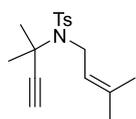
(PE/Et<sub>2</sub>O =8: 2) 0.3.

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>)  $\delta$  7.86 – 7.80 (m, 4H), 7.72 – 7.69 (m, 2H), 7.63 (dd,  $J$  = 8.6, 1.8 Hz, 1H), 7.48 – 7.44 (m, 2H), 7.23 (d,  $J$  = 8.1 Hz, 2H), 4.99 (s, 2H), 2.39 (s, 3H), 2.28 (s, 1H), 1.64 (s, 6H).

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>)  $\delta$  143.4 (C), 139.7 (C), 137.3 (C), 133.6 (C), 133.0 (C), 129.6 (CH x 2), 128.3 (CH), 128.2 (CH), 127.9 (CH), 127.8 (CH x 2), 126.7 (CH), 126.3 (CH), 126.0 (CH), 125.9 (CH), 86.5 (C), 72.7 (CH), 57.4 (C), 52.6 (CH<sub>2</sub>), 31.3 (CH<sub>3</sub> x 2), 21.7 (CH<sub>3</sub>).

**IR** (neat) v: 3284, 2987, 2942, 2111, 1633, 1599, 1330, 1148, 1089, 936, 812, 655, 572 cm<sup>-1</sup>.

**MS** m/z (ESI-MS) calcd. for ([M+H<sup>+</sup>]): C<sub>23</sub>H<sub>24</sub>NO<sub>2</sub>S<sup>+</sup> 378.15, Found 378.26.



**4-Methyl-N-(3-methylbut-2-en-1-yl)-N-(2-methylbut-3-yn-2-yl)benzenesulfonamide (35)** was prepared according to procedure C using 1-bromo-3-methylbut-2-ene, obtained: 544 mg (89%), white solid;  $R_f$  (PE/Et<sub>2</sub>O

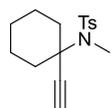
=8: 2) 0.4.

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>)  $\delta$  7.74 (d,  $J$  = 8.3 Hz, 2H), 7.25 (d,  $J$  = 6.7 Hz, 2H), 5.38 (t,  $J$  = 6.3 Hz, 1H), 4.16 (d,  $J$  = 6.3 Hz, 2H), 2.41 (s, 3H), 2.32 (s, 1H), 1.72 (s, 3H), 1.68 (s, 6H), 1.66 (s, 3H).

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>)  $\delta$  143.0 (C), 140.5 (C), 133.6 (C), 129.6 (CH x 2), 127.5 (CH x 2), 123.9 (CH), 87.1 (C), 72.0 (CH), 56.5 (C), 46.8 (CH<sub>2</sub>), 31.0 (CH<sub>3</sub> x 2), 26.0 (CH<sub>3</sub>), 21.8 (CH<sub>3</sub>), 18.2 (CH<sub>3</sub>).

**IR** (neat) v: 3289, 2990, 2945, 2112, 1598, 1444, 1263, 1149, 1089, 925, 813, 707, 652, 572 cm<sup>-1</sup>.

**MS** m/z (ESI-MS) calcd. for ([M+H<sup>+</sup>]): C<sub>17</sub>H<sub>24</sub>NO<sub>2</sub>S<sup>+</sup> 306.15, Found 306.16.



**N-(1-Ethynylcyclohexyl)-N,4-dimethylbenzenesulfonamide (36)** was prepared according to procedure C; obtained: 542 mg (93%), colorless oil;  $R_f$  (PE/Et<sub>2</sub>O =9:1) 0.45.

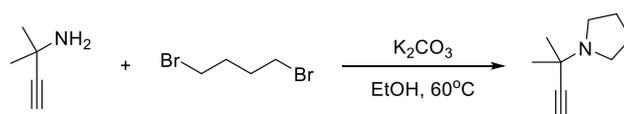
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.73 (d,  $J$  = 8.3 Hz, 2H), 7.28 (d,  $J$  = 8.0 Hz, 2H), 3.08 (s, 3H), 2.42 (s, 3H), 2.26 (s, 1H), 2.13 (d,  $J$  = 12.4 Hz, 2H), 1.94 (dd,  $J$  = 12.0, 3.2 Hz, 2H), 1.74 – 1.54 (m, 5H), 1.23 – 1.17 (m, 1H).

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>)  $\delta$  143.2 (C), 138.8 (C), 129.5 (CH x 2), 127.7 (CH x 2), 83.2 (C), 75.0 (CH), 61.1 (C), 37.4 (CH<sub>2</sub> x 2), 33.8 (CH<sub>3</sub>), 25.2 (CH<sub>2</sub>), 23.5 (CH<sub>2</sub> x 2), 21.8 (CH<sub>3</sub>).

**IR** (neat)  $\nu$ : 3267, 2934, 2859, 2105, 1598, 1450, 1331, 1154, 858, 669, 548 cm<sup>-1</sup>.

**MS**  $m/z$  (ESI-MS) calcd. for ([M+H<sup>+</sup>]): C<sub>16</sub>H<sub>22</sub>NO<sub>2</sub>S 292,14, Found 292,10.

### 1-(2-Methylbut-3-yn-2-yl)pyrrolidine (37)<sup>7</sup>



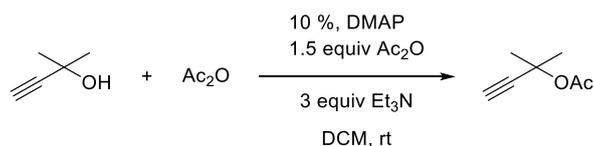
To a solution of 2-methylbut-3-yn-2-amine (1.7 g, 20 mmol) and K<sub>2</sub>CO<sub>3</sub> (1.4 g, 10 mmol) in EtOH was added 1,4-dibromobutane (2.2 g, 10 mmol). The resulting mixture was stirred for 72 h at 60 °C. After cooling to room temperature, the mixture was treated with 10% K<sub>2</sub>CO<sub>3</sub> (20 mL) and extracted with Et<sub>2</sub>O (3 x 20 mL). The combined extracts were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated under vacuo. The crude solid was purified by recrystallization (PE/EA 1/1) to give 2.3 g (82%) of desired adduct as a white solid.

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>)  $\delta$  2.74 – 2.69 (m, 4H), 2.23 (s, 1H), 1.82 – 1.77 (m, 4H), 1.41 (s, 6H).

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>)  $\delta$  85.0 (C), 70.4 (CH), 53.0 (C), 47.33 (CH<sub>2</sub> x 2), 28.97 (CH<sub>2</sub> x 2), 23.05 (CH<sub>3</sub> x 2).

### 2-Methylbut-3-yn-2-yl acetate (38)

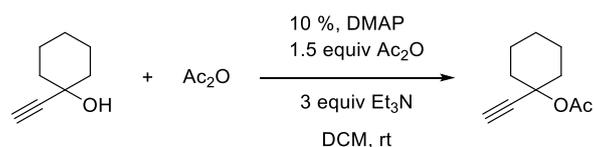
<sup>7</sup> S. Bertrand, N. Hoffmann, S. Humbel, J. P. Pete, *J. Org. Chem.* **2000**, 65, 8690-8703.



2-methylbut-3-yn-2-yl acetate was prepared according to reported literature.<sup>8</sup> To a mixture of DMAP (4-dimethylaminopyridine, 0.61 g, 5.0 mmol), the dimethyl propargylic alcohol (4.2 g, 50.0 mmol) and CH<sub>2</sub>Cl<sub>2</sub> (50 mL) was added Ac<sub>2</sub>O (9.3 mL, 75 mmol) dropwise. Then the mixture was stirred overnight under the disappearance of dimethyl propargylic alcohol on TLC. After completion of reaction, the solution was concentrated under vacuo, and the crude reaction mixture was purified on column chromatography (pentane:diethyl ether 10:1) to afford the propargylic acetate as a colorless oil (5.7 g, 90% yield), *R<sub>f</sub>* (PE/Et<sub>2</sub>O = 9: 1) 0.4.

<sup>1</sup>H NMR (400 MHz, Chloroform-*d*) δ 7.26 (s, 1H), 2.52 (s, 4H), 2.02 (s, 10H).

### 1-Ethynylcyclohexyl acetate (39)



Ethynylcyclohexyl acetate was prepared according to reported literature.<sup>9</sup> To a mixture of DMAP (4-dimethylaminopyridine, 0.61 g, 5.0 mmol), the propargylic alcohol (6.3 g, 50.0 mmol) and CH<sub>2</sub>Cl<sub>2</sub> (50 mL) was added Ac<sub>2</sub>O (9.3 mL, 75 mmol) dropwise. Then the mixture was stirred overnight under the disappearance of 1-ethynylcyclohexanol on TLC. After completion of reaction, the solution was concentrated under vacuo, and the crude reaction mixture was purified on column chromatography (pentane:diethyl ether 10:1) to afford the propargylic acetate as a colorless oil (7.2 g, 87% yield).

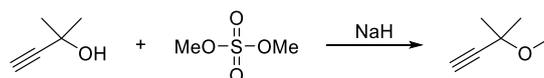
<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 2.59 (s, 1H), 2.16 – 2.09 (m, 2H), 2.04 (s, 3H), 1.89 – 1.80 (m, 2H), 1.69 – 1.59 (m, 4H), 1.55 – 1.48 (m, 1H), 1.33 (dq, *J* = 13.2, 6.5 Hz, 1H).

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 169.0 (C), 83.8 (C), 75.2 (CH), 74.5 (C), 37.1 (CH<sub>2</sub> x 2), 25.3 (CH<sub>2</sub>), 22.6 (CH<sub>2</sub> x 2), 22.0 (CH<sub>3</sub>).

<sup>8</sup> A. Bartels, R. Mahrwald, K. Müller, *Adv. Synth. Catal.* **2004**, 346, 483-485.

<sup>9</sup> Zhao, T. S. N.; Yang, Y.; Lessing, T.; Szabó, K. J. *J. Am. Chem. Soc.* **2014**, 136, 7563–7566.

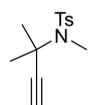
### 3-Methoxy-3-methylbut-1-yne (40)



3-methoxy-3-methylbut-1-yne was prepared according to reported literature.<sup>10</sup> A magnetically stirred solution of compound 2-methylbut-3-yn-2-ol (4.2 g, 0.050 mmol) in DMF (50 mL) was treated with sodium hydride (3.05 g of 60% w/w dispersion in mineral oil, 0.076 mmol) and the resulting mixture stirred at 0 °C for 0.5 h. Dimethyl sulfate (7.25 mL, 0.076 mmol) was then added dropwise and after the addition was complete the reaction mixture was warmed to 20 °C over 0.75 h. After this time, acetic acid (5 mL) was added to the reaction mixture to consuming excess NaH and the solution was then distilled to give the title compound 3-methoxy-3-methylbut-1-yne (4.35 g, 89%) as a clear, colorless oil, bp = 78~80 °C @ 760 mm Hg.

<sup>1</sup>H NMR (300 MHz, Chloroform-*d*) δ 3.36 (s, 3H), 2.42 (s, 1H), 1.46 (s, 6H).

<sup>13</sup>C NMR (75 MHz, Chloroform-*d*) δ 85.9 (C), 72.4 (CH), 70.6 (C), 51.8 (CH<sub>3</sub>), 28.5 (CH<sub>3</sub> x 2).



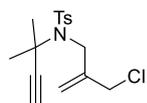
**N,4-Dimethyl-N-(2-methylbut-3-yn-2-yl)benzenesulfonamide (55)** was prepared according to procedure C using iodomethane, obtained: 462 mg (92%), white solid; R<sub>f</sub> (PE/Et<sub>2</sub>O =9: 1) 0.5.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.72 (d, *J* = 8.3 Hz, 2H), 7.27 (d, *J* = 8.5 Hz, 2H), 3.08 (s, 3H), 2.41 (s, 3H), 2.23 (s, 1H), 1.67 (s, 6H).

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 143.4 (C), 138.8 (C), 129.7 (CH x 2), 127.7 (CH x 2), 85.8 (C), 72.1 (CH), 55.9 (C), 34.5 (CH<sub>3</sub>), 30.2 (CH<sub>3</sub> x 2), 21.8 (CH<sub>3</sub>).

IR (neat) v: 3271, 2989, 2942, 2112, 1968, 1495, 1461, 1365, 1245, 905, 706, 546 cm<sup>-1</sup>.

MS m/z (ESI-MS) calcd. for ([M+H<sup>+</sup>]): C<sub>13</sub>H<sub>18</sub>NO<sub>2</sub>S<sup>+</sup> 252.11, Found 252.10.



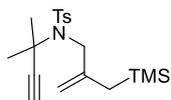
**N-(2-(Chloromethyl)allyl)-4-methyl-N-(2-methylbut-3-yn-2-yl)benzenesulfo**

<sup>10</sup> Pinkerton, D. M.; Banwell, M. G.; Willis, A. C. *Org. Lett.* **2009**, *11*, 4290-4293.

**namide (56)** was prepared according to procedure **A**, obtained: 541 mg (83%), colorless oil;  $R_f$  (PE/Et<sub>2</sub>O =9: 1) 0.5.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.73 (d,  $J$  = 8.3 Hz, 2H), 7.28 (d,  $J$  = 8.1 Hz, 2H), 5.46 (s, 1H), 5.38 (s, 1H), 4.27 (s, 2H), 4.15 (s, 2H), 2.42 (s, 3H), 2.20 (s, 1H), 1.67 (s, 6H).

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 143.7 (C), 142.6 (C), 138.9 (C), 129.7 (CH x 2), 127.9 (CH x 2), 117.3 (CH<sub>2</sub>), 85.9 (C), 72.2 (CH), 57.0 (C), 51.0 (CH<sub>2</sub>), 46.7 (CH<sub>2</sub>), 31.3 (CH<sub>3</sub> x 2), 21.8 (CH<sub>3</sub>).



**4-Methyl-N-(2-methylbut-3-yn-2-yl)-N-(2-((trimethylsilyl)methyl)allyl)benzenesulfonamide (57)** was prepared according to procedure **A**; obtained:

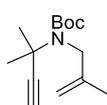
516 mg (71%), colorless oil;  $R_f$  (PE/Et<sub>2</sub>O =9: 1) 0.5.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.73 (d,  $J$  = 8.3 Hz, 2H), 7.25 (d,  $J$  = 8.1 Hz, 2H), 5.04 (m, 1H), 4.76 (s, 1H), 4.01 (s, 2H), 2.41 (s, 3H), 2.18 (s, 1H), 1.66 (s, 6H), 1.55 (s, 2H), 0.07 (s, 9H).

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 145.4 (C), 144.3 (C), 140.5 (C), 130.5 (CH x 2), 128.9 (CH x 2), 110.6 (CH<sub>2</sub>), 87.4 (C), 72.7 (CH), 57.5 (C), 55.7 (CH<sub>2</sub>), 32.2 (CH<sub>3</sub> x 2), 25.5 (CH<sub>2</sub>), 22.8 (CH<sub>3</sub>), 0.09 (CH<sub>3</sub> x 3).

IR (neat) v: 3268, 2988, 2951, 2112, 1645, 1418, 1149, 1089, 889, 838, 659, 541 cm<sup>-1</sup>.

MS m/z (ESI-MS) calcd. for ([M+Na<sup>+</sup>]): C<sub>19</sub>H<sub>29</sub>NO<sub>2</sub>SNaSi<sup>+</sup> 386.16, Found 386.28.



**Tert-butyl (2-methylallyl)(2-methylbut-3-yn-2-yl)carbamate (58)** was prepared according to procedure **B**; obtained: 403 mg (85%), colorless oil;  $R_f$  (PE/Et<sub>2</sub>O =8: 2) 0.5.

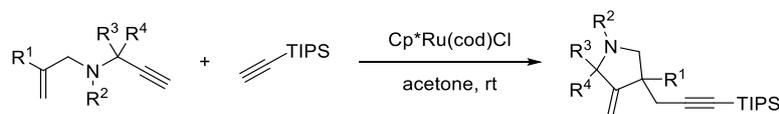
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 4.86 (dd,  $J$  = 1.7, 0.9 Hz, 1H), 4.85 – 4.82 (m, 1H), 3.98 (td,  $J$  = 1.7, 0.8 Hz, 2H), 2.36 (s, 1H), 1.71 (dt,  $J$  = 1.6, 0.8 Hz, 3H), 1.70 (s, 6H), 1.46 (s, 9H).

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 155.1 (C), 143.4 (C), 110.0 (CH<sub>2</sub>), 88.5 (C), 80.2 (C), 70.6 (CH), 53.8 (C), 51.5 (CH<sub>2</sub>), 29.6 (CH<sub>3</sub> x 2), 28.7 (CH<sub>3</sub> x 3), 20.3 (CH<sub>3</sub>).

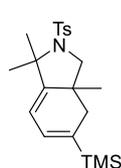
MS m/z (ESI-MS) calcd. for ([M+H<sup>+</sup>]): C<sub>14</sub>H<sub>24</sub>NO<sub>2</sub><sup>+</sup> 238.18, Found 238.17.

## Cp\*Ru(cod)Cl-catalyzed cyclization reactions

### Cross-coupling reaction of 1,6-enynes with alkynes



**Procedure D:** To a solution of 1, 6-enyne (0.2 mmol) and alkyne (1 mmol) in acetone was added Cp\*Ru(cod)Cl (0.01 mmol). The reaction mixture was stirred at room temperature until complete consumption of 1, 6-enynes (monitoring by TLC), filtered over celite, and concentrated in vacuo. The residue was purified by flash column chromatography to afford corresponding adducts.



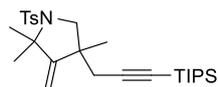
**1,1,3a-Trimethyl-2-tosyl-5-(trimethylsilyl)-2,3,3a,4-tetrahydro-1H-isindole (8)** was obtained according to procedure **D**, obtained: 58.4 mg (75%), colorless oil,  $R_f$  (PE/Et<sub>2</sub>O 8/2) 0.55.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.75 (d,  $J$  = 8.3 Hz, 2H), 7.27 (d,  $J$  = 8.5 Hz, 2H), 6.18 (dd,  $J$  = 5.0, 3.0 Hz, 1H), 5.65 (d,  $J$  = 5.0 Hz, 1H), 3.39 (d,  $J$  = 9.1 Hz, 1H), 3.00 (d,  $J$  = 9.1 Hz, 1H), 2.41 (s, 3H), 2.19 (d,  $J$  = 16.2 Hz, 1H), 2.03 (dd,  $J$  = 16.2, 3.0 Hz, 1H), 1.67 (s, 3H), 1.45 (s, 3H), 0.95 (s, 3H), 0.05 (s, 9H).

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$  156.2 (C), 143.1 (C), 138.3 (C), 135.9 (C), 131.3 (CH), 129.7 (CH x 2), 127.8 (CH x 2), 114.2 (CH), 67.6 (C), 61.4 (CH<sub>2</sub>), 38.8 (C), 37.3 (CH<sub>2</sub>), 31.2 (CH<sub>3</sub>), 28.5 (CH<sub>3</sub>), 21.8 (CH<sub>3</sub>), 21.2 (CH<sub>3</sub>), -2.33 (CH<sub>3</sub> x 3).

**IR** (neat)  $\nu$ : 2960, 2923, 2861, 1597, 1449, 1341, 1156, 1093, 1016, 912, 813, 663, 548 cm<sup>-1</sup>.

**HRMS** (ESI-MS) calcd. for C<sub>21</sub>H<sub>32</sub>NO<sub>2</sub>SSi<sup>+</sup> ([M+H]<sup>+</sup>): 390.1918, found 390.1917.



**2,2,4-Trimethyl-3-methylene-1-tosyl-4-(3-(triisopropylsilyl)prop-2-yn-1-yl)pyrrolidine (10)** was obtained according to procedure **D**, obtained:

90.0 mg (95%), colorless oil,  $R_f$  (PE/Et<sub>2</sub>O 8/2) 0.45.

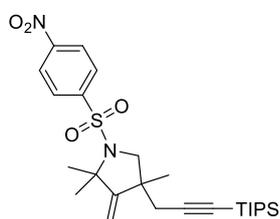
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.74 (d,  $J$  = 8.3 Hz, 2H), 7.26 (d,  $J$  = 8.0 Hz, 2H), 4.87 (s, 2H), 3.37 (d,  $J$  = 9.7 Hz, 1H), 3.12 (d,  $J$  = 9.7 Hz, 1H), 2.40 (s, 3H), 2.32 (d,  $J$  = 16.9 Hz, 1H),

2.24 (d,  $J = 16.9$  Hz, 1H), 1.56 (s, 3H), 1.52 (s, 3H), 1.20 (s, 3H), 1.07 (s, 2H), 1.04 – 0.99 (m, 19H).

$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  163.7 (C), 143.2 (C), 138.4 (C), 129.7 (CH x 2), 127.7 (CH x 2), 105.3 (C), 105.2 ( $\text{CH}_2$ ), 82.9 (C), 68.7 (C), 57.3 ( $\text{CH}_2$ ), 44.1 (C), 31.3 ( $\text{CH}_2$ ), 29.7 ( $\text{CH}_3$ ), 29.4 ( $\text{CH}_3$ ), 24.6 ( $\text{CH}_3$ ), 21.8 ( $\text{CH}_3$ ), 18.9 ( $\text{CH}_3$  x 6), 11.6 (CH x 3).

IR (neat)  $\nu$ : 2940, 2891, 2864, 2170, 1462, 1338, 1159, 1149, 1091, 1027, 753, 658, 581, 548  $\text{cm}^{-1}$ .

HRMS (ESI-MS) calcd. for  $\text{C}_{27}\text{H}_{44}\text{NO}_2\text{SSi}^+$  ( $[\text{M}+\text{H}]^+$ ): 474.2857, found 474.2855.



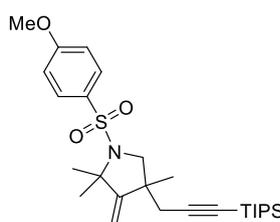
**2,2,4-Trimethyl-3-methylene-1-((4-nitrophenyl)sulfonyl)-4-(3-(triisopropylsilyl)prop-2-yn-1-yl)pyrrolidine (20)** was obtained according to procedure **D**, obtained: 87.8 mg (87%), colorless oil,  $R_f$  (PE/ $\text{Et}_2\text{O}$  8/2) 0.45.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.33 (d,  $J = 8.9$  Hz, 2H), 8.05 (d,  $J = 8.9$  Hz, 2H), 4.92 (s, 1H), 4.91 (s, 1H), 3.50 (d,  $J = 10.0$  Hz, 1H), 3.20 (d,  $J = 10.0$  Hz, 1H), 2.30 (d,  $J = 16.9$  Hz, 1H), 2.23 (d,  $J = 16.9$  Hz, 1H), 1.57 (s, 3H), 1.52 (s, 3H), 1.22 (s, 3H), 1.07 (s, 2H), 1.02 (d,  $J = 4.2$  Hz, 19H).

$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  162.6 (C), 150.1 (C), 147.1 (C), 128.8 (CH x 2), 124.5 (CH x 2), 105.9 ( $\text{CH}_2$ ), 104.8 (C), 83.4 (C), 69.4 (C), 57.4 ( $\text{CH}_2$ ), 44.3 (C), 31.2 ( $\text{CH}_2$ ), 30.0 ( $\text{CH}_3$ ), 29.4 ( $\text{CH}_3$ ), 24.4 ( $\text{CH}_3$ ), 18.9 ( $\text{CH}_3$  x 6), 11.5 (CH x 3).

IR (neat)  $\nu$ : 2941, 2890, 2865, 2170, 1606, 1531, 1463, 1349, 1165, 1090, 1029, 919, 883, 677, 614, 571  $\text{cm}^{-1}$ .

HRMS (ESI-MS) calcd. for  $\text{C}_{26}\text{H}_{41}\text{N}_2\text{O}_4\text{SSi}^+$  ( $[\text{M}+\text{H}]^+$ ): 505.2551, found 505.2553.



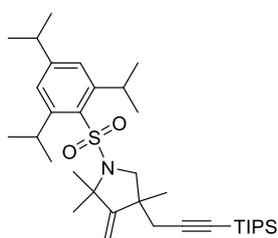
**1-((4-Methoxyphenyl)sulfonyl)-2,2,4-trimethyl-3-methylene-4-(3-(triisopropylsilyl)prop-2-yn-1-yl)pyrrolidine (21)** was obtained according to procedure **D**, obtained: 81.3 mg (83%), colorless oil,  $R_f$  (PE/ $\text{Et}_2\text{O}$  8/2) 0.43.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.79 (d, *J* = 9.0 Hz, 2H), 6.93 (d, *J* = 8.9 Hz, 2H), 4.88 (s, 2H), 3.85 (s, 3H), 3.35 (d, *J* = 9.7 Hz, 1H), 3.09 (d, *J* = 9.7 Hz, 1H), 2.33 (d, *J* = 16.8 Hz, 1H), 2.24 (d, *J* = 16.8 Hz, 1H), 1.56 (s, 3H), 1.53 (s, 3H), 1.20 (s, 3H), 1.01 (d, *J* = 4.7 Hz, 21H).

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>) δ 163.6 (C), 163.9 (C), 133.0 (C), 129.8 (CH x 2), 114.2 (CH x 2), 105.3 (C), 105.3 (CH<sub>2</sub>), 82.8 (C), 68.6 (C), 57.2 (CH<sub>2</sub>), 55.8 (CH<sub>3</sub>), 44.0 (C), 31.3 (CH<sub>2</sub>), 29.6 (CH<sub>3</sub>), 29.4 (CH<sub>3</sub>), 24.5 (CH<sub>3</sub>), 18.9 (CH<sub>3</sub> x 6), 11.6 (CH x 3).

**IR** (neat) v: 2941, 2864, 2170, 1597, 1579, 1497, 1462, 1338, 1258, 1157, 1092, 1026, 968, 883, 817, 677, 584, 560 cm<sup>-1</sup>.

**HRMS** (ESI-MS) calcd. for C<sub>27</sub>H<sub>44</sub>NO<sub>3</sub>SSi<sup>+</sup> ([M+H]<sup>+</sup>): 490.2806, found 490.2807.



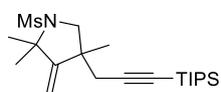
**2,2,4-Trimethyl-3-methylene-1-((2,4,6-triisopropylphenyl)sulfonyl)-4-(3-(triisopropylsilyl)prop-2-yn-1-yl)pyrrolidine (22)** was obtained according to procedure **D**, obtained: 111 mg (95%), colorless oil, *R<sub>f</sub>* (PE/Et<sub>2</sub>O 9/1) 0.40.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.14 (s, 2H), 4.92 (s, 2H), 4.36 (hept, *J* = 6.8 Hz, 2H), 3.24 (d, *J* = 8.9 Hz, 1H), 3.02 (d, *J* = 8.9 Hz, 1H), 2.89 (hept, *J* = 6.9 Hz, 1H), 2.46 (d, *J* = 16.8 Hz, 1H), 2.22 (d, *J* = 16.8 Hz, 1H), 1.71 (s, 3H), 1.69 (s, 3H), 1.29 – 1.21 (m, 23H), 0.95 – 0.91 (m, 19H).

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 164.6 (C), 153.4 (C), 151.9 (C x 2), 132.7 (C), 124.1 (CH x 2), 105.2 (C), 104.9 (CH<sub>2</sub>), 82.8 (C), 69.9 (C), 56.6 (CH<sub>2</sub>), 44.1 (C), 34.4 (CH x 2), 32.0 (CH<sub>2</sub>), 30.0 (CH), 29.3 (CH<sub>3</sub>), 29.0 (CH<sub>3</sub>), 25.3 (CH<sub>3</sub> x 2), 25.0 (CH<sub>3</sub> x 2), 24.3 (CH<sub>3</sub>), 23.9 (CH<sub>3</sub>), 23.8 (CH<sub>3</sub>), 18.9 (CH<sub>3</sub> x 3), 18.9 (CH<sub>3</sub> x 3), 11.5 (CH x 3).

**IR** (neat) v: 2958, 2855, 2170, 1600, 1462, 1364, 1317, 1163, 1146, 1076, 950, 882, 676, 582 cm<sup>-1</sup>.

**HRMS** (ESI-MS) calcd. for C<sub>35</sub>H<sub>60</sub>NO<sub>2</sub>SSi<sup>+</sup> ([M+H]<sup>+</sup>): 586.4109, found 586.4115.



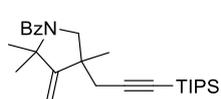
**2,2,4-Trimethyl-3-methylene-1-(methylsulfonyl)-4-(3-(triisopropylsilyl)prop-2-yn-1-yl)pyrrolidine (23)** was obtained according to procedure **D**, obtained: 56.5 mg (71%), colorless oil, *R<sub>f</sub>* (PE/Et<sub>2</sub>O 7/3) 0.30.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 4.96 (s, 1H), 4.93 (s, 1H), 3.54 (d, *J* = 9.7 Hz, 1H), 3.20 (d, *J* = 9.7 Hz, 1H), 2.91 (s, 3H), 2.51 (d, *J* = 16.9 Hz, 1H), 2.38 (d, *J* = 16.9 Hz, 1H), 1.55 (s, 6H), 1.30 (s, 3H), 1.06 (d, *J* = 3.9 Hz, 21H).

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 163.2 (C), 105.7 (CH<sub>2</sub>), 105.2 (C), 83.4 (C), 68.0 (C), 57.5 (CH<sub>2</sub>), 44.0 (C), 40.6 (CH<sub>3</sub>), 31.4 (CH<sub>2</sub>), 29.6 (CH<sub>3</sub>), 29.3 (CH<sub>3</sub>), 24.8 (CH<sub>3</sub>), 19.0 (CH<sub>3</sub> x 6), 11.6 (CH x 3).

**IR** (neat) v: 2940, 2892, 2864, 2171, 1463, 1332, 1159, 1141, 1027, 960, 882, 763, 661, 522 cm<sup>-1</sup>.

**HRMS** (ESI-MS) calcd. for C<sub>21</sub>H<sub>40</sub>NO<sub>2</sub>SSi<sup>+</sup> ([M+H]<sup>+</sup>): 398.2544, found 398.2543.



**Phenyl(2,2,4-trimethyl-3-methylene-4-(3-(triisopropylsilyl)prop-2-yn-1-yl)pyrrolidin-1-yl)methanone (24)** was obtained according to procedure

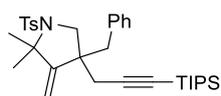
**D**, obtained: 61.9 mg (73%), colorless oil, *R<sub>f</sub>* (PE/Et<sub>2</sub>O 8/2) 0.35.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.39 (s, 5H), 5.01 (s, 1H), 4.95 (s, 1H), 3.59 (d, *J* = 11.2 Hz, 1H), 3.24 (d, *J* = 11.2 Hz, 1H), 2.50 (d, *J* = 16.9 Hz, 1H), 2.36 (d, *J* = 16.9 Hz, 1H), 1.72 (s, 3H), 1.71 (s, 3H), 1.28 (s, 3H), 1.12 (s, 2H), 1.02 – 0.98 (m, 19H).

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 170.6 (C), 164.2 (C), 139.0 (C), 129.4 (CH), 128.7 (CH x 2), 126.5 (CH x 2), 105.3 (C), 105.1 (CH<sub>2</sub>), 83.0 (C), 66.1 (C), 59.4 (CH<sub>2</sub>), 44.4 (C), 31.2 (CH<sub>2</sub>), 28.0 (CH<sub>3</sub>), 27.8 (CH<sub>3</sub>), 24.6 (CH<sub>3</sub>), 18.9 (CH<sub>3</sub> x 6), 11.6 (CH x 3).

**IR** (neat) v: 2959, 2940, 2863, 2170, 1640, 1460, 1395, 1118, 1027, 993, 882, 698, 674, 595 cm<sup>-1</sup>.

**HRMS** (ESI-MS) calcd. for C<sub>27</sub>H<sub>42</sub>NOSi<sup>+</sup> ([M+H]<sup>+</sup>): 424.3030, found 424.3027.



**4-Benzyl-2,2-dimethyl-3-methylene-1-tosyl-4-(3-(triisopropylsilyl)prop-2-yn-1-yl)pyrrolidine (25)** was obtained according to procedure **D**,

obtained: 78.1 mg (71%), colorless oil, *R<sub>f</sub>* (PE/Et<sub>2</sub>O 8/2) 0.65.

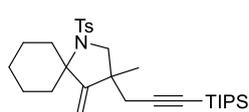
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.74 (d, *J* = 8.3 Hz, 2H), 7.28 (d, *J* = 8.1 Hz, 2H), 7.23 – 7.20 (m, 3H), 7.08 – 7.06 (m, 2H), 4.94 (s, 1H), 4.67 (s, 1H), 3.37 (d, *J* = 9.8 Hz, 1H), 3.13 (d, *J* =

9.8 Hz, 1H), 2.84 (d,  $J = 13.5$  Hz, 1H), 2.80 (d,  $J = 13.5$  Hz, 1H), 2.42 (s, 3H), 2.31 (d,  $J = 17.0$  Hz, 1H), 2.23 (d,  $J = 17.0$  Hz, 1H), 1.67 (s, 3H), 1.48 (s, 3H), 1.06 – 1.02 (d,  $J = 3.8$  Hz, 21H).

$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  160.4 (C), 143.4 (C), 138.0 (C), 137.2 (C), 131.0 (CH x 2), 129.8 (CH x 2), 128.3 (CH x 2), 127.9 (CH x 2), 126.9 (CH), 107.3 ( $\text{CH}_2$ ), 105.4 (C), 84.0 (C), 69.0 (C), 55.6 ( $\text{CH}_2$ ), 48.0 (C), 42.6 ( $\text{CH}_2$ ), 30.3 ( $\text{CH}_3$ ), 28.7 ( $\text{CH}_3$ ), 27.9 ( $\text{CH}_2$ ), 21.8 ( $\text{CH}_3$ ), 19.0 ( $\text{CH}_3$  x 6), 11.7 (CH x 3).

IR (neat) v: 2940, 2863, 2170, 1600, 1462, 1303, 1151, 1091, 991, 908, 730, 671, 577, 549  $\text{cm}^{-1}$ .

HRMS (ESI-MS) calcd. for  $\text{C}_{33}\text{H}_{48}\text{NO}_2\text{SSi}^+$  ( $[\text{M}+\text{H}]^+$ ): 554.3170, found 554.3170.



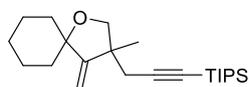
**3-Methyl-4-methylene-1-tosyl-3-(3-(triisopropylsilyl)prop-2-yn-1-yl)-1-azaspiro[4.5]decane (26)** was obtained according to procedure D, obtained: 88.4 mg (86%), colorless oil,  $R_f$  (PE/Et<sub>2</sub>O 8/2) 0.42.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.75 (d,  $J = 8.3$  Hz, 2H), 7.25 (d,  $J = 7.2$  Hz, 2H), 5.35 (s, 1H), 4.88 (s, 1H), 3.37 (d,  $J = 9.9$  Hz, 1H), 3.13 (d,  $J = 9.9$  Hz, 1H), 2.65 – 2.55 (m, 2H), 2.40 (s, 3H), 2.28 (d,  $J = 16.8$  Hz, 1H), 2.19 (d,  $J = 16.8$  Hz, 1H), 1.82 (d,  $J = 12.8$  Hz, 1H), 1.71 – 1.64 (m, 7H), 1.16 (s, 3H), 1.08 (s, 2H), 1.03 – 0.99 (m, 19H).

$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  161.7 (C), 143.1 (C), 139.2 (C), 129.7 (CH x 2), 127.6 (CH x 2), 107.6 ( $\text{CH}_2$ ), 105.5 (C), 82.8 (C), 71.4 (C), 56.9 ( $\text{CH}_2$ ), 44.9 (C), 35.7 ( $\text{CH}_2$ ), 35.2 ( $\text{CH}_2$ ), 31.7 ( $\text{CH}_2$ ), 24.8 ( $\text{CH}_3$ ), 24.6 ( $\text{CH}_2$ ), 22.5 ( $\text{CH}_2$ ), 22.4 ( $\text{CH}_2$ ), 21.8 ( $\text{CH}_3$ ), 18.9 ( $\text{CH}_3$  x 6), 11.6 (CH x 3).

IR (neat) v: 2938, 2890, 2864, 2171, 1598, 1460, 1304, 1155, 1092, 1033, 967, 881, 671, 587  $\text{cm}^{-1}$ .

HRMS (ESI-MS) calcd. for  $\text{C}_{30}\text{H}_{48}\text{NO}_2\text{SSi}^+$  ( $[\text{M}+\text{H}]^+$ ): 514.3170, found 514.3167.



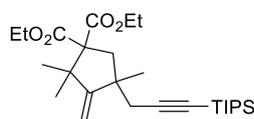
**Triisopropyl(3-(3-methyl-4-methylene-1-oxaspiro[4.5]decan-3-yl)prop-1-yn-1-yl)silane (27)** was obtained according to procedure D, obtained: 59.1 mg (82%), colorless oil,  $R_f$  (PE/Et<sub>2</sub>O 19/1) 0.65.

$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  4.85 (s, 1H), 4.78 (s, 1H), 3.89 (d,  $J = 9.0$  Hz, 1H), 3.55 (d,  $J = 9.0$  Hz, 1H), 2.44 (d,  $J = 16.8$  Hz, 1H), 2.27 (d,  $J = 16.8$  Hz, 1H), 1.77 – 1.55 (m, 8H), 1.35 – 1.25 (m, 2H), 1.24 (s, 3H), 1.09 – 1.03 (m, 21H).

$^{13}\text{C NMR}$  (75 MHz,  $\text{CDCl}_3$ )  $\delta$  164.2 (C), 106.4 (C), 103.4 ( $\text{CH}_2$ ), 84.7 (C), 82.1 (C), 75.1 ( $\text{CH}_2$ ), 46.4 (C), 37.4 ( $\text{CH}_2$ ), 36.7 ( $\text{CH}_2$ ), 31.4 ( $\text{CH}_2$ ), 25.8 ( $\text{CH}_2$ ), 24.1 ( $\text{CH}_3$ ), 22.8 ( $\text{CH}_2 \times 2$ ), 19.0 ( $\text{CH}_3 \times 6$ ), 11.7 ( $\text{CH} \times 3$ ).

**IR** (neat)  $\nu$ : 2930, 2863, 2170, 1461, 1447, 1145, 1057, 1043, 935, 883, 674, 637  $\text{cm}^{-1}$ .

**HRMS** (ESI-MS) calcd. for  $\text{C}_{23}\text{H}_{41}\text{OSi}^+$  ( $[\text{M}+\text{H}]^+$ ): 361.2921, found 361.2924.



**Diethyl**

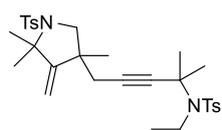
**2,2,4-trimethyl-3-methylene-4-(3-(triisopropylsilyl)prop-2-yn-1-yl)cyclopentane-1,1-dicarboxylate (28)** was obtained according to procedure **D**, obtained: 76.8 mg (83%), colorless oil,  $R_f$  (PE/Et<sub>2</sub>O 8/2) 0.40.

$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  4.92 (s, 1H), 4.87 (s, 1H), 4.23 – 4.12 (m, 4H), 2.64 (d,  $J = 15.0$  Hz, 1H), 2.45 (d,  $J = 17.0$  Hz, 1H), 2.31 (d,  $J = 15.0$  Hz, 1H), 2.30 (d,  $J = 17.0$  Hz, 1H), 1.33 (s, 3H), 1.28 – 1.23 (m, 9H), 1.21 (s, 3H), 1.09 – 1.03 (m, 21H).

$^{13}\text{C NMR}$  (101 MHz,  $\text{CDCl}_3$ )  $\delta$  171.4 (C), 171.1 (C), 167.4 (C), 107.3 (C), 104.4 ( $\text{CH}_2$ ), 81.8 (C), 65.7 (C), 61.3 ( $\text{CH}_2 \times 2$ ), 49.5 (C), 43.2 ( $\text{CH}_2$ ), 43.1 (C), 35.4 ( $\text{CH}_2$ ), 30.1 ( $\text{CH}_3$ ), 26.8 ( $\text{CH}_3$ ), 25.5 ( $\text{CH}_3$ ), 19.0 ( $\text{CH}_3 \times 6$ ), 14.4 ( $\text{CH}_3$ ), 14.47 ( $\text{CH}_3$ ), 11.7 ( $\text{CH} \times 3$ ).

**IR** (neat)  $\nu$ : 2959, 2941, 2865, 2168, 1731, 1463, 1365, 1268, 1234, 1119, 1031, 883, 675, 637  $\text{cm}^{-1}$ .

**HRMS** (ESI-MS) calcd. for  $\text{C}_{27}\text{H}_{47}\text{O}_4\text{Si}^+$  ( $[\text{M}+\text{H}]^+$ ): 463.3238, found 463.3240.



**N-Ethyl-4-methyl-N-(2-methyl-5-(3,5,5-trimethyl-4-methylene-1-tosylpyrrolidin-3-yl)pent-3-yn-2-yl)benzenesulfonamide (42)** was obtained

according to procedure **D**, obtained: 88.4 mg (83%), colorless oil,  $R_f$  (PE/Et<sub>2</sub>O 6/4) 0.35.

