UNIVERSITÀ DI PARMA

# UNIVERSITA' DEGLI STUDI DI PARMA

**DOTTORATO DI RICERCA IN**

**"SCIENZE CHIMICHE"**

**CICLO XXXII**

# Sequences of enynes in the presence of oxygen nucleophiles and transition metals


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*Chapter 1*

# Introduction to gold and platinum catalysis in cycloisomerization reactions of enynes

## 1.1 Gold and Platinum Catalysis of Enyne Cycloisomerization

While the use of noble metals for the activation π-bonds has a long history, their application started to grow exponentially shortly before the 2000s.[1]

The coordination of a transition metal complex to an unsaturated ligand (alkene or alkyne) is described by the Dewar-Chatt-Duncanson (DCD) model (Figure 1).[2] According to the latter, the interaction between *p* orbitals of the alkyne and *d* orbitals of the metal can occur in two different ways. The first interaction consists in a *σ*-symmetric donation between the filled orbitals of the *π*-system of the alkyne and the empty *d* orbital of the metal (ligand to metal). The second corresponds to a *π* back donation from an occupied *d* orbital of the metal to an empty antibonding orbital π* of the alkyne (metal to ligand). Moreover, the second filled *π* orbital of the alkyne, perpendicular to the equatorial plane, can be involved in a another $\pi_{\perp}$ retrodonation interaction.

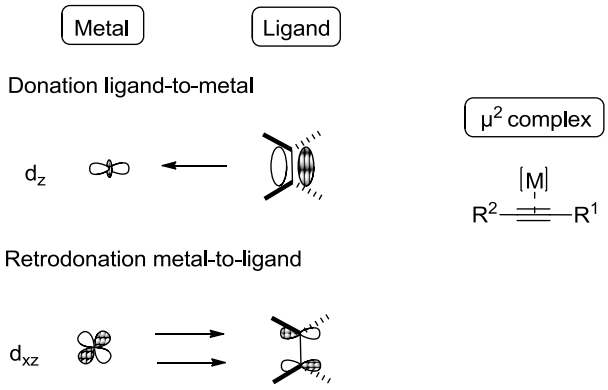
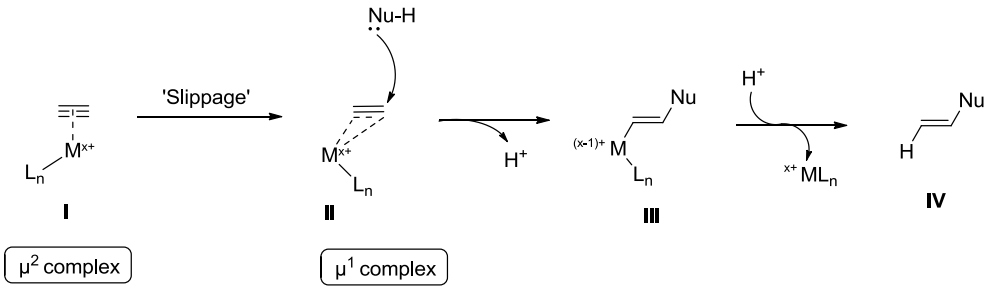



**Figure 1.** Interaction between an alkyne ligand and a transition metal.

According the DCD model, the $\mu^2$-complexation results in a deformation of the triple bond. The latter undergoes elongation by transfer of the electron density,

[1] L. Zhang, J. Sun and S. Kozmin, *Adv. Synth. Catal*., 2006, **348**, 2271.
[2] (a) M.J.S Dewar, *Bull.Soc.Chim.Fr*. 1951, **18**, C71. (b) J. Chatt and L. A. Duncanson, *J.Chem.Soc.* 1953, 2939.

from the bonding π orbitals to the antibonding π*orbitals. Consequently, the the electrophilicity of the alkyne is enhanced, and the triple bond is more prone to nucleophilic attack. The nucleophile adds in anti to the metal forming intermediate **III**, which undergoes protometallation yielding product **IV** (Scheme 1).

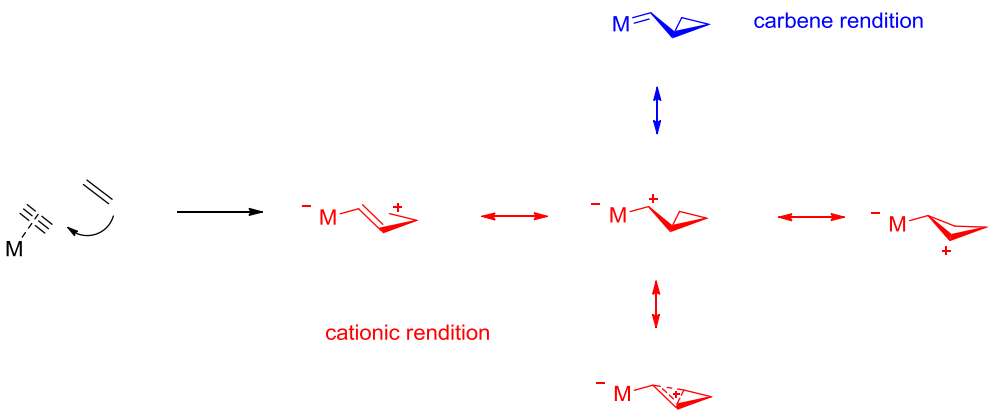



**Scheme 1** Basic mechanism for noble metal activation of alkynes

Particularly, in the cycloisomerization of enynes, the triple bond is selectively activated by complexation to the metal, and the resulting $\mu^2$-intermediate is then attacked by the alkene moiety which acts as nucleophile.

Investigations on [Au(I)]–ethyne and [Au(I)]–ethylene bonding demonstrated that Au(I)–alkyne complexes have lower LUMO for the addition of a nucleophile compared to that of Au(I)–alkene complexes. This is probably the source of the 'alkynophilicity' noticed in gold(I)-catalysed reaction. [3] The attack of the double bond on the activated triple bond is described in Scheme 2. The resulting intermediates can be depicted as either cationic (Scheme 2, in red) or carbenoid resonance extremes (Scheme 2, in blue).[4]

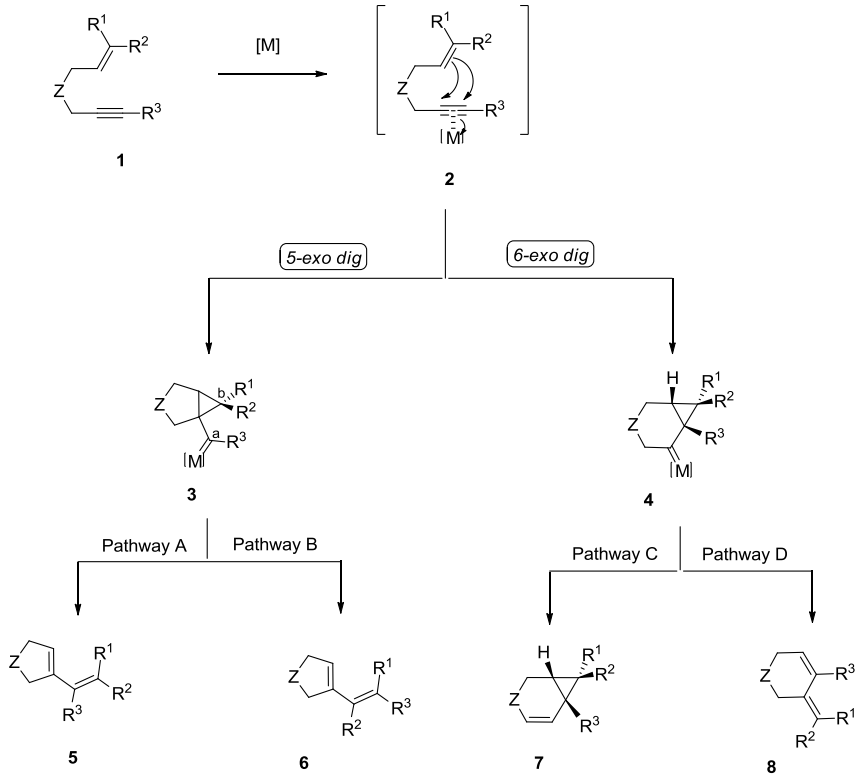
[3] D.J. Gorin and F.D. Toste, *Nature,* 2007, **446**, 395.
[4]G. Seidel, R. Mynott and A. Fürstner, *Angew.Chem.Int.Ed.* 2009, **48**, 2510.




**Scheme 2** Attack of an alkene on an triple bond activated by a metal fragment

## 1.2 Cycloisomerization of 1,6-enynes in the absence of nucleophiles

For cycloisomerization of 1,6-enynes different reaction pathways are proposed, as shown in Scheme 3.[5]

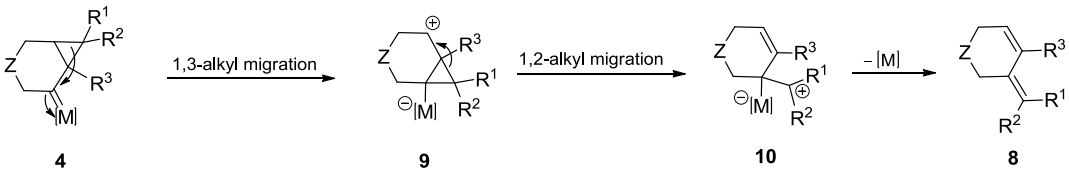



**Scheme 3** Mechanistic pathways for platinum or gold-catalyzed cycloisomerization of 1,6-enynes

As previously reported, the activation of the triple bond by the metal fragment led to $\mu^2$-complex **2**. At this point, addition of the alkene moiety to the alkyne can occur in a *5-exo-dig* or *6-endo-dig* fashion giving cyclopropyl carbenoid intermediate **3** and **4** respectively. Intermediate **3** can give product **5** through sequential formal retro-[2+1] cycloaddition/carbene dimerization steps

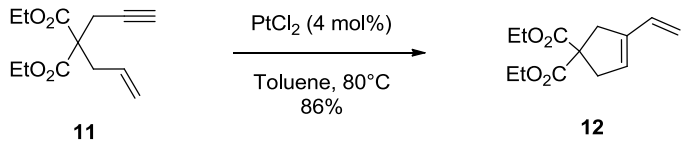
[5] Michelet, Comprehensive organic synthesis II, 2014, **5**, 1483.

(Pathway **A**, Scheme 3). Derivative **6** is obtained by double-cleavage process which involves the break of the bond between $R^3$ and the carbenic carbon *a* and that between $R^2$ and carbon *b* (Pathway **B**). The cyclopropyl metal-carbene **4** from *6-endo-dig* cyclization can afford bicyclic adduct **7** (Pathway **C**) and 1,3-diene derivative **8** (Pathway **D**). The first product is obtained by a protodemetallation step. On the other hand, **8** is delivered through a process involving a 1,3-alkyl migration, to give intermediate **9**, followed by a 1,2-alkyl migration to form species **10** and a final demetallation step (Scheme 4).




**Scheme 4** Fomation of product **8**

In 1996 Murai and co-workers reported the first rearrangement of 1,6-enyne **11**, catalysed by $PtCl_2$ leading to 1,3-diene **12** (Scheme 5).[6] Different products, corresponded to derivative of type **5** (pathway **A,** Scheme 3), were obtained in good yield reacting 1,6-enynes in the presence of 4 mol% $PtCl_2$ in toluene at 80°C.



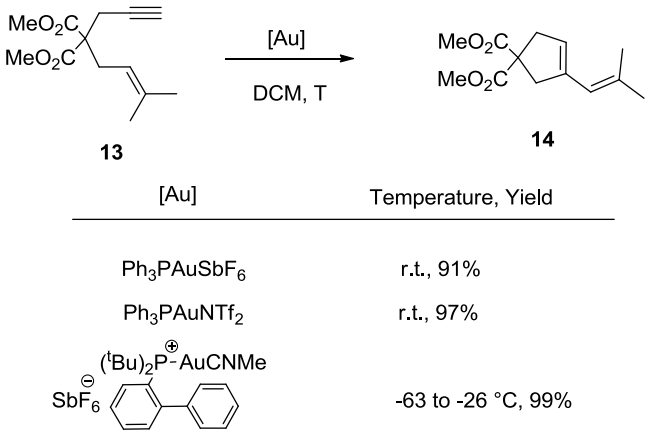

**Scheme 5** Cycloisomerization of 1,6-enynes with $PtCl_2$

The reactivity of gold(I) complexes in the cycloisomerizations of enynes **13** is also noteworthy. The formation of *5-exo-dig* product **14** was studied in

[6] N. Chatani, N. Furukawa, H. Sakurai and S. Murai, *Organometallics*, 1996, **15**, 901.

different conditions (Scheme 6). Echavarren and co workers[7] carried out this reaction employing the cationic species [$PPh_3Au^+$], formed *in situ* by the addition of $AuClPPh_3$ and $AgSbF_6$ (Y = 91%).

The replacement of $AuClPPh_3$ with gold(I) complexes such as [$Ph_3PAuNTf_2$] allowed the elimination of $AgSbF_6$, which is difficult to handle because highly hygroscopic.[8] Substituting $PPh_3$ with a bulkier ligand increased significantly the catalyst activity.[9] In this case, the cyclization occurred quantitatively even at a temperature as low as -63 °C. Regarding the mechanism, the formation of **14** occurred through pathway **A** illustrated in Scheme 3.

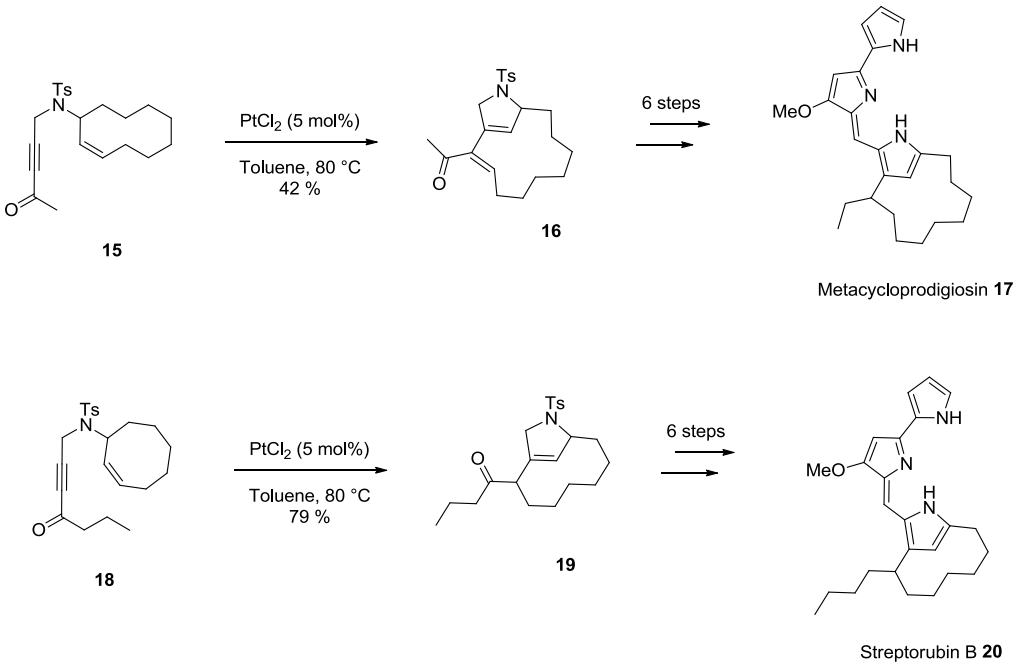



**Scheme 6** Cycloisomerization of 1,6-enynes with gold complexes

Enynes cycloisomerizations allowed access to several natural products. In 1998 Furstner's group employed a platinum-catalysed enyne cycloisomerization for the construction of the bicyclic core of

[7] C. Nieto-Oberhuber, M. P. Muñoz, E. Buñuel, C. Nevado, D. J. Càrdenas and A. M. Echavarren *Angew. Chem. Int. Ed*. 2004, **43**, 2402.
[8] N. Mézailles, L. Ricard and F. Gagosz, *Org. Lett.* 2005, **7**, 4133.
[9] C. Nieto-Oberhuber, S. Lopez, E. Jiménez-Nùñez and A.M. Echavarren, *Chem.–Eur.J.* 2006, **11**, 5916.

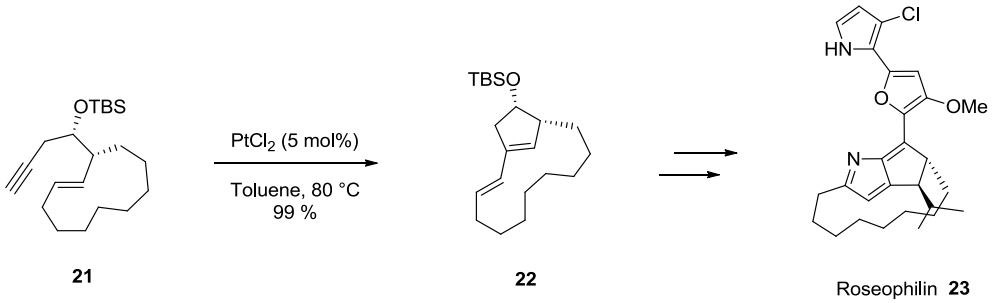
metacycloprodigiosin and streptorubin B (Scheme 7).[10] In both cases such transformation allowed the expansion of the 1,6-enyne (**15** and **18**) by two carbon atoms and the subsequent formation of a bridged bicyclic species (**16** and **19**). The formation of such key intermediates occurs via *5-exo* cyclization. Then, **16** and **19** were converted into the final products (**17** and **20**) by six additional reaction steps.




**Scheme 7** Platinum-catalysed cycloisomerization of enynes for the synthesis of Metacycloprodigiosin and Steptorubin B

In 2000 Trost and Doherty reported the synthesis of roseophilin (Scheme 8). In this case a cycloisomerization process allowed the isolation of bicyclic diene **22** via *5-exo* cyclization starting from enyne **21**.[11] The natural product was then isolated after several reaction steps.

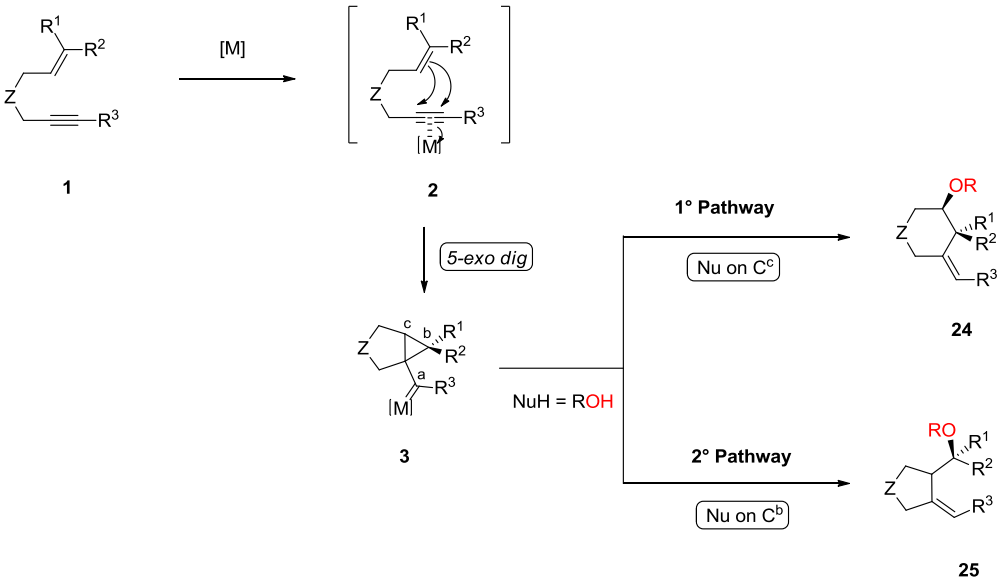
[10] A. Fürstner, H. Szillat, B. Gabor and R. Mynott, *J. Am. Chem. Soc.,* 1998, **120**, 8305.
[11] B.M Trost and G.A. Doherty, *J.Am.Chem.Soc.,* 2000, **122**, 3801.




**Scheme 8** Platinum-catalysed cycloisomerization of enynes for the synthesis of Roseophilin

## 1.3 Cycloisomerization of 1,n-enynes in the presence of oxygen nucleophiles

Enyne cycloisomerizations can also occur in the presence of oxygen nucleophile as shown in Scheme 9 for 1,6 enynes.




**Scheme 9** General mechanism for cycloisomerization of enynes in the presence of an oxygen nucleophile

Using oxygen nucleophiles two main products can be obtained (**24** and **25**, Scheme 9) which derived from *5-exo-dig* **3** intermediate. Six-membered ring **24** is afforded by addition of ROH on carbon *c* of the cyclopropanyl moiety, whereas **25** is yielded through the attack of the oxygen nucleophile on carbon *b*. Palladium(II)[12] and gold(I)[13]-based catalysts, in the presence of water and alcohols respectively, have led to the formation of cylic derivatives of type **25**

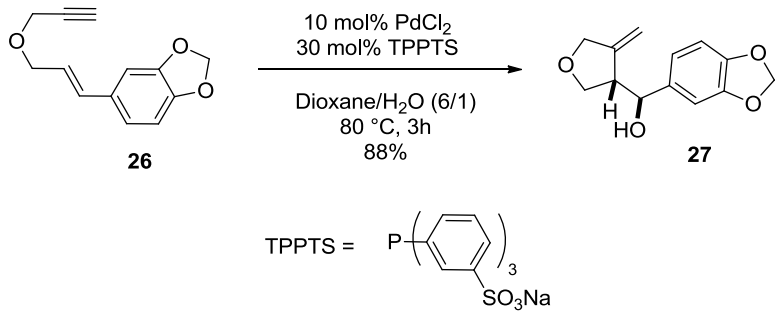
[12] (a) J.C Galland, M. Savignac and J.P. Genêt, *Tetrahedron Lett.*, 1997, **38**, 8695.(b) J.C Galland, S. Diaz, M. Savignac and J.P. Genêt, *Tetrahedron,* 2001, **57**, 5137. (c) L. Charruault, V. Michelet and J.P. Genêt, *Tetrahedron Lett.*, 2002, **43**, 4757

[13] C. Nieto-Oberhuber, M.P. Muñoz, S. López, E. Jiménez-Nùñez, C. Nevado, E. Herrero-Gómez, M. Raducan and A.M Echavarren *Chem.–Eur.J.*, 2006, **12**, 1677.

in high yield. On the other hand, a gold(III) complex[14] with methanol as nucleophile selectively delivered compounds of type **24**. Platinum chloride is less efficient compared the other metal-based complexes affording a mixture of both types of product (**24** and **25**) in the presence of methanol. [15]

### 1.3.1 Oxygen nucleophiles: Hydroxy- and alkoxycyclization reactions with 1,6-enynes

Cycloisomerization of enynes in the presence of oxygen compounds as nucleophiles was reported for the first time by Gênet and co-workers (Scheme 10).[12] The reaction was carried out dissolving substrate **26** in 1,4 dioxane/water and adding $PdCl_2$ and TPPTS (a water-soluble phosphine ligand). A diasteroselective process delivered product **27**. Starting from unsaturated substrate **26**, the final product **27** has the hydroxyl group bound to the benzylic position. This reaction occurs following the 2nd pathway displayed in Scheme 9.

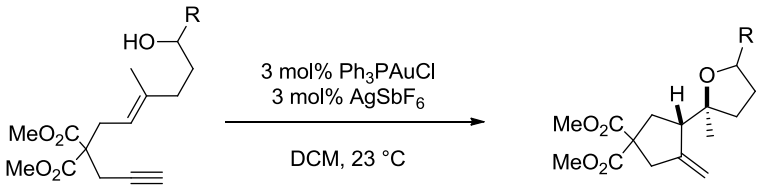



**Scheme 10** Hydroxycyclization of enynes

In addition, investigations on intramolecular cycloisomerizations of 1,6-enynes bearing an hydroxyl group on the alkene chain were carried out.[13] Particularly, such substrates were transformed into the corresponding *5-exo-dig* cyclic

[14]E. Genin, L. Leseurre, P.Y. Toullec, J.-P. Genêt and V. Michelet, 2007, *Synlett*, **11**, 1780.
[15] M. Méndez, M.P Muñoz, C. Nevado, D.J. Cárdenas and A.M.Echavarren, *J.Am.Chem.Soc.*, 2001, **123**, 10511.

products using $Ph_3PAuCl/AgSbF_6$ as catalytic system (Scheme 11). Starting from **28** the intramolecular attack of the hydroxy group on the cyclopropyl gold carbene species led to the formation of cyclic derivatives **29** following the second reaction pathway of Scheme 9.

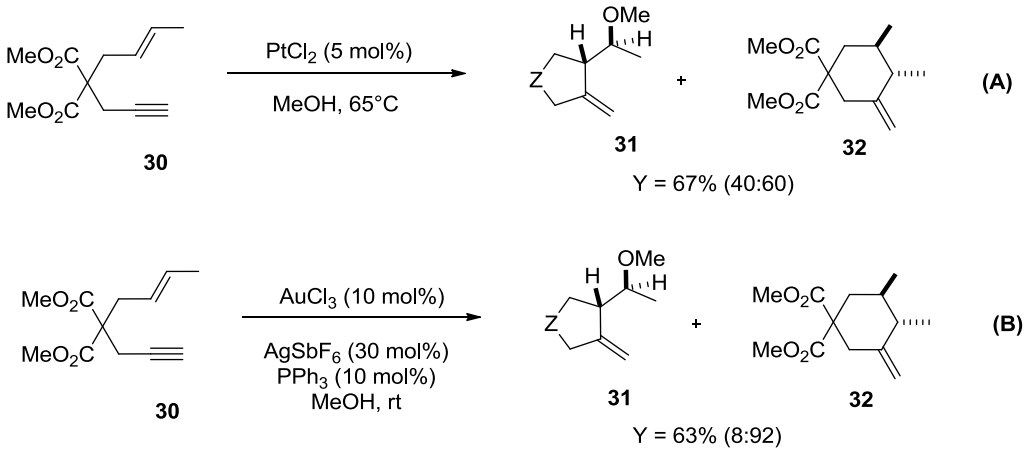



**28** **29**

| R | Yield |
|---|---|
| H | 76% |
| $^t$Bu | 85% (1:1) |

**Scheme 11** a) Intramolecular cycloisomerization reaction of 1,6-enynols bearing a hydroxyl group as nucleophile: a mixture of diateroisomers (1:1) was obtained when R = Bu$^t$.

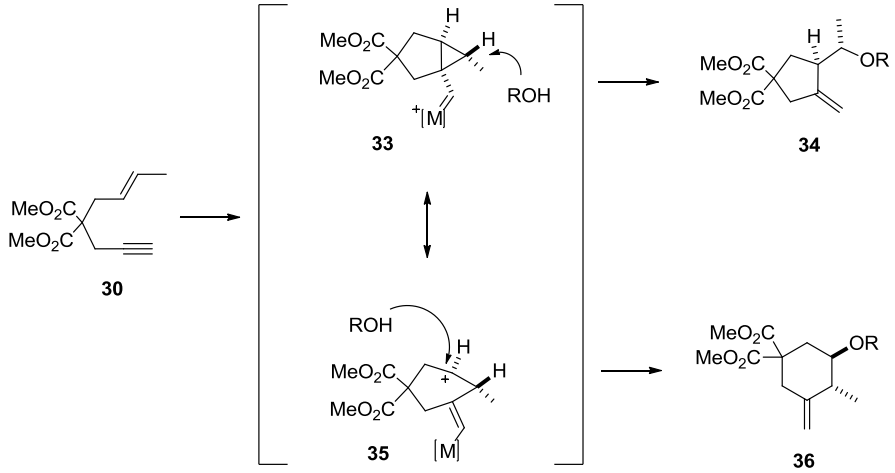
In some cases the formation of product **24** and **25** (Scheme 9) have been shown to be competitive. Indeed, reacting 1,6-enyne **30** in the presence of $PtCl_2$ and methanol, which acts as nucleophile, afforded a mixture of products **31** and **32** (5- and 6- membered ring respectively) in a ratio 40:60 (Scheme 12, reaction **A**).[15] Interestingly, repeating the same reaction with a gold(III)-based complex (Scheme 12, reaction **B**) significantly favoured the formation of the 6-membered ring **32**over that of **31** (ratio 8:92). [14]




**Scheme 12** Alkoxycyclization of 1,6-enyne **30** with $PtCl_2$ (reaction **A**) and $AuCl_3$ (reaction **B**)

From DFT calculations emerged the influence of the catalyst electrophilicity on the structural parameters of the cyclopropyl carbene species (Scheme 13).[16] Using $PtCl_2$, the species obtained by nucleophilic attack of the alkene on the activated alkyne can be described as a major cyclopropyl carbene of type **33**. On the other hand, the intermediate afforded from the reaction of the enyne with a gold-based catalyst would be best depicted as a cationic vinylaurate intermediate **35**. Therefore the attack of the oxygen nucleophile would be favored on intermediate of type **35**, leading to the 6-membered cyclic derivative.

[16] (a) C. Nieto-Oberhuber, M.P. Muñoz, C. Nevado, D.J Cárdenas and A.M Echavarren, *Angew.Chem.Int.Ed.*, 2004, **43**, 2402. (b) C. Nieto-Oberhuber, S. López, E. Jimenez-Nùñez and A.M Echavarren, Chem. Eur. J., 2006, **12**, 5916.

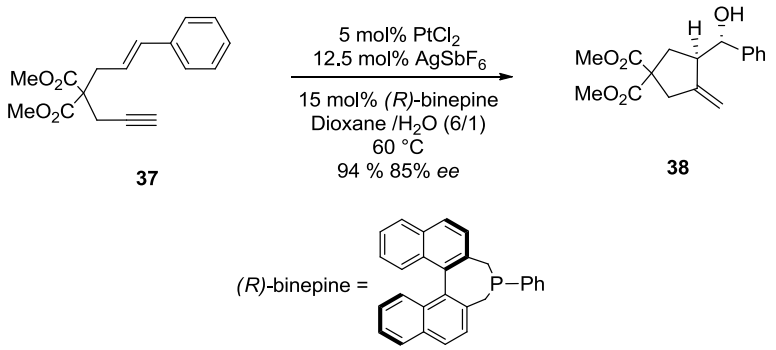



**Scheme 13** Carbenic and carbocationic intermediates in gold and platinum catalysis[17]

[17] E. Genin, L. Leseurre, P. Yves Toullec, J.P. Genêt,V. Michelet, *Synlett*, 2007, **11**, 1780.

### 1.3.2 Asymmetric catalysis

The first enantioselective enyne alkoxycyclization was reported by the group of Genêt (Scheme 14).[18] The reaction was performed using $PtCl_2$ with $AgSbF_6$ and an atropisomeric monophosphine ligand (*(R)*-binepine).



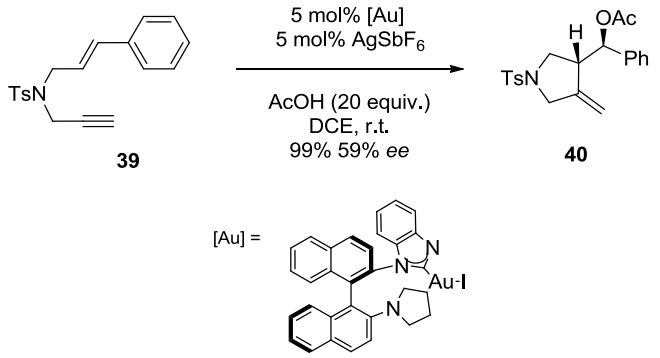

**Scheme 14** Enantioselective enyne alkoxycyclization

Starting from substrate **37** the *5-exo* product **38** was obtained in 94% yield and 85% *ee.* Similar catalytic systems with other ligands such as *(S)*-Tol-BINAP or *(R)*-BINAP were studied but no improvement emerged.[19] Also chiral NHC ligands were employed for the asymmetric cycloisomerization of 1,6-enynes (Scheme 15).[20] In this case, in the presence of acetic acid, substrate **39** was quantitatively transformed to cyclopentane derivative **40** with 59% *ee*.

[18] (a) L. Charruault, V. Michelet, R. Taras, S. Gladiali and J.P. Genêt, *Chem.Commun.,* 2004, 850. (b) V. Michelet, L. Charruault, S. Gladiali and J.P Genêt, *Pure Appl. Chem.*, 2006, **78**, 397.

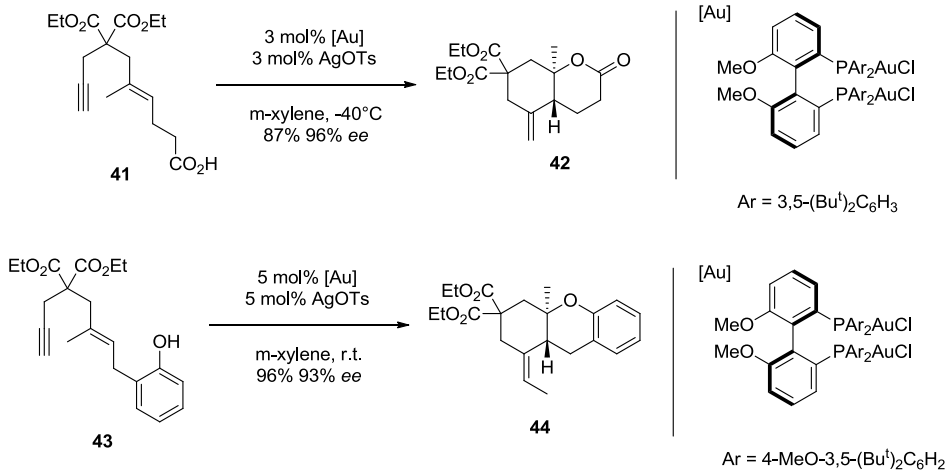
[19] M. P. Muñoz, J. Adrio, C. Carretero and A.M Echavarren, *Organometallics*, 2005, **24**, 1293.

[20] (a) W. Wang, J. Yang, F. Wang and M. Shi, *Organometallics*, 2011, **30**, 3859 (b) J .Yang, R. Zhang, W. Wang, Z. Zhang and M. Shi, *Tetrahedron: Asymmetry*, 2011, **22**, 2029.




**Scheme 15** Chiral NHC–Au(I) complex catalyzed asymmetric cycloisomerization of 1,6-enynes

Noteworthy, Toste and co-workers reported the enantioselective variant of phenoxy- and carboxycyclization.[21] Several chiral ligands were employed for the optimization of the reaction conditions. Di-tert-butyl- and di-tert-butyl-methoxy-MeOBIPHEP allowed to achieve the best results (Scheme 16). Through this method different polycyclic compounds were stereoselectively isolated.




**Scheme 16** Enantioselective variant of phenoxy- and carboxycyclization

[21] S.G. Sethofer, T. Meyer and F.D. Toste, *J.Am.Chem.Soc.,* 2010, **132**, 8276.

*Chapter 2*

# Complementary reactivity of 1,6-enynes with all-metal aromatic complexes and carboxylic acids

## 2.1 Introduction

### 2.1.1 Catalysis with all-metal aromatic clusters

All-metal aromatic clusters represent a fascinating class of organometallic compounds featured by delocalized metal–metal bonds, similarly to their classical carbon based counterparts.[22] Recently, different compounds of this type have been reported in literature.[23] In this regard, our group developed a synthetic route which easily allowed the isolation of a family of bench-stable $Pd_3^+$ complexes,[24] demonstrating their utility as competent catalysts for the selective reduction of internal alkynes and for the polycyclization of terminal 1,6-enynes and internal dienynes (Figure 2).[25,26]

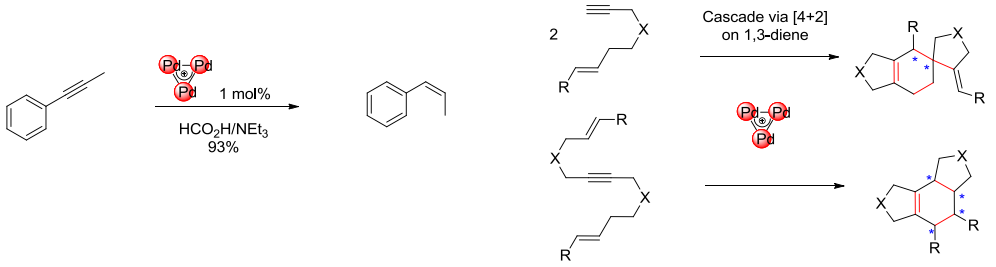



**Figure 2** Reactivity of triangular tripalladium clusters: (a) Selective reduction of internal alkynes. (b) Polycyclization of terminal 1,6-enynes and internal dienynes

[22] (a) A.I. Boldyrev and L.-S Wang, *Chem. Rev.*, 2005, **105**, 3716. (b) J. M. Mercero, A. I. Boldyrev, G. Merino and J. M. Ugalde, *Chem. Soc. Rev.*, 2015, **44**, 6519. (c) I. Fernández, G. Frenking and G. Merino, *Chem. Soc. Rev.*, 2015, **44**, 6452.

[23] (a) F. Fu, J. Xiang, H. Cheng, L. Cheng, H. Chong, S. Wang, P. Li, S. Wei, M.Zhu and Y. Li, *ACS Catal.*, 2017, **7**, 1860. (b) Y. Yun, H. Sheng, J.Yu, L. Bao, Y. Du, F. Xu, H. Yu, P. Li and M. Zhu, *Adv. Synth.Cat.*, 2018, **360**, 4731 (c) C. J. Diehl,T. Scattolin,U. Englert and F. Schoenebeck, *Angew.Chem.Int.Ed.*, 2019, **58**, 211. (d) N. W. J. Scott, M. J. Ford, C. Schotes, R. R. Parker, A. C. Whitwood and I. J. S. Fairlamb, *Chem. Sci.*, 2019, **10**, 7898.

[24] Y. Wang, P.A Deyris, T. Caneque, F. Blanchard, Y. Li, F. Bigi, R. Maggi, S. Blanchard, G. Maestri and M. Malacria, *Chem. Eur. J.*, 2015, **21**, 12271.

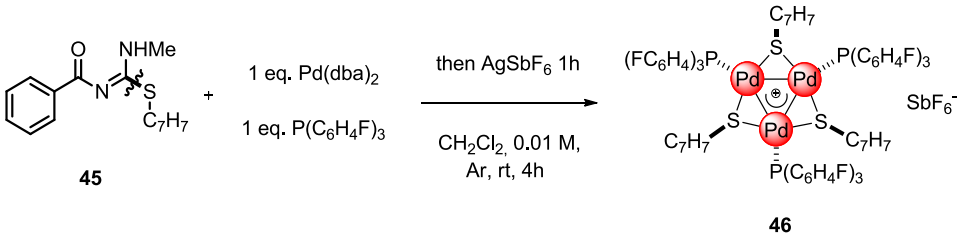
[25] (a) A. Monfredini, V. Santacroce, P.A. Deyris, R. Maggi, F. Bigi, G. Maestri, M. Malacria, *Dalton Trans.*, 2016, **45**, 15786. (b) A. Monfredini, V. Santacroce, L. Marchiò, R. Maggi, F. Bigi, G. Maestri and M. Malacria, *ACS Sustainable Chem.Eng.*, 2017, **5**, 8205.

[26] M. Lanzi, T. Caneque, L. Marchiò, R. Maggi, F. Bigi, M. Malacria and G. Maestri, *ACS Catalysis*, 2018, **8**, 144.

### 2.1.2 Synthesis of all-metal aromatic clusters

#### 2.1.2.1 First generation synthesis of $Pd_3^+$clusters

The first $Pt^{3+}$ all-metal aromatic cluster was serendipitously isolated by our group when isothiourea **45** was added to $[Pd(dba)_2]$ and tris(4-fluorophenyl) phosphine in degassed DCM (Scheme 17).[27]




**Scheme 17** First generation synthesis of $Pd^{3+}$ clusters

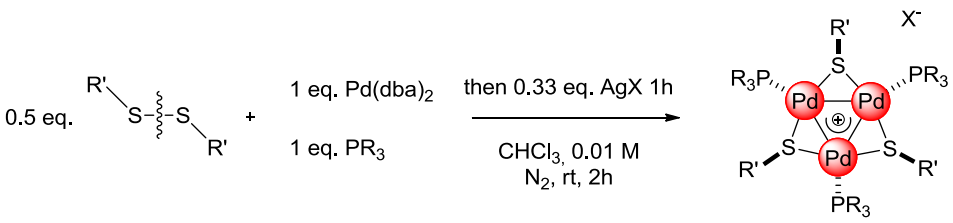
The powder obtained was analysed by mass spectrometry. The resulting mass peaks corresponded to the cation $[(SC_7H_7P(C_6H_4F)_3Pd)_3]^+$, which showed the pattern of the thiol fragment but not that of the rest of the isothiourea. The addition of 1 equivalent of $AgSbF_6$, upon the full conversion of the thiourea, led us to isolate the tripalladium cluster (Scheme 17) which has been subsequently crystallized. The crystal structure, obtained by X-ray analyses, revealed that each phosphinic ligand coordinates a palladium atom, whereas thiolates occupy the bridging position between metal centres. Interestingly, such crystals were found to be air- and moisture stable. Using this methodology several tripalladium complexes, with different steric and electronic proprieties, were isolated changing the organic fragment on ligands. However, poor reaction yields were obtained with alkyl substituents and the scope was restricted to aryl isothioureas and aryl phosphines. Moreover, since the two-

[27] S. Blanchard, L. Fensterbank, G. Gontard, E. Lacôte, G. Maestri, M. Malacria, *Angew. Chem Int. Ed*., **2014**, *53*, 1987.

steps synthesis of isothioureas[28] was not convenient, our research group decided to study a simpler procedure to obtain $Pd^{3+}$ clusters.

### 2.1.2.2 Second generation synthesis of $Pd_3^+$clusters

A novel synthetic method for the preparation of $Pd_3^+$ clusters was presented in 2015.[24] Through this new procedure isothioureas were substituted by disulfides, which were reacted in the presence $Pd(dba)_2$ and the desired phosphine (Scheme 18).




**Scheme 18** Second generation synthesis of $Pd^{3+}$ clusters

The reaction was carried out in chloroform and after two hours of stirring $AgSbF_6$ was added. Besides the desired cluster, no relevant byproduct was detected at the end of the reaction. Purification of the crude mixture was performed by filtration through celite. Afterwards, the solvent was evaporated under vacuum and the solid obtained washed three times with a chloroform/hexane solution (1:30 v/v) for the removal of dibenzylideneacetone (dba).

This synthetic method was found to be much more effective compared to the previous one. Firstly, it did not require the time consuming preparation of isothioureas thanks to the use commercial reagents. Moreover, it allowed to expand the reaction scope employing alkyl fragments (both on thiolates and

[28] G. Maestri, M.-H. Larraufie, C. Ollivier, M. Malacria, L. Fensterbank and E. Lacúte, *Org. Lett.*, 2012, **14**, 5538

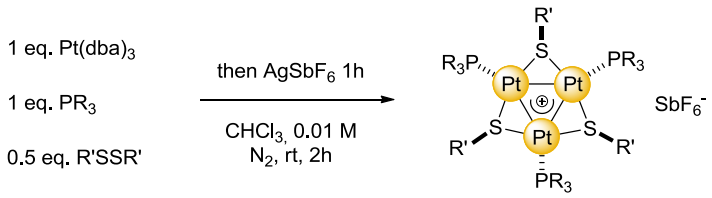
phosphines) which were well tolerated. Other non-coordinating counterions such as triflate or tetrafluoroborate could be also introduced, simply varying the silver salt. $Pd^{3+}$ structures obtained with this second generation synthetic method are showed in Table 1.

| Entry | Complex | R' | R | X | Yield (%) | Yield 1st gen. synth. (%) |
|---|---|---|---|---|---|---|
| **1** | 46 | 4-Me-$C_6H_4$ | 4-F-$C_6H_4$ | $SbF_6$ | 89 | 93 |
| **2** | 47 | 4-Cl-$C_6H_4$ | 4-Me-$C_6H_4$ | $SbF_6$ | 97 | 91 |
| **3** | 48 | Ph | Ph | $SbF_6$ | 99 | 88 |
| **4** | 49 | Me | Ph | $SbF_6$ | 97 | |
| **5** | 50 | 4-Cl-$C_6H_4$ | 4-F-$C_6H_4$ | $SbF_6$ | 90 | |
| **6** | 51 | 4-Cl-$C_6H_4$ | 4-Me-$C_6H_4$ | $CF_3COO$ | 89 | |
| **7** | 52 | 4-Cl-$C_6H_4$ | 4-MeO-$C_6H_4$ | $SbF_6$ | 80 | |
| **8** | 53 | Me | 4-F-$C_6H_4$ | $SbF_6$ | 85 | |
| **9** | 54 | Me | 4-Me-$C_6H_4$ | $SbF_6$ | 94 | |
| **10** | 55 | 4-Me-$C_6H_4$ | Et | $SbF_6$ | 98 | |
| **11** | 56 | 4-Cl-$C_6H_4$ | Et | $SbF_6$ | 97 | |
| **12** | 57 | Me | Ph | $BF_4$ | 91 | |

**Table 1** Tripalladium clusters obtained with the second generation synthetic method

#### 2.1.2.2.1 Synthesis of $Pt_3^+$ clusters

In order to synthesize $Pt_3^+$ clusters, the second generation synthetic method was repeated replacing the metal precursor $Pd(dba)_2$ with $Pt(dba)_3$. In this case the reaction scope was limited to two examples and the yields obtained were lower compared to those of palladium clusters (Table 2).




| Entry | Complex | R' | R | Yield (%) |
|---|---|---|---|---|
| **1** | 58 | 4-Cl-$C_6H_4$ | 4-F-$C_6H_4$ | 60 |
| **2** | 59 | Me | 4-Me-$C_6H_4$ | 40 |

**Table 2** Synthesis of triplatinum complexes

Such results were probably due to the requirement of an additional purification step. Indeed, after washings with chloroform/hexane, for the removal of dba, a flash column chromatography was performed in order to remove the remaining byproducts and deliver the pure cluster. Moreover, the reaction could have also been hampered by the higher difficulty of $Pt(dba)_3$ to lose three ligands instead of two as in the case of $Pd(dba)_2$. Interestingly, when palladium and platinum precursors were mixed in 2:1 and 1:2 ratio, hetereonuclear clusters $[Pd_2Pt]^+$ and $[PdPt_2]^+$ were afforded respectively.

#### 2.1.2.2.2 Structural features of $Pd_3^+$and $Pt_3^+$ clusters

The atomic radii of Nickel, Palladium and Platinum are 1.25 Å, 1.37 Å and 1.39 Å respectively. Since these values almost overlap for Palladium and Platinum, because of the lanthanide contraction effect, and aromatic systems are featured by equal bond lengths, the X-ray structures of $Pt_3^+$ and $Pd_3^+$ are similar. Indeed, they show a perfectly equilateral core, with a single metal–metal distance and three equal 60.0° angles and display almost identical M-M, M-S and M-P distances, with differences below 0.03 Å at the solid state (Figure 3). They also have 44 core valence electrons and each metal atom has a formal oxidation state of +4/3.

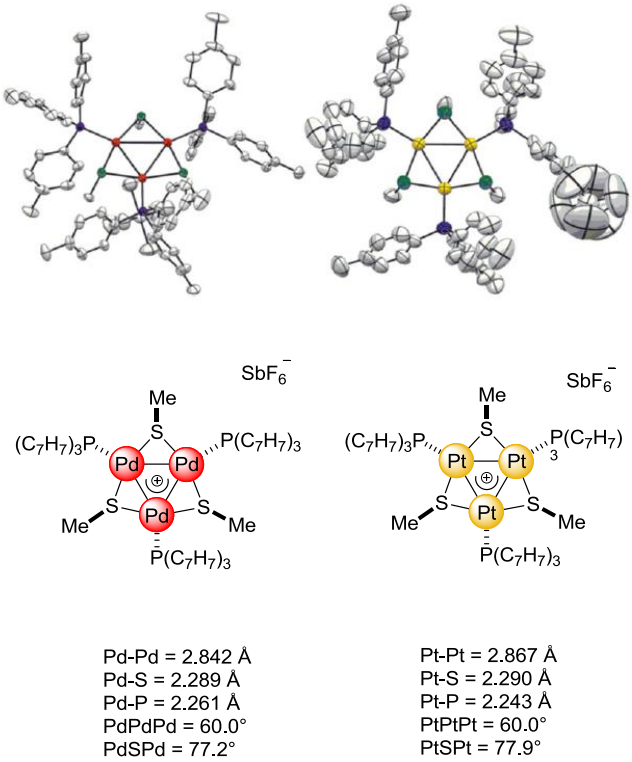



**Figure 3** Comparison of the main structural features of **54** and **59** at the solid state

These data led us to speculate that trinuclear platinum complexes could have held a good potential as catalysts. Hence, to further explore the applications of this family of all-metal aromatic clusters we decided to focus our attention on the reactivity of $Pt_3^{+}$ complexes.

## 2.2 Results and discussion

In the last few years, mononuclear platinum salts have found wide application in cycloisomerization reactions. Many important examples have been reported in the literature by Echavarren,[29] Fürstner,[30] and others[31]. At the same time, many platinum *triangulo*-clusters of general formula $[Pt_3(\mu\text{–}X)_3L_3]$ have been prepared and characterized[32], with more than 100 X-ray structures deposited in the CCDC[33]. Surprisingly, for these complexes, no catalytic reactivity have been reported. For this reasons, we supposed it could have been interesting to test our $Pt^{3+}$ triangles in the selective formation of C–C bonds from unsaturated

[29] (a) C. Nevado and A.M. Echavarren, *Chem.Eur.J.,* 2005, **11**, 3155. (b) C. Nevado, C. Ferrer and A.M. Echavarren, *Org. Lett.,* 2004, **6**,3191.

[30] (a) A. Fürstner, P.W. Davies and T. Gress, *J. Am. Chem. Soc.,* 2005, **127**, 8244. (b) V. Mamane, T.Gress, H. Krause and A. Fürstner, *J. Am. Chem. Soc.,* 2004, **126**, 8654. (c) A. Fürstner, F. Stelzer and H. Szillat, *J. Am. Chem. Soc,* 2001, **123**, 11863. (d) A. Fürstner, H. Szillat and F.Stelzer, *J. Am. Chem. Soc.,* 2000, **122**, 6785.

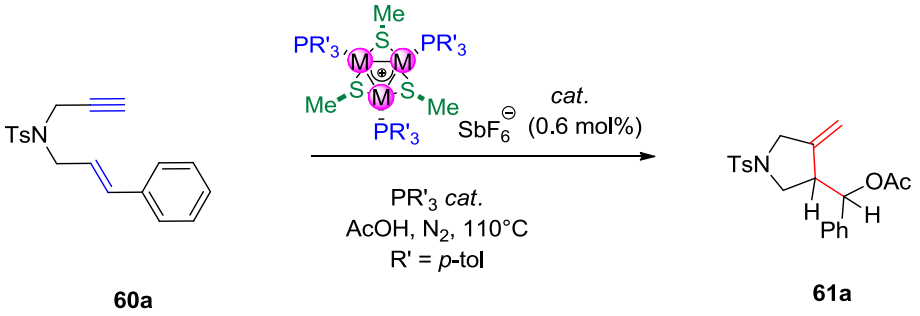
[31] For selected reviews, see: (a) A. Fürstner, *Chem. Soc. Rev.* 2009, **38**, 3208. (b) A. Fürstner and P.W. Davies, *Angew. Chem. Int. Ed.,* 2007, **46**, 3410. (c) C. Blaszykowski, Y. Harrak, C. Brancour, K.Nakama, A.L. Dhimane, L. Fensterbank and M. Malacria, *Synthesis,* 2007, 2037. (d) L. Zhang, J. Sun and S.A Kozmin, *Adv. Synth.Catal.,* 2006, **348**, 2271. For a seminal contribution, see: (e) N. Chatani, H.Inoue, T. Ikeda, S. Murai, *J. Org. Chem.,* 2000, **65**, 4913. (f) R. Zriba, V. Gandon, C. Aubert, L. Fensterbank and M. Malacria, *Chem. Eur. J.,* 2008, **14**, 1482. (g) F. Marion, J. Coulomb, C. Courillon, L. Fensterbank and M. Malacria, *Org. Lett.,* 2004, **6**, 1509. (h) Y. Harrak, C. Blaszykowski, M. Bernard, K. Cariou, E. Mainetti, V. Mouriès, A.L. Dhimane, L. Fensterbank, M. Malacria, *J. Am. Chem. Soc.,* 2004, **126**, 8656. (i) E. Mainetti, V. Mouriès, L. Fensterbank, M. Malacria and J. Marco-Contelles, *Angew. Chem. Int.Ed.,* 2002, **41**, 2132. For recent examples, see: (j) H. Jullien, D. Brissy, R. Sylvain,P. Retailleau, J.V. Naubron, S. Gladiali and A. Marinetti, *Adv.Synth. Catal.,* 2011, **353**, 1109. (k) Z. Ni, L. Giordano and A. Tenaglia, *Chem. Eur. J.,* 2014, **20**, 11703. (l) A. Pradal, S. Gladiali, V. Michelet and P.Y. Toullec, *Chem. Eur. J.* 2014, **20**, 7128.

[32] R. Ros, A. Tassan,G. Laurenczy and R. Roulet, *Inorg. Chim. Act.,* 2000, **303**, 94.

[33] T. Funaioli, P. Leoni, L. Marchetti, A. Albinati, S. Rizzato, F. Fabrizi de Biani, A. Ienco, G. Manca and C. Mealli, *Inorg. Chem*., 2013, **52**, 4635.

substrates.[34]

We started by synthetizing triplatinum complex **59** (procedure in paragraph 2.4 pag. 62) and then test it in the presence of 1,6-enyne *(E)*-**60a** and 1 equivalent of acetic acid. The reaction was carried out at 110 °C under nitrogen atmosphere and using 0.3 mol% of the catalyst. Firstly, the reaction system was investigated by changing different solvents. No reaction was observed using 1,4-dioxane and 1,2-dichloroethane (Table 3, entries 1-2), whereas toluene allowed the isolation of pyrrolidine derivative **61a** (entry 3). A test carried out without the acidic additive, showed the importance of the former (entry 4). Afterwards we decided to use AcOH as solvent. In this case **61a** was obtained in 42% yield (entry 5).




**60a** **61a**

M = Pt , R' = p-Tol (*cat.* **59**) **61a**: 71%

M = Pd , R' = Ph (*cat.* **49**) **61a**: 16%

| Entry | Complex 59 (mol%) | Solvent | PR'$_3$ (mol%) | Time (h) | Yield (%)[b] |
|---|---|---|---|---|---|
| **1** | 0.3 | 1,4 Dioxane | -- | 16 | N.R. |
| **2** | 0.3 | 1,2-DCE | -- | 16 | N.R |
| **3** | 0.3 | Toluene | -- | 16 | 29 |
| **4**[c] | 0.3 | Toluene | -- | 16 | N.R |

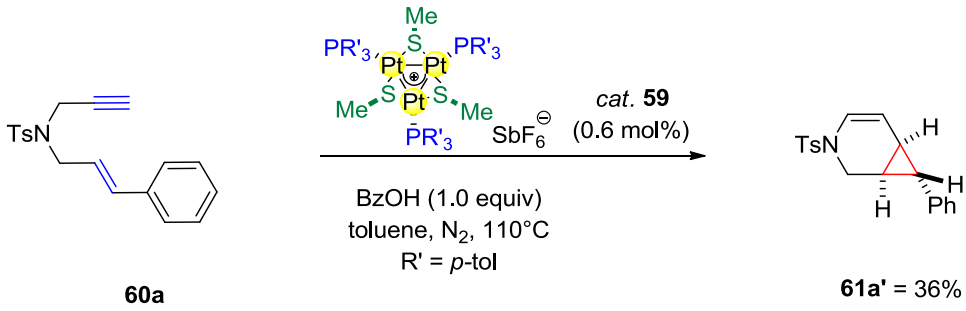
[34] C. Cecchini, M. Lanzi, G. Cera, M. Malacria and G. Maestri, *Synthesis,* 2019, **51**, 1216.

| | | | | | |
|---|---|---|---|---|---|
| **5**[d] | 0.3 | AcOH | -- | 16 | 42 |
| **6** | 0.3 | AcOH | 0.9 | 16 | 53 |
| **7** | 0.3 | AcOH | 1.8 | 24 | 57 |
| **8** | 0.3 | AcOH | 2.7 | 44 | 72 |
| **9** | 0.6 | AcOH | 1.8 | 16 | 71 |
| **10**[e] | 0.6 | AcOH | 1.8 | 16 | 16 |
| **11**[f] | -- | Toluene | -- | 16 | -- |

**Table 3** Optimization of reaction conditions. [a]Reaction conditions: **60a** (0.15 mmol) **59** (0.6 mol%), AcOH (0.15 mmol), solvent (0.3 M), isolated yields. [b]N. R.: No reaction. [c]Reaction without AcOH. [d]Conditions: **60a** (0.15 mmol)**, 59** (0.3 mol%), AcOH (500 µL, 0.3 M). [e]Reaction with complex **49** (0.6 mol%). [f]Reaction without catalyst **59**, using p-toluensolfonic acid (1 equiv) and **60a** (1 equiv.).

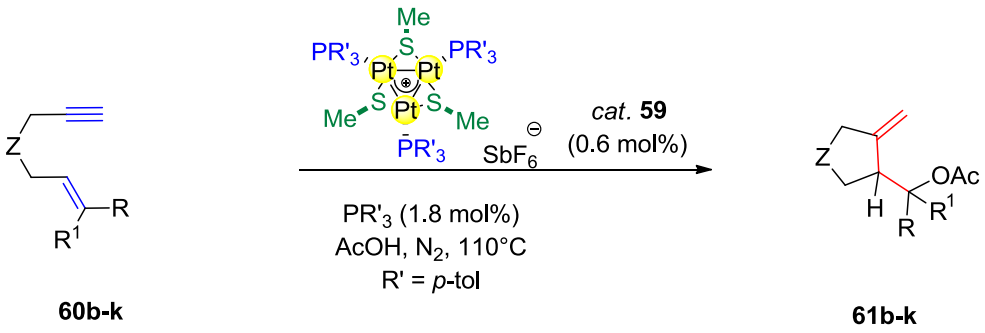
A strong improvement was achieved when the system was studied in the presence of different co-catalytic amounts of the phosphine ligand which ensures a more stabilizing environment. The increase of P(p-tolyl)$_3$ in the reaction media, with a constant catalyst loading (0,3 mol%), resulted in higher yields (entry 6-8). Nonetheless longer reaction times were required for the complete conversion of the substrate. Comparable efficacy was reached slightly increasing the catalyst loading from 0.3 mol% to 0.6 mol% (entry 9). In this case, the reaction proceeded for 16 hours with a yield of 71%. Lastly, the palladium analogue **49** was tested (entry 10). The latter was found to be less competent compared to complex **59**, affording **61a** in a 16% yield. In addition a test without catalyst **59** was performed (entry 11). In this case the reaction was carried out in Toluene with substrate **60a** (1 equiv.) in the presence of p-toluensolfonic acid (1 equiv). The latter was used to create an acidic environment. No conversion of the starting material was observed after 16h.

Subsequently, we decided to carry out the reaction with **59** in toluene, using one equivalent of benzoic acid as acidic additive. (Scheme 19).



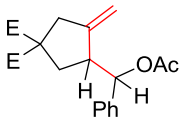

**Scheme 19** Acid-dependent cycloisomerizations of 1,6-enynes with trinuclear platinum complex

This test led us to isolate the bicyclic product **61a'** as major product. Thus, the chemoselectivity of the catalyst is highly influenced by the nature of the carboxylic acid additive. Different substituted *(E)*-1,6-enynes of type **60** were synthesized in order to investigate the scope of this catalytic synthetic methodology (Scheme 20).

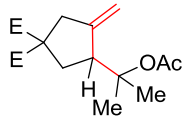



**60b-k**

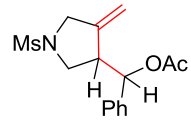
**61b-k**



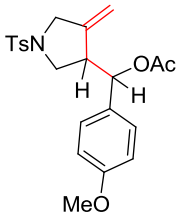

**E** = $CO_2Me$ **61b** = 70%



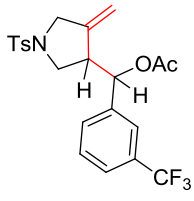

**E** = $CO_2Me$ **61c** = 56%



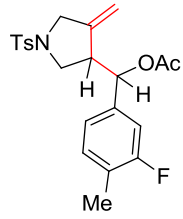

**61d**: 40%



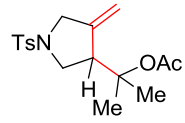

**61e**: 44% (*d.r.* 1:1)



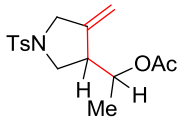

**61f**: 36%



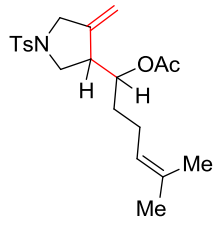

**61g**: 41%



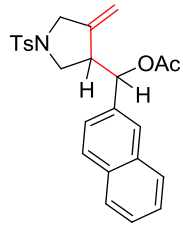

**61h**: 70%




**61i**: 59%




**61j**: 43%




**61k**: 43%

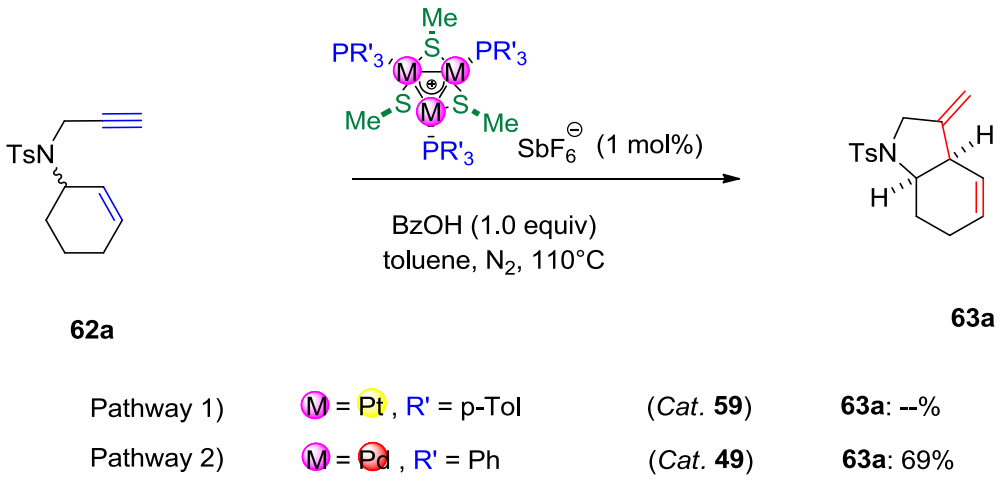
**Scheme 20** Scope of the platinum-catalysed rection with *(E)*-1,6-enynes

Initially we studied different tethering groups. Dialkyl malonyl groups were found suitable for the cycloisomerization providing the corresponding carbocyclic compound **61b** and **61c** in good yields, 70% and 56% respectively. The sulphonamide was tolerated as tethering group and substrate **61d** was converted in moderate yield (40%).

Next, we studied the reactivity of **60a** with a substituted phenyl ring. Different functional groups were investigated such as ether, fluoro and trifluoro units and their corresponding pyrrolidines were obtained in moderate yield (Scheme 20, **61e-g**).

Afterwards, we tested different starting materials by varying the alkene moiety of compound **60a**. In particular, the phenyl ring of **60a** was replaced first with two methyl groups (**60h**), then with one methyl group (**60i**) and finally with a geranyl moiety (**60j**). For these substrates, the corresponding products were obtained in synthetically useful yields (**61h-j**). Interestingly, the phenyl ring could be also replaced by a naphthalene ring (**60k**). In this case, the cycloisomerization product was obtained in 43% yield (**61k**). Derivatives **61a–d** and **61f–k** were afforded with high diastereocontrol (*dr* >20:1).

At this point we set out to focus our attention on the reactivity of *cis*-1,6-enynes in the presence of all-metal aromatic clusters. To this end, compound **62a** was synthesized and tested with $Pt^{3+}$ complex **59** under the same previously optimized catalytic conditions. Unexpectedly, no conversion was observed. Afterwards, we decided to repeat the experiment using reaction conditions similar to those employed for the cycloisomerization of enynes with $Pd^{3+}$ complex **49**[26] (Scheme 21). The test was carried out in toluene, with just one equivalent of benzoic acid and in the absence of the co-catalytic amount of phosphine. Also in this case no reaction occurred (Scheme 21, Pathway 1).



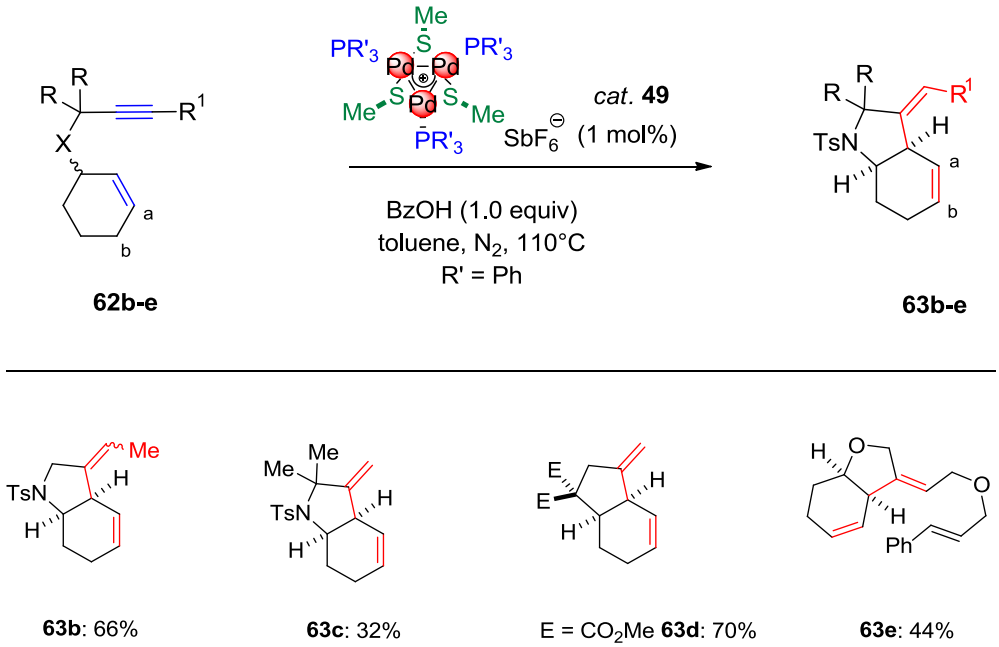

**Scheme 21**. Reactivity of *cis*-1,6-enynes in the presence of all-metal aromatic clusters

On the contrary, reacting **62a** with palladium cluster **49**, instead of platinum complex **59**, allowed us to isolate product **63a** in 69% yield (Scheme 21, Pathway 2).[35] Once again, as shown in the literature,[36] the presence of a mild carboxylic acid revealed to be decisive for promoting any reactivity, no enyne conversion being otherwise observed. In this case the addition of phosphine is not necessary for the complete conversion of the substrate because, as observed in previous studies,[25,26] the catalyst loading is not lower than 1 mol%. In addition, $Pd_3^+$ complexes are generally more robust than $Pt_3^+$ analogues. In order to prove the generality of this method we prepared different *cis*-1,6-

[35] For recent examples of cycloisomerizations with palladium, see: (a) Y.A. Qiu, B. Yang, T. Jiang, C. Zhu and J.E. Backvall, *Angew.Chem.Int.Ed.*, 2017, **56**, 3221. (b) D.A. Petrone, I. Franzoni, J. Ye, J. F. Rodriguez, A. I. Poblador-Bahamonde and M. Lautens, *J. Am. Chem. Soc.,* 2017, **139**, 3546. For reviews, see: (c) A. Düfert and D.B. Werz, *Chem. Eur. J.* 2016, **22**, 16718. (d) L.F. Tietze and T. Kinzel, *Pure Appl. Chem.,* 2007, **79**, 629.

[36] (a) G. Cera, M. Lanzi, D. Balestri, N. Della Ca', R. Maggi, F. Bigi, M. Malacria and G. Maestri, *Org. Lett.,* 2018, **20**, 3220. (b) G. Cera, M. Lanzi, F. Bigi, R. Maggi, M. Malacria and G. Maestri, *Chem. Commun.,* 2018, **54**, 14021. (c) J.F. Rodriguez, K.I. Burton, I. Franzoni, D. A. Petrone, I. Scheipers and M. Lautens, *Org. Lett.,* 2018, **20**, 6915. (d) A.M. Haydl, B. Breit, T. Lang and M.J. Krische, *Angew. Chem. Int. Ed.,* 2017, **56**, 11312. (e) M. D. Peacock, C.B. Roos and J.F Hartwig, *ACS Cent. Sci.,* 2016, **2**, 647.

enynes from which we were able to obtained a family of bicyclic compounds **63** (Scheme 22, **63b-e**).