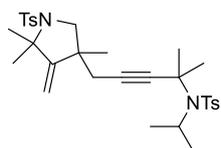
$^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.71 (dd,  $J = 9.7, 7.5$  Hz, 4H), 7.27 (s, 2H), 7.25 (s, 2H), 4.86

(s, 1H), 4.81 (s, 1H), 3.48 (q,  $J = 7.0$  Hz, 2H), 3.25 (d,  $J = 9.7$  Hz, 1H), 3.01 (d,  $J = 9.7$  Hz, 1H), 2.41 (s, 3H), 2.40 (s, 3H), 2.18 (d,  $J = 16.7$  Hz, 1H), 2.06 (d,  $J = 16.7$  Hz, 1H), 1.56 (s, 6H), 1.51 (s, 3H), 1.50 (s, 3H), 1.29 (t,  $J = 7.0$  Hz, 3H), 1.08 (s, 3H).

$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  163.3 (C), 143.4 (C), 143.0 (C), 140.4 (C), 138.1 (C), 129.7 (CH x 2), 129.7 (CH x 2), 127.7 (CH x 2), 127.4 (CH x 2), 105.4 ( $\text{CH}_2$ ), 85.3 (C), 80.6 (C), 68.5 (C), 57.2 ( $\text{CH}_2$ ), 56.7 (C), 43.9 (C), 43.7 ( $\text{CH}_2$ ), 31.2 ( $\text{CH}_3$  x 2), 30.0 ( $\text{CH}_2$ ), 29.7 ( $\text{CH}_3$ ), 29.3 ( $\text{CH}_3$ ), 24.5 ( $\text{CH}_3$ ), 21.8 ( $\text{CH}_3$ ), 21.7 ( $\text{CH}_3$ ), 17.9 ( $\text{CH}_3$ ).

IR (neat) v: 2996, 2931, 2859, 2253, 1456, 1329, 1160, 902, 722, 649, 548  $\text{cm}^{-1}$ .

HRMS (ESI-MS) calcd. for  $\text{C}_{30}\text{H}_{41}\text{N}_2\text{O}_4\text{S}_2^+$  ( $[\text{M}+\text{H}]^+$ ): 557.2502, found 557.2502.



***N*-Isopropyl-4-methyl-*N*-(2-methyl-5-(3,5,5-trimethyl-4-methylene-1-tosylpyrrolidin-3-yl)pent-3-yn-2-yl)benzenesulfonamide (43)** was

obtained according to procedure **D**, obtained: 104 mg (91%), colorless oil,

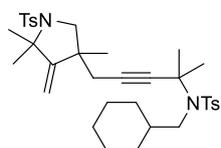
$R_f$  (PE/Et<sub>2</sub>O 6/4) 0.35.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.72 (d,  $J = 7.6$  Hz, 4H), 7.27 (s, 2H), 7.25 (s, 2H), 4.87 (s, 1H), 4.83 (s, 1H), 4.08 (p,  $J = 6.9$  Hz, 1H), 3.30 (d,  $J = 9.7$  Hz, 1H), 3.05 (d,  $J = 9.7$  Hz, 1H), 2.41 (s, 3H), 2.39 (s, 3H), 2.25 (d,  $J = 16.7$  Hz, 1H), 2.16 (d,  $J = 16.7$  Hz, 1H), 1.57 (d,  $J = 6.7$  Hz, 6H), 1.52 (s, 3H), 1.51 (s, 3H), 1.50 – 1.49 (m, 6H), 1.13 (s, 3H).

$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  162.5 (C), 142.4 (C), 141.7 (C), 137.3 (C), 128.8 (CH x 2), 128.7 (CH x 2), 126.8 (CH x 2), 126.0 (CH x 2), 104.4 ( $\text{CH}_2$ ), 85.3 (C), 79.2 (C), 67.6 (C), 56.5 (C), 56.3 ( $\text{CH}_2$ ), 53.1 (CH), 43.0 (C), 30.4 ( $\text{CH}_3$ ), 29.5 ( $\text{CH}_3$ ), 29.1 ( $\text{CH}_2$ ), 28.7 ( $\text{CH}_3$ ), 28.4 ( $\text{CH}_3$ ), 23.6 ( $\text{CH}_3$ ), 22.7 ( $\text{CH}_3$ ), 22.6 ( $\text{CH}_3$ ), 20.8 ( $\text{CH}_3$ ), 20.7 ( $\text{CH}_3$ ) (Attention: one carbon connecting the methyl of tosylate around 140 ppm is not visible in  $^{13}\text{C}$  NMR).

IR (neat) v: 2987, 2911, 2257, 1424, 1333, 1218, 1195, 1112, 907, 735, 523  $\text{cm}^{-1}$ .

HRMS (ESI-MS) calcd. for  $\text{C}_{31}\text{H}_{46}\text{N}_3\text{O}_4\text{S}_2$  ( $[\text{M}+\text{NH}_4]^+$ ): 588.2924, found 588.2926.



***N*-(Cyclohexylmethyl)-4-methyl-*N*-(2-methyl-5-(3,5,5-trimethyl-4-methylene-1-tosylpyrrolidin-3-yl)pent-3-yn-2-yl)benzenesulfonamide (44)**

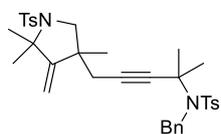
was obtained according to procedure **D**, obtained: 101 mg (81%), colorless oil,  $R_f$  (PE/Et<sub>2</sub>O 6/4) 0.35.

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>)  $\delta$  7.74 (d,  $J$  = 8.3 Hz, 2H), 7.66 (d,  $J$  = 8.3 Hz, 2H), 7.28 (s, 2H), 7.24 (s, 2H), 4.87 (s, 1H), 4.82 (s, 1H), 3.36 (d,  $J$  = 6.8 Hz, 2H), 3.27 (d,  $J$  = 9.7 Hz, 1H), 3.03 (d,  $J$  = 9.7 Hz, 1H), 2.41 (s, 6H), 2.16 (d,  $J$  = 16.7 Hz, 1H), 2.06 (d,  $J$  = 16.7 Hz, 1H), 1.86 – 1.71 (m, 6H), 1.54 (s, 6H), 1.51 (s, 3H), 1.51 (s, 3H), 1.30 – 1.18 (m, 3H), 1.09 (s, 3H), 1.00 – 0.89 (m, 2H).

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>)  $\delta$  162.4 (C), 142.4 (C), 141.8 (C), 140.2 (C), 137.3 (C), 128.8 (CH x 2), 128.6 (CH x 2), 126.8 (CH x 2), 126.3 (CH x 2), 104.4 (CH<sub>2</sub>), 84.6 (C), 80.3 (C), 67.6 (C), 56.4 (CH<sub>2</sub>), 55.8 (C), 54.4 (CH<sub>2</sub>), 42.9 (C), 38.2 (CH), 30.6 (CH<sub>3</sub>), 30.5 (CH<sub>3</sub>), 30.4 (CH<sub>2</sub> x 2), 29.1 (CH<sub>2</sub>), 28.7 (CH<sub>3</sub>), 28.4 (CH<sub>3</sub>), 25.9 (CH<sub>2</sub>), 25.6 (CH<sub>2</sub> x 2), 23.7 (CH<sub>3</sub>), 20.8 (CH<sub>3</sub>), 20.7 (CH<sub>3</sub>).

**IR** (neat) v: 2955, 2931, 2892, 2250, 1493, 1364, 1239, 1132, 1099, 903, 729, 524 cm<sup>-1</sup>.

**HRMS** (ESI-MS) calcd. for C<sub>35</sub>H<sub>52</sub>N<sub>3</sub>O<sub>4</sub>S<sub>2</sub> ([M+NH<sub>4</sub>]<sup>+</sup>): 642.3394, found 642.3401.



***N*-Benzyl-4-methyl-*N*-(2-methyl-5-(3,5,5-trimethyl-4-methylene-1-tosylpyrrolidin-3-yl)pent-3-yn-2-yl)benzenesulfonamide (**45**)** was obtained according to procedure **D**, obtained: 103 mg (83%), colorless oil,  $R_f$

(PE/Et<sub>2</sub>O 7/3) 0.40.

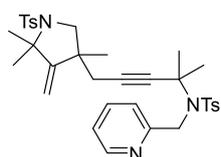
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.71 (d,  $J$  = 8.3 Hz, 2H), 7.62 (d,  $J$  = 8.3 Hz, 2H), 7.41 (d,  $J$  = 7.4 Hz, 2H), 7.31 (t,  $J$  = 7.4 Hz, 3H), 7.23 (d,  $J$  = 7.4 Hz, 4H), 4.83 (s, 1H), 4.76 (s, 1H), 4.72 (s, 2H), 3.21 (d,  $J$  = 9.7 Hz, 1H), 2.96 (d,  $J$  = 9.7 Hz, 1H), 2.40 (s, 3H), 2.38 (s, 3H), 2.10 (d,  $J$  = 16.7 Hz, 1H), 1.98 (d,  $J$  = 16.7 Hz, 1H), 1.51 (s, 6H), 1.49 (s, 3H), 1.48 (s, 3H), 1.01 (s, 3H).

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>)  $\delta$  163.3 (C), 143.4 (C), 143.2 (C), 139.8 (C), 139.8 (C), 138.1 (C), 129.7 (CH x 2), 129.6 (CH x 2), 128.5 (CH x 2), 127.7 (CH x 2), 127.6 (CH x 2), 127.65 (CH x 2), 127.2 (CH), 105.3 (CH<sub>2</sub>), 85.2 (C), 81.4 (C), 68.5 (C), 57.6 (C), 57.2 (CH<sub>2</sub>), 52.3 (CH<sub>2</sub>), 43.7 (C), 31.5 (CH<sub>3</sub> x 2), 29.9 (CH<sub>2</sub>), 29.7 (CH<sub>3</sub>), 29.3 (CH<sub>3</sub>), 24.5 (CH<sub>3</sub>), 21.8 (CH<sub>3</sub> x

2).

**IR** (neat) v: 2956, 2869, 2551, 1731, 1454, 1149, 1090, 914, 735, 572  $\text{cm}^{-1}$ .

**HRMS** (ESI-MS) calcd. for  $\text{C}_{35}\text{H}_{46}\text{N}_3\text{O}_4\text{S}_2^+$  ( $[\text{M}+\text{NH}_4]^+$ ): 636.2924, found 636.2926.



**4-Methyl-N-(2-methyl-5-(3,5,5-trimethyl-4-methylene-1-tosylpyrrolidin-3-yl)pent-3-yn-2-yl)-N-(pyridin-2-ylmethyl)benzenesulfonamide (46)**

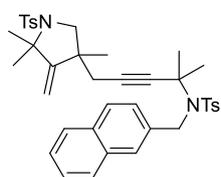
was obtained according to procedure **D**, obtained: 99.2 mg (80%), colorless oil,  $R_f$  (PE/Et<sub>2</sub>O 5/5) 0.35.

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>)  $\delta$  8.50 (s, 1H), 7.72 (dd,  $J = 14.1, 5.8$  Hz, 6H), 7.27 (d,  $J = 8.2$  Hz, 4H), 7.14 (s, 1H), 4.80 (s, 3H), 4.72 (s, 1H), 3.15 (d,  $J = 9.2$  Hz, 1H), 2.93 (d,  $J = 9.2$  Hz, 1H), 2.42 (s, 3H), 2.39 (s, 3H), 1.99 (d,  $J = 16.8$  Hz, 1H), 1.86 (d,  $J = 16.8$  Hz, 1H), 1.51 (s, 6H), 1.47 (s, 6H), 0.95 (s, 3H).

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>)  $\delta$  163.3 (C), 160.2 (C), 148.9 (CH), 143.5 (C), 143.4 (C), 138.9 (C), 138.2 (C), 136.9 (CH), 129.8 (CH x 4), 128.0 (CH x 2), 127.7 (CH x 2), 122.2 (CH), 122.1 (CH), 105.3 (CH<sub>2</sub>), 84.5 (C), 81.3 (C), 68.5 (C), 57.4 (C), 57.2 (CH<sub>2</sub>), 54.3 (CH<sub>2</sub>), 43.6 (C), 31.5 (CH<sub>3</sub>), 31.5 (CH<sub>3</sub>), 29.9 (CH<sub>2</sub>), 29.7 (CH<sub>3</sub>), 29.2 (CH<sub>3</sub>), 24.3 (CH<sub>3</sub>), 21.8 (CH<sub>3</sub>), 21.7 (CH<sub>3</sub>).

**IR** (neat) v: 2973, 2882, 2247, 1655, 1379, 1327, 1087, 1044, 897, 803, 644  $\text{cm}^{-1}$ .

**HRMS** (ESI-MS) calcd. for  $\text{C}_{34}\text{H}_{42}\text{N}_3\text{O}_4\text{S}_2^+$  ( $[\text{M}+\text{H}]^+$ ): 620.2611, found 620.2612.



**4-Methyl-N-(2-methyl-5-(3,5,5-trimethyl-4-methylene-1-tosylpyrrolidin-3-yl)pent-3-yn-2-yl)-N-(naphthalen-2-ylmethyl)benzenesulfonamide (47)**

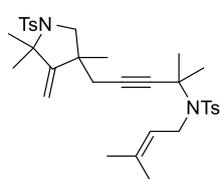
was obtained according to procedure **D**, obtained: 110 mg (82%), colorless oil,  $R_f$  (PE/Et<sub>2</sub>O 6/4) 0.35.

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>)  $\delta$  7.84 – 7.75 (m, 4H), 7.73 – 7.64 (m, 4H), 7.56 (dd,  $J = 8.7, 1.7$  Hz, 1H), 7.46 (hept,  $J = 4.5$  Hz, 2H), 7.21 (d,  $J = 8.1$  Hz, 4H), 4.89 (s, 2H), 4.82 (s, 1H), 4.74 (s, 1H), 3.22 (d,  $J = 9.7$  Hz, 1H), 2.96 (d,  $J = 9.7$  Hz, 1H), 2.38 (s, 3H), 2.35 (s, 3H), 2.11 (d,  $J = 16.7$  Hz, 1H), 1.98 (d,  $J = 16.6$  Hz, 1H), 1.55 (s, 6H), 1.49 (s, 3H), 1.47 (s, 3H), 1.00 (s, 3H).

$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  163.4 (C), 143.4 (C), 143.2 (C), 139.9 (C), 138.2 (C), 137.4 (C), 133.6 (C), 133.0 (C), 129.7 (CH x 2), 129.6 (CH x 2), 128.3 (CH), 128.2 (CH), 128.0 (CH), 127.7 (CH x 4), 126.5 (CH), 126.4 (CH), 126.0 (CH), 125.9 (CH), 105.3 ( $\text{CH}_2$ ), 85.4 (C), 81.6 (C), 68.5 (C), 57.9 (C), 57.2 ( $\text{CH}_2$ ), 52.5 ( $\text{CH}_2$ ), 43.8 (C), 31.6 ( $\text{CH}_3$ ), 31.5 ( $\text{CH}_3$ ), 30.0 ( $\text{CH}_2$ ), 29.7 ( $\text{CH}_3$ ), 29.3 ( $\text{CH}_3$ ), 24.6 ( $\text{CH}_3$ ), 21.8 ( $\text{CH}_3$  x 2).

IR (neat) v: 2975, 2928, 2868, 2254, 1599, 1364, 1146, 1089, 907, 728, 544  $\text{cm}^{-1}$ .

HRMS (ESI-MS) calcd. for  $\text{C}_{39}\text{H}_{48}\text{N}_3\text{O}_4\text{S}_2$  ( $[\text{M}+\text{NH}_4]^+$ ): 686.3081, found 686.3082.



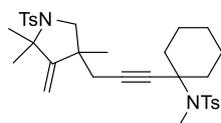
**4-Methyl-N-(2-methyl-5-(3,5,5-trimethyl-4-methylene-1-tosylpyrrolidin-3-yl)pent-3-yn-2-yl)-N-(3-methylbut-2-en-1-yl)benzenesulfonamide (48)** was obtained according to procedure **D**, obtained: 96.7 mg (81%), colorless oil,  $R_f$  (PE/Et<sub>2</sub>O 6/4) 0.35.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.71 (dd,  $J = 12.6, 8.3$  Hz, 4H), 7.26 (d,  $J = 8.1$  Hz, 2H), 7.25 (d,  $J = 8.1$  Hz, 2H), 5.33 (tq,  $J = 4.8, 1.5$  Hz, 1H), 4.85 (s, 1H), 4.81 (s, 1H), 4.08 (d,  $J = 6.1$  Hz, 2H), 3.27 (d,  $J = 9.7$  Hz, 1H), 3.02 (d,  $J = 9.7$  Hz, 1H), 2.40 (s, 3H), 2.40 (s, 3H), 2.17 (d,  $J = 16.7$  Hz, 1H), 2.07 (d,  $J = 16.7$  Hz, 1H), 1.71 (s, 3H), 1.64 (s, 3H), 1.56 (s, 6H), 1.50 (s, 3H), 1.49 (s, 3H), 1.08 (s, 3H).

$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  162.9 (C), 142.8 (C), 142.3 (C), 140.2 (C), 137.8 (C), 132.8 (C), 129.2 (CH x 2), 129.0 (CH x 2), 127.1 (CH x 2), 126.9 (CH x 2), 123.6 (CH), 104.7 ( $\text{CH}_2$ ), 85.1 (C), 80.1 (C), 68.0 (C), 56.7 ( $\text{CH}_2$ ), 56.2 (C), 46.1 ( $\text{CH}_2$ ), 43.3 (C), 30.6 ( $\text{CH}_3$  x 2), 29.5 ( $\text{CH}_2$ ), 29.1 ( $\text{CH}_3$ ), 28.8 ( $\text{CH}_3$ ), 25.4 ( $\text{CH}_3$ ), 23.9 ( $\text{CH}_3$ ), 21.2 ( $\text{CH}_3$ ), 21.1 ( $\text{CH}_3$ ), 17.6 ( $\text{CH}_3$ ).

IR (neat) v: 2961, 2918, 2850, 2253, 1734, 1598, 1494, 1363, 1149, 1090, 970, 814, 673, 547  $\text{cm}^{-1}$ .

HRMS (ESI-MS) calcd. for  $\text{C}_{33}\text{H}_{45}\text{N}_2\text{O}_4\text{S}_2^+$  ( $[\text{M}+\text{H}]^+$ ): 597.2815, found 597.2814.



**N,4-Dimethyl-N-(1-(3-(3,5,5-trimethyl-4-methylene-1-tosylpyrrolidin-3-yl)prop-1-yn-1-yl)cyclohexyl)benzenesulfonamide (49)** was obtained according to procedure **D**, obtained: 100 mg (86%), colorless oil,  $R_f$

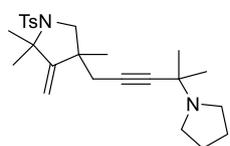
(PE/Et<sub>2</sub>O 6/4) 0.30.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.72 (d, *J* = 8.3 Hz, 2H), 7.66 (d, *J* = 8.3 Hz, 2H), 7.27 (d, *J* = 6.0 Hz, 2H), 7.25 (d, *J* = 6.7 Hz, 2H), 4.84 (s, 1H), 4.78 (s, 1H), 3.22 (d, *J* = 9.6 Hz, 1H), 2.99 (d, *J* = 9.6 Hz, 1H), 2.96 (s, 3H), 2.40 (s, 6H), 2.11 (d, *J* = 16.7 Hz, 1H), 1.99 (d, *J* = 16.6 Hz, 1H + 2 H), 1.85 (tt, *J* = 12.3, 3.5 Hz, 2H), 1.70 – 1.58 (m, 2H), 1.50 (s, 3H), 1.50 (s, 3H), 1.48 – 1.33 (m, 3H), 1.22 – 1.10 (m, 1H), 1.06 (s, 3H).

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>) δ 163.5 (C), 143.4 (C), 143.0 (C), 138.9 (C), 138.1 (C), 129.7 (CH x 2), 129.5 (CH x 2), 127.7 (CH x 2), 127.7 (CH x 2), 105.2 (CH<sub>2</sub>), 83.7 (C), 81.7 (C), 68.6 (C), 61.4 (C), 57.2 (CH<sub>2</sub>), 43.8 (C), 37.7 (CH<sub>2</sub>), 37.6 (CH<sub>2</sub>), 33.8 (CH<sub>3</sub>), 30.0 (CH<sub>2</sub>), 29.6 (CH<sub>3</sub>), 29.4 (CH<sub>3</sub>), 25.2 (CH<sub>2</sub>), 24.6 (CH<sub>3</sub>), 23.7 (CH<sub>2</sub>), 23.6 (CH<sub>2</sub>), 21.8 (CH<sub>3</sub>), 21.7 (CH<sub>3</sub>).

**IR** (neat) v: 2931, 2859, 2254, 1598, 1332, 1157, 1089, 911, 707, 579, 548 cm<sup>-1</sup>.

**HRMS** (ESI-MS) calcd. for C<sub>32</sub>H<sub>43</sub>N<sub>2</sub>O<sub>4</sub>S<sub>2</sub> ([M+H]<sup>+</sup>): 583.2659, found 583.2659.



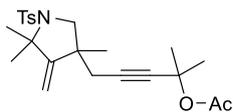
**2,2,4-Trimethyl-4-(4-methyl-4-(pyrrolidin-1-yl)pent-2-yn-1-yl)-3-methylene-1-tosylpyrrolidine (50)** was obtained according to procedure D, obtained: 66.9 mg (78%), colorless oil, *R<sub>f</sub>* (EA with 3‰ of Et<sub>3</sub>N) 0.30.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.75 (d, *J* = 8.3 Hz, 2H), 7.27 (d, *J* = 8.3 Hz, 2H), 4.87 (s, 1H), 4.86 (s 1H), 3.38 (d, *J* = 9.7 Hz, 1H), 3.08 (d, *J* = 9.7 Hz, 1H), 2.63 (br s, 4H), 2.41 (s, 3H), 2.30 (d, *J* = 16.6 Hz, 1H), 2.18 (d, *J* = 16.6 Hz, 1H), 1.77 – 1.74 (m, 4H), 1.54 (s, 3H), 1.53 (s, 3H), 1.31 (s, 6H), 1.17 (s, 3H).

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 163.7 (C), 143.3 (C), 138.5 (C), 129.7 (CH x 2), 127.7 (CH x 2), 105.1 (CH<sub>2</sub>), 84.0 (C), 80.6 (C), 68.6 (C), 57.2 (CH<sub>2</sub>), 54.2 (C), 48.4 (CH<sub>2</sub> x 2), 44.1 (C), 30.1 (CH<sub>3</sub> x 2), 30.0 (CH<sub>2</sub>), 29.6 (CH<sub>3</sub>), 29.5 (CH<sub>3</sub>), 24.7 (CH<sub>3</sub>), 24.1 (CH<sub>2</sub> x 2), 21.8 (CH<sub>3</sub>).

**IR** (neat) v: 3358, 3200, 2923, 2906, 2856, 2166, 1512, 1445, 1301, 1129, 997, 898, 679, 590 cm<sup>-1</sup>.

**HRMS** (ESI-MS) calcd. for C<sub>25</sub>H<sub>37</sub>N<sub>2</sub>O<sub>2</sub>S<sup>+</sup> ([M+H]<sup>+</sup>): 429.2570, found 429.2569.



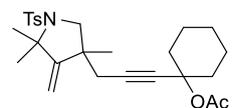
**4-(4-Methoxy-4-methylpent-2-yn-1-yl)-2,2,4-trimethyl-3-methylene-1-tosylpyrrolidine (51)** was obtained according to procedure **D**, obtained: 35.1 mg (42%), colorless oil,  $R_f$  (PE/Et<sub>2</sub>O 7/3) 0.35.

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>)  $\delta$  7.76 (d,  $J$  = 8.3 Hz, 2H), 7.28 (d,  $J$  = 8.1 Hz, 2H), 4.88 (s, 1H), 4.87 (s, 1H), 3.39 (d,  $J$  = 9.8 Hz, 1H), 3.10 (d,  $J$  = 9.8 Hz, 1H), 2.41 (s, 3H), 2.27 (d,  $J$  = 16.7 Hz, 1H), 2.17 (d,  $J$  = 16.7 Hz, 1H), 1.99 (s, 3H), 1.57 (s, 3H), 1.57 (s, 3H), 1.52 (s, 6H), 1.17 (s, 3H).

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>)  $\delta$  168.6 (C), 162.6 (C), 142.2 (C), 137.6 (C), 128.7 (CH x 2), 126.8 (CH x 2), 104.4 (CH<sub>2</sub>), 82.9 (C), 80.6 (C), 71.5 (C), 67.6 (C), 56.4 (CH<sub>2</sub>), 43.1 (C), 29.1 (CH<sub>2</sub>), 28.6(CH<sub>3</sub> x 2), 28.5 (CH<sub>3</sub>), 28.4 (CH<sub>3</sub>), 23.5 (CH<sub>3</sub>), 21.3 (CH<sub>3</sub>), 20.8 (CH<sub>3</sub>).

**IR** (neat) v: 2972, 2857, 2250, 1964, 1744, 1459, 1179, 1065, 907, 737, 656 cm<sup>-1</sup>.

**HRMS** (ESI-MS) calcd. for C<sub>23</sub>H<sub>32</sub>NO<sub>4</sub>S ([M+H]<sup>+</sup>): 418.2047, found 418.2042.



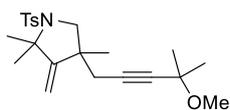
**1-(3-(3,5,5-Trimethyl-4-methylene-1-tosylpyrrolidin-3-yl)prop-1-yn-1-yl)cyclohexyl acetate (52)** was obtained according to procedure **D**, obtained: 33.9 mg (37%), colorless oil,  $R_f$  (PE/Et<sub>2</sub>O 7/3) 0.35.

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>)  $\delta$  7.75 (d,  $J$  = 8.2 Hz, 2H), 7.27 (d,  $J$  = 7.5 Hz, 2H), 4.88 (s, 1H), 4.87 (s, 1H), 3.38 (d,  $J$  = 9.8 Hz, 1H), 3.10 (d,  $J$  = 9.8 Hz, 1H), 2.40 (s, 3H), 2.31 (d,  $J$  = 16.7 Hz, 1H), 2.21 (d,  $J$  = 16.7 Hz, 1H), 2.00 (s, 5H), 1.76 (ddd,  $J$  = 13.0, 9.5, 3.7 Hz, 2H), 1.58 – 1.53 (m, 2H), 1.52 (s, 3H), 1.51 (s, 3H), 1.49 – 1.43 (m, 3H), 1.35 – 1.27 (m, 1H), 1.18 (s, 3H).

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>)  $\delta$  169.4 (C), 163.5 (C), 143.2 (C), 138.4 (C), 129.7 (CH x 2), 127.7 (CH x 2), 105.4 (CH<sub>2</sub>), 83.4 (C), 82.6 (C), 76.0 (C), 68.6 (C), 57.3 (CH<sub>2</sub>), 44.1 (C), 37.6 (CH<sub>2</sub>), 37.5 (CH<sub>2</sub>), 30.2 (CH<sub>2</sub>), 29.53 (CH<sub>3</sub>), 29.51 (CH<sub>3</sub>), 25.5 (CH<sub>2</sub>), 24.4 (CH<sub>3</sub>), 23.0 (CH<sub>2</sub>), 22.9 (CH<sub>2</sub>), 22.3 (CH<sub>3</sub>), 21.8 (CH<sub>3</sub>).

**IR** (neat) v: 2939, 2892, 2253, 1734, 1450, 1326, 1266, 902, 722, 649, 548 cm<sup>-1</sup>.

**HRMS** (ESI-MS) calcd. for C<sub>26</sub>H<sub>36</sub>NO<sub>4</sub>S ([M+H]<sup>+</sup>): 458.2360, found 458.2361.



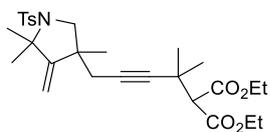
**4-(4-Methoxy-4-methylpent-2-yn-1-yl)-2,2,4-trimethyl-3-methylene-1-tosylpyrrolidine (53)** was obtained according to procedure **D**, obtained: 18.7 mg (24%), colorless oil,  $R_f$  (PE/Et<sub>2</sub>O 7/3) 0.35.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.75 (d,  $J$  = 8.3 Hz, 2H), 7.28 (d,  $J$  = 8.4 Hz, 2H), 4.89 (s, 1H), 4.87 (s, 1H), 3.37 (d,  $J$  = 9.7 Hz, 1H), 3.25 (s, 3H), 3.10 (d,  $J$  = 9.7 Hz, 1H), 2.41 (s, 3H), 2.30 (d,  $J$  = 16.7 Hz, 1H), 2.19 (d,  $J$  = 16.7 Hz, 1H), 1.55 (s, 3H), 1.53 (s, 3H), 1.35 (s, 6H), 1.17 (s, 3H).

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>)  $\delta$  162.6 (C), 142.3 (C), 137.4 (C), 128.7 (CH x 2), 126.8 (CH x 2), 104.3 (CH<sub>2</sub>), 83.5 (C), 80.4 (C), 69.8 (C), 67.7 (C), 56.3 (CH<sub>2</sub>), 50.8 (CH<sub>3</sub>), 43.1 (C), 29.1 (CH<sub>2</sub>), 28.6 (CH<sub>3</sub>), 28.5 (CH<sub>3</sub>), 27.9 (CH<sub>3</sub>), 27.8 (CH<sub>3</sub>), 23.7 (CH<sub>3</sub>), 20.8 (CH<sub>3</sub>).

**IR** (neat) v: 2980, 2912, 2253, 1467, 9, 903, 723, 649 cm<sup>-1</sup>.

**HRMS** (ESI-MS) calcd. for C<sub>22</sub>H<sub>32</sub>NO<sub>3</sub>S ([M+H]<sup>+</sup>): 390.2097, found 390.2097.



**Diethyl 2-(2-methyl-5-(3,5,5-trimethyl-4-methylene-1-tosylpyrrolidin-3-yl)pent-3-yn-2-yl)malonate (54)** was obtained according to procedure **D**,

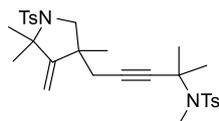
obtained: 24.8 mg (24%), colorless oil,  $R_f$  (PE/Et<sub>2</sub>O 8/2) 0.35.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.76 (d,  $J$  = 8.3 Hz, 2H), 7.28 (d,  $J$  = 8.0 Hz, 2H), 4.85 (d,  $J$  = 1.7 Hz, 2H), 4.19 (q,  $J$  = 7.1 Hz, 4H), 3.37 (d,  $J$  = 9.9 Hz, 1H), 3.35 (s, 1H), 3.09 (d,  $J$  = 9.9 Hz, 1H), 2.41 (s, 3H), 2.19 (d,  $J$  = 16.6 Hz, 1H), 2.09 (d,  $J$  = 16.6 Hz, 1H), 1.51 (s, 3H), 1.50 (s, 3H), 1.36 (s, 3H), 1.35 (s, 3H), 1.26 (t,  $J$  = 7.1 Hz, 6H), 1.15 (s, 3H).

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$  167.6 (C), 167.6 (C), 163.8 (C), 143.2 (C), 138.6 (C), 129.7 (CH x 2), 127.7 (CH x 2), 105.1 (CH<sub>2</sub>), 87.3 (C), 78.2 (C), 68.6 (C), 61.5 (CH<sub>2</sub> x 2), 60.9 (CH), 57.3 (CH<sub>2</sub>), 44.1 (C), 33.0 (C), 30.2 (CH<sub>2</sub>), 29.5 (CH<sub>3</sub> x 2), 28.1 (CH<sub>3</sub>), 28.0 (CH<sub>3</sub>), 24.2 (CH<sub>3</sub>), 21.8 (CH<sub>3</sub>), 14.5 (CH<sub>3</sub> x 2).

**IR** (neat) v: 2988, 2931, 2258, 1728, 1421, 1389, 12179, 1123, 903, 723, 649 cm<sup>-1</sup>.

**HRMS** (ESI-MS) calcd. for C<sub>28</sub>H<sub>43</sub>N<sub>2</sub>O<sub>6</sub>S<sup>+</sup> ([M+NH<sub>4</sub>]<sup>+</sup>): 535.2836, found 535.2836.



***N*,4-Dimethyl-*N*-(2-methyl-5-(3,5,5-trimethyl-4-methylene-1-tosylpyrrolidin-3-yl)pent-3-yn-2-yl)benzenesulfonamide (59)** was obtained according to procedure **D**, obtained: 84.7 mg (78%), colorless oil,  $R_f$

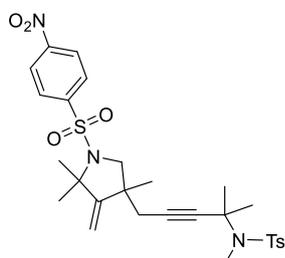
(PE/Et<sub>2</sub>O 6/4) 0.35.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.69 (dd,  $J = 20.3, 8.3$  Hz, 4H), 7.27 (s, 2H), 7.25 (s, 2H), 4.84 (s, 1H), 4.78 (s, 1H), 3.23 (d,  $J = 9.7$  Hz, 1H), 2.99 (d,  $J = 9.7$  Hz, 1H), 2.97 (s, 3H), 2.40 (s, 6H), 2.12 (d,  $J = 16.7$  Hz, 1H), 2.00 (d,  $J = 16.7$  Hz, 1H), 1.55 (s, 3H), 1.54 (s, 3H), 1.49 (s, 3H), 1.48 (s, 3H), 1.05 (s, 3H).

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>) δ 163.4 (C), 143.4 (C), 143.2 (C), 139.0 (C), 138.2 (C), 129.8 (CH x 2), 129.7 (CH x 2), 127.6 (CH x 2), 127.5 (CH x 2), 105.3 (CH<sub>2</sub>), 84.5 (C), 81.0 (C), 68.5 (C), 57.2 (CH<sub>2</sub>), 56.3 (C), 43.9 (C), 34.5 (CH<sub>3</sub>), 30.4 (CH<sub>3</sub> x 2), 29.9 (CH<sub>2</sub>), 29.7 (CH<sub>3</sub>), 29.3 (CH<sub>3</sub>), 24.5 (CH<sub>3</sub>), 21.8 (CH<sub>3</sub> x 2).

**IR** (neat) v: 2976, 2869, 2239, 1598, 1364, 1160, 1090, 947, 741, 580 cm<sup>-1</sup>.

**HRMS** (ESI-MS) calcd. for C<sub>29</sub>H<sub>39</sub>N<sub>2</sub>O<sub>4</sub>S<sub>2</sub><sup>+</sup> ([M+H]<sup>+</sup>): 543.2346, found 543.2344.

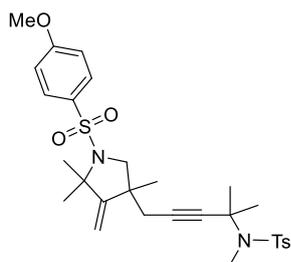


***N*,4-Dimethyl-*N*-(2-methyl-5-(3,5,5-trimethyl-4-methylene-1-((4-nitrophenyl)sulfonyl)pyrrolidin-3-yl)pent-3-yn-2-yl)benzenesulfonamide (60)** was obtained according to procedure **D**, obtained: 86.0 mg (75%), colorless oil,  $R_f$  (PE/Et<sub>2</sub>O 5/5) 0.35;

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 8.32 (d,  $J = 8.9$  Hz, 2H), 8.04 (d,  $J = 8.9$  Hz, 2H), 7.70 (d,  $J = 8.3$  Hz, 2H), 7.28 (d,  $J = 8.1$  Hz, 2H), 4.88 (s, 1H), 4.84 (s, 1H), 3.43 (d,  $J = 9.9$  Hz, 1H), 3.11 (d,  $J = 9.9$  Hz, 1H), 2.97 (s, 3H), 2.42 (s, 3H), 2.15 (d,  $J = 16.7$  Hz, 1H), 2.06 (d,  $J = 16.7$  Hz, 1H), 1.57 (s, 3H), 1.57 (s, 3H), 1.50 (s, 6H), 1.10 (s, 3H).

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 162.6 (C), 150.1 (C), 146.9 (C), 143.3 (C), 139.1 (C), 129.7 (CH x 2), 128.8 (CH x 2), 127.6 (CH x 2), 124.5 (CH x 2), 105.9 (CH<sub>2</sub>), 85.1 (C), 80.4 (C), 69.2 (C), 57.5 (CH<sub>2</sub>), 55.9 (C), 44.1 (C), 34.1 (CH<sub>3</sub>), 30.5 (CH<sub>3</sub>), 30.4 (CH<sub>3</sub>), 29.9 (CH<sub>2</sub>), 29.7 (CH<sub>3</sub>), 29.6 (CH<sub>3</sub>), 24.5 (CH<sub>3</sub>), 21.8 (CH<sub>3</sub>).

**HRMS** (ESI-MS) calcd. for C<sub>28</sub>H<sub>39</sub>N<sub>4</sub>O<sub>6</sub>S<sub>2</sub><sup>+</sup> ([M+NH<sub>4</sub>]<sup>+</sup>): 591.2306, found 591.2310.

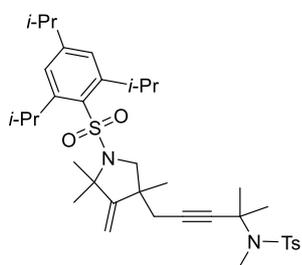


***N*-(5-(1-((4-Methoxyphenyl)sulfonyl)-3,5,5-trimethyl-4-methylene-2-methylpent-3-yn-2-yl)-*N*,4-dimethylbenzenesulfonamide (61)** was obtained according to procedure **D**, obtained: 88.3 mg (79%), colorless oil;  $R_f$  (PE/Et<sub>2</sub>O 6/4) 0.45;

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>)  $\delta$  7.77 (d,  $J$  = 8.9 Hz, 2H), 7.67 (d,  $J$  = 8.3 Hz, 2H), 7.27 (d,  $J$  = 8.2 Hz, 2H), 6.94 (d,  $J$  = 8.9 Hz, 2H), 4.85 (s, 1H), 4.79 (s, 1H), 3.85 (s, 3H), 3.21 (d,  $J$  = 9.6 Hz, 1H), 2.97 (d,  $J$  = 9.6 Hz, 1H), 2.97 (s, 3H), 2.40 (s, 3H), 2.13 (d,  $J$  = 16.7 Hz, 1H), 2.00 (d,  $J$  = 16.7 Hz, 1H), 1.55 (s, 3H), 1.54 (s, 3H), 1.50 (s, 3H), 1.49 (s, 3H), 1.05 (s, 3H).

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>)  $\delta$  163.4 (C), 162.9 (C), 143.2 (C), 138.8 (C), 132.8 (C), 129.8 (CH x 2), 129.7 (CH x 2), 127.6 (CH x 2), 114.2 (CH x 2), 105.3 (CH<sub>2</sub>), 84.5 (C), 81.0 (C), 68.5 (C), 57.1 (CH<sub>2</sub>), 56.3 (C), 55.9 (CH<sub>3</sub>), 43.8 (C), 34.5 (CH<sub>3</sub>), 30.5 (CH<sub>3</sub>), 30.4 (CH<sub>3</sub>), 29.9 (CH<sub>2</sub>), 29.7 (CH<sub>3</sub>), 29.3 (CH<sub>3</sub>), 24.5 (CH<sub>3</sub>), 21.8 (CH<sub>3</sub>).

**HRMS** (ESI-MS) calcd. for C<sub>29</sub>H<sub>39</sub>N<sub>2</sub>O<sub>5</sub>S<sub>2</sub><sup>+</sup> ([M+H]<sup>+</sup>): 559.2295, found 559.2997.



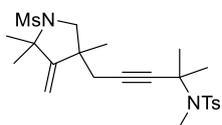
***N*,4-Dimethyl-*N*-(2-methyl-5-(3,5,5-trimethyl-4-methylene-1-((2,4,6-triisopropylphenyl)sulfonyl)pyrrolidin-3-yl)pent-3-yn-2-yl)benzenesulfonamide (62)** was obtained according to procedure **D**, obtained: 79.9 mg (61%), colorless oil;  $R_f$  (PE/Et<sub>2</sub>O 9/1) 0.45.

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>)  $\delta$  7.65 (d,  $J$  = 7.8 Hz, 2H), 7.27 – 7.25 (m, 2H), 7.15 (s, 2H), 4.92 (d,  $J$  = 2.5 Hz, 1H), 4.85 (d,  $J$  = 2.5 Hz, 1H), 4.34 (p,  $J$  = 6.9 Hz, 2H), 3.14 (d,  $J$  = 9.7 Hz, 1H), 2.97 (d,  $J$  = 9.7 Hz, 1H), 2.89 – 2.91 (m, 1H), 2.87 (s, 3H), 2.42 (s, 3H), 2.27 (d,  $J$  = 16.7 Hz, 1H), 1.92 (d,  $J$  = 16.7 Hz, 1H), 1.71 (s, 3H), 1.67 (s, 3H), 1.40 (s, 6H), 1.28 – 1.24 (m, 18H), 1.08 (s, 3H).

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>)  $\delta$  164.3 (C), 153.5 (C), 151.8 (C x 2), 143.1 (C), 139.0 (C), 132.7 (C), 129.6 (CH x 2), 127.6 (CH x 2), 124.1 (CH x 2), 104.9 (CH<sub>2</sub>), 84.5 (C), 81.0 (C), 69.9 (C), 56.2 (C), 56.1 (CH<sub>2</sub>), 44.0 (C), 34.5 (CH x 2), 34.4 (CH<sub>3</sub>), 30.6 (CH<sub>2</sub>), 30.4 (CH<sub>3</sub>), 30.3 (CH<sub>3</sub>), 30.1 (CH<sub>3</sub>), 29.3 (CH), 28.6 (CH<sub>3</sub>), 25.2 (CH<sub>3</sub> x 2), 25.0 (CH<sub>3</sub> x 2), 23.9 (CH<sub>3</sub>),

23.8 (CH<sub>3</sub>), 23.7 (CH<sub>3</sub>), 21.8 (CH<sub>3</sub>).