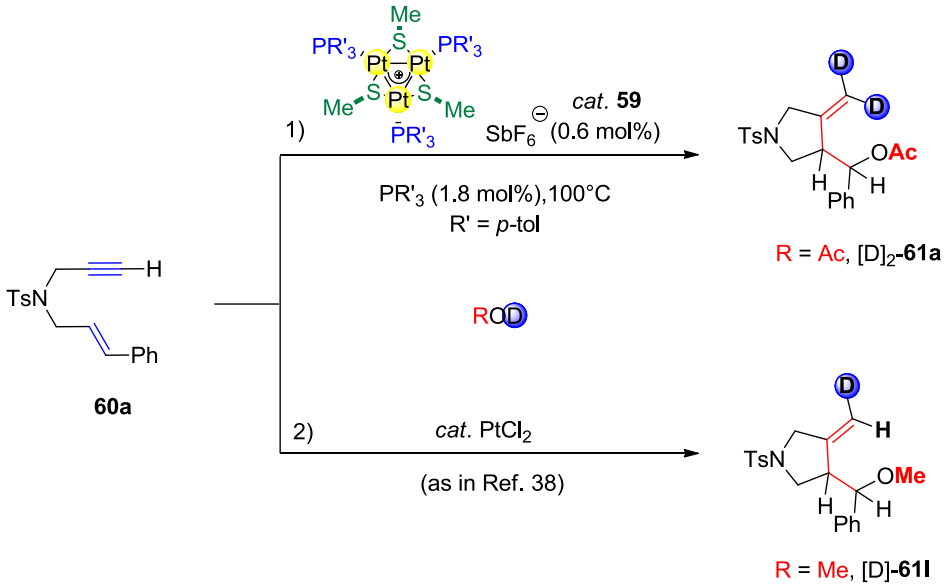

**Scheme 22.** Scope of the tripalladium-catalysed reaction with *(Z)*-enynes

Derivatives **63** show a formal shift of the double bond and no traces of the corresponding 1,3-diene have been detected. In all cases, a high level of diastereoselection was observed (*dr* >20:1), even though racemic substrates were used. The *syn*-configuration of bridgehead CH groups has been assigned through NMR correlation experiments.

Interestingly, the complete selectivity to 1,4-dienes was observed by Trost and co-workers using similar reagents.[37] In such studies, the *(E)*-alkene moiety of enynes had a C($sp^3$)-H group at his alpha position (as in our case: carbon *b* Scheme 22) and the resulting alkyl-palladium eventually provides the 1,4-diene through a beta-hydride elimination.

[37] (a)B. M. Trost, C. D. Haffner, D. J. Jebaratnam, M. J. Krische and A. P. Thomas, *J. Am. Chem. Soc.*, 1999, **121**, 6183. (b) B. M. Trost and M. Lautens, *J. Am. Chem. Soc.*, 1985, **107**, 1781.

In order to provide further insight into the reaction mechanism with the triplatinum cluster, we decided to carry out some labelling experiments. The first test was performed using substrate **60a** and AcOH-$d_4$ as solvent (Scheme 23).

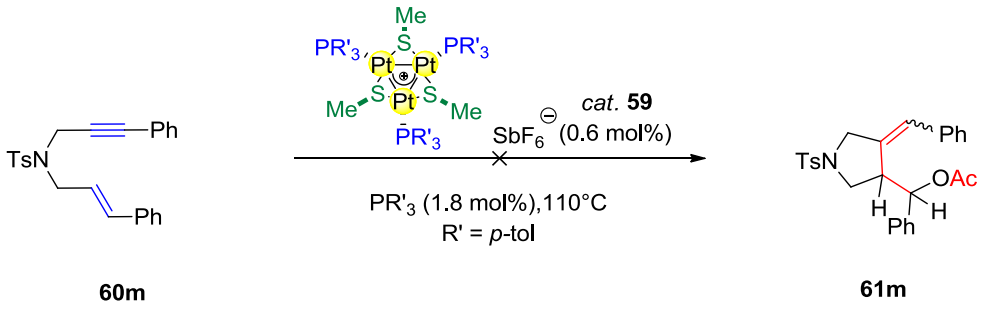



**Scheme 23** Mechanistic probes

This reaction led to the unusual incorporation of two deuterium atoms on *gem*-methylene unit giving product [D]$_2$-**61a** in good yield (57%, Scheme 23, pathway 1). In particular, D-labeling occurred with 90% and 63%, respectively. This result completely differs from previous studies on $PtCl_2$-catalyzed alkoxycyclization of enynes in which only one deuterium atom was singularly incorporated under similar reaction conditions (Scheme 23, pathway 2). [38]

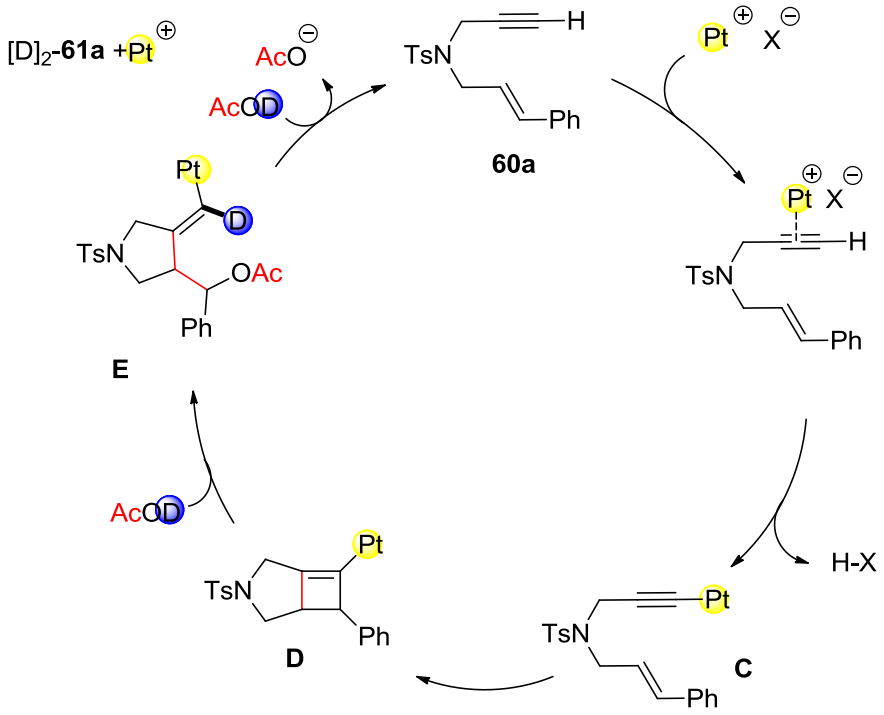
Notably, treating **60a** with AcOH-$d_4$ did not provide any H/D exchange. Moreover, the internal alkyne substrate **60m** was found not to be reactive under standard reaction conditions (Scheme 24).

[38]M. Méndez, M.P Mũnoz and A.M. Echavarren, *J. Am.Chem. Soc.,* 2000, **122**, 11549.




**Scheme 24** Test with internal alkyne **60m**

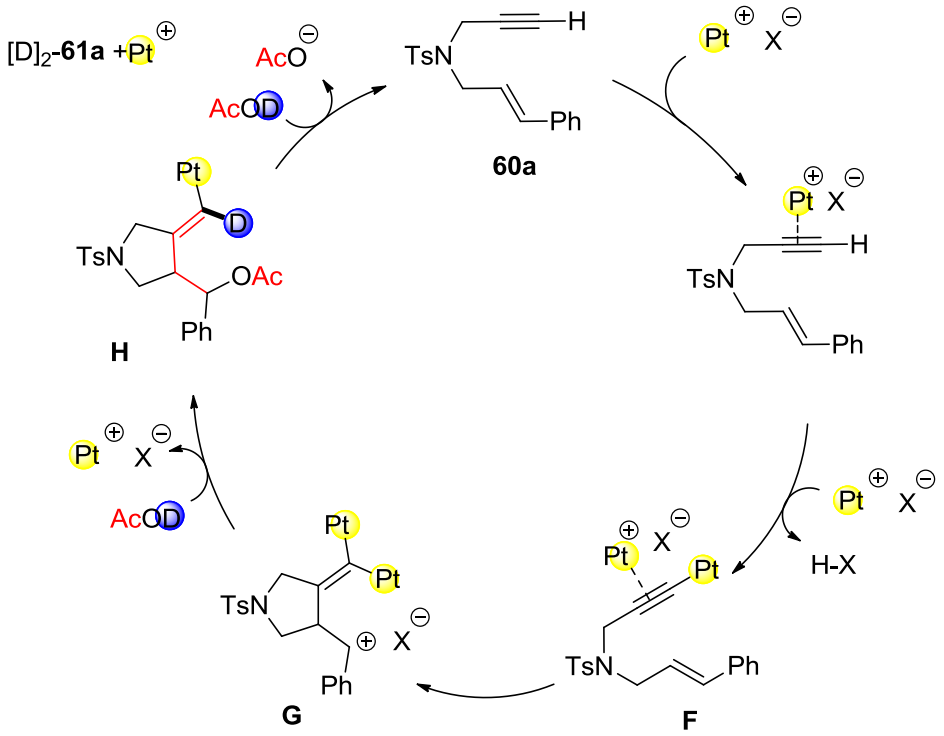
These results suggest that the presence of a terminal alkyne unit is essential to promote any transformation with the triplatinum cluster and that their acetylenic CH is most likely activated during the catalytic cycle. Finally we monitored the reaction by $^{31}P$ NMR. After four hours, complex **59** underwent decomposition together with the formation of new, not yet identified species. On the contrary, for sake of comparison, complex **49** was stable under similar conditions.[26]




**Scheme 25** First plausible catalytic cycle for the synthesis of $[D]_2$-**61a**

Based on the deuterium labelling experiment, we suppose an initial σ-activation of the triple bond with the formation of platinum acetylide complex **C** which then afforded metalated cyclobutene **D** (Scheme 25). The latter undergoes ring opening by the attack of AcOH, forming vinylplatinum complex **E**. The desired product $[D]_2$-**61a** was finally delivered by a protodemetallation step. At the same time we can not rule out a dual σ,π-activation.[39]

[39] A. S. K. Hashmi, *Acc. Chem. Res.,* 2014, **47**, 864.




**Scheme 26** Second plausible catalytic cycle for the synthesis of $[D]_2$-**61a**

The second plausible reaction pathway (Scheme 26) includes the formation of diplatinum complex **F** whose electron rich-alkene arm attacks the electrophilic alkyne carbon affording the carbocationic species **G**. Then, a quenching by an acetate molecule followed by a dual protodemetalation process affords species $[D]_2$-**61a**.

The first reaction mechanism could be supported by the absence of reactivity noticed for substrates **62**. Indeed, their cycloisomerization could have been hampered by the steric strain associated to the formation of the tricyclic intermediate **D**. However, the loss of stereocontrol observed for the reaction with **60e** might be more consistent with the second pathway proposed. Indeed,

the electron-rich anisole group on substrate **60e** could have stabilized the benzylic carbocation of intermediate **G**.

## 2.3 Conclusions

We have described the unprecedented use of trinuclear all-metal aromatic clusters in the presence of 1,6-enynes and carboxylic acids. Substrates, with the proper choice of the catalyst, were chemoselectively converted to cyclic and bicyclic compounds in good yields and functional group tolerance. Moreover, two reaction mechanisms were proposed on the bases of deuterium labelling experiments. Results obtained with this work will be useful for further expanding the applications of multinuclear complexes in catalytic synthesis.

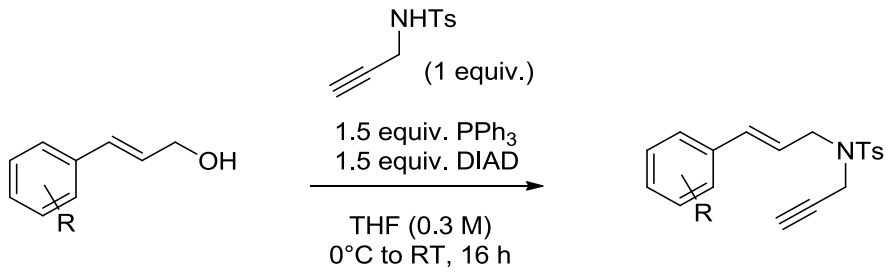
## 2.4 Experimental section

### General remarks

All chemicals those syntheses are not reported hereafter were purchased from commercial sources and used as received. $^{1}H$ and $^{13}C$ NMR spectra were recorded at 300 K on a Bruker 400 MHz or Bruker 300 MHz using solvents as internal standards (7.26 ppm for $^{1}H$ NMR and 77.00 ppm for $^{13}C$ NMR for $CDCl_3$, 2.05 ppm for $^{1}H$ NMR and 29.84 ppm for $^{13}C$ NMR for Acetone-$d_6$, 7.16 ppm for $^{1}H$-NMR and 128.06 for $^{13}C$ NMR for Benzene-$d_6$). $^{19}F$-NMR spectra were recorded in $CDCl_3$ at 298 K on a Bruker 400 MHz spectrometer fitted with a BBFO probe head at 263 MHz. The terms m, s, d, t, q and quint represent multiplet, singlet, doublet, triplet, quadruplet and quintuplet respectively, and the term br means a broad signal. LC-MS were recorded on an Agilent LQ Mass Spectrometer (ESI source) and exact masses were recorded on a LTQ ORBITRAP XL Thermo Mass Spectrometer (ESI source). Allylic alcohol derivatives were synthesized according to known procedures.[2640]

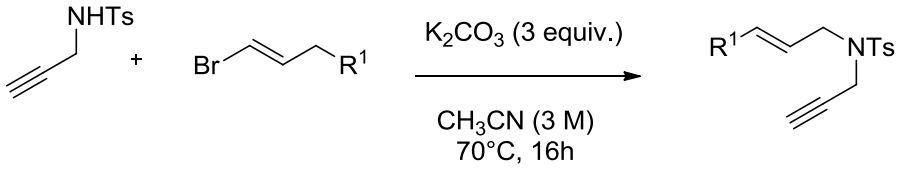
[40] M. J. Zhong, H.T. Zhu, P. Gao, Y.F. Qiu and Y.M. Liang, *RSC Adv,.* 2014, ***4***, 8914.

**General Procedure for synthesis of enynes (GP-1)**




To the solution of the desired allyl alcohol (1.1 equiv.) in dry THF (0.3 M) was added $PPh_3$ (1.5 equiv.) and 4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide (1.0 equiv.). The mixture was cooled to 0 °C and DIAD (1.5 equiv.) was added dropwise. The resulting mixture was stirred at room temperature until complete conversion monitored by TLC. Hence, the solution was carefully concentrated under reduced pressure and purified by flash chromatography (isocratic *n*-Hexane/EtOAc 8:2) affording the desired product.

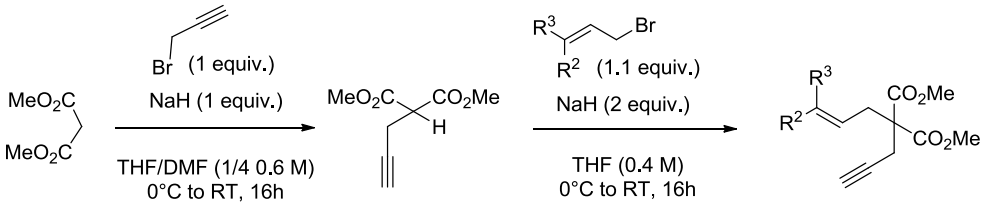
**General Procedure for synthesis of enynes (GP-2)**




To a solution of 4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide 0.628 g (1.0 equiv., 3 mmol) in $CH_3CN$ (0.2 M) was added $K_2CO_3$ 1.24 g (3.0 equiv., 9 mmol)

and the desired bromide (1.5 equiv.). Subsequently, the mixture was heated to 70 °C and stirred overnight. Upon complete conversion, the reaction was cooled to room temperature, quenched with water (~50 mL) and extracted with EtOAc (3 x 20 mL). The combined organic phases were dried over anhydrous $Na_2SO_4$, concentrated under reduced pressure and purified by column chromatography (isocratic *n*-Hexane/EtOAc 8:2).

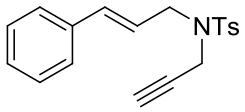
**General Procedure for synthesis of enynes (GP-3)**




NaH (340 mg, 60% dispersion in mineral oil, 8.5 mmol, 1 equiv.) was carefully added to a solution of dimethyl malonate (1.95 mL, 17 mmol, 2.0 equiv.) in THF/DMF (28 mL, 1/4, 0.6 M) at 0 °C. The reaction was stirred for half an hour, then propargyl bromide (0.92 mL, 80% in toluene, 8.5 mmol, 1.0 equiv.) was syringed dropwise. The resulting mixture was stirred at room temperature until complete conversion monitored by TLC. Hence, the reaction was quenched with water (~50 mL) and extracted with EtOAc (3 x 20 mL). The combined organic extracts were dried over anhydrous $Na_2SO_4$, filtered and concentrated under reduced pressure. Afterwards, the crude was carefully purified by flash chromatography (isocratic *n*-Hexane/EtOAc 8:2), yielding dimethyl 2-(prop-2-yn-1-yl)malonate as colourless oil (41 %, 3.5 mmol, 590 mg).

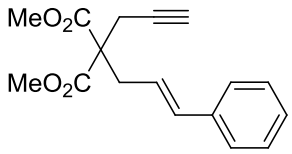
To a solution of the former (3.5 mmol, 1.0 equiv) in THF (9 ml, 0.4 M) at 0 °C, was added NaH (0.280 g, 60% dispersion in mineral oil, 7 mmol, 2.0 equiv.). The reaction system was stirred for half an hour, then the desired bromide (3.9 mmol, 1.1 equiv.) was added dropwise. The mixture was allowed to warm up to room temperature and stirred until complete conversion. Subsequently, the reaction was quenched with water (~25 mL) and extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried over anhydrous $Na_2SO_4$, filtered and concentrated under reduced pressure. The crude was carefully purified by flash chromatography (isocratic *n*-Hexane/EtOAc 8:2).

***N*-Cinnamyl-4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide (60a)**



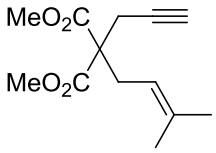

**60a** was isolated following procedure **GP-2** using cinnamyl bromide (0.66 ml, 4.5 mmol). Purification by column chromatography afforded **60a** (70 %, 683 mg) as a white solid. Spectra correspond to the literature.[26] **$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.3 Hz, 2H), 7.33 – 7.29 (m, 7H), 6.57 (d, *J* = 15.8 Hz, 1H), 6.08 (dt, *J* = 15.8, 6.9 Hz, 1H), 4.13 (d, *J* = 2.5 Hz, 2H), 3.99 (dd, *J* = 6.9, 1.1 Hz, 2H), 2.44 (s, 3H), 2.04 (t, *J* = 2.5 Hz, 1H).

**Dimethyl 2-cinnamyl-2-(prop-2-yn-1-yl)malonate (60b)**



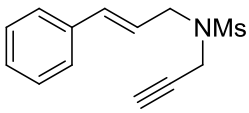

**60b** was isolated following procedure **GP-3** using cinnamyl bromide (0.570 ml, 3.9 mmol). Purification by column chromatography afforded **60b** as colourless oil. (28 %, 306 mg). Spectra correspond to the literature.[40] **$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.34 – 7.22 (m, 5H), 6.52 (d, *J* = 15.7 Hz, 1H), 6.00 (dt, *J* = 15.5, 7.6 Hz, 1H), 3.76 (s, 6H), 2.97 (dd, *J* = 7.6, 1.2 Hz, 2H), 2.85 (d, *J* = 2.7 Hz, 2H), 2.06 (t, *J* = 2.7 Hz, 1H).

**Dimethyl 2-(3-methylbut-2-en-1-yl)-2-(prop-2-yn-1-yl)malonate (60c)**




**60c** was isolated following procedure **GP-3** using 3,3-dimethylallyl bromide (0.445 ml, 3.9 mmol). Purification by column chromatography afforded **60c** as yellow oil (48%, 400 mg). Spectra correspond to the literature.[41] **$^1$H NMR** (400 MHz, $CDCl_3$) δ 4.90 (t, *J* = 7.6 Hz, 1H), 3.74 (s, 6H), 2.79 – 2.77 (m, 4H), 2.00 (t, *J* = 2.7 Hz, 1H), 1.70 (s, 3H), 1.65 (s, 3H).

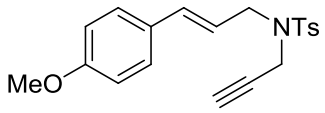
***N*-Cinnamyl-*N*-(prop-2-yn-1-yl)methanesulfonamide (60d)**




**60d** was isolated following procedure **GP-2** using cinnamyl bromide (0.66ml, 4.5 mmol) and 4-Methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide (400 mg, 3mmol). Purification by column chromatography afforded **60d** as white solid. (92 %, 688 mg). **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.41 – 7.26 (m, 5H), 6.67 (d, *J* = 15.8 Hz, 1H), 6.17 (dt, *J* = 15.8, 6.8 Hz, 2H), 4.11 (d, *J* = 2.5 Hz, 2H), 4.06 (dd, *J* = 6.8, 1.3 Hz, 2H), 2.99 (s, 3H). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 135.9, 135.0, 128.6, 128.1, 126.5, 122.7, 77.3, 74.4, 48.7, 38.4, 35.7. **LC-MS** calcd for $C_{13}H_{16}NO_2S$ $[M+H]^+$ 250.1, found 250.1.

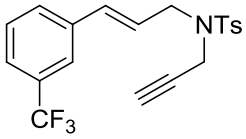
[41] S. Ferrer and A. M. Echavarren, *Organometallics* 2018, ***37***, 781.

***(E)*-*N*-(3-(4-Methoxyphenyl)allyl)-4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide (60e)**



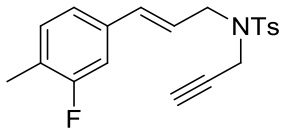

**60e** was obtained following procedure **GP-1** using *(E)*-3-(4-Methoxyphenyl)prop-2-en-1-ol (170 mg, 1.0 mmol) and 4-Methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide (0.200 mg, 0.9 mmol). Purification by column chromatography afforded **60e** as a white solid (54 %, 186 mg). **$^{1}$H NMR** (300 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.3 Hz, 2H), 7.32 – 7.26 (m, 5H), 6.85 (d, *J* = 8.7 Hz, 1H), 6.51 (d, *J* = 15.8 Hz, 1H), 5.93 (dt, *J* = 15.8, 6.9 Hz, 1H), 4.12 (d, *J* = 2.5 Hz, 2H), 3.96 (dd, *J* = 6.9, 1.3 Hz, 2H), 3.81 (s, 3H), 2.43 (s, 3H), 2.03 (t, *J* = 2.5 Hz, 1H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 159.6, 143.5, 136.1, 134.5, 129.5, 128.9, 127.8, 127.8, 120.5, 114.0, 77.2, 73.7, 55.3, 48.6, 35.7, 21.5. **HRMS** calcd for $C_{20}H_{21}NNaO_3S$ $[M+Na]^+$ 378.1134, found 378.1132.

***(E)*-4-Methyl-*N*-(prop-2-yn-1-yl)-*N*-(3-(3-(trifluoromethyl)phenyl)allyl) benzenesulfonamide (60f)**



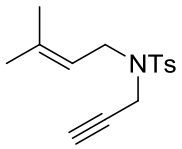

**60f** was obtained following procedure **GP-1** using *(E)*-3-[3 (trifluoromethyl)phenyl]prop-2-en-1-ol (429 mg, 2.1 mmol) and 4-Methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide (404 mg, 1.9 mmol). Purification by column chromatography afforded **60f** as a white solid (25 %, 216 mg). **$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.3 Hz, 2H), 7.54 – 7.50 (m, 3H), 7.45 – 7.41 (m, 1H), 7.31 (d, *J* = 8.0 Hz, 2H), 6.60 (d, *J* = 15.8 Hz, 1H), 6.15 (dt, *J* = 15.8, 6.7 Hz, 1H), 4.14 (d, *J* = 2.5 Hz, 2H), 4.02 (dd, *J* = 6.7, 1.4 Hz, 2H), 2.43 (s, 3H), 2.08 (t, *J* = 2.4 Hz, 1H). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 143.8, 136.9, 136.0, 133.2, 131.0 (q, $^{2}J_{C\text{-}F}$ = 32.2 Hz), 129.6, 129.6, 129.1, 127.7, 125.2, 124.5 (q, $^{4}J_{C\text{-}F}$ = 3.7 Hz), 124.0 (q, $^{1}J_{C\text{-}F}$ = 272.5 Hz), 123.2 (q, $^{3}J_{C\text{-}F}$ = 3.8 Hz), 76.5, 74.0, 48.4, 36.2, 21.5. $^{19}$F NMR (376 MHz, $CDCl_3$) δ -62.5, **LC-MS** calcd for $C_{20}H_{18}F_3NNaO_2S$ $[M+Na]^+$ 416.1, found 416.1.

***(E)*-*N*-[3-(3-Fluoro-4-methylphenyl)allyl]-4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide (60g)**



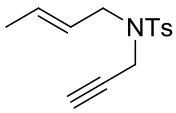

**60g** was isolated following procedure **GP-1** using *(E)*-3-(3-Fluoro-4-methylphenyl)prop-2-en-1-ol (200 mg, 1.2 mmol) and 4-Methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide (230 mg, 1.1 mmol). Purification by column chromatography afforded **60g** as a white solid (76 %, 294 mg). **$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.3 Hz, 2H), 7.31 (d, *J* = 8.3 Hz, 2H), 7.11 (t, *J* = 7.9 Hz, 1H), 7.00 – 6.95 (m, 2H), 6.50 (d, *J* = 15.8 Hz, 1H), 6.02 (dt, *J* = 15.8, 6.8 Hz, 1H), 4.12 (d, *J* = 2.4 Hz, 2H), 3.98 (d, *J* = 6.8 Hz, 2H), 2.43 (s, 3H), 2.25 (s, 3H), 2.06 (t, *J* = 2.4 Hz, 1H). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 161.4 (d, $^{1}J_{C\text{-}F}$ = 244.6 Hz), 143.7, 136.0, 135.8 (d, $^{4}J_{C\text{-}F}$ = 7.7 Hz), 133.7 (d, $^{8}J_{C\text{-}F}$ = 2.4 Hz), 131.5 (d, $^{5}J_{C\text{-}F}$ = 5.5 Hz), 129.6, 127.8, 124.7 (d, $^{3}J_{C\text{-}F}$ = 17.5 Hz), 123.3, 122.2 (d, $^{7}J_{C\text{-}F}$ = 3.1 Hz), 112.7 (d, $^{2}J_{C\text{-}F}$ = 22.8 Hz), 76.6, 73.9, 48.5, 36.0, 21.6, 14.4 (d, $^{6}J_{C\text{-}F}$ = 3.4 Hz). **$^{19}$F NMR** (376 MHz, $CDCl_3$) δ -117.6. **LC-MS** calcd for $C_{22}H_{25}NNaO_5S$ $[M+Na]^+$ 438.1, found 438.3.

**4-Methyl-*N*-(3-methylbut-2-en-1-yl)-*N*-(prop-2-yn-1-yl)benzenesulfonamide (60h)**




**60h** was isolated following procedure **GP-2** using 3,3-dimethylallyl bromide (0.520 ml, 4.5 mmol). Purification by column chromatography afforded **60h** as pale yellow oil. (57 %, 474 mg). Spectra correspond to the literature.[42] **$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.2 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 5.10 (t, *J* = 7.3 Hz, 1H), 4.07 (d, *J* = 2.3 Hz, 2H), 3.81 (d, *J* = 7.3 Hz, 2H), 2.42 (s, 3H), 1.98 (t, *J* = 2.4 Hz, 1H), 1.72 (s, 3H), 1.67 (s, 3H).

***(E)*-*N*-(But-2-en-1-yl)-4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide (60i)**

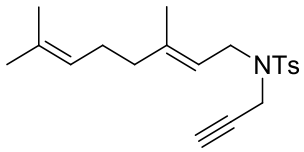



**60i** was isolated following procedure **GP-2**, using crotyl bromide (0.463 ml, 4.5 mmol). Purification by column chromatography afforded **60i** as a white

[42] J. A. Johnson, B. M. Petersen, A. Kormos, E. Echeverría and Y.S. Chen, J. Zhang, *J. Am. Chem. Soc.*, 2016, ***138***, 10293.

solid.(90%, 711 mg). Spectra correspond to the literature.[43] **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.2 Hz, 2H), 7.31 (d, *J* = 8.1 Hz, 2H), 5.78 – 5.69 (m, 1H), 5.42 – 5.34 (m, 1H), 4.10 (d, *J* = 2.5 Hz, 2H), 3.77 (d, *J* = 6.8 Hz, 2H), 2.44 (s, 3H), 2.01 (t, *J* = 2.5 Hz, 1H), 1.72 – 1.70 (m, 3H).

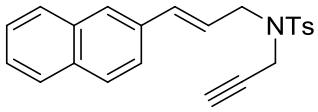
### *(E)-N*-(3,7-Dimethylocta-2,6-dien-1-yl)-4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide (60j)




**60j** was isolated following procedure **GP-2** using geranyl bromide (0.893 ml, 4.5 mmol). Purification by column chromatography afforded **60j** as a yellow oil. (38%, 393 mg). **$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.3 Hz, 2H), 7.29 (d, *J* = 7.8 Hz, 2H), 5.11 – 5.01 (m, 2H), 4.07 (d, *J* = 2.4 Hz, 2H), 3.84 (d, *J* = 7.3 Hz, 2H), 2.42 (s, 3H), 2.095 – 1.98 (m, 5H), 1.67 (d, *J* = 3.1 Hz, 6H), 1.59 (s, 3H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 143.4, 142.5, 136.1, 131.8, 129.4, 127.8, 123.7, 117.8, 77.0, 73.4, 43.8, 39.6, 35.2, 26.1, 25.7, 21.5, 17.7, 16.1. **LC-MS** calcd for $C_{20}H_{27}NNaO_2S$ $[M+Na]^+$ 368.2, found 368.2.

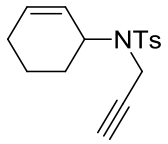
[43] M. Dieckmann, Y.S. Jang and N. Cramer, *Angew.Chem.Int.Ed.,* 2015, **54**, 12149.

***(E)*-4-Methyl-*N*-(3-(naphthalen-2-yl)allyl)-*N*-(prop-2-yn-1-yl)benzenesulfonamide (60k)**



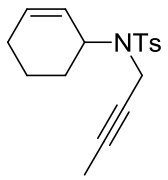

**60k** was obtained following procedure **GP-1** using *(E)*-3-(naphthalen-2-yl)prop-2-en-1-ol (300 mg, 0.25 mmol) and 4-Methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide (0.580 mg, 0.27 mmol). Purification by column chromatography afforded **60k** as a white solid (50%, 0.476 mg). **$^{1}$H NMR** (300 MHz, $CDCl_3$) δ 7.84 – 7.79 (m, 5H), 7.71 (brs, 1H), 7.57 – 7.54 (m, 1H), 7.50 – 7.46, 2H), 7.35 – 7.33 (m, 2H), 6.76 (d, *J* = 15.8 Hz, 1H), 6.22 (dt, *J* = 15.8, 6.9 Hz, 1H), 4.19 (d, *J* = 2.5 Hz, 2H), 4.07 (dd, *J* = 6.9, 1.3 Hz, 2H), 2.46 (s, 3H), 2.09 (t, *J* = 2.5 Hz, 1H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 143.6, 136.1, 134.9, 133.5, 133.4, 133.1, 129.5, 128.3, 128.0, 127.8, 127.7, 126.7, 126.4, 126.1, 123.4, 123.3, 76.6, 73.8, 48.6, 31.6, 21.5. **LC-MS** calcd for $C_{23}H_{21}NNaO_2S$ $[M+Na]^+$ 398.1, found 398.1.

***N*-(Cyclohex-2-en-1-yl)-4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide (62a)**




**62a** was isolated following procedure **GP-2** using 3-bromocyclohexene (0.518 ml, 4.5 mmol). Purification by column chromatography afforded **62a** as white solid (95 %, 0.825 g). Spectra correspond to the literature.[44] **$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.3 Hz, 2H), 7.29 (d, *J* = 7.7 Hz, 2H), 5.91 – 5.88 (m, 1H), 5.31 (d, *J* = 10.2 Hz, 1H), 4.52 – 4.47 (m, 1H), 4.13 (dd, *J* = 18.4, 2.4 Hz, 1H), 3.92 (dd, *J* = 18.5, 2.4 Hz, 1H), 2.43 (s, 3H), 2.18 (t, *J* = 2.4 Hz, 1H), 1.97 – 1.50 (m, 6H).

***N*-(But-2-yn-1-yl)-*N*-(cyclohex-2-en-1-yl)-4-methylbenzenesulfonamid**e (**62b)**

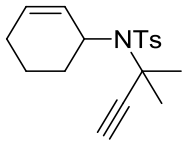



To the solution of 2-butyn-1-ol 116 mg 0.124 ml (1.65 mmol, 1.1 equiv) in dry THF (0.3 M) was added $PPh_3$ 0.425g (1.65 mmol, 1.5 equiv) and *N*-(cyclohex-2-en-1-yl)-4-methylbenzenesulfonamide 0.377 g (1.5 mmol, 1.0 equiv). The

[44] T. Kitamura, Y. Kuzuba, Y. Sato, H. Wakamatsu, R. Fujita and M. Mori, *Tetrahedron,* 2004, **60**, 7375

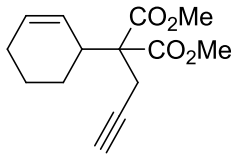
mixture was cooled to 0 °C and DIAD (0.325ml (1.65 mmol, 1.5 equiv) was added dropwise. The resulting mixture was stirred at room temperature until complete conversion monitored by TLC. Hence, the solution was carefully concentrated under reduced pressure and purified by flash chromatography (isocratic Hexane/EtOAc 8:2). **62b** was isolated as a white solid (45 %, 200 mg). Spectra correspond to the literature.[44] **$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.1 Hz, 1H), 7.29 (d, *J* = 7.7 Hz, 1H), 5.89 – 5.85 (m, 1H), 5.33 (d, *J* = 10.1 Hz, 1H), 4.53 – 4.49 (m, 1H), 4.07 (dd, *J* = 18.2, 2.5 Hz, 1H), 3.88 (dd, *J* = 18.2, 2.4 Hz, 1H), 2.44 (s, 3H), 1.97 – 1.54 (m, 6H), 1.70 (t, *J* = 2.4 Hz, 3H).

***N*-(Cyclohex-2-en-1-yl)-4-methyl-*N*-(2-methylbut-3-yn-2-yl)benzenesulfonamide (62c)**



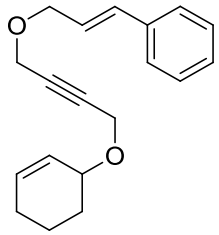

**62c** was isolated following procedure **GP-2** using 3-bromocyclohexene (0.518 ml, 4.5 mmol) and 4-methyl-*N*-(2-methylbut-3-yn-2-yl)benzenesulfonamide (0.712 g, 4.3 mmol). Purification by column chromatography afforded **62c** as white solid (45%, 420 mg). **$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.78 (d, J = 8.2 Hz 2H), 7.27 (d, J = 8.2 Hz 2H), 5.99-5-79 (s, 1H), 5.74 – 5.60 (m, 1H), 4.66 – 5.53 (s, 1H), 2.52 – 2.48 (m, 1H), 2.42 (s, 3H), 2.40 (s, 1H), 2.10 – 1.91 (m, 4H), 1.83 – 1.50 (m, 7H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 142.6, 131.2, 129.4, 126.9, 87.1, 71.4, 58.8, 56.8, 30.2, 29.6, 24.2, 23.4, 21.4. **HRMS** calcd for $C_{18}H_{23}NNaO_2S$ $[M+Na]^+$ 340.1342, found. 340.1345.

**Dimethyl 2-(cyclohex-2-en-1-yl)-2-(prop-2-yn-1-yl)malonate (62d)**




**62d** was isolated following procedure **GP-3** using 3-bromocyclohexene (0.443 ml, 3.85 mmol). Purification by column chromatography afforded **62d** as colourless oil (90 %, 900 mg). Spectra data correspond to the literature. [45] **$^1$H NMR** (300 MHz, $CDCl_3$) δ 5.78 – 5.65 (m, 2H), 3.74 (s, 3H), 3.70 (s, 3H), 3.13 – 3.08 (m, 1H), 2.87 (dd, *J* = 17.2, 2.7 Hz, 1H), 2.78 (dd, *J* = 17.2, 2.7 Hz, 1H), 2.00 (t, *J* = 2.7 Hz, 1H), 1.95 – 1.26 (m, 6H).

***(E)*-(3-((4-(Cyclohex-2-en-1-yloxy)but-2-yn-1-yl)oxy)prop-1-en-1-yl)benzene (62e)**




To the solution of 4-(cinnamyloxy)but-2-yn-1-ol (300 mg, 1.5 mmol, 1 equiv) in dry THF/DMF (2.5 mL, 4/1, 0.6 M) at 0 °C was dropwise added NaH (80 mg, 60 % dispersion in mineral oil, 1.8 mmol., 1.2 equiv). The mixture was kept under stirring for half an hour. Then, 2-bromo-cyclohexane was dropwise

[45] M. P. Muñoz, M. Méndez, C. Nevado, D. J. Cárdenas, A. M. Echavarren, *Synthesis*, **35**, 2003, 2898.

added (0.2 mL, 1.8 mmol, 1.2 equiv). The reaction was stirred at room temperature overnight, quenched with ethanol, diluted with AcOEt and washed with water and dried. The crude was purified by flash chromatography yielding **62e** as transparent oil. (50 %, 209 mg). **$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 7.40 – 7.23 (m, 5H), 6.64 (d, *J* = 15.9 Hz, 1H), 6.28 (dt, *J* = 15.9, 6.2 Hz, 1H), 5.91 – 5.77 (m, 2H), 4.27 – 4.22 (m, 6H), 4.09 (brs, 1H), 2.08 – 1.94 (m, 2H), 1.87 – 1.68 (m, 3H), 1.61 – 1.54 (m, 1H). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 136.5 (Cq), 133.2 (CH), 131.4 (CH), 128.5 (CH), 127.7 (CH), 127.1 (CH), 126.5(CH), 125.2 (CH), 83.1 (Cq), 81.7 (Cq), 71.7 ($CH_2$), 70.2 ($CH_2$), 57.4 ($CH_2$), 55.5 ($CH_2$), 28.0 ($CH_2$), 25.1 ($CH_2$), 19.0 ($CH_2$). **HRMS** calcd for $C_{19}H_{22}KO_2$ $[M+K]^+$ 321.1251, found 321.1252.

## Synthesis of Complex 59

$Pt(dba)_3$ (90 mg, 0.1 mmol, 1 equiv) was added to a 50 mL Schlenk flask, which underwent at least three vacuum/$N_2$ cycles. $P(p\text{-}tol)_3$ (31 mg, 0.1 mmol, 1 equiv) was added under $N_2$. Then, freshly degassed $CHCl_3$ (10 mL) and dimethyl disulfide (9.5 mg, 0.05 mmol, 0.5 equiv) were immediately syringed through the septum. The resulting solution was kept under stirring at r.t. for 2 h and $AgSbF_6$ (12 mg, 0.033 mmol, 0.33 equiv) was then added under $N_2$. The solution was kept in the dark. Stirring was maintained for 1 h and the mixture was then filtered under $N_2$ through a short pad of Celite to remove traces of black metals. The solvent was removed under vacuum to leave a deep yellow-brown solid that was washed with a $CHCl_3$/hexane solution (1:30 v/v, 3 × 20 mL). Desired cluster was purified by chromatography on silica gel using acetone/hexane under gradient as eluent. Recrystallization by vapor diffusion using THF/hexane eventually provided the pure complex as yellow crystals; yield: 15 mg (30%). Their spectroscopic data correspond to the literature. [24]

## Synthesis of complex 49

$Pd(dba)_2$ (115 mg, 0.2 mmol, 1 equiv) was added to a 100 mL Schlenk flask, which underwent at least three vacuum/$N_2$ cycles. $PPh_3$ (53 mg, 0.2 mmol, 1 equiv) was added under $N_2$. Then, freshly degassed $CHCl_3$ (20 mL) and dimethyl disulfide (19 mg, 0.1 mmol, 0.5 equiv) were immediately syringed through the septum. The resulting solution was kept under stirring at r.t. for 2 h and $AgSbF_6$ (12 mg, 0.033 mmol, 0.33 equiv) was then added under $N_2$. The solution was kept in the dark. Stirring was maintained for 1 h and the mixture was then filtered under $N_2$ through a short pad of Celite to remove traces of black metals. The solvent was removed under vacuum to leave a deep red solid that was washed with a $CHCl_3$/hexane solution (1:30 v/v, 3 × 30 mL). Desired cluster was directly purified by recrystallization via vapor diffusion using

acetone/hexane, eventually providing the pure complex as red crystals; yield: 88 mg (97%). Their spectroscopic data correspond to the literature.[24]

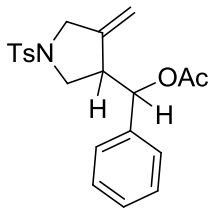
**Catalytic Synthesis of 61; General Procedure 1 (GP-4)**

Complex **59** (1.7 mg, 0.9 mmol, 0.6 mol%) and freshly degassed AcOH (0.5 mL) were added under $N_2$ to a Schlenk-type flask. The desired substrate **60** (0.15 mmol, 1 equiv) and P(p-tolyl)$_3$ (0.8 mg, 2.7 mmol, 1.8 mol%) were sequentially added. The mixture was heated at 110 °C and the conversion was followed by analyzing samples via TLC. Upon complete conversion of the substrate, the solution was diluted with EtOAc (5 mL) and purified.

**Catalytic Synthesis of 63; General Procedure 2 (GP-5)**

Complex **49** (3 mg, 0.002 mmol, 1 mol%) and freshly degassed toluene (3.5 mL) were added under $N_2$ to a Schlenk-type flask. The desired substrate **62** (0.2 mmol, 0.06 M) and benzoic acid (24.5 mg, 0.2 mmol, 1 equiv) were sequentially added. The mixture was heated at 100 °C and the conversion was followed by analyzing samples via TLC. Upon complete conversion of the substrate, the solution was diluted with EtOAc (5 mL) and purified.

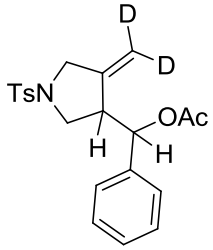
**(4-Methylene-1-tosylpyrrolidin-3-yl)(phenyl)methyl Acetate (61a)**




Product **61a** was isolated following **GP-4** as a pale yellow oil (71%, 42 mg, 0.105 mmol) using **60a** (50 mg, 0.15 mmol) as reagent. Spectra correspond to the literature. [42]

**$^1$H NMR** (300 MHz, CDCl3): δ = 7.71 (d, *J* = 8.2 Hz, 2 H), 7.37–7.25 (m, 7 H), 5.71 (d, *J* = 7.1 Hz, 1 H), 4.92 (d, *J* = 2.0 Hz, 1 H), 4.53 (d, *J* = 2.1 Hz,1 H), 3.87–3.73 (m, 2 H), 3.43–3.33 (m, 2 H), 3.18–3.12 (m, 1 H), 2.46 (s, 3 H), 2.01 (s, 3 H).

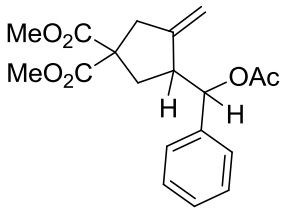
**[4-(Methylene-*$d_2$*)-1-tosylpyrrolidin-3-yl](phenyl)methyl Acetate-*$d_3$* ([D]$_2$-61a)**




Product **[D]$_2$-61a** was isolated following **GP-4** as a pale yellow oil (57%, 33 mg, 0.086 mmol) using **60a** (50 mg, 0.15 mmol) and AcOH-$d_4$ as solvent. **IR (neat)**: 3032, 2921, 1740, 1344, 1158, 1042, 583 cm$^{-1}$. **$^1$H NMR** (300 MHz, $CDCl_3$): δ = 7.71 (d, J = 8.2 Hz, 2 H), 7.37–7.23 (m, 7H), 5.72 (d, J = 7.1 Hz, 1 H), 4.90 (d, J = 2.0 Hz, 0.1 H), 4.52 (d, J = 2.1 Hz,0.37 H), 3.86–3.74 (m, 2 H), 3.43–3.34 (m, 2 H), 3.18–3.13 (m, 1 H), 2.46 (s, 3 H). **$^{13}$C NMR** (101 MHz, $CDCl_3$): δ =

169.7, 143.8, 142.7, 138.4, 132.7, 129.7, 128.5, 128.3, 127.8, 126.8, 109.9, 75.3, 52.5, 49.9, 48.1, 45.5, 21.6. **LC-MS**: m/z calcd for $C_{21}H_{21}D_2NO_4SNa$ $[M + Na]^+$: 410.2; found: 410.7.

**Dimethyl 3-[Acetoxy(phenyl)methyl]-4-methylenecyclopentane-1,1-dicarboxylate (61b)**

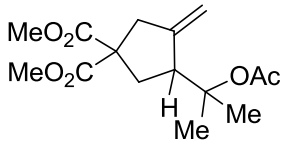



Product **61b** was isolated following **GP-4** as a pale yellow oil (70%, 36 mg, 0.105 mmol) using **60b** (42 mg, 0.15 mmol) as reagent.

**IR (neat)**: 2952, 2362, 1730, 1372, 1226, 1022, 895, 699 $cm^{-1}$.

**$^1$H NMR** (300 MHz, $CDCl_3$): δ = 7.35–7.25 (m, 5 H), 5.91 (d, J = 5.8 Hz, 1 H), 4.98 (d, J = 2.2 Hz, 1 H), 4.64 (d, J = 2.2 Hz, 1 H), 3.73 (s, 3 H), 3.69 (s, 3 H), 3.17–3.09 (m, 1 H), 2.94 (s, 2 H), 2.48–2.41 (m, 1 H), 2.23–2.15 (m, 1 H), 2.07 (s, 3 H). **$^{13}$C NMR** (75 MHz, $CDCl_3$): δ = 171.9, 171.7, 170.1, 146.9, 139.2, 128.4, 127.9, 126.6, 109.4, 76.3, 58.3, 52.8, 52.7, 47.6, 41.8, 35.4, 21.0. **LC-MS**: m/z calcd for $C_{19}H_{22}O_6Na$ $[M + Na]^+$: 369.1; found: 369.2.

**Dimethyl 3-(2-Acetoxypropan-2-yl)-4-methylenecyclopentane-1,1-dicarboxylate (61c)**

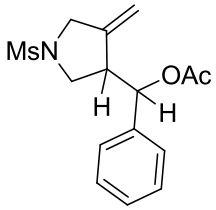



Product **61c** was isolated following **GP-4** as a colorless oil (56%, 25 mg,0.084 mmol) using **60c** (42 mg, 0.15 mmol) as reagent.

**IR (neat)**: 2953, 1729, 1367, 1230, 1076, 1018, 896, 610 $cm^{-1}$.

**$^1$H NMR** (300 MHz, $CDCl_3$): δ = 5.07 (s, 1 H), 4.96 (s, 1 H), 3.73 (s, 3 H), 3.71 (s, 3 H), 3.17–3.11 (m, 1 H), 2.88 (s, 2 H), 2.64–2.56 (m, 1 H), 2.04–1.99 (m, 1 H), 1.96 (s, 3 H), 1.49 (s, 3 H), 1.45 (s, 3 H). **$^{13}$C NMR** (75 MHz, $CDCl_3$): δ = 171.8, 171.7, 170.3, 147.5, 111.2, 84, 58.5, 52.8, 50.3, 43.6, 35.7, 23.6, 22.8, 22.4. **LC-MS**: *m/z* calcd for $C_{15}H_{22}O_6Na$ $[M + Na]^+$: 321.1; found: 321.2.

**[4-Methylene-1-(methylsulfonyl)pyrrolidin-3-yl](phenyl)methyl Acetate (61d)**

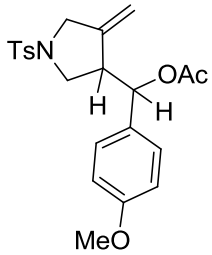



Product **61d** was isolated following **GP-4** as a colorless oil (40%, 18.5mg, 0.06 mmol) using **60d** (37 mg, 0.15 mmol) as reagent.

**IR (neat):** 2926, 1740, 1328, 1225, 1148, 1049, 959, 699 $cm^{-1}$.

**$^{1}$H NMR** (400 MHz, $CDCl_3$): δ = 7.35–7.29 (m, 5 H), 5.87 (d, J = 6.9 Hz, 1 H), 5.02 (s, 1 H), 4.68 (s, 1 H), 4.01–3.88 (m, 2 H), 3.55–3.44 (m, 2 H), 3.31–3.25 (m, 1 H), 2.82 (s, 3 H), 2.09 (s, 3 H). **$^{13}$C NMR** (101 MHz, $CDCl_3$): δ = 169.9, 142.8, 138.2, 128.6, 128.5, 126.8, 110.6, 75.0, 52.3, 49.7, 48.7, 35.3, 21.1. **LC-MS**: m/z calcd for $C_{15}H_{19}NO_4SNa$ $[M + Na]^+$: 332.093; found: 332.217.

**(4-Methoxyphenyl)(4-methylene-1-tosylpyrrolidin-3-yl)methyl Acetate (61e)**



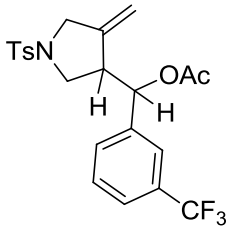

Product **61e** was isolated following **GP-4** as a colorless oil (44%, 27 mg, 0.066 mmol, dr 6:4) using **60e** (53 mg, 0.15 mmol) as reagent.

**IR (neat)**: 2922, 1737, 1513, 1344, 1227, 1159, 1027, 661 $cm^{-1}$.

**$^1$H NMR** (400 MHz, $CDCl_3$): δ = 7.69 (d, J = 8.3 Hz, 2 H), 7.63 (d, J = 8.3 Hz, 2 H), 7.33 (t, J = 7.9 Hz, 4 H), 7.16 (d, J = 7.9 Hz, 4 H), 6.85–6.82 (m, 4 H), 5.62–5.56 (m, 2 H), 5.04 (d, J = 18.2 Hz, 2 H), 4.87 (d, J = 2.0 Hz, 1 H), 4.47 (d, J = 2.1 Hz, 1 H), 3.88–3.69 (m, 4 H), 3.80 (s, 3 H), 3.78 (s, 3 H), 3.44–3.40 (m, 1 H), 3.33–3.29 (m, 1 H), 3.16–2.96 (m, 4 H), 2.44 (s, 3 H), 1.99 (s, 3 H), 1.98 (s, 3 H). **$^{13}$C NMR** (101 MHz, $CDCl_3$): δ = 169.8 (*d*a), 169.7 (*d*b), 159.7 (*d*a), 159.5 (*d*b), 144.2, 143.8 (*d*a), 143.8 (*d*b), 142.9, 132.8 (*d*a), 132.7 (*d*b), 130.5 (*d*a), 130.0 (*d*b), 129.7 (*d*a), 129.7 (*d*b), 128.7 (*d*a), 128.3 (*d*b), 127.8, 114.0 (*d*a), 113.8 (*d*b), 110.6 (*d*a), 110.3 (*d*b), 75.3 (*d*a), 75.3 (*d*b), 55.3 (*d*a), 55.3 (*d*b), 52.5 (*d*a), 52.1 (*d*b), 50.2 (*d*a), 50.0 (*d*b), 48.3 (*d*a), 48.0 (*d*b), 21.6, 21.1 (*d*a), 21.0 (*d*b).

**LC-MS**: m/z calcd for $C_{22}H_{25}NO_5SNa$ $[M + Na]^+$: 438.1; found: 438.3.

**(4-Methylene-1-tosylpyrrolidin-3-yl)[3-(trifluoromethyl)phenyl] methyl Acetate (61f)**

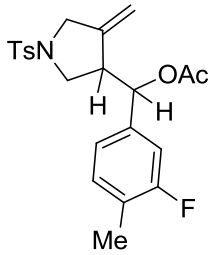



Product **61f** was isolated following **GP-4** as a colorless oil (36%, 20 mg, 0.044 mmol) using **60f** (59 mg, 0.15 mmol) as reagent.

**IR (neat)**: 2979, 1751, 1329, 1226, 1163, 903, 722, 650 $cm^{-1}$.

**$^{1}$H NMR** (400 MHz, $CDCl_3$): δ = 7.69 (d, J = 8.2 Hz, 2 H), 7.47–7.33 (m, 6H), 5.70 (d, J = 7.3 Hz, 1 H), 4.92 (d, J = 1.7 Hz, 1 H), 4.46 (d, J = 1.7 Hz, 1 H), 3.78 (s, J = 6.2 Hz, 2 H), 3.41–3.30 (m, 2 H), 3.12–3.08 (m, 1 H), 2.44 (s, 3 H), 2.02 (s, 3 H). **$^{13}$C NMR** (101 MHz, $CDCl_3$): δ = 169.6, 144.0, 142.5, 139.5, 130.4, 129.8, 129.0, 127.8, 127.2, 126.4, 125.2 (q, 2JC,F = 3.7 Hz), 123.5 (q, 3JC,F = 3.7 Hz), 123.0 (d, 1JC,F = 273 Hz), 110.8, 74.7, 52.3, 49.8, 48.3, 21.5, 20.9. **$^{19}$F NMR** (376 MHz, $CDCl_3$): δ = –62.7. **LC-MS**: m/z calcd for $C_{22}H_{22}F_3NO_4SNa$ $[M + Na]^+$: 476.1; found: 476.1.

**(3-Fluoro-4-methylphenyl)(4-methylene-1-tosylpyrrolidin-3-yl)methyl Acetate (61g)**




Product **61g** was isolated following **GP-4** as a colorless oil (41%, 25 mg, 0.062 mmol) using **60g** (52 mg, 0.15 mmol) as reagent.

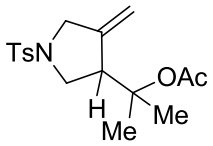
**IR (neat):** 2926, 1740, 1371, 1344, 1223, 1160, 662, 588 $cm^{-1}$.

**$^{1}$H NMR** (400 MHz, $CDCl_3$): δ = 7.69 (d, J = 8.3 Hz, 2 H), 7.33 (d, J = 8.4 Hz, 2 H), 7.11 (t, J = 7.8 Hz, 1 H), 6.90–6.84 (m, 2 H), 5.62 (d, J = 7.1 Hz, 1 H), 4.91 (s, 1 H), 4.54 (s, 1 H), 3.84–3.71 (m, 2 H), 3.39–3.30 (m, 2 H), 3.10–3.06 (m, 1 H), 2.44 (s, 3 H), 2.23 (s, 3 H), 1.99 (s, 3 H). **$^{13}$C NMR** (101 MHz, $CDCl_3$): δ = 169.6, 161.1 (d, $^{1}J_{C,F}$ = 245 Hz), 143.9, 142.7, 138.1, 132.7, 131.5 (d, $^{4}J_{C,F}$ = 5.3 Hz), 129.7, 127.8, 124.9 (d, $^{3}J_{C,F}$ = 17 Hz), 122.3 (d, $^{5}J_{C,F}$ = 3 Hz), 113.3 (d, $^{2}J_{C,F}$ = 23 Hz), 110.4, 74.6, 52.4, 49.8, 48.1, 21.6, 20.9, 14.3 (d, $^{6}J_{C,F}$ = 3 Hz).

**$^{19}$F NMR** (376 MHz, $CDCl_3$): δ = –116.

**LC-MS**: m/z calcd for $C_{22}H_{24}FNO_4SNa$ $[M + Na]^+$: 440.1; found: 440.2.

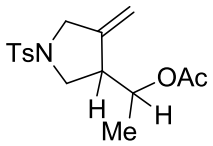
**2-(4-Methylene-1-tosylpyrrolidin-3-yl)propan-2-yl Acetate (61h)**




Product **61h** was isolated following **GP-4** as a pale yellow oil (70%, 35 mg, 0.105 mmol) using **60h** (41 mg, 0.15 mmol) as reagent. Spectra correspond to the literature.[46]

**1H NMR** (300 MHz, $CDCl_3$): δ = 7.68 (d, *J* = 8.2 Hz, 2 H), 7.34 (d, *J* = 8.0 Hz, 2 H), 5.04 (d, *J* = 10.6 Hz, 1 H), 3.86 (d, *J* = 12.1 Hz, 1 H), 3.71 (d, *J* = 13.7 Hz, 1 H), 3.71 (d, *J* = 13.7 Hz, 1 H), 3.41 (dd, *J* = 9.6, 3.1 Hz, 1 H), 3.33–3.31 (m, 1 H), 3.25–3.19 (m, 1 H), 2.42 (s, 3 H), 1.91 (s, 3 H), 1.45 (s, 3 H), 1.46 (s, 3 H).

**1-(4-Methylene-1-tosylpyrrolidin-3-yl)ethyl Acetate (61i)**



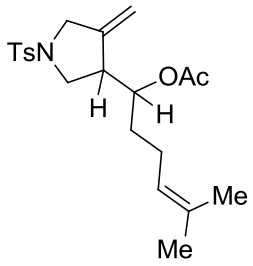

Product **61i** was isolated following **GP-4**as a colorless oil (59%, 28 mg, 0.087 mmol) using **60i** (35 mg, 0.15 mmol) as reagent.
**IR (neat)**: 2926, 1734, 1372, 1343, 1159, 1092, 662, 547 $cm^{-1}$.

**$^1$H NMR** (400 MHz, $CDCl_3$): δ = 7.71 (d, J = 8.2 Hz, 2 H), 7.34 (d, J = 8.0 Hz, 2 H), 5.01 (dd, J = 18.6, 2.0 Hz, 2 H), 4.96–4.93 (m, 1 H), 3.85–3.72 (m, 2 H), 3.43 (dd,

[46]W. Wang, J. Yang, F. Wang and M. Shi, *Organometallics,* 2011, **30**, 3859.

J = 9.8, 7.9 Hz, 1 H), 3.27–3.23 (m, 1 H), 2.82–2.79 (m, 1 H), 2.43 (s, 3 H), 1.92 (s, 3 H), 1.18 (dd, J = 10.2, 5.9 Hz, 3 H). **$^{13}$C NMR** (101 MHz, $CDCl_3$): δ = 170.1, 143.8, 143.8, 132.8, 129.7, 127.8, 109.4, 70.1, 52.5, 49.3, 47.5, 21.5, 21.0, 17.8. **LC-MS**: m/z calcd for $C_{16}H_{21}NO_4SNa$ $[M + Na]^+$: 346.1; found: 346.2.

**6-Methyl-2-(4-methylene-1-tosylpyrrolidin-3-yl)hept-5-en-2-yl Acetate (61j)**

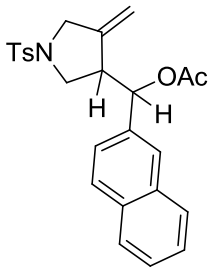



Product **61j** was isolated following **GP-4** as a pale yellow oil (43%, 26 mg, 0.065 mmol) using **60j** (35 mg, 0.15 mmol) as reagent.

**IR (neat)**: 2923, 1734, 1345, 1237, 1160, 1094, 660, 589 $cm^{-1}$.

**$^1$H NMR** (300 MHz, $CDCl_3$): δ = 7.70 (d, J = 8.3 Hz, 2 H), 7.33 (d, J = 7.9 Hz, 2 H), 5.05–4.98 (m, 2 H), 3.92–3.67 (m, 2 H), 3.54–3.48 (m, 2 H), 3.23–3.17 (m, 2 H), 2.43 (s, 3 H), 2.06–2.89 (m, 2 H), 1.96 (s, 3 H), 1.81–1.72 (m, 1 H), 1.66 (s, 3 H), 1.67 (s, 3 H), 1.46–1.38 (m, 1 H), 1.31 (s, 3 H). **$^{13}$C NMR** (75 MHz, $CDCl_3$): δ = 170.2, 143.7, 132.5, 132.0, 129.7, 127.8, 127.2, 123.4, 111.5, 85.4, 53.2, 49.6, 49.1, 35.3, 25.7, 22.2, 22.0, 21.5, 20.6, 17.6. **HRMS**: m/z calcd for $C_{22}H_{31}NO_4SNa$ $[M + Na]^+$: 428.1875; found:428.1869.

**(4-Methylene-1-tosylpyrrolidin-3-yl)(naphthalen-2-yl)methyl Acetate (61k)**

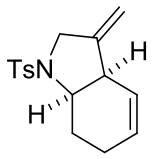



Product **61k** was isolated following **GP-4** as a colorless oil (43%, 28 mg,0.065 mmol) using **60k** (56 mg, 0.15 mmol) as reagent.

**IR (neat)**: 2924, 1737, 1344, 1223, 1160, 1093, 814, 547 $cm^{-1}$.

**$^1$H NMR** (400 MHz, $CDCl_3$): δ = 7.82–7.80 (m, 3 H), 7.70–7.68 (m, 3 H), 7.50–7.48 (m, 2 H), 7.36–7.31 (m, 3 H), 5.86 (d, J = 7.2 Hz, 1 H), 4.88 (s, 1 H), 4.51 (s, 1 H), 3.86–3.77 (m, 2 H), 3.42–3.41 (m, 2 H), 3.28–3.21 (m, 1 H), 2.44 (s, 3 H), 2.03 (s, 3 H). **$^{13}$C NMR** (101 MHz, $CDCl_3$): δ = 169.7, 143.8, 142.9, 135.7, 133.2, 132.9, 132.8, 127.9, 128.4, 128.1, 127.9, 127.7, 126.4, 126.4, 126.3, 124.3, 110.4, 75.6, 52.5, 50.0, 48.0, 21.6, 21.0. **LC-MS**: m/z calcd for $C_{25}H_{25}NO_4SNa$ $[M + Na]^+$: 458.1; found: 458.3.

**(3a,7a)-3-Methylene-1-tosyl-2,3,3a,6,7,7a-hexahydro-1H-indole (63a)**




Product **63a** was isolated following **GP-5** as a colorless oil (69%, 60.1 mg, 0.21 mmol) using **62a** (87 mg, 0.3 mmol) as reagent. Spectroscopic data correspond to the literature.[42]

**$^1$H NMR** (300 MHz, $CDCl_3$): δ = 7.73 (d, J = 8.3 Hz, 2 H), 7.30 (d, J = 8.0 Hz, 2 H), 5.80–5.77 (m, 1 H), 5.65–5.60 (m, 1 H), 4.98 (d, J = 2.2 Hz, 1 H), 4.84 (d, J = 2.3 Hz, 1 H), 4.01–3.84 (m, 3 H), 2.73 (br s, 1 H), 2.42 (s, 3 H), 2.11–1.89 (m, 3 H), 1.63–1.51 (m, 1 H). The *syn*-configuration was determinated by NOESY NMR experiment (see Figure 4).

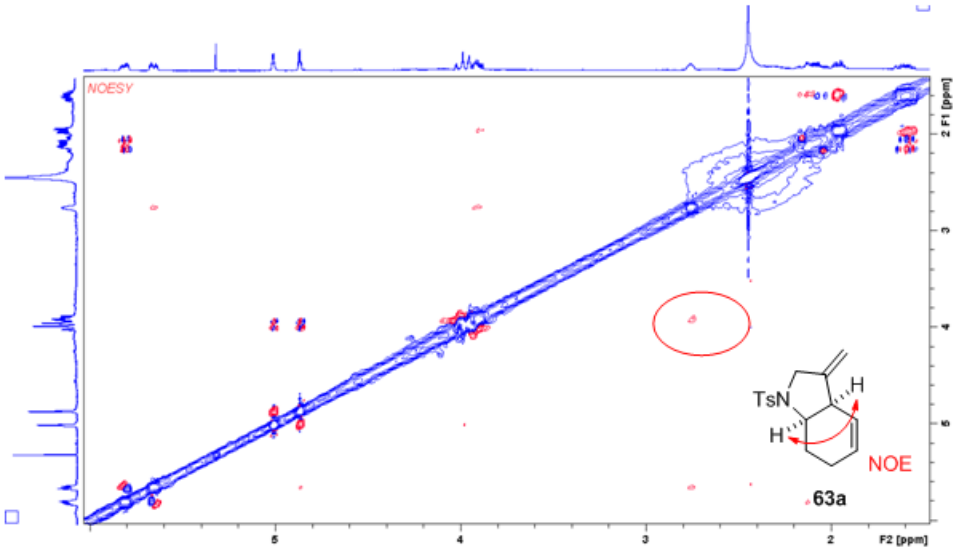
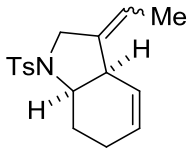



**Figure 4** NOESY NMR spectrum of product **63a**

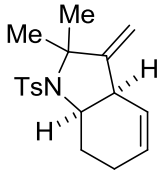
**3-Ethylidene-1-tosyl-2,3,3a,6,7,7a-hexahydro-1H-indole (63b)**




Product **63b** was isolated following **GP-5** as a colorless oil (66%, 60 mg, 0.2 mmol) using **62b** (91 mg, 0.3 mmol) as reagent.
**IR (neat)**: 2922, 1597, 1333, 1157, 1092, 814, 663, 545 $cm^{-1}$.

**$^1$H NMR** (400 MHz, $CDCl_3$): δ = 7.73 (d, J = 8.3 Hz, 2 H), 7.30 (d, J = 8.1 Hz, 2 H), 5.77–5.75 (m, 1 H), 5.62–5.57 (m, 1 H), 5.24–5.17 (m, 1 H), 4.07–4.01 (m, 1 H), 3.86–3.79 (m, 1 H), 2.71 (br s, 1 H), 2.42 (s, 3 H), 2.20–1.86 (m, 4 H), 1.64–1.55 (m, 4 H). **$^{13}$C NMR** (101 MHz, $CDCl_3$): δ = 143.3, 138.6, 129.7, 128.1, 127.3, 124.7, 117.9, 115.7, 58.8, 48.6, 42.6, 26.1, 23.3, 21.5, 14.5. **HRMS**: m/z calcd for $C_{17}H_{22}NO_2S$ $[M + H]^+$: 304.1373; found: 304.1368.

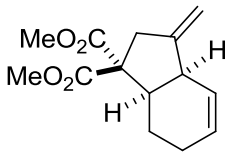
**(3a,7a)-2,2-Dimethyl-3-methylene-1-tosyl-2,3,3a,6,7,7a-hexahydro- 1H-indole (63c)**




Product **63c** was isolated following **GP-5** as a colorless oil (32%, 20.3 mg, 0.06 mmol) using **62c** (63.5 mg, 0.2 mmol) as reagent.
**IR (neat)**: 2917, 1567, 1331, 1167, 1390, 878, 623, 555 $cm^{-1}$.

**$^{1}$H NMR** (300 MHz, $CDCl_3$): δ = 7.78 (d, J = 8.2 Hz, 2 H), 7.27 (d, J = 4.9 Hz, 2 H), 5.90–5.50 (m, 2 H), 4.98 (d, J = 2.9 Hz, 1 H), 4.78 (d, J = 2.4 Hz, 1 H), 3.88 (dt, J = 9.0, 6.6 Hz, 1 H), 2.81 (br s, 1 H), 2.41 (s, 3 H), 2.17– 1.86 (m, 2 H), 1.73 (s, 3 H), 1.48 (s, 3 H), 1.33–1.25 (m, 2 H). **$^{13}$C NMR** (75 MHz, $CDCl_3$): δ = 157.0, 142.6, 129.4, 129.4, 127.0, 123.9, 123.8, 103.4, 67.1, 56.4, 37.8, 30.0, 29.9, 29.2, 23.5, 21.5. **LC-MS**: m/z calcd for $C_{18}H_{24}NO_2S$ $[M + H]^+$: 318.1; found: 318.1.

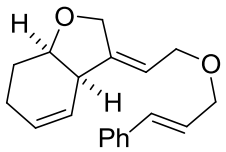
**Dimethyl (3a,7a)-3-Methylene-2,3,3a,6,7,7a-hexahydro-1H-indene-1,1-dicarboxylate (63d)**




Product **63d** was isolated following **GP-5** as a colorless oil (70%, 52.3 mg, 0.21 mmol) using **62d** (75 mg, 0.3 mmol) as reagent.
**IR (neat)**: 2950, 1725, 1434, 1297, 1218, 1039, 895, 701 $cm^{-1}$.