**HRMS** (ESI-MS) calcd. for C<sub>37</sub>H<sub>55</sub>N<sub>2</sub>O<sub>4</sub>S<sub>2</sub><sup>+</sup> ([M+H]<sup>+</sup>): 655.3598, found 655.3600.



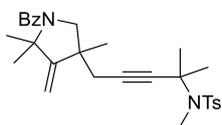
**N,4-Dimethyl-N-(2-methyl-5-(3,5,5-trimethyl-4-methylene-1-(methylsulfonyl)pyrrolidin-3-yl)pent-3-yn-2-yl)benzenesulfonamide (63)** was obtained according to procedure **D**, obtained: 60.7 mg (65%), colorless oil;

R<sub>f</sub> (PE/Et<sub>2</sub>O 7/3) 0.35.

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 7.72 (d, *J* = 8.3 Hz, 2H), 7.29 (d, *J* = 8.6 Hz, 2H), 4.92 (s, 1H), 4.87 (s, 1H), 3.41 (d, *J* = 9.7 Hz, 1H), 3.10 (d, *J* = 9.7 Hz, 1H), 3.04 (s, 3H), 2.91 (s, 3H), 2.43 (s, 3H), 2.29 (d, *J* = 16.7 Hz, 1H), 2.16 (d, *J* = 16.7 Hz, 1H), 1.64 (s, 6H), 1.54 (s, 3H), 1.53 (s, 3H), 1.18 (s, 3H).

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 163.0 (C), 143.2 (C), 138.9 (C), 129.7 (CH x 2), 127.6 (CH x 2), 105.6 (CH<sub>2</sub>), 84.7 (C), 80.8 (C), 67.8 (C), 57.4 (CH<sub>2</sub>), 56.1 (C), 43.7 (C), 40.3 (CH<sub>3</sub>), 34.3 (CH<sub>3</sub>), 30.5 (CH<sub>3</sub> x 2), 30.0 (CH<sub>2</sub>), 29.5 (CH<sub>3</sub>), 29.2 (CH<sub>3</sub>), 24.8 (CH<sub>3</sub>), 21.8 (CH<sub>3</sub>).

**HRMS** (ESI-MS) calcd. for C<sub>23</sub>H<sub>38</sub>N<sub>3</sub>O<sub>4</sub>S<sub>2</sub><sup>+</sup> ([M+NH<sub>4</sub>]<sup>+</sup>): 484.2298, found 484.2297.



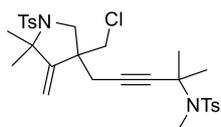
**N-(5-(1-Benzoyl-3,5,5-trimethyl-4-methylenepyrrolidin-3-yl)-2-methylpent-3-yn-2-yl)-N,4-dimethylbenzenesulfonamide (64)** was obtained according to procedure **D**, obtained: 79.8 mg (81%), colorless oil; R<sub>f</sub>

(PE/Et<sub>2</sub>O 7/3) 0.35.

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 7.64 (d, *J* = 8.3 Hz, 2H), 7.39 – 7.32 (m, 5H), 7.22 (d, *J* = 8.1 Hz, 2H), 4.95 (s, 1H), 4.84 (s, 1H), 3.39 (d, *J* = 11.2 Hz, 1H), 3.08 (d, *J* = 11.2 Hz, 1H), 2.92 (s, 3H), 2.38 (s, 3H), 2.24 (d, *J* = 16.7 Hz, 1H), 2.05 (d, *J* = 16.7 Hz, 1H), 1.67 (s, 3H), 1.64 (s, 3H), 1.54 (s, 6H), 1.08 (s, 3H).

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 170.4 (C), 163.8 (C), 143.1 (C), 138.9 (C), 138.6 (C), 129.6 (CH x 2), 129.5 (CH), 128.8 (CH x 2), 127.6 (CH x 2), 126.6 (CH x 2), 105.2 (CH<sub>2</sub>), 84.5 (C), 81.0 (C), 66.0 (C), 59.1 (CH<sub>2</sub>), 56.2 (C), 44.2 (C), 34.4 (CH<sub>3</sub>), 30.50 (CH<sub>3</sub>), 30.47 (CH<sub>3</sub>), 29.8 (CH<sub>2</sub>), 28.2 (CH<sub>3</sub>), 27.5 (CH<sub>3</sub>), 24.1 (CH<sub>3</sub>), 21.8 (CH<sub>3</sub>).

**HRMS** (ESI-MS) calcd. for C<sub>29</sub>H<sub>37</sub>N<sub>2</sub>O<sub>3</sub>S<sup>+</sup> ([M+H]<sup>+</sup>): 493.2519, found 493.2519.



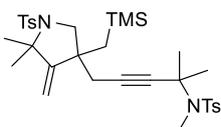
***N*-(5-(3-(Chloromethyl)-5,5-dimethyl-4-methylene-1-tosylpyrrolidin-3-yl)-2-methylpent-3-yn-2-yl)-*N*,4-dimethylbenzenesulfonamide (65)**

was obtained according to procedure **D**, obtained: 27.7 mg (24%), colorless oil;  $R_f$ (PE/Et<sub>2</sub>O 7/3) 0.35.

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>)  $\delta$  7.70 (dd,  $J$  = 15.1, 8.2 Hz, 4H), 7.32 – 7.26 (m, 4H), 5.00 (s, 1H), 4.94 (s, 1H), 3.41 (m, 3H), 3.19 (d,  $J$  = 10.2 Hz, 1H), 2.96 (s, 3H), 2.41 (s, 6H), 2.33 (s, 2H), 1.56 (s, 3H), 1.55 (s, 3H), 1.51 (s, 3H), 1.46 (s, 3H).

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>)  $\delta$  158.5 (C), 143.7 (C), 143.3 (C), 138.8 (C), 137.9 (C), 129.9 (CH x 2), 129.7 (CH x 2), 127.7 (CH x 2), 127.6 (CH x 2), 108.6 (CH<sub>2</sub>), 85.3 (C), 70.7 (C), 68.9 (C), 56.0 (C), 53.9 (CH<sub>2</sub>), 49.3 (CH<sub>2</sub>), 48.5 (C), 34.3 (CH<sub>3</sub>), 30.5 (CH<sub>3</sub>), 30.4 (CH<sub>3</sub>), 29.5 (CH<sub>3</sub>), 29.1 (CH<sub>3</sub>), 25.4 (CH<sub>2</sub>), 21.9 (CH<sub>3</sub> x 2).

**HRMS** (ESI-MS) calcd. for C<sub>29</sub>H<sub>38</sub>ClN<sub>2</sub>O<sub>4</sub>S<sub>2</sub><sup>+</sup> ([M+H]<sup>+</sup>): 577.1956, found 577.1956.



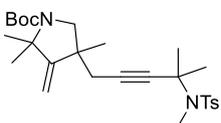
***N*-(5-(5,5-Dimethyl-4-methylene-1-tosyl-3-((trimethylsilyl)methyl)pyrrolidin-3-yl)-2-methylpent-3-yn-2-yl)-*N*,4-dimethylbenzenesulfonamide (66)**

was obtained according to procedure **D**, obtained: 87.3 mg (71%), colorless oil;  $R_f$ (PE/Et<sub>2</sub>O 7/3) 0.35.

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>)  $\delta$  7.69 (dd,  $J$  = 11.9, 8.3 Hz, 4H), 7.28 – 7.24 (m, 4H), 4.84 (s, 1H), 4.80 (s, 1H), 3.20 (d,  $J$  = 9.5 Hz, 1H), 3.05 (d,  $J$  = 9.5 Hz, 1H), 2.99 (s, 3H), 2.40 (s, 6H), 2.15 (s, 2H), 1.56 (s, 6H), 1.49 (s, 3H), 1.47 (s, 3H), 1.06 (d,  $J$  = 15.1 Hz, 1H), 0.76 (d,  $J$  = 15.0 Hz, 1H), -0.04 (s, 9H).

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>)  $\delta$  162.2 (C), 142.4 (C), 142.2 (C), 138.1 (C), 136.9 (C), 128.7 (CH x 2), 128.6 (CH x 2), 126.8 (CH x 2), 126.6 (CH x 2), 105.0 (CH<sub>2</sub>), 84.0 (C), 80.3 (C), 67.1 (C), 56.7 (CH<sub>2</sub>), 55.4 (C), 45.4 (C), 33.5 (CH<sub>3</sub>), 29.37 (CH<sub>3</sub>), 29.35 (CH<sub>3</sub>), 29.3 (CH<sub>2</sub>), 29.1 (CH<sub>3</sub>), 28.4 (CH<sub>3</sub>), 25.3 (CH<sub>2</sub>), 20.8 (CH<sub>3</sub>), 20.7 (CH<sub>3</sub>), 0.2 (CH<sub>3</sub> x 3).

**HRMS** (ESI-MS) calcd. for C<sub>32</sub>H<sub>50</sub>N<sub>3</sub>O<sub>4</sub>S<sub>2</sub>Si<sup>+</sup> ([M+NH<sub>4</sub>]<sup>+</sup>): 632.3007, found 632.3010.



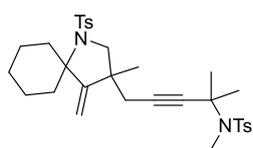
***Tert*-butyl 4-(4-(*N*,4-dimethylphenylsulfonamido)-4-methylpent-2-yn-1-yl)-2,2-dimethylpyrrolidine-3-carboxylate (67)**

**4-trimethyl-3-methylenepyrrolidine-1-carboxylate (67)** was obtained according to procedure **D**, obtained: 81.1 mg (83%), colorless oil;  $R_f$  (PE/Et<sub>2</sub>O 8/2) 0.35.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.71 (d,  $J$  = 8.0 Hz, 2H), 7.27 (s,  $J$  = 8.7 Hz, 2H), 4.87 (s, 1H), 4.80 (s, 1H), 3.39 (d,  $J$  = 11.3 Hz, 1H), 3.17 (d,  $J$  = 11.3 Hz, 1H), 3.06 (s, 3H), 2.41 (s, 3H), 2.18 – 2.04 (m, 2H), 1.63 (s, 6H), 1.55 – 1.39 (m, 15H), 1.11 (s, 3H).

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>)  $\delta$  164.9 (C), 155.1 (C), 143.1 (C), 139.1 (C), 129.6 (CH x 2), 127.7 (CH x 2), 105.2 (CH<sub>2</sub>), 84.2 (C), 81.6 (C), 77.8 (C), 63.8 (C), 56.9 (CH<sub>2</sub>), 56.4 (C), 43.2 (C), 34.6 (CH<sub>3</sub>), 30.6 (CH<sub>3</sub> x 2), 30.1 (CH<sub>2</sub>), 28.9 (CH<sub>3</sub> x 3), 28.2 (CH<sub>3</sub>), 27.6 (CH<sub>3</sub>), 25.6 (CH<sub>3</sub>), 21.8 (CH<sub>3</sub>).

**HRMS** (ESI-MS) calcd. for C<sub>27</sub>H<sub>41</sub>N<sub>2</sub>O<sub>4</sub>S<sup>+</sup> ([M+H]<sup>+</sup>): 489.2782, found 489.2777.



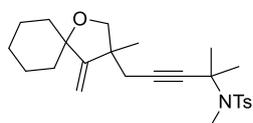
***N*,4-Dimethyl-*N*-(2-methyl-5-(3-methyl-4-methylene-1-tosyl-1-azaspiro[4.5]decan-3-yl)pent-3-yn-2-yl)benzenesulfonamide (68)** was obtained according to procedure **D**, obtained: 73.4 mg (63%), colorless

oil;  $R_f$  (PE/Et<sub>2</sub>O 6/4) 0.35.

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>)  $\delta$  7.74 (d,  $J$  = 8.2 Hz, 2H), 7.68 (d,  $J$  = 8.3 Hz, 2H), 7.27 (d,  $J$  = 6.8 Hz, 4H), 5.33 (s, 1H), 4.80 (s, 1H), 3.22 (d,  $J$  = 9.8 Hz, 1H), 3.02 (d,  $J$  = 9.8 Hz, 1H), 2.98 (s, 3H), 2.66 – 2.49 (m, 2H), 2.42 (s, 3H), 2.41 (s, 3H), 2.09 (d,  $J$  = 16.7 Hz, 1H), 1.97 (d,  $J$  = 16.7 Hz, 1H), 1.79 – 1.63 (m, 7H), 1.56 (s, 3H), 1.55 (s, 3H), 1.35 (m, 1H), 1.02 (s, 3H).

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>)  $\delta$  161.3 (C), 143.24 (C), 143.18 (C), 138.95 (C), 138.94 (C), 129.68 (CH x 2), 129.66 (CH x 2), 127.58 (CH x 2), 127.56 (CH x 2), 107.7 (CH<sub>2</sub>), 84.4 (C), 81.1 (C), 71.3 (C), 56.7 (CH<sub>2</sub>), 56.3 (C), 44.7 (C), 35.4 (CH<sub>2</sub>), 35.3 (CH<sub>2</sub>), 34.5 (CH<sub>3</sub>), 30.4 (CH<sub>3</sub> x 2), 30.2 (CH<sub>2</sub>), 24.6 (CH<sub>3</sub>), 24.5 (CH<sub>2</sub>), 22.4 (CH<sub>2</sub>), 22.3 (CH<sub>2</sub>), 21.8 (CH<sub>3</sub> x 2).

**HRMS** (ESI-MS) calcd. for C<sub>32</sub>H<sub>43</sub>N<sub>2</sub>O<sub>4</sub>S<sub>2</sub><sup>+</sup> ([M+H]<sup>+</sup>): 583.2659, found 583.2659.



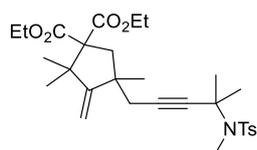
***N*,4-Dimethyl-*N*-(2-methyl-5-(3-methyl-4-methylene-1-oxaspiro[4.5]decan-3-yl)pent-3-yn-2-yl)benzenesulfonamide (69)** was obtained according to procedure **D**, obtained: 70.5 mg (82%), colorless oil;  $R_f$

(PE/Et<sub>2</sub>O 7/3) 0.45.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.70 (d, *J* = 8.3 Hz, 2H), 7.27 (d, *J* = 8.1 Hz, 2H), 4.76 (s, 2H), 3.65 (d, *J* = 8.9 Hz, 1H), 3.41 (d, *J* = 8.9 Hz, 1H), 3.06 (s, 3H), 2.41 (s, 3H), 2.18 (d, *J* = 16.6 Hz, 1H), 2.01 (d, *J* = 16.6 Hz, 1H), 1.73 – 1.66 (m, 3H), 1.63 (s, 6H), 1.59 – 1.54 (m, 4H), 1.35 – 1.16 (m, 3H), 1.07 (s, 3H).

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 163.9 (C), 143.1 (C), 139.1 (C), 129.6 (CH x 2), 127.7 (CH x 2), 103.4 (CH<sub>2</sub>), 84.6 (C), 83.7 (C), 82.0 (C), 74.9 (CH<sub>2</sub>), 56.5 (C), 46.2 (C), 37.5 (CH<sub>2</sub>), 36.5 (CH<sub>2</sub>), 34.6 (CH<sub>3</sub>), 30.6 (CH<sub>3</sub> x 2), 30.0 (CH<sub>2</sub>), 25.7 (CH<sub>2</sub>), 23.9 (CH<sub>3</sub>), 22.8 (CH<sub>2</sub>), 22.7 (CH<sub>2</sub>), 21.8 (CH<sub>3</sub>).

**HRMS** (ESI-MS) calcd. for C<sub>25</sub>H<sub>36</sub>NO<sub>3</sub>S<sup>+</sup> ([M+H]<sup>+</sup>): 430.2410, found 430.2410.



**Diethyl**

**4-(4-(*N*,4-dimethylphenylsulfonamido)-4-methylpent-2-yn-1-yl)-2,2,4-trimethyl-3-methylenecyclopentane-1,1-dicarboxylate (70)** was

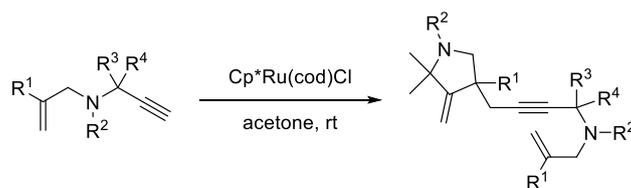
obtained according to procedure **D**, obtained: 88.3 mg (83%), colorless oil; *R<sub>f</sub>* (PE/Et<sub>2</sub>O 9/1) 0.35.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.71 (d, *J* = 8.3 Hz, 2H), 7.27 (d, *J* = 8.5 Hz, 2H), 4.90 (s, 1H), 4.79 (s, 1H), 4.20 – 4.14 (m, 4H), 3.08 (s, 3H), 2.45 (d, *J* = 14.9 Hz, 1H), 2.40 (s, 3H), 2.21 (d, *J* = 16.7 Hz, 1H), 2.17 (d, *J* = 14.9 Hz, 1H), 2.06 (d, *J* = 16.7 Hz, 1H), 1.64 (s, 6H), 1.27 – 1.19 (m, 12H), 1.15 (s, 3H).

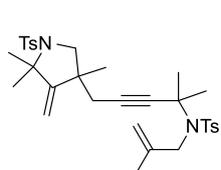
**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 171.2 (C), 171.0 (C), 167.2 (C), 143.0 (C), 139.1 (C), 129.7 (CH x 2), 127.6 (CH x 2), 104.4 (CH<sub>2</sub>), 85.3 (C), 82.7 (C), 65.6 (C), 61.28 (CH<sub>2</sub>), 61.26 (CH<sub>2</sub>), 56.5 (C), 49.4 (C), 43.3 (CH<sub>2</sub>), 42.9 (C), 34.6 (CH<sub>3</sub>), 34.2 (CH<sub>2</sub>), 30.6 (CH<sub>3</sub>), 30.5 (CH<sub>3</sub>), 29.9 (CH<sub>3</sub>), 26.3 (CH<sub>3</sub>), 25.9 (CH<sub>3</sub>), 21.7 (CH<sub>3</sub>), 14.3 (CH<sub>3</sub> x 2).

**HRMS** (ESI-MS) calcd. for C<sub>29</sub>H<sub>45</sub>N<sub>2</sub>O<sub>6</sub>S<sup>+</sup> ([M+NH<sub>4</sub>]<sup>+</sup>): 549.2993, found 549.2993.

*Self-coupling reactions of various 1,6-enynes*



Cross-adducts **71-82** were obtained according to procedure **D** in the absence of alkyne partners.



**4-Methyl-N-(2-methyl-5-(3,5,5-trimethyl-4-methylene-1-tosylpyrrolidin-3-yl)pent-3-yn-2-yl)-N-(2-methylallyl)benzenesulfonamide (71),**

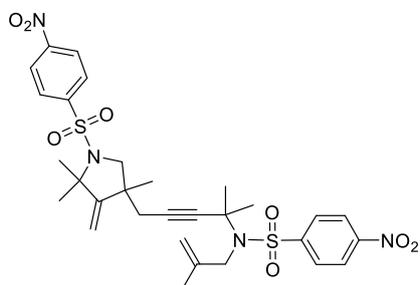
obtained: 51.0 mg (91%), colorless oil;  $R_f$  (PE/Et<sub>2</sub>O 6/4) 0.35.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.70 (dd,  $J$  = 15.8, 8.4 Hz, 4H), 7.28 – 7.24 (m, 4H), 5.03 (s, 1H), 4.91 (s, 1H), 4.84 (s, 1H), 4.78 (s, 1H), 4.02 (s, 2H), 3.23 (d,  $J$  = 9.7 Hz, 1H), 2.98 (d,  $J$  = 9.7 Hz, 1H), 2.40 (s, 6H), 2.09 (d,  $J$  = 16.7 Hz, 1H), 1.99 (d,  $J$  = 16.7 Hz, 1H), 1.76 (s, 3H), 1.54 (s, 6H), 1.50 (s, 3H), 1.48 (s, 3H), 1.04 (s, 3H).

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$  163.1 (C), 143.3 (C), 143.2 (C), 143.0 (C), 139.5 (C), 138.0 (C), 129.6 (CH x 2), 129.4 (CH x 2), 127.6 (CH x 2), 127.5 (CH x 2), 112.1 (CH<sub>2</sub>), 105.2 (CH<sub>2</sub>), 84.7 (C), 80.6 (C), 68.3 (C), 57.0 (CH<sub>2</sub>), 56.9 (C), 54.0 (CH<sub>2</sub>), 43.6 (C), 31.3 (CH<sub>3</sub>), 31.2 (CH<sub>3</sub>), 29.7 (CH<sub>2</sub>), 29.5 (CH<sub>3</sub>), 29.1 (CH<sub>3</sub>), 24.4 (CH<sub>3</sub>), 21.6 (CH<sub>3</sub> x 2), 20.4 (CH<sub>3</sub>).

**IR** (neat) v: 2978, 2931, 2250, 1657, 1494, 1330, 1148, 1090, 905, 724, 570 cm<sup>-1</sup>.

**HRMS** (ESI-MS) calcd. for C<sub>32</sub>H<sub>46</sub>N<sub>3</sub>O<sub>4</sub>S<sub>2</sub><sup>+</sup> ([M+NH<sub>4</sub>]<sup>+</sup>): 600.2924, found 600.2925.



**N-(2-Methyl-5-(3,5,5-trimethyl-4-methylene-1-((4-nitrophenyl)sulfonyl)pyrrolidin-3-yl)pent-3-yn-2-yl)-N-(2-methylallyl)-4-nitrobenzenesulfonamide (72),** obtained:

58.7 mg (91%), pale yellow oil;  $R_f$  (PE/Et<sub>2</sub>O 6/4) 0.30.

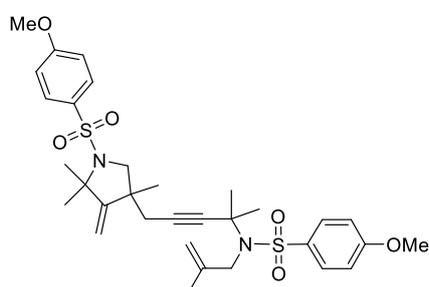
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.33 (dd,  $J$  = 8.8, 6.0 Hz, 4H), 8.04 – 8.00 (m, 4H), 4.97 (s, 1H), 4.94 (p,  $J$  = 1.5 Hz, 1H), 4.88 (d,  $J$  = 1.2 Hz, 1H), 4.82 (d,  $J$  = 1.2 Hz, 1H), 4.10 (s, 2H), 3.41 (d,  $J$  = 9.8 Hz, 1H), 3.04 (d,  $J$  = 9.8 Hz, 1H), 2.13 (d,  $J$  = 16.7 Hz, 1H), 2.02 (d,  $J$  = 16.7 Hz, 1H), 1.77 (s, 3H), 1.61 (s, 6H), 1.51 (s, 3H), 1.45

(s, 3H), 1.06 (s, 3H).

$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  162.4 (C), 150.1 (C), 150.0 (C), 148.5 (C), 146.8 (C), 142.5 (C), 128.9 (CH x 2), 128.8 (CH x 2), 124.5 (CH x 2), 124.2 (CH x 2), 113.2 ( $\text{CH}_2$ ), 106.0 ( $\text{CH}_2$ ), 85.3 (C), 81.2 (C), 69.1 (C), 57.5 ( $\text{CH}_2$ ), 57.4 (C), 53.8 ( $\text{CH}_2$ ), 43.9 (C), 31.4 ( $\text{CH}_3$ ), 31.3 ( $\text{CH}_3$ ), 29.9 ( $\text{CH}_2$ ), 29.9 ( $\text{CH}_3$ ), 29.3 ( $\text{CH}_3$ ), 24.6 ( $\text{CH}_3$ ), 20.5 ( $\text{CH}_3$ ).

IR (neat) v: 2986, 2895, 2254, 1531, 1349, 1165, 1149, 903, 724, 613  $\text{cm}^{-1}$ .

HRMS (ESI-MS) calcd. for  $\text{C}_{30}\text{H}_{40}\text{N}_5\text{O}_8\text{S}_2^+$  ( $[\text{M}+\text{NH}_4]^+$ ): 662.2313, found 662.2316.



**4-Methoxy-N-(5-(1-((4-methoxyphenyl)sulfonyl)-3,5,5-trimethyl-4-methylenepyrrolidin-3-yl)-2-methylpent-3-yn-2-yl)-N-(2-methylallyl)benzenesulfonamide (73)**, obtained: 53.5 mg (87%), colorless oil;  $R_f$  (PE/Et<sub>2</sub>O 6/4) 0.25.

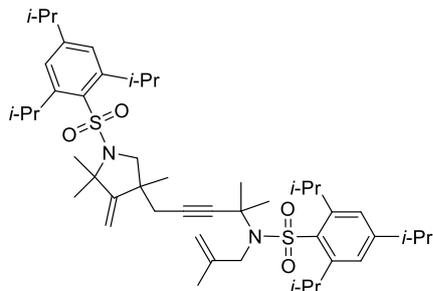
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.76 (dd,  $J = 16.0, 8.9$  Hz, 4H), 6.96 – 6.90 (m, 4H), 5.02 (s, 1H), 4.90 (p,  $J = 1.6$  Hz, 1H), 4.85 (s, 1H), 4.78 (s, 1H), 3.99 (s, 2H), 3.86 (s, 3H), 3.85 (s, 3H), 3.21 (d,  $J = 9.6$  Hz, 1H), 2.96 (d,  $J = 9.6$  Hz, 1H), 2.11 (d,  $J = 16.7$  Hz, 1H), 2.01 (d,  $J = 16.7$  Hz, 1H), 1.75 (s, 3H), 1.55 (s, 6H), 1.50 (s, 3H), 1.48 (s, 3H), 1.05 (s, 3H).

$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  163.4 (C), 162.9 (C), 162.8 (C), 143.3 (C), 134.3 (C), 132.8 (C), 129.8 (CH x 2), 129.8 (CH x 2), 114.2 (CH x 2), 114.1 (CH x 2), 112.1 ( $\text{CH}_2$ ), 105.3 ( $\text{CH}_2$ ), 85.0 (C), 80.7 (C), 68.4 (C), 57.2 ( $\text{CH}_2$ ), 57.0 (C), 55.9 ( $\text{CH}_3$ ), 55.9 ( $\text{CH}_3$ ), 54.0 ( $\text{CH}_2$ ), 43.8 (C), 31.4 ( $\text{CH}_3$  x 2), 30.0 ( $\text{CH}_2$ ), 29.7 ( $\text{CH}_3$ ), 29.2 ( $\text{CH}_3$ ), 24.5 ( $\text{CH}_3$ ), 20.6 ( $\text{CH}_3$ ).

IR (neat) v: 2974, 2932, 2256, 1595, 1497, 1145, 1090, 907, 677, 552  $\text{cm}^{-1}$ .

HRMS (ESI-MS) calcd. for  $\text{C}_{32}\text{H}_{43}\text{N}_2\text{O}_6\text{S}_2^+$  ( $[\text{M}+\text{H}]^+$ ): 615.2557, found 615.2557.

**N-(5-(1-((2,6-Diisopropyl-4-nitrophenyl)sulfonyl)-3,5,5-trimethyl-4-methylenepyrrolidin-3-yl)-2-methylpent-3-yn-2-yl)-2,6-diisopropyl-N-(2-methylallyl)-4-nitrobenzenesulfonamide (74)**, obtained: 76.7 mg (95%), colorless oil;  $R_f$  (PE/Et<sub>2</sub>O 9/1) 0.45.

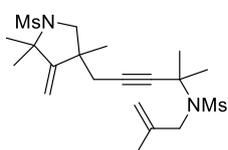


**$^1\text{H NMR}$**  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.11 (s, 2H), 7.08 (s, 2H), 4.90 (s, 1H), 4.88 (s, 1H), 4.85 (s, 1H), 4.74 (s, 1H), 4.31 (hept.  $J = 6.7$  Hz, 2H), 4.06 (hept.  $J = 6.7$  Hz, 2H), 4.04 (s, 2H), 3.13 (d,  $J = 8.9$  Hz, 1H), 2.96 (d,  $J = 8.9$  Hz, 1H), 2.91 – 2.80 (m, 2H), 2.30 (d,  $J = 16.6$  Hz, 1H), 1.97 (d,  $J = 16.6$  Hz, 1H), 1.69 (s, 6H), 1.65 (s, 3H), 1.36 (s, 6H), 1.23 (m, 36H), 1.12 (s, 3H).

**$^{13}\text{C NMR}$**  (101 MHz,  $\text{CDCl}_3$ )  $\delta$  164.3 (C), 153.5 (C), 152.7 (C), 151.8 (C x 2), 150.2 (C x 2), 143.5 (C), 136.8 (C), 132.7 (C), 124.1 (CH x 2), 124.0 (CH x 2), 113.6 ( $\text{CH}_2$ ), 104.9 ( $\text{CH}_2$ ), 85.9 (C), 81.3 (C), 69.9 (C), 57.5 (C), 56.2 ( $\text{CH}_2$ ), 53.5 ( $\text{CH}_2$ ), 44.0 (C), 34.4 (CH x 2), 34.4 (CH x 2), 30.8 ( $\text{CH}_2$ ), 30.6 (CH), 30.5 (CH), 30.0 ( $\text{CH}_3$ ), 29.3 ( $\text{CH}_3$  x 2), 29.2 ( $\text{CH}_3$  x 2), 28.7 ( $\text{CH}_3$ ), 25.2 ( $\text{CH}_3$ ), 25.1 ( $\text{CH}_3$  x 2), 25.0 ( $\text{CH}_3$  x 2), 24.98 ( $\text{CH}_3$ ), 24.0 ( $\text{CH}_3$ ), 23.9 ( $\text{CH}_3$ ), 23.88 ( $\text{CH}_3$ ), 23.86 ( $\text{CH}_3$ ), 23.7 ( $\text{CH}_3$ ), 20.8 ( $\text{CH}_3$ ).

**IR** (neat) v: 2962, 2911, 2254, 1600, 1462, 1384, 1143, 1038, 902, 723, 583  $\text{cm}^{-1}$ .

**HRMS** (ESI-MS) calcd. for  $\text{C}_{48}\text{H}_{78}\text{N}_3\text{O}_4\text{S}_2^+$  ( $[\text{M}+\text{NH}_4]^+$ ): 824.5428, found 824.5427.



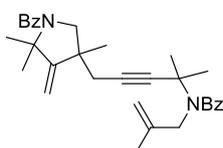
***N*-(2-Methyl-5-(3,5,5-trimethyl-4-methylene-1-(methanesulfonyl)pyrrolidin-3-yl)pent-3-yn-2-yl)-*N*-(2-methylallyl)methanesulfonamide (75)**, obtained: 39.6 mg (92%), colorless oil;  $R_f$  (PE/Et<sub>2</sub>O 6/4) 0.40.

**$^1\text{H NMR}$**  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  5.02 (s, 1H), 4.94 (s, 1H), 4.93 (s, 2H), 3.88 (s, 2H), 3.49 (d,  $J = 9.6$  Hz, 1H), 3.14 (d,  $J = 9.6$  Hz, 1H), 3.00 (s, 3H), 2.91 (s, 3H), 2.46 (d,  $J = 16.8$  Hz, 1H), 2.33 (d,  $J = 16.8$  Hz, 1H), 1.74 (s, 3H), 1.67 (s, 6H), 1.54 (s, 3H), 1.52 (s, 3H), 1.26 (s, 3H).

**$^{13}\text{C NMR}$**  (75 MHz,  $\text{CDCl}_3$ )  $\delta$  162.0 (C), 142.1 (C), 110.8 ( $\text{CH}_2$ ), 104.8 ( $\text{CH}_2$ ), 84.5 (C), 79.9 (C), 66.8 (C), 56.4 ( $\text{CH}_2$ ), 55.5 (C), 51.5 ( $\text{CH}_2$ ), 42.8 (C), 40.7 ( $\text{CH}_3$ ), 39.3 ( $\text{CH}_3$ ), 30.3 ( $\text{CH}_3$  x 2), 29.1 ( $\text{CH}_2$ ), 28.7 ( $\text{CH}_3$ ), 28.0 ( $\text{CH}_3$ ), 23.8 ( $\text{CH}_3$ ), 19.5 ( $\text{CH}_3$ ).

**IR** (neat) v: 2975, 2933, 2871, 2255, 1659, 1322, 1138, 961, 765, 518  $\text{cm}^{-1}$ .

**HRMS** (ESI-MS) calcd. for  $\text{C}_{20}\text{H}_{38}\text{N}_3\text{O}_4\text{S}_2^+$  ( $[\text{M}+\text{NH}_4]^+$ ): 448.2298, found 448.2298.



***N*-(5-(1-Benzoyl-3,5,5-trimethyl-4-methylenepyrrolidin-3-yl)-2-methylpent-3-yn-2-yl)-*N*-benzylmethanesulfonamide**

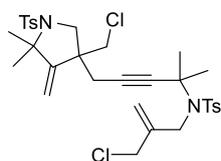
**pent-3-yn-2-yl)-N-(2-methylallyl)benzamide (76)**, obtained: 35.2 mg (73%), colorless oil;  $R_f$  (PE/Et<sub>2</sub>O 4/6) 0.35.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.45 – 7.30 (m, 10H), 5.01 (s, 2H), 4.96 (s, 1H), 4.89 (s, 1H), 3.87 (s, 2H), 3.57 (d,  $J$  = 11.1 Hz, 1H), 3.20 (d,  $J$  = 11.1 Hz, 1H), 2.45 (d,  $J$  = 16.7 Hz, 1H), 2.29 (d,  $J$  = 16.7 Hz, 1H), 1.81 (s, 3H), 1.79 (s, 3H), 1.74 (s, 3H), 1.69 (s, 3H), 1.48 (s, 3H), 1.23 (s, 3H).

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$  172.8 (C), 163.9 (C), 143.5 (C x 2), 138.9 (C), 138.8 (C), 129.5 (CH x 2), 128.7 (CH x 2), 128.4 (CH x 2), 126.6 (CH x 2), 126.3 (CH x 2), 112.1 (CH<sub>2</sub>), 105.2 (CH<sub>2</sub>), 86.6 (C), 80.4 (C), 66.0 (C), 59.2 (CH<sub>2</sub>), 56.0 (C), 54.8 (CH<sub>2</sub>), 44.4 (C), 30.1 (CH<sub>2</sub>), 28.77 (CH<sub>3</sub> x 2), 28.75 (CH<sub>3</sub> x 2), 24.2 (CH<sub>3</sub>), 20.4 (CH<sub>3</sub>).

**IR** (neat)  $\nu$ : 2974, 2933, 2244, 1630, 1396, 1156, 904, 724, 646 cm<sup>-1</sup>.

**HRMS** (ESI-MS) calcd. for C<sub>32</sub>H<sub>39</sub>N<sub>2</sub>O<sub>2</sub><sup>+</sup> ([M+H]<sup>+</sup>): 483.3006, found 483.3006.



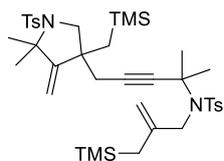
**N-(5-(3-(Chloromethyl)-5,5-dimethyl-4-methylene-1-tosylpyrrolidin-3-yl)-2-methylpent-3-yn-2-yl)-N-(2-(chloromethyl)allyl)-4-methylbenzenesulfonamide (77)**, obtained: 24.8 mg (19%), colorless oil,  $R_f$  (PE/Et<sub>2</sub>O 6/4) 0.35.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.71 (dd,  $J$  = 12.9, 8.3 Hz, 4H), 7.29 (dd,  $J$  = 8.0, 3.6 Hz, 4H), 5.40 (s, 1H), 5.35 (s, 1H), 5.00 (d,  $J$  = 1.2 Hz, 1H), 4.91 (d,  $J$  = 1.2 Hz, 1H), 4.17 (s, 2H), 4.12 (s, 2H), 3.38 (m, 3H), 3.19 (d,  $J$  = 10.3 Hz, 1H), 2.42 (s, 6H), 2.30 (d,  $J$  = 3.6 Hz, 2H), 1.56 (s, 6H), 1.49 (s, 3H), 1.47 (s, 3H).

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$  158.5 (C), 143.71 (C), 143.65 (C), 142.6 (C), 139.0 (C), 138.0 (C), 129.9 (CH x 2), 129.8 (CH x 2), 128.0 (CH x 2), 127.7 (CH x 2), 117.1 (CH<sub>2</sub>), 108.6 (CH<sub>2</sub>), 85.6 (C), 79.7 (C), 68.6 (C), 57.3 (C), 54.0 (CH<sub>2</sub>), 50.8 (CH<sub>2</sub>), 49.2 (CH<sub>2</sub>), 48.5 (C), 46.8 (CH<sub>2</sub>), 31.3 (CH<sub>3</sub>), 31.2 (CH<sub>3</sub>), 29.3 (CH<sub>3</sub>), 29.2 (CH<sub>3</sub>), 25.4 (CH<sub>2</sub>), 21.8 (CH<sub>3</sub>), 21.7 (CH<sub>3</sub>).

**IR** (neat)  $\nu$ : 2923, 2871, 2244, 1730, 1377, 1151, 1090, 929, 707, 572, 548 cm<sup>-1</sup>.

**HRMS** (ESI-MS) calcd. for C<sub>32</sub>H<sub>41</sub>Cl<sub>2</sub>N<sub>2</sub>O<sub>4</sub>S<sub>2</sub><sup>+</sup> ([M+H]<sup>+</sup>): 651.1879, found 651.1880.



***N*-(5-(5,5-Dimethyl-4-methylene-1-tosyl-3-((trimethylsilyl)methyl)pyrrolidin-3-yl)-2-methylpent-3-yn-2-yl)-4-methyl-*N*-(2-((trimethylsilyl)methyl)allyl)benzenesulfonamide (78)**, obtained: 35.9 mg (50%),

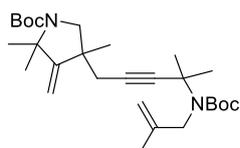
colorless oil;  $R_f$  (PE/Et<sub>2</sub>O 6/4) 0.40.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.74 (dd,  $J = 10.6, 8.3$  Hz, 4H), 7.32 – 7.26 (m, 4H), 5.03 (d,  $J = 1.6$  Hz, 1H), 4.88 (s, 1H), 4.84 (s, 1H), 4.77 (s, 1H), 3.98 (s, 2H), 3.24 (d,  $J = 9.5$  Hz, 1H), 3.08 (d,  $J = 9.5$  Hz, 1H), 2.44 (s, 3H), 2.44 (s, 3H), 2.15 (d,  $J = 1.9$  Hz, 2H), 1.59 (s, 6H), 1.56 (s, 2H), 1.54 (s, 3H), 1.50 (s, 3H), 1.09 (d,  $J = 15.0$  Hz, 1H), 0.78 (d,  $J = 15.0$  Hz, 1H), 0.10 (s, 9H), 0.00 (s, 9H).

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$  164.2 (C), 145.5 (C), 144.4 (C), 144.0 (C), 140.8 (C), 139.0 (C), 130.7 (CH x 2), 130.5 (CH x 2), 128.8 (CH x 2), 128.8 (CH x 2), 110.4 (CH<sub>2</sub>), 107.0 (CH<sub>2</sub>), 86.5 (C), 81.9 (C), 69.1 (C), 58.7 (CH<sub>2</sub>), 57.9 (C), 55.6 (CH<sub>2</sub>), 47.4 (C), 32.6 (CH<sub>3</sub>), 32.5 (CH<sub>3</sub>), 31.5 (CH<sub>2</sub>), 31.3 (CH<sub>3</sub>), 30.3 (CH<sub>3</sub>), 27.2 (CH<sub>2</sub>), 25.5 (CH<sub>2</sub>), 22.8 (CH<sub>3</sub> x 2), 1.8 (CH<sub>3</sub> x 3), 0.1 (CH<sub>3</sub> x 3).

**IR** (neat)  $\nu$ : 2952, 2897, 2255, 1599, 1333, 1149, 1090, 837, 708, 571 cm<sup>-1</sup>.

**HRMS** (ESI-MS) calcd. for C<sub>38</sub>H<sub>62</sub>N<sub>3</sub>O<sub>4</sub>S<sub>2</sub>Si<sub>2</sub><sup>+</sup> ([M+NH<sub>4</sub>]<sup>+</sup>): 744.3715, found 744.3724.



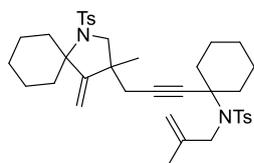
***Tert*-butyl-4-(4-((tert-butoxycarbonyl)(2-methylallyl)amino)-4-methylpent-2-yn-1-yl)-2,2,4-trimethyl-3-methylenepyrrolidine-1-carboxylate (79)**, obtained: 39.4 mg (83%), colorless oil;  $R_f$  (PE/Et<sub>2</sub>O 9/1) 0.50.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  4.89 (s, 2H), 4.81 (s, 2H), 4.00 (s, 2H), 3.48 (d,  $J = 11.1$  Hz, 1H), 3.18 (dd,  $J = 39.6, 11.1$  Hz, 1H), 2.37 – 2.23 (m, 2H), 1.68 (d,  $J = 5.0$  Hz, 9H), 1.49 – 1.42 (m, 24H), 1.20 (s, 3H).

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>)  $\delta$  164.6 (C), 154.2 (C x 2), 142.5 (C), 108.6 (CH<sub>2</sub>), 104.2 (CH<sub>2</sub>), 85.8 (C), 79.4 (C), 78.9 (C x 2), 63.4 (C), 56.0 (CH<sub>2</sub>), 53.7 (C), 51.2 (CH<sub>2</sub>), 41.7 (C), 29.8 (CH<sub>2</sub>), 28.9 (CH<sub>3</sub>), 28.8 (CH<sub>3</sub>), 28.3 (CH<sub>3</sub>), 27.9 (CH<sub>3</sub> x 3), 27.8 (CH<sub>3</sub> x 3), 25.8 (CH<sub>3</sub>), 24.4 (CH<sub>3</sub>), 19.5 (CH<sub>3</sub>).

**IR** (neat)  $\nu$ : 2979, 2899, 2252, 1680, 1388, 1238, 1164, 903, 732, 649 cm<sup>-1</sup>.

**HRMS** (ESI-MS) calcd. for  $C_{28}H_{47}N_2O_4^+$  ( $[M+H]^+$ ): 475.3530, found 475.3533.



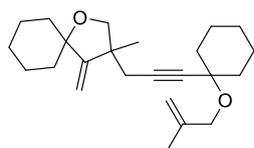
**4-Methyl-N-(1-(3-(3-methyl-4-methylene-1-tosyl-1-azaspiro[4.5]decane-3-yl)prop-1-yn-1-yl)cyclohexyl)-N-(2-methylallyl)benzenesulfonamide (80)**, obtained: 58.3 mg (88%), colorless oil;  $R_f$  (PE/Et<sub>2</sub>O 6/4) 0.35.

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>)  $\delta$  7.73 (d,  $J$  = 8.3 Hz, 2H), 7.67 (d,  $J$  = 8.3 Hz, 2H), 7.27 – 7.23 (m, 4H), 5.32 (s, 1H), 5.06 (s, 1H), 4.91 (s, 1H), 4.78 (s, 1H), 4.01 (s, 2H), 3.19 (d,  $J$  = 9.7 Hz, 1H), 2.99 (d,  $J$  = 9.7 Hz, 1H), 2.66 – 2.51 (m, 2H), 2.40 (s, 6H), 2.03 (d,  $J$  = 16.7, 1H), 1.99 (d,  $J$  = 16.7, 1H), 1.95 – 1.93 (m, 2H), 1.87 – 1.82 (dd,  $J$  = 12.6, 2.7 Hz, 2H), 1.77 (s, 3H), 1.71 – 1.65 (m, 6H), 1.59 – 1.46 (m, 4H), 1.41 – 1.19 (m, 4H), 1.00 (s, 3H).

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>)  $\delta$  161.4 (C), 143.7 (C), 143.3 (C), 143.0 (C), 139.9 (C), 138.9 (C), 129.7 (CH x 2), 129.5 (CH x 2), 127.8 (CH x 2), 127.6 (CH x 2), 112.0 (CH<sub>2</sub>), 107.6 (CH<sub>2</sub>), 84.0 (C), 82.0 (C), 71.4 (C), 63.0 (C), 57.0 (CH<sub>2</sub>), 53.7 (CH<sub>2</sub>), 44.7 (C), 38.2 (CH<sub>2</sub> x 2), 35.5 (CH<sub>2</sub>), 35.4 (CH<sub>2</sub>), 30.4 (CH<sub>2</sub>), 25.1 (CH<sub>2</sub>), 25.0 (CH<sub>3</sub>), 24.5 (CH<sub>2</sub>), 24.02 (CH<sub>2</sub>), 23.97 (CH<sub>2</sub>), 22.5 (CH<sub>2</sub>), 22.4 (CH<sub>2</sub>), 21.8 (CH<sub>3</sub> x 2), 20.7 (CH<sub>3</sub>).

**IR** (neat) v: 2988, 2930, 2253, 1626, 1398, 1299, 1152, 1096, 903, 739, 597 cm<sup>-1</sup>.

**HRMS** (ESI-MS) calcd. for  $C_{38}H_{54}N_3O_4S_2^+$  ( $[M+NH_4]^+$ ): 680.3550, found 680.3550.



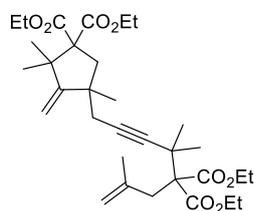
**3-Methyl-3-(3-(1-((2-methylallyl)oxy)cyclohexyl)prop-2-yn-1-yl)-4-methylene-1-oxaspiro[4.5]decane (81)**, obtained: 30.0 mg (84%), colorless oil;  $R_f$  (PE/Et<sub>2</sub>O 8/2) 0.35.

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>)  $\delta$  4.99 (s, 1H), 4.84 (s, 2H), 4.78 (s, 1H), 3.97 (s, 2H), 3.85 (d,  $J$  = 8.9 Hz, 1H), 3.53 (d,  $J$  = 8.9 Hz, 1H), 2.42 (d,  $J$  = 16.6 Hz, 1H), 2.25 (d,  $J$  = 16.6 Hz, 1H), 1.88 – 1.82 (m, 2H), 1.75 (s, 3H), 1.71 – 1.46 (m, 14H), 1.39 – 1.24 (m, 4H), 1.20 (s, 3H).

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>)  $\delta$  164.0 (C), 143.5 (C), 111.5 (CH<sub>2</sub>), 103.4 (CH<sub>2</sub>), 84.7 (C), 83.8 (C), 83.2 (C), 75.0 (CH<sub>2</sub>), 74.2 (C), 67.5 (CH<sub>2</sub>), 46.4 (C), 37.9 (CH<sub>2</sub>), 37.8 (CH<sub>2</sub>), 37.4 (CH<sub>2</sub>), 36.6 (CH<sub>2</sub>), 30.1 (CH<sub>2</sub> x 2), 25.9 (CH<sub>2</sub>), 25.7 (CH<sub>2</sub>), 24.1 (CH<sub>3</sub>), 23.3 (CH<sub>2</sub>), 22.8 (CH<sub>2</sub>), 22.7 (CH<sub>2</sub>), 20.2 (CH<sub>3</sub>).

**IR** (neat)  $\nu$ : 2933, 2856, 2245, 1721, 1447, 1143, 968, 774, 647  $\text{cm}^{-1}$ .

**HRMS** (ESI-MS) calcd. for  $\text{C}_{24}\text{H}_{40}\text{NO}_2^+$  ( $[\text{M}+\text{NH}_4]^+$ ): 374.3054, found 374.3054.



**Diethyl**

**4-(5,5-bis(ethoxycarbonyl)-4,4,7-trimethyloct-7-en-2-yn-1-yl)-2,2,4-trimethyl-3-methylenecyclopentane-1,1-dicarboxylate (82)**, obtained:

39.8 mg (71%), colorless oil;  $R_f$  (PE/Et<sub>2</sub>O 8/2) 0.50.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  4.91 (s, 1H), 4.86 (s, 1H), 4.76 (s, 1H), 4.70 (s, 1H), 4.20 – 4.14 (m, 8H), 2.96 (s, 2H), 2.60 (d,  $J = 15.0$  Hz, 1H), 2.36 (t,  $J = 16.7$  Hz, 1H), 2.27 (d,  $J = 15.0$ , 1H), 2.24 (t,  $J = 16.7$  Hz, 1H), 1.73 (s, 3H), 1.38 (s, 6H), 1.30 (s, 3H), 1.26 – 1.23 (m, 18H).

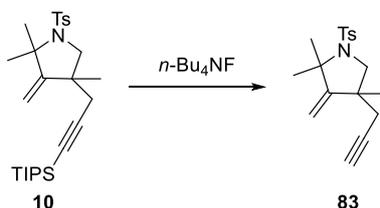
**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>)  $\delta$  170.3 (C), 170.22 (C), 169.0 (C x 2), 166.6 (C), 142.3 (C), 113.4 (CH<sub>2</sub>), 103.2 (CH<sub>2</sub>), 85.7 (C), 79.8 (C), 64.7 (C), 63.3 (C), 60.3 (CH<sub>2</sub>), 60.2 (CH<sub>2</sub>), 60.1 (CH<sub>2</sub> x 2), 48.5 (C), 42.4 (CH<sub>2</sub>), 42.2 (C), 39.7 (CH<sub>2</sub>), 37.3 (C), 33.5 (CH<sub>2</sub>), 29.1 (CH<sub>3</sub>), 26.7 (CH<sub>3</sub>), 26.6 (CH<sub>3</sub>), 25.5 (CH<sub>3</sub>), 24.8 (CH<sub>3</sub>), 23.3 (CH<sub>3</sub>), 13.4 (CH<sub>3</sub> x 2), 13.3 (CH<sub>3</sub> x 2).

**IR** (neat)  $\nu$ : 2978, 2937, 2255, 1725, 1446, 1365, 1232, 1095, 949, 769, 592  $\text{cm}^{-1}$ .

**HRMS** (ESI-MS) calcd. for  $\text{C}_{32}\text{H}_{52}\text{NO}_8^+$  ( $[\text{M}+\text{NH}_4]^+$ ): 578.3687, found 578.3687.

### *Transformation of cross-coupling products*

#### **2,2,4-Trimethyl-3-methylene-4-(prop-2-yn-1-yl)-1-tosylpyrrolidine (83)**



To a solution of **10** (1.9 g, 4 mmol) in THF (30 mL) was added  $n\text{-Bu}_4\text{NF}$  (8 mL, 8 mmol, 1.0 M in THF). The resulting mixture was stirred overnight at room temperature, and concentrated under vacuo. The crude residue was purified by flash chromatography to give 1.3 g (99%) of **83** as a colorless oil;  $R_f$  (PE/Et<sub>2</sub>O 8/2) 0.45.

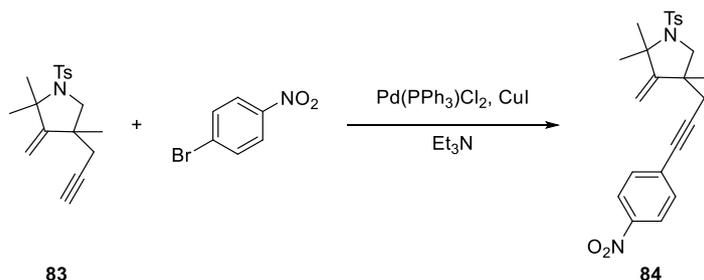
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.75 (d, *J* = 8.3 Hz, 2H), 7.28 (d, *J* = 8.0 Hz, 2H), 4.88 (s, 2H), 3.43 (d, *J* = 9.9 Hz, 1H), 3.11 (d, *J* = 9.9 Hz, 1H), 2.41 (s, 3H), 2.26 (dd, *J* = 16.7, 2.6 Hz, 1H), 2.19 (dd, *J* = 16.7, 2.6 Hz, 1H), 1.93 (t, *J* = 2.6 Hz, 1H), 1.53 (s, 3H), 1.51 (s, 3H), 1.18 (s, 3H).

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 163.5 (C), 143.3 (C), 138.5 (C), 129.7 (CH x 2), 127.7 (CH x 2), 105.4 (CH<sub>2</sub>), 81.2 (C), 70.7 (CH), 68.6 (C), 57.4 (CH<sub>2</sub>), 43.6 (C), 30.0 (CH<sub>2</sub>), 29.5 (CH<sub>3</sub>), 29.4 (CH<sub>3</sub>), 24.5 (CH<sub>3</sub>), 21.8 (CH<sub>3</sub>).

**IR** (neat) *v*: 2941, 2892, 2865, 1463, 1333, 1149, 1092, 995, 918, 881, 801, 673, 581, 549 cm<sup>-1</sup>.

**HRMS** (ESI-MS) calcd. for C<sub>18</sub>H<sub>24</sub>NO<sub>2</sub>S<sup>+</sup> ([M+H]<sup>+</sup>): 318.1522, found 318.1523.

#### 2,2,4-Trimethyl-3-methylene-4-(3-(4-nitrophenyl)prop-2-yn-1-yl)-1-tosylpyrrolidine (**84**)



To a solution of **83** (158.7 mg, 0.5 mmol) and 4-bromonitrobenzene (121.2 mg, 0.6 mmol) in Et<sub>3</sub>N (5 mL) was added Pd(PPh<sub>3</sub>)Cl<sub>2</sub> (17.5 mg, 0.025 mmol) and CuI (4.8 mg, 0.025 mmol). The resulting mixture was stirred at 50 °C for 15 h and then cooled to rt and diluted with MTBE (30 mL). The mixture was filtered over celite. The filtrate was washed with brine (10 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated under vacuo. The crude residue was purified by flash chromatography to give 144 mg (68%) of **84** as a pale yellow oil, R<sub>f</sub> (PE/Et<sub>2</sub>O 1/1) 0.50.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 8.15 (d, *J* = 8.9 Hz, 2H), 7.77 (d, *J* = 8.3 Hz, 2H), 7.45 (d, *J* = 8.3 Hz, 2H), 7.27 (d, *J* = 9.2 Hz, 2H), 4.95 (s, 2H), 3.49 (d, *J* = 9.8 Hz, 1H), 3.14 (d, *J* = 9.8 Hz, 1H), 2.56 (d, *J* = 17.0 Hz, 1H), 2.46 (d, *J* = 17.0 Hz, 1H), 2.39 (s, 3H), 1.59 (s, 3H), 1.52 (s, 3H), 1.24 (s, 3H).

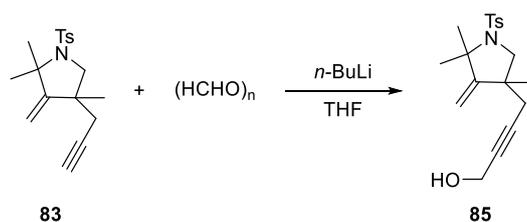
**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 163.3 (C), 147.1 (C), 143.4 (C), 138.3 (C), 132.6 (CH x 2),

130.7 (CH x 2), 129.7 (C), 127.7 (CH x 2), 123.8 (CH x 2), 105.7 (CH<sub>2</sub>), 93.1 (C), 81.4 (C), 68.6 (C), 57.4 (CH<sub>2</sub>), 44.1 (C), 31.0 (CH<sub>2</sub>), 29.7 (CH<sub>3</sub>), 29.2 (CH<sub>3</sub>), 24.7 (CH<sub>3</sub>), 21.8 (CH<sub>3</sub>).

**IR** (neat)  $\nu$ : 3078, 2974, 2930, 2869, 2221, 1592, 1516, 1340, 1158, 1148, 1090, 1033, 853, 583 cm<sup>-1</sup>.

**HRMS** (ESI-MS) calcd. for C<sub>24</sub>H<sub>27</sub>N<sub>2</sub>O<sub>4</sub>S<sup>+</sup> ([M+H]<sup>+</sup>): 439.1686, found 439.1690.

#### 4-(3,5,5-Trimethyl-4-methylene-1-tosylpyrrolidin-3-yl)but-2-yn-1-ol (**85**)



To a solution of enyne **83** (158.7 mg, 0.5 mmol) in dry THF (10 mL) was dropwise added *n*-BuLi (0.38 mL, 0.6 mmol, 1.6 M in hexanes) at -78 °C. The mixture was gradually warmed to 0 °C and stirred for an additional 1 h. The oven-dried paraformaldehyde (18.0 mg, 0.6 mmol) was added in one portion and the resulting mixture was warmed to room temperature, and then heated to 40 °C for 1 h. Saturated aqueous NH<sub>4</sub>Cl (20 mL) was added and the mixture was extracted with ethyl acetate (3×10 mL). The combined organic layers were washed with brine and dried over Na<sub>2</sub>SO<sub>4</sub>. After evaporation of the solvents, the residue was purified by column chromatography to afford 142.3 mg (82%) of **85** as a colorless oil, *R<sub>f</sub>* (PE/Et<sub>2</sub>O 2/3) 0.35.

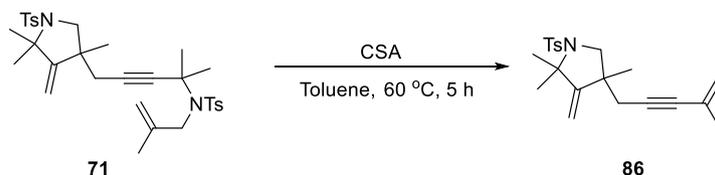
**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>)  $\delta$  7.75 (d, *J* = 8.3 Hz, 2H), 7.28 (d, *J* = 8.2 Hz, 2H), 4.88 (s, 1H), 4.87 (s, 1H), 4.19 (t, *J* = 2.0 Hz, 2H), 3.44 (d, *J* = 9.8 Hz, 1H), 3.08 (d, *J* = 9.8 Hz, 1H), 2.42 (s, 3H), 2.32 (dt, *J* = 16.7, 2.0 Hz, 1H), 2.22 (dt, *J* = 16.7, 2.0 Hz, 1H), 1.58 (br s, 1H), 1.55 (s, 3H), 1.49 (s, 3H), 1.17 (s, 3H).

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$  163.6 (C), 143.4 (C), 138.4 (C), 129.8 (CH x 2), 127.8 (CH x 2), 105.4 (CH<sub>2</sub>), 83.2 (C), 80.9 (C), 68.6 (C), 57.4 (CH<sub>2</sub>), 51.6 (CH<sub>2</sub>), 43.8 (C), 30.5 (CH<sub>2</sub>), 29.7 (CH<sub>3</sub>), 29.2 (CH<sub>3</sub>), 24.6 (CH<sub>3</sub>), 21.8 (CH<sub>3</sub>).

**IR** (neat)  $\nu$ : 3506, 2969, 2926, 2868, 1732, 1599, 1425, 1364, 1289, 1260, 1148, 1091, 815, 657, 582, 549  $\text{cm}^{-1}$ .

**HRMS** (ESI-MS) calcd. for  $\text{C}_{19}\text{H}_{26}\text{NO}_3\text{S}^+$  ( $[\text{M}+\text{H}]^+$ ): 348.1628, found 348.1630.

### 2,2,4-Trimethyl-3-methylene-4-(4-methylpent-4-en-2-yn-1-yl)-1-tosylpyrrolidie (**86**)



To a solution of the **71** (291 mg, 0.5 mmol) in toluene (5 mL) was added camphorsulfonic acid (139.4 mg, 0.6 mmol). The mixture was stirred for 5 h at 60  $^\circ\text{C}$ , and cooled to room temperature. After addition of saturated aqueous  $\text{NaHCO}_3$  (1 mL), the solution was washed with brine (10 mL), dried over  $\text{Na}_2\text{SO}_4$ , and concentrated under vacuo. The residue was purified by column chromatography to give 311.0 mg (87%) of **86** as a colorless oil,  $R_f$  (PE/ $\text{Et}_2\text{O}$  3/1) 0.65.

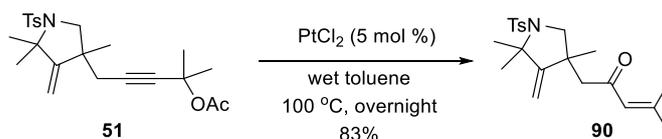
**$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.76 (d,  $J = 8.3$  Hz, 2H), 7.28 (d,  $J = 8.1$  Hz, 2H), 5.13 (s, 2H), 4.89 (s, 2H), 3.42 (d,  $J = 9.8$  Hz, 1H), 3.12 (d,  $J = 9.8$  Hz, 1H), 2.41 (s, 3H), 2.37 (d,  $J = 16.8$  Hz, 1H), 2.27 (d,  $J = 16.8$  Hz, 1H), 1.81 (s, 3H), 1.53 (s, 6H), 1.18 (s, 3H).

**$^{13}\text{C}$  NMR** (101 MHz,  $\text{CDCl}_3$ )  $\delta$  163.5 (C), 143.3 (C), 138.4 (C), 129.7 (CH x 2), 127.7 (CH x 2), 127.2 (C), 121.1 ( $\text{CH}_2$ ), 105.3 ( $\text{CH}_2$ ), 86.0 (C), 84.1 (C), 68.6 (C), 57.3 ( $\text{CH}_2$ ), 44.1 (C), 30.7 ( $\text{CH}_2$ ), 29.5 ( $\text{CH}_3$ ), 29.4 ( $\text{CH}_3$ ), 24.6 ( $\text{CH}_3$ ), 23.9 ( $\text{CH}_3$ ), 21.8 ( $\text{CH}_3$ ).

**IR** (neat)  $\nu$ : 2980, 2946, 2877, 1552, 1490, 1339, 1266, 1185, 979, 865, 773, 619, 578  $\text{cm}^{-1}$ .

**HRMS** (ESI-MS) calcd. for  $\text{C}_{21}\text{H}_{28}\text{NO}_2\text{S}^+$  ( $[\text{M}+\text{H}]^+$ ): 358.1835, found 358.1836.

### 4-Methyl-1-(3,5,5-trimethyl-4-methylene-1-tosylpyrrolidin-3-yl)pent-3-en-2-one (**90**)



To a solution of the **51** (291 mg, 0.5 mmol) in wet toluene (5 mL) was added  $\text{PtCl}_2$  (6.65 mg,

0.025 mmol). The mixture was stirred overnight at 60 °C, and cooled to room temperature. After concentrated under vacuo, the residue was purified by column chromatography to give 155.8 mg (83%) of **90** as a colorless oil,  $R_f$  (PE/Et<sub>2</sub>O 7/3) 0.40.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.69 (d,  $J$  = 8.3 Hz, 2H), 7.20 (d,  $J$  = 8.1 Hz, 2H), 5.87 (s, 1H), 4.77 (d,  $J$  = 1.1 Hz, 1H), 4.74 (d,  $J$  = 1.0 Hz, 1H), 3.40 (d,  $J$  = 10.0 Hz, 1H), 3.17 (d,  $J$  = 10.0 Hz, 1H), 2.47 (d,  $J$  = 15.9 Hz, 1H), 2.40 (d,  $J$  = 15.9 Hz, 1H), 2.34 (s, 3H), 2.02 (d,  $J$  = 1.2 Hz, 3H), 1.79 (d,  $J$  = 1.2 Hz, 3H), 1.47 (s, 3H), 1.46 (s, 3H), 1.09 (s, 3H).

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 197.8 (C), 164.7 (C), 154.9 (C), 142.2 (C), 137.5 (C), 128.7 (CH x 2), 126.8 (CH x 2), 124.1 (CH), 103.9 (CH<sub>2</sub>), 67.0 (C), 56.5 (CH<sub>2</sub>), 51.7 (CH<sub>2</sub>), 42.1 (C), 28.6 (CH<sub>3</sub> x 2), 27.0 (CH<sub>3</sub>), 24.2 (CH<sub>3</sub>), 20.8 (CH<sub>3</sub>), 20.0 (CH<sub>3</sub>).

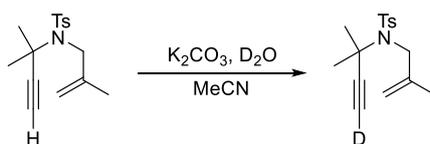
IR (neat) v: 3111, 2954, 2899, 2856, 1698, 1322, 979, 837, 662 cm<sup>-1</sup>.

HRMS (ESI-MS) calcd. for C<sub>21</sub>H<sub>30</sub>NO<sub>3</sub>S ([M+H]<sup>+</sup>): 376.1941, found 376.1941.

### *Deuterium labeling experiments*

#### **4-Methyl-*N*-(2-methylallyl)-*N*-(4-deutero-2-methylbut-3-yn-2-yl)benzenesulfonamide**

(**6-*d*<sub>1</sub>**)



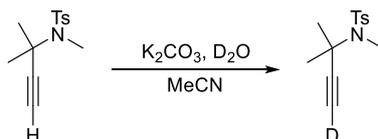
To a suspension of K<sub>2</sub>CO<sub>3</sub> (207 mg, 1.5 mmol) in dry MeCN (5 mL) was added **6** (291.4 mg, 1 mmol). The mixture was stirred for 2 h at room temperature. Then D<sub>2</sub>O (1 mL, 50 mmol) was added and the reaction solution was stirred overnight, then diluted with CH<sub>2</sub>Cl<sub>2</sub> (5 mL) and water was separated. The organic layers were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under vacuo to afford 290.6 mg (99%) **6-*d*<sub>1</sub>** (95% of deuteration determined by <sup>1</sup>H NMR).

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.73 (d,  $J$  = 8.1 Hz, 2H), 7.26 (t,  $J$  = 4.1 Hz, 2H), 5.08 (s, 1H), 4.94 (s, 1H), 4.11 (s, 2H), 2.41 (s, 3H), 2.19 (s, 0.05H), 1.79 (s, 3H), 1.66 (s, 6H).

$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  143.3 (C), 143.2 (C), 139.5 (C), 129.6 (CH x 2), 127.8 (CH x 2), 112.5 ( $\text{CH}_2$ ), [85.8, 85.7, 85.6](C), [71.9, 71.7, 71.5](CH), 56.7 (C), 54.2 ( $\text{CH}_2$ ), 31.1 ( $\text{CH}_3$  x 2), 21.8 ( $\text{CH}_3$ ), 20.6 ( $\text{CH}_3$ ).

HRMS (ESI-MS) calcd. for  $\text{C}_{16}\text{H}_{21}\text{DNO}_2\text{S}$  ( $[\text{M}+\text{H}]^+$ ): 293.1429, found 293.1429.

***N*-Ethyl-4-methyl-*N*-(4-deutero-2-methylbut-3-yn-2-yl)benzenesulfonamide (**55-*d*<sub>1</sub>**)**



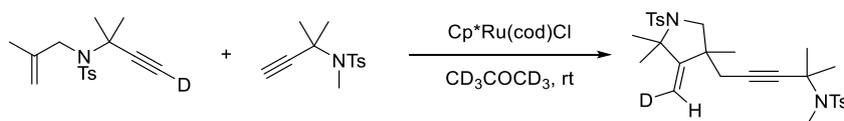
By using the above method, **55-*d*<sub>1</sub>** was obtained in 97% yield (97% of deuteration determined by  $^1\text{H}$  NMR).

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.72 (d,  $J$  = 8.2 Hz, 2H), 7.27 (d,  $J$  = 8.3 Hz, 2H), 3.08 (s, 3H), 2.42 (s, 3H), 2.24 (s, 0.03H), 1.67 (s, 6H).

$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  143.3 (C), 138.7 (C), 129.6 (CH x 2), 127.6 (CH x 2), [85.3, 85.2, 85.1] (C), [72.4, 72.2, 71.9](CH), 55.8 (C), 34.4 ( $\text{CH}_3$ ), 30.1 ( $\text{CH}_3$  x 2), 21.7 ( $\text{CH}_3$ ).

HRMS (ESI-MS) calcd. for  $\text{C}_{13}\text{H}_{17}\text{DNO}_2\text{S}^+$  ( $[\text{M}+\text{H}]^+$ ): 253.1116, found 253.1115.

***N*,4-Dimethyl-*N*-(2-methyl-5-(3,5,5-trimethyl-4-methylene-1-tosylpyrrolidin-3-yl)pent-3-yn-2-yl)benzenesulfonamide (**59-*d*<sub>1</sub>**)**



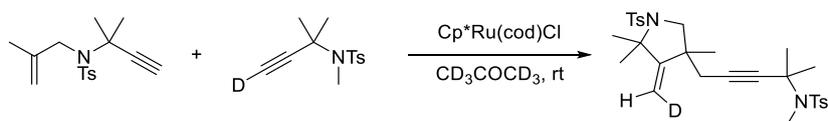
**59-*d*<sub>1</sub>** was prepared according procedure **D** using **6-*d*<sub>1</sub>** and **55** as coupling partners in  $\text{CD}_3\text{COCD}_3$ . Yield: 77%, colorless oil,  $R_f$  (PE/ $\text{Et}_2\text{O}$  6/4) 0.35.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.70 (dd,  $J$  = 20.2, 8.3 Hz, 4H), 7.28 (s, 2H), 7.26 (s, 2H), 4.84 (s, 0.06H), 4.77 (s, 1H), 3.23 (d,  $J$  = 9.7 Hz, 1H), 2.99 (d,  $J$  = 9.7 Hz, 1H), 2.97 (s, 3H), 2.40 (s, 3H), 2.40 (s, 3H), 2.13 (d,  $J$  = 16.7 Hz, 1H), 2.00 (d,  $J$  = 16.7 Hz, 1H), 1.56 (s, 3H), 1.55 (s, 3H), 1.50 (s, 3H), 1.49 (s, 3H), 1.05 (s, 3H).

$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  163.4 (C), 143.4 (C), 143.2 (C), 139.1 (C), 138.3 (C), 129.7 (CH x 2), 129.6 (CH x 2), 127.7 (CH x 2), 127.6 (CH x 2), [105.3, 105.0, 104.7]( $\text{CH}_2$ ), 84.5 (C), 81.0 (C), 68.5 (C), 57.2 ( $\text{CH}_2$ ), 56.3 (C), 43.8 (C), 34.4 ( $\text{CH}_3$ ), 30.4 ( $\text{CH}_3$  x 2), 29.9 ( $\text{CH}_2$ ), 29.6 ( $\text{CH}_3$ ), 29.3 ( $\text{CH}_3$ ), 24.5 ( $\text{CH}_3$ ), 21.8 ( $\text{CH}_3$  x 2).

HRMS (ESI-MS) calcd. for  $\text{C}_{29}\text{H}_{38}\text{DN}_2\text{O}_4\text{S}_2^+$  ( $[\text{M}+\text{H}]^+$ ): 544.2409, found 544.2410.

***N*,4-Dimethyl-*N*-(2-methyl-5-(3,5,5-trimethyl-4-methylene-1-tosylpyrrolidin-3-yl)pent-3-yn-2-yl)benzenesulfonamide (**59'-*d*<sub>1</sub>**)**



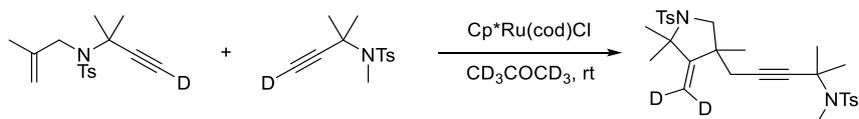
**59'-*d*<sub>1</sub>** was prepared according procedure **D** using **6** and **55-*d*<sub>1</sub>** as coupling partners in  $\text{CD}_3\text{COCD}_3$ . Yield: 79%, colorless oil,  $R_f$  (PE/ $\text{Et}_2\text{O}$  6/4) 0.35.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.70 (dd,  $J = 20.2, 8.3$  Hz, 4H), 7.28 (s, 2H), 7.26 (s, 2H), 4.83 (s, 1H), 4.79 (s, 0.07H), 3.23 (d,  $J = 9.7$  Hz, 1H), 2.99 (d,  $J = 9.7$  Hz, 1H), 2.97 (s, 3H), 2.41 (s, 3H), 2.40 (s, 3H), 2.13 (d,  $J = 16.7$  Hz, 1H), 2.01 (d,  $J = 16.7$  Hz, 1H), 1.56 (s, 3H), 1.55 (s, 3H), 1.50 (s, 3H), 1.49 (s, 3H), 1.06 (s, 3H).

$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  163.4 (C), 143.4 (C), 143.2 (C), 139.1 (C), 138.3 (C), 129.7 (CH x 2), 129.6 (CH x 2), 127.8 (CH x 2), 127.6 (CH x 2), [105.3, 105.0, 104.7]( $\text{CH}_2$ ), 84.6 (C), 81.0 (C), 68.5 (C), 57.2 ( $\text{CH}_2$ ), 56.3 (C), 43.9 (C), 34.4 ( $\text{CH}_3$ ), 30.4 ( $\text{CH}_3$  x 2), 30.0 ( $\text{CH}_2$ ), 29.65 ( $\text{CH}_3$ ), 29.34 ( $\text{CH}_3$ ), 24.5 ( $\text{CH}_3$ ), 21.8 ( $\text{CH}_3$  x 2).

HRMS (ESI-MS) calcd. for  $\text{C}_{29}\text{H}_{38}\text{DN}_2\text{O}_4\text{S}_2^+$  ( $[\text{M}+\text{H}]^+$ ): 544.2409, found 544.2408.

***N*,4-Dimethyl-*N*-(2-methyl-5-(3,5,5-trimethyl-4-methylene-1-tosylpyrrolidin-3-yl)pent-3-yn-2-yl)benzenesulfonamide (**59-*d*<sub>2</sub>**)**



**59-*d*<sub>2</sub>** was prepared according procedure **D** using **6-*d*<sub>1</sub>** and **55-*d*<sub>1</sub>** as coupling partners in

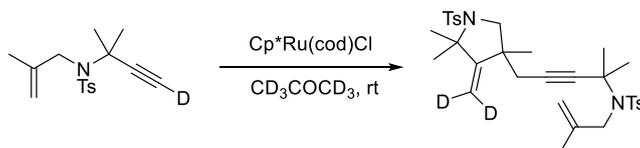
CD<sub>3</sub>COCD<sub>3</sub>. Yield: 73%, colorless oil, R<sub>f</sub> (PE/Et<sub>2</sub>O 6/4) 0.35.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.70 (dd, *J* = 20.1, 8.3 Hz, 4H), 7.27 (d, *J* = 7.5 Hz, 4H), 4.83 (s, 0.05H), 4.77 (s, 0.08H), 3.24 (d, *J* = 9.7 Hz, 1H), 2.99 (d, *J* = 9.7 Hz, 1H), 2.97 (s, 3H), 2.41 (d, *J* = 1.5 Hz, 6H), 2.13 (d, *J* = 16.7 Hz, 1H), 2.01 (d, *J* = 16.7 Hz, 1H), 1.56 (s, 3H), 1.55 (s, 3H), 1.50 (s, 3H), 1.49 (s, 3H), 1.06 (s, 3H).

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 163.2 (C), 143.4 (C), 143.2 (C), 139.1 (C), 138.3 (C), 129.7 (CH x 2), 129.7 (CH x 2), 127.8 (CH x 2), 127.6 (CH x 2), 84.6 (C), 81.0 (C), 68.5 (C), 57.2 (CH<sub>2</sub>), 56.3 (C), 43.8 (C), 34.4 (CH<sub>3</sub>), 30.4 (CH<sub>3</sub> x 2), 30.0 (CH<sub>2</sub>), 29.7 (CH<sub>3</sub>), 29.4 (CH<sub>3</sub>), 24.5 (CH<sub>3</sub>), 21.8 (CH<sub>3</sub> x 2).

HRMS (ESI-MS) calcd. for: C<sub>29</sub>H<sub>37</sub>D<sub>2</sub>N<sub>2</sub>O<sub>4</sub>S<sub>2</sub><sup>+</sup> ([M+H]<sup>+</sup>): 545.2471, found 545.2470.

**4-Methyl-*N*-(2-methyl-5-(3,5,5-trimethyl-4-dideuteromethylene-1-tosylpyrrolidin-3-yl)pent-3-yn-2-yl)-*N*-(2-methylallyl)benzenesulfonamide (71-*d*<sub>2</sub>)**



**71-*d*<sub>2</sub>** was prepared according procedure **D** using **6-*d*<sub>1</sub>** as reactant in CD<sub>3</sub>COCD<sub>3</sub>. Yield: 85%, colorless oil, R<sub>f</sub> (PE/Et<sub>2</sub>O 6/4) 0.35.

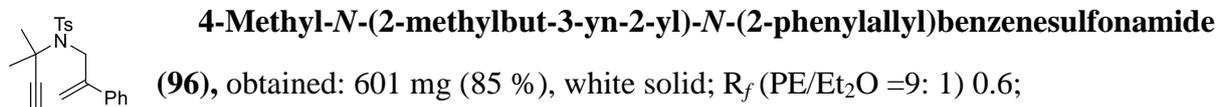
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.72 (d, *J* = 8.3 Hz, 2H), 7.68 (d, *J* = 8.3 Hz, 2H), 7.28 (s, 2H), 7.25 (d, *J* = 6.2 Hz, 2H), 5.02 (s, 1H), 4.90 (s, 1H), 4.83 (s, 0.05H), 4.76 (s, 0.07H), 4.02 (s, 2H), 3.23 (d, *J* = 9.7 Hz, 1H), 2.98 (d, *J* = 9.7 Hz, 1H), 2.40 (s, 6H), 2.10 (d, *J* = 16.7 Hz, 1H), 1.99 (d, *J* = 16.7 Hz, 1H), 1.76 (s, 3H), 1.54 (s, 6H), 1.50 (s, 3H), 1.48 (s, 3H), 1.04 (s, 3H).

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 163.3 (C), 143.4 (C), 143.3 (C), 143.1 (C), 139.8 (C), 138.3 (C), 129.7 (CH x 2), 129.5 (CH x 2), 127.8 (CH x 2), 127.7 (CH x 2), 112.3 (CH<sub>2</sub>), 85.1 (C), 80.8 (C), 68.5 (C), 57.3 (CH<sub>2</sub>), 57.1 (C), 54.1 (CH<sub>2</sub>), 43.8 (C), 31.4 (CH<sub>3</sub>), 31.3 (CH<sub>3</sub>), 30.0 (CH<sub>2</sub>), 29.7 (CH<sub>3</sub>), 29.3 (CH<sub>3</sub>), 24.5 (CH<sub>3</sub>), 21.8 (CH<sub>3</sub> x 2), 20.6 (CH<sub>3</sub>).

HRMS (ESI-MS) calcd. for ([M]<sup>+</sup>): C<sub>32</sub>H<sub>41</sub>D<sub>2</sub>N<sub>2</sub>O<sub>4</sub>S<sub>2</sub><sup>+</sup> ([M+H]<sup>+</sup>): 585.2784, found 585.2793.

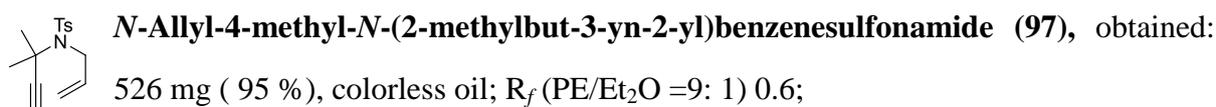
## Part II. Ruthenium-Catalyzed [2+2+2] Cycloaddition of 1,6-Enynes with Alkynes

1,6-Enynes **96**, **97** and **98** were prepared according to the Procedure A of part I of experimental section. Enyne **150** was prepared according to previous publication.<sup>3</sup>



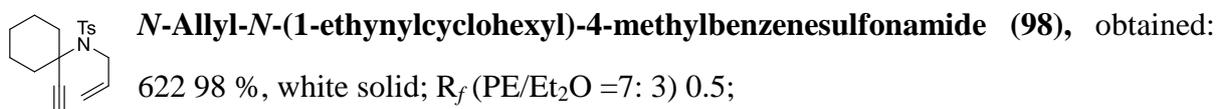
<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  7.77 (d,  $J$  = 8.3 Hz, 2H), 7.43 – 7.27 (m, 6H), 7.25 (s, 1H), 5.51 (q,  $J$  = 1.3 Hz, 1H), 5.46 (q,  $J$  = 1.5 Hz, 1H), 4.51 (t,  $J$  = 1.8 Hz, 2H), 2.42 (s, 3H), 2.16 (s, 1H), 1.71 (s, 6H).

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  145.7 (C), 143.5 (C), 140.2 (C), 139.1 (C), 129.6 (CH x 2), 128.7 (CH x 2), 128.1 (CH x 2), 128.1 (CH), 126.5 (CH x 2), 114.3 (CH<sub>2</sub>), 86.2 (C), 71.9 (CH), 57.0 (C), 52.2 (CH<sub>2</sub>), 31.2 (CH<sub>3</sub> x 2), 21.8 (CH<sub>3</sub>).



<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.74 (d,  $J$  = 8.2 Hz, 2H), 7.26 (d,  $J$  = 8.1 Hz, 2H), 6.08 – 5.98 (m, 1H), 5.27 (dd,  $J$  = 17.2, 1.5 Hz, 1H), 5.18 (dd,  $J$  = 10.3, 1.5 Hz, 1H), 4.17 (d,  $J$  = 5.9, 2H), 2.41 (s, 3H), 2.30 (s, 1H), 1.67 (s, 6H).

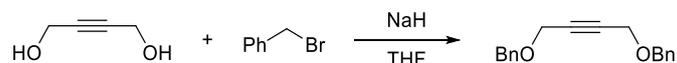
<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  143.1 (C), 139.7 (C), 136.8 (CH), 129.5 (CH x 2), 127.3 (CH x 2), 117.3 (CH<sub>2</sub>), 86.3 (C), 72.2 (CH), 56.4 (C), 50.6 (CH<sub>2</sub>), 30.7 (CH<sub>3</sub> x 2), 21.6 (CH<sub>3</sub>).



<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.73 (d,  $J$  = 8.3 Hz, 2H), 7.25 (d,  $J$  = 8.3 Hz, 2H), 6.04 (ddt,  $J$  = 17.2, 10.2, 5.7 Hz, 1H), 5.27 (dq,  $J$  = 17.2, 1.6 Hz, 1H), 5.16 (dq,  $J$  = 10.2, 1.4 Hz, 1H), 4.18 (dt,  $J$  = 5.8, 1.6 Hz, 2H), 2.40 (s, 3H), 2.36 (s, 1H), 2.09 – 2.06 (m, 2H), 1.91 (td,  $J$  = 12.5, 4.0 Hz, 2H), 1.68 – 1.59 (m, 3H), 1.56 – 1.51 (m, 2H), 1.17 – 1.06 (m, 1H).