**$^{1}$H NMR** (300 MHz, $CDCl_3$): δ = 5.88–5.83 (m, 1 H), 5.77–5.72 (m, 1 H), 4.97 (d, J = 2.2 Hz, 1 H), 4.83 (d, J = 2.6 Hz, 1 H), 3.73 (s, 3 H), 3.72 (s, 3 H), 3.32 (dq, J = 17.8, 2.5 Hz, 1 H), 3.21 (br s, 1 H), 2.89–2.81 (m, 2 H), 2.04–1.99 (m, 2 H), 1.35–1.07 (m, 2 H). **$^{13}$C NMR** (75 MHz, $CDCl_3$): δ = 172.3, 170.2, 151.1, 126.5, 126.4, 107.6, 62.4, 52.8, 52.5, 43.1, 42.9, 37.7, 24.5, 21.3. **LC-MS**: m/z calcd for $C_{14}H_{19}O_4$ [M + H]+: 251.1; found: 251.1.

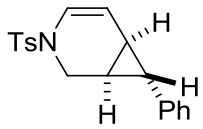
**(3a,7a,*Z*)-3-[2-(Cinnamyloxy)ethylidene]-2,3,3a,6,7,7a-hexahydrobenzofuran (63e)**




Product **63e** was isolated following **GP-5** as a colorless oil (44%, 37.3 mg, 0.13 mmol) using **62e** (85 mg, 0.3 mmol) as reagent.
**IR (neat)**: 2924, 1735, 1449, 1170, 1039, 963, 746, 692 cm–1.

**$^1$H NMR** (300 MHz, $CDCl_3$): δ = 7.42–7.23 (m, 5 H), 6.63 (d, J = 15.9 Hz, 1 H), 6.31 (dt, J = 15.9, 6.0 Hz, 1 H), 5.79–5.75 (m, 1 H), 5.57–5.54 (m, 2 H), 4.53 (d, J = 13.4 Hz, 1 H), 4.38 (d, J = 12.5 Hz, 1 H), 4.23 (td, J = 5.7, 2.8 Hz, 1 H), 4.15 (d, J = 6.1 Hz, 2 H), 3.98 (d, J = 6.6 Hz, 2 H), 3.18 (s, 1 H), 2.38–2.10 (m, 1 H), 2.00–1.87 (m, 2 H), 1.74–1.64 (m, 1 H). **$^{13}$C NMR** (75 MHz, $CDCl_3$): δ = 146.5, 136.6, 132.6, 128.5, 127.7, 127.0, 126.4, 126.2, 125.9, 117.2, 76.4, 70.8, 67.7, 67.4, 43.4, 24.5, 20.0. **LC-MS**: m/z calcd for $C_{19}H_{23}O_2$ [M + H]+: 283.2; found: 283.2.

**7-Phenyl-3-tosyl-3-azabicyclo[4.1.0]hept-4-ene (61a′)**




Complex **59** (1.7 mg, 0.9 mmol, 0.6 mol%) and freshly degassed toluene (0.5 mL) were added under $N_2$ to a Schlenk-type flask. Substrate **60a** (0.15 mmol) and benzoic acid (0.15 mmol, 1 equiv) were sequentially added. The mixture was heated at 110 °C and the conversion was followed analyzing samples via TLC. Upon complete conversion of the substrate (24 h), the solution was diluted with EtOAc (5 mL) and purified. Product **61a′** was obtained as a yellow oil; yield: 17 mg (36%, 0.054 mmol). Spectra correspond to the literature.[46]

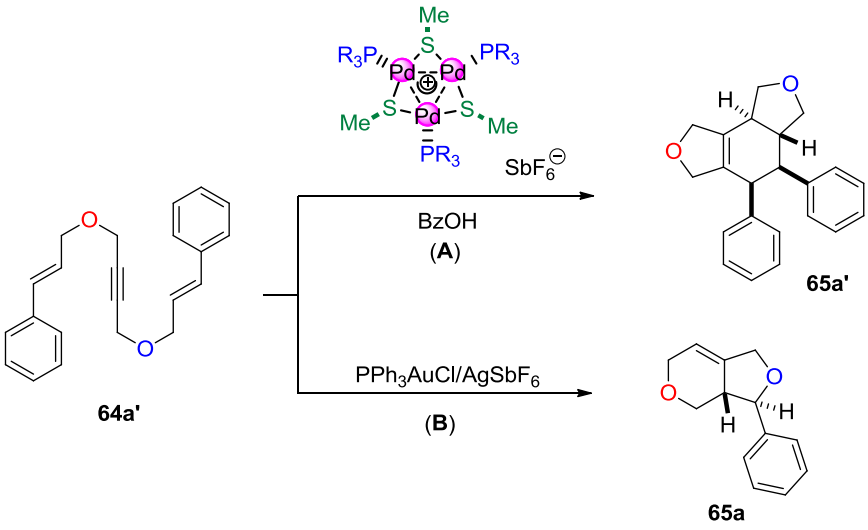
**$^1$H NMR** (300 MHz, $CDCl_3$): δ = 7.72 (d, J = 8.3 Hz, 2 H), 7.39 (d, J = 8.0 Hz, 2 H), 7.28–7.13 (m, 3 H), 6.82 (d, J = 7.1 Hz, 2 H), 6.45 (d, J = 8.0 Hz, 1 H), 5.53 (dd, J = 8.0, 5.4 Hz, 1 H), 4.06 (d, J = 12.0 Hz, 1 H), 3.18 (dd, J = 12.0, 2.9 Hz, 1 H), 2.49 (s, 3 H), 1.96–1.90 (m, 1 H), 1.66–1.63 (m, 1 H), 1.51–1.45 (m, 1 H).

*Chapter 3*

# Diasteroselective bicyclization of enynols via gold catalysis

## 3.1 Introduction

As previously reported, our group developed complex cascades catalysed by all-metal aromatic $Pd_3^+$ clusters starting from polyunsaturated substrates. [26] In that work we showed that a family of tricycle products could be isolated in high yield and diasterocontrol (Scheme 27, path A). To gain further insight in the reaction mechanism, we thought to synthesize a trinuclear alkyne-metal complex by ligand exchange with an ancillary phosphine. For this experiment substrate **64a'** was selected as starting material.




**Scheme 27** Discovery of the gold(I)-catalyzed cycloisomerizations of enynols.

Several phosphine scavengers were tested in order to break the Pd-P bond, including chloride dimethylsulphide complex.[47] Controlling the reaction at room temperature by $^{31}P$ NMR, led us to notice the rapid decomposition of the tripalladium cluster along with formation of $AuClPPh_3$. Interestingly, through the analysis of the $^1H$ NMR spectrum we discovered that dienyne **64a'** was

[47] Y. Wang, A. Monfredini, P.-A. Deyris, F. Blanchard, E. Derat, G. Maestri and M. Malacria, *Chem. Sci.*, 2017, **8**, 7394.

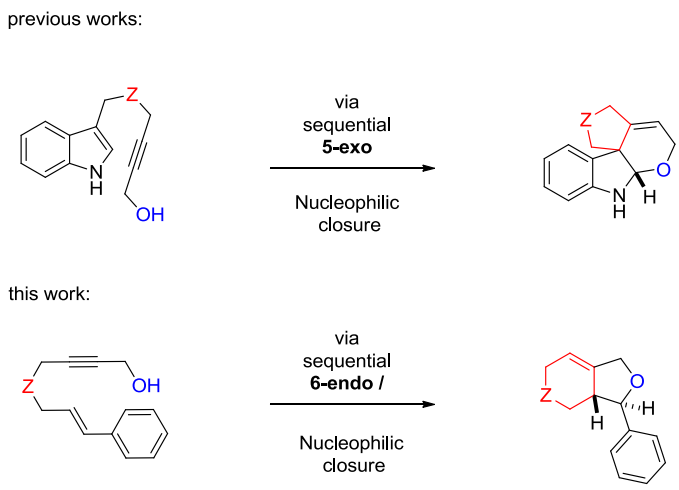
partially converted into a new species featured by different resonances compared to those of **65a'**.

Delighted by these results, we decided to test **64a'** in the presence of catalytic amount of $AuClPPh_3$ and $AgSbF_6$. Surprisingly, the reaction afforded a tetrahydro-3H-furo[3,4-C]pyran scaffold **65a** (Scheme 27, path B). The formation of product **65a** was allowed by the formal extrusion of a cinnamyl unit from substrate **64a'**.

## 3.2 Results and discussion

At this point, we thought to design a simpler starting material in order to improve the atom economy of the reaction and develop a mild catalytic method to access heterobicycles **65**. To this end, we focused our attention on the use of configurationally pure *(E)* 1,6-enynol **64a**. Substrates of type **64** are very little described in literature with few elegant examples reported by the group of Bandini which developed the intramolecular gold(I)-catalysed dearomatization of indoles (Scheme 28).[48] Prompted by the complementary reactivity observed in our system, which led to a challenging *6-endo* cyclization rather than the expected *5-exo* one, we decided to proceed with the optimization of the reaction conditions.

[48] (a) G. Cera, M. Chiarucci, A. Mazzanti, M. Mancinelli and M. Bandini, *Org. Lett.*, 2012, **14**, 1350; (b) G. Cera, P. Crispino, M. Monari and M. Bandini, *Chem. Commun*., 2011, **47**, 7803.



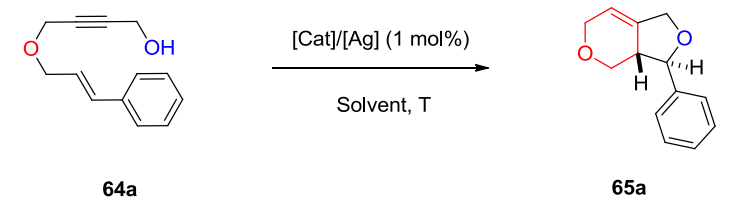

**Scheme 28** Enynols in gold(I)-catalysis.

The optimization process started using Au(III) salts and $CHCl_3$ as solvent at 0°C. This attempt resulted in no conversion of the starting material (Table 4, entry 1). Moreover, we did not observe any reactivity repeating the experiment at higher temperatures.

However, the previously employed catalytic system, obtained combing $PPh_3AuCl$ with $AgSbF_6$, allowed the isolation of **65a** in 50% yield (Table 4, entry 2). The product was delivered with an excellent diastereoselectivity (*d.r.* > 25:1) using a catalyst loading as low as 1 mol %.

Subsequently, different silver salts were tested to enhance the electrophilicity of $AuClPPh_3$ (entries 3-6). Particularly, adding $AgPF_6$ afforded product **65a** in 50% yield (entry 3) whereas the use of silver triflate and tetrafluoroborate resulted in diminished yields, 27% and 13%, respectively (entry 4-5). The reaction did not occur in the presence of acetate anions (entry 6). From this screening emerged that the coordinating properties of the counter anion and the reaction yield were strongly correlated. Indeed, less coordinating counterions had a positive effect in promoting the cycloisomerization process while more coordinating ones reduced the reactivity. Next, we investigated the

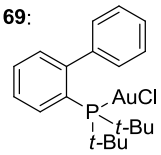
solvent effect. Dichloromethane and 1,2-dichloroethane (entries 7-8) afforded the desired product in a lower yield compared to that obtained with chloroform (20% and 17% respectively).



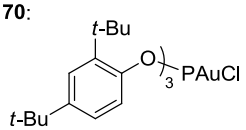

**64a** **65a**

**66**: $PPh_3AuCl$ **67**: $PAr_3AuCl$ Ar: 4-$FC_6H_4$ **68**: $PAr_3AuCl$ Ar: 4-$OMeC_6H_4$

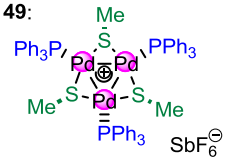
**69**:




**70**:




**49**:




| Entry | [Cat] | [Ag] | Solvent | T °C | Yield |
|---|---|---|---|---|---|
| **1** | $AuCl_3$ | -- | $CHCl_3$ | 0 | |
| **2**[a] | **66** | $AgSbF_6$ | $CHCl_3$ | 0 | 50 |
| **3** | **66** | $AgPF_6$ | $CHCl_3$ | 0 | 50 |
| **4** | **66** | AgOTf | $CHCl_3$ | 0 | 27 |
| **5** | **66** | $AgBF_4$ | $CHCl_3$ | 0 | 13 |
| **6** | **66** | AgOAc | $CHCl_3$ | 0 | -- |
| **7** | **66** | $AgSbF_6$ | $CH_2Cl_2$ | 0 | 20 |
| **8** | **66** | $AgSbF_6$ | 1,2-DCE | 0 | 17 |
| **9** | **66** | $AgSbF_6$ | MTBE | 0 | -- |
| **10** | **66** | $AgSbF_6$ | toluene | 0 | -- |
| **11** | **67** | $AgSbF_6$ | $CHCl_3$ | 25 | 46 |
| **12** | **68** | $AgSbF_6$ | $CHCl_3$ | 25 | 42 |

| | | | | | |
|---|---|---|---|---|---|
| **13** | **69** | $AgSbF_6$ | $CHCl_3$ | 0 | 16 |
| **14** | **70** | $AgSbF_6$ | $CHCl_3$ | 25 | 56 |
| **15** | **70** | $AgSbF_6$ | $CHCl_3$ | 25 | 91[b] |
| **16** | **49** | | $CHCl_3$ | 25 | -- |
| **17** | **--** | $AgSbF_6$ | $CHCl_3$ | 25 | -- |

**Table 4**. [a] Reaction conditions: **64a** (0.4 mmol), [Au] (1.0 mol %), [Ag] (1.0 mol %), solvent (0.3 M), 4 hs under inert atmosphere. [b] NMR yield using trimethoxybenzene as the internal standard.

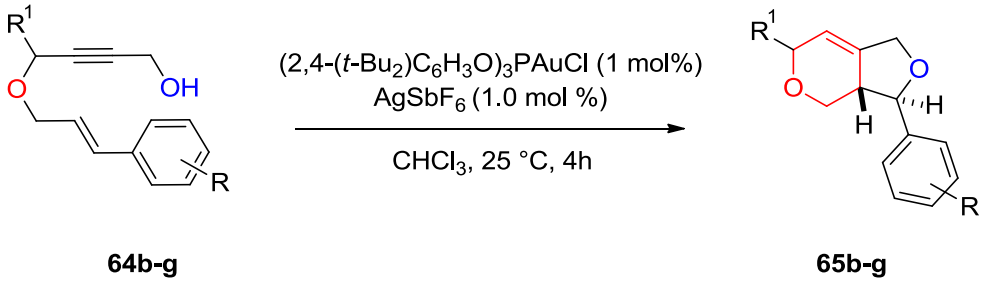
No conversion was noticed using non-chlorinated solvents, such as MTBE and Toluene (entries 9-10). These results showed that the use of a solvent with mild Brönsted acidity is crucial to obtain higher turnover numbers. At this point the reaction was studied in the presence of different Gold(I) complexes with phosphines bearing either electron-withdrawing or donating groups. Complexes **67** and **68** showed to be competent for the cycloisomerization reaction (entries 11-12), while Echavarren's catalyst **69** was found not suitable, delivering **65a** in a meagre 16% yield (entry 13). Finally, the best catalytic performance was achieved using phosphite gold(I) catalyst **70**,[49] which afforded **65a** in 56% (entry 14). As expected, the less donating ligand (tris(2,4-di-*tert*-butylphenyl)phosphate) turned out to be the best group able to enhance the electrophilic properties of gold (I) promoting significantly the activation of the substrate. Try as we might, we could not identify any by-product of the reaction despite a limited mass recovery. For this reason we set out to calculate the yield by $^1$H NMR spectroscopy using trimethoxybenzene as internal standard. Surprisingly, such analysis revealed that **65a** was formed in

[49] a) S. Fernández, J. González, J. Santamaría, and A.Ballesteros, *Angew. Chem. Int. Ed.*, 2019, **58**, 10703. b) M. M. Mastandrea, N. Mellonie, P. Giacinto, A. Collado, S. P. Nolan, G. P. Miscione, A. Bottoni and M. Bandini, *Angew. Chem. Int. Ed.*, 2015, **54**, 14885; c) M. C. B. Jaimes, F. Rominger, M. M. Pereira, R. M. B. Carrilho, S. A. C. Carabineiro and A. S. K. Hashmi, *Chem. Commun.*, 2014, **50**, 4937; d) C. Obradors and A. M. Echavarren, *Chem. Commun.*, 2014, **50**, 16.

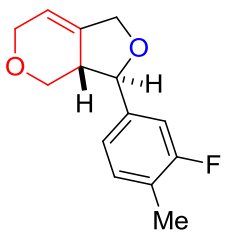
excellent yield: 91% (entry 15). Thanks to this experiment we were able to demonstrate the decomposition of the desired product during the purification process performed on silica gel. In particular, the limited stability of **65a** was likely due to the presence of allylic and benzylic C-H groups alpha to oxygen atoms. This was confirmed by repeating experiments of entries 3, 11 and 12, which were taken as representative examples. The corresponding yields of **65a** measured by NMR were 8–28% higher compared to the isolated ones (60%, 74% and 50%, respectively). A purification test using neutral alumina, instead of silica, was carried out. However, no improvement was noticed because **65a** was isolated in 50% yield. Try as we might, we were unable to detect any by-product of the reaction, despite a limited mass recovery. A control test carried out with tripalladium cluster **49** failed in delivering product **65a** (entry 16). Similarly, no reactivity was observed when we performed the reaction in the absence of a gold source (entry 17).

Subsequently, a family of *O*-tethered enynols of type **64** was synthesized in order to explore the scope of the cascade cycloisomerization (Figure 5). Substrates featured by halogenated styryl groups, and extended aromatic systems, such as 1- and 2-naphthyl units, were converted into the corresponding products **65b-e** in excellent diasteroselectivity and complete regiocontrol (33-64%, *d.r.* > 25:1). Also racemic substrates **64f-g** could be employed. Interestingly, the synthesis of **65f** proceeded in a stereoselective manner (50%, *d.r.* > 25:1). The relative configuration of the phenyl group on the pyrane ring has been assigned through NMR experiments, which showed NOE correlation between the benzylic and the head-bridging protons. On the other hand, **65g** was isolated with a significant loss of the diasterochemical purity (31%, *d.r.* = 2:1). Such result could be due to the presence of the smaller methyl substituent. As for **65a**, the yields of **65b-g** measured by NMR were generally higher than those obtained after purification with column

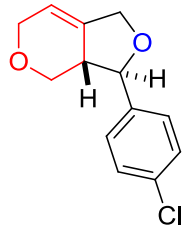
chromatography (by +2–40%, Figure 5). Interestingly, the major difference was observed for products **65d-e** bearing a naphthyl group.



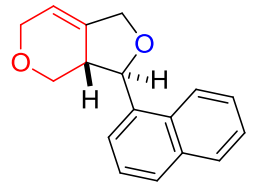

**64b-g** **65b-g**



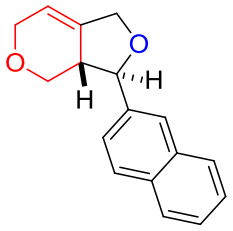

**65b**, 33%, *35%*
(*d.r.* > 25 : 1)



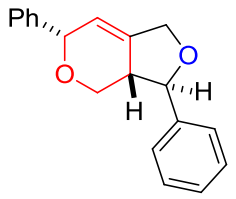

**65c**, 51%, *56%*
(*d.r.* > 25 : 1)



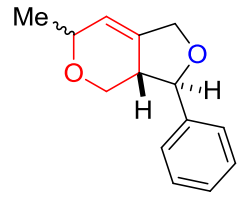

**65d**, 40%, *80%*
(*d.r.* > 25 : 1)




**65e**, 64%, *87%*
(*d.r.* > 25 : 1)




**65f**, 55%, *60%*
(*d.r.* > 25 : 1)




**65g**, 31%, *39%*
(*d.r.* = 2 : 1)

**Figure 5**. Scope for *O*-tethered enynols, the NMR yields are in italic.

The structure of tetrahydro-3H-furo[3,4-c]pyranes **65** was initially determinated through extensive NMR correlation experiments and then confirmed by X-ray analysis on crystals of **65e** (Figure 6).

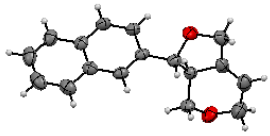
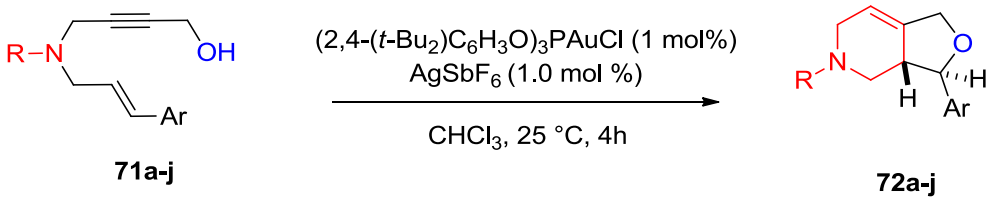


**Figure 6.** X-ray of compound **65e**

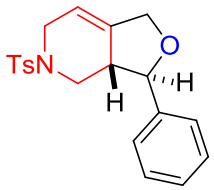
Different mono-, di- and trisubstituted alkenes, including non-conjugated ones were found unreactive under standard reaction conditions. Also attempts to extend the reaction to styryl arms with strongly withdrawing groups, such as *p*-$CF_3$ ones, proved fruitless at present stage. Similarly, replacing the oxygen tether with a diethyl or dimethyl malonate group did not allow to isolate the corresponding cycloisomerized products.

Next we decided to synthesize a family of *N*-tethered enynols of type **71**. Their reactivity was investigated under the optimized catalytic conditions. The reaction of **71a** proceeded with comparable regioselectivity affording hexahydrofuro[3,4-c] pyridines **72a** in 71% yield (Figure 7).

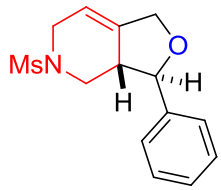



**71a-j**

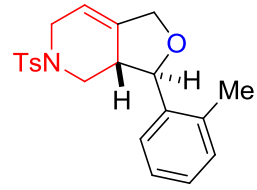
**72a-j**



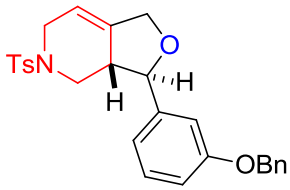

**72a**, 71%
(*d.r.* > 25 : 1)



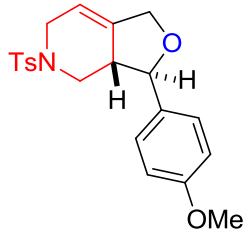

**72b**, 45%
(*d.r.* > 25 : 1)



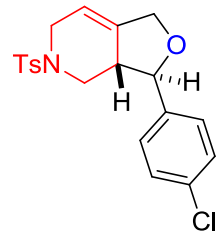

**72c**, 87%
(*d.r.* > 25 : 1)



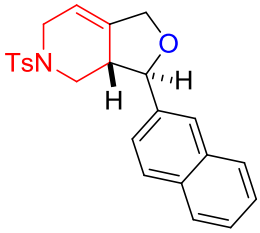

**72d**, 64%
(*d.r.* > 25 : 1)



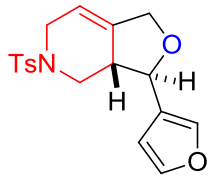

**72e**, 92%
(*d.r.* > 25 : 1)



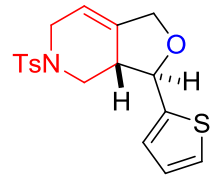

**72f**, 71%
(*d.r.* > 25 : 1)




**72g**, 63%
(*d.r.* > 25 : 1)




**72h**, 68%
(*d.r.* > 25 : 1)




**72i**, 68%
(*d.r.* > 25 : 1)

**Figure 7**. Scope of N-tethered enynols

Overall, 1,6-enynols **71** showed to be more robust compared to the *O*-tethered analogues **64**, delivering products **72** in higher yields and with complete diastereoselectivities. The replacement the tosyl group with the mesyl one lowered the yield to 45% (**72b**). Satisfyingly, a methyl group in *ortho*-position on the aromatic ring was well tolerated, delivering **72c** in excellent yield (87%). Afterwards, different functional groups, such as ethers (**71d-e**) and chloride (**71f**) were tested. The corresponding polycycles (**72d-f**) were afforded in synthetically useful yields (64-92%). Also the replacement of the phenyl ring with heterocycles, such as furane and thiophene (**71h-i**), was well tolerated allowing us to isolate the bicyclic derivatives **72h-i** in good yields (68%). It is worth noting that the trend showed by these results is highly reminiscent of a linear Hammet-like correlation between the electron density of the styryl fragment and the outcome of the sequence.

This aspect is particularly put in evidence when we compare the yield of **72a** with that of **72c** (71% and 87%, respectively). Ethereal aryls **72d** and **72e** followed suit, too. The best performance was obtained with substrate **72e** bearing the *para*-methoxy substituted ring (92% yield). The proposed structure of products **72** was further confirmed by X-ray analysis on **72a** (Figure 8).

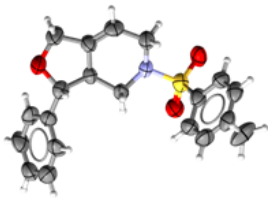
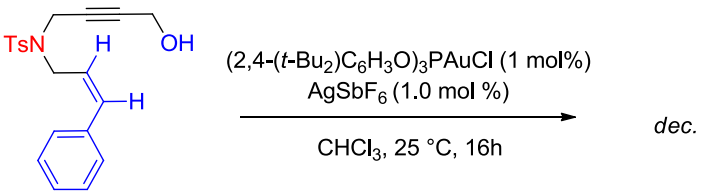


**Figure 8**. X-ray structure of **72a**.

Finally, *(Z)*-enynol **71j** was synthesized and submitted to the optimized catalytic conditions. Such substrate underwent slow decomposition without the formation of any product (Scheme 29).




(Z)-**71j**

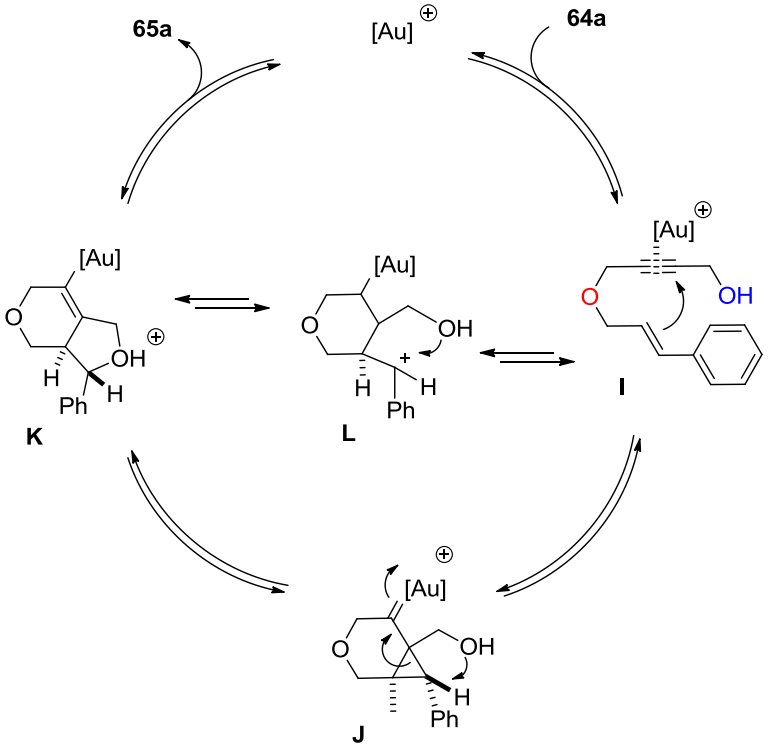
**Scheme 29** Decomposition of *(Z)*-enynol **71j**

Together with the observed requirement for an electron rich, highly nucleophilic alkene moiety (*vide supra*), this outcome could be due to an allyl strain,[50]which partially tilts the phenyl ring reducing the overall conjugation of a *(Z)*-styryl arm. In analogy to previous literature examples on similar substrates [51,48] we proposed the initial formation of $\eta^2$ adduct **I** (Scheme 30) through reversible coordination of enynol **64a** on the cationic gold catalyst. Such species is in equilibrium with the two corresponding $\eta^1$ intermediates, which in turn promote the activation of their uncoordinated alkyne carbons. Two competing pathways could then take place. In contrast to the reaction of indole derivatives,[48] regioselective *6-endo-dig* cyclopropanation would occur forming the strained bicyclo [4.1.0] gold-carbene complex **J**. The latter, after a concerted 1,2-carbon shift followed by a nucleophilic attack, affords species **K**.

[50] R. W. Hoffmann, *Chem. Rev.*, 1989, **89**, 1841

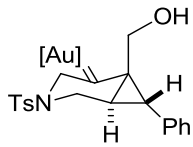
[51] For selected examples, see: (a) F. Gagosz, *Synthesis*, 2019, **51**, 1087. (b) D. Pflästerer and A.S.K. Hashmi, *Chem. Soc. Rev.*, 2016, **45**, 1331. (c) W. Zi and D.F. Toste, *Chem. Soc. Rev.*, 2016, **45**, 4567. (d) R. Dorel and A.M. Echavarren, *Chem. Rev.*, 2015, **115**, 9028; (e) M. Jia and M. Bandini, *ACS Catal.*, 2015, **5**, 1638. (f) L. Fensterbank and M. Malacria, *Acc.Chem.Res.*, 2014, **47**, 953, part of a special issue dedicated to gold catalysis. (g) G. Abbiati, E. Rossi and Beilstein *J.Org.Chem.*, 2014, **10**, 481. (h) D. Gerayalde and C. Nevado, *ACS Catal.*, 2012, **2**, 1462. (i) D. Qian and J. Zhang, Chem. *Soc. Rev.*, 2015, **44**, 677. (j) Y. Li, W. Li and J. Zhang, *Chem. Eur. J.*, 2017, **23**, 467. (k) P.C. Zhang, Y. Wang, Z.M. Zhang and J. Zhang, *Org. Lett.*, 2018, **20**, 7049.

Such intermediate finally yields product **65a** through a protodeauration process.

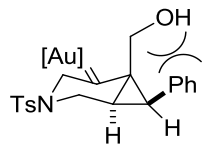



**Scheme 30**. Possible reaction mechanisms.

This last step is probably mediated by the mild acidity of the solvent because of the unfavourable 1,4-relation between the metal and the oxonium ion. The negative result obtained with *(Z)*-enynol **71j** could be related to the structure of intermediate **J** where the methylene group would be in a *syn*-configuration with respect to the phenyl ring (Figure 9). Such steric hinderance would have hampered the concerted ring expansion process.




*Anti*-**J**




*Cis*-**J**

**Figure 9**. Structure of intermediate **J**

The formation of bicycle complex **J** is also consistent with the relative configuration of the two contiguous stereocenters of products, which are invariably in *anti* relation. Nonetheless, the unsatisfactory results obtained with electron-deficient styrenes seems somehow in contrast with the formation of a dicarbenoid gold intermediates.[51]

For this reason we considered another reaction pathway involving the formation of the benzylic carbocation **L** which would be quenched by the hydroxy group to afford oxonium ion **K**. As before, a protodeauration step would finally deliver product **65a**. The restricted flexibility of the dihydropyrane ring could favour the nucleophilic oxygen attack and prevent any racemization of the resulting stereocenter. Even though the discrimination between the carbene- and vinyl-gold character is still far from trivial, in the literature[52] the former pathway is often considered a more accurate description of gold-catalyzed alkyne sequences. However, in our case, the second option suits better the observed trend on the electron density of styryl arms.

Reasoning on the greater electrophilicity of the phosphite–gold complex compared to that of phosphine–gold ones, [49] we supposed that the formation of benzylic cation **L** might become more favourable. This in turn could thus be

[52] (a) D. Benitez, N.D. Shapiro, E. Tkatchouk, Y. Wang, W. A. Goddard and D.F. Toste, *Nat.Chem.*, 2009, **1**, 482. (b) G. Seidel, R. Mynott and A. Fürstner, *Angew.Chem.Int.Ed.*, 2009, **48**, 2510.(c) A.S.K. Hashmi, *Angew.Chem.Int.Ed.*, 2008, **47**, 6754. (d) A. Correa, N. Marion, L. Fensterbank, M. Malacria, S. Nolan and L. Cavallo, *Angew.Chem.Int.Ed.*, 2008, **47**, 718.

responsible for the regiochemical switch in the first cyclization with respect to the reactivity described in the literature.[48]

## 3.3 Conclusions

We have documented the unprecedented cycloisomerization of *(E)*-1,6-enynols catalysed by a phosphite gold(I) complexes. 4.3.0 (hetero)bicycles were obtained with complete regio- and diastereoselection under mild conditions, with good yields and notable functional group tolerance.

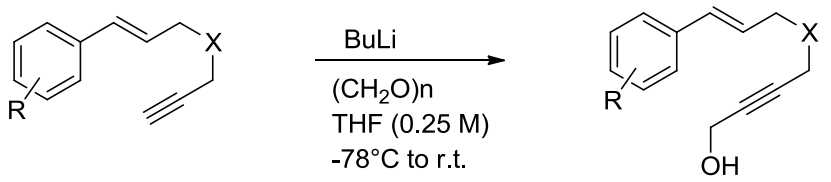
## 3.4. Experimental section

### General Remarks and Materials

All chemicals those syntheses are not reported hereafter were purchased from commercial sources and used as received. $^{1}H$, $^{13}C$, $^{31}P$ NMR spectra were recorded at 300 K on a Bruker 400 MHz or Bruker 300 MHz using solvents as internal standards (7.26 ppm for $^{1}H$ NMR and 77.00 ppm for $^{13}C$ NMR for $CDCl_3$ $^{19}F$-NMR spectra were recorded in $CDCl_3$ at 298 K on a JEOL 600 MHz spectrometer. The terms m, s, d, t, q and quint represent multiplet, singlet, doublet, triplet, quadruplet and quintuplet respectively, and the term brs means a broad signal. LC-MS were recorded on an Agilent LQ Mass Spectrometer (ESI source). Chromatographic purifications were performed under gradient using a Combiflash® system and prepacked disposable silica cartridges. The synthesis of enynes used in **GP-4** and substituted acetates employed in **GP-5** was carried out following known procedures.[26,34] Substituted *N*-cinnamyl-4-methylbenzenesulfonamides used in **GP-3** were prepared according to a previously employed protocol.[53] Gold complexes **67**, **68** and **70** were obtained following literature procedures.[54,55,56]

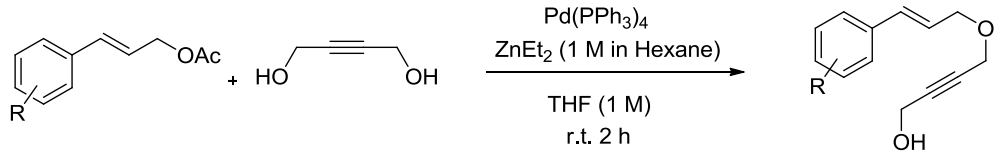
[53] C.A. Busacca and Y. Dong, *Tetrahedron Lett.*, 1996, **37**, 3947.
[54] J. Cordón, J.M. López-de-Luzuriaga and M. Monge, *Organometallics,* 2016, **35**, 732
[55] Y. Lu, X. Fu, H. Chen, X Du, X. Jia and Y. Liu, *Adv. Synth. Catal.,* 2009, **351**, 129
[56] S. López, E. Herrero-Gómez, P. Pérez-Galán, C, Nieto-Oberhuber and A. Echavarren, *Angew. Chem.Int.Ed.,* 2006, **45**, 6029

**General Procedure for synthesis of enynols (GP-4)**




A solution of the desired enyne (1 equiv.) in THF (0.25 M) was cooled to -78 °C and then BuLi (1.6 M in hexane, 1.3 equiv.) was added dropwise under a $N_2$ atmosphere. After 1 hour, paraformaldehyde (3 equiv.) was added and the mixture was stirred overnight at room temperature. Upon complete conversion, a saturated solution of $NH_4Cl$ (30 mL) was added and the resulting mixture was extracted with EtOAc (3 x 20 mL). The combined organic phases were dried over anhydrous $Na_2SO_4$, concentrated under reduced pressure and purified by column chromatography (eluent: gradient hexane/EtOAc).