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  143.1 (C), 140.1 (C), 137.5 (CH), 129.6 (CH x 2), 127.6 (CH x 2), 117.0 (CH<sub>2</sub>), 83.9 (C), 75.4 (CH), 62.4 (C), 50.4 (CH<sub>2</sub>), 37.8 (CH<sub>2</sub> x 2), 25.0 (CH<sub>2</sub>), 23.8 (CH<sub>2</sub> x 2), 21.8 (CH<sub>3</sub>).

### 1,4-Bis(benzyloxy)but-2-yne (110)<sup>11</sup>

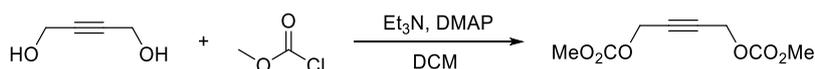


2-Butyne-1,4-diol (861 mg, 10 mmol) was added dropwise to a suspension of NaH (880 mg, 22 mmol, 60 % dispersion in mineral oil) in dry THF (50 mL) at 0 °C. The mixture was stirred for 1 h, and then benzyl bromide (4.1 g, 24 mmol) was added dropwise. The mixture was warmed to rt and stirred until completion (TLC monitoring), diluted with a saturated aqueous NH<sub>4</sub>Cl (30 mL), extracted with diethyl ether (3 x 15 mL). The combined extracts were washed with brine (30 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel to afford 1.7 g (65%) of the title compound as a colorless oil. R<sub>f</sub>(PE/Et<sub>2</sub>O 4/1) 0.45.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.47–7.28 (m, 10H), 4.64 (s, 4H), 4.27 (s, 4H).

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 137.6 (C x 2), 128.6 (CH x 4), 128.2 (CH x 4), 128.0 (CH x 2), 82.8 (C x 2), 71.8 (CH<sub>2</sub> x 2), 57.6 (CH<sub>2</sub> x 2).

### But-2-yne-1,4-diyl dimethyl bis(carbonate) (111)<sup>12</sup>



Methyl chloroformate (2.27 g, 24 mmol) was added dropwise to a solution of 2-butyne-1,4-diol (861 mg, 10 mmol), 4-dimethylaminopyridine (122 mg, 1 mmol) and triethylamine (4 g, 40 mmol) in dry dichloromethane (50 mL) at 0 °C. The mixture was stirred at room temperature overnight, then was washed with 10% HCl solution (50 mL), brine (30 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel to afford 1.8 g (91%) of the title compound as a white semisolid. R<sub>f</sub>(PE/Et<sub>2</sub>O 4/6) 0.35.

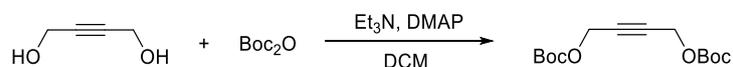
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 4.77 (m, 4H), 3.81 (m, 6H).

<sup>11</sup> A. Tenaglia, S. Marc, *J. Org. Chem.* **2008**, *73*, 1397-1402.

<sup>12</sup> J. Kijii, T. Okano, E. Fujii, J. Tsuji, *Synthesis* **1997**, 869-870.

$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  155.1 (C x 2), 80.9 (C x 2), 55.2 ( $\text{CH}_3$  x 2), 55.1 ( $\text{CH}_2$  x 2).

**But-2-yne-1,4-diyl di-tert-butyl bis(carbonate) (112)**<sup>13</sup>

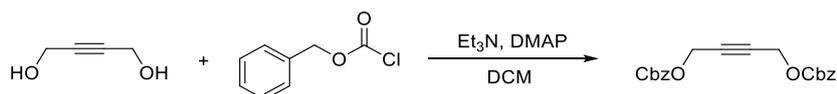


A solution of di-*tert*-butyl dicarbonate (5.24 g, 24 mmol) in dichloromethane (25 mL) was added to a solution of 2-butyne-1,4-diol (861 mg, 10 mmol), 4-dimethylaminopyridine (122 mg, 1 mmol) and triethylamine (4 g, 40 mmol) in dichloromethane (50 mL). The mixture was stirred overnight, then washed with 10% HCl solution (50 mL), brine (30 mL), dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel to afford 2.1 g (73%) of the title compound as a colorless oil.  $R_f$  (PE/Et<sub>2</sub>O 1/1) 0.35.

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  4.68 (s, 4H), 1.47 (s, 18H).

$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  152.9 (C x 2), 83.0 (C x 2), 81.1 (C x 2), 54.6 ( $\text{CH}_2$  x 2), 27.8 ( $\text{CH}_3$  x 6).

**Dibenzyl but-2-yne-1,4-diyl bis(carbonate) (113)**



Benzyl chloroformate (4.09 g, 24 mmol) was added to a solution of 2-butyne-1,4-diol (861 mg, 10 mmol), 4-dimethylaminopyridine (122 mg, 1 mmol) and triethylamine (4 g, 40 mmol) in dichloromethane (50 mL) at 0 °C. The resulting mixture was stirred overnight at room temperature, washed with 10% HCl solution (50 mL), brine (30 mL), dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel to afford 2.4 g (69%) of the title compound as a white solid, mp 74–75 °C.  $R_f$  (PE/Et<sub>2</sub>O 3/2) 0.45.

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.40–7.31 (m, 10H), 5.19 (s, 4H), 4.78 (s, 4H).

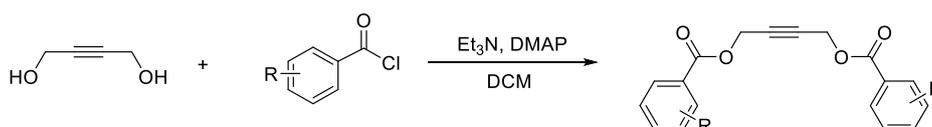
<sup>13</sup> A. Buzas, F. Gagosz, *Org. Lett.* **2006**, *8*, 515-518.

$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  154.8 (C x 2), 135.2 (C x 2), 128.9 (CH x 4), 128.9 (CH x 4), 128.6 (CH x 2), 81.3 (C x 2), 70.4 ( $\text{CH}_2$  x 2), 55.7 ( $\text{CH}_2$  x 2).

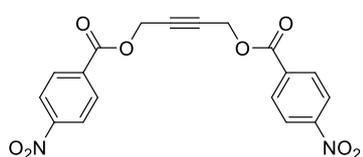
IR (neat)  $\nu$  3034, 2955, 1744, 1497, 1389, 1223, 1153, 932, 910, 751, 694, 576  $\text{cm}^{-1}$ .

HRMS (ESI-MS) calcd. for  $\text{C}_{20}\text{H}_{22}\text{NO}_6^+$  ( $[\text{M}+\text{NH}_4]^+$ ): 372.1442, found 372.1442.

General Procedure E for Acylation of 2-butyne-1,4-diol



Acyl chloride (24 mmol) was added dropwise to a solution of 2-butyne-1,4-diol (861 mg, 10 mmol), 4-dimethylaminopyridine (122 mg, 1 mmol) and triethylamine (4 g, 40 mmol) in dry dichloromethane (50 mL) at 0 °C. The resulting mixture was stirred overnight at room temperature, washed with 10% HCl solution (50 mL), brine (30 mL), dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel.



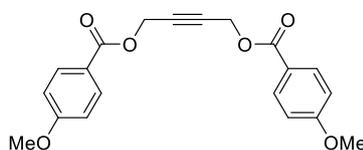
**But-2-yne-1,4-diyl bis(4-nitrobenzoate) (114).** The above procedure E afforded 2.8 g (72%) of the title compound as a white solid, mp 148–149 °C.  $R_f(\text{Et}_2\text{O})$  0.40.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.31 (d,  $J$  = 8.9 Hz, 4H), 8.25 (d,  $J$  = 9.0 Hz, 4H), 5.05 (s, 4H).

$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  164.2 (C x 2), 151.1 (C x 2), 135.0 (C x 2), 131.3 (CH x 4), 123.9 (CH x 4), 81.3 (C x 2), 53.6 ( $\text{CH}_2$  x 2).

IR (neat)  $\nu$  3113, 2913, 1729, 1522, 1344, 1262, 1094, 944, 878, 718  $\text{cm}^{-1}$ .

HRMS (ESI-MS) calcd. for  $\text{C}_{18}\text{H}_{16}\text{N}_3\text{O}_8^+$  ( $[\text{M}+\text{NH}_4]^+$ ): 402.0932, found 402.0928.



**But-2-yne-1,4-diyl bis(4-methoxybenzoate) (115).** The above procedure E afforded 2.9 g (82%) of the title compound as a

white solid, mp 117–118 °C.  $R_f$ (PE/AcOEt 4/1) 0.35.

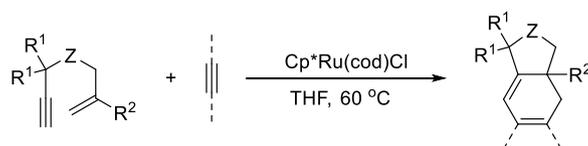
$^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.02 (d,  $J = 8.4$  Hz, 4H), 6.92 (d,  $J = 8.4$  Hz, 4H), 4.96 (s, 4H), 3.86 (s, 6H).

$^{13}\text{C NMR}$  (75 MHz,  $\text{CDCl}_3$ )  $\delta$  164.9 (C x 2), 163.0 (C x 2), 131.3 (CH x 4), 121.2 (C x 2), 113.1 (CH x 4), 80.4 (C x 2), 54.8 ( $\text{CH}_3$  x 2), 51.7 ( $\text{CH}_2$  x 2).

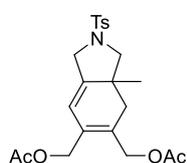
**IR** (neat)  $\nu$  2933, 2846, 1701, 1606, 1512, 1444, 1310, 1269, 1260, 1161, 1101, 842, 765, 693, 615  $\text{cm}^{-1}$ .

**HRMS** (ESI-MS) calcd. for  $\text{C}_{20}\text{H}_{19}\text{O}_6^+$  ( $[\text{M}+\text{H}]^+$ ): 355.1176, found 355.1172.

General procedure **F** for the Ru(II)-catalyzed coupling reaction of enynes and alkynes.



A solution of 1, 6-enyne (0.2 mmol) and alkyne (0.6 mmol) in THF (0.5 mL) was added to a solution of  $\text{Cp}^*\text{Ru}(\text{cod})\text{Cl}$  (3.80 mg, 0.01 mmol) in THF (0.5 mL). The mixture was stirred at 60 °C until completion of the reaction (TLC monitoring), cooled to room temperature, filtered over celite, and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel.



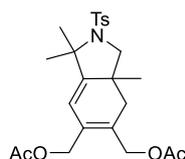
**(3a-Methyl-2-tosyl-2,3,3a,4-tetrahydro-1H-isoindole-5,6-diyl)bis(methylene)diacetate (94)**. General procedure **F** afforded 38.1 mg (44%) of the title compound as colorless oil.  $R_f$ (PE/ $\text{Et}_2\text{O}$  1/1) 0.30.

$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.70 (d,  $J = 8.2$  Hz, 2H), 7.33 (d,  $J = 7.9$  Hz, 2H), 5.70 (t,  $J = 2.1$  Hz, 1H), 4.77 (d,  $J = 12.5$  Hz, 1H), 4.70 (d,  $J = 12.4$  Hz, 1H), 4.62 (d,  $J = 12.4$  Hz, 1H), 4.54 (d,  $J = 12.5$  Hz, 1H), 4.20 (dd,  $J = 15.6, 2.1$  Hz, 1H), 3.75 (d,  $J = 15.6$  Hz, 1H), 3.54 (d,  $J = 9.0$  Hz, 1H), 2.78 (d,  $J = 9.0$  Hz, 1H), 2.43 (s, 3H), 2.20 (s, 2H), 2.03 (s, 3H), 2.02 (s, 3H), 0.99 (s, 3H).

$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  171.1 (C x 2), 144.1 (C), 144.0 (C), 133.2 (C), 130.1 (CH x 2), 129.2 (C), 128.7 (C), 128.0 (CH x 2), 116.9 (CH), 63.4 ( $\text{CH}_2$ ), 62.1 ( $\text{CH}_2$ ), 62.0 ( $\text{CH}_2$ ), 50.2 ( $\text{CH}_2$ ), 41.5 (C), 37.6 ( $\text{CH}_2$ ), 21.9 ( $\text{CH}_3$ ), 21.6 ( $\text{CH}_3$ ), 21.2 ( $\text{CH}_3$ ), 21.1 ( $\text{CH}_3$ ).

IR (neat)  $\nu$  2960, 2862, 1734, 1376, 1221, 1161, 1092, 1021, 817, 711, 664, 601, 549  $\text{cm}^{-1}$ .

HRMS (ESI-MS) calcd. for  $\text{C}_{22}\text{H}_{28}\text{NO}_6\text{S}^+$  ( $[\text{M}+\text{H}]^+$ ): 434.1632, found 434.1627.



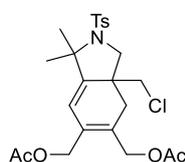
**(1,1,3a-Trimethyl-2-tosyl-2,3,3a,4-tetrahydro-1H-isoindole-5,6-diyl)bis(methylene) diacetate (95).** General procedure F afforded 89.5 mg (97%) of the title compound as a colorless oil.  $R_f$ (PE/Et<sub>2</sub>O 4/6) 0.35.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.74 (d,  $J = 8.3$  Hz, 2H), 7.27 (d,  $J = 8.9$  Hz, 2H), 5.65 (s, 1H), 4.80 (d,  $J = 12.5$  Hz, 1H), 4.74 (d,  $J = 12.4$  Hz, 1H), 4.66 (d,  $J = 12.4$  Hz, 1H), 4.57 (d,  $J = 12.5$  Hz, 1H), 3.40 (d,  $J = 9.2$  Hz, 1H), 3.01 (d,  $J = 9.2$  Hz, 1H), 2.41 (s, 3H), 2.20–2.14 (m, 2H), 2.04 (s, 3H), 2.03 (s, 3H), 1.69 (s, 3H), 1.46 (s, 3H), 0.96 (s, 3H).

$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  171.0 (C x 2), 156.6 (C), 143.2 (C), 138.2 (C), 129.6 (CH x 2), 129.4 (C), 128.7 (C), 127.7 (CH x 2), 115.3 (CH), 67.3 (C), 63.3 ( $\text{CH}_2$ ), 62.1 ( $\text{CH}_2$ ), 60.8 ( $\text{CH}_2$ ), 39.5 (C), 38.4 ( $\text{CH}_2$ ), 31.1 ( $\text{CH}_3$ ), 28.4 ( $\text{CH}_3$ ), 21.9 ( $\text{CH}_3$ ), 21.7 ( $\text{CH}_3$ ), 21.1 ( $\text{CH}_3$ ), 20.9 ( $\text{CH}_3$ ).

IR (neat)  $\nu$  3055, 2979, 2254, 1733, 1353, 1264, 1091, 907, 727  $\text{cm}^{-1}$ .

HRMS (ESI-MS) calcd. for  $\text{C}_{24}\text{H}_{32}\text{NO}_6\text{S}^+$  ( $[\text{M}+\text{H}]^+$ ): 462.1945, found 462.1947.



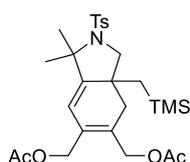
**(3a-(Chloromethyl)-1,1-dimethyl-2-tosyl-2,3,3a,4-tetrahydro-1H-isoindole-5,6-diyl)bis(methylene) diacetate (99).** General procedure F afforded 97.2 mg (98%) of the title compound as a colorless oil.  $R_f$ (PE/Et<sub>2</sub>O 4/6) 0.35.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.74 (d,  $J = 8.3$  Hz, 2H), 7.28 (d,  $J = 8.0$  Hz, 2H), 5.81 (s, 1H), 4.83 (d,  $J = 12.7$  Hz, 1H), 4.76 (dd,  $J = 12.5, 1.7$  Hz, 1H), 4.67 (d,  $J = 12.5$  Hz, 1H), 4.51 (d,  $J = 12.7$  Hz, 1H), 3.91 (d,  $J = 10.2$  Hz, 1H), 3.22 (dd,  $J = 10.9, 1.6$  Hz, 1H), 3.17 (d,  $J = 10.9$  Hz, 1H), 2.97 (dd,  $J = 10.2, 1.6$  Hz, 1H), 2.78 (d,  $J = 17.0$  Hz, 1H), 2.41 (s, 3H), 2.05 (s, 3H), 2.03 (s, 3H), 2.01 (br s, 1H), 1.61 (s, 3H), 1.49 (s, 3H).

$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  171.0 (C), 170.9 (C), 152.3 (C), 143.5 (C), 138.4 (C), 129.8 (CH x 2), 129.6 (C), 129.5 (C), 127.4 (CH x 2), 118.8 (CH), 66.9 (C), 62.6 ( $\text{CH}_2$ ), 61.9 ( $\text{CH}_2$ ), 56.0 ( $\text{CH}_2$ ), 44.7 (C), 44.2 ( $\text{CH}_2$ ), 32.4 ( $\text{CH}_2$ ), 30.3 ( $\text{CH}_3$ ), 28.9 ( $\text{CH}_3$ ), 21.7 ( $\text{CH}_3$ ), 21.2 ( $\text{CH}_3$ ), 21.1 ( $\text{CH}_3$ ).

IR (neat)  $\nu$  2975, 2871, 1735, 1364, 1220, 1150, 1112, 1089, 991, 728, 576  $\text{cm}^{-1}$ .

HRMS (ESI-MS) calcd. for  $\text{C}_{24}\text{H}_{31}\text{ClNO}_6\text{S}^+$  ( $[\text{M}+\text{H}]^+$ ): 496.1555, found 496.1553.



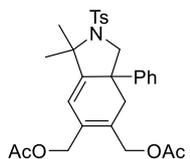
**(1,1-Dimethyl-2-tosyl-3a-((trimethylsilyl)methyl)-2,3,3a,4-tetrahydro-1H-isoindole-5,6-diyl)bis(methylene) diacetate (100)**. General procedure F afforded 77.9 mg (73%) of the title compound as a colorless oil.  $R_f$ (PE/Et<sub>2</sub>O 4/6) 0.38.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.75 (d,  $J$  = 8.3 Hz, 2H), 7.28 (d,  $J$  = 8.0 Hz, 2H), 5.59 (s, 1H), 4.71–4.69 (m, 4H), 3.45 (d,  $J$  = 9.3 Hz, 1H), 2.94 (dd,  $J$  = 9.3, 2.0 Hz, 1H), 2.40 (s, 3H), 2.32 (d,  $J$  = 16.9 Hz, 1H), 2.20 (d,  $J$  = 16.9 Hz, 1H), 2.04 (s, 3H), 2.03 (s, 3H), 1.76 (s, 3H), 1.47 (s, 3H), 0.88 (dd,  $J$  = 14.9, 2.0 Hz, 1H), 0.72 (dd,  $J$  = 14.9, 1.3 Hz, 1H), -0.12 (s, 9H).

$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  171.0 (C x 2), 158.5 (C), 143.4 (C), 138.1 (C), 130.1 (C), 129.7 (CH x 2), 128.4 (C), 127.9 (CH x 2), 114.3 (CH), 67.0 (C), 63.7 ( $\text{CH}_2$ ), 62.3 ( $\text{CH}_2$ ), 59.8 ( $\text{CH}_2$ ), 41.9 (C), 38.1 ( $\text{CH}_2$ ), 31.4 ( $\text{CH}_3$ ), 28.7 ( $\text{CH}_3$ ), 23.1 ( $\text{CH}_2$ ), 21.7 ( $\text{CH}_3$ ), 21.1 ( $\text{CH}_3$  x 2). 0.7 ( $\text{CH}_3$  x 3).

IR (neat)  $\nu$  2976, 2869, 2257, 1733, 1364, 1221, 1141, 1023, 959, 729  $\text{cm}^{-1}$ .

HRMS (ESI-MS) calcd. for  $\text{C}_{27}\text{H}_{40}\text{NO}_6\text{SSi}^+$  ( $[\text{M}+\text{H}]^+$ ): 534.2340, found 534.2339.



**(1,1-Dimethyl-3a-phenyl-2-tosyl-2,3,3a,4-tetrahydro-1H-isoindole-5,6-diyl)bis(methylene) diacetate (101)**. General procedure F afforded 64.9 mg (62%) of the title compound as a colorless oil.  $R_f$ (PE/Et<sub>2</sub>O 4/6) 0.43.

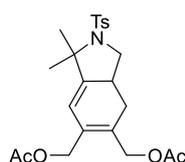
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.28 (d,  $J$  = 8.3 Hz, 2H), 7.19–7.11 (m, 5H), 6.99 (d,  $J$  = 8.0 Hz, 2H), 6.11 (s, 1H), 4.79 (d,  $J$  = 12.4 Hz, 1H), 4.69 (d,  $J$  = 12.4 Hz, 1H), 4.56 (d,  $J$  = 12.5 Hz, 1H), 4.31 (d,  $J$  = 12.5 Hz, 1H), 4.16 (d,  $J$  = 10.0 Hz, 1H), 3.49 (d,  $J$  = 10.0 Hz, 1H), 2.57

(d,  $J = 16.1$  Hz, 1H), 2.52 (d,  $J = 16.1$  Hz, 1H), 2.32 (s, 3H), 2.05 (s, 3H), 1.64 (s, 3H), 1.62 (s, 3H), 1.53 (s, 3H).

$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  170.9 (C), 170.5 (C), 152.7 (C), 142.8 (C), 140.7 (C), 138.6 (C), 130.6 (C), 129.3 (CH x 2), 129.1 (C), 128.3 (CH x 2), 127.1 (CH x 2), 127.1 (CH), 127.0 (CH x 2), 119.4 (CH), 66.8 (C), 62.6 ( $\text{CH}_2$ ), 61.9 ( $\text{CH}_2$ ), 61.4 ( $\text{CH}_2$ ), 48.0 (C), 40.4 ( $\text{CH}_2$ ), 29.1 ( $\text{CH}_3$ ), 29.0 ( $\text{CH}_3$ ), 21.6 ( $\text{CH}_3$ ), 21.1 ( $\text{CH}_3$ ), 20.7 ( $\text{CH}_3$ ).

IR (neat)  $\nu$  2932, 2868, 2252, 1734, 1218, 1090, 1023, 728, 581  $\text{cm}^{-1}$ .

HRMS (ESI-MS) calcd. for  $\text{C}_{29}\text{H}_{34}\text{NO}_6\text{S}^+$  ( $[\text{M}+\text{H}]^+$ ): 524.2101, found 524.2101.



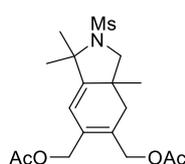
**(1,1-Dimethyl-2-tosyl-2,3,3a,4-tetrahydro-1H-isoindole-5,6-diyl)bis(methylene) diacetate (102).** General procedure F afforded 82.3 mg (92%) of the title compound as a colorless oil.  $R_f(\text{PE}/\text{Et}_2\text{O}$  2/3) 0.37.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.73 (d,  $J = 8.3$  Hz, 2H), 7.27 (d,  $J = 8.0$  Hz, 2H), 5.69 (d,  $J = 2.7$  Hz, 1H), 4.79 (d,  $J = 12.6$  Hz, 1H), 4.72 (dd,  $J = 12.4, 1.4$  Hz, 1H), 4.65 (d,  $J = 12.4$  Hz, 1H), 4.57 (d,  $J = 12.6$  Hz, 1H), 3.82 (t,  $J = 7.8$  Hz, 1H), 3.01–2.88 (m, 2H), 2.41 (s, 4H), 2.04 (s, 6H), 2.02 – 1.99 (m, 1H), 1.59 (s, 3H), 1.53 (s, 3H).

$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  171.0 (C x 2), 151.8 (C), 143.3 (C), 138.3 (C), 130.4 (C), 129.7 (CH x 2), 129.6 (C), 127.6 (CH x 2), 115.8 (CH), 67.3 (C), 63.2 ( $\text{CH}_2$ ), 62.2 ( $\text{CH}_2$ ), 54.0 ( $\text{CH}_2$ ), 36.0 (CH), 30.6 ( $\text{CH}_2$ ), 30.5 ( $\text{CH}_3$ ), 27.3 ( $\text{CH}_3$ ), 21.7 ( $\text{CH}_3$ ), 21.1 ( $\text{CH}_3$  x 2).

IR (neat)  $\nu$  2995, 2938, 1717, 1410, 1229, 1159, 1086, 723, 589  $\text{cm}^{-1}$ .

HRMS (ESI-MS) calcd. for  $\text{C}_{23}\text{H}_{29}\text{NO}_6\text{SNa}^+$  ( $[\text{M}+\text{Na}]^+$ ): 470.1608, found 470.1607.



**(1,1,3a-Trimethyl-2-(methylsulfonyl)-2,3,3a,4-tetrahydro-1H-isoindole-5,6-diyl)bis(methylene) diacetate (103).** General procedure F afforded 71.7 mg (93%) of the title compound as a colorless oil.  $R_f(\text{PE}/\text{Et}_2\text{O}$  3/7) 0.35.

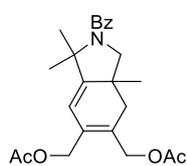
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  5.70 (s, 1H), 4.83 (d,  $J = 12.5$  Hz, 1H), 4.78 (d,  $J = 12.4$  Hz, 1H), 4.69 (d,  $J = 12.4$  Hz, 1H), 4.60 (d,  $J = 12.5$  Hz, 1H), 3.53 (d,  $J = 9.2$  Hz, 1H), 3.10 (d,  $J$

= 9.2 Hz, 1H), 2.91 (s, 3H), 2.29 (d,  $J = 16.4$  Hz, 1H), 2.24 (d,  $J = 16.4$  Hz, 1H), 2.05 (s, 3H), 2.05 (s, 3H), 1.64 (s, 3H), 1.52 (s, 3H), 1.12 (s, 3H).

$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  171.0 (C x 2), 156.2 (C), 129.4 (C), 128.8 (C), 115.7 (CH), 66.6 (C), 63.3 ( $\text{CH}_2$ ), 62.1 ( $\text{CH}_2$ ), 61.1 ( $\text{CH}_2$ ), 40.3 ( $\text{CH}_3$ ), 39.4 (C), 38.4 ( $\text{CH}_2$ ), 30.9 ( $\text{CH}_3$ ), 28.2 ( $\text{CH}_3$ ), 22.2 ( $\text{CH}_3$ ), 21.1 ( $\text{CH}_3$ ), 21.0 ( $\text{CH}_3$ ).

IR (neat)  $\nu$  2998, 2819, 2254, 1761, 1395, 1210, 1159, 1034, 719, 537  $\text{cm}^{-1}$ .

HRMS (ESI-MS) calcd. for  $\text{C}_{18}\text{H}_{31}\text{N}_2\text{O}_6\text{S}^+$  ( $[\text{M}+\text{NH}_4]^+$ ): 403.1897, found 403.1897.



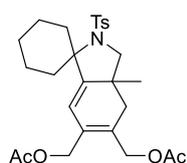
**(2-Benzoyl-1,1,3a-trimethyl-2,3,3a,4-tetrahydro-1H-isoindole-5,6-diyl)bis(methylene) diacetate (104)**. General procedure **F** afforded 74.9 mg (91%) of the title compound as a colorless oil.  $R_f(\text{PE}/\text{Et}_2\text{O}$  1/1) 0.36.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.37 (s, 5H), 5.76 (s, 1H), 4.81 (d,  $J = 12.5$  Hz, 1H), 4.78 (d,  $J = 12.4$  Hz, 1H), 4.69 (d,  $J = 12.4$  Hz, 1H), 4.58 (d,  $J = 12.5$  Hz, 1H), 3.49–3.44 (m, 1H), 3.20 (d,  $J = 10.7$  Hz, 1H), 2.23 (d,  $J = 16.4$  Hz, 1H), 2.13 (d,  $J = 16.4$  Hz, 1H), 2.06 (s, 3H), 2.02 (s, 3H), 1.83 (s, 3H), 1.64 (s, 3H), 1.09 (s, 3H).

$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  170.9 (C), 170.8 (C), 170.2 (C), 157.1 (C), 138.9 (C), 129.4 (C), 129.3 (CH), 128.6 (CH x 2), 128.2 (C), 126.3 (CH x 2), 115.1 (CH), 64.6 (C), 63.3 ( $\text{CH}_2$ ), 62.9 ( $\text{CH}_2$ ), 62.1 ( $\text{CH}_2$ ), 39.7 (C), 38.4 ( $\text{CH}_2$ ), 29.2 ( $\text{CH}_3$ ), 26.1 ( $\text{CH}_3$ ), 22.1 ( $\text{CH}_3$ ), 21.0 ( $\text{CH}_3$ ), 20.8 ( $\text{CH}_3$ ).

IR (neat)  $\nu$  2974, 2891, 2252, 1734, 1628, 1445, 1225, 904, 723, 647  $\text{cm}^{-1}$ .

HRMS (ESI-MS) calcd. for  $\text{C}_{24}\text{H}_{30}\text{NO}_5^+$  ( $[\text{M}+\text{H}]^+$ ): 412.2118, found 412.2118.



**(3a'-Methyl-2'-tosyl-2',3',3a',4'-tetrahydrospiro[cyclohexane-1,1'-isoindole]-5',6'-diyl)bis(methylene) diacetate (105)**. General procedure **F** afforded 93.3 mg (93%) of the title compound as a colorless oil.  $R_f(\text{PE}/\text{Et}_2\text{O}$  2/3) 0.33.

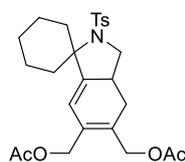
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.74 (d,  $J = 8.3$  Hz, 2H), 7.26 (d,  $J = 8.0$  Hz, 2H), 6.10 (s, 1H), 4.79 (d,  $J = 12.5$  Hz, 1H), 4.74 (d,  $J = 12.4$  Hz, 1H), 4.69 (d,  $J = 12.4$  Hz, 1H), 4.56 (d,  $J = 12.5$  Hz, 1H), 3.26 (d,  $J = 9.3$  Hz, 1H), 3.10 (d,  $J = 9.3$  Hz, 1H), 2.87–2.79 (m, 1H), 2.47–

2.42 (m, 1H), 2.40 (s, 3H), 2.22 (d,  $J = 16.3$  Hz, 1H), 2.10 (d,  $J = 16.3$  Hz, 1H), 2.03 (s, 3H), 2.02 (s, 3H), 1.85 (d,  $J = 13.0$  Hz, 1H), 1.74–1.59 (m, 6H), 1.42–1.33 (m, 1H), 0.86 (s, 3H).

$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  171.0 (C), 170.9 (C), 154.4 (C), 143.1 (C), 138.8 (C), 129.6 (C), 129.6 (CH x 2), 128.6 (C), 127.5 (CH x 2), 117.9 (CH), 70.8 (C), 63.2 ( $\text{CH}_2$ ), 62.4 ( $\text{CH}_2$ ), 60.3 ( $\text{CH}_2$ ), 40.2 (C), 38.3 ( $\text{CH}_2$ ), 36.3 ( $\text{CH}_2$ ), 36.1 ( $\text{CH}_2$ ), 24.5 ( $\text{CH}_2$ ), 22.7 ( $\text{CH}_2$ ), 22.2 ( $\text{CH}_2$ ), 22.1 ( $\text{CH}_3$ ), 21.7 ( $\text{CH}_3$ ), 21.1 ( $\text{CH}_3$ ), 20.9 ( $\text{CH}_3$ ).

IR (neat)  $\nu$  2931, 2872, 2255, 1733, 1225, 1154, 905, 724, 603  $\text{cm}^{-1}$ .

HRMS (ESI-MS) calcd. for  $\text{C}_{27}\text{H}_{36}\text{NO}_6\text{S}^+$  ( $[\text{M}+\text{H}]^+$ ): 502.2258, found 502.2258.



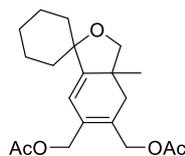
(2'-Tosyl-2',3',3a',4'-tetrahydrospiro[cyclohexane-1,1'-isoindole]-5',6'-diyl)bis(methylene) diacetate (**106**). General procedure **F** afforded 84.8 mg (87%) of the title compound as a colorless oil.  $R_f$ (PE/Et<sub>2</sub>O 4/6) 0.33.

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.65 (d,  $J = 8.0$  Hz, 2H), 7.19 (d,  $J = 7.9$  Hz, 2H), 6.07 (s, 1H), 4.74–4.49 (m, 4H), 3.70 (t,  $J = 8.1$  Hz, 1H), 2.95–2.77 (m, 2H), 2.55–2.45 (td,  $J = 12.5, 4.6$  Hz, 2H), 2.34 (s, 3H), 2.30–2.25 (m, 1H), 1.98 (s, 3H), 1.97 (s, 3H), 1.80–1.75 (m, 1H), 1.67–1.41 (m, 7H), 1.35–1.19 (m, 1H).

$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  171.1 (C x 2), 149.6 (C), 143.1 (C), 139.2 (C), 130.6 (C), 129.7 (CH x 2), 129.5 (C), 127.5 (CH x 2), 118.5 (CH), 70.9 (C), 63.2 ( $\text{CH}_2$ ), 62.5 ( $\text{CH}_2$ ), 53.8 ( $\text{CH}_2$ ), 36.7 (CH), 36.1 ( $\text{CH}_2$ ), 35.2 ( $\text{CH}_2$ ), 30.7 ( $\text{CH}_2$ ), 24.7 ( $\text{CH}_2$ ), 22.9 ( $\text{CH}_2$  x 2), 21.8 ( $\text{CH}_3$ ), 21.2 ( $\text{CH}_3$ ), 21.2 ( $\text{CH}_3$ ).

IR (neat)  $\nu$  2925, 2869, 1736, 1376, 1221, 1155, 1044, 663, 588  $\text{cm}^{-1}$ .

HRMS (ESI-MS) calcd. for  $\text{C}_{26}\text{H}_{37}\text{N}_2\text{O}_6\text{S}^+$  ( $[\text{M}+\text{NH}_4]^+$ ): 505.2367, found 505.2368.



(3a'-Methyl-3a',4'-dihydro-3'H-spiro[cyclohexane-1,1'-isobenzofuran]-5',6'-diyl)bis(methylene) diacetate (**107**). General procedure **F** afforded 59.2 mg (85%) of the title compound as a colorless oil.  $R_f$ (PE/Et<sub>2</sub>O 4/1) 0.45.

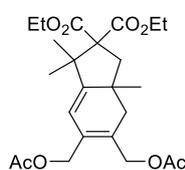
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  5.64 (s, 1H), 4.83 (d,  $J = 12.4$  Hz, 1H), 4.79 (dd,  $J = 12.3, 1.3$  Hz, 1H), 4.70 (d,  $J = 12.3$  Hz, 1H), 4.61 (d,  $J = 12.4$  Hz, 1H), 3.83 (d,  $J = 8.3$  Hz, 1H), 3.51

(d,  $J = 8.3$  Hz, 1H), 2.25 (d,  $J = 16.4$  Hz, 1H), 2.16 (d,  $J = 16.4$  Hz, 1H), 2.07 (s, 3H), 2.06 (s, 3H), 1.80–1.51 (m, 8H), 1.30–1.21 (m, 2H), 1.06 (s, 3H).

$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  170.7 (C), 170.6 (C), 157.3 (C), 129.5 (C), 128.1 (C), 113.6 (CH), 82.3 (C), 77.8 ( $\text{CH}_2$ ), 63.2 ( $\text{CH}_2$ ), 62.0 ( $\text{CH}_2$ ), 42.1 (C), 38.4 ( $\text{CH}_2$ ), 37.1 ( $\text{CH}_2$ ), 35.5 ( $\text{CH}_2$ ), 25.2 ( $\text{CH}_2$ ), 22.4 ( $\text{CH}_2$ ), 22.1 ( $\text{CH}_2$ ), 21.2 ( $\text{CH}_3$ ), 20.8 ( $\text{CH}_3$ ), 20.7 ( $\text{CH}_3$ ).

IR (neat)  $\nu$  2932, 2855, 2255, 1734, 1375, 1221, 1021, 959, 727  $\text{cm}^{-1}$ .

HRMS (ESI-MS) calcd. for  $\text{C}_{20}\text{H}_{32}\text{NO}_5^+$  ( $[\text{M}+\text{NH}_4]^+$ ): 366.2275, found 366.2275.



Diethyl

**5,6-bis(acetoxymethyl)-1,1,3a-trimethyl-1,3,3a,4-tetrahydro-2H-indene-2,2-dicarboxylate (108).** General procedure F afforded 79.3 mg (88%) of the

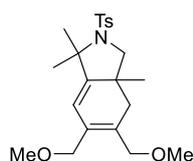
title compound as a colorless oil.  $R_f$ (PE/Et<sub>2</sub>O 3/1) 0.40.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  5.61 (s, 1H), 4.81 (d,  $J = 12.5$  Hz, 1H), 4.75–4.68 (m, 2H), 4.50 (d,  $J = 12.5$  Hz, 1H), 4.22 (q,  $J = 7.1$  Hz, 2H), 4.10 (qd,  $J = 7.2, 1.5$  Hz, 2H), 2.60–2.54 (m, 2H), 2.05 (s, 3H), 2.04 (s, 3H), 2.03 (d,  $J = 16.4$  Hz, 1H), 1.98 (d,  $J = 16.4$  Hz, 1H), 1.38 (s, 3H), 1.29 (t,  $J = 7.1$  Hz, 3H), 1.22–1.13 (m, 9H).

$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  171.8 (C), 171.2 (C), 171.1 (C), 170.7 (C), 158.5 (C), 129.8 (C), 129.6 (C), 114.8 (CH), 68.0 (C), 63.5 ( $\text{CH}_2$ ), 62.4 ( $\text{CH}_2$ ), 61.3 ( $\text{CH}_2$ ), 61.2 ( $\text{CH}_2$ ), 48.3 (C), 44.3 ( $\text{CH}_2$ ), 41.6 ( $\text{CH}_2$ ), 38.8 (C), 26.5 ( $\text{CH}_3$ ), 25.9 ( $\text{CH}_3$ ), 23.2 ( $\text{CH}_3$ ), 21.3 ( $\text{CH}_3$ ), 21.1 ( $\text{CH}_3$ ), 14.4 ( $\text{CH}_3$ ), 14.2 ( $\text{CH}_3$ ).

IR (neat)  $\nu$  2913, 2900, 1796, 1431, 1185, 1025, 997, 835, 775, 564  $\text{cm}^{-1}$ .

HRMS (ESI-MS) calcd. for  $\text{C}_{24}\text{H}_{38}\text{NO}_8^+$  ( $[\text{M}+\text{NH}_4]^+$ ): 468.2592, found 468.2593.



**5,6-Bis(methoxymethyl)-1,1,3a-trimethyl-2-tosyl-2,3,3a,4-tetrahydro-1H-isoindole (122).** General procedure F afforded 76.2 mg (94%) of the title compound as a colorless oil.  $R_f$ (PE/Et<sub>2</sub>O 4/6) 0.37.

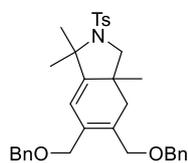
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.74 (d,  $J = 8.2$  Hz, 2H), 7.27 (d,  $J = 8.2$  Hz, 2H), 5.71 (s, 1H), 4.05 (d,  $J = 12.0$  Hz, 1H), 4.04 (dd,  $J = 11.6, 1.7$  Hz, 1H), 3.98 (d,  $J = 11.6$  Hz, 1H), 3.92 (d,

$J = 12.0$  Hz, 1H), 3.40 (d,  $J = 9.1$  Hz, 1H), 3.27 (s, 3H), 3.26 (s, 3H), 3.01 (d,  $J = 9.1$  Hz, 1H), 2.41 (s, 3H), 2.27 (d,  $J = 16.4$  Hz, 1H), 2.24 (d,  $J = 16.4$  Hz, 1H), 1.70 (s, 3H), 1.46 (s, 3H), 1.00 (s, 3H).

$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  155.3 (C), 143.2 (C), 138.4 (C), 130.0 (C), 129.9 (C), 129.7 (CH x 2), 127.7 (CH x 2), 115.7 (CH), 71.1 ( $\text{CH}_2$ ), 70.1 ( $\text{CH}_2$ ), 67.5 (C), 61.1 ( $\text{CH}_2$ ), 58.1 ( $\text{CH}_2$  x 2), 39.5 (C), 38.3 ( $\text{CH}_2$ ), 31.1 ( $\text{CH}_3$ ), 28.6 ( $\text{CH}_3$ ), 22.4 ( $\text{CH}_3$ ), 21.7 ( $\text{CH}_3$ ).

IR (neat)  $\nu$  3441, 2926, 2819, 1726, 1598, 1379, 1156, 1089, 663, 549  $\text{cm}^{-1}$ .

HRMS (ESI-MS) calcd. for  $\text{C}_{22}\text{H}_{32}\text{NO}_4\text{S}^+$  ( $[\text{M}+\text{H}]^+$ ): 406.2047, found 406.2047.



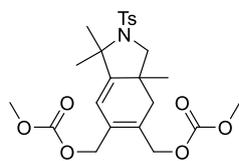
**5,6-Bis((benzyloxy)methyl)-1,1,3a-trimethyl-2-tosyl-2,3,3a,4-tetrahydro-1H-isoindole (123).** General procedure F afforded 103 mg (92%) of the title compound as a colorless oil.  $R_f$ (PE/Et<sub>2</sub>O 6/4) 0.45.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.76 (d,  $J = 8.3$  Hz, 2H), 7.36 – 7.26 (m, 12H), 5.76 (s, 1H), 4.43 (dd,  $J = 11.8, 5.0$  Hz, 2H), 4.37 (dd,  $J = 11.8, 2.7$  Hz, 2H), 4.11 (d,  $J = 11.8$  Hz, 1H), 4.09 (dd,  $J = 11.5, 1.5$  Hz, 1H), 4.03 (d,  $J = 11.5$  Hz, 1H), 3.98 (d,  $J = 11.8$  Hz, 1H), 3.42 (d,  $J = 9.1$  Hz, 1H), 3.03 (d,  $J = 9.1$  Hz, 1H), 2.42 (s, 3H), 2.34 (d,  $J = 16.5$  Hz, 1H), 2.20 (d,  $J = 16.5$  Hz, 1H), 1.72 (s, 3H), 1.47 (s, 3H), 1.04 (s, 3H).

$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  155.3 (C), 143.2 (C), 138.6 (C), 138.4 (C), 138.4 (C), 130.2 (C), 130.0 (C), 129.7 (CH x 2), 128.7 (CH x 2), 128.6 (CH x 2), 128.2 (CH x 2), 128.0 (CH), 127.9 (CH), 127.9 (CH x 2), 127.7 (CH x 2), 115.9 (CH), 72.2 ( $\text{CH}_2$ ), 72.1 ( $\text{CH}_2$ ), 68.7 ( $\text{CH}_2$ ), 67.5 ( $\text{CH}_2$ ), 67.4 (C), 61.1 ( $\text{CH}_2$ ), 39.6 (C), 38.5 ( $\text{CH}_2$ ), 31.2 ( $\text{CH}_3$ ), 28.6 ( $\text{CH}_3$ ), 22.5 ( $\text{CH}_3$ ), 21.8 ( $\text{CH}_3$ ).

IR (neat)  $\nu$  2919, 2893, 2230, 1317, 1153, 1094, 1039, 721, 544  $\text{cm}^{-1}$ .

HRMS (ESI-MS) calcd. for  $\text{C}_{34}\text{H}_{43}\text{N}_2\text{O}_4\text{S}^+$  ( $[\text{M}+\text{NH}_4]^+$ ): 575.2938, found 575.2938.



**Dimethyl ((1,1,3a-trimethyl-2-tosyl-2,3,3a,4-tetrahydro-1H-isoindole-5,6-diyl) bis(methylene)) bis(carbonate) (124).** General procedure F afforded

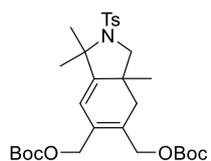
93.8 mg (95%) of the title compound as a colorless oil.  $R_f$ (PE/Et<sub>2</sub>O 1/1) 0.30.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.73 (d, *J* = 8.3 Hz, 2H), 7.27 (d, *J* = 8.1 Hz, 2H), 5.69 (s, 1H), 4.88 (d, *J* = 12.5 Hz, 1H), 4.85 (d, *J* = 12.3 Hz, 1H), 4.73 (d, *J* = 12.3 Hz, 1H), 4.63 (d, *J* = 12.5 Hz, 1H), 3.76 (s, 3H), 3.75 (s, 3H), 3.40 (d, *J* = 9.2 Hz, 1H), 3.00 (d, *J* = 9.2 Hz, 1H), 2.40 (s, 3H), 2.23 (s, 2H), 1.68 (s, 3H), 1.45 (s, 3H), 0.96 (s, 3H).

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 157.2 (C), 155.9 (C), 155.8 (C), 143.3 (C), 138.2 (C), 129.7 (CH x 2), 129.5 (C), 128.7 (C), 127.7 (CH x 2), 115.0 (CH), 67.4 (C), 66.6 (CH<sub>2</sub>), 65.4 (CH<sub>2</sub>), 60.7 (CH<sub>2</sub>), 55.2 (CH<sub>3</sub> x 2), 39.4 (C), 38.2 (CH<sub>2</sub>), 31.0 (CH<sub>3</sub>), 28.4 (CH<sub>3</sub>), 21.9 (CH<sub>3</sub>), 21.7 (CH<sub>3</sub>).

**IR** (neat) ν 2998, 2890, 1710, 1495, 1220, 1106, 895, 698 cm<sup>-1</sup>.

**HRMS** (ESI-MS) calcd. for C<sub>24</sub>H<sub>32</sub>NO<sub>8</sub>S<sup>+</sup> ([M+H]<sup>+</sup>): 494.1843, found 494.1842.



**Di-tert-butyl**  
**((1,1,3a-trimethyl-2-tosyl-2,3,3a,4-tetrahydro-1H-isoindole-5,6-diyl)**

**bis(methylene)) bis(carbonate) (125)**. General procedure **F** afforded 103 mg (89%) of the title compound as a colorless oil. *R<sub>f</sub>*(PE/Et<sub>2</sub>O 7/3) 0.48.

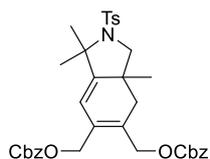
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.73 (d, *J* = 8.3 Hz, 2H), 7.27 (d, *J* = 8.0 Hz, 2H), 5.68 (s, 1H), 4.81 (d, *J* = 12.5 Hz, 1H), 4.77 (d, *J* = 12.3 Hz, 1H), 4.65 (d, *J* = 12.3 Hz, 1H), 4.53 (d, *J* = 12.5 Hz, 1H), 3.38 (d, *J* = 9.2 Hz, 1H), 2.99 (d, *J* = 9.2 Hz, 1H), 2.41 (s, 3H), 2.24 (d, *J* = 16.7 Hz, 1H), 2.19 (d, *J* = 16.7 Hz, 1H), 1.68 (s, 3H), 1.46 (s, 9H), 1.44 (s, 12H), 0.96 (s, 3H).

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 156.7 (C), 153.7 (C), 153.7 (C), 143.3 (C), 138.3 (C), 129.7 (CH x 2), 129.5 (C), 128.8 (C), 127.7 (CH x 2), 115.3 (CH), 82.6 (C), 82.5 (C), 67.5 (C), 65.7 (CH<sub>2</sub>), 64.5 (CH<sub>2</sub>), 60.8 (CH<sub>2</sub>), 39.5 (C), 38.2 (CH<sub>2</sub>), 31.1 (CH<sub>3</sub>), 28.5 (CH<sub>3</sub>), 28.1 (CH<sub>3</sub> x 6), 21.9 (CH<sub>3</sub>), 21.8 (CH<sub>3</sub>).

**IR** (neat) ν 2980, 2259, 1737, 1270, 1149, 906, 725 cm<sup>-1</sup>.

**HRMS** (ESI-MS) calcd. for C<sub>30</sub>H<sub>47</sub>N<sub>2</sub>O<sub>8</sub>S<sup>+</sup> ([M+NH<sub>4</sub>]<sup>+</sup>): 595.3048, found 595.3052.

## Dibenzyl



**((1,1,3a-trimethyl-2-tosyl-2,3,3a,4-tetrahydro-1H-isoindole-5,6-diyl)bis(methylene)) bis(carbonate) (126).** General procedure **F** afforded 112 mg

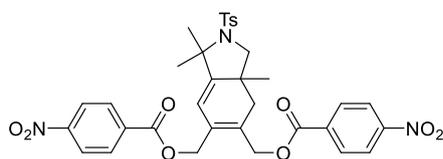
(87%) of the title compound as a white waxy oil.  $R_f$ (PE/Et<sub>2</sub>O 1/1) 0.53.

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>)  $\delta$  7.76 (d,  $J$  = 7.3 Hz, 2H), 7.45–7.26 (m, 12H), 5.69 (s, 1H), 5.15 (s, 4H), 4.91 (d,  $J$  = 12.4 Hz, 1H), 4.87 (d,  $J$  = 12.2 Hz, 1H), 4.77 (d,  $J$  = 12.2 Hz, 1H), 4.66 (d,  $J$  = 12.4 Hz, 1H), 3.40 (d,  $J$  = 8.7 Hz, 1H), 3.01 (d,  $J$  = 8.7 Hz, 1H), 2.44 (s, 3H), 2.22 (s, 2H), 1.68 (s, 3H), 1.46 (s, 3H), 0.92 (s, 3H).

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>)  $\delta$  157.2 (C), 155.3 (C), 155.2 (C), 143.2 (C), 138.2 (C), 135.4 (C x 2), 129.7 (CH x 2), 129.5 (C), 128.9 (CH x 5), 128.6 (C), 128.6 (CH x 5), 127.7 (CH x 2), 115.0 (CH), 70.0 (CH<sub>2</sub> x 2), 67.4 (C), 66.7 (CH<sub>2</sub>), 65.5 (CH<sub>2</sub>), 60.7 (CH<sub>2</sub>), 39.4 (C), 38.1 (CH<sub>2</sub>), 31.0 (CH<sub>3</sub>), 28.4 (CH<sub>3</sub>), 21.8 (CH<sub>3</sub>), 21.7 (CH<sub>3</sub>).

**IR** (neat)  $\nu$  3086, 2916, 2230, 1711, 1236, 1244, 945, 726, 684 cm<sup>-1</sup>.

**HRMS** (ESI-MS) calcd. for C<sub>36</sub>H<sub>43</sub>N<sub>2</sub>O<sub>8</sub>S<sup>+</sup> ([M+NH<sub>4</sub>]<sup>+</sup>): 663.2735, found 663.2734.



**((1,1,3a-Trimethyl-2-tosyl-2,3,3a,4-tetrahydro-1H-isoindole-5,6-diyl)bis(methylene) bis(4-nitrobenzoate) (127).** General procedure **F** afforded 112 mg (83%) of

the title compound as a white solid. mp 156-158 °C,  $R_f$ (PE/Et<sub>2</sub>O 4/6) 0.50.

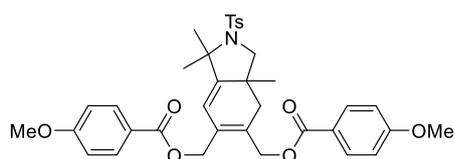
**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>)  $\delta$  8.26 (d,  $J$  = 8.7 Hz, 4H), 8.14 (d,  $J$  = 8.7 Hz, 4H), 7.74 (d,  $J$  = 8.1 Hz, 2H), 7.28 (d,  $J$  = 7.2 Hz, 2H), 5.78 (s, 1H), 5.22 (d,  $J$  = 12.5 Hz, 1H), 5.14 (d,  $J$  = 12.5 Hz, 1H), 5.07 (d,  $J$  = 12.5 Hz, 1H), 4.94 (d,  $J$  = 12.5 Hz, 1H), 3.42 (d,  $J$  = 9.2 Hz, 1H), 3.06 (d,  $J$  = 9.2 Hz, 1H), 2.41 (s, 3H), 2.35 (d,  $J$  = 6.4 Hz, 2H), 1.70 (s, 3H), 1.51 (s, 3H), 0.99 (s, 3H).

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>)  $\delta$  164.8 (C), 164.7 (C), 157.9 (C), 151.1 (C), 151.0 (C), 143.5 (C), 138.2 (C), 135.5 (C), 135.5 (C), 131.0 (CH x 2), 131.0 (CH x 2), 130.0 (C), 129.8 (CH x 2), 128.8 (C), 127.7 (CH x 2), 124.0 (CH x 2), 123.9 (CH x 2), 115.2 (CH), 67.4 (C), 64.8

(CH<sub>2</sub>), 63.6 (CH<sub>2</sub>), 60.7 (CH<sub>2</sub>), 39.7 (C), 38.6 (CH<sub>2</sub>), 31.2 (CH<sub>3</sub>), 28.5 (CH<sub>3</sub>), 22.1 (CH<sub>3</sub>), 21.8 (CH<sub>3</sub>).

**IR** (neat)  $\nu$  3639, 3020, 2257, 1755, 1558, 1298, 1178, 1091, 862, 731, 647 cm<sup>-1</sup>.

**HRMS** (ESI-MS) calcd. for C<sub>34</sub>H<sub>34</sub>N<sub>3</sub>O<sub>10</sub>S<sup>+</sup> ([M+H]<sup>+</sup>): 676.1959, found 676.1959.



**(1,1,3a-Trimethyl-2-tosyl-2,3,3a,4-tetrahydro-1H-isoindole-5,6-diyl)bis(methylene) bis(4-methoxybenzoate)**

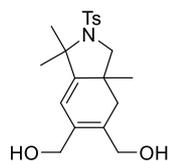
**(128)**. General procedure **F** afforded 120 mg (93%) of the title compound as a colorless oil.  $R_f$ (PE/Et<sub>2</sub>O 4/6) 0.32.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.93 (d,  $J$  = 9.0 Hz, 4H), 7.73 (d,  $J$  = 8.3 Hz, 2H), 7.27 (d,  $J$  = 8.0 Hz, 2H), 6.88 (d,  $J$  = 1.7 Hz, 2H), 6.86 (d,  $J$  = 1.7 Hz, 2H), 5.77 (s, 1H), 5.10 (d,  $J$  = 12.5 Hz, 1H), 5.03 (d,  $J$  = 12.4 Hz, 1H), 4.97 (d,  $J$  = 12.4 Hz, 1H), 4.85 (d,  $J$  = 12.5 Hz, 1H), 3.84 (s, 3H), 3.83 (s, 3H), 3.40 (d,  $J$  = 9.2 Hz, 1H), 3.03 (d,  $J$  = 9.2 Hz, 1H), 2.40 (s, 3H), 2.31 (s, 2H), 1.69 (s, 3H), 1.48 (s, 3H), 1.00 (s, 3H).

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  166.3 (C x 2), 163.8 (C), 163.7 (C), 156.6 (C), 143.2 (C), 138.2 (C), 131.9 (CH x 2), 131.8 (CH x 2), 129.9 (C), 129.7 (CH x 2), 129.2 (C), 127.7 (CH x 2), 122.7 (C), 122.6 (C), 115.6 (CH), 114.0 (CH x 2), 113.9 (CH x 2), 67.4 (C), 63.7 (CH<sub>2</sub>), 62.6 (CH<sub>2</sub>), 60.8 (CH<sub>2</sub>), 55.7 (CH<sub>3</sub> x 2), 39.6 (C), 38.6 (CH<sub>2</sub>), 31.2 (CH<sub>3</sub>), 28.5 (CH<sub>3</sub>), 22.0 (CH<sub>3</sub>), 21.7 (CH<sub>3</sub>).

**IR** (neat)  $\nu$  2967, 2865, 1701, 1604, 1510, 1249, 1164, 1087, 815, 608, 549 cm<sup>-1</sup>.

**HRMS** (ESI-MS) calcd. for C<sub>36</sub>H<sub>43</sub>N<sub>2</sub>O<sub>8</sub>S<sup>+</sup> ([M+NH<sub>4</sub>]<sup>+</sup>): 663.2735, found 663.2739.



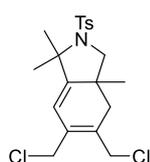
**(1,1,3a-Trimethyl-2-tosyl-2,3,3a,4-tetrahydro-1H-isoindole-5,6-diyl)dimethanol (129)**. General procedure **F** afforded 64.9 mg (86%) of the title compound as a colorless oil.  $R_f$ (AcOEt) 0.36.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.74 (d,  $J$  = 8.3 Hz, 2H), 7.28 (d,  $J$  = 8.0 Hz, 2H), 5.69 (s, 1H), 4.26–4.08 (m, 4H), 3.38 (d,  $J$  = 9.1 Hz, 1H), 3.00 (d,  $J$  = 9.1 Hz, 1H), 2.41 (br s, 5H, CH<sub>3</sub> + 2OH), 2.26 (d,  $J$  = 16.6 Hz, 1H), 2.20 (d,  $J$  = 16.6 Hz, 1H), 1.68 (s, 3H), 1.45 (s, 3H), 0.98 (s, 3H).

$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  155.6 (C), 143.4 (C), 138.3 (C), 131.8 (C x 2), 129.8 (CH x 2), 127.7 (CH x 2), 116.3 (CH), 67.5 (C), 62.4 ( $\text{CH}_2$ ), 61.3 ( $\text{CH}_2$ ), 61.1 ( $\text{CH}_2$ ), 39.6 (C), 39.1 ( $\text{CH}_2$ ), 31.2 ( $\text{CH}_3$ ), 28.6 ( $\text{CH}_3$ ), 22.1 ( $\text{CH}_3$ ), 21.8 ( $\text{CH}_3$ ).

IR (neat)  $\nu$  3516, 3086, 2965, 1680, 1236, 1185, 1055, 980, 796, 663, 544  $\text{cm}^{-1}$ .

HRMS (ESI-MS) calcd. for  $\text{C}_{20}\text{H}_{27}\text{NO}_4\text{SNa}^+$  ( $[\text{M}+\text{Na}]^+$ ): 400.1553, found 400.1553.



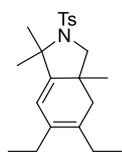
**5,6-Bis(chloromethyl)-1,1,3a-trimethyl-2-tosyl-2,3,3a,4-tetrahydro-1H-isoindole (130).** General procedure F afforded 73.7 mg (89%) of the title compound as a colorless oil.  $R_f$ (PE/Et<sub>2</sub>O 7/3) 0.38.

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.75 (d,  $J$  = 8.2 Hz, 2H), 7.28 (d,  $J$  = 8.2 Hz, 2H), 5.68 (s, 1H), 4.30 (d,  $J$  = 11.5 Hz, 1H), 4.19 (d,  $J$  = 11.6 Hz, 1H), 4.11 (d,  $J$  = 11.6 Hz, 1H), 4.06 (d,  $J$  = 11.5 Hz, 1H), 3.43 (d,  $J$  = 9.2 Hz, 1H), 3.04 (d,  $J$  = 9.2 Hz, 1H), 2.41 (s, 3H), 2.33 (d,  $J$  = 16.4 Hz, 1H), 2.23 (d,  $J$  = 16.4 Hz, 1H), 1.71 (s, 3H), 1.49 (s, 3H), 1.02 (s, 3H).

$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  157.8 (C), 143.4 (C), 138.2 (C), 130.8 (C), 129.7 (CH x 2), 129.4 (C), 127.7 (CH x 2), 115.3 ( $\text{CH}_2$ ), 67.4 (C), 60.7 ( $\text{CH}_2$ ), 43.9 ( $\text{CH}_2$ ), 41.6 ( $\text{CH}_2$ ), 39.8 (C), 38.9 ( $\text{CH}_2$ ), 31.1 ( $\text{CH}_3$ ), 28.5 ( $\text{CH}_3$ ), 22.4 ( $\text{CH}_3$ ), 21.8 ( $\text{CH}_3$ ).

IR (neat)  $\nu$  2931, 2878, 2255, 1733, 1375, 1225, 1154, 905, 724, 588  $\text{cm}^{-1}$ .

HRMS (ESI-MS) calcd. for  $\text{C}_{20}\text{H}_{26}\text{NO}_2\text{SCl}_2^+$  ( $[\text{M}+\text{H}]^+$ ): 414.1056, found 414.1056.



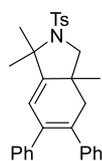
**5,6-Diethyl-1,1,3a-trimethyl-2-tosyl-2,3,3a,4-tetrahydro-1H-isoindole (131).** General procedure F afforded 73.2 mg (98%) of the title compound as a colorless oil.  $R_f$ (PE/Et<sub>2</sub>O 8/2) 0.55.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.68 (d,  $J$  = 8.3 Hz, 2H), 7.20 (d,  $J$  = 7.2 Hz, 2H), 5.41 (s, 1H), 3.31 (d,  $J$  = 9.0 Hz, 1H), 2.91 (d,  $J$  = 9.0 Hz, 1H), 2.34 (s, 3H), 2.15 – 2.03 (m, 3H), 1.99 – 1.81 (m, 3H), 1.60 (s, 3H), 1.38 (s, 3H), 0.90 – 0.84 (m, 9H).

$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  152.5 (C), 143.1 (C), 138.6 (C), 129.9 (C), 129.7 (C), 129.6 (CH x 2), 127.8 (CH x 2), 117.7 (CH), 67.5 (C), 61.3 ( $\text{CH}_2$ ), 40.2 ( $\text{CH}_2$ ), 39.9 (C), 31.4 ( $\text{CH}_3$ ), 28.7 ( $\text{CH}_3$ ), 25.9 ( $\text{CH}_2$ ), 24.4 ( $\text{CH}_2$ ), 22.0 ( $\text{CH}_3$ ), 21.8 ( $\text{CH}_3$ ), 14.3 ( $\text{CH}_3$ ), 13.0 ( $\text{CH}_3$ ).

**IR** (neat)  $\nu$  2963, 2867, 1598, 1362, 1288 1148, 1014, 926, 799, 709, 548  $\text{cm}^{-1}$ .

**HRMS** (ESI-MS) calcd. for  $\text{C}_{22}\text{H}_{32}\text{NO}_2\text{S}^+$  ( $[\text{M}+\text{H}]^+$ ): 374.2148, found 374.2146.



**1,1,3a-Trimethyl-5,6-diphenyl-2-tosyl-2,3,3a,4-tetrahydro-1H-isoindole (132).**

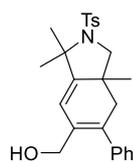
General procedure F afforded 19.7 mg (21%) of the title compound as a colorless oil.  $R_f$ (PE/Et<sub>2</sub>O 8/2) 0.45.

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>)  $\delta$  7.79 (d,  $J$  = 8.2 Hz, 2H), 7.30 (d,  $J$  = 8.1 Hz, 2H), 7.16–7.08 (m, 6H), 7.01–6.96 (m, 4H), 5.88 (s, 1H), 3.49 (d,  $J$  = 9.1 Hz, 1H), 3.14 (d,  $J$  = 9.1 Hz, 1H), 2.76 (d,  $J$  = 16.1 Hz, 1H), 2.48 (d,  $J$  = 16.1 Hz, 1H), 2.43 (s, 3H), 1.76 (s, 3H), 1.56 (s, 3H), 1.21 (s, 3H).

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>)  $\delta$  155.0 (C), 143.3 (C), 142.5 (C), 141.2 (C), 138.4 (C), 132.9 (C), 131.2 (C), 129.8 (CH x 2), 129.4 (CH x 2), 129.1 (CH x 2), 128.3 (CH x 2), 128.3 (CH x 2), 127.8 (CH x 2), 126.8 (CH), 126.7 (CH), 119.1 (CH), 67.67 (C), 61.1 (CH<sub>2</sub>), 43.2 (CH<sub>2</sub>), 40.1 (CH<sub>3</sub>), 31.4 (CH<sub>3</sub>), 28.7 (CH<sub>3</sub>), 22.1 (CH<sub>3</sub>), 21.8 (CH<sub>3</sub>).

**IR** (neat)  $\nu$  2965, 2918, 1612, 1497, 1381, 1153, 1036, 930, 723, 706, 528  $\text{cm}^{-1}$ .

**HRMS** (ESI-MS) calcd. for  $\text{C}_{30}\text{H}_{32}\text{NO}_2\text{S}^+$  ( $[\text{M}+\text{H}]^+$ ): 470.2148, found 470.2146.



**(3,3,7a-Trimethyl-6-phenyl-2-tosyl-2,3,7,7a-tetrahydro-1H-isoindol-5-yl)methanol (134).**

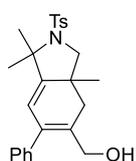
General procedure F afforded 41.5 mg (49%) of the title compound as a white solid, mp 61-62°C.  $R_f$ (PE/Et<sub>2</sub>O 1/1) 0.42.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.77 (d,  $J$  = 8.2 Hz, 2H), 7.36 – 7.26 (m, 5H), 7.15 (d,  $J$  = 7.2 Hz, 2H), 5.93 (s, 1H), 4.16 (d,  $J$  = 5.5 Hz, 2H), 3.43 (d,  $J$  = 9.2 Hz, 1H), 3.06 (d,  $J$  = 9.2 Hz, 1H), 2.60 (d,  $J$  = 16.2 Hz, 1H), 2.42 (s, 3H), 2.34 (d,  $J$  = 16.2 Hz, 1H), 1.75 (s, 3H), 1.54 (s, 3H), 1.24 (t,  $J$  = 5.4 Hz, 1H), 1.13 (s, 3H).

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>)  $\delta$  155.1 (C), 143.2 (C), 141.3 (C), 138.3 (C), 132.8 (C), 130.6 (C), 129.7 (CH x 2), 128.6 (CH x 2), 128.2 (CH x 2), 127.7 (CH x 2), 127.5 (CH), 115.9 (CH), 67.6 (C), 62.0 (CH<sub>2</sub>), 61.0 (CH<sub>2</sub>), 42.8 (CH<sub>2</sub>), 39.9 (C), 31.3 (CH<sub>3</sub>), 28.7 (CH<sub>3</sub>), 22.1 (CH<sub>3</sub>), 21.8 (CH<sub>3</sub>).

**IR** (neat)  $\nu$  3520, 2974, 2929, 1598, 136, 1149, 1090, 1028, 703, 572, 549  $\text{cm}^{-1}$ .

**HRMS** (ESI-MS) calcd. for  $\text{C}_{25}\text{H}_{29}\text{NO}_3\text{SNa}^+$  ( $[\text{M}+\text{Na}]^+$ ): 446.1760, found 446.1759.



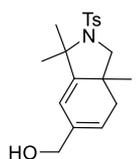
**(1,1,3a-Trimethyl-6-phenyl-2-tosyl-2,3,3a,4-tetrahydro-1H-isoindol-5-yl)methanol (134')**. General procedure **F** afforded 32.2 mg (38%) of the title compound as a white solid, mp 68-69 °C.  $R_f$ (PE/Et<sub>2</sub>O 1/1) 0.40.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.77 (d,  $J$  = 8.2 Hz, 2H), 7.37 – 7.26 (m, 5H), 7.14 (d,  $J$  = 7.0 Hz, 2H), 5.72 (s, 1H), 4.19 (d,  $J$  = 11.7 Hz, 1H), 4.04 (d,  $J$  = 11.7 Hz, 1H), 3.47 (d,  $J$  = 9.2 Hz, 1H), 3.11 (d,  $J$  = 9.2 Hz, 1H), 2.44 (d,  $J$  = 16.3 Hz, 1H), 2.43 (s, 3H), 2.34 (d,  $J$  = 16.3 Hz, 1H), 1.70 (s, 3H), 1.50 (s, 3H), 1.22 (dt,  $J$  = 6.9, 4.3 Hz, 1H), 1.11 (s, 3H).

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>)  $\delta$  155.3 (C), 143.3 (C), 140.1 (C), 138.4 (C), 134.1 (C), 129.8 (C), 129.7 (CH x 2), 128.6 (CH x 2), 128.5 (CH x 2), 127.8 (CH x 2), 127.5 (CH), 118.0 (CH), 67.6 (C), 63.2 (CH<sub>2</sub>), 61.1 (CH<sub>2</sub>), 39.7 (C), 38.0 (CH<sub>2</sub>), 31.2 (CH<sub>3</sub>), 28.7 (CH<sub>3</sub>), 22.2 (CH<sub>3</sub>), 21.8 (CH<sub>3</sub>).

**IR** (neat)  $\nu$  3515, 2972, 2927, 1598, 1363, 1224, 1147, 973, 780, 701, 581  $\text{cm}^{-1}$ .

**HRMS** (ESI-MS) calcd. for  $\text{C}_{25}\text{H}_{29}\text{NO}_3\text{SNa}^+$  ( $[\text{M}+\text{Na}]^+$ ): 446.1760, found 446.1757.



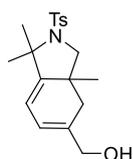
**(3,3,7a-Trimethyl-2-tosyl-2,3,7,7a-tetrahydro-1H-isoindol-5-yl)methanol (138)**. General procedure **F** afforded 34.1 mg (49%) of the title compound as a colorless oil.  $R_f$ (PE/Et<sub>2</sub>O 4/6) 0.30.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.74 (d,  $J$  = 8.3 Hz, 2H), 7.27 (d,  $J$  = 8.1 Hz, 2H), 5.57-5.54 (m, 1H), 5.66 (s, 1H), 4.14–4.07 (m, 2H), 3.37 (d,  $J$  = 9.1 Hz, 1H), 3.00 (d,  $J$  = 9.1 Hz, 1H), 2.41 (s, 3H), 2.14 (d,  $J$  = 4.4 Hz, 2H), 1.69 (s, 3H), 1.47 (s, 3H), 1.42 (br s, 1H), 1.01 (s, 3H).

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$  156.2 (C), 143.3 (C), 138.3 (C), 135.8 (C), 129.7 (CH x 2), 127.8 (CH x 2), 119.1 (CH), 113.9 (CH), 67.4 (C), 65.5 (CH<sub>2</sub>), 61.1 (CH<sub>2</sub>), 39.6 (C), 35.3 (CH<sub>2</sub>), 31.2 (CH<sub>3</sub>), 28.7 (CH<sub>3</sub>), 22.3 (CH<sub>3</sub>), 21.8 (CH<sub>3</sub>).

**IR** (neat)  $\nu$  3490, 2929, 2899, 1738, 1318, 1209, 953, 749, 559  $\text{cm}^{-1}$ .

**HRMS** (ESI-MS) calcd. for  $\text{C}_{19}\text{H}_{26}\text{NO}_3\text{S}^+$  ( $[\text{M}+\text{H}]^+$ ): 348.1628, found 348.1630.



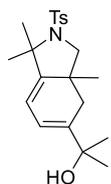
**(1,1,3a-Trimethyl-2-tosyl-2,3,3a,4-tetrahydro-1H-isoindol-5-yl)methanol (138')**. General procedure **F** afforded 33.4 mg (48%) of the title compound as a colorless oil.  $R_f$ (PE/Et<sub>2</sub>O 4/6) 0.28.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.75 (d,  $J$  = 8.3 Hz, 2H), 7.28 (d,  $J$  = 8.1 Hz, 2H), 5.92–5.89 (m, 1H), 5.62 (d,  $J$  = 5.4 Hz, 1H), 4.13–4.05 (m, 2H), 3.39 (d,  $J$  = 9.1 Hz, 1H), 3.03 (d,  $J$  = 9.1 Hz, 1H), 2.41 (s, 3H), 2.19 – 2.11 (m, 1H), 2.06 (d,  $J$  = 16.4 Hz, 1H), 1.68 (s, 3H), 1.45 (s, 3H), 1.41 (br s, 1H), 1.00 (s, 3H).

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$  154.6 (C), 143.3 (C), 138.3 (C), 135.4 (C), 129.7 (CH x 2), 127.8 (CH x 2), 119.2 (CH), 113.5 (CH), 67.4 (C), 66.4 (CH<sub>2</sub>), 61.0 (CH<sub>2</sub>), 39.9 (C), 36.6 (CH<sub>2</sub>), 31.2 (CH<sub>3</sub>), 28.7 (CH<sub>3</sub>), 22.2 (CH<sub>3</sub>), 21.8 (CH<sub>3</sub>).

**IR** (neat)  $\nu$  3501, 2917, 2900, 1696, 1299, 1152, 949, 687, 660, 593 cm<sup>-1</sup>.

**HRMS** (ESI-MS) calcd. for C<sub>19</sub>H<sub>26</sub>NO<sub>3</sub>S<sup>+</sup> ([M+H]<sup>+</sup>): 348.1628, found 348.1631.



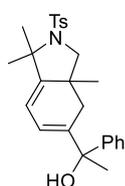
**2-(1,1,3a-Trimethyl-2-tosyl-2,3,3a,4-tetrahydro-1H-isoindol-5-yl)propan-2-ol (144)**. General procedure **F** using 10 mol % of Cp\**Ru*(cod)Cl afforded 64.6 mg (86%) of the title compound as a colorless oil.  $R_f$ (PE/Et<sub>2</sub>O 1/1) 0.23.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.75 (d,  $J$  = 8.3 Hz, 2H), 7.28 (d,  $J$  = 8.0 Hz, 2H), 5.95 (dd,  $J$  = 5.5, 2.9 Hz, 1H), 5.63 (d,  $J$  = 5.5 Hz, 1H), 3.41 (d,  $J$  = 9.1 Hz, 1H), 3.03 (d,  $J$  = 9.1 Hz, 1H), 2.41 (s, 3H), 2.19 (d,  $J$  = 16.1 Hz, 1H), 2.09 (dd,  $J$  = 16.1, 2.9 Hz, 1H), 1.67 (s, 3H), 1.45 (s, 3H), 1.37 (s, 1H), 1.33 (s, 3H), 1.31 (s, 3H), 0.98 (s, 3H).

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>)  $\delta$  153.8 (C), 143.2 (C), 142.3 (C), 138.3 (C), 129.7 (CH x 2), 127.7 (CH x 2), 115.7 (CH), 113.8 (CH), 72.6 (C), 67.4 (C), 61.1 (CH<sub>2</sub>), 40.0 (C), 35.8 (CH<sub>2</sub>), 31.2 (CH<sub>3</sub>), 28.6 (CH<sub>3</sub>), 28.6 (CH<sub>3</sub>), 28.4 (CH<sub>3</sub>), 21.8 (CH<sub>3</sub>), 21.6 (CH<sub>3</sub>).

**IR** (neat)  $\nu$  3510, 3054, 2304, 1670, 1421, 1264, 1158, 730, 702 cm<sup>-1</sup>.

**HRMS** (ESI-MS) calcd. for C<sub>21</sub>H<sub>30</sub>NO<sub>3</sub>S<sup>+</sup> ([M+H]<sup>+</sup>): 376.1941, found 376.1938.



**Phenyl-1-(1,1,3a-trimethyl-2-tosyl-2,3,3a,4-tetrahydro-1H-isoindol-5-yl)ethan-1-ol (145)**. General procedure **F** using 10 mol % of Cp\**Ru*(cod)Cl afforded 74.4

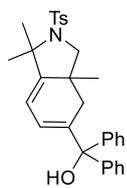
mg (85%) of the title compound as a white solid in a 1:1 mixture of diastereomers. Mp 75–76 °C.  $R_f$ (PE/Et<sub>2</sub>O 1/1) 0.54.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.69 (d,  $J$  = 8.2 Hz, 2H), 7.39–7.36 (m, 2H), 7.34–7.27 (m, 2H), 7.25–7.20 (m, 3H), 6.17 (dd,  $J$  = 5.5, 2.9 Hz, 0.5H), 6.11 (dd,  $J$  = 5.5, 2.9 Hz, 0.5H), 5.67 (dd,  $J$  = 5.4, 2.4 Hz, 1H), 3.28 (d,  $J$  = 9.0 Hz, 0.5H), 3.25 (d,  $J$  = 9.1 Hz, 0.5H), 2.91 (d,  $J$  = 9.2 Hz, 0.5H), 2.88 (d,  $J$  = 9.1 Hz, 0.5H), 2.39 (s, 3H), 1.97–1.80 (m, 2H), 1.78 (s, 0.5H), 1.76 (s, 0.5 H), 1.71–1.66 (m, 6H), 1.44 (s, 1.5H), 1.43 (s, 1.5H), 0.82 (s, 1.5H), 0.73 (s, 1.5H).

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  154.3 (C x 0.5), 154.1 (C x 0.5), 145.6 (C x 0.5), 145.4 (C x 0.5), 143.1 (C), 141.0 (C x 0.5), 140.8 (C x 0.5), 138.3 (C x 0.5), 138.2 (C x 0.5), 129.6 (CH x 2), 128.4 (CH x 2), 127.7 (CH x 2 x 0.5), 127.7 (CH x 2 x 0.5), 127.3 (CH x 0.5), 127.2 (CH x 0.5), 125.81(CH x 2 x 0.5), 125.7 (CH x 2 x 0.5), 117.5 (CH<sub>2</sub> x 0.5), 117.2 (CH<sub>2</sub> x 0.5), 113.6 (CH<sub>2</sub> x 0.5), 113.59 (CH<sub>2</sub> x 0.5), 76.6 (C x 0.5), 76.2 (C x 0.5), 67.3 (C), 61.0 (CH<sub>2</sub> x 0.5), 60.95 (CH<sub>2</sub> x 0.5), 40.0 (C x 0.5), 39.9 (C x 0.5), 35.8 (CH<sub>2</sub> x 0.5), 35.7 (CH<sub>2</sub> x 0.5), 31.4 (CH<sub>3</sub> x 0.5), 31.2 (CH<sub>3</sub> x 0.5), 28.6 (CH<sub>3</sub>), 28.5 (CH<sub>3</sub> x 0.5), 28.1 (CH<sub>3</sub> x 0.5), 22.2 (CH<sub>3</sub> x 0.5), 21.8 (CH<sub>3</sub> x 0.5), 21.7 (CH<sub>3</sub>).

IR (neat)  $\nu$  2997, 2868, 2253, 1373, 1150, 1121, 904, 701, 593, 549 cm<sup>-1</sup>.

HRMS (ESI-MS) calcd. for C<sub>26</sub>H<sub>32</sub>NO<sub>3</sub>S<sup>+</sup> ([M+H]<sup>+</sup>): 438.2097, found 438.2096.



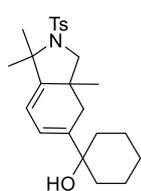
**Diphenyl(1,1,3a-trimethyl-2-tosyl-2,3,3a,4-tetrahydro-1H-isoindol-5-yl)methanol (146).** General procedure F using 10 mol % of Cp\*<sub>2</sub>Ru(cod)Cl afforded 90.9 mg (91 %) of the title compound as a white solid. Mp 112-113 °C.  $R_f$ (PE/Et<sub>2</sub>O 1/1) 0.60.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.63 (d,  $J$  = 8.3 Hz, 2H), 7.28–7.23 (m, 8H), 7.23–7.19 (m, 2H), 7.19–7.17 (m, 2H), 5.58 (dd,  $J$  = 5.5, 2.7 Hz, 1H), 5.52 (d,  $J$  = 5.5 Hz, 1H), 3.24 (d,  $J$  = 9.1 Hz, 1H), 2.86 (d,  $J$  = 9.1 Hz, 1H), 2.33 (s, 3H), 2.30 (s, 1H), 2.08 (d,  $J$  = 16.3 Hz, 1H), 1.98 (dd,  $J$  = 16.3, 2.7 Hz, 1H), 1.59 (s, 3H), 1.37 (s, 3H), 0.84 (s, 3H).

$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  154.7 (C), 144.6 (C), 144.6 (C), 143.2 (C), 140.3 (C), 138.3 (C), 129.7 (CH x 2), 128.3 (CH x 2), 128.25 (CH x 2), 128.0 (CH x 2), 127.9 (CH x 2), 127.7 (CH x 2), 127.6 (CH x 2), 122.2 (CH), 113.6 (CH), 82.6 (C), 67.3 (C), 61.1 ( $\text{CH}_2$ ), 40.3 (C), 36.5 ( $\text{CH}_2$ ), 31.3 ( $\text{CH}_3$ ), 28.5 ( $\text{CH}_3$ ), 22.5 ( $\text{CH}_3$ ), 21.8 ( $\text{CH}_3$ ).

IR (neat)  $\nu$  3018, 2947, 1610, 1508, 1485, 1112, 1023, 742, 712  $\text{cm}^{-1}$ .

HRMS (ESI-MS) calcd. for  $\text{C}_{31}\text{H}_{34}\text{NO}_3\text{S}^+$  ( $[\text{M}+\text{H}]^+$ ): 500.2254, found 500.2256.



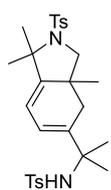
**1-(1,1,3a-Trimethyl-2-tosyl-2,3,3a,4-tetrahydro-1H-isoindol-5-yl)cyclohexan-1-ol (147).** General procedure **F** using 10 mol % of  $\text{Cp}^*\text{Ru}(\text{cod})\text{Cl}$  afforded 58.2 mg (70%) of the title compound as a white solid. Mp 71-73  $^\circ\text{C}$ .  $R_f$ (PE/Et<sub>2</sub>O 1/1) 0.41.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.75 (d,  $J$  = 8.3 Hz, 2H), 7.27 (d,  $J$  = 8.4 Hz, 2H), 5.96 (dd,  $J$  = 5.5, 2.9 Hz, 1H), 5.63 (d,  $J$  = 5.5 Hz, 1H), 3.41 (d,  $J$  = 9.1 Hz, 1H), 3.03 (d,  $J$  = 9.1 Hz, 1H), 2.41 (s, 3H), 2.24 (d,  $J$  = 16.0 Hz, 1H), 2.06 (dd,  $J$  = 16.0, 2.9 Hz, 1H), 1.67 (s, 3H), 1.65–1.51 (m, 9H), 1.45 (s, 3H), 1.26–1.13 (s, 2H), 0.98 (s, 3H).

$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  153.9 (C), 143.2 (C), 142.5 (C), 138.4 (C), 129.7 (CH x 2), 127.8 (CH x 2), 116.5 (CH), 113.9 (CH), 73.3 (C), 67.4 (C), 61.2 ( $\text{CH}_2$ ), 40.0 (C), 35.7 ( $\text{CH}_2$ ), 35.6 ( $\text{CH}_2$ ), 35.5 ( $\text{CH}_2$ ), 31.2 ( $\text{CH}_3$ ), 28.6 ( $\text{CH}_3$ ), 25.9 ( $\text{CH}_2$ ), 22.2 ( $\text{CH}_2$ ), 22.1 ( $\text{CH}_2$ ), 21.8 ( $\text{CH}_3$ ), 21.5 ( $\text{CH}_3$ ).