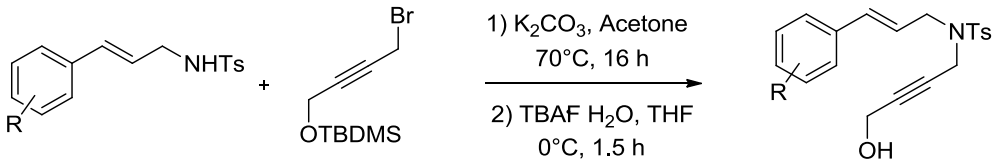
**General Procedure for synthesis of enynols (GP-5)**




To a solution of but-2-yne-1,4-diol (5 equiv.) in THF, $Et_2Zn$ (0.9 M in hexane, 0.5 equiv.) was added dropwise. The resulting mixture was stirred until it turned cloudily white (30 min). At this point the desired acetate (1 equiv.) and

$Pd(PPh_3)_4$ (5 mol%) were then added and the reaction was stirred overnight at room temperature. Upon complete conversion, the mixture was concentrated and carefully purified by column chromatography (eluent: gradient hexane/EtOAc).

**General Procedure for synthesis of enynols (GP-6)**




The desired *N*-cinnamyl-4-methylbenzenesulfonamides (1 equiv.) was dissolved in acetone and then $K_2CO_3$ (2 equiv.) was added. After 15 minutes, ((4-bromobut-2-yn-1-yl)oxy)(tert-butyl))dimethylsilane (1.5 equiv.) was syringed and the resulting mixture was stirred overnight at 70°C. Upon complete conversion, the reaction was diluted with water and the solution was extracted with EtOAc (3 x 30 mL). The combined organic phases were dried over anhydrous $Na_2SO_4$, filtered and concentrated under reduced pressure. The crude was dissolved in THF (0.4 M) cooled at 0 °C and subsequently TBAF·$H_2O$ (1.3 equiv.) was added to the mixture. The reaction was stirred for 1.5 hours. Upon complete conversion, the reaction was diluted with a saturated solution of $NH_4Cl$ and extracted with EtOAc (3 x 20 mL). The combined organic extracts were dried over anhydrous $Na_2SO_4$, concentrated under reduced pressure and purified by column chromatography (eluent: gradient hexane/EtOAc).

**Gold catalyst 67**

Complex **67** was isolated following the reported procedure.[54] Spectra correspond to the literature.[54] **$^{31}$P NMR** (162 MHz, $CDCl_3$) δ 30.8.

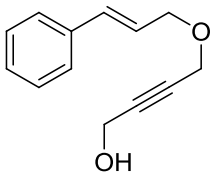
**Gold catalyst 68**

Complex **68** was isolated following the reported procedure.[55] Spectra correspond to the literature.[55] **$^{31}$P NMR** (162 MHz, $CDCl_3$) δ 29.3.

**Gold catalyst 70**

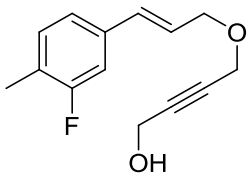
Complex **70** was isolated following the reported procedure.[56] Spectra correspond to the literature.[56] **$^{31}$P NMR** (162 MHz, $CDCl_3$) δ 100.8.

**4-(cinnamyloxy)but-2-yn-1-ol (64a)**




**64a** was isolated following the reported procedure.[26] Spectra correspond to the literature.[26] **$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.43 – 7.27 (m, 5H), 6.66 (d, *J* = 16.0 Hz, 1H), 6.30 (dt, *J* = 15.9, 6.2 Hz, 1H), 4.35 (s, 2H), 4.26 – 4.24 (m, 4H).

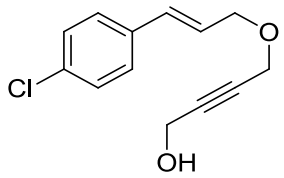
***(E)*-4-[(3-(3-fluoro-4-methylphenyl)allyl)oxy]but-2-yn-1-ol (64b)**




**64b** was isolated following procedure **GP-5** using but-2-yne-1,4-diol (925 mg, 10.8 mmol) and *(E)*-3-(3-fluoro-4-methylphenyl)allyl acetate (448 mg, 2.1 mmol). Purification by column chromatography afforded **64b** (39 %, 196 mg, 0.8 mmol) as a brown oil. **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.13 – 7.01 (m, 3H), 6.56 (d, *J* = 15.9 Hz, 1H), 6.22 (dt, *J* = 15.9, 6.1 Hz, 1H), 4.32 (s, 2H), 4.23 – 4.20 (m, 4H), 2.25 (s, 3H). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 161.5 (d, $^1J_{C\text{-}F}$ = 244.2 Hz, $C_q$), 136.2 (d, $^4J_{C\text{-}F}$ = 7.8 Hz, $C_q$), 132.2 (d, $^8J_{C\text{-}F}$ = 2.2 Hz, CH), 131.5 (d, $^5J_{C\text{-}F}$ = 5.3 Hz, CH), 125.4 (CH), 124.4 (d, $^3J_{C\text{-}F}$ = 17.6 Hz, $C_q$), 122.1 (d, $^7J_{C\text{-}F}$ = 3.2 Hz, CH), 112.6 (d, $^2J_{C\text{-}F}$ = 22.8 Hz, CH), 84.9 ($C_q$), 81.6 ($C_q$), 70.2 ($CH_2$), 57.5 ($CH_2$), 51.1 ($CH_2$),

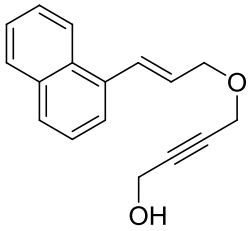
14.4 (d, $^{6}J_{C\text{-}F}$ = 3.6 Hz, $CH_3$). **$^{19}$F NMR** (565 MHz,$CDCl_3$) δ -117.7. **LC-MS** calcd for $C_{14}H_{15}FNaO_2$ $[M+Na]^+$ 257.10, found 257.19.

### *(E)*-4-[(3-(4-chlorophenyl)allyl)oxy]but-2-yn-1-ol (64c)



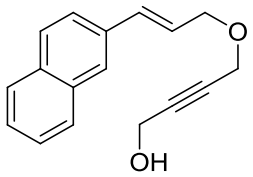

**64c** was isolated following procedure **GP-5** using but-2-yne-1,4-diol (851 mg, 9.9 mmol) and *(E)*-3-(4-chlorophenyl)allyl acetate (417 mg, 1.9 mmol). Purification by column chromatography afforded **64c** (54 %, 255 mg, 1.1 mmol) as a pale yellow oil. **$^{1}$H NMR** (300 MHz, $CDCl_3$) δ 7.33 – 7.26 (m, 4H), 6.59 (d, *J* = 16.0 Hz, 1H), 6.25 (dt, *J* = 15.9, 6.0 Hz, 1H), 4.33 (t, *J* = 1.8 Hz, 2H), 4.24 (t, *J* = 1.8 Hz, 2H), 4.21 (dd, *J* = 6.1, 1.4 Hz, 2H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 135.0 ($C_q$), 133.5 ($C_q$), 131.9 (CH), 128.8 (CH), 127.7 (CH), 125.8 (CH), 84.8 ($C_q$), 81.7 ($C_q$), 70.2 ($CH_2$), 57.5 ($CH_2$), 51.2 ($CH_2$). **LC-MS** calcd for $C_{13}H_{13}ClNaO_2$ $[M+Na]^+$ 259.05, found 259.12.

***(E)*-4-[(3-(naphthalen-1-yl)allyl)oxy]but-2-yn-1-ol (64d)**



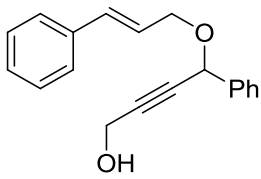

**64d** was isolated following procedure **GP-5** using but-2-yne-1,4-diol (1040 mg, 12.0 mmol) and *(E)*-3-(4-chlorophenyl)allyl acetate (550 mg, 2.4 mmol). Purification by column chromatography afforded **64d** (32 %, 200 mg, 0.8 mmol) as a yellow oil. **$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 8.12 (d, *J* = 7.8 Hz, 1H), 7.86 (d, *J* = 7.1 Hz, 1H), 7.79 (d, *J* = 8.2 Hz, 1H), 7.61 (d, *J* = 7.2 Hz, 1H), 7.54 – 7.45 (m, 3H), 7.41 (d, *J* = 15.8 Hz, 1H), 6.31 (dt, *J* = 15.7, 6.1 Hz, 1H), 4.35 – 4.31 (m, 6H), 2.10 (s, 1H). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 134.3 ($C_q$), 133.6 ($C_q$), 131.1 ($C_q$), 130.5 (CH), 128.6 (CH), 128.3 (CH), 128.2 (CH), 126.1 (CH), 125.8 (CH), 125.6 (CH), 124.0 (CH), 123.8 (CH), 85.0 ($C_q$), 81.6 ($C_q$), 70.6 ($CH_2$), 57.6 ($CH_2$), 51.0 ($CH_2$). **LC-MS** calcd for $C_{17}H_{16}NaO_2$ $[M+Na]^+$ 245.10, found 245.16.

***(E)*-4-[(3-(naphthalen-2-yl)allyl)oxy]but-2-yn-1-ol (64e)**




**64e** was isolated following procedure **GP-5** using but-2-yne-1,4-diol (732 mg, 8.5 mmol) and *(E)*-3-(naphthalen-2-yl)allyl acetate (385 mg, 1.7 mmol). Purification by column chromatography afforded **64e** (43%, 184 mg, 0.7 mmol) as a pale yellow wax. **$^{1}$H NMR** (300 MHz, $CDCl_3$) δ 7.82 – 7.74 (m, 4H), 7.61 (dd, *J* = 8.6, 1.7 Hz, 1H), 7.49 – 7.42 (m, 2H), 6.81 (d, *J* = 16.0 Hz, 1H), 6.41 (dt, *J* = 15.8, 6.2 Hz, 1H), 4.36 – 4.27 (m, 6H). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 134.0 ($C_q$), 133.6 ($C_q$), 133.5 (CH), 133.1 ($C_q$), 128.3 (CH), 128.0 (CH), 127.7 (CH), 126.7 (CH), 126.3 (CH), 126.0 (CH), 125.5 (CH), 123.5 (CH), 84.8 ($C_q$), 81.8 ($C_q$), 70.5 ($CH_2$), 57.5 ($CH_2$), 51.2 ($CH_2$). **LC-MS** calcd for $C_{17}H_{16}NaO_2$ $[M+Na]^+$ 275.10, found 275.19.

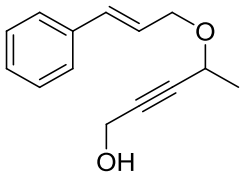
**4-(cinnamyloxy)-4-phenylbut-2-yn-1-ol (64f)**




**64f** was isolated following procedure **GP-4** using *(E)*-(1-(cinnamyloxy)prop-2-yn-1-yl)benzene (500 mg, 2.0 mmol) and paraformaldehyde (181 mg, 6.0 mmol). Purification by column chromatography afforded **64f** (40 %, 224 mg,

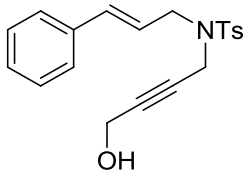
0.8 mmol) as a pale yellow oil. **$^{1}$H NMR** (300 MHz, $CDCl_3$) δ 7.57 – 7.54 (m, 2H), 7.45 – 7.28 (m, 8H), 6.68 (d, *J* = 16.0 Hz, 1H), 6.35 (dt, *J* = 15.9, 6.2 Hz, 1H), 5.32 (s, 1H), 4.38 (s, 2H), 4.35 – 4.29 (m, 2H), 1.96 (s, 1H). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 138.4 ($C_q$), 136.6 ($C_q$), 133.4 (CH), 128.7 (CH), 128.6 (CH), 128.6 (CH), 127.9 (CH), 127.5 (CH), 126.6 (CH), 125.4 (CH), 86.1 ($C_q$), 83.5 ($C_q$), 70.7 ($CH_2$), 69.0 (CH), 51.0 ($CH_2$). **LC-MS** calcd for $C_{14}H_{16}NaO_2$ $[M+Na]^+$ 301.12 found 301.16.

**4-(cinnamyloxy)pent-2-yn-1-ol (64g)**



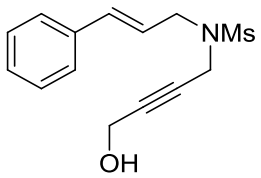

**64g** was isolated following procedure **GP-4** using *(E)*-(3-(but-3-yn-2-yloxy)prop-1-en-1-yl)benzene (432 mg, 2.3 mmol) and paraformaldehyde (209 mg, 7.0 mmol). Purification by column chromatography afforded **64g** (36 %, 183 mg, 0.8 mmol) as a pale yellow oil. **$^{1}$H NMR** (300 MHz, $CDCl_3$) δ 7.43 – 7.26 (m, 5H), 6.66 (d, *J* = 15.9 Hz, 1H), 6.43 (dt, *J* = 15.9, 6.0 Hz, 1H), 4.42 (ddd, *J* = 12.4, 5.7, 1.5 Hz, 1H), 4.35 – 4.31 (m, 3H), 4.16 (ddd, *J* = 12.4, 6.7, 1.3 Hz, 1H), 1.87 (s, 1H), 1.50 (d, *J* = 6.6 Hz, 3H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 136.6 ($C_q$), 133.0 (CH), 128.6 (CH), 127.8 (CH), 126.5 (CH), 125.5 (CH), 85.6 ($C_q$), 83.3 ($C_q$), 69.3 ($CH_2$), 64.5 (CH), 51.1 ($CH_2$), 22.1 ($CH_3$). **LC-MS** calcd for $C_{14}H_{16}NaO_2$ $[M+Na]^+$ 239,11, found 239.15.

***N*-cinnamyl-*N*-(4-hydroxybut-2-yn-1-yl)-4-methylbenzenesulfonamide (71a)**




**71a** was isolated following procedure **GP-4** using *N*-cinnamyl-4-methyl-N-(prop-2-yn-1-yl) benzenesulfonamide (2.83 g, 8.7 mmol) and paraformaldehyde (784 mg, 26.1 mmol). Purification by column chromatography afforded **71a** (60 %, 1.86 g, 8.7 mmol) as a white solid. **M. p.** = (75 – 78) °C **$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.2 Hz, 2H), 7.33 – 7.24 (m, 7H), 6.56 (d, *J* = 15.8 Hz, 1H), 6.08 (dt, *J* = 15.7, 6.8 Hz, 1H), 4.13 (s, 2H), 4.00 – 3.98 (m, 4H), 2.44 (s, 3H), 1.43 (brs, 1H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 143.7 ($C_q$), 136.2 ($C_q$), 136.1 ($C_q$), 134.8 (CH), 129.5 (CH), 128.7 (CH), 128.1 (CH), 128.0 (CH), 126.5 (CH), 123.0 (CH), 83.9 ($C_q$), 78.7 ($C_q$), 50.8 ($CH_2$), 48.9 ($CH_2$), 36.2 ($CH_2$), 21.5 ($CH_3$). **LC-MS** calcd for $C_{20}H_{21}NNaO_3S$ $[M+Na]^+$ 378.11, found 378.13.

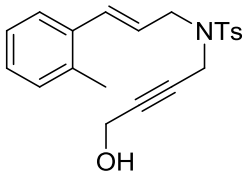
***N*-cinnamyl-*N*-(4-hydroxybut-2-yn-1-yl)methanesulfonamide (71b)**




**71b** was isolated following procedure **GP-4** using *N*-cinnamyl-*N*-(prop-2-yn-1-yl)methanesulfonamide (500 mg, 2.0 mmol) and paraformaldehyde (180 mg,

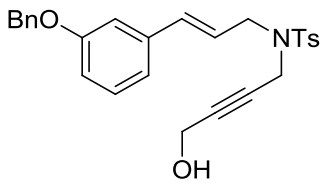
6.0 mmol). Purification by column chromatography afforded **71b** (40 %, 224 mg, 0.8 mmol) as a white solid. **M. p.** = (91 – 95) °C. **$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.41 – 7.26 (m, 5H), 6.65 (d, *J* = 15.8 Hz, 1H), 6.17 (dt, *J* = 15.8, 6.8 Hz, 1H), 4.32 (t, *J* = 1.7 Hz, 2H), 4.14 (t, *J* = 1.8 Hz, 2H), 4.05 (d, *J* = 6.8 Hz, 2H), 2.99 (s, 3H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 136.0 ($C_q$), 135.0 (CH), 128.7 (CH), 128.2 (CH), 126.6 (CH), 122.9 (CH), 84.4 ($C_q$), 79.3 ($C_q$), 51.0 ($CH_2$), 48.9 ($CH_2$), 38.7 ($CH_3$), 36.1 ($CH_2$). **LC-MS** calcd for $C_{14}H_{17}NNaO_3S$ $[M+Na]^+$ 302.08, found 302.15.

### *(E)-N*-(4-hydroxybut-2-yn-1-yl)-4-methyl-N-(3-(o-tolyl)allyl) benzenesulfonamide (71c)



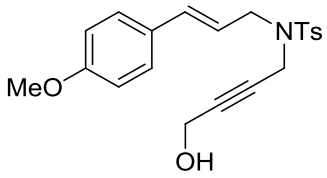

**71c** was isolated following procedure **GP-4** using *(E)*-4-methyl-*N*-(prop-2-yn-1-yl)-*N*-(3-(o-tolyl)allyl)benzenesulfonamide (399 mg, 1.2 mmol) and paraformaldehyde (106 mg, 3.5 mmol). Purification by column chromatography afforded **71c** (42 %, 189 mg, 0.5 mmol) as a yellow solid. **M. p.** = (76 – 79) °C. **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.4 Hz, 2H), 7.37 – 7.32 (m, 3H), 7.18 – 7.12 (m, 3H), 6.79 (d, *J* = 15.7 Hz, 1H), 5.95 (dt, *J* = 15.6, 6.8 Hz, 1H), 4.15 (t, *J* = 1.9 Hz, 2H), 4.02 – 4.00 (m, 4H), 2.44 (s, 3H), 2.31 (s, 3H), 1.40 (brs, 1H). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 143.7 ($C_q$), 136.1 ($C_q$), 135.5 ($C_q$), 135.2 ($C_q$), 133.0 (CH), 130.4 (CH), 129.5 (CH), 128.0 (2CH), 126.2 (CH), 125.8 (CH), 124.2 (CH), 83.9 ($C_q$), 78.7 ($C_q$), 50.8 ($CH_2$), 49.1 ($CH_2$), 36.2 ($CH_2$), 21.5 ($CH_3$), 19.8 ($CH_3$). **LC-MS** calcd for $C_{21}H_{23}NNaO_3S$ $[M+Na]^+$ 392.13, found 392.20

***(E)*-N-[3-(3-(benzyloxy)phenyl)allyl]-*N*-(4-hydroxybut-2-yn-1-yl)-4 methylbenzenesulfonamide (71d)**



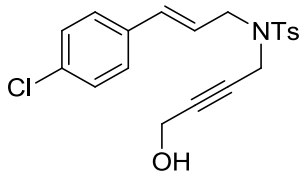

**71d** was isolated following procedure **GP-6** using *(E)-N*-(3-(3-(benzyloxy)phenyl)allyl)-4-methylbenzenesulfonamide (879 mg, 2.2 mmol) and ((4-bromobut-2-yn-1-yl)oxy)(tert-butyl)) dimethylsilane (880 mg, 3.3 mmol). Purification by column chromatography afforded **71d** (20%, 201 mg, 0.4 mmol) as a white solid. **M. p.** = (82 – 85) °C. **$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.3 Hz, 2H), 7.45 – 7.35 (m, 5H), 7.33 (d, *J* = 8.2 Hz, 2H), 7.23 (t, *J* = 7.9 Hz, 1H), 6.96– 6.87 (m, 3H), 6.53 (d, *J* = 15.8 Hz, 1H), 6.07 (dt, *J* = 15.7, 6.8 Hz, 1H), 5.06 (s, 2H), 4.13 (s, 2H), 4.00 – 3.97 (m, 4H), 2.43 (s, 3H). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 159.1 ($C_q$), 143.7 ($C_q$), 137.6 ($C_q$), 136.9 ($C_q$), 136.2 ($C_q$), 134.7 (CH), 129.7 (CH), 129.5 (CH), 128.6 (CH), 128.1 (CH), 128.0 (CH), 127.5 (CH), 123.4 (CH), 119.5 (CH), 114.6 (CH), 112.9 (CH), 83.9 ($C_q$), 78.7 ($C_q$), 70.0 ($CH_2$), 50.8 ($CH_2$), 48.8 ($CH_2$), 36.3 ($CH_2$), 21.6 ($CH_3$). **LC-MS** calcd for $C_{27}H_{27}NNaO_4S$ $[M+Na]^+$ 484.15 found 484.19

***(E)*-*N*-(4-hydroxybut-2-yn-1-yl)-N-(3-(4-methoxyphenyl)allyl)-4-methylbenzenesulfonamide (71e)**



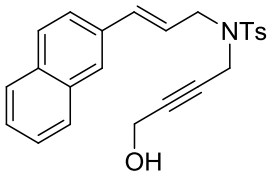

**71e** was isolated following procedure **GP-6** using *(E)*-*N*-(3-(4-methoxyphenyl)allyl)-4-methylbenzenesulfonamide (293 mg, 0.9 mmol) and ((4-bromobut-2-yn-1-yl)oxy)(tert-butyl)) dimethylsilane (364 mg, 1.4 mmol). Purification by column chromatography afforded **71e** (33 %, 120 mg, 0.3 mmol) as a white solid. **M. p.** = (83 – 87) °C. **$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.3 Hz, 2H,), 7.34 (d, *J* = 8.0 Hz, 2H,), 7.29 (d, *J* = 8.7 Hz, 2H,), 6.87 (d, *J* = 8.7 Hz, 2H), 6.52 (d, *J* = 15.8 Hz, 1H), 5.95 (dt, *J* = 15.7, 6.9 Hz, 1H), 4.15 (s, 2H), 4.03 – 3.97 (m, 4H), 3.83 (s, 3H), 2.46 (s, 3H), 1.32 (brs, 1H). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 159.6 ($C_q$), 143.6 ($C_q$), 136.3 ($C_q$), 134.4 (CH), 129.4 (CH), 128.9 ($C_q$), 128.0 (CH), 127.8 (CH), 120.6 (CH), 114.1 (CH), 83.8 ($C_q$), 78.8 ($C_q$), 55.3 ($CH_3$), 50.8 ($CH_2$), 49.0 ($CH_2$), 36.1 ($CH_2$), 21.5 ($CH_3$). **LC-MS** calcd for $C_{21}H_{23}NNaO_4S$ $[M+Na]^+$ 408.20, found 408.17.

***(E)*-*N*-(3-(4-chlorophenyl)allyl)-*N*-(4-hydroxybut-2-yn-1-yl)-4-methy lbenzenesulfonamide (71f)**



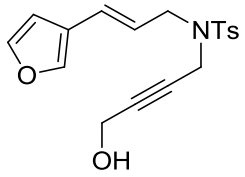

**71f** was isolated following procedure **GP-6** using *(E)*-*N*-(3-(4-chlorophenyl)allyl)-4-methylbenzenesulfonamide (413 mg, 1.3 mmol) and ((4-bromobut-2-yn-1-yl)oxy)(tert-butyl)) dimethylsilane (505 mg, 1.9 mmol). Purification by column chromatography afforded **71f** (31 %, 155 mg, 0.4 mmol) as a white solid. **M. p.** = (73 – 76) °C. **$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.3 Hz, 2H), 7.33 (d, *J* = 8.1 Hz, 2H), 7.29 – 7.24 (m, 4H), 6.52 (d, *J* = 15.8 Hz, 1H), 6.07 (dt, *J* = 15.8, 6.7 Hz, 1H), 4.13 (t, *J* = 1.7 Hz, 2H), 4.01 (t, *J* = 1.8 Hz, 2H), 3.98 (d, *J* = 5.8 Hz, 2H), 2.44 (s, 3H). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 143.7 ($C_q$), 136.2 ($C_q$), 134.6 ($C_q$), 133.8 ($C_q$), 133.4 (CH), 129.5 (CH), 128.8 (CH), 128.0 (CH), 127.7 (CH), 123.9 (CH), 83.9 ($C_q$), 78.6 ($C_q$), 50.8 ($CH_2$), 48.7 ($CH_2$), 36.4 ($CH_2$), 21.5 ($CH_3$). **LC-MS** calcd for $C_{20}H_{20}ClNNaO_3S$ $[M+Na]^+$ 412.08, found 412.14.

***(E)-N*-(4-hydroxybut-2-yn-1-yl)-4-methyl-N-(3-(naphthalen-2-yl)allyl)benzenesulfonamide (71g)**



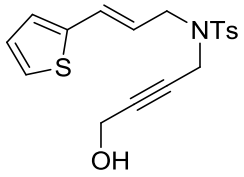

**71g** was isolated following procedure **GP-6** using *(E)*-4-methyl-*N*-(3-(naphthalen-2-yl)allyl) benzenesulfonamide (610 mg, 1.8 mmol) and ((4-bromobut-2-yn-1-yl)oxy)(tert-butyl)) dimethylsilane (714 mg, 2.7 mmol). Purification by column chromatography afforded **71g** (18 %, 175 mg, 0.3 mmol) as a yellow solid. **M. p.** = (78 – 81) °C. **$^{1}$H NMR** (300 MHz, $CDCl_3$) δ 7.81 – 7.77 (m, 5H), 7.69 (s, 1H), 7.55 – 7.52 (m, 1H), 7.48 – 7.44 (m, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 6.73 (d, *J* = 15.8 Hz, 1H), 6.21 (dt, *J* = 15.8, 6.8 Hz, 1H), 4.17 (t, *J* = 1.7 Hz, 2H), 4.05 – 4.02 (m, 4H), 2.44 (s, 3H). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 143.7 ($C_q$), 136.3 ($C_q$), 134.9 (CH), 133.5 ($C_q$), 133.5 ($C_q$), 133.2 ($C_q$), 129.5 (CH), 128.4 (CH), 128.0 (CH), 128.0 (CH), 127.7 (CH), 126.8 (CH), 126.4 (CH), 126.2 (CH), 123.4 (CH), 123.4 (CH), 84.0 ($C_q$), 78.7 ($C_q$), 50.8 ($CH_2$), 49.0 ($CH_2$), 36.3 ($CH_2$), 21.5 ($CH_3$). **LC-MS** calcd for $C_{24}H_{23}NNaO_3S$ $[M+Na]^+$ 428.13, found 428.18.

***(E)*-*N*-(3-(furan-3-yl)allyl)-*N*-(4-hydroxybut-2-yn-1-yl)-4-methylbenzenesulfonamide (71h)**



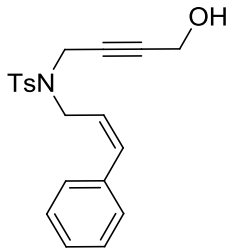

**71h** was isolated following procedure **GP-4** using *(E)*-*N*-(3-(furan-3-yl)allyl)-4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide (270 mg, 0.9 mmol) and paraformaldehyde (77 mg, 2.6 mmol). Purification by column chromatography afforded **71h** (30 %, 88 mg, 0.2 mmol) as a yellow solid. **M. p.** = (85 – 89) °C. **$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.3 Hz, 2H), 7.38 (d, *J* = 16.2 Hz, 2H), 7.32 (d, *J* = 8.1 Hz, 2H), 6.47 (s, 1H), 6.43 (d, *J* = 15.8 Hz, 2H), 5.80 (dt, *J* = 15.6, 6.8 Hz, 2H), 4.12 (s, 2H), 3.99 (s, 2H), 3.92 (d, *J* = 6.5 Hz, 2H), 2.43 (s, 3H), 1.29 (brs, 1H). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 143.7 (CH), 143.7 ($C_q$), 140.9 (CH), 136.2 ($C_q$), 129.4 (CH), 128.0 (CH), 124.6 (CH), 123.3 ($C_q$), 122.6 (CH), 107.5 (CH), 83.8 ($C_q$), 78.7 ($C_q$), 50.8 ($CH_2$), 48.7 ($CH_2$), 36.1 ($CH_2$), 21.5 ($CH_3$). **LC-MS** calcd for $C_{18}H_{19}NNaO_4S$ $[M+Na]^+$ 368.09, found 368.17.

***(E)*-*N*-(4-hydroxybut-2-yn-1-yl)-4-methyl-*N*-(3-(thiophen-2-yl)allyl)benzenesulfonamide (71i)**



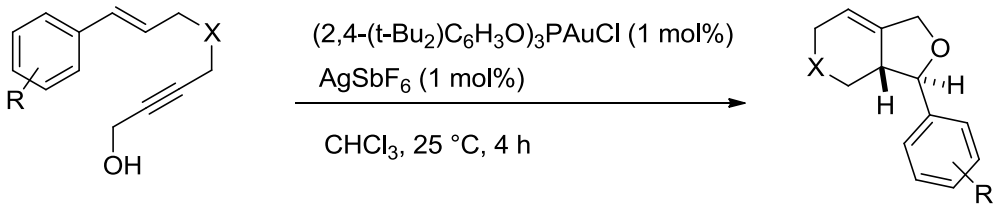

**71i** was isolated following procedure **GP-4** using *(E)*-4-methyl-*N*-(prop-2-yn-1-yl)-*N*-(3-(thiophen-2-yl)allyl)benzenesulfonamide (292 mg, 0.9 mmol) and paraformaldehyde (79 mg, 2.6 mmol). Purification by column chromatography afforded **71i** (37 %, 118 mg, 0.3 mmol) as a yellow solid. **M. p.** = (79 – 82) °C. **$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.3 Hz, 2H), 7.32 (d, *J* = 8.1 Hz, 2H), 7.18 – 7.16 (m, 1H), 6.96 – 6.94 (m, 2H), 6.69 (d, *J* = 15.6 Hz, 1H), 5.89 (dt, *J* = 15.5, 6.8 Hz, 1H), 4.13 (s, 2H), 4.00 (t, *J* = 1.8 Hz, 2H), 3.95 (d, *J* = 6.6 Hz, 2H), 2.44 (s, 3H). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 143.8 ($C_q$), 141.1 ($C_q$), 136.1 ($C_q$), 129.5 (CH), 128.0 (CH), 127.8 (CH), 127.5 (CH), 126.4 (CH), 124.9 (CH), 122.5 (CH), 83.9 ($C_q$), 78.7 ($C_q$), 50.8 ($CH_2$), 48.7 ($CH_2$), 36.3 ($CH_2$), 21.6 ($CH_3$). **LC-MS** calcd for $C_{18}H_{19}NNaO_3S_2$ $[M+Na]^+$ 384.07, found 384.11

***(Z)-N*-(4-hydroxybut-2-yn-1-yl)-4-methyl-N-(3-phenylallyl)benzenesulfonamide (71j)**



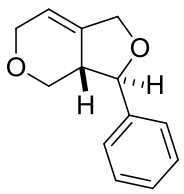

**71j** was isolated following procedure **GP-4** using *(Z)*-4-methyl-N-(3-phenylallyl)-N-(prop-2-yn-1-yl)benzenesulfonamide (498 mg, 1.53 mmol) and paraformaldehyde (137 mg, 4.59 mmol). Purification by column chromatography afforded **71j** (38%, 207 mg, 0.581 mmol) as a yellow oil.**$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.3 Hz, 2H), 7.30 (m, 7H), 6.72 (d, *J* = 11.6 Hz, 1H), 5.64 (dt, *J* = 11.6, 6.9 Hz, 1H), 4.15 (dd, *J* = 6.9, 1.5 Hz, 2H), 4.10 (s, 2H), 3.72 (s, 2H), 2.44 (s, 3H). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 143.7 ($C_q$), 136.2 ($C_q$), 135.9 ($C_q$), 134.0 (CH), 129.5 (CH), 128.9 (CH), 128.2 (CH), 127.8 (CH), 127.3 (CH), 126.1 (CH), 83.9 ($C_q$), 78.2 ($C_q$), 50.4 ($CH_2$), 44.1 ($CH_2$), 36.4 ($CH_2$), 21.5 ($CH_3$). **LC-MS** calcd for $C_{20}H_{21}NNaO_3S$ $[M+Na]^+$ 378.11, found 378.20.

**Catalytic Synthesis (GP-7)**




(2,4-(t-$Bu_2$)$C_6H_3O$)$_3$PAuCl (1 mol%) was dissolved with freshly degassed $CHCl_3$ (0.3 M) under $N_2$ in a two necked round bottom flask. Afterwards, the substrate (0.14 mmol or 0.2 mmol, 1 equiv.) and $AgSbF_6$ (a tip of a spatula) were added and the mixture was stirred at room temperature. The reaction was monitored by TLC. Upon complete conversion, the solution was diluted with DCM (5 mL) and purified by column chromatography (eluent: gradient hexane/ethyl acetate).