IR (neat)  $\nu$  2918, 2877, 2271, 1310, 1125, 1076, 959, 749, 544  $\text{cm}^{-1}$ .

HRMS (ESI-MS) calcd. for  $\text{C}_{24}\text{H}_{34}\text{NO}_3\text{S}^+$  ( $[\text{M}+\text{H}]^+$ ): 416.2254, found 416.2254.



**4-Methyl-N-(2-(1,1,3a-trimethyl-2-tosyl-2,3,3a,4-tetrahydro-1H-isoindol-5-yl)propan-2-yl)benzenesulfonamide (148).** General procedure **F** afforded 67.6 mg (64%) of the title compound as a pale yellow solid, mp 58-59  $^\circ\text{C}$ .  $R_f$ (PE/Et<sub>2</sub>O 4/6) 0.33.

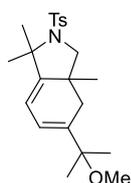
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.74 (d,  $J$  = 8.2 Hz, 2H), 7.70 (d,  $J$  = 8.2 Hz, 2H), 7.29 (d,  $J$  = 8.2 Hz, 2H), 7.24 (d,  $J$  = 8.2 Hz, 2H), 5.88 (dd,  $J$  = 5.5, 2.8 Hz, 1H), 5.58 (d,  $J$  = 5.5 Hz, 1H), 4.43 (s, 1H), 3.38 (d,  $J$  = 9.1 Hz, 1H), 2.89 (d,  $J$  = 9.1 Hz, 1H), 2.42 (s, 3H), 2.37 (s, 3H),

2.07 (d,  $J = 16.1$  Hz, 1H), 1.79 (dd,  $J = 16.1, 2.8$  Hz, 1H), 1.66 (s, 3H), 1.42 (s, 3H), 1.36 (s, 3H), 1.28 (s, 3H), 0.96 (s, 3H).

$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  153.6 (C), 142.3 (C), 142.2 (C), 139.3 (C), 138.8 (C), 137.3 (C), 128.8 (CH x 2), 128.7 (CH x 2), 126.8 (CH x 2), 126.4 (CH x 2), 117.1 (CH), 112.6 (CH), 66.3 (C), 60.1 ( $\text{CH}_2$ ), 58.1 (C), 39.1 (C), 34.4 ( $\text{CH}_2$ ), 30.3 ( $\text{CH}_3$ ), 27.5 ( $\text{CH}_3$ ), 27.0 ( $\text{CH}_3$ ), 25.3 ( $\text{CH}_3$ ), 20.8 ( $\text{CH}_3$  x 2), 20.7 ( $\text{CH}_3$ ).

IR (neat)  $\nu$  3276, 2977, 1598, 1450, 1382, 1146, 1090, 909, 661, 548  $\text{cm}^{-1}$ .

HRMS (ESI-MS) calcd. for  $\text{C}_{28}\text{H}_{37}\text{N}_2\text{O}_4\text{S}_2^+$  ( $[\text{M}+\text{H}]^+$ ): 529.2189, found 529.2188.



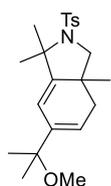
**5-(2-Methoxypropan-2-yl)-1,1,3a-trimethyl-2-tosyl-2,3,3a,4-tetrahydro-1H-indole (149).** General procedure F afforded 22.3 mg (28%) of the title compound as a colorless oil.  $R_f(\text{PE}/\text{Et}_2\text{O}$  3/1) 0.44.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.76 (d,  $J = 8.3$  Hz, 2H), 7.28 (d,  $J = 8.4$  Hz, 2H), 5.86 (dd,  $J = 5.5, 3.0$  Hz, 1H), 5.62 (d,  $J = 5.5$  Hz, 1H), 3.42 (d,  $J = 9.0$  Hz, 1H), 3.05 (s, 3H), 3.02 (d,  $J = 9.0$  Hz, 1H), 2.41 (s, 3H), 2.28 (d,  $J = 16.3$  Hz, 1H), 1.95 (dd,  $J = 16.3, 2.9$  Hz, 1H), 1.69 (s, 3H), 1.46 (s, 3H), 1.28 (s, 3H), 1.27 (s, 3H), 1.00 (s, 3H).

$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  154.5 (C), 143.2 (C), 139.9 (C), 138.3 (C), 129.7 (CH x 2), 127.8 (CH x 2), 119.2 (CH), 113.6 (CH), 76.8 (C), 67.4 (C), 61.3 ( $\text{CH}_2$ ), 50.8 ( $\text{CH}_3$ ), 40.1 (C), 35.0 ( $\text{CH}_2$ ), 31.3 ( $\text{CH}_3$ ), 28.6 ( $\text{CH}_3$ ), 25.4 ( $\text{CH}_3$ ), 25.1 ( $\text{CH}_3$ ), 22.4 ( $\text{CH}_3$ ), 21.8 ( $\text{CH}_3$ ).

IR (neat)  $\nu$  3018, 2932, 1698, 1454, 1214, 1156, 1090, 940, 751, 667, 570  $\text{cm}^{-1}$ .

HRMS (ESI-MS) calcd. for  $\text{C}_{22}\text{H}_{32}\text{NO}_3\text{S}$  ( $[\text{M}+\text{H}]^+$ ): 390.2097, found 390.2097.



**6-(2-Methoxypropan-2-yl)-1,1,3a-trimethyl-2-tosyl-2,3,3a,4-tetrahydro-1H-indole (149').** General procedure F afforded 26.8 mg (34%) of the title compound as a white solid. Slow evaporation technique from a petroleum ether solution of 7bg' yielded good single crystals for X-ray analysis. Mp 56–57 °C.  $R_f(\text{PE}/\text{Et}_2\text{O}$  1/1)

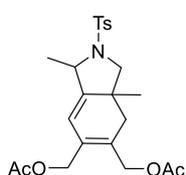
0.60.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.75 (d, *J* = 8.3 Hz, 2H), 7.22 (d, *J* = 8.2 Hz, 2H), 5.82 (s, 1H), 5.50 (t, *J* = 4.5 Hz, 1H), 3.41 (d, *J* = 9.1 Hz, 1H), 3.01 (d, *J* = 9.1 Hz, 1H), 2.99 (s, 3H), 2.41 (s, 3H), 2.14 (d, *J* = 4.5 Hz, 2H), 1.70 (s, 3H), 1.48 (s, 3H), 1.27 (s, 3H), 1.26 (s, 3H), 1.00 (s, 3H).

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>) δ 155.7 (C), 143.2 (C), 140.3 (C), 138.4 (C), 129.7 (CH x 2), 127.8 (CH x 2), 117.8 (CH), 113.4 (CH), 76.1 (C), 67.6 (C), 61.2 (CH<sub>2</sub>), 50.7 (CH<sub>3</sub>), 39.3 (C), 35.6 (CH<sub>2</sub>), 31.4 (CH<sub>3</sub>), 28.7 (CH<sub>3</sub>), 25.9 (CH<sub>3</sub>), 25.5 (CH<sub>3</sub>), 22.1 (CH<sub>3</sub>), 21.8 (CH<sub>3</sub>).

**IR** (neat) ν 2975, 2821, 1599, 1451, 1271, 1223, 1074, 951, 903, 784, 598 cm<sup>-1</sup>.

**HRMS** (ESI-MS) calcd. for C<sub>22</sub>H<sub>32</sub>NO<sub>3</sub>S ([M+H]<sup>+</sup>): 390.2097, found 390.2097.



**(1,3a-Dimethyl-2-tosyl-2,3,3a,4-tetrahydro-1H-isoindole-5,6-diyl)bis(methylene) diacetate (151)**; General procedure **F** afforded 59.1 mg (66%, 15:1 md) of the title compound as a colorless oil. R<sub>f</sub>(PE/Et<sub>2</sub>O 6/4) 0.35.

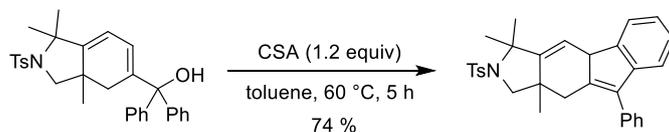
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.75 (d, *J* = 8.1 Hz, 0.8H), 7.69 (d, *J* = 8.1 Hz, 1.2H), 7.33 (d, *J* = 8.0 Hz, 1.2H), 7.30 (d, *J* = 8.0 Hz, 0.8H), 5.66 – 5.64 (m, 1H), 4.79 – 4.51 (m, 4H), 4.44 (q, *J* = 6.6 Hz, 0.4H), 3.89 (q, *J* = 6.6 Hz, 0.6H), 3.59 (d, *J* = 8.6 Hz, 0.6H), 3.56 (d, *J* = 10.8 Hz, 0.4H), 3.20 (d, *J* = 10.8 Hz, 0.4H), 2.65 (d, *J* = 8.6 Hz, 0.6H), 2.44 (s, 1.8H), 2.41 (s, 1.2H), 2.27 – 2.08 (m, 2H), 2.04 – 2.02 (m, 6H), 1.60 (d, *J* = 6.6 Hz, 1.8H), 1.45 (d, *J* = 6.6 Hz, 1.2H), 1.15 (s, 1.8H), 0.51 (s, 1.2H).

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 171.0 (C), 150.9 (C), 150.7 (C), 144.1 (C), 143.7 (C), 136.8 (C), 132.6 (C), 130.0 (CH), 129.9 (CH), 129.2 (C), 129.1 (C), 128.9 (C), 128.8 (C), 128.4 (CH), 127.6 (CH), 116.7 (CH), 116.4 (CH), 63.4 (CH<sub>2</sub>), 63.3 (CH<sub>2</sub>), 62.2 (CH<sub>2</sub>), 62.1 (CH<sub>2</sub>), 61.0 (CH<sub>2</sub>), 58.8 (CH), 57.4 (CH), 41.4 (C), 39.5 (C), 38.3 (CH<sub>2</sub>), 38.1 (CH<sub>2</sub>), 24.8 (CH<sub>3</sub>), 22.6 (CH<sub>3</sub>), 21.8 (CH<sub>3</sub>), 21.7 (CH<sub>3</sub>), 21.6 (CH<sub>3</sub>), 21.2 (CH<sub>3</sub>), 21.1 (CH<sub>3</sub>), 21.0 (CH<sub>3</sub>), 20.9 (CH<sub>3</sub>).

**IR** (neat) ν 2972, 2869, 1736, 1376, 1223, 1162, 1048, 915, 712, 549 cm<sup>-1</sup>.

**HRMS** (ESI-MS) calcd. for C<sub>23</sub>H<sub>30</sub>NO<sub>6</sub>S<sup>+</sup> ([M+H]<sup>+</sup>): 448.1788, found 448.1786.

**3,3,10a-Trimethyl-9-phenyl-2-tosyl-1,2,3,4a,10,10a-hexahydroindeno[1,2-f]isoindole (152).**



Camphorsulfonic acid (55.7 mg, 0.24 mmol) was added to a solution of dienol **146** (99.9 mg, 0.2 mmol) in toluene (10 mL). The mixture was stirred for 5 h at 60 °C, and then concentrated *in vacuo*. The crude residue was purified by flash chromatography on silica gel to give 69.4 mg (74%) of the title compound as a white solid. Mp 113–114 °C.  $R_f$  (PE/Et<sub>2</sub>O 2/3) 0.28.

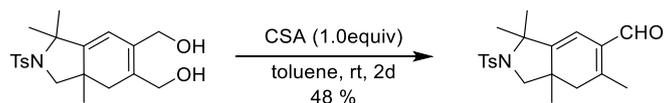
**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>)  $\delta$  7.73 (d,  $J$  = 8.2 Hz, 2H), 7.53 (d,  $J$  = 7.0 Hz, 1H), 7.48–7.34 (m, 5H), 7.30–7.22 (m, 5H), 5.92 (d,  $J$  = 3.8 Hz, 1H), 4.07 (d,  $J$  = 3.8 Hz, 1H), 3.20 (d,  $J$  = 9.1 Hz, 1H), 3.07 (d,  $J$  = 9.1 Hz, 1H), 2.79 (d,  $J$  = 12.2 Hz, 1H), 2.47 (d,  $J$  = 12.2 Hz, 1H), 2.40 (s, 3H), 1.62 (s, 3H), 1.59 (s, 3H), 0.71 (s, 3H).

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>)  $\delta$  154.1 (C), 145.1 (C), 144.6 (C), 143.9 (C), 143.2 (C), 139.1 (C), 138.4 (C), 134.8 (C), 129.7 (CH x 2), 129.4 (CH x 2), 128.9 (CH x 2), 127.7 (CH x 3), 127.2 (CH), 125.0 (CH), 123.0 (CH), 120.5 (CH), 115.9 (CH), 67.0 (C), 59.1 (CH<sub>2</sub>), 50.9 (CH), 46.2 (C), 35.8 (CH<sub>2</sub>), 30.7 (CH<sub>3</sub>), 29.0 (CH<sub>3</sub>), 26.7 (CH<sub>3</sub>), 21.8 (CH<sub>3</sub>).

**IR** (neat)  $\nu$  3025, 2930, 1598, 1363, 1156, 1038, 1015, 939, 702, 658, 546 cm<sup>-1</sup>.

**HRMS** (ESI-MS) calcd. for C<sub>31</sub>H<sub>32</sub>NO<sub>2</sub>S<sup>+</sup> ([M+H]<sup>+</sup>): 482.2148, found 482.2148.

**3,3,6,7a-Tetramethyl-2-tosyl-2,3,7,7a-tetrahydro-1H-isoindole-5-carbaldehyde (153).**



Camphorsulfonic acid (46.4 mg, 0.2 mmol) was added to a solution of diol **129** (75.5 mg, 0.2 mmol) in toluene (10 mL). The mixture was stirred for 2 days at room temperature, and then

concentrated *in vacuo*. The crude residue was purified by flash chromatography to give 34.5 mg (48 %) of the title compound as a yellow solid. Mp 144–145 °C,  $R_f$  (PE/Et<sub>2</sub>O 1/1) 0.37.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  10.08 (s, 1H), 7.75 (d,  $J = 8.3$  Hz, 2H), 7.28 (d,  $J = 8.0$  Hz, 2H), 6.18 (s, 1H), 3.42 (d,  $J = 9.2$  Hz, 1H), 3.02 (d,  $J = 9.2$  Hz, 1H), 2.43 (d,  $J = 17.3$  Hz, 1H), 2.41 (s, 3H), 2.24 (d,  $J = 1.4$  Hz, 3H), 2.14 (d,  $J = 17.3$  Hz, 1H), 1.70 (s, 3H), 1.47 (s, 3H), 0.98 (s, 3H).

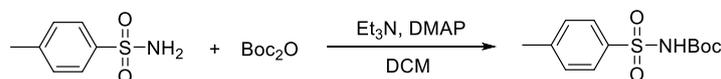
**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>)  $\delta$  187.9 (CH), 154.3 (C), 152.3 (C), 143.3 (C), 138.2 (C), 130.9 (C), 129.7 (CH x 2), 127.7 (CH x 2), 109.8 (CH), 67.5 (C), 60.7 (CH<sub>2</sub>), 44.8 (CH<sub>2</sub>), 39.1 (C), 31.0 (CH<sub>3</sub>), 28.5 (CH<sub>3</sub>), 22.7 (CH<sub>3</sub>), 21.8 (CH<sub>3</sub>), 19.1 (CH<sub>3</sub>).

**IR** (neat)  $\nu$  3019, 2975, 2866, 1668, 1449, 1214, 1150, 1121, 1033, 747, 667, 540 cm<sup>-1</sup>.

**HRMS** (ESI-MS) calcd. for C<sub>20</sub>H<sub>26</sub>NO<sub>3</sub>S<sup>+</sup> ([M+H]<sup>+</sup>): 360.1628, found 360.1628.

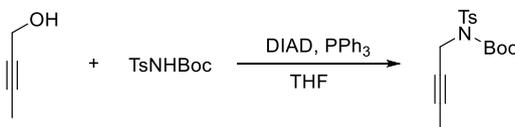
### Part III. Ruthenium-Catalyzed Cycloisomerization of *N*-Tethered 1,6-Enynes: Access to Aza-Bicyclo[4.1.0]heptenes

#### *Tert*-butyl tosylcarbamate<sup>14</sup>



A solution of di-*tert*-butyl dicarbonate (5.24 g, 24 mmol) in dichloromethane (25 mL) was added to a solution of *p*-Toluenesulfonamide (1.71g, 10 mmol), 4-dimethylaminopyridine (122 mg, 1 mmol) and triethylamine (4 g, 40 mmol) in dichloromethane (50 mL). The mixture was stirred overnight, then washed with 10% HCl solution (50 mL), brine (30 mL), dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel to afford 2.5 g (92%) of the title compound as white solid.  $R_f$  (PE/Et<sub>2</sub>O 5/5) 0.30.

#### *Tert*-butyl but-2-yn-1-yl(tosyl)carbamate<sup>15</sup>

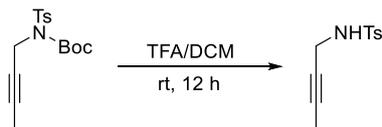


To a solution of but-2-yn-1-ol (350 mg, 5.0 mmol), *tert*-butyl tosylcarbamate (1.36 g, 5.0 mmol) and  $\text{PPh}_3$  (1.57 g, 6.0 mmol) in dry THF (50 mL) was slowly added diisopropyl azodicarboxylate (1.21 g, 6.0 mmol) at 0 °C. Then the resulting mixture was warmed to room temperature and stirred for 12 h. Then the solvent was removed under *vacuo* and the crude product was purified by flash chromatography to give 1.41 g (87 %) of desired product as a white solid;  $R_f$  (PE/Et<sub>2</sub>O =8: 2) 0.65.

#### *N*-(But-2-yn-1-yl)-4-Methylbenzenesulfonamide<sup>15</sup>

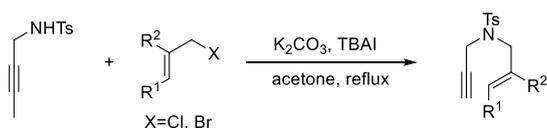
<sup>14</sup> P. Juszczak, L. Łankiewicz, A. S. Kołodziejczyk, *Lett. Pept. Sci.* **2002**, *9*, 187-192.

<sup>15</sup> Y. Kavanagh, M. O'Brien, P. Evans, *Tetrahedron* **2009**, *65*, 8259-8268.



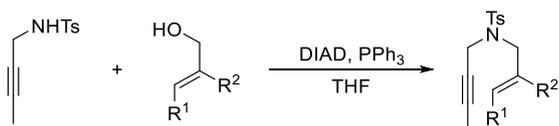
To a solution of *tert*-butyl but-2-yn-1-yl(tosyl)carbamate (1.62 g, 5.0 mmol) in dry DCM (30 mL) was added trifluoroacetic acid (5 mL). The resulting mixture was stirred for 12 h at room temperature. Then saturated NaHCO<sub>3</sub> solution (50 mL) was added, and the mixture was extracted with DCM (20 mL x 3). The organic phase was washed with brine (30 mL), dried with Na<sub>2</sub>SO<sub>4</sub>, and concentrated under vacuo. The crude product was purified by flash chromatography to give 1.11 g (99 %) of desired product as a white solid; R<sub>f</sub> (PE/Et<sub>2</sub>O =6: 4) 0.35.

### Procedure G



To a solution of *N*-(but-2-yn-1-yl)-4-methylbenzenesulfonamide (447 mg, 2 mmol) in acetone was added the allylic halide (4 mmol), potassium carbonate (552 mg, 4 mmol) and tetrabutylammonium iodide (73.8 mg, 0.2 mmol). The reaction solution was stirred overnight at 60 °C. The solvent was evaporated under vacuo. The residue was taken up in ethyl acetate, washed with distilled water (50 mL), brine (30 mL) and then dried over Na<sub>2</sub>SO<sub>4</sub>, concentrated under vacuo. The crude product was purified by flash chromatography.

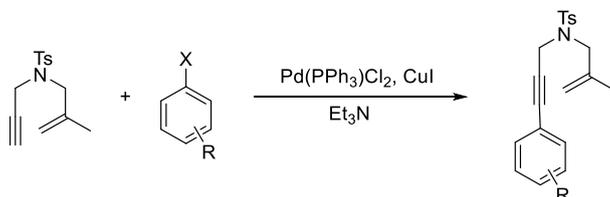
### Procedure H



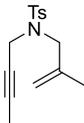
To a solution of *N*-(but-2-yn-1-yl)-4-methylbenzenesulfonamide (447 mg, 2.0 mmol), allylic alcohol (2.0 mmol) and PPh<sub>3</sub> (524 mg, 2.0 mmol) in dry THF (20 mL) was slowly added diisopropyl azodicarboxylate (404 mg, 2.0 mmol) at 0 °C. Then the resulting mixture was

warmed to room temperature and stirred for 12 h. Then the solvent was removed under vacuo and the crude product was purified by flash chromatography to give desired product.

### Procedure I

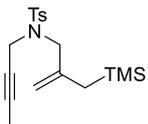


To a solution of 4-methyl-*N*-(2-methylallyl)-*N*-(prop-2-yn-1-yl)benzenesulfonamide (527 mg, 2 mmol) and aryl halide (2.4 mmol) in Et<sub>3</sub>N (20 mL) was added Pd(PPh<sub>3</sub>)Cl<sub>2</sub> (70 mg, 0.1 mmol) and CuI (19.2 mg, 0.1 mmol). The resulting mixture was stirred at 50 °C until the completion of the reaction (monitoring by TLC), and then cooled to rt and diluted with MTBE (30 mL). The mixture was filtered over celite. The filtrate was washed with brine (10 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated under vacuo. The crude residue was purified by flash chromatography to provide desired product.

 ***N*-(But-2-yn-1-yl)-4-methyl-*N*-(2-methylallyl)benzenesulfonamide (156)**<sup>16</sup> was prepared according to Procedure G, obtained: 505 mg (91%), white solid; R<sub>f</sub> (PE/Et<sub>2</sub>O 8/2) 0.5.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.75 (d, *J* = 8.0 Hz, 2H), 7.29 (d, *J* = 7.9 Hz, 2H), 4.95 (s, 2H), 3.97 (s, 2H), 3.70 (s, 2H), 2.42 (s, 3H), 1.76 (s, 3H), 1.51 (s, 3H).

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 143.5 (C), 139.9 (C), 136.7 (C), 129.5 (CH x 2), 128.3 (CH x 2), 115.4 (CH<sub>2</sub>), 81.8 (C), 71.9 (C), 52.8 (CH<sub>2</sub>), 36.4 (CH<sub>2</sub>), 21.8 (CH<sub>3</sub>), 20.1 (CH<sub>3</sub>), 3.5 (CH<sub>3</sub>).

 ***N*-(But-2-yn-1-yl)-4-methyl-*N*-(2-((trimethylsilyl)methyl)allyl)benzenesulfonamide (158)** was prepared according to Procedure G, obtained: 259 mg (37%), colorless oil; R<sub>f</sub> (PE/Et<sub>2</sub>O 9/1) 0.5.

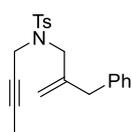
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.74 (d, *J* = 8.3 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 4.87 (s, 1H),

<sup>16</sup> E. Benedetti, A. Simonneau, A. Hours, H. Amouri, A. Penoni, G. Palmisano, M. Malacria, J.-P. Goddard, L. Fensterbank, *Adv. Synth. Catal.* **2011**, 353, 1908-1912.

4.74 (s, 1H), 4.00 (q,  $J = 2.4$  Hz, 2H), 3.62 (s, 2H), 2.42 (s, 3H), 1.56 (s, 2H), 1.50 (t,  $J = 2.4$  Hz, 3H), 0.05 (s, 9H).

$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  143.4 (C), 141.4 (C), 136.7 (C), 129.5 (CH x 2), 128.3 (CH x 2), 112.2 (CH<sub>2</sub>), 81.8 (C), 72.0 (C), 53.0 (CH<sub>2</sub>), 36.4 (CH<sub>2</sub>), 23.3 (CH<sub>2</sub>), 21.8 (CH<sub>3</sub>), 3.5 (CH<sub>3</sub>), -1.2 (CH<sub>3</sub> x 3).

MS  $m/z$  (ESI-MS) calcd. for ( $[\text{M}+\text{H}^+]$ ):  $\text{C}_{18}\text{H}_{28}\text{NO}_2\text{Si}^+$  350.16 Found 350.16.

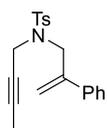


***N*-(2-Benzylallyl)-*N*-(but-2-yn-1-yl)-4-methylbenzenesulfonamide (159)** was prepared according to Procedure **H**, obtained: 488 mg (69%), colorless oil;  $R_f$  (PE/Et<sub>2</sub>O 8/2) 0.65.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.71 (d,  $J = 8.3$  Hz, 2H), 7.34 – 7.19 (m, 7H), 5.08 (s, 1H), 4.94 (s, 1H), 3.98 (q,  $J = 2.4$  Hz, 2H), 3.69 (s, 2H), 3.39 (s, 2H), 2.41 (s, 3H), 1.48 (t,  $J = 2.4$  Hz, 3H).

$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  143.5 (C), 143.4 (C), 139.2 (C), 136.5 (C), 129.6 (CH x 2), 129.5 (CH x 2), 128.7 (CH x 2), 128.3 (CH x 2), 126.6 (CH), 116.6 (CH<sub>2</sub>), 82.0 (C), 71.8 (C), 51.2 (CH<sub>2</sub>), 40.1 (CH<sub>2</sub>), 36.6 (CH<sub>2</sub>), 21.8 (CH<sub>3</sub>), 3.5 (CH<sub>3</sub>).

MS  $m/z$  (ESI-MS) calcd. for ( $[\text{M}+\text{H}^+]$ ):  $\text{C}_{21}\text{H}_{24}\text{NO}_2\text{S}^+$  354.15 Found 354.15.

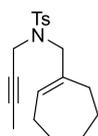


***N*-(But-2-yn-1-yl)-4-methyl-*N*-(2-phenylallyl)benzenesulfonamide (160)**<sup>16</sup> was prepared according to Procedure **G**, obtained: 631 mg (93%), pale yellow solid;  $R_f$  (PE/Et<sub>2</sub>O 8/2) 0.65.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.75 (d,  $J = 8.2$  Hz, 2H), 7.53 – 7.51 (m, 2H), 7.36 – 7.27 (m, 5H), 5.55 (s, 1H), 5.33 (s, 1H), 4.23 (s, 2H), 3.93 (q,  $J = 2.3$  Hz, 2H), 2.44 (s, 3H), 1.51 (t,  $J = 2.3$  Hz, 3H).

$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  143.6 (C), 142.0 (C), 138.3 (C), 136.3 (C), 129.5 (CH x 2), 128.7 (CH x 2), 128.5 (CH x 2), 128.4 (CH), 126.8 (CH x 2), 117.1 (CH<sub>2</sub>), 82.2 (C), 71.8 (C), 50.4 (CH<sub>2</sub>), 36.5 (CH<sub>2</sub>), 21.8 (CH<sub>3</sub>), 3.5 (CH<sub>3</sub>).

MS  $m/z$  (ESI-MS) calcd. for ( $[\text{M}+\text{H}^+]$ ):  $\text{C}_{20}\text{H}_{22}\text{NO}_2\text{S}^+$  340.14 Found 340.14.



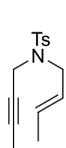
***N*-(But-2-yn-1-yl)-*N*-(cyclohept-1-en-1-ylmethyl)-4-methylbenzenesulfonamide**

(**161**) was prepared according to Procedure **H**; obtained: 583 mg (88%), white solid;  $R_f$  (PE/Et<sub>2</sub>O 8/2) 0.65.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.73 (d,  $J$  = 8.3 Hz, 2H), 7.28 (d,  $J$  = 8.0 Hz, 2H), 5.77 (t,  $J$  = 6.3 Hz, 1H), 3.96 (q,  $J$  = 2.4 Hz, 2H), 3.61 (s, 2H), 2.42 (s, 3H), 2.20 – 2.18 (m, 2H), 2.11 (q,  $J$  = 6.1 Hz, 2H), 1.76 – 1.70 (m, 2H), 1.50 – 1.44 (m, 7H).

<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 143.3 (C), 138.3 (C), 136.6 (C), 132.7 (CH), 129.4 (CH x 2), 128.2 (CH x 2), 81.7 (C), 71.9 (C), 54.8 (CH<sub>2</sub>), 35.9 (CH<sub>2</sub>), 32.6 (CH<sub>2</sub>), 30.4 (CH<sub>2</sub>), 28.7 (CH<sub>2</sub>), 27.3 (CH<sub>2</sub>), 27.0 (CH<sub>2</sub>), 21.8 (CH<sub>3</sub>), 3.5 (CH<sub>3</sub>).

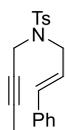
MS  $m/z$  (ESI-MS) calcd. for ([M+H<sup>+</sup>]): C<sub>19</sub>H<sub>26</sub>NO<sub>2</sub>S<sup>+</sup> 332.17 Found 332.17.



(**E**)-*N*-(But-2-en-1-yl)-*N*-(but-2-yn-1-yl)-4-methylbenzenesulfonamide (**162**)<sup>16</sup> was prepared according to Procedure **G**, obtained: 538 mg (97%), colorless oil;  $R_f$  (PE/Et<sub>2</sub>O 8/2) 0.70.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.73 (d,  $J$  = 8.3 Hz, 2H), 7.28 (d,  $J$  = 8.0 Hz, 2H), 5.74 – 5.64 (m, 1H), 5.40 – 5.32 (m, 1H), 4.01 – 3.99 (m, 2H), 3.72 (d,  $J$  = 6.8 Hz, 2H), 2.42 (s, 3H), 1.70 – 1.65 (m, 3H), 1.54 (t,  $J$  = 2.4 Hz, 3H).

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 143.4 (C), 136.8 (CH), 131.45 (CH), 129.5 (CH x 2), 128.2 (CH x 2), 125.24 (CH), 81.6 (C), 72.2 (CH), 48.6 (CH<sub>2</sub>), 36.4 (CH<sub>2</sub>), 21.8 (CH<sub>3</sub>), 18.0 (CH<sub>3</sub>), 3.5 (CH<sub>3</sub>).

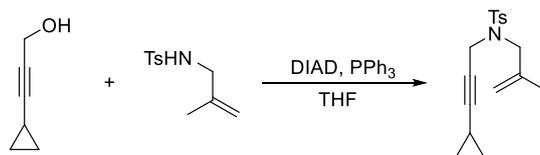


*N*-(But-2-yn-1-yl)-*N*-cinnamyl-4-methylbenzenesulfonamide (**163**)<sup>16</sup> was prepared according to Procedure **G**, obtained: 563 mg (83%), white solid;  $R_f$  (PE/Et<sub>2</sub>O 8/2) 0.55.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.80 (d,  $J$  = 8.3 Hz, 2H), 7.38 – 7.25 (m, 7H), 6.58 (d,  $J$  = 15.8 Hz, 1H), 6.11 (dt,  $J$  = 15.8, 6.8 Hz, 1H), 4.08 (q,  $J$  = 2.4 Hz, 2H), 4.00 (dd,  $J$  = 6.8, 0.8 Hz, 2H), 2.46 (s, 3H), 1.60 (t,  $J$  = 2.4 Hz, 3H).

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 143.4 (C), 136.4 (C), 136.4 (C), 134.5 (CH), 129.4 (CH x 2), 128.7 (CH x 2), 128.0 (CH), 128.0 (CH x 2), 126.6 (CH x 2), 123.5 (CH), 81.9 (C), 71.9 (C), 48.8 (CH<sub>2</sub>), 36.7 (CH<sub>2</sub>), 21.6 (CH<sub>3</sub>), 3.4 (CH<sub>3</sub>).

***N*-(3-cyclopropylprop-2-yn-1-yl)-4-methyl-*N*-(2-methylallyl)benzenesulfonamide (164)**<sup>17</sup>



To a solution of 3-cyclopropylprop-2-yn-1-ol (192 mg, 2.0 mmol), 4-methyl-*N*-(2-methylallyl)benzenesulfonamide (451 mg, 2.0 mmol) and PPh<sub>3</sub> (524 mg, 2.0 mmol) in dry THF (20 mL) was slowly added diisopropyl azodicarboxylate (404 mg, 2.0 mmol) at 0 °C. Then the resulting mixture was warmed to room temperature and stirred for 12 h. Then the solvent was removed under vacuo and the crude product was purified by flash chromatography to give 285 mg (47%) desired product as a white solid; *R<sub>f</sub>* (PE/Et<sub>2</sub>O 8/2) 0.65.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.72 (d, *J* = 8.2 Hz, 2H), 7.29 (d, *J* = 8.1 Hz, 2H), 4.95 (s, 2H), 3.98 (d, *J* = 1.5 Hz, 2H), 3.70 (s, 2H), 2.43 (s, 3H), 1.76 (s, 3H), 0.99 – 0.89 (m, 1H), 0.63 – 0.56 (m, 2H), 0.32 – 0.26 (m, 2H).

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 143.5 (C), 139.7 (C), 136.6 (C), 129.5 (CH x 2), 128.0 (CH x 2), 115.4 (CH<sub>2</sub>), 89.6 (C), 67.8 (C), 52.6 (CH<sub>2</sub>), 36.3 (CH<sub>2</sub>), 21.7 (CH<sub>3</sub>), 20.0 (CH<sub>3</sub>), 8.1 (CH<sub>2</sub> x 2), 0.7 (CH).

**4-Methyl-*N*-(2-methylallyl)-*N*-(3-phenylprop-2-yn-1-yl)benzenesulfonamide (165)**<sup>18</sup> was prepared according to Procedure I; obtained: 536 mg (79%), white solid; *R<sub>f</sub>* (PE/Et<sub>2</sub>O 8/2) 0.50.

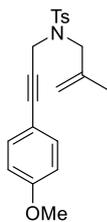
<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.80 (d, *J* = 8.1 Hz, 2H), 7.32 – 7.22 (m, 5H), 7.06 (d, *J* = 7.5 Hz, 2H), 5.03 (s, 2H), 4.28 (s, 2H), 3.82 (s, 2H), 2.35 (s, 3H), 1.83 (s, 3H).

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 143.7 (C), 139.7 (C), 136.5 (C), 131.8 (CH x 2), 129.8 (CH x 2), 128.7 (CH), 128.4 (CH x 2), 128.2 (CH x 2), 122.6 (C), 115.8 (CH<sub>2</sub>), 86.0 (C), 82.0 (C), 53.1 (CH<sub>2</sub>), 36.8 (CH<sub>2</sub>), 21.7 (CH<sub>3</sub>), 20.1 (CH<sub>3</sub>).

***N*-(3-(4-Methoxyphenyl)prop-2-yn-1-yl)-4-methyl-*N*-(2-methylallyl)benzenesulfonamide**

<sup>17</sup> S. Y. Kim, S. I. Lee, S. Y. Choi, Y. K. Chung, *Angew. Chem., Int. Ed.* **2008**, *47*, 4914-4917.

<sup>18</sup> S. Y. Kim, Y. K. Chung, *J. Org. Chem.* **2010**, *75*, 1281-1284.

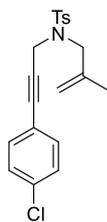


**(166)** was prepared according to Procedure **I**, obtained: 133 mg (18%), white solid;  $R_f$  (PE/Et<sub>2</sub>O 6/4) 0.55.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.77 (d,  $J$  = 8.3 Hz, 2H), 7.25 (d,  $J$  = 8.2 Hz, 2H), 6.98 (d,  $J$  = 8.9 Hz, 2H), 6.75 (d,  $J$  = 8.9 Hz, 2H), 5.01 – 4.99 (m, 2H), 4.24 (s, 2H), 3.79 (s, 5H), 2.35 (s, 3H), 1.81 (s, 3H).

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  159.9 (C), 143.6 (C), 139.7 (C), 136.5 (C), 133.2 (CH x 2), 129.7 (CH x 2), 128.1 (CH x 2), 115.7 (CH<sub>2</sub>), 114.6 (C), 114.0 (CH x 2), 85.9 (C), 80.5 (C), 55.6 (CH<sub>3</sub>), 52.9 (CH<sub>2</sub>), 36.8 (CH<sub>2</sub>), 21.7 (CH<sub>3</sub>), 20.0 (CH<sub>3</sub>).

MS  $m/z$  (ESI-MS) calcd. for ([M+H<sup>+</sup>]): C<sub>21</sub>H<sub>24</sub>NO<sub>3</sub>S<sup>+</sup> 370.15 Found 370.15.

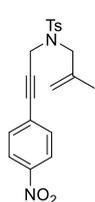


**N-(3-(4-Chlorophenyl)prop-2-yn-1-yl)-4-methyl-N-(2-methylallyl)benzenesulfonamide (167)** was prepared according to Procedure **I**, obtained: 680 mg (91%), white solid;  $R_f$  (PE/Et<sub>2</sub>O 8/2) 0.75.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.77 (d,  $J$  = 8.3 Hz, 2H), 7.25 (d,  $J$  = 8.1 Hz, 2H), 7.21 (d,  $J$  = 8.6 Hz, 2H), 6.96 (d,  $J$  = 8.6 Hz, 2H), 4.99 (s, 2H), 4.24 (s, 2H), 3.78 (s, 2H), 2.34 (s, 3H), 1.80 (s, 3H).

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  143.7 (C), 139.6 (C), 136.4 (C), 134.7 (C), 132.9 (CH x 2), 129.7 (CH x 2), 128.7 (CH x 2), 128.1 (CH x 2), 121.0 (C), 115.8 (CH<sub>2</sub>), 84.8 (C), 83.1 (C), 53.1 (CH<sub>2</sub>), 36.6 (CH<sub>2</sub>), 21.7 (CH<sub>3</sub>), 20.0 (CH<sub>3</sub>).

MS  $m/z$  (ESI-MS) calcd. for ([M+H<sup>+</sup>]): C<sub>20</sub>H<sub>21</sub>ClNO<sub>2</sub>S<sup>+</sup> 374.10 Found 374.10.



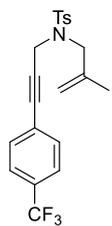
**4-Methyl-N-(2-methylallyl)-N-(3-(4-nitrophenyl)prop-2-yn-1-yl)benzenesulfonamide (168)** was prepared according to Procedure **I**, obtained: 569 mg (74%), white solid;  $R_f$  (PE/Et<sub>2</sub>O 6/4) 0.55.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.11 (d,  $J$  = 8.9 Hz, 2H), 7.78 (d,  $J$  = 8.3 Hz, 2H), 7.28 – 7.25 (m, 2H), 7.18 (d,  $J$  = 8.9 Hz, 2H), 5.02 (s, 1H), 4.99 (s, 1H), 4.28 (s, 2H), 3.80 (s, 2H), 2.35 (s, 3H), 1.81 (s, 3H).

<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  147.4 (C), 143.9 (C), 139.4 (C), 136.3 (C), 132.5 (CH x 2), 129.8 (CH x 2), 129.3 (C), 128.1 (CH x 2), 123.6 (CH x 2), 116.0 (CH<sub>2</sub>), 87.7 (C), 84.0 (C),

53.3 (CH<sub>2</sub>), 36.6 (CH<sub>2</sub>), 21.7 (CH<sub>3</sub>), 20.0 (CH<sub>3</sub>).

MS m/z (ESI-MS) calcd. for ([M+H<sup>+</sup>]): C<sub>20</sub>H<sub>21</sub>N<sub>2</sub>O<sub>4</sub>S<sup>+</sup> 385.12 Found 385.12.

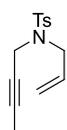


**4-Methyl-N-(2-methylallyl)-N-(3-(4-(trifluoromethyl)phenyl)prop-2-yn-1-yl)benzenesulfonamide (169)** was prepared according to Procedure I, obtained: 766 mg (94%), white solid; R<sub>f</sub>(PE/Et<sub>2</sub>O 8/2) 0.65.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.77 (d, *J* = 8.3 Hz, 2H), 7.49 (d, *J* = 8.1 Hz, 2H), 7.25 (d, *J* = 8.5 Hz, 2H), 7.13 (d, *J* = 8.0 Hz, 2H), 5.01 (s, 1H), 5.00 (s, 1H), 4.27 (s, 2H), 3.80 (s, 2H), 2.33 (s, 3H), 1.81 (s, 3H).

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 143.8 (C), 139.6 (C), 136.4 (C), 132.0 (CH x 2), 129.8 (CH x 2), 130.4 (q, *J* = 32.6 Hz, C), 128.1 (CH x 2), 126.4 (C), 125.3 (q, *J* = 3.7 Hz, CH x 2), 124.1 (q, *J* = 272.6 Hz, C), 115.9 (CH<sub>2</sub>), 84.8 (C), 84.6 (C), 53.2 (CH<sub>2</sub>), 36.6 (CH<sub>2</sub>), 21.6 (CH<sub>3</sub>), 20.0 (CH<sub>3</sub>).

MS m/z (ESI-MS) calcd. for ([M+H<sup>+</sup>]): C<sub>21</sub>H<sub>21</sub>F<sub>3</sub>NO<sub>2</sub>S<sup>+</sup> 408.12 Found 408.12.