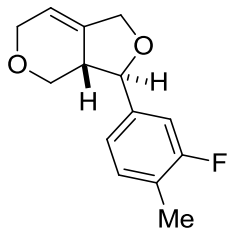
**3-phenyl-3,3a,4,6-tetrahydro-1H-furo[3,4-c]pyran (65a)**




Represented procedure **GP-7** was followed using **64a** (40.4 mg, 0.20 mmol). Purification by column chromatography (Eluent: gradient hexane/ethyl acetate.) yielded **65a** as a pale yellow oil (56 %, 22.2 mg, 0.11 mmol, *d.r.* > 25:1). $\mathbf{R_f}$ = 0.45 (eluent: Hexane/ethyl acetate = 8:2). **$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.40 – 7.33 (m, 5H), 5.65 (s, 1H), 4.73 (d, *J* = 12.4 Hz, 1H), 4.48 (d, *J* = 12.5 Hz,

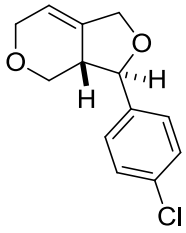
1H), 4.35 (d, *J* = 9.9 Hz, 1H), 4.29 – 4.22 (m, 1H), 4.16 – 4.11 (m, 2H), 3.34 (t, *J* = 10.1 Hz, 1H), 2.79 (brs, 1H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 140.4 ($C_q$), 138.8 ($C_q$), 128.6 (CH), 128.1 (CH), 126.0 (CH), 116.2 (CH), 83.4 (CH), 69.7 ($CH_2$), 65.9 ($CH_2$), 64.3 ($CH_2$), 46.5 (CH). **LC-MS** calcd for $C_{13}H_{14}NaO_2$ $[M+Na]^+$ 225.09, found 225.12.

**3-(3-fluoro-4-methylphenyl)-3,3a,4,6-tetrahydro-1H-furo[3,4-c]pyran (65b)**



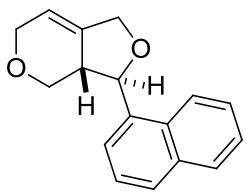

Represented procedure **GP-7** was followed using **64b** (46.8 mg, 0.20 mmol). Purification by column chromatography (Eluent: gradient hexane/ethyl acetate.) yielded **65b** as a pale yellow oil (33 %, 16.4 mg, 0.07 mmol, *d.r.* > 25:1). $\mathbf{R_f}$ = 0.41 (Eluent: Hexane/ethyl acetate = 8:2). **$^{1}$H NMR** (300 MHz, $CDCl_3$) δ 7.19 – 7.13 (m, 1H), 7.05 – 6.97 (m, 2H), 5.63 (s, 1H), 4.68 (d, *J* = 12.3 Hz, 1H), 4.44 (d, *J* = 12.6 Hz, 1H), 4.27 (d, *J* = 9.8 Hz, 1H), 7.21 – 7.07 (m, 3H), 3.30 (t, *J* = 10.1 Hz, 1H), 2.70 (brs, 1H), 2.27 (s, 3H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 161.4 (d, $^{1}J_{C\text{-}F}$ = 245.0 Hz, $C_q$), 140.3 (d, $^{4}J_{C\text{-}F}$ = 7.2 Hz, $C_q$), 138.5 ($C_q$), 131.6 (d, $^{5}J_{C\text{-}F}$ = 5.4 Hz, CH), 124.5 (d, $^{3}J_{C\text{-}F}$ = 17.3 Hz, $C_q$), 121.2 (d, $^{7}J_{C\text{-}F}$ = 3.3 Hz, CH), 116.4 (CH), 112.5 (d, $^{2}J_{C\text{-}F}$ = 23.1 Hz, CH), 82.6 (d, $^{8}J_{C\text{-}F}$ = 1.6 Hz, CH), 69.7 ($CH_2$), 65.8 ($CH_2$), 64.3 ($CH_2$), 46.6 (CH), 14.4 (d, $^{6}J_{C\text{-}F}$ = 3.5 Hz, $CH_3$). **$^{19}$F NMR** (565 MHz,$CDCl_3$) δ -117.0. **LC-MS** calcd for $C_{14}H_{15}FNaO_2$ $[M+Na]^+$ 257.10 found 257.12.

**3-(4-chlorophenyl)-3,3a,4,6-tetrahydro-1H-furo[3,4-c]pyran (65c)**




Represented procedure **GP-7** was followed using **64c** (47.3 mg, 0.20 mmol). Purification by column chromatography (Eluent: gradient hexane/ethyl acetate.) yielded **65c** as a colourless oil (51 %, 23.7 mg, 0.10 mmol, *d.r.* > 25:1). $\mathbf{R_f}$ = 0.30 (Eluent: Hexane/ethyl acetate = 8:2). **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.34 (d, *J* = 8.6 Hz, 2H), 7.28 (d, *J* = 8.5 Hz, 2H), 5.64 (s, 1H), 4.69 (d, *J* = 12.6 Hz, 1H), 4.45 (d, *J* = 12.6 Hz, 1H), 4.29 (d, *J* = 9.9 Hz, 1H), 4.25 – 4.20 (m, 1H), 4.146 – 4.06 (m, 2H), 3.30 (t, *J* = 10.2 Hz, 1H), 2.69 (brs, 1H). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 139.0 ($C_q$), 138.4 ($C_q$), 133.7 ($C_q$), 128.8 (CH), 127.3 (CH), 116.5 (CH), 82.7 (CH), 69.8 ($CH_2$), 65.7 ($CH_2$), 64.3 ($CH_2$), 46.7 (CH). **LC-MS** calcd for $C_{13}H_{13}ClNaO_2$ $[M+Na]^+$ 259,05 found 259.09.

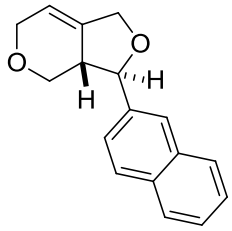
**3-(naphthalen-1-yl)-5-tosyl-1,3,3a,4,5,6-hexahydrofuro[3,4-c]pyridine (65d)**




Represented procedure **GP-7** was followed using **64d** (50.4 mg, 0.20 mmol). Purification by column chromatography (Eluent: gradient hexane/ethyl acetate.) yielded **65d** as a white solid (40 %, 20.2 mg, 0.08 mmol, *d.r.* > 25:1).

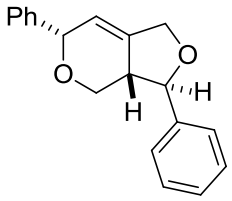
**M. p.** = (98 – 100) °C. $\mathbf{R_f}$ = 0.35 (Eluent: Hexane/ethyl acetate = 8:2). **$^1$H NMR** (300 MHz, $CDCl_3$) δ 8.09 – 8.05 (m, 1H), 7.90 – 7.87 (m, 1H), 7.84 (d, *J* = 8.2 Hz, 1H), 7.69 (d, *J* = 7.1 Hz, 1H), 7.55 – 7.47 (m, 3H), 5.70 (bs , 1H), 5.08 (d, *J* = 10.0 Hz, 1H), 4.83 – 4.78 (m, 1H), 4.61 – 4.56 (m, 1H), 4.31 – 4.09 (m, 3H), 3.42 (t, *J* = 10.2 Hz, 1H), 3.12 (brs, 1H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 139.0 ($C_q$), 135.3 ($C_q$), 133.9 ($C_q$), 131.3 ($C_q$), 128.9 (CH), 128.8 (CH), 126.2 (CH), 125.7 (CH), 125.5 (CH), 123.6 (CH), 123.3 (CH), 116.3 (CH), 80.6 (CH), 69.6 ($CH_2$), 66.5 ($CH_2$), 64.5 ($CH_2$), 45.4 (CH). **LC-MS** calcd for $C_{17}H_{16}NaO_2$ $[M+Na]^+$ 275.10, found 275.14.

**3-(naphthalen-2-yl)-3,3a,4,6-tetrahydro-1H-furo[3,4-c]pyran (65e)**



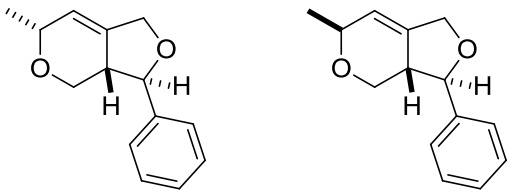

Represented procedure **GP-7** was followed using **64e** (50.4 mg, 0.20 mmol). Purification by column chromatography (Eluent: gradient hexane/ethyl acetate.) yielded **65e** as a white solid (64 %, 32.8 mg, 0.13 mmol, *d.r.* > 25:1). **M. p.** = (82 – 85) °C. $\mathbf{R_f}$ = 0.30 (Eluent: Hexane/ethyl acetate = 8:2). **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.88 – 7.81 (m, 4H), 7.51 – 7.46 (m, 3H), 5.66 (s, 1H), 4.77 (d, *J* = 12.5 Hz, 1H), 4.55 – 4.49 (m, 2H), 4.28 – 4.13 (m, 3H), 3.38 (t, *J* = 10.1 Hz, 1H), 2.86 (s, 1H). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 138.8 ($C_q$), 137.9 ($C_q$), 133.3 ($C_q$), 133.3 ($C_q$), 128.5 (CH), 128.0 (CH), 127.7 (CH), 126.2 (CH), 126.0 (CH), 125.0 (CH), 123.8 (CH), 116.3 (CH), 83.6 (CH), 69.9 ($CH_2$), 66.0 ($CH_2$), 64.4 ($CH_2$), 46.6 (CH). **LC-MS** calcd for $C_{17}H_{16}NaO_2$ $[M+Na]^+$ 275.10, found 275.12.

**3,6-diphenyl-3,3a,4,6-tetrahydro-1H-furo[3,4-c]pyran (65f)**




Represented procedure **GP-7** was followed using **64f** (55.6 mg, 0.20 mmol). Purification by column chromatography (Eluent: gradient hexane/ethyl acetate.) yielded **65f** as a yellow oil (55 %, 30.6 mg, 0.11 mmol, *d.r.* > 25:1). $\mathbf{R_f}$ = 0.55 (Eluent: Hexane/ethyl acetate = 8:2). **$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.40 – 7.30 (m, 10H), 5.68 (s, 1H), 5.13 (s, 1H), 4.77 (d, *J* = 12.8 Hz, 1H), 4.52 (d, *J* = 12.7 Hz, 1H), 4.41 (d, *J* = 9.8 Hz, 1H), 4.27 (dd, *J* = 10.5, 5.6 Hz, 1H), 3.62 (t, *J* = 10.2 Hz, 1H), 2.95 (brs, 1H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 140.8 ($C_q$), 140.2 ($C_q$), 139.4 ($C_q$), 128.7 (CH), 128.6 (CH), 128.2 (CH), 128.1 (CH), 127.2 (CH), 126.0 (CH), 119.8 (CH), 83.4 (CH), 76.3 (CH), 69.7 ($CH_2$), 67.0 ($CH_2$), 46.6 (CH). **LC-MS** calcd for $C_{19}H_{18}NaO_2$ $[M+Na]^+$ 301.12, found 301.16.

**6-methyl-3-phenyl-3,3a,4,6-tetrahydro-1H-furo[3,4-c]pyran (65g)**

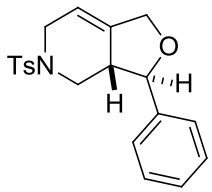



***d*a + *d*b**

Represented procedure **GP-7** was followed using **64g** (43.3 mg, 0.20 mmol). Purification by column chromatography (Eluent: gradient hexane/ethyl acetate) yielded **65g** as a pale yellow oil (31 %, 13.0 mg, 0.06 mmol, *d.r.* ≈ 2:1). $\mathbf{R_f}$ = 0.6 (Eluent: Hexane/ethyl acetate = 8:2). **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.40

– 7.37 (m, 5H, *d*a), 7.36 – 7.33 (m, 5H , *d*b) 5.62 – 5.60 (m, 1H , *d*a), 5.57 – 5.56 (m, 1H, *d*b), 4.75 – 4.71 (m, 1H, *d*a), 4.70 – 4.68 (m, 1H, *d*b), 4.50 – 4.47 (m, 1H, *d*a), 4.46 – 4.44 (m, 1H, *d*b), 4.41 – 4.38 (m, 1H, *d*a), 4.35 (d, *J* = 9.9 Hz, 1H, *d*a), 4.34 (d, *J* = 9.9 Hz, 1H, *d*b), 4.25 – 2.20 (m, 1H, *d*b), 4.13 (dd, *J* = 10.5, 5.7 Hz, 1H, *d*a), 3.91 (dd, *J* = 10.7, 5.9 Hz, 1H, *d*b), 3.50 – 3.47 (m, 1H, *d*a), 3.45 – 3.40 (m, 1H, *d*b), 2.83 – 2.76 (m, 1H, *d*a), 2.72 – 2.71 (m, 1H, *d*b), 1.33 – 1.29 (m, 3H, *d*b), 1.31 – 1.27 (m, 3H, *d*a). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 140.5 ($C_q$, *d*a), 140.4 ($C_q$, *d*b), 139.3 ($C_q$, *d*a), 138.9 ($C_q$, *d*b), 128.6 (CH, *d*a), 128.6 (CH, *d*b), 128.1 (CH, *d*a,*d*b), 126.0 (CH, *d*a), 126.0 (CH, *d*b), 121.3 (CH, *d*a), 121. 0 (CH, *d*b), 83.5 (CH, *d*a), 83.3 (CH, *d*b), 69.9 (CH, *d*a), 69.7 (CH, *d*b), 69.5 ($CH_2$, da), 67.6 ($CH_2$, *d*b), 66.5 (*d*a), 60.4 (*db*), 46.5 (CH, *d*a), 46.5 (CH, *d*b), 21.3 ($CH_3$, *d*a), 20.0 ($CH_3$, *d*b). **LC-MS** calcd for $C_{14}H_{16}NaO_2$ $[M+Na]^+$ 239.10 found 239.16.

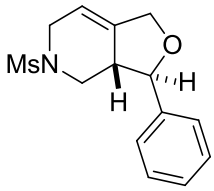
**3-phenyl-5-tosyl-1,3,3a,4,5,6-hexahydrofuro[3,4-c]pyridine (72a)**




Represented procedure **GP-7** was followed using **71a** (49.8 mg, 0.14 mmol). Purification by column chromatography (Eluent: gradient hexane/ethyl acetate) yielded **72a** as a sticky wax (71 %, 35.5 mg, 0.09 mmol, *d.r.* > 25:1). **$R_f$** = 0.31 (Eluent: Hexane/ethyl acetate = 7:3). **$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.65 (d, *J* = 8.2 Hz, 2H), 7.38– 7.31 (m, 7H), 5.53 (s, 1H), 4.66 (d, *J* = 12.8 Hz, 1H), 4.37 (d, *J* = 12.8 Hz, 1H), 4.22 (d, *J* = 9.8 Hz, 1H), 4.11 (d, *J* = 16.6 Hz, 1H), 4.02 (dd, *J* = 11.1, 5.7 Hz, 1H), 3.24 (d, *J* = 16.8 Hz, 1H), 2.79 (brs, 1H), 2.43 (s, 3H), 2.27 (t, *J* = 10.6 Hz, 1H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 143.7 ($C_q$), 130.0 ($C_q$), 139.4 ($C_q$), 133.5 ($C_q$), 129.8 (CH), 128.7 (CH), 128.5 (CH), 127.5 (CH), 126.2

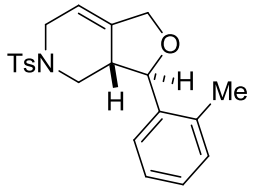
(CH), 113.0 (CH), 84.1 (CH), 69.5 ($CH_2$), 47.3 (CH), 44.5 ($CH_2$), 44.3 ($CH_2$), 21.6 ($CH_3$). **LC-MS** calcd for $C_{20}H_{21}NNaO_3S$ $[M+Na]^+$ 378.11, found 378.17.

**5-(methylsulfonyl)-3-phenyl-1,3,3a,4,5,6-hexahydrofuro[3,4-c]pyridine (72b)**



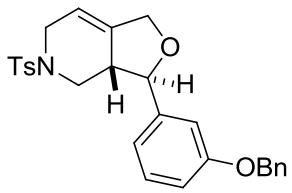

Represented procedure **GP-7** was followed using **71b** (55.9 mg, 0.20 mmol). Purification by column chromatography (Eluent: gradient hexane/ethyl acetate) yielded **72b** as a white solid (45 %, 25.1 mg, 0.09 mmol, *d.r.* > 25:1). **M. p.** = (116 – 119)°C. $\mathbf{R_f}$ = 0.27 (eluent: Hexane/ethyl acetate = 7:3). **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.40 – 7.30 (m, 5H), 5.62 (s, 1H), 4.72 (d, *J* = 12.9 Hz, 1H), 4.46 (d, *J* = 12.9 Hz, 1H), 4.31 (d, *J* = 9.7 Hz, 1H), 4.11 (d, *J* = 17.0 Hz, 1H), 3.98 (dd, *J* = 11.5, 5.6 Hz, 1H), 3.60 (d, *J* = 17.1 Hz, 1H), 2.80 – 2.74 (m, 4H), 2.64 (t, *J* = 10.0 Hz, 1H). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 140.3 ($C_q$), 139.4 ($C_q$), 128.8 (CH), 128.4 (CH), 126.0 (CH), 113.2 (CH), 84.1 (CH), 69.6 ($CH_2$), 47.5 (CH), 44.3 ($CH_2$), 44.1 ($CH_2$), 36.0 ($CH_3$). **LC-MS** calcd for $C_{14}H_{17}NNaO_3S$ $[M+Na]^+$ 302.08, found 302.21.

**3-(o-tolyl)-5-tosyl-1,3,3a,4,5,6-hexahydrofuro[3,4-c]pyridine (72c)**




Represented procedure **GP-7** was followed using **71c** (51.7 mg, 0.14 mmol). Purification by column chromatography (Eluent: gradient hexane/ethyl acetate) yielded **72c** as a white solid (87 %, 44.3 mg, 0.12 mmol, *d.r.* > 25:1). **M. p.** = (120 – 124) °C. $\mathbf{R_f}$ = 0.33 (Eluent: Hexane/ethyl acetate = 7:3). **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.67 (d, *J* = 8.2 Hz, 2H), 7.46 – 7.44 (m, 1H), 7.34 (d, *J* = 8.1 Hz, 2H), 7.30 – 7.18 (m, 3H), 5.55 (s, 1H), 4.67 (d, *J* = 13.0 Hz, 1H), 4.49 (d, *J* = 10.0 Hz, 1H), 4.39 (d, *J* = 12.9 Hz, 1H), 4.15 (d, *J* = 16.7 Hz, 1H), 4.04 (dd, *J* = 11.1, 5.6 Hz, 1H), 3.27 (d, *J* = 16.8 Hz, 1H), 2.94 (brs, 1H), 2.46 (s, 3H), 2.33 (s, 3H), 2.29 (t, *J* = 10.7 Hz, 1H). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 143.7 ($C_q$), 140.2 ($C_q$), 136.8 ($C_q$), 135.9 ($C_q$), 133.6 ($C_q$), 130.7 (CH), 129.8 (CH), 128.2 (CH), 127.5 (CH), 126.5 (CH), 126.1 (CH), 112.9 (CH), 80.8 (CH), 69.3 ($CH_2$), 46.5 (CH), 44.7 ($CH_2$), 44.3 ($CH_2$), 21.5 ($CH_3$), 19.3 ($CH_3$). **LC-MS** calcd for $C_{21}H_{23}NNaO_3S$ $[M+Na]^+$ 392.13, found 392.18.

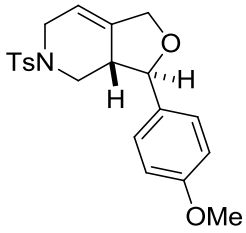
**3-(3-(benzyloxy)phenyl)-5-tosyl-1,3,3a,4,5,6-hexahydrofuro[3,4-c]pyridine (72d)**




Represented procedure **GP-7** was followed using **71d** (64.6 mg, 0.14 mmol). Purification by column chromatography (Eluent: gradient hexane/ethyl

acetate) yielded **72d** as a white solid (64 %, 41.5 mg, 0.09 mmol, *d.r.* > 25:1). **M. p.** = (134 – 137) °C. $\mathbf{R_f}$ = 0.38 (Eluent: Hexane/ethyl acetate = 7:3). **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.66 (d, *J* = 8.2 Hz, 2H), 7.48 – 7.28 (m, 8H), 6.99 – 6.91 (m, 3H), 5.52 (s, 1H), 5.09 (s, 2H), 4.66 (d, *J* = 12.8 Hz, 1H), 4.37 (d, *J* = 12.8 Hz, 1H), 4.19 (d, *J* = 9.8 Hz, 1H), 4.11 (d, *J* = 16.8 Hz, 1H), 4.03 (dd, *J* = 11.1, 5.7 Hz, 1H), 3.23 (d, *J* = 16.7 Hz, 1H), 2.78 (brs, 1H), 2.43 (s, 3H), 2.26 (t, *J* = 10.6 Hz, 1H). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 159.2 ($C_q$), 143.8 ($C_q$), 141.2 ($C_q$), 139.9 ($C_q$), 136.9 ($C_q$), 133.5 ($C_q$), 129.8 (CH), 129.8 (CH), 128.7 (CH), 128.1 (CH), 127.7 (CH), 127.5 (CH), 118.7 (CH), 114.5 (CH), 113.0 (CH), 112.8 (CH), 83.9 (CH), 70.1 ($CH_2$), 69.6 ($CH_2$), 47.4 (CH), 44.6 ($CH_2$), 44.3 ($CH_2$), 21.6 ($CH_3$). **LC-MS** calcd for $C_{27}H_{27}NNaO_4S$ $[M+Na]^+$ 484.16, found 484.19.

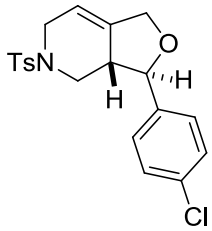
### 3-(4-methoxyphenyl)-5-tosyl-1,3,3a,4,5,6-hexahydrofuro[3,4-c]pyridine (72e)




Represented procedure **GP-7** was followed using **71e** (53.9 mg, 0.14 mmol). Purification by column chromatography (Eluent: gradient hexane/ethyl acetate) yielded **72e** as a white solid (92 %, 50.1 mg, 0.13 mmol, *d.r.* > 25:1). **M. p.** = (126 – 128) °C. $\mathbf{R_f}$ = 0.27 (Eluent: Hexane/ethyl acetate = 7:3). **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.65 (d, *J* = 8.3 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.26 (d, *J* = 8.7 Hz, 2H), 6.91 (d, *J* = 8.7 Hz, 2H), 5.51 (s, 1H), 4.63 (d, *J* = 12.8 Hz, 1H), 4.34 (d, *J* = 12.9 Hz, 1H), 4.15 (d, *J* = 10.0 Hz, 1H), 4.12 – 4.08 (m, 1H), 3.99 (dd, *J* = 11.1, 5.7 Hz, 1H), 3.83 (s, 3H), 3.24 (d, *J* = 16.7 Hz, 1H), 2.78 (brs, 1H), 2.43 (s,

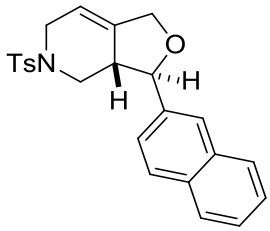
3H), 2.24 (t, *J* = 10.0 Hz, 1H). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 159. 8 ($C_q$), 143.7 ($C_q$), 140.1 ($C_q$), 133.6 ($C_q$), 131.2 ($C_q$), 129.8 (CH), 127.6 (CH), 127.5 (CH), 114.1 (CH), 112.9 (CH), 83.8 (CH), 69.4 ($CH_2$), 55.4 ($CH_3$), 47.0 (CH), 44.5 ($CH_2$), 44.3 ($CH_2$), 21.5 ($CH_3$). **LC-MS** calcd for $C_{21}H_{23}NNaO_4S$ $[M+Na]^+$ 408.12, found 408.17.

**3-(4-chlorophenyl)-5-tosyl-1,3,3a,4,5,6-hexahydrofuro[3,4-c]pyridine (72f)**



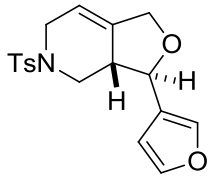

Represented procedure **GP-7** was followed using **71f** (54.6 mg, 0.14 mmol). Purification by column chromatography (Eluent: gradient hexane/ethyl acetate) yielded **72f** as a white solid (71 %, 39.0 mg, 0.01 mmol, *d.r.* > 25:1). **M. p.** = (140 – 144) °C. **$R_f$** = 0.28 (Eluent: Hexane/ethyl acetate = 7:3). **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.3 Hz, 2H), 7.38 (d, *J* = 8.5 Hz, 2H), 7.35 (d, *J* = 7.9 Hz, 2H), 7.29 (d, *J* = 8.4 Hz, 2H), 5.56 (s, 1H), 4.69 – 4.64 (m, 1H), 4.41 – 4.37 (m, 1H), 4.21 (d, *J* = 9.8 Hz, 1H), 4.16 – 4.11 (m, 1H), 4.02 (dd, *J* = 11.1, 5.7 Hz, 1H), 3.30 – 3.24 (m, 1H), 2.74 (brs, 1H), 2.46 (s, 3H), 2.32 – 2.27 (m, 1H). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 143.8 ($C_q$), 139.6 ($C_q$), 138.1 ($C_q$), 134.1 ($C_q$), 133.6 ($C_q$), 129.8 (CH), 128.92 (CH), 127.5 (2CH), 113.3 (CH), 83.3 (CH), 69.6 ($CH_2$), 47.5 (CH), 44.4 ($CH_2$), 44.3 ($CH_2$), 21.6 ($CH_3$). **LC-MS** calcd for $C_{20}H_{20}ClNNa_2O_3S$ $[M+Na]^+$ 412.08, found 412.13.

**3-(naphthalen-2-yl)-5-tosyl-1,3,3a,4,5,6-hexahydrofuro[3,4-c]pyridine (72g)**



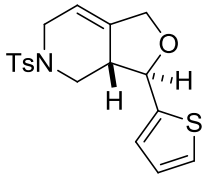

Represented procedure **GP-7** was followed using **71g** (56.8 mg, 0.14 mmol). Purification by column chromatography (Eluent: gradient hexane/ethyl acetate) yielded **72g** as a white solid (63 %, 36.5 mg, 0.09 mmol, *d.r.* > 25:1). **M. p.** = (177 – 180) °C. $\mathbf{R_f}$ = 0.27 (Eluent: Hexane/ethyl acetate = 7:3). **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.90 – 7.84 (m, 3H), 7.78 (s, 1H), 7.65 (d, *J* = 8.3 Hz, 2H), 7.52 – 7.55 (m, 3H), 7.32 (d, *J* = 8.3 Hz, 2H), 5.57 (s, 1H), 4.72 (d, *J* = 12.9 Hz, 1H), 4.45 – 4.41 (m, 1H), 4.39 (d, *J* = 9.8 Hz, 1H), 4.17 – 4.11 (m, 1H), 4.04 (dd, *J* = 11.2, 5.7 Hz, 1H), 3.32 – 3.26 (m, 1H), 2.88 (s, 1H), 2.43 (s, 3H), 2.35 (t, *J* = 10.0 Hz, 1H). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 143.7 ($C_q$), 140.0 ($C_q$), 136.8 ($C_q$), 133.7 ($C_q$), 133.5 ($C_q$), 133.3 ($C_q$), 129.8 (CH), 128.7 (CH), 128.0 (CH), 127.8 (CH), 127.5 (CH), 126.3 (CH), 126.2 (CH), 125.4 (CH), 123.8 (CH), 113.1 (CH), 84.3 (CH), 69.7 ($CH_2$), 47.3 (CH), 44.6 ($CH_2$), 44.3 ($CH_2$), 21.6 ($CH_3$). **LC-MS** calcd for $C_{24}H_{23}NNaO_3S$ $[M+Na]^+$ 428.13, found 428.16.

**3-(furan-2-yl)-5-tosyl-1,3,3a,4,5,6-hexahydrofuro[3,4-c]pyridine (72h)**




Represented procedure **GP-7** was followed using **71h** (48.4 mg, 0.14 mmol). Purification by column chromatography (Eluent: gradient hexane/ethyl acetate) yielded **72h** as a white solid (68 %, 34.5 mg, 0.10 mmol, *d.r.* > 25:1). **M.p.** = (149 – 152) °C. $\mathbf{R_f}$ = 0.27 (Eluent: Hexane/ethyl acetate = 7:3). **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.66 (d, *J* = 8.3 Hz, 2H), 7.45 – 7.44 (m, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 6.44 (s, 1H), 5.52 (s, 1H), 4.56 (d, *J* = 12.9 Hz, 1H), 4.30 (d, *J* = 12.9 Hz, 1H), 4.19 (d, *J* = 10.0 Hz, 1H), 4.12 (d, *J* = 16.7 Hz, 1H), 4.03 (dd, *J* = 11.2, 5.7 Hz, 1H), 3.23 (d, *J* = 16.8 Hz, 1H), 2.82 (brs, 1H), 2.43 (s, 3H), 2.18 (t, *J* = 10.0 Hz ,1H). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 143.9 (CH), 143.8 ($C_q$), 140.2 (CH), 139.7 ($C_q$), 133.5 ($C_q$), 129.8 (CH), 127.5 (CH), 123.9 ($C_q$), 113.1 (CH), 108.5 (CH), 76.3 (CH), 69.2 ($CH_2$), 45.7 (CH), 44.6 ($CH_2$), 44.3 ($CH_2$), 21.6 ($CH_3$). **LC-MS** calcd for $C_{18}H_{19}NNaO_4S$ $[M+Na]^+$ 368.09, found 368.13.

**3-(thiophen-2-yl)-5-tosyl-1,3,3a,4,5,6-hexahydrofuro[3,4-c]pyridine (72i)**




Represented procedure **GP-7** was followed using **71i** (50.6 mg, 0.14 mmol). Purification by column chromatography (Eluent: gradient hexane/ethyl acetate) yielded **72i** as a pale yellow solid (68 %, 36.1 mg, 0.10 mmol, *d.r.* > 25:1). **M. p.** = (132 – 135) °C. $\mathbf{R_f}$ = 0.24 (Eluent: Hexane/ethyl acetate = 7:3). **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.66 (d, *J* = 8.3 Hz, 2H), 7.33 – 7.31 (m, 3H), 7.03 – 6.99 (m, 2H), 5.52 (s, 1H), 4.61 (d, *J* = 12.9 Hz, 1H), 4.48 (d, *J* = 9.8 Hz, 1H), 4.33 (d, *J* = 12.9 Hz, 1H), 4.15 – 4.07 (m, 2H), 3.24 (d, *J* = 16.9 Hz, 1H), 2.90 (s, 1H), 2.43 (s, 3H), 2.25 (t, *J* = 10.0 Hz, 1H). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 143.80 ($C_q$), 142.38 ($C_q$), 139.3 ($C_q$), 133.6 ($C_q$), 129.8 (CH), 127.5 ( CH), 126.8 (CH), 125.8 (CH), 125.2 (CH), 113.4 (CH), 79.5 (CH), 69.4 ($CH_2$), 47.4 (CH), 44.5 ($CH_2$), 44.3 ($CH_2$), 21.6 ($CH_3$). **LC-MS** calcd for $C_{18}H_{19}NNaO_3S_2$ $[M+Na]^+$ 384.07, found 384.11.

*Chapter 4*

# $MnO_2$ promoted cascade reactions of 1,6-enynols

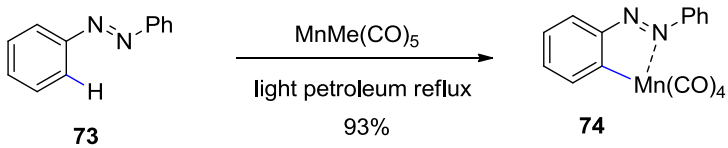
## 4.1 Introduction

### 4.1.1 Manganese catalysis for organic synthesis

Manganese is the third most abundant transition metal after iron and titanium. Since it is an inexpensive and non-toxic element, it represents a very attractive alternative to the use of precious metal based catalysts.[57] Different transformations have been reported using manganese catalysts; some of the most relevant are C–H activation, hydrosilylation and cross-coupling reactions.[58]

### 4.1.2 Manganese in C-H activation reactions

Stone and Bruce, in 1970, developed the first C-H activation operated by a manganese complex, using a stoichiometric amount of $MnMe(CO)_5$ (Scheme 31).[59]



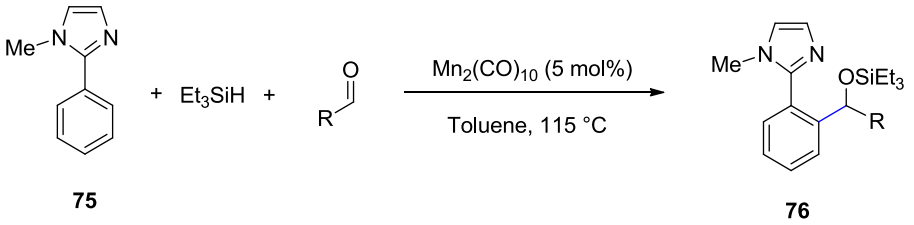

**73** **74**

**Scheme 31.** First C-H activation promoted by a manganese complex

After this seminal work, stoichiometric transformations were reported also by Liebeskind,[60] Nicholson, Main [61] and Woodgate[62].

[57] R. Cano, K. Mackeyab and G.P. McGlacken, *Catal.Sci.Technol.,* 2018, **8**, 1251.
[58] J. R. Carney, B. R. Dillon and S.P. Thomas, *Eur.J.Org.Chem.,* 2016, **23**, 3912.
[59] M.I. Bruce, M.Z. Iqbal and F.G.A. Stone, *J.Chem.Soc.A.,* 1970, 3204.
[60] L. S. Liebeskind, J. R. Gasdaska, J. S. McCallum and S. J. Tremont, *J. Org. Chem.*, 1989, **54,** 669.

Pioneering studies on C-H activation in the presence of a catalytic amount of manganese were carried out by Kuninobu and Takai in 2007.[63] In this case different imidazolines were reacted with benzaldehyde and triethylsilane, in the presence of manganese catalyst [$MnBr(CO)_5$] to give silyl ethers (Scheme 32).




**Scheme 32** Manganese-catalysed C–H activation.

The mechanism should start with the oxidative addition of the aromatic compound to the metal center followed by insertion of the aldehyde into the manganese–carbon (aryl) bond. At this point, after the introduction of a molecule of triethylsilane the desidered product is delivered. Important contributions involving catalysis were also given by the groups of Ackermann,[64] Wang[65] and others[66]. Overall different manganese catalysed C–H

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[61] (a)L.H.P. Gommans, L. Main and B. K. Nicholson, *J. Chem. Soc., Chem. Commun.*, 1987, 761. (b) N.P. Robinson, L. Main and B.K. Nicholson, J. *Organomet. Chem.*, 1989, **364**, C37(c) W. Tully, L. Main and B.K. Nicholson, *J. Organomet. Chem.*, 1998, **551**, 281.