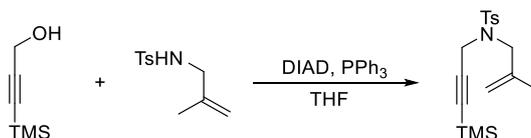


**N-Allyl-N-(but-2-yn-1-yl)-4-methylbenzenesulfonamide (170)**<sup>16</sup> was prepared according to Procedure G, obtained: 766 mg (94%), colorless oil; R<sub>f</sub> (PE/Et<sub>2</sub>O 8/2) 0.70.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.74 (d, *J* = 8.3 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 5.73 (ddt, *J* = 17.1, 10.0, 6.4 Hz, 1H), 5.27 (dq, *J* = 17.1, 1.4 Hz, 1H), 5.21 (dq, *J* = 10.0, 1.2 Hz, 1H), 4.02 (q, *J* = 2.4 Hz, 2H), 3.79 (dt, *J* = 6.4, 1.2 Hz, 2H), 2.42 (s, 3H), 1.54 (t, *J* = 2.4 Hz, 3H).

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 143.5 (C), 136.4 (C), 132.5 (CH), 129.5 (CH x 2), 128.0 (CH x 2), 119.6 (CH<sub>2</sub>), 81.8 (C), 71.8 (C), 49.2 (CH<sub>2</sub>), 36.5 (CH<sub>2</sub>), 21.6 (CH<sub>3</sub>), 3.3 (CH<sub>3</sub>).

#### 4-Methyl-N-(2-methylallyl)-N-(3-(trimethylsilyl)prop-2-yn-1-yl)benzenesulfonamide (171)



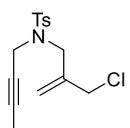
To a solution of 3-(trimethylsilyl)prop-2-yn-1-ol (266 mg, 2.0 mmol),

4-methyl-*N*-(2-methylallyl)benzenesulfonamide (451 mg, 2.0 mmol) and PPh<sub>3</sub> (524 mg, 2.0 mmol) in dry THF (20 mL) was slowly added diisopropyl azodicarboxylate (404 mg, 2.0 mmol) at 0 °C. Then the resulting mixture was warmed to room temperature and stirred for 12 h. Then the solvent was removed under vacuo and the crude product was purified by flash chromatography to give 564 mg (84%) desired product as a white solid; R<sub>f</sub> (PE/Et<sub>2</sub>O 8/2) 0.70.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.73 (d, *J* = 8.2 Hz, 2H), 7.28 (d, *J* = 8.1 Hz, 2H), 4.96 (s, 2H), 4.06 (s, 2H), 3.73 (s, 2H), 2.42 (s, 3H), 1.78 (s, 3H), -0.02 (s, 9H).

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 143.5 (C), 139.4 (C), 136.4 (C), 129.7 (CH x 2), 128.0 (CH x 2), 115.7 (CH<sub>2</sub>), 98.0 (C), 91.2 (C), 52.6 (CH<sub>2</sub>), 36.7 (CH<sub>2</sub>), 21.7 (CH<sub>3</sub>), 19.9 (CH<sub>3</sub>), 0.2 (CH<sub>3</sub> x 3).

MS m/z (ESI-MS) calcd. for ([M+H<sup>+</sup>]): C<sub>17</sub>H<sub>26</sub>NO<sub>2</sub>SSi<sup>+</sup> 336.14 Found 336.15.



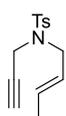
***N*-(But-2-yn-1-yl)-*N*-(2-(chloromethyl)allyl)-4-methylbenzenesulfonamide**

**(172)** was prepared according to Procedure G, obtained: 280 mg (45%), colorless oil; R<sub>f</sub> (PE/Et<sub>2</sub>O 8/2) 0.65.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.76 (d, *J* = 8.3 Hz, 2H), 7.31 (d, *J* = 8.5 Hz, 2H), 5.38 (s, 1H), 5.26 (s, 1H), 4.10 (s, 2H), 4.00 (q, *J* = 2.4 Hz, 2H), 3.87 (s, 2H), 2.43 (s, 3H), 1.53 (q, *J* = 2.4 Hz, 3H).

<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 143.8 (C), 139.9 (C), 136.2 (C), 129.6 (CH x 2), 128.3 (CH x 2), 119.3 (CH<sub>2</sub>), 82.3 (C), 71.7 (C), 49.1 (CH<sub>2</sub>), 45.3 (CH<sub>2</sub>), 37.1 (CH<sub>2</sub>), 21.9 (CH<sub>3</sub>), 3.5 (CH<sub>3</sub>).

MS m/z (ESI-MS) calcd. for ([M+H<sup>+</sup>]): C<sub>15</sub>H<sub>19</sub>ClNO<sub>2</sub>S<sup>+</sup> 312.08 Found 312.08.



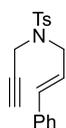
**(*E*)-*N*-(But-2-en-1-yl)-4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide** **(187)**<sup>16</sup>

was prepared according to Procedure G, obtained: 516 mg (98%), colorless oil; R<sub>f</sub> (PE/Et<sub>2</sub>O 8/2) 0.65.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.73 (d, *J* = 8.0 Hz, 2H), 7.29 (d, *J* = 8.1 Hz, 2H), 5.77 – 5.66 (m, 1H), 5.42 – 5.32 (m, 1H), 4.09 (s, 2H), 3.77 (d, *J* = 6.6 Hz, 2H), 2.43 (s, 3H), 2.01 (s, 1H),

1.70 (d,  $J = 6.2$  Hz, 3H).

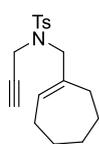
$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  143.7 (C), 136.5 (C), 131.9 (CH), 129.7 (CH x 2), 128.0 (CH x 2), 124.8 (CH), 77.1 (C), 73.8 (CH), 48.6 ( $\text{CH}_2$ ), 35.8 ( $\text{CH}_2$ ), 21.8 ( $\text{CH}_3$ ), 17.9 ( $\text{CH}_3$ ).



***N*-Cinnamyl-4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide (188)**<sup>16</sup> was prepared according to Procedure **G**, obtained: 625 mg (96%), white solid;  $R_f$  (PE/Et<sub>2</sub>O 8/2) 0.60.

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.79 (d,  $J = 8.1$  Hz, 2H), 7.37 – 7.27 (m, 7H), 6.60 (d,  $J = 15.8$  Hz, 1H), 6.10 (dt,  $J = 15.8, 6.8$  Hz, 1H), 4.15 (d,  $J = 2.4$  Hz, 2H), 4.02 (d,  $J = 6.8$  Hz, 2H), 2.45 (s, 3H), 2.07 (s, 1H).

$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  143.9 (C), 136.4 (C), 136.3 (C), 135.1 (CH), 129.8 (CH x 2), 128.9 (CH x 2), 128.3 (CH), 128.0 (CH x 2), 126.8 (CH x 2), 123.2 (CH), 77.0 (C), 74.1 (CH), 48.9 ( $\text{CH}_2$ ), 36.2 ( $\text{CH}_2$ ), 21.8 ( $\text{CH}_3$ ).



***N*-(Cyclohept-1-en-1-ylmethyl)-4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide (189)**<sup>19</sup> was prepared according to Procedure **H**, obtained: 324 mg (51%), white solid;  $R_f$  (PE/Et<sub>2</sub>O 8/2) 0.60.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.73 (d,  $J = 8.3$  Hz, 2H), 7.28 (d,  $J = 8.2$  Hz, 2H), 5.80 (t,  $J = 6.4$  Hz, 1H), 4.04 (d,  $J = 2.4$  Hz, 2H), 3.65 (s, 2H), 2.42 (s, 3H), 2.20 – 2.17 (m, 2H), 2.13 – 2.09 (m, 2H), 1.92 (t,  $J = 2.4$  Hz, 1H), 1.75 – 1.71 (m, 2H), 1.51 – 1.45 (m, 4H).

$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  143.7 (C), 138.0 (C), 136.6 (C), 133.2 (CH), 129.7 (CH x 2), 128.2 (CH x 2), 76.9 (C), 73.9 (CH), 54.8 ( $\text{CH}_2$ ), 35.5 ( $\text{CH}_2$ ), 32.5 ( $\text{CH}_2$ ), 30.4 ( $\text{CH}_2$ ), 28.8 ( $\text{CH}_2$ ), 27.3 ( $\text{CH}_2$ ), 27.0 ( $\text{CH}_2$ ), 21.8 ( $\text{CH}_3$ ).

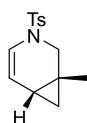
## General Procedure J

### Ru(II)-catalyzed Cycloisomerization Reaction of 1,6-Enynes.

A solution of enynes (0.2 mmol) in 1,4-dioxane (0.5 mL) was added to a solution of  $[\text{RuCl}_2(\text{CO})_3]_2$  (0.01 mmol) in 1,4-dioxane (0.5 mL). The resulting mixture was stirred at 90-110 °C until completion of the reaction. Then the reaction solution was cooled to room

<sup>19</sup> A. Fürstner, F. Stelzer, H. Szillat, *J. Am. Chem. Soc.* **2001**, *123*, 11863-11869.

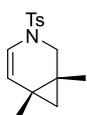
temperature, filtered over celite and concentrated under vacuo. The residue was purified by flash chromatography over Et<sub>3</sub>N treated silica gel.



**(1R,6R)-1-Methyl-3-tosyl-3-azabicyclo[4.1.0]hept-4-ene (154).**<sup>16</sup> General procedure **J** afforded 24.8 mg (47%) of the title compound as a white solid. R<sub>f</sub>(PE/Et<sub>2</sub>O 3/1) 0.65.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.64 (d, *J* = 8.3 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 6.27 (d, *J* = 7.9 Hz, 1H), 5.39 (dd, *J* = 7.9, 5.6 Hz, 1H), 3.83 (d, *J* = 11.4 Hz, 1H), 2.72 (dd, *J* = 11.4, 0.8 Hz, 1H), 2.42 (s, 3H), 1.10 (s, 3H), 0.91 (dt, *J* = 8.2, 4.9 Hz, 1H), 0.62 (ddd, *J* = 8.2, 4.4, 1.3 Hz, 1H), 0.56 (t, *J* = 4.4 Hz, 1H).

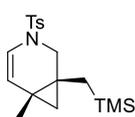
<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 143.90 (C), 135.4 (C), 130.04 (CH x 2), 127.34 (CH x 2), 120.66 (CH), 112.95 (CH), 46.33 (CH<sub>2</sub>), 26.03 (CH<sub>2</sub>), 22.27 (CH), 21.84 (CH<sub>3</sub>), 20.61 (CH<sub>2</sub>), 16.28 (CH<sub>3</sub>).



**(1R,6R)-1,6-Dimethyl-3-tosyl-3-azabicyclo[4.1.0]hept-4-ene (157).**<sup>16</sup> General procedure **J** afforded 44.9 mg (81%) of the title compound as a white solid. R<sub>f</sub>(PE/Et<sub>2</sub>O 3/1) 0.65.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.64 (d, *J* = 7.9 Hz, 2H), 7.30 (d, *J* = 7.8 Hz, 2H), 6.25 (d, *J* = 7.8 Hz, 1H), 5.17 (d, *J* = 7.8 Hz, 1H), 3.76 (d, *J* = 11.3 Hz, 1H), 2.68 (d, *J* = 11.3 Hz, 1H), 2.41 (s, 3H), 1.10 (s, 6H), 0.72 (d, *J* = 3.8 Hz, 1H), 0.31 (d, *J* = 3.8 Hz, 1H).

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 143.9 (C), 135.4 (C), 130.0 (CH x 2), 127.3 (CH x 2), 120.3 (CH), 118.5 (CH), 47.0 (CH<sub>2</sub>), 29.7 (C), 26.6 (CH<sub>2</sub>), 21.8 (CH<sub>3</sub>), 19.0 (CH<sub>3</sub>), 17.9 (C), 17.8 (CH<sub>3</sub>).



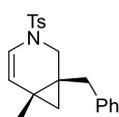
**(1S,6R)-6-Methyl-3-tosyl-1-((trimethylsilyl)methyl)-3-azabicyclo[4.1.0]hept-4-ene (173).** General procedure **J** afforded 46.8 mg (67%) of the title compound as a colorless oil. R<sub>f</sub>(PE/Et<sub>2</sub>O 17/3) 0.45.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.64 (d, *J* = 8.3 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 6.24 (dd, *J* = 7.9, 0.8 Hz, 1H), 5.20 (d, *J* = 7.9 Hz, 1H), 3.84 (d, *J* = 11.7 Hz, 1H), 2.62 (d, *J* = 11.7 Hz, 1H), 2.42 (s, 3H), 1.08 (s, 3H), 0.82 (d, *J* = 15.1 Hz, 1H), 0.62 (d, *J* = 4.4 Hz, 1H), 0.58 (d, *J*

= 15.1 Hz, 1H), 0.24 (dd,  $J = 4.4, 0.8$  Hz, 1H), 0.04 (s, 9H).

$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  143.9 (C), 135.5 (C), 130.0 (CH x 2), 127.4 (CH x 2), 120.1 (CH), 119.2 (CH), 46.9 ( $\text{CH}_2$ ), 32.8 (C), 26.5 ( $\text{CH}_2$ ), 21.8 ( $\text{CH}_3$ ), 19.6 ( $\text{CH}_2$ ), 19.5 ( $\text{CH}_3$ ), 18.0 (C), -0.1 ( $\text{CH}_3$  x 3).

HRMS (ESI-MS) calcd. for  $\text{C}_{18}\text{H}_{28}\text{NO}_2\text{SSi}^+$  ( $[\text{M}+\text{H}]^+$ ): 350.1605, found 350.1605.



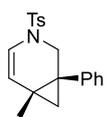
**(1*S*,6*R*)-1-Benzyl-6-methyl-3-tosyl-3-azabicyclo[4.1.0]hept-4-ene** (174).

General procedure **J** afforded 59.4 mg (84%) of the title compound as a colorless oil.  $R_f(\text{PE}/\text{Et}_2\text{O}$  3/1) 0.45.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.53 (d,  $J = 8.3$  Hz, 2H), 7.32 – 7.21 (m, 5H), 7.15 (d,  $J = 6.9$  Hz, 2H), 6.27 (dd,  $J = 7.9, 0.7$  Hz, 1H), 5.24 (d,  $J = 7.9$  Hz, 1H), 3.63 (d,  $J = 11.8$  Hz, 1H), 2.81 (d,  $J = 15.2$  Hz, 1H), 2.75 (d,  $J = 11.8$  Hz, 1H), 2.70 (d,  $J = 15.2$  Hz, 1H), 2.42 (s, 3H), 1.25 (s, 3H), 0.67 (dd,  $J = 4.5, 0.7$  Hz, 1H), 0.60 (dd,  $J = 4.5, 0.7$  Hz, 1H).

$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  143.8 (C), 138.9 (C), 135.3 (C), 129.9 (CH x 2), 128.9 (CH x 2), 128.8 (CH x 2), 127.2 (CH x 2), 126.7 (CH), 120.7 (CH), 118.7 (CH), 45.1 ( $\text{CH}_2$ ), 38.3 ( $\text{CH}_2$ ), 34.1 (C), 26.3 ( $\text{CH}_2$ ), 21.8 ( $\text{CH}_3$ ), 19.6 ( $\text{CH}_3$ ), 18.2 (C).

HRMS (ESI-MS) calcd. for  $\text{C}_{21}\text{H}_{24}\text{NO}_2\text{S}^+$  ( $[\text{M}+\text{H}]^+$ ): 354.1522, found 354.1522.



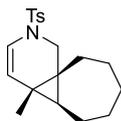
**(1*R*,6*R*)-6-Methyl-1-phenyl-3-tosyl-3-azabicyclo[4.1.0]hept-4-ene** (175).<sup>16</sup>

General procedure **J** afforded 50.2 mg (74%) of the title compound as a white solid.  $R_f(\text{PE}/\text{Et}_2\text{O}$  17/3) 0.65.

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.67 (d,  $J = 8.2$  Hz, 2H), 7.33 (d,  $J = 7.5$  Hz, 2H), 7.30 – 7.22 (m, 5H), 6.40 (d,  $J = 8.0$  Hz, 1H), 5.38 (d,  $J = 8.0$  Hz, 1H), 3.98 (d,  $J = 11.5$  Hz, 1H), 3.02 (d,  $J = 11.5$  Hz, 1H), 2.45 (s, 3H), 1.22 (d,  $J = 4.6$  Hz, 1H), 0.99 (d,  $J = 4.6$  Hz, 1H), 0.87 (s, 3H).

$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  144.0 (C), 139.3 (C), 135.4 (C), 130.1 (CH x 2), 130.0 (CH x 2), 128.8 (CH x 2), 127.5 (CH), 127.4 (CH x 2), 121.2 (CH), 118.3 (CH), 48.5 ( $\text{CH}_2$ ), 40.0 (C), 24.5 ( $\text{CH}_2$ ), 21.9 ( $\text{CH}_3$ ), 21.2 ( $\text{CH}_3$ ), 19.2 (C).

**(4*aR*,4*bS*,9*aR*)-4*a*-Methyl-2-tosyl-2,4*a*,4*b*,5,6,7,8,9-octahydro-1*H*-cyclohepta[1,3]cyclopr**

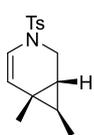


**opa[1,2-c]pyridine (176).** General procedure **C** afforded 61.0 mg (92%) of the title compound as a colorless oil.  $R_f$ (PE/Et<sub>2</sub>O 3/1) 0.55.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.66 (d,  $J$  = 8.3 Hz, 2H), 7.31 (d,  $J$  = 8.0 Hz, 2H), 6.24 (d,  $J$  = 8.0 Hz, 1H), 5.21 (d,  $J$  = 8.0 Hz, 1H), 3.98 (d,  $J$  = 11.6 Hz, 1H), 2.59 (d,  $J$  = 11.6 Hz, 1H), 2.41 (s, 3H), 1.88 – 1.82 (m, 1H), 1.78 – 1.61 (m, 4H), 1.44 – 1.27 (m, 2H), 1.10 – 0.89 (m, 6H), 0.69 (dd,  $J$  = 10.5, 6.7 Hz, 1H).

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  143.8 (C), 135.6 (C), 130.0 (CH x 2), 127.4 (CH x 2), 120.7 (CH), 120.0 (CH), 46.4 (CH<sub>2</sub>), 37.6 (C), 33.7 (CH<sub>3</sub>), 32.8 (CH<sub>2</sub>), 28.9 (CH<sub>2</sub>), 28.6 (CH<sub>2</sub>), 27.0 (CH<sub>2</sub>), 25.9 (CH<sub>2</sub>), 23.4 (C), 21.8 (CH<sub>3</sub>), 14.3 (CH).

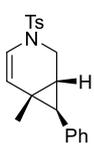
**HRMS** (ESI-MS) calcd. for C<sub>19</sub>H<sub>26</sub>NO<sub>2</sub>S<sup>+</sup> ([M+H]<sup>+</sup>): 332.1679, found 332.1679.



**(1R,6S,7R)-6,7-Dimethyl-3-tosyl-3-azabicyclo[4.1.0]hept-4-ene (177).**<sup>16</sup> General procedure **J** afforded 36.1 mg (65%) of the title compound as a colorless oil.  $R_f$ (PE/Et<sub>2</sub>O 17/3) 0.55.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.64 (d,  $J$  = 8.3 Hz, 2H), 7.30 (d,  $J$  = 8.0 Hz, 2H), 6.26 (dd,  $J$  = 8.2, 1.0 Hz, 1H), 5.20 (dd,  $J$  = 8.2, 1.0 Hz, 1H), 3.88 (d,  $J$  = 11.4 Hz, 1H), 2.93 (dd,  $J$  = 11.4, 2.8 Hz, 1H), 2.42 (s, 3H), 1.05 (s, 3H), 0.94 (d,  $J$  = 6.3 Hz, 3H), 0.86 (dt,  $J$  = 4.1, 1.8 Hz, 1H), 0.62 (p,  $J$  = 6.2 Hz, 1H).

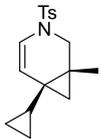
<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  143.8 (C), 135.4 (C), 130.0 (CH x 2), 127.4 (CH x 2), 120.0 (CH), 118.4 (CH), 40.7 (CH<sub>2</sub>), 32.7 (CH), 25.5 (CH), 21.8 (CH<sub>3</sub>), 17.5 (CH<sub>3</sub>), 16.6 (C), 13.2(CH<sub>3</sub>).



**(1R,6S,7S)-6-Methyl-7-phenyl-3-tosyl-3-azabicyclo[4.1.0]hept-4-ene (178).**<sup>16</sup> General procedure **J** afforded 53.0 mg (78%) of the title compound as a colorless oil.  $R_f$ (PE/Et<sub>2</sub>O 4/1) 0.55.

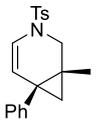
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.67 (d,  $J$  = 8.3 Hz, 2H), 7.30 (d,  $J$  = 8.0 Hz, 2H), 7.27 – 7.21 (m, 2H), 7.18 – 7.14 (m, 1H), 6.97 (d,  $J$  = 7.1 Hz, 2H), 6.41 (d,  $J$  = 8.1 Hz, 1H), 5.31 (d,  $J$  = 8.1 Hz, 1H), 4.02 (d,  $J$  = 11.6 Hz, 1H), 3.14 (dd,  $J$  = 11.6, 2.8 Hz, 1H), 2.40 (s, 3H), 1.90 (d,  $J$  = 5.9 Hz, 1H), 1.81 – 1.78 (m, 1H), 0.85 (s, 3H).

$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  144.06 (C), 137.58 (C), 135.13 (C), 130.13 (CH x 2), 128.91 (CH x 2), 128.32 (CH x 2), 127.36 (CH x 2), 126.42 (CH), 121.04 (CH), 117.64 (CH), 40.69 ( $\text{CH}_2$ ), 36.20 (CH), 29.73 (CH), 21.80 ( $\text{CH}_3$ ), 20.69 (C), 17.88 ( $\text{CH}_3$ ).

 **(1R,6S)-6-Cyclopropyl-1-methyl-3-tosyl-3-azabicyclo[4.1.0]hept-4-ene (179).**<sup>17</sup>  
General procedure **J** afforded 30.9 mg (51%) of the title compound as a colorless.  
 $R_f(\text{PE}/\text{Et}_2\text{O}$  17/3) 0.65.

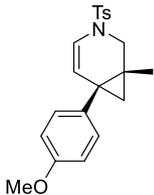
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.65 (d,  $J = 8.3$  Hz, 2H), 7.31 (d,  $J = 8.0$  Hz, 2H), 6.27 (dd,  $J = 8.1, 1.0$  Hz, 1H), 5.30 (d,  $J = 8.1$  Hz, 1H), 3.79 (dd,  $J = 11.4, 0.8$  Hz, 1H), 2.70 (d,  $J = 11.4$  Hz, 1H), 2.42 (s, 3H), 1.17 (s, 3H), 0.88 – 0.81 (m, 1H), 0.56 – 0.50 (m, 1H), 0.46 (d,  $J = 4.6$  Hz, 1H), 0.42 – 0.37 (m, 1H), 0.31 (d,  $J = 4.6$  Hz, 1H), 0.20 – 0.12 (m, 2H).

$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  143.9 (C), 135.4 (C), 130.0 (CH x 2), 127.4 (CH x 2), 120.5 (CH), 117.3 (CH), 47.0 ( $\text{CH}_2$ ), 30.6 (C), 23.9 (C), 22.5 ( $\text{CH}_2$ ), 21.8 ( $\text{CH}_3$ ), 17.6 ( $\text{CH}_3$ ), 12.7 (CH), 5.3 ( $\text{CH}_2$ ), 3.1 ( $\text{CH}_2$ ).

 **(1R,6R)-1-Methyl-6-phenyl-3-tosyl-3-azabicyclo[4.1.0]hept-4-ene (180).**<sup>18</sup>  
General procedure **J** afforded 54.3 mg (80%) of the title compound as a white solid.  
 $R_f(\text{PE}/\text{Et}_2\text{O}$  4/1) 0.65.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.73 (d,  $J = 8.3$  Hz, 2H), 7.38 (d,  $J = 8.0$  Hz, 2H), 7.31 – 7.26 (m, 2H), 7.24 – 7.20 (m, 1H), 7.17 – 7.15 (m, 2H), 6.43 (dd,  $J = 8.0, 0.9$  Hz, 1H), 5.37 (d,  $J = 8.0$  Hz, 1H), 3.96 (d,  $J = 11.6$  Hz, 1H), 2.81 (d,  $J = 11.6$  Hz, 1H), 2.48 (s, 3H), 1.24 (d,  $J = 5.4$  Hz, 1H), 1.06 (d,  $J = 4.9$  Hz, 1H), 0.81 (s, 3H).

$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  144.1 (C), 141.6 (C), 135.4 (C), 130.2 (CH x 2), 129.4 (CH x 2), 128.4 (CH x 2), 127.4 (CH x 2), 126.7 (CH), 120.9 (CH), 117.6 (CH), 46.8 ( $\text{CH}_2$ ), 32.9 (C), 28.6 (C), 23.7 ( $\text{CH}_2$ ), 21.9 ( $\text{CH}_3$ ), 19.1 ( $\text{CH}_3$ ).

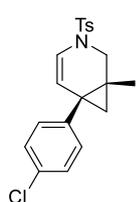
 **(1R,6R)-6-(4-Methoxyphenyl)-1-methyl-3-tosyl-3-azabicyclo[4.1.0]hept-4-ene (181).** General procedure **J** afforded 62.8 mg (85%) of the title compound as a white solid.  $R_f(\text{PE}/\text{Et}_2\text{O}$  3/2) 0.55.

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.70 (d,  $J = 8.2$  Hz, 2H), 7.35 (d,  $J = 8.1$  Hz,

2H), 7.05 (d,  $J = 8.7$  Hz, 2H), 6.80 (d,  $J = 8.7$  Hz, 2H), 6.37 (d,  $J = 8.0$  Hz, 1H), 5.32 (d,  $J = 8.0$  Hz, 1H), 3.92 (d,  $J = 11.5$  Hz, 1H), 3.77 (s, 3H), 2.77 (d,  $J = 11.5$  Hz, 1H), 2.45 (s, 3H), 1.14 (dd,  $J = 4.8$  Hz, 1H), 1.00 (d,  $J = 4.8$  Hz, 1H), 0.79 (s, 3H).

$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  158.5 (C), 144.0 (C), 135.5 (C), 133.7 (C), 130.4 (CH x 2), 130.1 (CH x 2), 127.4 (CH x 2), 120.7 (CH), 118.0 (CH), 113.9 (CH x 2), 55.5 ( $\text{CH}_3$ ), 46.8 ( $\text{CH}_2$ ), 32.7 (C), 27.9 (C), 24.0 ( $\text{CH}_2$ ), 21.9 ( $\text{CH}_3$ ), 19.2 ( $\text{CH}_3$ ).

HRMS (ESI-MS) calcd. for  $\text{C}_{21}\text{H}_{24}\text{NO}_3\text{S}^+$  ( $[\text{M}+\text{H}]^+$ ): 370.1471, found 370.1472.

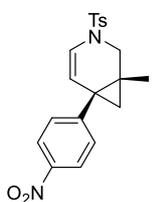


**(1R,6R)-6-(4-Chlorophenyl)-1-methyl-3-tosyl-3-azabicyclo[4.1.0]hept-4-ene (182).** General procedure J afforded 62.8 mg (84%) of the title compound as a white solid.  $R_f(\text{PE}/\text{Et}_2\text{O}$  4/1) 0.65.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.70 (d,  $J = 8.3$  Hz, 2H), 7.35 (d,  $J = 8.0$  Hz, 2H), 7.23 (d,  $J = 8.5$  Hz, 2H), 7.07 (d,  $J = 8.5$  Hz, 2H), 6.41 (dd,  $J = 8.0, 0.8$  Hz, 1H), 5.28 (d,  $J = 8.0$  Hz, 1H), 3.93 (d,  $J = 11.6$  Hz, 1H), 2.76 (d,  $J = 11.6$  Hz, 1H), 2.45 (s, 3H), 1.17 (d,  $J = 4.9$  Hz, 1H), 1.05 (d,  $J = 4.9$  Hz, 1H), 0.78 (s, 3H).

$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  144.1 (C), 140.2 (C), 135.3 (C), 132.6 (C), 130.7 (CH x 2), 130.2 (CH x 2), 128.6 (CH x 2), 127.4 (CH x 2), 121.3 (CH), 116.8 (CH), 46.6 ( $\text{CH}_2$ ), 33.0 (C), 28.0 (C), 24.0 ( $\text{CH}_2$ ), 21.9 ( $\text{CH}_3$ ), 19.1 ( $\text{CH}_3$ ).

HRMS (ESI-MS) calcd. for  $\text{C}_{20}\text{H}_{21}\text{ClNO}_2\text{S}^+$  ( $[\text{M}+\text{H}]^+$ ): 374.0976, found 374.0976.



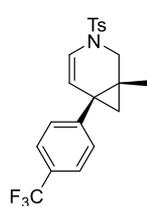
**(1R,6R)-1-Methyl-6-(4-nitrophenyl)-3-tosyl-3-azabicyclo[4.1.0]hept-4-ene (183).** General procedure J afforded 56.0 mg (73%) of the title compound as a pale yellow solid.  $R_f(\text{PE}/\text{Et}_2\text{O}$  3/2) 0.30.

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.13 (d,  $J = 8.6$  Hz, 2H), 7.71 (d,  $J = 8.2$  Hz, 2H), 7.36 (d,  $J = 8.0$  Hz, 2H), 7.31 (d,  $J = 8.6$  Hz, 2H), 6.49 (d,  $J = 8.0$  Hz, 1H), 5.28 (d,  $J = 8.0$  Hz, 1H), 3.96 (d,  $J = 11.7$  Hz, 1H), 2.79 (d,  $J = 11.7$  Hz, 1H), 2.46 (s, 3H), 1.32 (d,  $J = 5.1$  Hz, 1H), 1.19 (d,  $J = 5.1$  Hz, 1H), 0.80 (s, 3H).

$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  149.5 (C), 147.0 (C), 144.4 (C), 135.3 (C), 130.3 (CH x 2), 130.2 (CH x 2), 127.5 (CH x 2), 123.8 (CH x 2), 122.2 (CH), 115.3 (CH), 46.5 ( $\text{CH}_2$ ), 34.0

(C), 28.7 (C), 24.4 (CH<sub>2</sub>), 21.9 (CH<sub>3</sub>), 19.1 (CH<sub>3</sub>).

**HRMS** (ESI-MS) calcd. for C<sub>20</sub>H<sub>21</sub>N<sub>2</sub>O<sub>4</sub>S<sup>+</sup> ([M+H]<sup>+</sup>): 385.1217, found 385.1216.

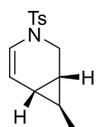


**(1R,6R)-1-Methyl-3-tosyl-6-(4-(trifluoromethyl)phenyl)-3-azabicyclo[4.1.0]hept-4-ene (184)**. General procedure **J** afforded 57.9 mg (71%) of the title compound as a white solid. R<sub>f</sub>(PE/Et<sub>2</sub>O 4/1) 0.65.

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 7.71 (d, *J* = 8.2 Hz, 2H), 7.52 (d, *J* = 8.1 Hz, 2H), 7.36 (d, *J* = 8.1 Hz, 2H), 7.26 (d, *J* = 8.2 Hz, 2H), 6.45 (d, *J* = 8.0 Hz, 1H), 5.29 (d, *J* = 8.0 Hz, 1H), 3.95 (d, *J* = 11.7 Hz, 1H), 2.79 (d, *J* = 11.7 Hz, 1H), 2.46 (s, 3H), 1.26 (d, *J* = 5.0 Hz, 1H), 1.11 (d, *J* = 5.0 Hz, 1H), 0.79 (s, 3H).

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 145.8 (C), 144.2 (C), 135.3 (C), 130.2 (CH x 2), 129.7 (CH x 2), 129.5 (q, *J* = 32.7 Hz, C), 127.4 (CH x 2), 125.5 (q, *J* = 3.8 Hz, CH x 2), 124.1 (q, *J* = 272.1 Hz, C), 121.6 (CH), 116.2 (CH), 46.6 (CH<sub>2</sub>), 33.3 (C), 28.5 (C), 24.0 (CH<sub>2</sub>), 21.9 (CH<sub>3</sub>), 19.1 (CH<sub>3</sub>).

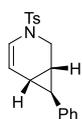
**HRMS** (ESI-MS) calcd. for C<sub>21</sub>H<sub>21</sub>F<sub>3</sub>NO<sub>2</sub>S<sup>+</sup> ([M+H]<sup>+</sup>): 408.1240, found 408.1245.



**(1R,6S,7S)-7-Methyl-3-tosyl-3-azabicyclo[4.1.0]hept-4-ene (191)**.<sup>16</sup> General procedure **J** afforded 21.1 mg (40%) of the title compound as a colorless oil. R<sub>f</sub>(PE/Et<sub>2</sub>O 4/1) 0.55.

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 7.64 (d, *J* = 8.3 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 6.29 (d, *J* = 8.1 Hz, 1H), 5.41 (dd, *J* = 8.1, 5.4 Hz, 1H), 3.88 (d, *J* = 11.5 Hz, 1H), 2.96 (dd, *J* = 11.5, 3.1 Hz, 1H), 2.42 (s, 3H), 1.25 – 1.19 (m, 1H), 0.97 (d, *J* = 6.1 Hz, 3H), 0.84 (ddd, *J* = 8.8, 5.4, 3.8 Hz, 1H), 0.75 – 0.67 (m, 1H).

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 143.9 (C), 135.3 (C), 130.0 (CH x 2), 127.4 (CH x 2), 121.1 (CH), 112.1 (CH), 41.1 (CH<sub>2</sub>), 26.7 (CH), 22.1 (CH), 21.8 (CH<sub>3</sub>), 17.7 (CH<sub>3</sub>), 15.8 (CH).

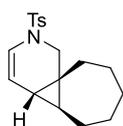


**(1S,6S,7S)-7-Phenyl-3-tosyl-3-azabicyclo[4.1.0]hept-4-ene (192)**.<sup>16</sup> General procedure **J** afforded 26.7 mg (41%) of the title compound as a colorless oil. R<sub>f</sub>(PE/Et<sub>2</sub>O 4/1) 0.55.

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 7.70 (d, *J* = 8.3 Hz, 2H), 7.36 (d, *J* = 8.1 Hz, 2H), 7.21 (dd, *J*

= 8.1, 6.4 Hz, 2H), 7.16 – 7.10 (m, 1H), 6.82 – 6.79 (m, 2H), 6.43 (d,  $J = 8.0$  Hz, 1H), 5.51 (dd,  $J = 8.0, 5.4$  Hz, 1H), 4.03 (d,  $J = 12.0$  Hz, 1H), 3.17 (dd,  $J = 12.0, 2.9$  Hz, 1H), 2.47 (s, 3H), 1.93 – 1.87 (m, 1H), 1.64 (dd,  $J = 5.1, 3.8$  Hz, 1H), 1.46 (ddd,  $J = 9.0, 5.4, 3.8$  Hz, 1H).

$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  144.1 (C), 140.8 (C), 135.2 (C), 130.2 (CH x 2), 128.7 (CH x 2), 127.5 (CH x 2), 126.2 (CH), 125.7 (CH x 2), 121.8 (CH), 111.5 (CH), 40.6 ( $\text{CH}_2$ ), 31.6 (CH), 29.2 (CH), 21.9 ( $\text{CH}_3$ ), 19.7 (CH).

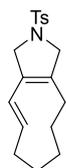


**(4aR,4bS,9aR)-2-Tosyl-2,4a,4b,5,6,7,8,9-octahydro-1H-cyclohepta[1,3]cyclopropana[1,2-c]pyridine (193).**<sup>19</sup> General procedure **J** afforded 14.6 mg (23%) of the title compound as a colorless oil.  $R_f(\text{PE}/\text{Et}_2\text{O} 17/3)$  0.40.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.65 (d,  $J = 8.3$  Hz, 2H), 7.31 (d,  $J = 8.0$  Hz, 2H), 6.24 (d,  $J = 7.9$  Hz, 1H), 5.44 (dd,  $J = 7.9, 5.6$  Hz, 1H), 3.97 (d,  $J = 11.5$  Hz, 1H), 2.67 (d,  $J = 11.5$  Hz, 1H), 2.42 (s, 3H), 2.04 – 1.93 (m, 2H), 1.81 – 1.76 (m, 1H), 1.68 – 1.59 (m, 2H), 1.45 – 1.40 (m, 1H), 1.19 – 1.09 (m, 3H), 0.93 – 0.77 (m, 3H).

$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  143.9 (C), 135.5 (C), 130.1 (CH x 2), 127.4 (CH x 2), 120.6 (CH), 113.9 (CH), 46.8 ( $\text{CH}_2$ ), 35.3 (C), 34.2 ( $\text{CH}_2$ ), 32.5 ( $\text{CH}_2$ ), 31.3 (CH), 30.8 ( $\text{CH}_2$ ), 29.1 ( $\text{CH}_2$ ), 27.2 ( $\text{CH}_2$ ), 26.1 (CH), 21.9 ( $\text{CH}_3$ ).

HRMS (ESI-MS) calcd. for  $\text{C}_{18}\text{H}_{24}\text{NO}_2\text{S}^+$  ( $[\text{M}+\text{H}]^+$ ): 318.1522, found 318.1522.



**(E)-2-Tosyl-1,2,3,4,5,6,7,8-octahydrocyclonona[c]pyrrole (197),** General procedure **J** afforded 34.9 mg (55%) of the title compound as a colorless oil.  $R_f(\text{PE}/\text{Et}_2\text{O} 3/2)$  0.40.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.72 (d,  $J = 8.3$  Hz, 2H), 7.32 (d,  $J = 8.0$  Hz, 2H), 5.71 – 5.60 (m, 2H), 4.08 – 4.03 (m, 4H), 2.42 (s, 3H), 2.00 – 1.98 (m, 2H), 1.93 – 1.89 (m, 2H), 1.48 – 1.37 (m, 6H).

$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  143.7 (C), 136.0 (CH), 134.5 (C), 130.0 (CH x 2), 129.5 (C x 2), 127.8 (CH x 2), 123.2 (CH), 58.8 ( $\text{CH}_2$ ), 58.5 ( $\text{CH}_2$ ), 29.5 ( $\text{CH}_2$ ), 29.2 ( $\text{CH}_2$ ), 28.4 ( $\text{CH}_2$ ), 26.3 ( $\text{CH}_2$ ), 24.8 ( $\text{CH}_2$ ), 21.8 ( $\text{CH}_3$ ).

## ABSTRACT

This dissertation focuses on cyclization reactions of 1,6-enynes involving ruthenium catalysts. Three different types of cyclization were developed from readily available precursors, such as 1,6-enynes and alkynes. In one application, a novel ruthenium-catalyzed hydroalkynylation cyclization of 1,6-enynes using terminal alkynes as co-reactants was explored. This reaction provides an entry to five-membered rings featuring an exocyclic 1,5-enyne motif. A neutral electron-rich ruthenium complex  $\text{Cp}^*\text{Ru}(\text{cod})\text{Cl}$  proved to be the catalyst of choice for these transformations. In another application, using the same complex, the ruthenium-catalyzed [2+2+2] cycloaddition of 1,6-enynes and alkynes was developed. Both internal and terminal alkynes were suitable substrates to access bicyclohexadienes with high yields in a single step. An intriguing ruthenium-catalyzed bicycloannulation of nitrogen-tethered 1,6-enynes has also been developed. For these cyclizations, only the electrophilic and alkynophilic ruthenium complex  $[\text{RuCl}_2(\text{CO})_3]_2$  was able to perform the reaction. The exclusive formation of 3-azabicyclo[4.1.0]hept-1-enes was observed with 1,6-enynes featuring an internal alkyne unit. These cyclization reactions fulfil the atom-economical reactions principle and are discussed on the basis of their mechanisms of formation.

## RESUME

Cette thèse porte sur les réactions de cyclisation des 1,6-enynes impliquant des catalyseurs de ruthénium. Trois types différents de cyclisation ont été élaborés à partir de précurseurs facilement disponibles, tels que les 1,6-enynes et alcynes. Dans un premier temps, une nouvelle cyclisation hydroalcynylante des 1,6-enynes, à l'aide d'alcynes terminaux comme co-réactifs, catalysée par le ruthénium a été explorée. Cette réaction fournit une méthode de synthèse de cycles à cinq chaînons doté d'un motif 1,5-enyne exocyclique. Un complexe du ruthénium neutre et riche en électrons,  $\text{Cp}^*\text{Ru}(\text{cod})\text{Cl}$ , s'est avéré être le catalyseur de choix de ces transformations. Dans un deuxième temps, en utilisant le même complexe, la cycloaddition [2+2+2] des 1,6-enynes et alcynes catalysée par le ruthénium a été développée. Les alcynes internes et terminaux sont appropriés pour accéder en une seule étape aux bicyclohexadienes avec de hauts rendements. Une bicycloannulation inhabituelle des 1,6-enynes, intégrant un atome d'azote, catalysée par le ruthénium a également été élaborée. Pour ces cyclisations, seul un complexe du ruthénium électrophile et alkynophile tel que  $[\text{RuCl}_2(\text{CO})_3]_2$  a été en mesure d'effectuer la réaction. La formation exclusive des 3-azabicyclo[4.1.0]hept-1-enes a été observée avec les 1,6-enynes dotés d'une unité alcyne interne. Ces réactions de cyclisation, respectant le principe des réactions à économie d'atome, sont discutées et sur la base de leur mécanisme de formation.