[62] (a) R. C. Cambie, M. R. Metzler, P. S. Rutledge and P. D. Woodgate, J. *Organomet. Chem.,* 1990, **381**, C26. (b) R.C. Cambie, M.R. Metzler, P.S. Rutledge and P.D. Woodgate, *J.Organomet.Chem.*, 1990, **398**, C22. (c) R.C. Cambie, M.R. Metzler, P.S. Rutledge and P.D.Woodgate, *J. Organomet. Chem.*, 1992, **429**, 41.

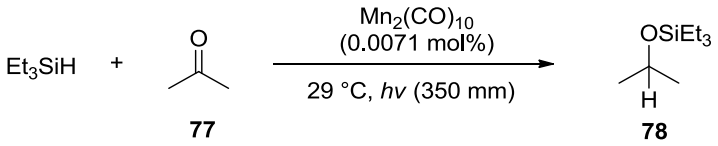
[63] Y. Kuninobu, Y. Nishina, T. Takeuchi and K. Takai, *Angew.Chem.Int. Ed.,* 2007, **43**, 6518.

[64] (a) W. Liu, D. Zell, M. John and L. Ackermann, *Angew. Chem., Int. Ed.*, 2015, **54**, 4092. (b) W. Liu, J. Bang, Y. Zhang and L. Ackermann, *Angew. Chem., Int. Ed.*, 2015, **54**, 14137. (c) W. Liu, G. Cera, J. C. A. Oliveira, Z. Shen, and L. Ackermann, *Chem. Eur. J.* 2017, **23**, 11524.

alkenylations, C–H alkynylations, C–H allylations, C–H halogenations and C–H hydroarylations have been successfully accomplished.

### 4.1.3 Manganese in hydrosilylation reactions

Manganese-mediated hydrosilylation reactions have seen great advances over the last few decades. The first example was reported in 1982 by Yates co-workers who performed the hydrosilylation of ketones under UV irradiation using $Mn_2(CO)_{10}$ (Scheme 33).[67]




**Scheme 33** first manganese-promoted hydrosilylation

After this work many other studies were carried out with hydrosilylation of ketones,[68] esters,[69] aldehydes[70] and carboxylic acids[71]. Poor results were obtained when alkynes and alkenes were used as substrates.

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[65] B. Zhou, H. Chen and C. Wang, *J. Am. Chem. Soc.*, 2013, **135**, 1264. (b) R. He, Z.-T. Huang, Q.-Y. Zheng and C. Wang, *Angew. Chem., Int. Ed.*, 2014, **53**, 4950. (c) B. Zhou, P. Ma, H. Chen and C. Wang, *Chem. Commun.*, 2014, 50, 14558.

[66] (a) L. Shi, X. Zhong, H. She, Z. Lei and F. Li, *Chem. Commun*., 2015, **51**, 7136. (b) S.M. Paradine, J.R. Griffin, J. Zhao, A.L. Petronico, S.M. Miller and M.C. White, *Nat. Chem.*, 2015, **7**, 987.

[67] R.L. Yates, *J. Catal.,* 1982, **78**, 111.

[68] M. DiBiase Cavanaugh, B.T. Gregg and A.R. Cutler, *Organometallics,* 1996, **15**, 2764.

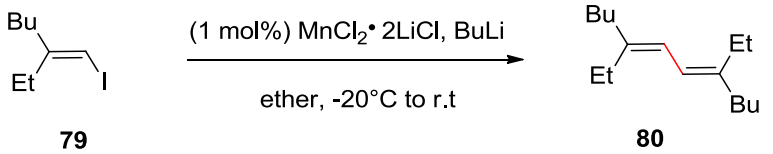
[69] Z. Mao, B.T. Gregg and A.R. Cutler, *J. Am. Chem. Soc.*, 1995, **117**, 10139.

[70] a) J. Zheng, S. Elangovan, D.A. Valyaev, R. Brousses, V. César, J.B. Sortais, C. Darcel, N. Lugan and G. Lavigne, *Adv. Synth. Catal.,* 2014, **356**, 1093 b) D.A. Valyaev, D. Wei, S. Elangovan, M. Cavailles, V. Dorcet, J.B. Sortais, C. Darcel and N. Lugan, *Organometallics,* 2016, **35**, 4090. (c) M. Pinto, S. Friães, F. Franco, J. Lloret-Fillol and B. Royo, *Chem.Cat.Chem.,* 2018, **10**, 2734.

[71] J. Zheng, S. Chevance, C. Darcel and J.B. Sortais, *Chem. Commun.*, 2013, **49**, 10012.

### 4.1.4 Manganese in coupling reactions

Manganese-based complexes have been also employed in coupling reactions. In this case, the first examples dates back to 1976 when the group of Cahiez and Normant developed a manganese-catalysed homocoupling using alkenyl iodides and BuLi (Scheme 34).[72]




**79** **80**

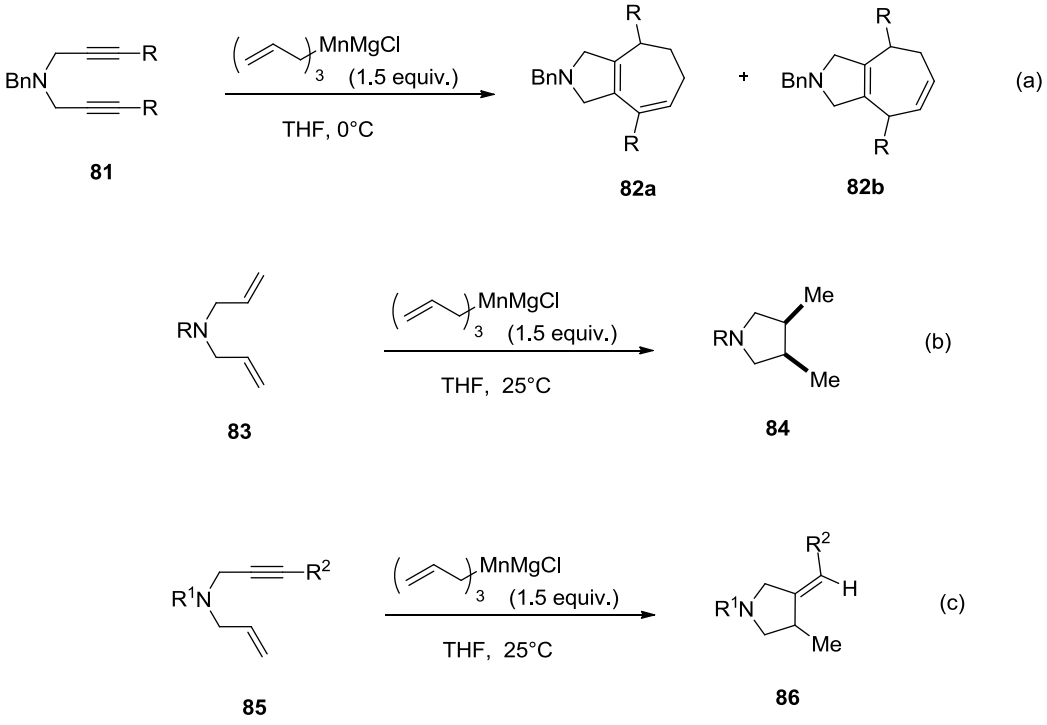
**Scheme 34** Manganese-catalyzed homocoupling

The construction of aryl-aryl bonds was investigated too. A Stille-type cross-coupling reaction, catalysed by manganese, was reported by Choi and co-workers.[73] In this case, products were delivered in high yield, but harsher conditions were required compared to those of analogous palladium-catalysed reactions. Interestingly, also Grignard reagents were used as coupling partners with good results.[74]

[72] G. Cahiez, D. Bernard and J.F Normant, *J.Organomet.Chem.* 1976, **113**, 99.
[73] S.K. Kang, J.S. Kim and S. C. Choi, *J. Org. Chem.* 1997, **62**, 4208.
[74] (a) G. Cahiez, C. Duplais and J. Buendia, *Chem. Rev.,* 2009, ***109***, 1434. (b)G. Cahiez, D. Luart and F. Lecomte, *Org. Lett.,* 2004, ***6***, 4395. (c)M. Rueping and W. Ieawsuwan, *Synlet.,t* 2007, 247 (d) H. Kakiya, R. Inoue, H. Shinokubo, K. Oshima, *Tetrahedron,* 2000, ***56***, 2131.

### 4.1.5 Manganese-catalysed cyclization reactions

Manganese-catalysed cyclization reactions are rare, only few studies are present in literature. To the best of our knowledge, the first example was reported by the group of Oshima in 1998. They investigated the intramolecular cycloaddition of diynes in the presence of triallylmanganate to give bicyclized derivatives containing a 7-membered ring (Scheme 35, reaction (a)).[75] In this case, the allylic moiety was included in the products. Using the same manganese-based complex they also carried out the cyclization of dienes and enynes (Scheme 35, reaction (b) and (c)).




**Scheme 35** Reaction of diynes(a), dienes (b) and enynes (c) with triallylmanganate.

[75] J. Tang, H. Shinokubo and K. Oshima, *Organometallics,* 1998, **17**, 290.

More recently, Matsubara and co-workers designed a manganese-based complex with a porphyrin ligand bearing a weakly coordinating axial counteranion ligand (Figure 10).[76]

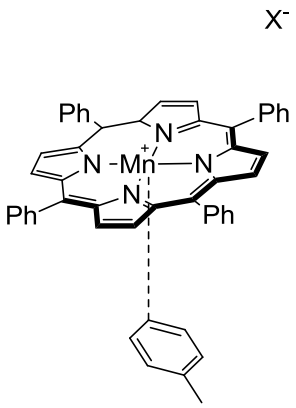
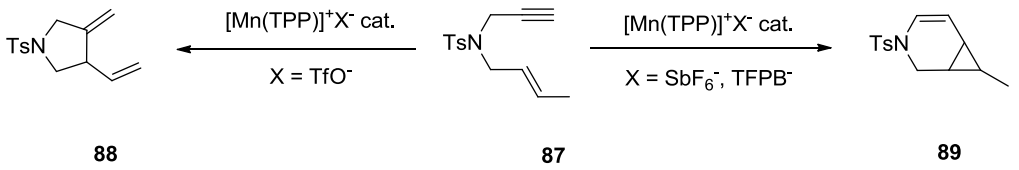



**Figure 10** $[Mn(TPP)]^+X^-$ Catalyst (X = $SbF_6^-$, $TfO^-$, $TFPB^-$)

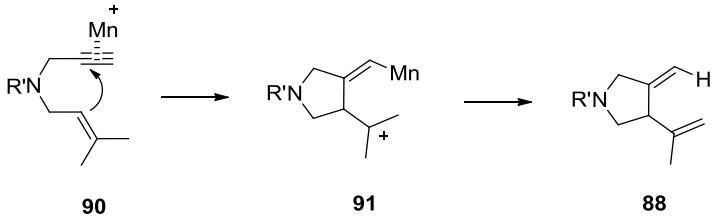
Such system made the metal centre sufficiently electrophilic to activate a triple bond. Interestingly, by changing the nature of the counteranion, six- or five-membered ring systems can be delivered (Scheme 36).




**Scheme 36** Two possible pathways for manganese porphyrin catalyzed cycloisomerization of enynes

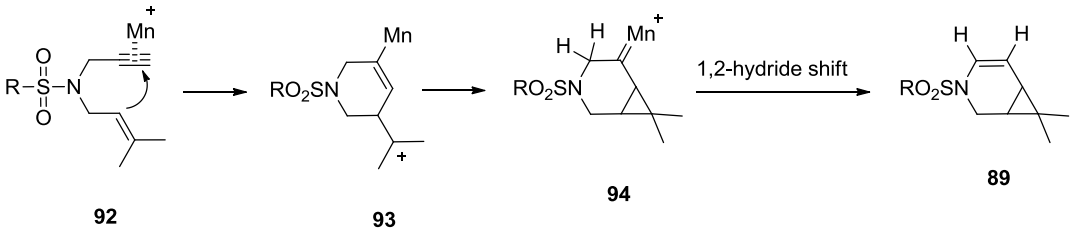
Synthesis of **88** occurred via *5-exo* cyclization. In particular it was supposed the formation of a vinyl metal intermediate **91** which after proton shift affords the desidered product **88** (Scheme 37).

[76] T. Ozawa, T. Kurahashi and S. Matsubara, *Org.Lett.*, 2012, **14**, 3008.




**Scheme 37** *5-exo* pathway for manganese porphyrin catalyzed cycloisomerization of enynes

On the other hand, the reaction pathway for the formation of compound **89** consisted in a *6-endo* cyclization which involved the formation of intermediate **93**. The latter after isomerisation and subsequent 1,2-hydride shift would deliver the six-membered ring (Scheme 38).

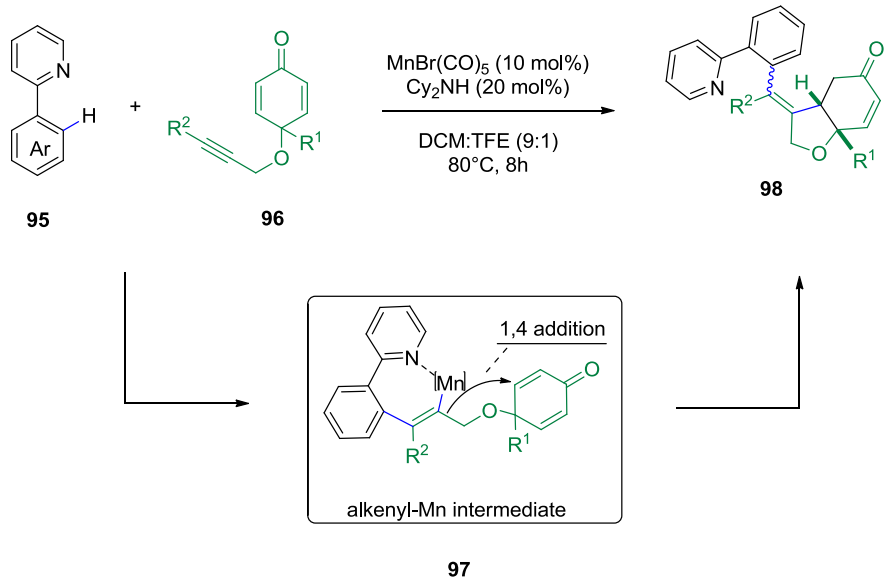



**Scheme 38** *6-endo* pathway for manganese porphyrin catalyzed cycloisomerization of enynes

Another interesting study was carried out by the group of Lin.[77] In particular they designed a Mn(I)-based catalytic system that operates the activation of the aromatic C-H bond of 2-pyridyl derivatives **95** to give an intermediate which subsequently coordinates with **96** and undergoes regioselective syn-insertion to the C≡C bond to form alkenyl-Mn species **97** (Scheme 39). The latter finally undergoes Michael addition and protonation to

[77] Y.X. Tan, X.Y. Liu, Y.S. Zhao, P. Tian and G.Q. Lin, *Org. Lett.*, 2019, **21**, 5.

afford the desired cyclized adduct **98**. All the products were chemoselectively delivered.




**Scheme 39** Cyclized products obtained through manganese-catalysed coupling reaction between arenes and 1,6-enynes

## 4.2 Results and discussion

Product **99a** was serendipitously obtained when we attempted to oxidize enynol **64a** to the corresponding aldehyde (Scheme 40). The cascade reaction should start with the initial oxidation of the hydroxyl group to give the linear aldehyde which in turn undergoes cyclization. A final aromatization step would deliver product **99a**.


**64a** **99a**

**Scheme 40** Synthesis of product **99a**

The reaction was carried out in DCE, at room temperature with four equiv. of $MnO_2$. Upon full conversion, the mixture was purified by filtration on a short pad of celite followed by chromatographic column, which afforded product **99a** in 20% yield. After the isolation of such interesting cyclic derivative, we decided to further investigate the reactivity of enynol **64a**, in the presence of $MnO_2$, optimizing the reaction conditions (Table 5).

Firstly, we increased the temperature to 50°C and the amount of $MnO_2$ from 4 equiv. to 40 equiv. (entry 1). In this way the yield has more than doubled (44%). Different solvents were tested, both chlorinated and non-chlorinated. Toluene and MTBE (entries 2-3) were less efficient compared to chloroform and dichloromethane (entries 4-5) which gave the desired product in 44% and 38% yield respectively. At this point, using dichloromethane as solvent, we changed the concentration and repeated the reaction at room temperature. Comparable efficiency was observed diluting the system to 0.025 M (entry 6), whereas a greater improvement was achieved when we further

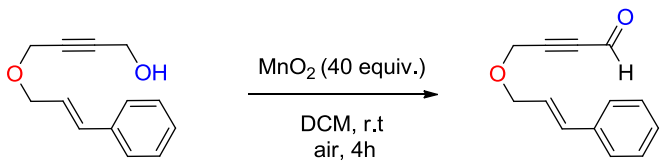
lowered the concentration to 0.0125 M (entry 7). The reaction was also tested under $N_2$ atmosphere but no increase in the yield value was noticed.


**64a** **99a**

| Entry | Solvent | M (Mol/L) | T (°C) | Y (%) |
|---|---|---|---|---|
| **1** | DCE | 0.12 | 50 | 45 |
| **2** | Toluene | 0.12 | 50 | 29 |
| **3** | MTBE | 0.12 | 50 | 15 |
| **4** | $CHCl_3$ | 0.12 | 50 | 44 |
| **5** | DCM | 0.12 | 50 | 38 |
| **6** | DCM | 0.025 | rt | 34 |
| **7** | DCM | 0.0125 | rt | 51 |

**Table 5** Optimization of the reaction conditions

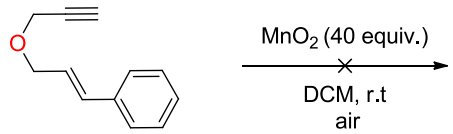
When we stopped the reaction after four hours, we observed the formation of another product different from **99a**. It consisted in the linear aldehyde **100a**. Such finding confirmed that the first reaction step consisted in the oxidation of the hydroxyl group (Scheme 41).




**64a** **100a**

**Scheme 41** Formation of linear aldehyde **100a**

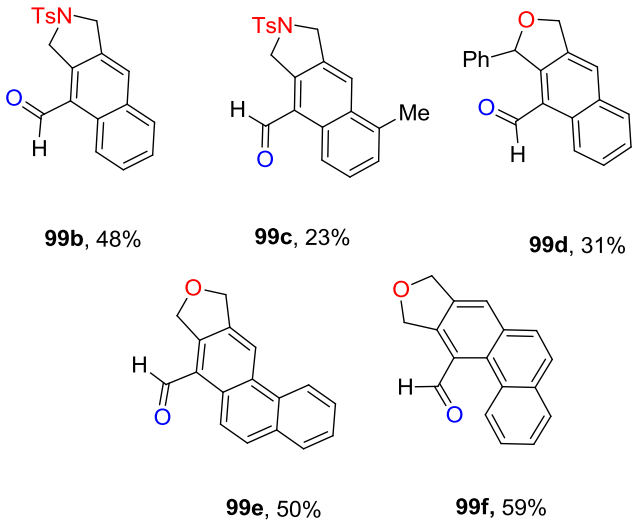
Interestingly, terminal enyne **101a** was unreactive under standard conditions (Scheme 42). Such result showed that the presence of a propargyl alcohol moiety is essential to promote the reaction.




**101a**

**Scheme 42** No reactivity observed with terminal enynes **101a**

With the optimized conditions in hand, the substrate scope was investigated. A good result was achieved when we changed the tethering group of **64a** with a tosyl moiety (**99b**, 48%), whereas the presence of a methyl group in the *ortho*-position of the phenyl ring (**99c**) lowered the yield to 23 % (Scheme 43). Afterwards we decided to test different *O*-tethered enynols of type **64**. Increasing the steric hindrance with a phenyl ring in α position to oxygen, afforded product **99d** in meagre 31% yields. The aromatic ring of the cinnamyl unit could be replaced by 1- and 2-naphthyl group and the corresponding products, **99e** and **99f**, were delivered in 59% and 50% yield respectively. Interestingly, compound **99f** was obtained as single regioisomer.




**99b**, 48% **99c**, 23% **99d**, 31%

**99e**, 50% **99f,** 59%

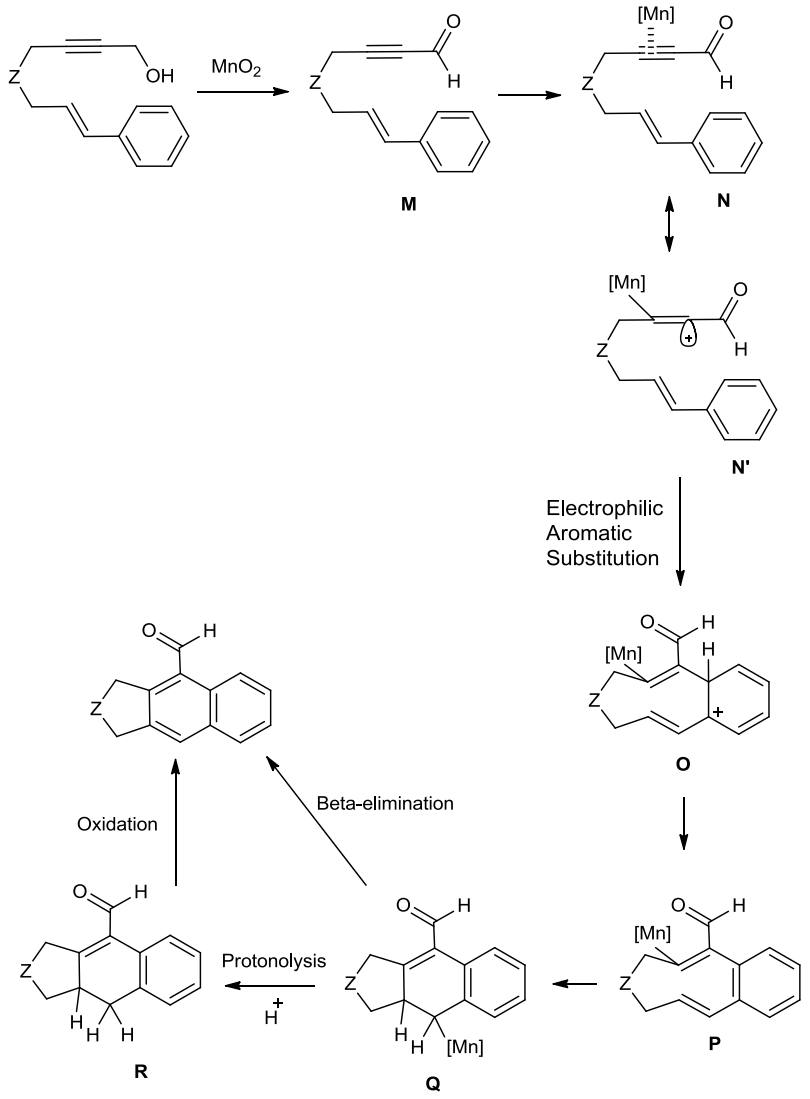
**Scheme 43** Reaction scope

The cyclized product did not form when we employed styryl arms with electron withdrawing substituents such as chloro and fluoro. These enynols were transformed to the corresponding aldehydes which did not undergo further cyclization. Such results along with the negative outcome obtained using a terminal 1,6-enyne (Scheme 42), suggest that the formal activation of the aromatic C-H could proceed through a process similar to an electrophilic aromatic substitution.

Regarding the mechanism, we supposed the initial oxidation of the enynol to the corresponding aldehyde **M** (Scheme 44). Then, the triple bond is activated by the metal giving intermediate **N**. It is not possible at present stage to assert which Mn species is coordinated by the electron-poor alkyne. The resulting vinyl manganese complex can then undergo an electrophilic aromatic substituion, in agreement with the observed trend of yields using electron-rich substrates, delivering Wheland-type intermediate **O**.

The latter undergoes an aromatization step forming **P** which in turn allows the insertion of the Mn species to give **Q**. Such intermediate could finally deliver

the desired product through two different pathways: protonolysis followed by an oxidation step or a β-elimination process.




**Scheme 44** Possible reaction mechanisms.

## 4.3 Conclusions

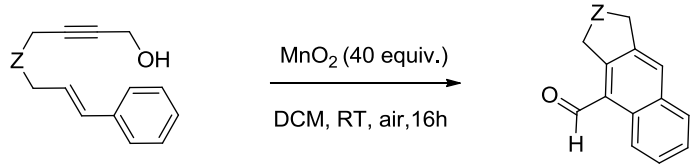
In conclusion, we have described the unprecedented use of $MnO_2$ in a cascade reactions of 1,6-enynols, involving the formation of products bearing 5- and 6-membered rings. The optimization of the reaction conditions was carried out by screening different solvents and temperatures. A small library of substrates, both *O*-tethered and *N*-tethered enynols, was synthesized in order to prove the generality of this methodology. The corresponding cyclic products were chemoselectively delivered in synthetically useful yields.

## 4.4 Experimental section

## General remarks

$^{1}H$ and $^{13}C$ NMR spectra were recorded at 300 K on a Bruker 400 MHz or Bruker 300 MHz using solvents as internal standards (7.26 ppm for $^{1}H$ NMR and 77.00 ppm for $^{13}C$ NMR for $CDCl_3$, 2.05 ppm for $^{1}H$ NMR and 29.84 ppm for $^{13}C$ NMR for Acetone-$d_6$, 7.16 ppm for $^{1}H$-NMR and 128.06 for $^{13}C$ NMR for Benzene-d6). The terms m, s, d, t, q and quint represent multiplet, singlet, doublet, triplet, quadruplet and quintuplet respectively, and the term br means a broad signal. LC-MS were recorded on an Agilent LQ Mass Spectrometer (ESI source). The synthesis of the1,6-enynols **64** is reported in paragraph 3.4.

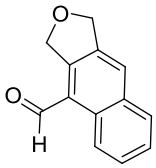
**General procedure for the synthesis of products 99 (GP-8)**




**99**

The 1,6-enynol was dissolved in DCM (0.0125 Mol/L) and then $MnO_2$ was added. The reaction stirred overnight at room temperature. Upon complete conversion the metal was removed filtering the mixture over a pad of celite and the crude was concentrated under reduced pressure. Purification by column chromatography (Hexane : EtOAc = 8: 2) afforded the desired product.

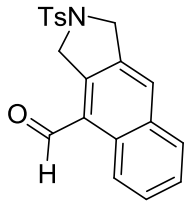
**1,3-dihydronaphtho[2,3-c]furan-4-carbaldehyde (99a)**



Product **99a** was isolated following **GP-8** as a white solid (51%, 25.2 mg, 0.12 mmol) using **64a** (50.5 mg, 0.25 mmol) as reagent.

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 10.95 (s, 1H, CHO), 8.77 (d, *J* = 8.6 Hz, 1H), 7.92 – 7.90 (m, 1H), 7.68 – 7.64 (m, 1H), 7.59 – 7.55 (m, 1H), 5.54 (s, 2H), 5.22 (s, 2H). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 190.2 (C=O), 144.2 ($C_q$), 138.5 ($C_q$), 133.7 ($C_q$), 131.7 ($C_q$), 128.9 (CH), 128.2 (CH), 126.4 (CH), 126.2 (CH), 123.8 ($C_q$), 122.4 (CH), 74.1 ($CH_2$), 71.7 ($CH_2$). **LC MS** calcd for $C_{13}H_{10}NaO_2$ $[M+Na]^+$ 221.05, found 221.02.

**2-tosyl-2,3-dihydro-1H-benzo[f]isoindole-4-carbaldehyde (99b)**

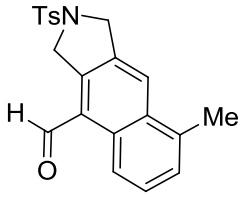


Product **99d** was isolated following **GP-8** as a white solid (48 %, 42 mg, 0.12 mmol) using **71a** (88 mg, 0.25 mmol) as reagent.

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 10.93 (s, 1H), 8.71 (d, *J* = 8.6 Hz, 1H), 7.90 – 7.80 (m, 4H), 7.68 – 7.61 (m, 1H), 7.61 – 7.52 (m, 1H), 7.32 (d, *J* = 8.0 Hz, 2H), 5.06 (s, 2H), 4.75 (s, 2H). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 190.0 (C=O), 143.9 ($C_q$), 140.2 ($C_q$), 135.4 ($C_q$), 133.6 ($C_q$), 133.4 ($C_q$), 131.7 ($C_q$), 129.9 (CH), 128.9 (CH), 128.5 (CH), 127.9 (CH), 127.7 (CH), 126.7 (CH), 124.5 ($C_q$), 122.2 (CH), 54.3 ($CH_2$),

52.1 ($CH_2$), 21.5 ($CH_3$). **LC MS** calcd for $C_{20}H_{17}NNaO_3S$ $[M+Na]^+$ 374.08, found 374.07.

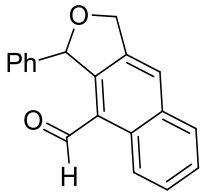
**8-methyl-2-tosyl-2,3-dihydro-1H-benzo[f]isoindole-4-carbaldehyde (99c)**




Product **99f** was isolated following **GP-8** as a white solid (23%, 22 mg, 0.06 mmol) using **71c** (92 mg, 0.25 mmol) as reagent.

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 10.94 (s, 1H), 8.55 (d, *J* = 8.7 Hz, 1H), 8.06 (s, 1H), 7.83 (d, *J* = 8.3 Hz, 2H), 7.56 – 7.49 (m, 1H), 7.39 (d, *J* = 7.0 Hz, 1H), 7.32 (d, *J* = 8.0 Hz, 2H), 5.05 (s, 2H), 4.77 (s, 2H), 2.69 (s, 3H), 2.38 (s, 3H). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 190.4 (C=O), 143.8 ($C_q$), 139.3 ($C_q$), 135.2 ($C_q$), 135.2 ($C_q$), 133.4 ($C_q$), 132.9 ($C_q$), 132.2 ($C_q$), 129.9 (CH), 128.1 (CH), 127.7 (CH), 127.5 (CH), 124.9 ($C_q$), 124.1 (CH), 120.2 (CH), 54.5 ($CH_2$), 52.4 ($CH_2$), 21.5 ($CH_3$), 19.9 ($CH_3$). **LC-MS** calcd for $C_{21}H_{19}NNaO_3S$ $[M+Na]^+$ 388.04 found 388.07.

**3-phenyl-1,3-dihydronaphtho[2,3-c]furan-4-carbaldehyde (99d)**

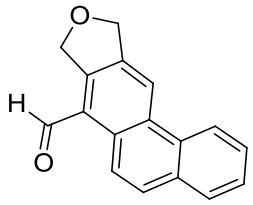



Product **99d** was isolated following **GP-8** as a white solid (31%, 21 mg, 0.08 mmol) using **64f** (69 mg, 0.25 mmol) as reagent.

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 10.54 (s, 1H), 9.01 (d, *J* = 8.5 Hz, 1H), 8.02 (s, 1H), 7.95 (d, *J* = 7.9 Hz, 1H), 7.72 – 7.55 (m, 2H), 7.34 – 7.27 (m, 3H), 7.22 – 7.16 (m,

2H), 6.82 (s, 1H), 5.37 (d, *J* = 12.8 Hz, 1H), 5.27 (d, *J* = 12.8 Hz, 1H). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 190.5 (C=O), 146.7 ($C_q$), 141.3 ($C_q$), 139.1 ($C_q$), 134.2 ($C_q$), 131.2 ($C_q$), 128.8 (CH), 128.7 (CH), 128.7 (CH), 128.5 (CH), 127.8 (CH), 126.9 (CH), 126.4 (CH), 124.6 (CH), 124.4 ($C_q$), 85.6 (CH), 71.0 ($CH_2$). **LC-MS** calcd for $C_{19}H_{14}NaO_2$ $[M+Na]^+$ 297.09, found 297.03.

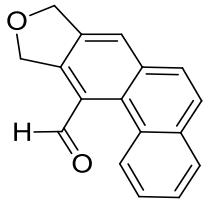
**8,10-dihydrophenanthro[2,3-c]furan-7-carbaldehyde (99e)**




Product **99e** was isolated following **GP-8** as a white solid (50%, 32 mg, 0.13 mmol) using **64d** (63 mg, 0.25 mmol) as reagent.

**$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 10.97 (s, 1H), 8.72 (s, 1H), 8.63 – 8.55 (m, 2H), 7.93 (d, *J* = 7.6 Hz, 1H), 7.89 (d, *J* = 9.2 Hz, 1H), 7.75 – 7.62 (m, 2H), 5.54 (s, 2H), 5.28 (s, 2H).**$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 190.4 (C=O), 142.8 ($C_q$), 139.1 ($C_q$), 131.4 ($C_q$), 131.2 ($C_q$), 130.8 ($C_q$), 130.0 ($C_q$), 129.4 (CH), 128.7 (CH), 127.4 (CH), 127.3 (CH), 124. 8 ($C_q$), 122.6 (CH), 120.6 (CH), 120.1 (CH), 74.5 ($CH_2$), 72.3 ($CH_2$). **LC-MS** calcd for $C_{17}H_{12}NaO_2$ $[M+Na]^+$ 271.21, found 271.01.

**8,10-dihydrophenanthro[2,3-c]furan-11-carbaldehyde (99f)**



Product **99c** was isolated following **GP-8** as a white solid (59%, 36 mg, 0.15 mmol) using **64e** (63 mg, 0.25 mmol) as reagent.

**$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 10.58 (s, 1H), 8.05 (d, *J* = 7.7 Hz, 1H), 7.98 (d, *J* = 7.3 Hz, 1H), 7.90 (s, 1H), 7.84 – 7.74 (m, 2H), 7.73 – 7.64 (m, 2H), 5.50 (s, 2H), 5.29 (s, 2H). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 192.4 (C=O), 141.9 ($C_q$), 139.1 ($C_q$), 133.5 ($C_q$), 133.1 ($C_q$), 130.5 ($C_q$), 129.2 (CH), 128.6 (CH), 128.5 ($C_q$), 127.9 ($C_q$), 127.8 (CH), 127.6 (CH), 126.7 (CH), 126.6 (CH), 124.8 (CH), 74.8 ($CH_2$), 72.4 ($CH_2$). **LC-MS** calcd for $C_{17}H_{12}NaO_2$ $[M+Na]^+$ 271.21, found 271.05.